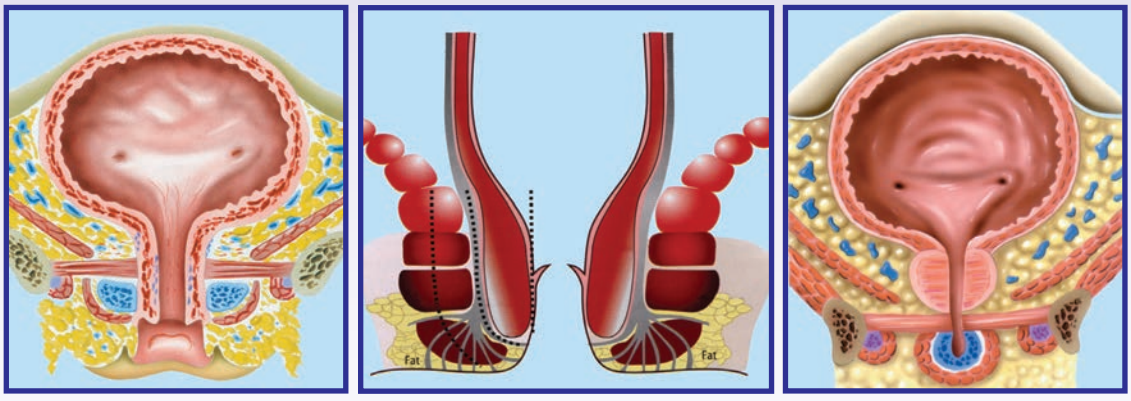
INCONTINENCE

EDITORS

PAUL ABRAMS - LINDA CARDOZO -
SAAD KHOURY - ALAN WEIN



5th International Consultation on Incontinence, Paris February, 2012

European Association of Urology

5th EDITION 2013

ICUD

Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

The Publishers have made every effort to trace the copyright holders for borrowed material. If they have inadvertently overlooked any, they will be pleased to make the necessary arrangements at the first opportunity.

The great tragedy of science :
The slaying of a beautiful hypothesis by an ugly fact
Thomas Huxley (1825-1895)

ISBN : 978-9953-493-21-3

LAYOUT: SMART-DOT marketing & web consultants - www.smart-dot.com

PREFACE

Paul Abrams

The 5th International Consultation on Incontinence was held in Paris in February 2012, made possible by the generous support of the European Association of Urology. The four previous ICI Consultations were held as stand-alone meetings. However, by holding the 5th ICI during the annual meeting of EAU this made possible the attendance of a wider range of participants than had previously occurred.

The 23 committees included almost 200 experts from every corner of the globe: all selected according to their pre-eminence in their topic area within the overall subject in incontinence. The committees prepared their chapters making full use of modern technology and in particular email discussions. Hence they arrived at the 5th ICI with their committees' work in final draft. The principle of the Consultation is to present the final draft to a wider audience and then to finalize the chapter following the discussions at the Consultation.

The 1st Consultation occurred in 1998 and since then the scope had gradually broadened so that, once again this year, the Consultation included faecal incontinence, pelvic organ prolapse, bladder pain syndrome and obstetric fistula.

Whilst some conditions afflict either men or women, many conditions affect both sexes. The ICUD also held a Consultation in 2012 on Male Urinary Tract Symptoms and consideration could be given to combining these Consultations in the next cycle. Both Consultations deal with functional pelvic disorders, usually of a benign nature, although some patient's problems emanate from treatment of malignancy, for example, stress incontinence after a radical prostatectomy for prostate cancer. However, the principles of management are similar in both men and women, in most conditions. It is of interest that there is increasing discussion of a new speciality that combines female urology, urogynaecology and benign coloproctology.

This book, produced by the huge efforts of the 23 committees has once again vigorously examined and summarised the latest scientific evidence, and remains a unique publication and reference source. The reference source is invaluable to all those who commit their professional lives to men and women suffering from these often miserable conditions. The conditions we deal with are not "glamorous" medicine and remain "Cinderella" subjects. However, we have seen the emphasis move towards measuring outcomes by assessing improved quality of life. As the population ages then maintaining or improving quality of life in the latest stages of all our lives will attract greater attention. Hence the work of the ICI remains vitally important to the many millions of women and men who suffer from these conditions.

Paul Abrams, Chairman of the 5th International Consultation on Incontinence.

November 2012

Faculty

Editors

P. Abrams, *U.K*
L. Cardozo, *U.K*
S. Khoury, *France*
A. Wein, *USA*

Members of the Commitees

(Alphabetical order - Chairmen in bold print)

- 18	ABRAMS, PAUL	UK
- 1	ALTMAN, D.	Sweden
- 7	AMARENCO, G.	France
- 8	**ANDERSSON, KARL-ERIK**	**USA**
- 10	APOSTOLIDIS, A.	Greece
- 14	ATHANASIOU, STAVROS	Greece
- 9	AUSTIN, PAUL	USA
- 9	BAEL, AN	Belgium
- 15	BAESSLER, KAVEN	Germany
- 15	BARBER, MATTHEW	USA
- 5A	BASRA, CRAMAN	UK
- 16	BERGHMANS, B.	The Netherlands
- 3	**BIRDER, L.**	**USA**
- 20	BLISS, D.Z.	USA
- 16	**BLISS, DZ.**	**USA**
- 23	BO, K.	Norway
- 5A	BOSCH, RUUD	The Netherlands
- 12	BRADLEY, C.	USA
- 23	**BRUBAKER, L.**	**USA**
- 13	BRUSCHINI, HOMERO	Brazil
- 20	BUCKLEY, B.	Ireland
- 21	BUCKLEY, BRIAN	UK/Ireland
- 12	BURGIO, K.	USA
- 8	CARDOZO, LINDA	UK
- 1	CARTWRIGHT, R.	UK
- 2	CHACKO, S.	USA
- 3	CHAI, T.	USA
- 12	CHAMBERS, T.	Canada
- 8	CHAPPLE, CHRISTOPHER R	UK
- 9	CHASE, JANET	Australia
- 11	CHEN, LIANG KUNG	Taiwan
- 15	CHEON, CECILIA	Hong Kong
- 5A	CHERIAN, PRASEETHA	USA
- 5B	CHERIAN, PRASEETHA	USA
- 16	CHIARIONI, G.	Italy
- 23	CHOO, M.S.	Korea
- 13	COMITER, CRAIG	USA
- 23	COOK, J.	UK
- 20	**COTTENDEN, A.**	**UK**
- 5A	COTTERILL, NIKKI	UK
- 5B	COTTERILL, NIKKI	UK
- 5A	COYNE, KARIN	USA
- 5B	COYNE, KARIN	USA
- 8	CRUZ, FRANCISCO	Portugal
- 6	DE GENNARO, MARIO	Italy
- 18	**DE RIDDER, DIRK**	**Belgium**
- 18	DE VRIES, CATHERINE	USA
- 22	DE WACHTER, STEFAN	The Netherlands
- 2	DE WACHTER, S.	Belgium
- 15	DEITZ, VIVIANNE	The Netherlands
- 7	DELANCEY, JOHN O. L.	USA
- 15	DETAYRAC, RENAUD	France
- 19	DINIS, P.	Portugal
- 14	**DMOCHOWSKI, ROGER**	**USA**
- 7	DOUMOUCHTSIS, STERGIOS K.	UK
- 10	**DRAKE, M.J.**	**UK**
- 22	DUDDING, THOMAS	England
- 12	**DUMOULIN, C.**	**Canada**
- 18	ELNEIL, SUZY	UK
- 18	EMASU, ALICE	Uganda
- 16	EMMANUEL, A.	UK
- 10	EMMANUEL, A.	UK
- 18	ESEGBONO, GLORIA	UK/Nigeria
- 20	FADER, M.	UK
- 7	FERNANDO, RUWAN	UK
- 2	**FRY, CH.**	**UK**
- 10	GAJEWSKI, J.	Canada
- 20	GARTLEY, C.	USA
- 21	GARTLEY, CHERYLE	USA
- 13	GOLDMAN, HOWARD B.	USA
- 14	GOMELSKY, ALEX	USA
- 21	GORDON, DEBORAH	Australia
- 8	GRATZKE, CHRISTIAN	Germany
- 21	GRIEBLING, TOMAS L.	USA
- 3	GRIFFITHS, D.	Canada
- 13	GRISE, PHILIPPE	France
- 3	GRUNDY, D.	UK
- 18	GUEYE, SERIGNE	Senegal
- 15	GUTMAN, ROBERT	USA
- 12	HAGEN, S.	UK
- 19	**HANNO, P.**	**USA**
- 13	HANUS, TOMAS	Czech Republic
- 10	HARRISON, S.C.W.	UK
- 6	HASHIM, HASHIM	UK

- 20	HAYDER, D.	Germany
- 10	HEESAKKERS, J.	The Netherlands
- 11	KIRSCHNER HERMANNS, RUTH	Germany
- 13	**HERSCHORN, SENDER**	**Canada**
- 18	HILTON, PAUL	UK
- 6	HOBSON, PHILIP TOOSZ	UK
- 23	HOMMA, Y.	Japan
- 22	HU, TEH-WEI	USA
- 12	HUNTER, K.	Canada
- 4	IGAWA, TY.	Japan
- 12	IMAMURA, M.	UK
- 11	JOHNSON 2ND, THEODORE	USA
- 6	KAKIZAKI, HIDEHIRO	Japan
- 2	KANAI, AJ.	USA
- 15	KARRAM, MICKEY	USA
- 5A	KELLEHER, CON	UK
- **5B**	**KELLEHER, CON**	**UK**
- 7	KHULLAR, VIK	UK
- 4	**KOELBL, H.**	**Germany**
- 5A	KOPP, ZOE	USA
- 5B	KOPP, ZOE	USA
- 14	KRAUS, STEVEN	USA
- 11	KUCHEL, GEORGE A.	USA
- 6	KUO, HANN-CHORNG	Taiwan
- 23	KUSEK, J.	USA
- 1	LAPITAN, M.C.	The Philippines
- 4	LATERZA, R.M.	Germany
- 17	LAURBERG, S.	Denmark
- 8	LEE, KYU-SUNG	Korea
- 17	LEHUR, P.	France
- 10	LEMACK, G.	USA
- 19	LIN, A.	Taiwan
- 4	LOWRY, A.	USA
- 10	MADERSBACHER, H.	Austria
- 17	**MADOFF, R. D.**	**USA**
- 15	**MAHER, CHRISTOPHER**	**Australia**
- 11	MARKLAND, ALAYNE	USA
- 17	MATZEL, K. E.	Germany
- 23	MEIKLE, S.	USA
- 16	MELLGREN, A.	USA
- 17	MELLGREN, A.F.	USA
- 1	**MILSOM, IAN**	**Sweden**
- 16	MIMURA, T.	Japan
- 17	MIMURA, T.	Japan
- 18	MOHAMMAD, RAHMAT	Nigeria
- 12	MOORE, K.	Canada
- 22	**MOORE, KATE H.**	**Australia**
- 18	MOURAD, SHERIF	Egypt
- 18	MULETA, MULU	Ethiopia
- 1	NELSON, R.	UK
- 21	**NEWMAN, DIANE K.**	**USA**
- 19	NICKEL, C.	Canada
- 9	**NIJMAN, RIEN**	**The Netherlands**
- 14	NITTI, VICTOR	USA
- 19	NORDLING, J.	Denmark
- 16	NORTHWOOD, M.	Canada
- 21	NORTON, NANCY	USA
- 23	NYGAARD, I.	USA
- 17	O'CONNELL, P. R.	Ireland
- 20	OSTASZKIEWICZ, J.	Australia
- 11	OSTASZKIEWICZ, JOAN	Australia
- 11	PALMER, MARY H.	USA
- 10	PANICKER, J.	UK
- 23	PAYNE, C.	USA
- 16	PEDEN-MCALPINE, C.	USA
- 21	PETTY, LEIGH E.	Australia
- 18	PICKARD, ROBERT	UK
- 7	PODNAR, S.	Slovenia
- 7	PUCCINI, F.	Italy
- 10	RADZISZEWSKI, P.	Poland
- 14	REID, FIONA	UK
- 14	ROBINSON, DUDLEY	UK
- 5A	ROSENBERG, MATTHEW	USA
- 6	**ROSIER, PETER F.W.M.**	**The Netherlands**
- 18	ROVNER, ERIC	USA
- 3	SADANANDA, P.	UK
- 10	SAKAKIBARA, R.	Japan
- 4	SALVATORE, S.	Italy
- 16	SANTORO, GA	Italy
- 15	SENTILHES, LOIC	France
- 4	SIEVERT, K-D.	Germany
- 1	SILLÉN, U.	Sweden
- 16	SLIEKER-TEN HOVE, M.	The Netherlands
- 14	SMITH, A.R.B.	UK
- 18	STANFORD, EDWARD	USA
- 5A	STASKIN, DAVID	USA
- 5B	STASKIN, DAVID	USA
- 22	SUBAK, LESLEE	USA
- 4	SULTAN, A.	UK
- 5A	SYMONDS, TARA	
- 5B	SYMONDS, TARA	
- 11	SZONYI, GEORGE	Australia
- 2	TAKEDA, M.	Japan
- 5A	TANNENBAUM, CARA	Canada
- 8	TANNENBAUM, CARA	Canada
- 9	TEKGUL, SERDAR	Turkey
- 12	THAKAR, R.	UK
- 3	THOR, K.	USA
- 1	TIKKINEN, K.	Finland
- 23	TINCELLO, D.G.	UK
- 7	**TUBARO, A.**	**ITALY**
- 19	UEDA, T.	Japan
- 12	VALE, L.	UK
- 3	VALENTINO, R.	USA
- 6	VAN MEEL, TOM DAVID	Belgium
- 19	VAN OPHOVEN, A.	Germany
- 17	VARMA, M. G.	USA
- 7	VODUŠEK, DAVID B.	Slovenia
- 9	VON GONTARD, ALEXANDER	Germany
- 11	**WAGG, ADRIAN S.**	**Canada**
- 22	WAGNER, TODD H.	USA
- 21	WANG, KEFANG	China
- 8	WEIN, ALAN J	USA
- 16	WHITEHEAD, WE	USA
- 20	WILDE, M.	USA
- 12	WILLIAMS, K.	UK
- 13	WOODHOUSE, CHRISTOPHER	UK
- 10	WYNDAELE, J.-J.	Belgium
- 5A	YOSHIDA, MASAKI	Japan
- 2	YOUNG, JS.	UK
- 16	ZBAR, A.	Israel

Members of the Commitees
(by committee - Chairmen in bold print)

1. Epidemiology

ALTMAN, D.	Sweden
CARTWRIGHT, R.	UK
LAPITAN, M.C.	The Philippines
MILSOM, IAN	**Sweden**
NELSON, R.	UK
SILLÉN, U.	Sweden
TIKKINEN, K.	Finland

2. Cell Biology

CHACKO, S.	USA
DE WACHTER, S.	Belgium
FRY, CH.	**UK**
KANAI, AJ.	USA
TAKEDA, M.	Japan
YOUNG, JS.	UK

3. Neural Control

BIRDER, L.	**USA**
CHAI, T.	USA
GRIFFITHS, D.	Canada
GRUNDY, D.	UK
SADANANDA, P.	UK
THOR, K.	USA
VALENTINO, R.	USA

4. Pathophysiology

IGAWA, TY.	Japan
KOELBL, H.	**Germany**
LATERZA, R.M.	Germany
LOWRY, A.	USA
SALVATORE, S.	Italy
SIEVERT, K-D.	Germany
SULTAN, A.	UK

5A. Initial Assessment of Urinary Incontinence

BASRA, CRAMAN	UK
BOSCH, RUUD	The Netherlands
CHERIAN, PRASEETHA	USA
COTTERILL, NIKKI	UK
COYNE, KARIN	USA
KELLEHER, CON	UK
KOPP, ZOE	USA
ROSENBERG, MATTHEW	USA
STASKIN, DAVID	**USA**
SYMONDS, TARA	USA
TANNENBAUM, CARA	Canada
YOSHIDA, MASAKI	Japan

5B. Patient-Reported Outcome Assessment

CHERIAN, PRASEETHA	USA
COTTERILL, NIKKI	UK
COYNE, KARIN	USA
KELLEHER, CON	**UK**
KOPP, ZOE	USA
STASKIN, DAVID	USA
SYMONDS, TARA	USA

6. Urodynamic Testing

DE GENNARO, MARIO	Italy
HASHIM, HASHIM	UK
HOBSON, PHILIP TOOSZ	UK
KAKIZAKI, HIDEHIRO	Japan
KUO, HANN-CHORNG	Taiwan
ROSIER, PETER F.W.M.	**The Netherlands**
VAN MEEL, TOM DAVID	Belgium

7. Imaging, Neurophysiological Testing and other Tests

AMARENCO, G.	France
DELANCEY, JOHN O. L.	USA
FERNANDO, RUWAN	UK
DOUMOUCHTSIS, STERGIOS K.	UK
KHULLAR, VIK	UK
PODNAR, S.	Slovenia
PUCCINI, F.	Italy
TUBARO, A.	**Italy**
VODUŠEK, DAVID B.	Slovenia

8. Pharmacological Treatment of Urinary Incontinence

ANDERSSON, KARL-ERIK	**USA**
CARDOZO, LINDA	UK
CHAPPLE, CHRISTOPHER R	UK
CRUZ, FRANCISCO	Portugal
GRATZKE, CHRISTIAN	Germany
LEE, KYU-SUNG	Korea
TANNENBAUM, CARA	Canada
WEIN, ALAN J	USA

9. Diagnosis and Management of Urinary Incontinence in Childhood

AUSTIN, PAUL	USA
BAEL, AN	Belgium
CHASE, JANET	Australia
VON GONTARD, ALEXANDER	Germany
NIJMAN, RIEN	**The Netherlands**
TEKGUL, SERDAR	Turkey

10. Neurologic Urinary and Faecal Incontinence

APOSTOLIDIS, A.	Greece
DRAKE, M.J.	**UK**
EMMANUEL, A.	UK
GAJEWSKI, J.	Canada
HARRISON, S.C.W.	UK
HEESAKKERS, J.	The Netherlands
LEMACK, G.	USA
MADERSBACHER, H.	Austria
PANICKER, J.	UK
RADZISZEWSKI, P.	Poland
SAKAKIBARA, R.	Japan
WYNDAELE, J.-J.	Belgium

11. Incontinence in the Frail Elderly

WAGG, ADRIAN S.	**Canada**
CHEN, LIANG KUNG	Taiwan
JOHNSON 2ND, THEODORE	USA
KIRSCHNER HERMANNS, RUTH	Germany
KUCHEL, GEORGE A.	USA
MARKLAND, ALAYNE	USA
OSTASZKIEWICZ, JOAN	Australia
PALMER, MARY H.	USA
SZONYI, GEORGE	Australia

12. Adult Conservative Management

BRADLEY, C.	USA

DUMOULIN, C.	**Canada**
BURGIO, K.	USA
HUNTER, K.	Canada
WILLIAMS, K.	UK
VALE, L.	UK
IMAMURA, M.	UK
MOORE, K.	**Canada**
THAKAR, R.	UK
HAGEN, S.	UK
CHAMBERS, T.	Canada

13. Surgical Treatment of Urinary Incontinence in Men

GOLDMAN, HOWARD B.	USA
BRUSCHINI, HOMERO	Brazil
COMITER, CRAIG	USA
GRISE, PHILIPPE	France
HANUS, TOMAS	Czech Republic
HERSCHORN, SENDER	**Canada**
WOODHOUSE, CHRISTOPHER	UK

14. Surgery for Urinary Incontinence in Women

ATHANASIOU, STAVROS	Greece
DMOCHOWSKI, ROGER	**USA**
GOMELSKY, ALEX	USA
KRAUS, STEVEN	USA
NITTI, VICTOR	USA
REID, FIONA	UK
ROBINSON, DUDLEY	UK
SMITH, A.R.B.	UK

15. Pelvic Organ Prolapse Surgery

BAESSLER, KAVEN	Germany
BARBER, MATTHEW	USA
CHEON, CECILIA	Hong Kong
DEITZ, VIVIANNE	The Netherlands
DETAYRAC, RENAUD	France
GUTMAN, ROBERT	USA
KARRAM, MICKEY	USA
MAHER, CHRISTOPHER	**Australia**
SENTILHES, LOIC	France

16. Assessment and Conservative Management of Faecal Incontinence and Quality of Life in Adults

BERGHMANS, B.	The Netherlands
BLISS, DZ.	**USA**
CHIARIONI, G.	Italy
EMMANUEL, A.	UK
MELLGREN, A.	USA
MIMURA, T.	Japan
NORTHWOOD, M.	Canada
PEDEN-MCALPINE, C.	USA
SANTORO, GA	Italy
SLIEKER-TEN HOVE, M.	The Netherlands
WHITEHEAD, WE	USA
ZBAR, A.	Israel

17. Surgery For Faecal Incontinence

LAURBERG, S.	Denmark
LEHUR, P.	France
MADOFF, R. D.	**USA**
MATZEL, K. E.	Germany
MELLGREN, A.F.	USA
MIMURA, T.	Japan
O'CONNELL, P. R.	Ireland
VARMA, M. G.	USA

18. Fistula

ABRAMS, PAUL	UK
DE RIDDER, DIRK	**Belgium**
DE VRIES, CATHERINE	USA
ELNEIL, SUZY	UK
EMASU, ALICE	Uganda
ESEGBONO, GLORIA	UK/Nigeria
GUEYE, SERIGNE	Senegal
HILTON, PAUL	UK
MOHAMMAD, RAHMAT	Nigeria
MOURAD, SHERIF	Egypt
MULETA, MULU	Ethiopia
PICKARD, ROBERT	UK
ROVNER, ERIC	USA
STANFORD, EDWARD	USA

19. Bladder Pain Syndrome

DINIS, P.	Portugal
HANNO, P.	**USA**
LIN, A.	Taiwan
NICKEL, C.	Canada
NORDLING, J.	Denmark
VAN OPHOVEN, A.	Germany
UEDA, T.	Japan

20. Management Using Continence Products

BLISS, D.Z.	USA
BUCKLEY, B.	Ireland
COTTENDEN, A.	**UK**
FADER, M.	UK
GARTLEY, C.	USA
HAYDER, D.	Germany
OSTASZKIEWICZ, J.	Australia
WILDE, M.	USA

21. Continence Promotion, Education & Primary Prevention

BUCKLEY, BRIAN	UK/Ireland
GARTLEY, CHERYLE	USA
GORDON, DEBORAH	Australia
GRIEBLING, TOMAS L.	USA
NEWMAN, DIANE K.	**USA**
NORTON, NANCY	USA
PETTY, LEIGH E.	Australia
WANG, KEFANG	China

22. Economics of Urinary & Faecal Incontinence, and Prolapse

DUDDING, THOMAS	England
DE WACHTER, STEFAN	The Netherlands
HU, TEH-WEI	USA
MOORE, KATE H.	**Australia**
SUBAK, LESLEE	USA
WAGNER, TODD H.	USA

23. Research Methodology

BO, K.	Norway
BRUBAKER, L.	**USA**
CHOO, M.S.	Korea
COOK, J.	UK
HOMMA, Y.	Japan
KUSEK, J.	USA
MEIKLE, S.	USA
NYGAARD, I.	USA
PAYNE, C.	USA
TINCELLO, D.G.	UK

EVIDENCE – BASED MEDICINE OVERVIEW OF THE MAIN STEPS FOR DEVELOPING AND GRADING GUIDELINE RECOMMENDATIONS.

INTRODUCTION

The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). In the last ten years Consultations have been organised on BPH, Prostate Cancer, Urinary Stone Disease, Nosocomial Infections, Erectile Dysfunction and Urinary Incontinence. These consultations have looked at published evidence and produced recommendations at four levels; highly recommended, recommended, optional and not recommended. This method has been useful but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001 http://minerva.minervation.com/cebm/docs/levels.html). The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the Consultations organised by ICUD. It is highly desirable that the recommendations made by the Consultations follow an accepted grading system supported by explicit levels of evidence.

The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly 'mapped' onto the Oxford system.

1. **1st Step: Define the specific questions or statements that the recommendations are supposed to address.**
2. **2nd Step: Analyse and rate (level of evidence) the relevant papers published in the literature.**

The analysis of the literature is an important step in preparing recommendations and their guarantee of quality.

2.1 What papers should be included in the analysis?

- Papers published, or accepted for publication in the peer reviewed issues of journals.
- The committee should do its best to search for papers accepted for publication by the peer reviewed journals in the relevant field but not yet published.
- Abstracts published in peer review journals should be identified. If of sufficient interest the author(s) should be asked for full details of methodology and results. The relevant committee members can then 'peer review' the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue – it may actually increase publication bias as "uninteresting" abstracts commonly do not progress to full publication.
- Papers published in non peer reviewed supplements will not be included.

An exhaustive list should be obtained through:

I. the **major database**s covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index)

II. the **table of contents** of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

It is expected that the highly experienced and expert committee members provide additional assurance that no important study would be missed using this review process.

2.2 How papers are analysed?

Papers published in peer reviewed journals have differing quality and level of evidence.

Each committee will rate the included papers according to levels of evidence (see below).

The level (strength) of evidence provided by an individual study depends on the ability of the study design to minimise the possibility of bias and to maximise attribution.

is influenced by:

• the type of study

The hierarchy of study types are:

- Systematic reviews and meta-analysis of randomised

controlled trials

- Randomised controlled trials
- Non-randomised cohort studies
- Case control studies
- Case series
- Expert opinion

• how well the study was designed and carried out

Failure to give due attention to key aspects of study methodology increase the risk of bias or confounding factors, and thus reduces the study's reliability.

The use of **standard check lists** is recommended to insure that all relevant aspects are considered and that a consistent approach is used in the methodological assessment of the evidence.

The objective of the check list is to give a quality rating for individual studies.

• how well the study was reported

The ICUD has adopted the CONSORT statement and its widely accepted check list. The CONSORT statement and the checklist are available at

http: //www.consort-statement.org

2.3 How papers are rated?

Papers are rated following a **«Level of Evidence scale»**.

ICUD has modified the Oxford Center for Evidence-Based Medicine levels of evidence.

The levels of evidence scales vary between types of studies (ie therapy, diagnosis, differential diagnosis/symptom prevalence study).

the Oxford Center for Evidence-Based Medicine Website: http://minerva.minervation.com/cebm/docs/ levels.html

3. 3rd Step: Synthesis of the evidence

After the selection of the papers and the rating of the level of evidence of each study, the next step is to compile a summary of the individual studies and the overall direction of the evidence in an **Evidence Table**.

4. 4th Step: Considered judgment (integration of individual clinical expertise)

Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgement as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgement based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence based medicine requires the integration of individual clinical expertise with best

available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannised by evidence, for even excellent external evidence may be inapplicable to, or inappropriate for, an individual patient: without current bestevidence, practice quickly becomes out of date. Although it is not practical to lay our "rules" for exercising judgement, guideline development groups are asked to consider theevidence in terms of quantity, quality, and consistency; applicability; generalisability; and clinical impact.

5. 5th Step: Final Grading

The grading of the recommendation is intended to strike an appropriate balance between incorporating the complexity of type and quality of the evidence and maintaining clarity for guideline users.

The recommendations for grading follow the Oxford Centre for Evidence-Based Medicine.

The levels of evidence shown below have again been modified in the light of previous consultations. There are now 4 levels of evidence instead of 5.

The grades of recommendation have not been reduced and a "no recommendation possible" grade has been added.

6. Levels of Evidence and Grades of Recommendation Therapeutic Interventions

All interventions should be judged by the body of evidence for their efficacy, tolerability, safety, clinical effectiveness and cost effectiveness. It is accepted that at present little data exists on cost effectiveness for most interventions.

6.1 Levels of Evidence

Firstly, it should be stated that any level of evidence may be positive (the therapy works) or negative (the therapy doesn't work). A level of evidence is given to each individual study.

- **Level 1** evidence (incorporates Oxford 1a, 1b) usually involves meta-anaylsis of trials (RCTs) or a good quality randomised controlled trial, or 'all or none' studies in which no treatment is not an option, for example in vesicovaginal fistula.
- **Level 2** evidence (incorporates Oxford 2a, 2b and 2c) includes "low" quality RCT (e.g. < 80% follow up) or metaanalysis (with homogeneity) of good quality prospective 'cohort studies'. These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.
- **Level 3** evidence (incorporates Oxford 3a, 3b and 4) includes:

good quality retrospective 'case-control studies' where a group of patients who have a condition are matched appropriately (e.g. for age, sex etc) with control individuals who do not have the condition.

good quality 'case series' where a complete group of patients all, with the same condition/disease/therapeutic intervention, are described, without a comparison control group.

- **Level 4** evidence (incorporates Oxford 4) includes expert opinion were the pinion is based not on evidence but on 'first principles' (e.g. physiological or anatomical) or bench research. The Delphi process can be used to give 'expert opinion' greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of 'options'; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made.

6.2 Grades of Recommendation

The ICUD will use the four grades from the Oxford system. As with levels of evidence the grades of evidence may apply either positively (do the procedure) or negatively (don't do the procedure). Where there is disparity of evidence, for example if there were three well conducted RCT's indicating that Drug A was superior to placebo, but one RCT whose results show no difference, then there has to be an individual judgement as to the grade of recommendation given and the rationale explained.

- **Grade A** recommendation usually depends on consistent level 1 evidence and often means that the recommendation is effectively mandatory and placed within a clinical care pathway. However, there will be occasions where excellent evidence (level 1) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous or unethical. Grade A recommendation can follow from Level 2 evidence. However, a Grade A recommendation needs a greater body of evidence if based on anything except Level 1 evidence
- **Grade B** recommendation usually depends on consistent level 2 and or 3 studies, or 'majority evidence' from RCT's.
- **Grade C** recommendation usually depends on level 4 studies or 'majority evidence' from level 2/3 studies or Dephi processed expert opinion.
- **Grade D** "No recommendation possible" would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Dephi.

7. Levels of Evidence and Grades of Recommendation for Methods of Assessment and Investigation

From initial discussions with the Oxford group it is clear that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions.

The ICUD recommend, that, as a minimum, any test should be subjected to three questions:

1. does the test have good technical performance, for example, do three aliquots of the same urine sample give the same result when subjected to 'stix' testing?
2. Does the test have good diagnostic performance, ideally against a "gold standard" measure?
3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management, does the use of the test improve outcome?

For the third component (therapeutic performance) the same approach can be used as for section 6.

8. Levels of Evidence and Grades of Recommendation for Basic Science and Epidemiology Studies

The proposed ICUD system does not easily fit into these areas of science. Further research needs to be carried out, in order to develop explicit levels of evidence that can lead to recommendations as to the soundness of data in these important aspects of medicine.

CONCLUSION

The ICUD believes that its consultations should follow the ICUD system of levels of evidence and grades of recommendation, where possible. This system can be mapped to the Oxford system.

There are aspects to the ICUD system that require further research and development, particularly diagnostic performance and cost effectiveness, and also factors such as patient preference.

P. Abrams, S. Khoury, A. Grant 19/1/04

Contents

Preface 3
Faculty 4
Level of Evidence and Grades of Recommendation 8

Committee 1: Epidemiology of Urinary Incontinence (UI) and other Lower Urinary Tract Symptoms (LUTS), Pelvic Organ Prolapse (POP) and Anal Incontinence (AI) 15
Ian Milsom (Sweden), *D. Altman (Sweden), R. Cartwright (UK), M.C., Lapitan (The Philippines), R. Nelson (UK), U. Sillén (Sweden), K. Tikkinen (Finland)*

Committee 2: Cell Biology 109
CH Fry (U.K), *S Chacko (USA), S de Wachter (Belguim), AJ Kanai (USA), M Takeda (Japan), JS Young (UK)*

Committee 3: Neural Control 179
L. Birder (USA), *T. Chai (USA), D. Griffiths (CAN), D. Grundy (UK), K. Thor (USA), R. Valentino (USA), P. Sadananda (UK)*

Committee 4: Pathophysiology of Urinary Incontinence, Faecal Incontinence and Pelvic Organ Prolapse 261
H. Koelbl (Germany), *Ty. Igawa (Japan), S. Salvatore (Italy), R.M. Laterza (Germany), A. Lowry (Usa), K-D. Sievert (Germany), A. Sultan (U.K.)*

Committee 5A: Initial Assessment of Urinary Incontinence in Adult Male and Female Patients 361
David Staskin (US), *Con Kelleher (UK), Ruud Bosch (NL), Nikki Cotterill (UK), Karin Coyne (USA), Con Kelleher (UK), Zoe Kopp (USA), Matthew Rosenberg (US), David Staskin (US), Tara Symonds (USA), Cara Tannenbaum (Canada), Masaki Yoshida (JP), Raman Basra (UK), Praseetha Cherian (USA)*

Committee 5B: Patient-Reported Outcome Assessment (5B) 389
Con Kelleher (UK), *David Staskin (US), Praseetha Cherian (USA), Nikki Cotterill (UK), Karin Coyne (USA), Zoe Kopp (USA), Tara Symonds (USA)*

Committee 6: Urodynamic Testing 429
Peter F.W.M. Rosier (The Netherlands), *Hann-Chorng Kuo (Taiwan), Mario De Gennaro (Italy), Hidehiro Kakizaki (Japan), Hashim Hashim (United Kingdom), Tom David Van Meel (Belgium), Philip Toosz Hobson (United Kingdom)*

Committee 7: Imaging, Neurophysiological Testing and Other Tests 507
A. Tubaro (Italy), *David B. Vodušek (Slovenia), G. Amarenco (France), Stergios K. Doumouchtsis (UK), John O. L. DeLancey (USA), Ruwan Fernando (UK), Vik Khullar (UK), F. Puccini (Italy), S. Podnar (Slovenia)*

Committee 8: Pharmacological Treatment of Urinary Incontinence 623
Karl-Erik Andersson (USA), *Christopher R Chapple (UK), Linda Cardozo, (UK), Francisco Cruz, (Portugal), Christian Gratzke, (Germany), Kyu-Sung Lee, (Korea), Cara Tannenbaum, (Canada), Alan J Wein (USA)*

Committee 9: Diagnosis and Management of Urinary Incontinence in Childhood 729
Rien Nijman (The Netherlands), *Serdar Tekgul (Turkey), Janet Chase (Australia), An Bael (Belgium), Paul Austin (USA), Alexander von Gontard (Germany)*

Committee 10: Neurologic Urinary and Faecal Incontinence 827
M.J. Drake (U.K.), *A. Apostolidis (Greece), A. Emmanuel (U.K.), J. Gajewski (Canada), S.C.W. Harrison (U.K.), J. Heesakkers (Netherlands), G. Lemack (U.S.A.), H. Madersbacher (Austria), J. Panicker (U.K.), P. Radziszewski (Poland), R. Sakakibara (Japan), J.-J. Wyndaele (Belgium)*

Committee 11: Incontinence in the Frail Elderly 1001
Adrian S. Wagg, (Canada), *Liang Kung Chen (Taiwan), Ruth Kirschner – Hermanns (Germany), George A. Kuchel (USA), Theodore Johnson 2nd (USA), Joan Ostaszkiewicz (Australia), Alayne Markland, (USA) Mary H. Palmer(USA), George Szonyi (Australia)*

Committee 12: Adult Conservative Management **1101**
K. Moore (Canada), C. Dumoulin (Canada), *C. Bradley (USA), K. Burgio (USA), T. Chambers (Canada), S. Hagen (UK), K. Hunter (Canada), M. Imamura (UK), R. Thakar (UK), K. Williams (UK), L. Vale (UK)*

Committee 13: Surgical Treatment of Urinary Incontinence in Men **1229**
Sender Herschorn (Canada), *Homero Bruschini (Brazil), Craig Comiter (USA), Howard B. Goldman (USA), Philippe Grise (France), Tomas Hanus (Czech Republic), Christopher Woodhouse (U.K.)*

Committee 14: Surgery for Urinary Incontinence in Women **1307**
Roger Dmochowski (U.S.), *Stavros Athanasiou (Greece), Fiona Reid (U.K.), Steven Kraus (U.S.), Victor Nitti (U.S.), Alex Gomelsky (U.S.), Dudley Robinson (U.K.), A.R.B. Smith (U.K.)*

Committee 15: Pelvic Organ Prolapse Surgery **1377**
Christopher Maher (AUST), *Kaven Baessler (Germany), Matthew Barber (USA),Cecilia Cheon (Hong Kong), Vivianne Deitz (Netherlands), Renaud DeTayrac (France), Robert Gutman (USA), Loic Sentilhes (France), Mickey Karram (USA)*

Committee 16: Assessment and Conservative Management of Faecal Incontinence and Quality of Life in Adults **1443**
Bliss DZ (USA), *Mellgren A (USA), Whitehead WE (USA), Chiarioni G (Italy), Emmanuel A (UK), Santoro GA (Italy), Zbar A (Israel), Peden-McAlpine C (USA), Northwood M (Canada), Slieker-ten Hove M (Netherlands), Berghmans B (Netherlands), Mimura T. (Japan)*

Committee 17: Surgery For Faecal Incontinence **1487**
R. D. Madoff (USA), *S. Laurberg (Denmark), P. Lehur (France), K. E. Matzel (Germany), A.F. Mellgren (Usa), T. Mimura (Japan), P. R. O'connell (Ireland), M. G. Varma (Usa)*

Committee 18: Fistula **1527**
Dirk De Ridder (Belgium), *Paul Abrams (UK), Catherine De Vries (USA), Suzy Elneil (UK), Alice Emasu (Uganda), Gloria Esegbono (UK/Nigeria), Serigne Gueye (Senegal), Rahmat Mohammad (Nigeria), Sherif Mourad (Egypt), Mulu Muleta (Ethiopia),* **Non-obstetrical fistula**, *Paul Hilton (UK), Sherif Mourad (Egypt), Robert Pickard (UK), Edward Stanford (USA), Eric Rovner (USA)*

Committee 19: Bladder Pain Syndrome **1581**
P. Hanno (USA), *P. Dinis (Portugal), A. Lin (Taiwan), C. Nickel (Canada), J. Nordling (Denmark), A. van Ophoven (Germany), T. Ueda (Japan)*

Committee 20: Management Using Continence Products **1651**
A. Cottenden (UK), *D.Z. Bliss (USA), B. Buckley (Ireland), M. Fader (UK), C. Gartley (USA), D. Hayder (Germany), J. Ostaszkiewicz (Australia), M. Wilde (USA)*

Committee 21: Continence Promotion, Education & Primary Prevention **1787**
Diane K. Newman, (USA), *Brian Buckley (UK/Ireland), Deborah Gordon (Australia), Tomas L. Griebling (USA), Leigh E. Petty (Australia), Kefang Wang (China), Cheryle Gartley (USA), Nancy Norton (USA)*

Committee 22: Economics of Urinary & Faecal Incontinence, and Prolapse **1829**
Kate H. Moore (Australia), *Todd H. Wagner (USA), Leslee Subak (USA), Stefan de Wachter (Netherlands), Thomas Dudding (England), Teh-wei Hu (USA)*

Committee 23: Research Methodology **1863**
L. Brubaker (US), *I. Nygaard (US), K. Bo (Norway), D.G. Tincello (UK), Y. Homma (Japan), J. Cook (UK), M.S. Choo (Korea), J. Kusek (US), S. Meikle (US), C. Payne (US)*

Recommendations of the International Scientific Committee: Evaluation and Treatment of Urinary Incontinence, Bladder Pain Syndrome,Pelvic Organ Prolapse and Faecal Incontinence. **1895**

Detailed Contents

INCONTINENCE

EDITORS

P. ABRAMS, L. CARDOZO,

S. KHOURY, A. WEIN

Committee 1

Epidemiology of Urinary Incontinence (UI) and other Lower Urinary Tract Symptoms (LUTS), Pelvic Organ Prolapse (POP) and Anal Incontinence (AI)

Chair

Ian Milsom (Sweden)

Members

D. Altman (Sweden)

R. Cartwright (UK)

M.C. Lapitan (The Philippines)

R. Nelson (UK)

U. Sillén (Sweden)

K. Tikkinen (Finland)

CONTENTS

A. INTRODUCTION

B. BASIC EPIDEMIOLOGICAL CONSIDERATIONS

C. EPIDEMIOLOGY OF ENURESIS AND UI IN CHILDREN

I. GENERAL COMMENTS AND DEFINITIONS

II. PREVALENCE OF NOCTURNAL ENURESIS (NE)

III. POTENTIAL RISK FACTORS FOR NE

IV. PREVALENCE OF FUNCTIONAL INCONTINENCE IN CHILDREN

V. POTENTIAL RISK FACTORS FOR DAY WETTING

VI. SUMMARY POINTS

D. EPIDEMIOLOGY OF UI IN WOMEN

I. GENERAL COMMENTS AND DEFINITIONS

II. PREVALENCE

III. INCIDENCE AND REMISSION

IV. RISK FACTORS

V. SUMMARY POINTS

VI. FUTURE DIRECTIONS

E. EPIDEMIOLOGY OF UI IN MEN

I. GENERAL COMMENTS

II. PREVALENCE

III. POTENTIAL RISK FACTORS FOR UI

IV. FACTORS OF UNCLEAR ASSOCIATION WITH UI IN MEN

V. SUMMARY POINTS

F. EPIDEMIOLOGY OF OVERACTIVE BLADDER AND NOCTURIA

I. OVERACTIVE BLADDER

II. NOCTURIA

G. EPIDEMIOLOGY OF POP

I. GENERAL COMMENTS AND DEFINITIONS

II. PREVALENCE OF POP

III. INCIDENCE

IV. POTENTIAL RISK FACTORS

V. SUMMARY POINTS

H. THE GENETIC EPIDEMIOLOGY OF UI AND POP IN ADULT WOMEN

I. FAMILY STUDIES

II. TWIN STUDIES

III. SEGREGATION ANALYSES

IV. LINKAGE STUDIES

V. GENE ASSOCIATED STUDIES

VI. SUMMARY POINTS

I. EPIDEMIOLOGY OF ANAL INCONTINENCE

I. GENERAL COMMENTS AND DEFINITIONS

II. PREVALENCE

III. INCIDENCE

IV. RISK FACTORS

V. PREVENTION

VI. SUMMARY POINTS

VII. FUTURE NEEDS

J. WHY DO PREVALENCE ESTIMATES DIFFER?

I. GENERAL PROBLEMS IN SURVEY RESEARCH

II. DIFFERENT DEFINITIONS AND MEASUREMENT

III. SUMMARY POINTS

K. HELP SEEKING BEHAVIOUR

I. URINARY INCONTINENCE

II. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE

III. SUMMARY POINTS

L. EPIDEMIOLOGY AND CLINICAL WORK: FROM RESPONDENT TO PATIENT

I. WORLDWIDE ESTIMATES OF CURRENT AND FUTURE INDIVIDUALS (≥20 YEARS) WITH LOWER URINARY TRACT SYMPTOMS INCLUDING URINARY INCONTINENCE AND OVERACTIVE BLADDER

II. SUMMARY POINTS

M. RECOMMENDATIONS FOR FURTHER RESEARCH

I. URINARY INCONTINENCE

II. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE

REFERENCES

Epidemiology of Urinary Incontinence (UI) and other Lower Urinary Tract Symptoms (LUTS), Pelvic Organ Prolapse (POP) and Anal Incontinence (AI)

Ian Milsom

D. Altman, R. Cartwright, M.C. Lapitan, r. nelson, U. Sillén, K. Tikkinen

A. INTRODUCTION

In this report we focus on the epidemiology (distribution and determinants) of urinary incontinence (UI) and other lower urinary tract symptoms (LUTS), pelvic organ prolapse (POP) and anal incontinence (AI). We also discuss important topics such as differences between epidemiological and clinical approaches to health problems, help seeking behaviour, and methodological issues for this research.

We have included a section on overactive bladder and nocturia which are commonly occurring LUTS. A worldwide estimation of the current and future number of individuals with LUTS [1,2] including UI and overactive bladder (OAB) is also included at the end of this chapter.

The epidemiological population under study for this review will mainly be community dwelling non-institutionalised persons. The review will include discussion of the prevalence, incidence, natural history, and presence of racial and ethnic differences. We also review correlates and potential risk factors that have been revealed in epidemiological studies. Progress has clearly been made during the 4 years since our previous report when the 4th International Consultation on Incontinence (4th ICI) was published. Some new important areas have been studied with increasing regularity and quality. We have searched the literature for relevant new articles, thus reviewing a large number of high-quality and population based studies, as well as clinical trials that might include relevant epidemiological data. Because of an abundant number of studies, only a small fraction can be presented in a text like this. Other studies not presented here may have equally useful information, but lack of space precluded their inclusion.

Summary points:

- This review includes discussion of the prevalence, incidence, natural history, and presence of racial and ethnic differences in the epidemiology of UI, OAB, nocturia, POP and AI.
- Correlates and potential risk factors that have been revealed in epidemiological studies are also reviewed.

B. BASIC EPIDEMIOLOGICAL CONSIDERATIONS

Epidemiology is the scientific study of the distribution and determinants of disease in people. *Descriptive epidemiology* is the description of disease prevalence, incidence, (and mortality) by persons, place and time, while the term *analytical epidemiology* describes the search for determinants of disease risk. The discovery of risk factors and protective factors may then in turn lead to primary or secondary prevention.

In order to collect knowledge about risk factors or natural history, observational studies are needed. Cohort studies and case-control studies are the most common. However, caution is always needed when interpreting the results from such studies, as associations found in epidemiological studies may not be the same as causes. Longitudinal study designs and appropriate control for confounding factors are preferred, as these increase the validity of epidemiologic studies. For practical and ethical reasons, experimental designs are seldom used.

Recommendations and conclusions should always be based on the best available evidence. Studies of interventions, and studies of risk factors generally cannot be randomised because they relate to inherent human characteristics or practices, and exposing subjects to harmful risk factors is unethical. No uniform guidelines for assessing the results of observational studies exist, and the level of evidence for risk factors from observational studies should be judged on the soundness of the exclusion of alternative explanations by statistical and other controls. But some initiatives for how to report meta-analyses of observational studies have been taken [3].

Studies of disease frequency should rely on a very specific definition of the condition under investigation. The absence of unifying definitions for the conditions reviewed here is a fundamental problem which has not been resolved. Definitions used and problems associated with them are discussed in the subsections for the particular populations below.

Prevalence is defined as the probability of experiencing a symptom or having a condition or a disease within a defined population and at a defined time point. The concept is important for establishing the distribution of the condition in the population and for projecting the need for health and medical services.

Incidence is defined as the probability of developing the condition under study during a defined time period. Incidence is usually reported for one-, two- or five-year time intervals.

Even in many of the recent studies reviewed analyses are very simple. Often only proportions or percentages are used to describe differences in different subgroups. Many analyses do not control for confounders (by stratification or multivariate analysis techniques). There is an obvious need for more advanced epidemiological analyses of risk factors and comorbidity, and strength of associations should be determined by relative risks and odds ratios.

The relative risk (RR) estimates the magnitude of an association between exposure and a condition, and indicates the likelihood of having the condition in the exposed group relative to those who are not exposed (e.g. do not have the risk factor). A RR of 1.0 indicates that the rates in the exposed and non-exposed groups are identical and thus that there is no association between the exposure and the condition in that specific dataset. A value greater than 1.0 indicates a positive association or an increased risk. A RR of 2.5 for UI indicates that there is a 2.5 times increased risk or that the persons in question are 150 percent more likely to have incontinence than those without the risk factor.

The odds ratio (OR) is the odds for having a risk factor in persons with a condition divided by the odds among those without the condition. An OR of 2.5 for UI my be interpreted as meaning that in this sample the odds in favour of having incontinence are 2.5 times higher among those with the risk factor than among those without.

For a condition with high prevalence, like UI or POP, OR and RR will not be identical, but in practice the results can be interpreted similarly. Results should always be given with a 95% confidence interval (CI).

Words like well established and established may be used about risk factors and findings with a high level of evidence in the literature. For less documented findings words like " indications of" or " data are suggestive" may be used.

Summary points:

- Descriptive epidemiology reports disease incidence, prevalence (and mortality) by persons, place and time.
- Analytical epidemiology searches for determinants of disease risk. There is a need for good longitudinal cohort studies.
- Variations in definitions and measurement issues are fundamental, and lead to problems with assessing the findings in epidemiological studies.
- There is a need for more advanced epidemiological analyses of risk factors and comorbidity using multivariable techniques, and strength of associations should be determined by relative risks and odds ratios.

C. EPIDEMIOLOGY OF ENURESIS AND UI IN CHILDREN

I. GENERAL COMMENTS AND DEFINITIONS

The International Children's Continence Society (ICCS) has issued new recommendations regarding terminology of bedwetting or *nocturnal enuresis* (NE) [4]. NE is now the term for all urinary incontinence during sleep taking place in discrete episodes, regardless of the presence or absence of concomitant daytime symptoms. *Monosymptomatic nocturnal enuresis* (MNE) denotes bedwetting without any other LUTS symptoms, and *non-monosymptomatic nocturnal enuresis* (NMNE) should be used for those with any concomitant LUTS.

NE is caused by relative nocturnal polyuria [5] and/or nocturnal bladder over-activity [6], combined with the lack of arousal at the time when the bladder needs to be emptied. The most important cause is, of course, the lack of arousal, otherwise the child would have had nocturia.

Any other leakage of urine in children during both the day and night is referred to as UI, just as it is in the adult population. UI with no obvious cause, i.e. without neurological or congenital anatomic alterations, is often seen together with other urinary symptoms such as frequency, urgency and infections. Altogether these symptoms are referred to as functional LUT dysfunction, which is the term used to describe the entire spectrum of functional filling-voiding disturbances. Several sub-classifications have been used for children who present with varying degrees of "functional" urinary symptoms. Some are based on urodynamic patterns, others on clinical presentation.

According to recent definitions by the ICCS [4], based on symptoms and flow-residual studies rather than invasive urodynamic investigations, incontinence as a result of a filling-phase dysfunction, is in most cases due to an OAB, which can also be referred to as "urgency syndrome" and "urge incontinence". Children with OAB usually have detrusor overactivity, but this label cannot be applied to them without cystometric evaluation. When incontinence is the result of a voiding-phase dysfunction, the diagnosis is often dysfunctional voiding (DV), which is induced by increased activity in the sphincter and pelvic floor during voiding. It is subdivided into staccato and fractionated voiding, and the terms cannot be applied unless repeat uroflow measurements have been performed. Voiding postponement (VD) is another common LUT dysfunction causing UI in children, but differs from the other since it is induced by a habitual postponement of voiding and not a LUT dysfunction per se.

NE and UI due to functional LUT dysfunction are the wetting problems addressed in this chapter. Both can be either primary (the child has not been dry for more than six months) or secondary (the wetting has recurred after a dry period lasting more than six months). If the complaints are secondary, they may signify psychological, neurological or even structural anomalies and therefore require careful consideration.

The healthy infant is socially incontinent but physiologically continent, because micturitions (about once every hour) are discrete and there is no leakage of urine between micturition [7]. Bladder control develops during the first four to six years of life and is a highly complex process, which is still not fully understood. Most children are toilet trained by the age of three years, although there is huge social and cultural variation. By the age of five years, the child is normally able to void at will and to postpone voiding in a socially acceptable manner [8]. By this age, night-time and daytime involuntary wetting becomes a social problem and a cause for therapeutic intervention.

II. PREVALENCE OF NOCTURNAL ENURESIS (NE)

As bladder control is something that develops over time, longitudinal studies are the best way of defining the dynamics of this process. Studies giving us the prevalence for all children between five and 15 years of age, for example, are not appropriate, as all the developmental stages are clustered together. It is therefore better to give the prevalence for an age cohort, such as seven-year-olds. Furthermore, random sampling should preferably be used in order to be able to say anything about the population. These problems associated with understanding epidemiology were summarised by Krantz [9], who also reviewed the epidemiological studies that had been published by 1993.

One explanation for the variation in prevalence in different studies is the fact that some studies include only monosymptomatic enuresis (MNE), whereas others also include what is defined as non-monosymptomatic enuresis (NMNE). Another explanatory factor is that the frequency of enuretic episodes differs or is not taken into account in some studies. Moreover, most epidemiological studies link primary and secondary enuresis together.

1. PREVALENCE OF ALL NIGHT WETTING (MNE+ NMNE) ACCORDING TO AGE

Longitudinal cohort studies should be the ideal when analysing epidemiology in childhood NE, as there is a successive reduction in prevalence. Only a few of these studies are available [10-15] and cross-sectional studies at different ages therefore have to be used.

Most studies investigate cohorts of children in an age span of six to 12 years of age, for example, and give the prevalence for the entire group. Some of them also give the age-related prevalence [13, 16-26] which is summarised in **Table 1**. Cross-sectional studies of a specific age are also included [27-31] in **Table 1**.

In most studies (Table 1), the prevalence for seven-year-olds was between 7% and 10%. In two studies, the prevalence was higher; 15.1% and 16.4% for Turkish [20] and Korean [18] children respectively, despite the fact that the inclusion criteria were very similar in all the studies dealing with seven-year-olds (NE=night wetting once/month or more), apart from the studies by Hellström [27] (once/3 months or more) and Järvelin [28] (once/6 months or more). The prevalence of more frequent wetting (once/week or more) was lower compared to the prevalence for all wetting (once/month or more) by age, which have been illustrated in **Figure 1**.

In nine studies at age seven years [12,16,19,21-24,27-28], (Table 1) the numbers of both non-enuretic and enuretic children were given and the definitions

Table 1. Prevalence of nocturnal enuresis (NE) (= Monosymptomatic nocturnal enuresis (MNE) + Non-monosymptomatic nocturnal enuresis (NMNE) together) grouped according to age.

Author and year	Prevalence of NE (%)		
	7 years	11-12 years	16-17 years
Chiozza [16]	6.8	2	
Järvelin [28]	8		
Spee-van der Wekke [18]	8	4.6	
Cher [19]	9.3	1.7	
Hellström [27, 29]	9.5		0.5
Ferguson [12]	10.3		
Kanaheswari [25]	10.3	3.3	
Serel [20]	15.1	4	
Lee [21]	16.4	4.5	
Swithinbank [30, 31]		4.7	1.1
Soderstrom [23]	7.0	2.6	
Kajiwara [22]	10.1	3.7	
Yeung [24]	10.1	2.0	1.7
Butler[15]	14.2		
Su [26]		1.9	

for enuresis were similar (MNE and NMNE, wetting once/1-3 months or more). A prevalence of 10% was obtained by meta-analyses of these studies (cohort of 14372 seven-year-old children, of whom 1422 were enuretic). Only four studies included groups of children that were chosen at random from the population [16,21,24,28].

At age 11-12 years, the prevalence of NE had decreased and from the studies shown in **Table I** the prevalence varied between 1.7% and 4.7%. In seven of the studies, the number of non-enuretics and enuretics were available and the definition of NE was similar (once/month or more), apart from Swithinbank's [30] study (once/3 months or more). In these studies, the total number of children included was 8947, while the number of children with NE was 278, giving a prevalence of 3.1%. So, of those children with NE at age seven years, almost 15% spontaneously grow out of the wetting every year. In a recent Japanese study a higher resolution rate was reported in children with MNE compared to NMNE in children 7 to 12 years of age (21% and 15%, respectively) [22]. Similar results were found in a study from Hong Kong in which the proportion of children with NMNE was significantly greater in adolescent boys than in boys aged 5-10 years (32% vs 14.6%), even if the total prevalence of NE was decreasing as in other studies [24].

The variation in the prevalence of NE at 11-12 years between the studies is less than that seen at age seven years. The highest prevalence is no longer found in Turkey or Korea, as was the case at age seven years, but instead comes from a non-randomised cross-sectional study of 11- to 12-year-old schoolchildren (n=1145) in the UK (4.7%). It can therefore be suggested that the high prevalence seen in the studies from Turkey and Korea at age seven is not due to differences in genetic predisposition, but rather to phenotypic differences, such as the age of toilet training and the subsequent attainment of bladder control, socio-economic status, or cultural differences.

At age 16-17, three cross-sectional studies show a further reduction in prevalence to 0.5-1.7%. Two of the studies re-investigated children who had

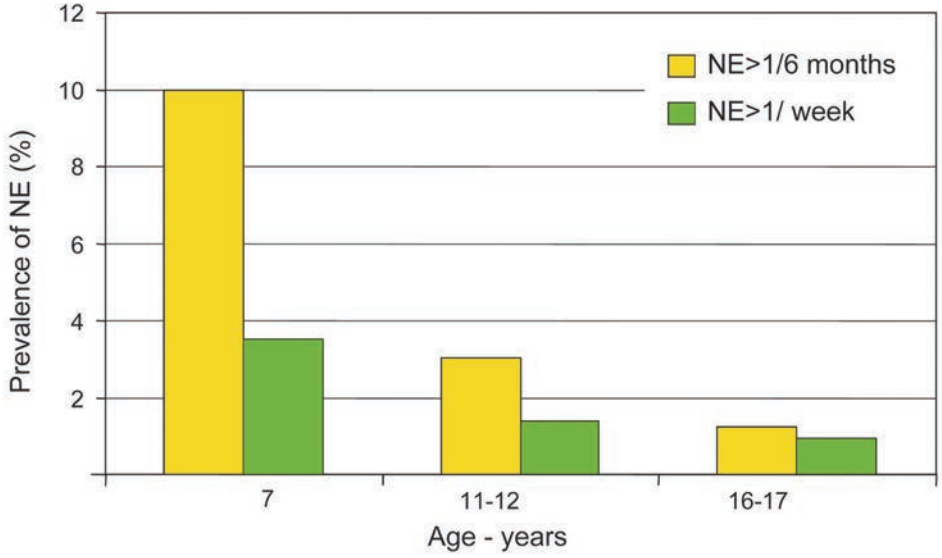


Figure 1. Prevalence of nocturnal enuresis (NE) by frequency of enuretic episodes and age. The data were obtained from metaanalyses of the epidemiological studies included in table III.1. NE>1 episode/6months: at 7 years [16, 19, 21-25, 27-28,], 11-12 years [16, 19, 21-24, 30] and 16-17 years [24, 29, 31]. NE>1 episode/ week: at age 7 years [23, 24, 27, 28], 11-12 years [23, 24, 30] and 16-17 years [24, 29].

previously been studied; at age seven years [29] and 11-12 years [30] respectively. The prevalence when the cohorts were added together was 1.3% (cohort=3819, NE=51) [24,29,31], which gives a spontaneous cure rate of 11% a year among those who wet at age 11-12 years.

In a study of 13,081 adults randomly sampled in the Netherlands [32], an overall prevalence of NE of 0.5% was found. There was no significant difference between age groups. Primary NE was reported by 50% of the men and 19% of the women, indicating that a small group of the enuretic children remain enuretic as adults.

2. PREVALENCE OF MONOSYMPTOMATIC ENURESIS (MNE)

Very few studies make a distinction between MNE and NMNE and it is therefore difficult to obtain relevant figures for MNE (**Table 2**). In two studies from Scandinavia dealing exclusively with seven-year-olds, there was agreement between the studies; 6.4% [28] and 7.4% [27]. Recently, a Japanese study gave similar figures for MNE; 6.2% at age 7 years. In this latter study MNE corresponded to approximately 60% of all NE in ages from 7 to 12 years [19]. When it comes to studies in which all ages were mixed (5-12 years), four studies were identified in which those without daytime voiding problems could be identified.

However, the difference in prevalence of MNE varied in these studies; 3.5% [17], 6.9% [33], 9.4% [21] and 15% [34].

3. PREVALENCE OF NE VERSUS GENDER

Almost all epidemiological studies of NE report a higher prevalence in boys than in girls, with a ratio of 2:1 in western countries [16-23,26-28,30,33-35]. It appears that the gender difference diminishes with age and becomes less visible and less proven among older children [29,31,36] (**Figure 2**).

Table 2. Prevalence of Monosymptomatic nocturnal enuresis (MNE) at age seven years and overall (including all ages).

Author and year	Prevalence of MNE (%)	
	Age 7 years	All ages included
Järvelin [28]	6.4	
Hellström [27]	7.4	
Kanaheswari [25]	9.0	6.2
Lee [21]	13.6	9.4
Yeung [17]		3.5
Neveus [33]		6.9
Bower [34]		15.0
Kajiwara [22]	6.2	3.5

4. PREVALENCE OF NE VERSUS ETHNICITY

In a study from The Netherlands [18], a higher prevalence was reported in the Turkish/Moroccan group (14%) than in the Dutch children (6%) (OR 3.76 (95%CI 1.98-7.12)). An equally high prevalence was found in a Turkish study of children with NE [20] at age seven years (15.1%). In a study from Korea [18], the same high prevalence at age 7 years was identified (16.4%). However, other studies from South-East Asia had comparable [19,22,24] or even lower levels of prevalence to those in western countries. In fact, two Chinese studies have shown a low prevalence of nocturnal enuresis [17,37], 3.6% and 4.3% for children aged 4-12 and 6-16 respectively, which they attribute to earlier nocturnal urinary control in Chinese children, due to earlier toilet training.

5. PREVALENCE OF NE VERSUS FREQUENCY OF WET NIGHTS AND AGE

Yeung et al [24]showed in a large epidemiological study that the relative proportion of subjects with frequent bed-wetting increased with age. Overall 82% of the adolescents had >3 wet nights/week versus enuretic children aged 5-10 (42%) (**Figure 3**). Such a relationship is also evident in fig 1, in which the proportion of children with severe NE increase with age, even if the total number decrease. Further support for severe NE to remain in a higher proportion as compared to children with infrequent bedwetting was shown in a recent study [15]. Findings in epidemiological studies also show a correlation between severity of the NE and NMNE [15-16,38], meaning that NE in adolescents often are combined with LUT dysfunction.

III. POTENTIAL RISK FACTORS FOR NE

Several risk factors have been established or suggested by epidemiological studies and the most important ones will be discussed here.

1. DAYTIME UI AND LUT DYSFUNCTION

Daytime UI, a symptom of LUT dysfunction, has in epidemiological studies been shown to be the strongest predictor for NE (OR 4.8 (2.9-7.9)) and has been identified in a third of the patients (NMNE) [38]. However, poor concordance was revealed (kappa 0.25), which confirmed the two to be separate entities that should be evaluated and treated separately.

2. FAMILY HISTORY

NE is a hereditary disorder and this has been demonstrated in many studies (for example, [16,17,20,28,33,34,39]. The mode of inheritance appears to be autosomal dominant. Järvelin [28]

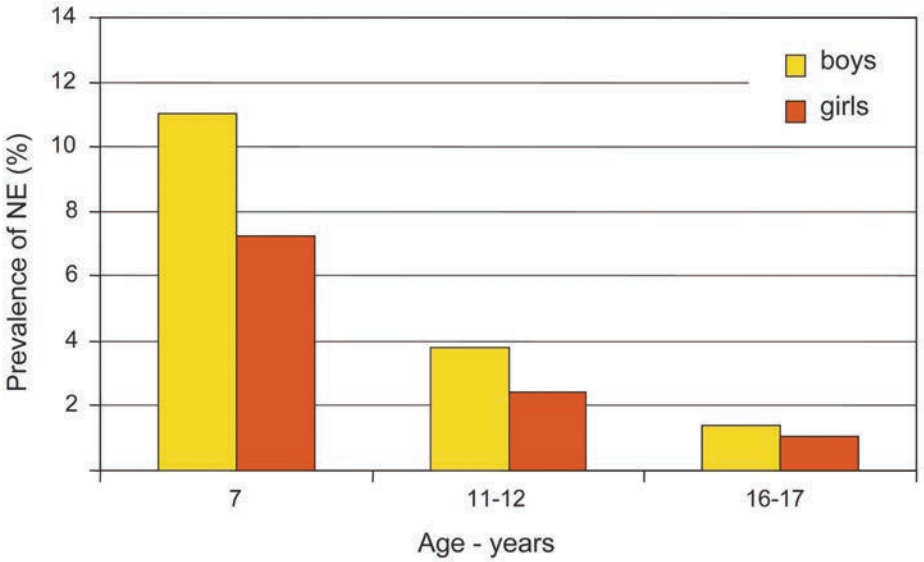


Figure 2. Prevalence of nocturnal enuresis (NE) >1 episode/6months, by gender and age. The prevalence data were obtained from metaanalyses of the following epidemiological studies: at age 7 [16, 22-24, 27, 28], age 11-12 [16, 22-24, 30] and age 16-17 [24, 29, 31].

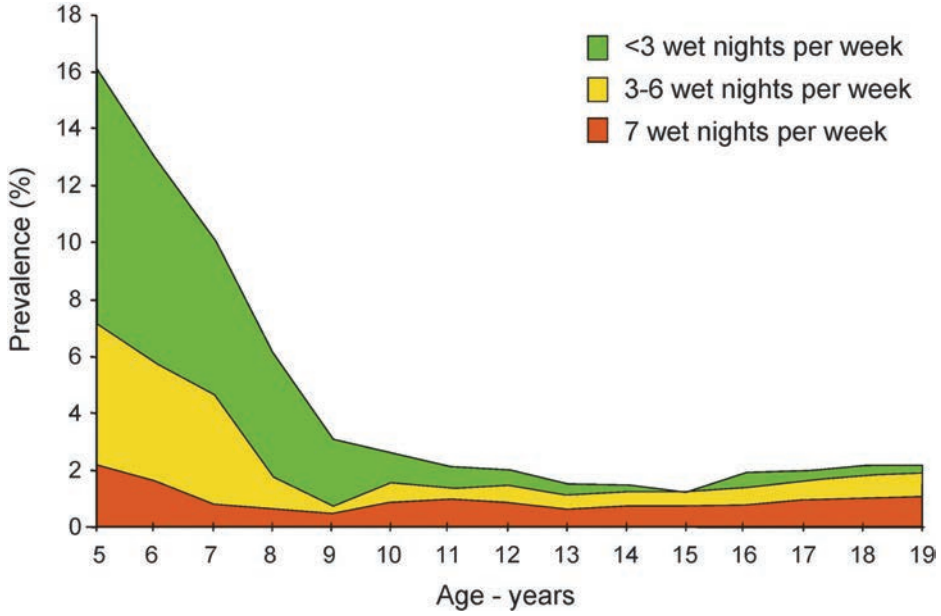


Figure 3. Prevalence of nocturnal enuresis by frequency of enuretic episodes and age. Data from [21].

showed that, if both parents were enuretics as children, the RR (95% CI) for the child to have NE was 16 (6.3-20.1), while if only one was enuretic, the RR was 7.8 (5.1-9.8). It has recently been shown that the risk for the child to have hereditary NE is increased with the severity of the enuresis. Children with severe NE (>2 episodes/week) were combined with odds ratio for maternal NE 3.63 (2.56-5.14), whereas mild and moderate NE (<2 episodes/week) had 2.14 (1.74-2-64) [40]. The association with paternal NE was less pronounced, but a similar increased association to severe NE was observed. Using molecular genetic methods, foci have been found on chromosomes 13, 12, 8 and 22 [41-42. A picture of pronounced heterogeneity for both genotype and phenotype emerges [43].

3. PSYCHOPATHOLOGY

There are evident connections between childhood enuresis and mental well-being 13-14,37,39,44-47]. Evidence is accumulating to show that psychological consequences are probably caused by the enuresis and not a cause of primary NE, which has

been thought for a long time [45]. The findings presented by Feehan [14] support this latter statement, as he only found an association between psychopathology and secondary NE, while children with primary NE did not display a connection of this kind.

4. DEVELOPMENTAL DELAY AND ADHD

Children with developmental delay and mental retardation have been shown to have a higher prevalence of NE [12,18,28,48]. Spee-van der Wekke [18] found that children who were given special education in school, including both those with and without mental retardation, had an OR of 3.74 (95%CI 2.32-6.03) for NE.

Perinatal events such as toxaemia and low birth weight, possibly involving an increased risk of minor neurological dysfunction, have also been shown to be associated with NE [12,28,39]. A connection between NE and minor neurological dysfunction of this kind has also been shown by Lunsing [49] in 12-year-old enuretic children. Furthermore, children with attention deficit hyperactivity disorders (ADHD) are more likely to have enuresis than the general child population [46,50-52].

5. SLEEP AND AROUSAL

The main pathology behind NE in children is the inability to wake up to the sensation of a full bladder. Parents often say that their enuretic child " sleeps very deeply". Some recent studies support this view. By using auditory signals [53], computerised EEG [54] or questionnaires [33], a defect in arousal has been largely validated. In the study by Neveus [33], the odds ratios were significantly high for a high arousal threshold (2.7), pavour nocturnus (2.4) and confusion when awoken from sleep (3.4). Computerised EEG energy analysis has indicated both greater depth of sleep and impaired arousal in enuretics [55]. Difficult arousal from sleep has also been shown in children with NE compared to children with isolated day-wetting problems and controls, by using a scoring system in a questionnaire [56].

6. SOCIO-CULTURAL FACTORS

Differences in the prevalence of NE [17,20-21,37,57] at early ages in different parts of the world are probably partly due to socio-cultural differences and not to differences in genetic predisposition [18]. It has been suggested that socio-economic status correlates with NE in some studies [16,46], whereas in others no correlation was found [12].

7. OTHER RISK FACTORS

Obstructive sleep apnoea (OSA) has been associated with enuresis in some patients [58]. In an epidemiological study association between severe OSA and NE in girls was shown [26], but when including both sexes and all forms of OSA no difference was seen. In another study dealing with OSA patients versus controls, a significant correlation between NE and OSA was found (OR 5.1 (2.4-10.7) [59]. Removal of large adenoids or tonsils causing upper airway obstruction in children with NE significantly reduced or cured NE [60]. Constipation (see co-morbidity below) may cause secondary NE or make primary NE persist [58]. Enkopresis was shown as a risk factor for NE in an epidemiological study (OR 2.7 (1.6-4.4)), while no association with constipation could be identified [38]. Sexual abuse must also be included among the factors that may lead to NE [62]. Organic conditions such as infravesical obstruction and neuropathic bladder may also present as NE. In most cases, however, additional symptoms are present to make detection possible. Type1 diabetes was reported to be a risk factor for secondary MNE due to the polyuria seen at presentation [63].

IV. PREVALENCE OF FUNCTIONAL INCONTINENCE IN CHILDREN

In children with functional LUT dysfunction, OAB is far more common than dysfunctional voiding. In a urodynamic study of 1,000 patients with functional LUT dysfunction, approximately two-thirds had an OAB and one-third had dysfunctional voiding [64]. Based on clinical information, another study comprising 226 children revealed that 76% were considered to have an OAB and only 1% dysfunctional voiding. The difference illustrates that different inclusion criteria influence the rate of prevalence [65].

When considering the total prevalence of UI (all frequencies of UI included) (**Table 3**), there was a variation between 3.2% and 9% in different studies at the age of seven years. In the earliest studies the prevalence was lower (3.2%-5.0%), whereas in the studies performed later in the 2000 [21, 23, 66-68], the prevalence was higher 6.3%-9.0%. One explanation for the difference was probably an increased recognition of the problem in the population through information via media etc. At 11-13 years the reported prevalence varied between 1.1% and 12.5%. Swithinbank's study [30] showed a very high prevalence (12.5%) and differed most from the rest (1.1%-4.2%). The difference could probably partly be explained by different limits for frequency of UI (occasionally [30] vs once/month or more). The fact that the studies were performed in different parts of the world was also a possible explanatory factor (UK and Korea).

The frequency of UI decreased with age (**Table 3**), which was clearly demonstrated in the subjects with frequent episodes of UI (>1/week) (**figure 4**). The prevalence at 7 years, 11-13 years and 15-17 years was 2.6%, 1.1% and 0.3% respectively. There were only two authors who investigated the same cohort of children on two occasions; Hellström [27, 29] in Sweden and Swithinbank [27, 28] in the UK.

Table 3. Day urinary incontinence (UI) (including mixed day/night)

Author (ref)	Sample size	Prevalence (%)			
		<1/ week	>1/ week	Total day+ night	Total day only
Children 7 years:					
Järvelin [28]	Total: 2892			3.2[1]	1.8
	Boys: 1444			2.7	1.3
	Girls: 1445			3.7	2.3
Hellström [27]	Total: 3555	2.3	2.5	4.9[2]	2.7
	Boys: 1834	1.7	2.1	3.8	1.7
	Girls: 1721	2.9	3.1	6.0	3.7
Lee [21]	Total: 1325			6.7[3]	3.9
Kajiwara [66]	Total: 984			9.0[3]	9.0
	Boys: 532			9.2	9.2
	Girls: 452			8.9	8.9
Söderstrom [23]	Total: 715			6.3[3]	
	Boys: 367	3.0	3.8	6.8	
Joinson [67]	Girls: 348	3.2	2.6	5.8	
	Total: 8213			7.8[3]	
	Boys: 4222			6.9	
Swithinbank [68]	Girls: 3991			8.8	
	Total: 13973	6.4	0.9	7.3	
	Boys: 7217	6.0	0.7	6.8	3.3
	Girls: 3991	7.0	1.2	8.8	5.8
Children aged 11-13 years:					
Swithinbank [27]	Total: 1171	11.9	0.6	12.5[5]	
	Boys: 510	7.0	0.2	7.2	
	Girls: 661	15.7	0.9	16.6	
Lee [21]	Total: 913			1.1[3]	0.9
Kajiwara [66]	Total: 761			2.5[3]	
	Boys: 366			1.0	
	Girls: 395			3.9	
Söderstrom [23]	Total: 763			4.2[3]	
	Boys: 398	1.8	2.3	4.1	
	Girls: 365	3.0	1.3	4.3	
Children aged 15-17 years:					
Hellström [29]	Total: 651	1.5	0.3	1.8[2]	1.8
	Boys: 344	0.3	0.0	0.3	0.3
	Girls: 307	2.9	0.7	3.6	3.6
Swithinbank [31]	Total: 940			3.0[2]	
	Boys: 411			0.9	
	Girls: 529			4.7	

Episodes of UI: 1>1/6 months, 2>1/3 months, 3> 1/ month, 4>1/2 weeks, 5 occasionally

According to the studies by Hellström, the reduction from seven years to 17 years was 0.2% per year in those with wetting at least once a week and 0.3% when including all kinds of wetting. Swithinbank reported a far higher frequency for all kinds of wetting at age 11-12 years but not at 15-16 years and the reduction in his cohort of children was therefore approximately 2% per year.

UI was more common in girls in most studies, especially in the older age groups (**Table 3, figure 4**). From the prevalence found in the different studies, daytime UI could be suggested to be 1.5 times more common in girls than in boys at age seven years, whereas at age 16 years the difference was even more pronounced: 5-10 times more common in girls than in boys (**Table 3**). Overall in a population based study of 2856 children between 4.8-12.8 years, female gender was an independent risk factor for UI (OR 5.4 (2.6-11.1), [69].

1. PREVALENCE OF OVERACTIVE BLADDER (OAB)

In a Japanese study [66], the prevalence in children between 7 and 12 years of age, OAB was seen in 17.8%, with no significant difference between boys and girls. There was a gradual decrease in prevalence from 19.8% at the age of 7 years to 12.8% at 12 years.

2. COMORBIDITY:

a) Prevalence of NE

NE in combination with UI is denoted as NMNE as mentioned above. NE has been identified as an independent risk-factor for day-UI (OR 7.2 (3.4-15.2)) [69]. Association of NE to day UI was more often reported in children with frequent UI (≥ 2 episodes/ week), as compared to infrequent UI (< 2 episodes/ week) at 7.5 years [68]. In boys NE was seen in 70-80% of those with frequent day UI compared to about 50% in those with infrequent. Corresponding figures for girls was about 55% and 30%, respectively.

b) Prevalence of Bowel problems

Urinary and faecal incontinence often coexist in different combinations. Constipation in childhood is a very common condition and when functional faecal incontinence is seen, constipation is often the cause. The term encopresis can be used synonymously with functional faecal incontinence. An increasing number of epidemiological studies reporting the frequency of bowel problems are accumulating, either in terms of constipation or functional faecal incontinence, in children with daytime wetting. **Table 4** shows that the prevalence of bowel problems in day-wetting children approximately corresponded to a third of the children (21%-35%) [23,56,66-67,69-70], with even higher prevalence in the subgroup with dysfunctional voiding (43%) [70]. A significant association between day-wetting and bowel problems was shown [23]. These results support the new treatment concept of day-wetting children, with treatment of bowel problems as the first step. MNE, on the other hand, seldom have bowel problems (0%-1%), whereas in NMNE it is more common (16%-24%) [56,70].

In an epidemiological study from Japan including 5282 children, ages between 7-12 years, 81.5% were reported to have daily bowel movements. A significant higher prevalence of NMNE was found in those with constipation, compared to hose with regular daily bowel movements (3.4% vs 2.2%) [22].

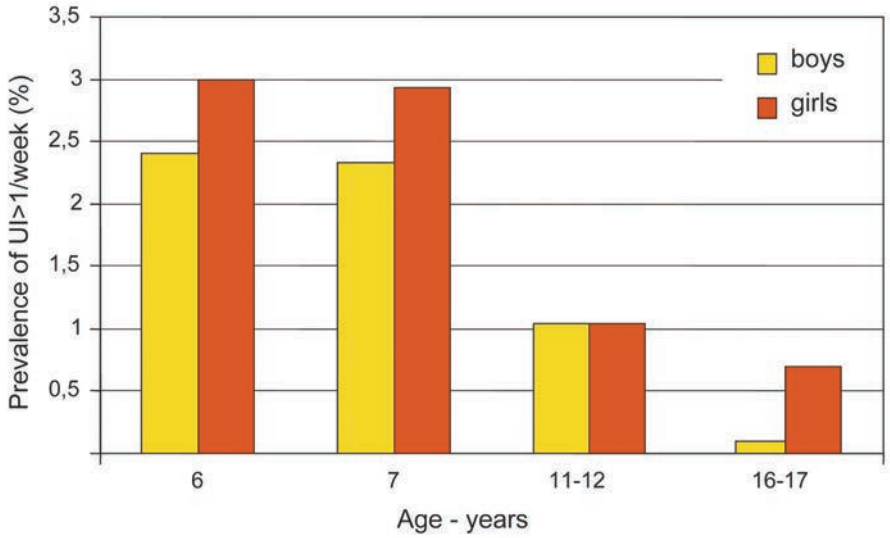


Figure 4. Prevalence of day UI (including mixed day/night) >1 episode/week by age and gender. Data are from: at age 6 years [71], 7 years [23, 27], 11-12 years [23, 30] and 16-17 years [29].

V. POTENTIAL RISK FACTORS FOR DAY WETTING

1. FAMILY HISTORY

Day wetting, also including those subjects with mixed day and night wetting, has been shown to be correlated with hereditary factors, in parallel to what is known about children with NE. However, the number of studies is limited (**Table 5**). Like for NE hereditary factors have been shown to be more pronounced in those with severe UI (>2 episodes/week), especially when paternal day UI is present (**table 5**) [40].

Table 4. Comobidities. The prevalence of concommittant bowel problems in children with day-wetting and nocturnal enuresis.

Author	Number bowel problems in day-wetting group	OR (95%CI)	Number children bowel problems in NE	OR (95%CI)
Söderstrom 2004 [23]	35%	7.2 (4.1-12.7)		1.2 (0.6-2.5)[2] 2.0 (0.6-6.3)[3]
Kajiwara 2004 [66]	33%			
Von Gontard 2004 [70]	25%[4]		0%-16%[1]	
Chandra 2004 [56]	24%		1%-24%[1]	
Joinson 2006 [67]	33%			
Sureshkumar 2009 [69]	21%	3.3 (1.4-7.7) [2]		

Episodes of UI: 1>1/6 months, 2>1/3 months, 3> 1/ month, 4>1/2 weeks, 5 occasionally

2. PSYCHOPATHOLOGY

Children under stress as a result of marital separation, for example, have a higher incidence of diurnal or mixed UI, according to some authors [16,39,71]. Moreover, psychopathology investigated by Järvelin [39] using the Children's Apperception Test (CAT) revealed a significant increase in the signs of repression, including an inability to express one's emotions and feelings (p=0.027), when comparing day wetting children with controls. Neveus [33] found that day-wetting children had more difficulty falling asleep (OR 2.4, CI 1.4-4) and he interpreted them as "anxious children". Lettgren [72] found a significant increase in attention problems and delinquent behaviour in a certain form of day-wetting children (voiding postponement) using the Child Behaviour Check List (CBCL, Achenbach). In a recent paper [73] similar results were found with the highest rate of psychiatric comorbidity in children with UI due to voiding postponement and the lowest in children with MNE. In the group with encopresis 65% were considered to have severe behavioural problems [70], meaning that children with both wetting and bowel problems are at the highest risk for psychopathology.

In a population-based study investigating psychological problems associated with day UI, 8213 children were included of whom 643 suffered from daytime wetting at median age 7.5 years [67]. Overall the results indicated a rate of psychological problems that was twice the rate reported for children with no daytime wetting, particularly notable was the increase in externalising problems. After adjustment for developmental delay, gender, stressful life events, variables associated with family socio-demographic background and soiling, there was still an independent association of daytime wetting and behaviour problems

Table 5. Day wetting vs family history (including mixed day/night wetting).

Author	RR (95%CI)	OR (95%CI)	Positive history (%)
Järvelin [39]			
-enuresis in mother	10.1 (3.4-29.3)		
-enuresis in father	5.9 (1.9-17.8)		
Sureshkumar [71]			
daytime wetting in			
-male sibling		5.3 (1.6-18.2)	
-paternal lineage		9.3 (3.2-27.3)	
Chiozza [16]*			
-enuresis in parents		12.3	
Bower [34]			
-family history of enuresis			70**
Neveus [33]			
-family history		2.0 (1.1-3.7)	
Von Gontard [40]<2 episodes/week			
-maternal NE		1.2 (0.9-1.6	
-paternal NE		1.3 (0.9-1.8)	
-maternal day UI		2.6 (1.4-5.1)	
-paternal day UI		5.5 (2.4-12.5)	
>2 episodes/week			
-maternal NE		2.1 (1.2-4.0)	
-paternal NE		2.1 (1.0-4.3)	
-maternal day UI		3.3 (0.8-13.7)	
-paternal day UI		10.1(2.3-44.1)	

**Only children with mixed day and night wetting, **compared with 45% in dry children*

(OR 2.04, CI 1.67-2.51). In another epidemiological study UI was found to be associated with parenteral concerns about the child's social behaviour (OR 3.4 (1.4-8.3)), [69]. It is not clear whether the behavioural problems described in these studies are a cause or a consequence of daytime wetting.

3. MINOR NEUROLOGICAL DYSFUNCTION AND DEVELOPMENTAL DELAY

Children with minor neurological dysfunction have also been shown to have an increased rate of day wetting. Duel [50] found that children with ADHD are three times more likely to have day UI than controls ($p<0.0005$). Also in children with delayed maturation or with mental retardation, the risk of day wetting is increased (OR 1.9 and 4 respectively), according to studies by Järvelin [28]. Perinatal events, which can also be suggestive of minimal brain dysfunction, have also been shown to be over-represented in day-wetting children. For example, Järvelin [39] found that the children of mothers who had suffered from toxaemia had RR of 8.5 (CI1.4-51.9) for day UI.

4. OTHER RISK FACTORS FOR DAY UI

Sometimes, functional day UI is difficult to distinguish from UI due to organic anomalies. The most prominent examples are the adolescent form of posterior urethral valves in boys and epispadias in girls.

In many papers, UTI is regarded as a risk factor for day UI. Järvelin [39] found RR of 8.6 (2.3-32.3) for UTI in day UI children. Neveus [33] was able to demonstrate similar connections; OR 2.3 (1.3-3.9) and similar results were seen in the Sureshkumar study [69]; OR 5.6 (2.0-15.6). However, these infections should probably be regarded as a consequence of the functional bladder disturbance with UI and not the other way round as a cause of the UI.

VI. SUMMARY POINTS

Nocturnal enuresis (NE)

- The prevalence of NE at age 7 seems to be around 10% for most countries, at age 11-12 years around 3% and at age 16 around 1.3%.
- The spontaneous resolution rate seems to be around 15% annually between 7 and 12 years, and between 12 and 17 years 11%.
- In an adult population the prevalence of NE seems to be 0.5%. The prevalence was 0.1% when including only those with a history of NE during childhood. Thus the risk for NE as adult if having the condition at 7 years of age can be calculated to 1%.
- Potential risk factors for NE in children include OAB, polyuria, family history, psychopathology, developmental delay, mental retardation, socio-cultural factors, sleep and arousal problems, sleep apnoea, constipation, sexual abuse and organic conditions such as infravesical obstruction.

• Functional incontinence

- Children who are and remain dry in the day seem to attain their diurnal continence between age 4 and 5 years.
- Diurnal UI, or combined diurnal and nocturnal UI, in children is caused by overactive bladder in the great majority of cases.
- Prevalence of functional UI decreases with age. At age 7 years prevalence figures vary between 3.2% and 9%, with the highest prevalence in recent studies. At age 15-17 years the corresponding prevalence is 1.2-3%.
- Variation in prevalence figures is mainly dependant on differences in frequency of incontinence episodes in the studies.
- Potential risk factors for diurnal UI in children include bowel problems such as constipation and functional faecal incontinence, family history, psychopathology, socio-cultural factors, minor neurological dysfunction, developmental delay, organic anomalies such as infravesical obstruction in boys and sexual abuse.

D. EPIDEMIOLOGY OF UI IN WOMEN

I. GENERAL COMMENTS AND DEFINITIONS

In this section we address the epidemiology of female UI, including its common subtypes, stress UI, urgency UI, and mixed UI. Current terminology for female UI is drawn from the 2010 IUGA/ICS joint terminology report [2] but in most instances is entirely compatible with current terminology for men [1] , and children [4] In considering the epidemiology of female UI, we mainly address the epidemiology of *the symptom of UI*, defined as complaint of involuntary loss of urine. There remains a paucity of work at a population level concerning either *the sign of UI*, defined as observation of involuntary loss of urine on examination, or on the formal diagnoses of urodynamic stress incontinence or detrusor overactivity.

A large majority of epidemiological studies have either not considered subtypes of UI, or only reported on *stress UI* (complaint of involuntary loss of urine on effort or physical exertion or on sneezing or coughing), *urgency UI* (complaint of involuntary loss of urine associated with urgency), and *mixed UI* (complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing). A small number of studies have reported prevalence and risk factors for adult *nocturnal enuresis* (complaint of involuntary urinary loss of urine which occurs during sleep). With a lack of validated questionnaire items for less common subtypes, the current literature is almost silent regarding the population prevalence and risks for *postural incontinence, continuous incontinence, insensible incontinence,* and *coital incontinence*, although they are sometimes grouped as “other incontinence”.

The validity of urinary symptom questionnaires employed in epidemiological research is considered in detail in Chapter 5. Most questionnaires were initially developed using secondary care samples, with criterion validity demonstrated in comparison to bladder diaries, pad tests, or urodynamic diagnoses. Quite widely varying terminology is used in the items assessing stress incontinence and urgency incontinence in different questionnaires and some items do not capture all aspects of the standardised definitions. Even the surrounding context for the items is known to strongly affect prevalence estimates [74], and small variations in terminology from different questionnaires may have similar effects.

The optimal assessment of incontinence subtype remains controversial [75-76], but it is clear that self-report of symptoms differs systematically from detailed clinical evaluation. In particular, for women mixed incontinence is more common than would be expected by chance using questionnaire evaluation [77], and is reproduced less frequently using urodynamics [78-79]. Stress and urgency incontinence have different treatment options, and are presumed to have different underlying pathophysiology. Caution is therefore needed when comparing epidemiological studies that either do or do not report a separate mixed incontinence subgroup, and when generalising from population level data on mixed incontinence to clinical practice.

Self-report of incontinence symptoms should reflect the woman’s own experience of incontinence, but may bear little relationship to expressed need for treatment. Across multiple measures, incontinence severity is shown to be only a moderate predictor of incontinence specific quality of life impairment [80-81]. It is important therefore to characterise both the severity of symptoms, through frequency of leakage and/or quantity of loss, and the perceived bother or impact on activities. Most questionnaires in contemporary use, including the ICIQ-SF, ICIQ-FLUTS and DAN-PSS, therefore ask patients to report both the frequency of UI, and its perceived bother. Cautious interpretation should be made of high prevalence rates obtained with case definitions that do not incorporate a measure of symptom bother.

Incontinence is a stigmatising condition in many populations [82], which creates a high risk for respondent bias in incontinence epidemiology [83-84]. Perhaps because of stigma, incontinence is also associated with low rates of presentation for care. Surveys assessing incontinence may therefore also be highly prone to both medical surveillance bias and Berksonian bias. In this section we therefore focus on community or population based samples with high response rate. To further minimise differential effects of such biases, where possible we report outcomes stratified by age, by type of incontinence, and by major subgroups of interest.

The majority of work reviewed in previous editions of this chapter, originated from developed countries. There have been many recent studies from both developing and developed countries [85], which are now reviewed. Subsequent discussion excludes however the epidemiology of obstetric vesico-vaginal fistula, which is covered in a later chapter.

II. PREVALENCE

Among general population studies included in previous ICI editions, crude prevalence estimates for the most inclusive definitions of UI ('ever' 'any' or 'at least once in the past 12 months') have ranged from 5% to 69%, with most studies reporting a prevalence of any UI in the range of 25% to 45% (**Table 6**). This enormous variation between studies is seen both within and between countries, with few studies reporting age standardised rates, largely precludes meaningful comparison between countries. If there is variation in true prevalence rates between countries, it is obscured by cultural differences in the perception of UI and willingness to report UI, as well as methodological differences [86], including in the wording of questionnaire items, in the method of administration of questionnaires, and perhaps most importantly, with differences in case definitions employed [87-88].

Only four studies have used the same survey tools and methods to report female UI general population prevalence in more than one country (**Table 7**). Three studies have attempted to assess the relative prevalence in western nations [89-91]. Across all countries surveyed, all these three studies find that SUI is the most common subtype, followed by MUI, and then UUI. Hunskaar and colleagues surveyed 29,500 women in France, Germany, the UK and Spain [89]. By demonstration of similar age trends across all countries, they suggested both lower overall prevalence of incontinence in Spain, and a relative excess of urgency incontinence in France. The EPIC and EpiLUTS studies [90-91], used similar questionnaire items explicitly based on standard definitions. However, there was inconsistency between studies. The EpiLUTS study found similar prevalence of each UI subtype in the US, UK, and Sweden, while the EPIC study reported a more than 3-fold variation in prevalence between countries, with Sweden having a prevalence of 29.5% and Italy only 9.3%. The disparity in results could be explained by differences in sampling methods, or different response rates (58%, 33% and 59% respectively). A further recent study set in Senegal, Mauritania, and Chad, reports substantial variation in prevalence across countries, even after age stratification [92] The lack of consistency in between country comparisons, even for large surveys set in western nations, makes it impossible to assess the extent of true variation between countries. It remains difficult to establish stable, meaningful prevalence rates for female UI, when there is no consensus about what constitutes significant UI. Again, extreme caution is needed in making direct comparison of crude prevalence rates.

Although between study comparisons of female UI prevalence are largely unrewarding, we can meaningfully compare within study distributions of UI by age and UI subtype. **Table 8** summarises prevalence estimates by age for female UI from community or population based studies with response rate >60%, over the period January 2008 through December 2011. Again a 10 fold variation in crude prevalence is evident between studies, so where available, overall prevalence rates are given by UI subtype, while age trends are depicted with sparklines.

As in the studies comparing prevalence between countries, although absolute prevalence rates vary widely in recent cross-sectional work, the distribution of UI subtypes is consistent. Isolated stress incontinence accounts for approximately half of all incontinence, with most studies reporting 10-39% prevalence. With few exceptions mixed incontinence is found to be next most common, with most studies report 7.5-25% prevalence. Isolated urgency incontinence is uncommon, with 1-7% prevalence, and where recorded at all, other causes of incontinence occur with approximately 0.5-1% prevalence.

In summary, current data provide very disparate estimates of population prevalence for UI in women. Approximately 10% of all adult women report leakage at least weekly. Occasional leakage is much more common, affecting 25%-45% of all adult women. Prevalence rates from cross-sectional studies uniformly demonstrate an association with age, which is explored in more detail in the section on risk factors.

III. INCIDENCE AND REMISSION

Many prospective longitudinal studies have examined UI in women, either in the general population, or focused on pregnancy, menopause or old age. However, interpretation and comparison of incidence and remission rates is fraught with difficulties. Incontinence is not intuitively a condition, with fluctuating severity, indeed the popular perception in both the medical community and the laity, is of a chronic condition. However misclassification due to the unreliability of symptom assessment tools may cause the appearance of symptom fluctuation. Measuring the short term test re-test reliability for the BFLUTS questionnaire [116], the DAN-PSS [117], the IIQ[118], or any of the other commonly used questionnaires suggests that only 80-85% of item responses are stable over even a brief retest period. Thus even when a longitudinal study is able to use the exact same item for assessment across even relatively long periods of follow up, the effect of misclassification due to questionnaire unreliability may obscure a true effect of incidence or

Table 6. Population prevalence rates for female UI from studies assessing more than one country.

Reference	Method	Age	Country	Sample	Overall Prevalence %			
Hunskaa (89)	Postal	18+	France	3,881	All UI SUI UUI MUI Other UI	44 13.6 11.9 15.0 4.0		
			Germany	3,824	All UI SUI UUI MUI Other UI	41 16.4 6.6 15.6 2.9		
			Spain	6,444	All UI SUI UUI MUI Other UI	23 9.0 4.8 6.0 3.5		
			UK	2,931	All UI SUI UUI MUI Other UI	42 17.2 6.7 14.3 3.8		
Niang (92)	Postal	16+			Age Groups	<30	30-59	60+
			Senegal	682	All UI	31.4	30.9	25.0
			Mauritania	740	All UI	8.0	13.2	22.7
			Chad	648	All UI	8.0	17.5	95.0
Irwin (90)	Direct or telephone interview	18+	Sweden	19,165	All UI	29.5		
			Italy		All UI	9.3		
			Canada		All UI	13.0		
			Germany		All UI	11.4		
			UK		All UI	14.9		
Coyne (93)	Web Based	40+	US	10,584	All UI SUI UUI MUI Other UI	67.0 23.1 6.7 21.1 5.3		
			UK	3,983	All UI SUI UUI MUI Other UI	69.0 28.6 7.1 19.6 4.9		
			Sweden	1,293	All UI SUI UUI MUI Other UI	67.1 26.9 7.9 16.9 5.0		

Table 7. Population based studies with response rate >60%, reporting prevalence of female UI by age.

Reference	Country	Sample Size	Survey Method	Age Range	Overall Prevalence (%)		Age Trend
Espuna-Pons(94)	Spain	9,063	Postal	15+	All UI	12.2	
Herschorn (95)	Canada	518	Telephone	18-90	SUI UUI	25.5 9.3	
Tahtinen (96)	Finland	2,002	Postal	18-79	SUI UUI	11.2 3.1	
Tennstedt (97)	US	3,205	Direct Interview	30-79	All UI SUI UUI MUI Other UI	10.4 2.8 1.1 5.9 0.7	
Lee (98)	South Korea	13,484	Direct Interview	19+	All UI SUI UUI MUI Other UI	24.4 11.9 1.9 10.2 0.5	
Zhu (99)	China	5,300	Direct Interview	20+	All UI SUI UUI MUI	38.5 22.9 2.8 12.4	
Nygaard (100)	US	1,961	Direct Interview	20+	All UI	15.7	
Martinez-Agullo (101)	Spain	3,090	Direct Interview	25-64	All UI	4.0	
Bodhare (102)	India	552	Direct Interview	35+	All UI	9.6	
Ojengbede (103)	Nigeria	5,001	Direct Interview	15+	All UI SUI UUI MUI	2.8 2.3 1.0 0.6	
Ahmadi (104)	Iran	800	Direct Interview	40-95	All UI	38.4	
Liapis (105)	Greece	2,000	Direct Interview	20-80	All UI SUI UUI MUI Other UI	27.0 11.9 3.0 11.1 1.1	
Amaro (106)	Brazil	685	Postal	22-96	All UI	27.0	
Lopez (107)	Puerto Rico	276	Direct Interview	21-64	All UI SUI UUI MUI	34.8 16.7 4.0 14.1	
Correia (108)	Portugal	1,483	Telephone	40+	All UI	21.4	
Slieker-ten Hove (109)	Netherlands	1,397	Postal	45-84	All UI SUI UUI MUI	58.8 30.6 6.1 23.2	
Ge (110)	China	3,058	Direct Interview	20-96	All UI SUI UUI MUI	22.1 12.9 1.7 7.5	
Botlero (86)	Aus	504	Postal	24-80	All SUI UUI MUI	6.8 4.8 0.7 1.3	
Wennberg (111)	Sweden	1,023	Postal	20+	1991 All 2007 All	14.7 27.8	
Franzen (112)	Sweden	4,609	Postal	18-79	All	28.9	
Zhu (113)	China	19,024	Direct Interview	20-99	All SUI UUI MUI	30.9 18.9 2.6 9.4	
Lasserre (114)	France	2,183	Direct Interview	18+	All SUI UUI MUI	26.8 12.1 2.9 11.2	
Onur (115)	Turkey	2,275	Direct Interview	17-80	All SUI UUI MUI	46.3 21.3 19.9 16.7	

Table 8. Studies reporting incidence and/or remission for UI in women.

Study	Country	Period (yr)	♀Sample Size	Loss to Follow Up (%)	Baseline Age	Case Definition	Prevalence at baseline (%)	Prevalence at follow up (%)	Annual Incidence (%)	Annual Remission (%)
Samuelsson (121)	Sweden	5	457	16.4	20-59	Any UI	23.5	27.5	2.9	5.9
Hagglund (122)	Sweden	4	338	26.6	20-50	Any UI	45.6	47.5	4.2	4.0
Wehrberger (123)	Austria	6.5	925	52.3	20+	Any UI Weekly UI	32.0 n/a	43.3 n/a	3.9 2.1	2.9 n/a
Townsend (124)	US	2	64,650	18.4	36-55	Monthly UI Weekly UI	52.5 n/a	48.3 n/a	6.9 1.9	7.0 n/a
Dallosso (125)	UK	1	6,424	48.9	40+	Monthly SUI	17.3	n/a	8.3	n/a
McGrother (126)	UK	1	12,036	20.2	40+	Any UI	34.2	n/a	8.8	25.2
Donaldson (127)	UK	3	12,750	33.0	40+	Any SUI	16.9	n/a	6.1-7.3	33.7-34.9
Waetjen (128)	US	5	3,301	18.1	40-55	Monthly UI Weekly UI Monthly SUI Monthly UUI Monthly MUI Other UI	46.7 15.3 32.2 9.2 13.8 2.7	n/a	11.1 1.2 5.0 3.2 2.4 0.5	n/a
Liu (129)	Australia	2	2,272 (♂&♀)	13.9	65+	Any SUI Any UUI	12.1 38.4	15.4 37.4	15.4 18.8	n/a n/a
Goode (130)	US	3	490	5.0	65+	Monthly UI	0.41	n/a	9.7	13.0
Ostbye (131)	Canada	10	5,332	60.2	65+	Any UI	19.5	28.8	1.8	n/a
Wennberg (120)	Sweden	16	2,911	51.6	20+	Any UI	14.6	27.8	1.3	2.1
Moller (132)	Denmark	1	2,860	20.1	40-60	Weekly SUI Weekly UUI	13.1 7.3	11.0 6.7	4.0 2.7	41.4 42.0
Hotledahl (133)	Norway	1	507	3.6	50-74	Monthly UI	30.6	29.8	0.9	1.4
Byles (134)	Australia	9	12,432	42.4	70-75	Sometimes UI	20.7	27.3	1.62	n/a
Lifford (135)	US	2	58,703	10.4	54-79	Monthly UI Weekly UI	45.2 n/a	51.6 n/a	4.6 1.8	6.6 4.4
Jackson (136)	US	2	1,017	19.0	55-75	Any UI	66.0	63.1	9.6	7.1
Nygaard (137)	US	6	2,025	n/a	65+	Any SUI Any UUI	40.3 36.3	n/a n/a	4.77 4.75	5.02 3.68
Gavira Iglesias (138)	Spain	5	486	34.9	65+	Any UI	41.0	54.0	7.2	2.8
Herzog (139)	US	2	1,154	30.2	60+	Any UI	37.7	52.7	15.8	7.5
Burgio (140)	US	3	541	61.9	42-50	Monthly UI	30.7	n/a	2.7	n/a
Melville (141)	US	6	5,820	18.1	57-67	Monthly UI	13.5	n/a	3.5	n/a
Jahanlu (142)	Norway	10	2331	13.0	40-44	Any UI	38.9	43.9	4.9	n/a
Botlero (143)	Australia	2	506	12.6	26-82	Any UI	41.6	44.6	8.5	8.4

remission. Even non-differential misclassification bias, can have devastating consequences both for estimates of absolute cumulative incidence, and relative incidence risk, and such effects are largest for conditions such as UI, with high prevalence and low incidence [119].

Other methodological differences may also cause wide variation. Questionnaires that use different recall periods (e.g. any leakage in last week, any leakage in last year, any leakage ever), will produce different estimates of incidence and remission. Due to changes in standard definitions, many studies also use different case definitions at baseline and follow-up. Finally, although loss to follow up itself is very variable between studies, differential loss to follow-up is observed in almost all studies, and must substantially decrease generalisability.

Annual incidence rates for broad definitions of UI ("monthly" or "any") range from 0.9% to 18.8%, while rates for weekly UI show less variation at 1.2-4.0% (**Table 8**). There is a significant negative correlation between the length of a study and its reported annualised incidence rate, suggesting that short studies of 1-2 years overestimate incidence due to a dominating effect of misclassification.

Limiting comparisons to studies with >5yr follow up suggests incidence of 1.3-4.9% even for inclusive definitions of UI. Fewer studies have reported remission rates, and again estimates vary widely between 1.2 and 42%. Again limiting comparisons to longer studies of >5yrs suggests rates of 2.1 to 5.0%. Overall these results are compatible with findings from cross-sectional studies, with modest increases in UI prevalence across the whole female population of 0.5-1% per year. Although the extent of cohort effects has rarely been reported, current data suggests that earlier cohorts are less likely to report incontinence, consistent with evidence of increased care seeking among later cohorts[111,120],

IV. RISK FACTORS

In this section we summarise the most important reported demographic, social, environmental, and lifestyle correlates of urinary incontinence in women. Genetic risk factors for incontinence and prolapse are considered together in a later section. While a majority of previously cited studies have reported associations with incontinence, some caution is again needed in judging whether these may be causal risk factors.

As already seen, a large majority of studies are cross-sectional in design, providing limited evidence of causation, since the temporal association of the putative risk factor and the onset of incontinence cannot be assessed. Where possible we therefore try to focus on risk factors for incident UI, from longitudinal studies. Again though, with the exceptions of mode of delivery, menopause hormone therapy, and weight loss, there remains a dearth of interventional studies. Even the highest quality observational studies may suffer from residual or unmeasured confounding.

1. AGE

The age distribution for incontinence of all causes reported in the widely cited EPINCONT study[144], depicts a steady increase in moderate and severe incontinence throughout the adult lifespan, but with a distinct peak in slight incontinence around the time of the menopause. Other large studies have however, reported a steady increase in prevalence for both slight and severe UI, without a distinct menopausal peak[145]. The timing and causes of a fifth and sixth decade peak have been explored in a number of high quality longitudinal studies of menopausal transition, discussed subsequently. Where such a peak is identified from cross-sectional studies, it is most pronounced for stress incontinence[89,146]. Across most cross-sectional studies isolated stress incontinence declines into old age, as mixed incontinence becomes relatively more common[144,147]. Besides methodological differences, disparity in age ranges, severity thresholds, and proportion of each subtype of incontinence probably therefore explains the differences in age trends seen in **Table 3**. These age trends from cross-sectional studies may in any case be biased by cohort or period effects.

While most cross-sectional studies find an increase in crude prevalence into old age, some recent studies identify a peak in all causes of incontinence, with a decline in the eighth and ninth decade. Such a large disparity might be explained by sampling strategies that include or exclude institutionalised adults. The epidemiology of UI in this vulnerable group deserves special attention. Only one study provides data from more than one country, allowing cross-border comparisons. From a population of 279,191 elderly people in care homes, from Denmark, France, Iceland, Italy, Japan, Sweden, and the US, the prevalence of female urinary incontinence was relatively stable at 42.0-72.5%[148], with much of that variation accounted for by differences in age structure, and proportion of residents with functional or cognitive impairment. Indeed variability in prevalence estimates for female care home residents across the entire literature is much less than for the general population[149], ranging from 42.0% in Japan [78] through to 78.4% in the US (using a much more inclusive definition) [150]. Urinary incontinence is associated with nursing home admission from the community [151]. This may in part explain the apparent steeper increase in prevalence with age in nursing homes compared to community dwelling samples [150]. Loss to follow up certainly limits our ability to accurately assess age trends in the elderly from cross-sectional studies.

Given the difficulties in establishing robust incidence estimates, most longitudinal studies do not provide good evidence of age trends in incidence. Many studies have either reported no change in incidence with age, or a stable incidence in middle age, with a sharp increase in old age. However, the large Nurse's Health Study cohort [145], provided good evidence of a decrease in incidence of stress UI following the menopause, which has more recently been explored in analyses of the SWAN study[152], the 1946 British Birth Cohort[146], and the Hordaland Women's Cohort [142,153]. All these studies provide consistent evidence of a peak in incontinence at the time of the menopause, with pre and peri-menopausal status being associated with increased incidence of UI and decreased remission of UI compared to postmenopause. As will be discussed in the section on menopausal replacement therapy, part of this peak may be iatrogenic. Consistent with evidence from cross-sectional studies [89,144], the peak is attributable mainly to slight stress incontinence.

While the association between age and female UI is clearly important for planning healthcare resource allocation, in many studies this is not an independent association. Other risk factors associated with age, including parity, co-morbidities, and BMI attenuate the association with UI [145], and additional adjustment for relevant co-morbidities typically eliminates the association [97]. Confounding factors adequately explain the association between age and UI, and therefore UI in women should not be considered as an intrinsic consequence of the aging process itself.

2. OBESITY AND ADIPOSITY

Perhaps even more than age, obesity is the most clearly established risk factor for UI in women. There is a wealth of cross-sectional, longitudinal, and interventional data demonstrating a positive association between BMI and UI, which has recently been subject to two systematic reviews [154-155]. Across a wide range of studies obese women have approximately double the risk of UI. A typical pattern of association, taken from the large Nurses' Health Study II [156]. (n=83,355) is demonstrated in **figure 5**. The ORs for UI by severity are plotted against BMI, from underweight through to obese. Although the Nurses' Health Study II is limited to middle aged women, such findings are consistent across all age groups, both within studies[157], and between studies[154]. This association is quite minimally attenuated by adjustment for other risks for UI.

Data from the EPINCONT survey also demonstrate the same positive association between BMI and more severe incontinence. Additionally they indicate that such associations hold for the major subtypes of incontinence (**Figure 6**), but are most pronounced for mixed UI, and relatively modest for UUI. Similar findings were reported for data from HERS [158]. and the 1946 British Birth Cohort[159]. with the associations with BMI being greater for stress or mixed UI compared with urgency UI.

The temporal association between BMI and UI is also established with data from the 1946 British Birth Cohort [161]., SWAN [128]., MRC Incontinence [125]. and the Nurses' Health II studies [162]. demonstrating that earlier onset of obesity is associated with increased risk for UI in middle age[161], and that both higher BMI and greater weight gain are associated with increased risk of incident UI [125,128,162]. Although again it is hard to compare between studies, it appears that BMI may be a greater risk factor for incident UI than for prevalent UI adding credence to its causal association [128]. As for cross-sectional studies, the association is stronger for incident stress UI and mixed UI, compared with incident urgency UI [125, 128].

There is adequate evidence [163-164], that obesity increases intraabdominal pressure, predisposing to stress incontinence, while coexisting

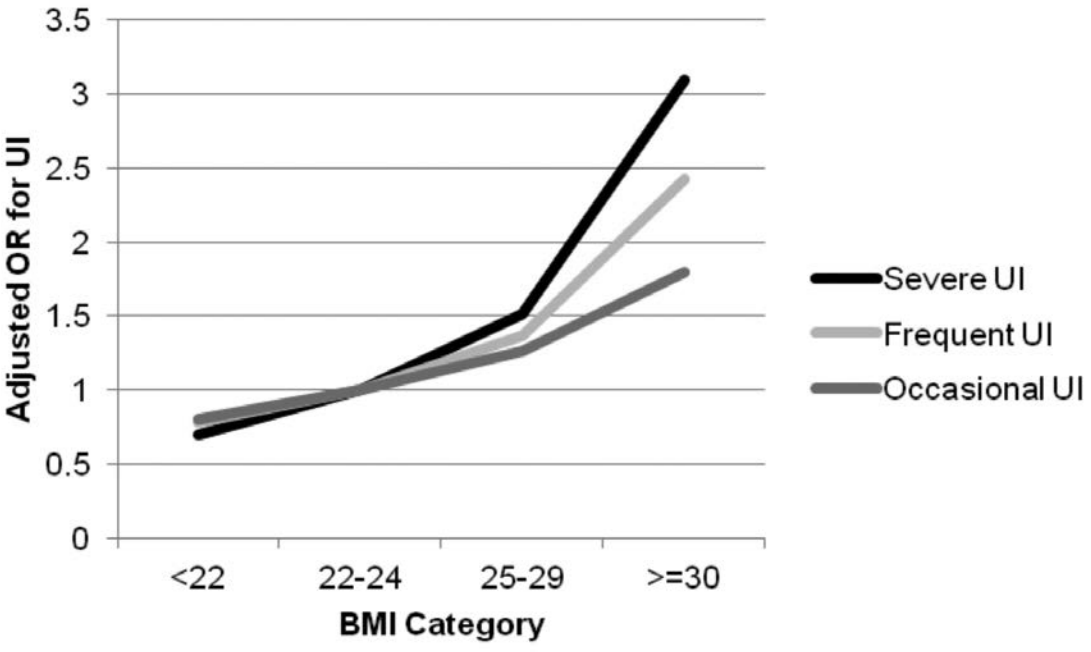


Figure 5. Associations between BMI and UI severity from [156].

metabolic syndrome predisposes to urgency incontinence [165-168]. Consistent with this hypothesis waist circumference and waist to hip ratio appeared to be associated only with stress UI, and not with urgency UI in the SWAN [128] and HERS studies[158]. More recent data from BACH [159] and KNHNES [170]. indicate that measures of central adiposity are also correlated with urgency UI.

Finally, intervention studies for weight reduction have reported that even modest weight loss is associated with improvement or resolution of both stress and urgency UI, with the probability of resolution correlated to the degree of weight loss [163,171-174]. Despite the complex interplay between weight and other risk factors for UI, we therefore have very robust evidence to support a causal role of BMI in the development of UI.

3. PARITY, PREGNANCY AND MODE OF DELIVERY

Parity is considered by the laity as among the most important risk factors for UI. This is reflected in almost all large cross-sectional surveys (**Figure 7**). Some early studies reported a threshold effect at one delivery and little or no additional risk with increasing parity [175-177], but in most subsequent work, increasing parity is associated with increased risk of UI. A single delivery is typically associated with adjusted OR of around 1.3-1.6 for UI, and further deliveries linearly increasing the risk up to an adjusted OR of 1.5-2.0 [128,145,156,178]. As expected these effects are strongest in the third and fourth decades, with substantial attenuation through middle age, and in many studies no persistent effect in old age [157,178-180], as other risk factors come to dominate. Although the EPINCONT[178] and SWAN [128] studies reported only association between parity and stress or mixed UI, other studies have suggested, a reduced but significant association with urge UI also [181-182].

There is a substantial difference in effect between vaginal delivery and caesarean delivery, that has also been subject of a systematic review [183]. Meta-analysing data from four large cross-sectional studies [184-187], suggested a significant protective effect of caesarean on stress UI (OR 0.56) and mixed UI (OR 0.70), consistent with data both from more recent cross-sectional [179,181], and longitudinal studies [188-191]. While the existing interventional studies remain significantly underpowered, even in aggregate, a trend towards protective effect of caesarean is still seen [192].

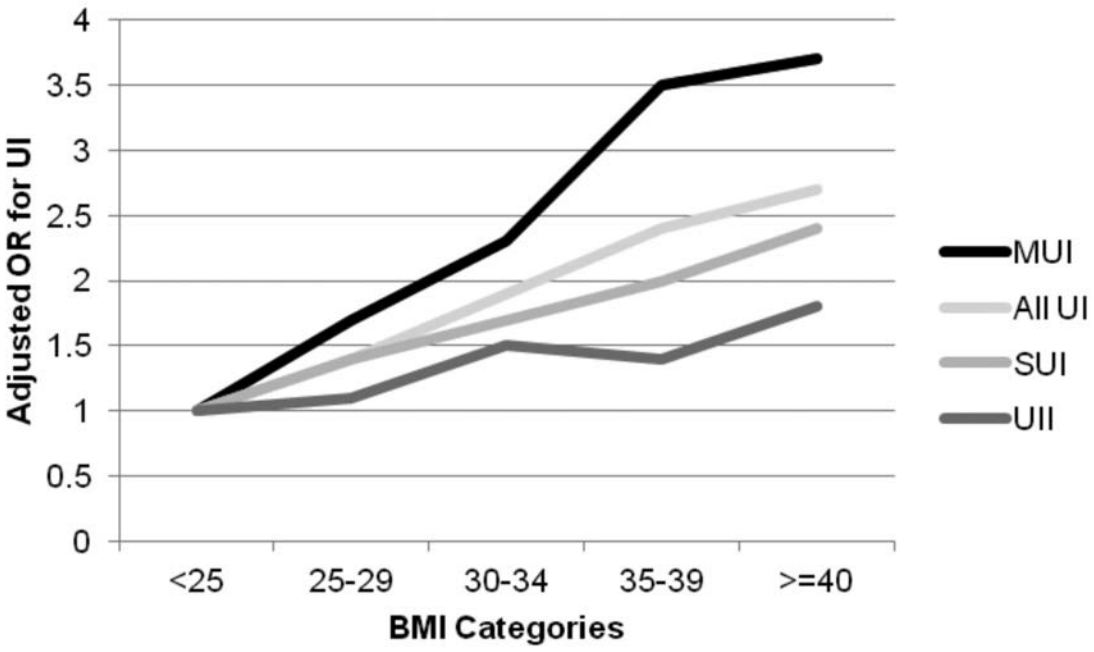


Figure 6. Associations between BMI and UI subtype from [160].

Figure 7. Adjusted OR for UI from large cross-sectional surveys grouped according to number of deliveries(128,145,156,178)

Pregnant women, and those in the early postpartum period are typically excluded from population-based studies of UI, but a large body of work considers the specific epidemiology of UI in and around pregnancy. A recent systematic review including 33 population based studies, each with response rate over 50% [193], concluded that the prevalence of UI in the first three months postdelivery was 30%, and with infrequent stress UI being most common. As demonstrated in **Table 9**, there is a gradual decrease in prevalence during the first post-partum year. The difference in UI rates between women delivering vaginally and those delivering by caesarean is evident immediately after delivery.

Despite the protective effect of caesarean, for many women the onset of incontinence is during pregnancy itself. Point prevalence of UI is low in the first trimester, rising rapidly in the second trimester and increasing slightly in the 3rd trimester [204-205]. In the population based Norwegian Mother and Child Cohort Study, (n=43,279), the prevalence of stress incontinence from before to during pregnancy, rose from 9% to 31% in nulliparous women, and from 24% to 42% in parous women. In contrast, mixed incontinence showed a similar rise in both groups (from 6% to 16% and from 8% to 20%, respectively). Urge incontinence remained virtually unchanged in both groups at less than 5%. In follow up of these women, onset of incontinence during pregnancy was strongly predictive of post-partum UI, with little modification by mode of delivery. Such an effect seems to persist even into long term follow up [189-190, 206-207], even for women who return to full continence in the immediate post-partum period. It seems that the temporary physiological changes during pregnancy may reveal women with a predisposition to incontinence in later life, in a manner analogous to gestational diabetes.

There are other suggested potentially modifiable obstetric risk factors, including induction of labour, forceps delivery, and use of episiotomy. Regardless of conflicting observational evidence of an effect of episiotomy (for example [195,203,208-209]), there are a large number of interventional studies that have not shown either harm or benefit [210]. Similarly while forceps delivery has conflicting evidence from observational studies (for example [199,209,211-212]), within the context of the second stage of labour, maternal urinary incontinence is of secondary importance in decision making regarding choice of delivery instrument [213]. In a similar vein, while induction and augmentation of labour, and use of epidural anaesthesia have each been identified as being associated with both early postpartum and persistent UI [198,214-216], it is doubtful whether this should have any effect on current obstetric practice.

Many other suggested obstetric risk factors, including age at first delivery, and birth weight, are perhaps not meaningfully modifiable. Several studies have suggested that older age at either first or last birth is associated with UI [159,217-219], although more recent data from the RRISK study suggested a U shaped distribution [216], with very young mothers also at increased risk. Inadequate adjustment for

Table 9. Prevalence of urinary incontinence in the first post-partum year among primiparous women by type of delivery

						Prevalence (%) by months post partum		
Reference	**Country**	**Type of delivey**	**N**	**Type of UI**	**Freq. of UI**	**1 to 3 months**	**4 to 6 months**	**7 to 12 months**
Chaliha (194)	UK	VD	289	All Stress	Any	15 13		
		CS	131	All Stress	Any	9 8		
Eason (195)	Canada	VD	467	All	Any ≥weekly Daily	31 10 3		
		CS	104	All	Any >weekly Daily	12 2 1		
Eftekhar(196)	Iran	VD	357	Stress	Any		16*	
		CS ECS CSL	345	Stress	Any		12* 11* 25*	
Ekstrom (197)	Sweden	VD	197	Stress Urge	Any	20 4		15 6
		CS	192	Stress Urge	Any	4 3		5 5
Pregazzi (198)	Italy	VD	379	Stress Urge	Any	8 6		
		SVD	218	Stress Urge	Any	16 1		
Farrell (199)	Canada	SVD	313	All	Any	23*	22*	
		CS ECS CSL	125 27 98	All	Any	8* 4* 9*	10* 5* 12*	
Groutz (200)	Israel	SVD	145	Stress	2+/mo.			10*
		ECS CSL	118 100	Stress	2+/mo.			3* 12*
Glazener(201)	New Zealand, UK	VD SVD IVD	2805 1954 851	All	Any	32, 29* 31, 28* 33, 30*		
		CS	569	All	Any	16, 12*		
Schytt (202)	Sweden	VD SVD IVD	750 617 133	SUI	Any			20 19 22
		CS ECS CSL	165 43 122	Stress	Any			9 0 11
Borello-France (203)	USA	VD	356	All Stress Urge Mixed	Any	35 17 4 15	31 14 3 14	
		ECS	116	All Stress Urge Mixed	Any	25 11 4 10	23 14 1 8	

** Restricted to women with no UI prior to pregnancy*
VD=all vaginal deliveries; SVD=spontaneous vaginal delivery; IVD=instrumental vaginal delivery (forceps and/or vacuum); CS=all Cesarean sections; ECS=elective Cesarean section (prior to labour); CSL=Cesarean section after onset of labour

socio-economic class may explain all these effects. Numerous studies have suggested that greater birth weight at a single delivery, or maximum weight of infant across all deliveries may also be associated with UI [177,179,201,216,220], but again randomized interventional trials of elective caesarean are needed before making clinical recommendations.

4. ETHNICITY AND RACE

With wide variations in UI prevalence between studies, comparison by race and ethnicity can be made only where such data have been reported within one study. Almost all population-based studies comparing the prevalence of UI among women from one or more racial or ethnic groups originate from the US, which may limit generalisability of conclusions. Results are summarised in Table 10. In general, across all studies, white women have a higher prevalence of UI, and in particular stress UI than all other groups.

The starkest and most consistent contrast is in rates of stress UI for black and white women. In most studies, black women have half the prevalence of stress UI compared to white women, with differences persisting after adjustment for age, parity and BMI. In comparing prevalence of mixed and urge UI for white and black women, there is less consistency. Most studies suggest similar prevalence of urge UI and mixed UI, however, the recent BACH survey found very high rates of mixed UI [27] among black women, while the EPI study reported very high rates of pure urgency UI [221].(**Table 10**) These cross-sectional data are supplemented by longitudinal studies. In SWAN [128], black women were at half the risk of incident stress UI, but nearly double the risk of incident urgency UI. In the Nurses Health Studies [222], black women had lower risk of both overall UI, and stress UI after adjustment. The consistency of this difference across both cross-sectional and longitudinal studies, employing different case definitions suggests a real difference in prevalence rather than simply reporting bias.

Typically smaller groups of east Asian or Hispanic women have been included in these studies, which precludes clear conclusions. Broadly though, Asian women report lower prevalence of both stress and urgency UI. There is less consistency in comparisons of Hispanic and non-Hispanic white women, with some studies reporting higher, and others lower overall prevalence. This heterogeneity may be explained, at least in part, by differences in prevalence among sub-populations, with Mexican-American women being at higher risk than other Hispanic women [226], or differences in extent of adjustment for covariates.

5. MENOPAUSAL REPLACEMENT THERAPY

Menopausal oestrogen replacement therapy was widely prescribed as a treatment for urinary incontinence during or after menopause, on the basis of rather heterogenous data from clinical trials [231] and inconsistent associations in cross-sectional studies [215,232]. While current evidence overall continues to support prescribing of topical oestrogen [233], the Nurse's Health Study[234], the Heart Estrogen/Progestin Replacement Study (HERS) [235], and Womens' Health Initiative (WHI) Hormone Replacement Trial [165] all provided strong evidence that oral oestrogens, with or without combined progestogens were associated with increased incident UI. In the placebo controlled HERS trial, women randomized to conjugated oral oestrogen plus medroxyprogesterone were more likely to experience worsening of their incontinence over 4 years (39% vs 27%, p<.001)[164]. In the randomized WHI trial, continent women receiving oestrogen, with or without progestogen, were approximately twice as likely to have developed stress incontinence at 1 year (16% vs 9%, p<.0001) [236]. The risks of mixed and urge incontinence were also significantly increased, though more modestly. Further trials including oestrogen arms have subsequently been reported during development of selective oestrogen receptor modulators (SERMs), confirming these findings [237]. Some SERMs, have themselves been associated with an increased risk of UI [238] although raloxifene appears safe.

6. HYSTERECTOMY

Hysterectomy is among the most common major procedures performed for women in Western nations. Many women date the onset of incontinence to a hysterectomy, but uncontrolled case series and small randomised trials produced conflicting results. Evidence from large population based observational studies has increasingly suggested a causal link, although the underlying pathophysiological mechanism is poorly understood.

Among a sample of 1,517 Taiwanese women aged 65+, hysterectomy was associated with OR 1.8 for UI, with no difference by hysterectomy route [239]. Earlier trials had however suggested either no effect [121,135] or rather more modest effects [240]. Where an association is found, it is strongest with case defintions consistent with "severe UI" [136,156,185], perhaps reflecting high rates of mild UI in controls. Using a sample of more than 900,000 women from the Swedish Population Register, abdominal hysterectomy for benign disease was associated with hazard ratio 2.1 for subsequent stress UI surgery, while vaginal hysterectomy for prolapse was associated with hazard ratio 6.3 [241]. Similar results were observed comparing hysterectomy and endometrial ablation in the Scottish Morbidity Returns database [242]. Recent data from a randomised trial of levonorgestrel-IUS versus hysterectomy [243] does confirm this effect. In follow up of 236 women, increased incidence of both stress UI (OR 1.83) and urgency UI (OR 1.48) was first noticed only at 10 years, with corresponding higher rates of treatment.

Table 10. Prevalence of UI by Race/Ethnicity in Population-based Studies.

Reference	Age	Sample	Case Definition	White	Hispanic	Black	Asian
Fultz (223)	70+	3,991	Any UI	23	-	16	-
Nygaard (224)	50-69	5,701	Any UI	17	10	10	-
Nygaard (100)	20+	1,961	Monthly UI	16	16	14	-
Burgio (140)	42-50	541	Monthly UI	32	-	18	-
Grodstein (145)	50-75	82,936	Monthly UI Weekly UI	35 18	28 16	21 10	26 13
Danforth (156)	37-54	85,670	Monthly UI Weekly UI	18 26	19 26	14 22	14 18
Sampselle (225)	42-52	3,258	Any UI	66	42	50	52
Waetjen (128)	42-52	3,002	Monthly UI Weekly UI Monthly SUI Monthly UUI Monthly MUI	57 20 32 8 16	28 11 21 1 5	39 13 13 12 13	39 9 27 4 7
Anger (226)	60+	23,477,726	Any UI Monthly UI Weekly UI Daily UI	41 35 25 15	31 27 25 8	20 17 15 11	-
Jackson (227)	70-79	1,558	Weekly UI Weekly SUI Weekly UUI	27 12 11	-	14 5 7	-
Dooley (228)	20+	4,229	Any UI Any SUI Any UUI Any MUI	53 27 8 19	50 26 8 17	38 12 11 15	-
Fenner (221)	35-64	2,814	Monthly UI Weekly UI Monthly SUI Monthly UUI Monthly MUI	33 21 13 4 7	-	15 9 4 4 4	-
Thom (83)	40-69	2109	Monthly UI Weekly UI Daily UI Weekly SUI Weekly UUI Weekly MUI	45 30 12 15 9 3	51 36 17 18 10 5	37 25 12 8 14 2	34 19 9 8 7 3
Markland (229)	65+	421	Any UI	45	29	-	-
Markland (230)	65+	490	Monthly UI	41		25	
Tennstedt (97)	30-79	3,205	Weekly SUI Weekly UUI Weekly MUI Weekly Other UI	35 13 44 7	14 11 69 6	9 3 82 5	-

Overall hysterectomy by any route appears to be associated with development of subsequent incontinence symptoms, and particularly with need for stress UI surgery. The data from observational studies should still be considered cautiously, as findings may be influenced by both healthy responder bias and medical surveillance bias, the latter of which may also affect unblinded interventional studies.

7. DIET

Studying diet as a risk factor for UI remains challenging. While some dietary constituents such as coffee, alcohol or carbonated beverages have been suspected as worsening UI, there is little theoretical reason to suspect other dietary constituents as causing, or protecting from, UI. Dietary data are difficult to obtain reliably. Studies of dietary factors must adjust for confounders, notably age and body mass, and should consider the trade-offs made with other constituents. Finally, women may change dietary intake in response to UI, making cross- sectional studies of diet and UI difficult to interpret.

Several studies have examined the consumption of coffee as a risk factor for UI. While some studies report a positive association with an increased risk of UI [131,244-245], others have either reported no association [246], or a protective effect [125,247]. Even within the large EPINCONT study there appeared to be conflicting findings with a positive association with mixed UI, but a negative association with stress UI [160]. The WHI study demonstrates a dose-dependent positive association between caffeinated coffee and urgency UI, but not for decaffeinated coffee or other UI subtypes [248]. The overall picture is therefore unclear.

The EPINCONT study suggested a positive association between tea drinking and stress UI or mixed UI [160], while analysis of the Swedish Twin Registry Cohort showed an association only with overactive bladder [247]. The Leicester MRC Incontinence study is one of two studies to have used food frequency questionnaires, and found no association with tea [125]. It is unclear whether tea consumption contributed significantly to the overall association between UI and dietary caffeine in the WHI study [248]. A positive association between alcohol consumption and UI has been reported by some studies [249], but is found to be either protective [125,250], or of no significance [160] in other studies.

The most comprehensive assessment of diet as a risk factor for UI comes from the Leicester MRC study [125]. Besides effects reported above, this study also found an increased incidence of stress UI with carbonated drinks, and reduced incidence of overactive bladder with bread, potato and vegetable consumption. While these effects certainly provide interesting avenues for further research, there is a concern that they may be surrogates for other unidentified socioeconomic risks, rather than truly causal. Overall there is a lack of consistency in reports of dietary associations with UI that most likely reflects methodological limitations rather than differences between populations.

8. SOCIOECONOMIC STATUS

Socio-economic status (SES) is strongly correlated with many of the other risk factors for UI including parity, BMI, diabetes, depression, smoking and timing of menopause. Higher SES is consistently associated with increased care seeking for UI, but there is conflicting evidence of association between SES and UI prevalence, or bother. While many studies do include some measure of SES as a potential confounder, its effect is frequently not reported. **Table 11** summarises some of the major studies that have reported associations, to highlight inconsistencies both by SES definition and UI definition. In the table a positive association is cited where women of higher SES, i.e. higher income, more education, report a greater prevalence of UI.

9. SMOKING

Data from observational studies on smoking are again quite inconsistent. It has been reported to be an independent risk factor for UI in women in some cross-sectional studies [108,156,160,225,256] but not in many others [96-97,110]. Within studies that do find an association, former smokers have a risk intermediate between never smokers and current smokers, and some dose response effect is evident, adding plausibility.

However, with one exception longitudinal studies have consistently failed to find a significant association between either past or current smoking and incident UI in multivariate analysis [121,128,131,135,257]. Only in the Leicester MRC study [125] was current smoking associated with increased risk for incident stress UI. The conflicting data from cross-sectional studies and lack of association between smoking and incident UI in most prospective studies suggests that smoking is probably not a causal risk factor for UI.

10. PHYSICAL ACTIVITY

Evaluating associations between physical activity and incontinence remains complex. It is clear that high impact exercise such as gymnastics [258-259] or trampolining [260-261]. is a direct cause of stress UI, with a dose dependent deleterious effect. However, women who suffer from UI, and particularly stress UI, may feel less able to engage in such sports [262]. Furthermore with increasing interest in core training as a treatment for UI [263], there are theoretical reasons to believe that low impact exercise might have a direct therapeutic effect. With these competing mechanisms at play, unsurprisingly cross-sectional studies have again

Table 11. Selected studies reporting associations between socioeconomic status and UI in women.

Reference	Country	♀Sample	SES Measure	Incontinence Definition	Association
Huang (251)	US	2,109	Educational level	Bothersome UI	Negative
Sampselle (225)	US	3,302	Educational level Financial strain	Any UI Bothersome UI	Positive Negative
Waetjen (128)	US	2,702	Educational level Social Support	Monthly UI Monthly UUI	Negative Positive
Kraus (252)	US	654	Occupation	Bothersome UI	Negative
Tennstedt (97)	US	3,205	Composite Index	Weekly UI	Nil
Melville (185)	US	3,506	Educational level Income	Monthly UI Monthly UI	Negative Negative
Saadoun (253)	France	2,640	Educational level Occupation	Monthly UI Monthly UI	Nil Nil
Roe (254)	UK	2,699	Occupation	Monthly UI	Nil
Kuh (159)	UK	1,333	Educational level Educational level	Monthly SUI Monthly UUI	Positive Nil
Coyne (255)	US/UK/ Sweden	15,861	Educational level Occupation	Monthly UI Monthly UI	Negative Negative
Ge (110)	China	3,058	Educational level Occupation	Monthly UI Monthly UI	Negative Negative

produced conflicting evidence (see for example [97,264-265]). However, among cross-sectional studies, comparison of low impact and high impact exercise is suggestive that, as hypothesised, high impact sports might be harmful, while low impact sports might be protective [160,266].

Evidence from longitudinal studies overall suggests that exercise does have a protective effect against incident UI, but perhaps only mediated via an effect on weight. In the Leicester MRC study, women who reported that they exercised less frequently were at increased risk for both incident stress UI and OAB in a model that adjusted for physical functioning, although notably this association was eliminated in a full model, adjusting for obesity[125]. In a study of 4,291 older women exercise at baseline was not associated with incident UI at 10 year follow up after multivariate adjustment [131]. Perhaps the strongest evidence comes from the Nurses' Health Study [267]. In this population of US nurses aged 54-79, a higher level of physical activity across 14 years of follow-up, was associated with a reduced risk of UI overall, and specifically stress UI, although after adjustment for BMI and other factors, the overall effect was small.

11. COMORBIDITIES: DIABETES, UTI, COGNITIVE IMPAIRMENT, ISCHAEMIC HEART DISEASE, PHYSICAL IMPAIRMENT AND DEPRESSION

In cross-sectional studies many different comorbidities have been associated with UI in univariate analysis [232,255,268]. However, in most cases these have no explicatory power, being neither a cause nor consequence of UI, but only associated with other known or unknown mediators of UI, or differentially diagnosed due to medical surveillance bias. In this section, we therefore concentrate on studies that are able to adjust for a wide range of confounders, and give priority to associations of incident UI.

Many, though not all, cross sectional studies have reported urinary incontinence to be more common in women with either type 1 or type 2 diabetes than among women with normal glucose levels even after extensive adjustment for known risk factors [128,135,185,258,269-271]. There are conflicting data regarding a dose dependent association [270,272]. Longitudinal evidence is also conflicting. In the Nurses' Health Study cohort, diabetes was a slight but significant predictor of incident UI

(RR=1.21), and the strength of the association was seen to increase both with duration of diabetes and with severity of incontinence. Despite strong associations with prevalent UI in the SWAN study, no association with either incident UI[128], or worsening UI was found [128]. Despite a host of plausible pathophysiological mechanisms by which diabetes might induce incontinence, it remains unclear whether it truly has a causal role.

Acute urinary tract infection (UTI) is a direct cause of transient UI [273], but caution is required regarding a causal association with chronic UI. UTIs are often diagnosed and treated based on symptoms alone, and there may therefore be a risk of misclassification between exposure and outcome. Many cross-sectional studies have found that women with UI are more likely to report having had one or more lifetime UTIs [221,246,274-275], and longitudinal data suggest both that UI can cause UTI, and that UTI can lead to UI. Two recent prospective studies found that baseline UI was a risk for incident UTI [273,276], among middle aged and elderly women, and in the Leicester MRC study, a history of cystitis was associated with both incident stress UI (OR 1.9) and incident OAB (OR 2.1) in women aged >40.

Prevalent UI has a clear dose dependent association with dementia [277-278], but until recently longitudinal studies did not identify an association with incident UI. One longitudinal study of 6,349 community dwelling women found that a decrease in mental functioning as measured by the modified mini mental status exam (MMSE) was not associated with increased frequency of UI over 6 years, but did predict a greater impact [279]. Despite strong associations with baseline UI in the Canadian Study of Health and Aging, moderate or severe cognitive impairment, again defined by the modified MMSE, was not associated with incident UI over 10 years [131]. However, in a sample of 12,432 women aged 70-75, followed up for 9 years, the Australian Longitudinal Survey of Women's Health did demonstrate a strong longitudinal association with diagnosed dementia (OR 2.34) [134]. In 9 year follow up of 1,453 women aged 65+ enrolled in a US HMO diagnosed dementia was strongly associated with incident diagnosis of UI (RR 3.0) [280]. Given the strength and consistency of associations with prevalent and incident UI, and given that treatment for reversible dementias can improve UI [210,211], a causal role seems certain.

Ischaemic heart disease is associated with many risk factors for UI, but perhaps because of Neyman's bias, cross-sectional studies have often failed to identify an association with UI itself even in univariate analysis [227,232]. The BACH study reported a strong association only among Black participants (OR 2.52) in multivariate analysis [97]. In the Leicester MRC study [268], a history of ischaemic heart disease was associated with baseline stress UI and OAB only in univariate analysis, and with no association with incident symptoms. In contrast, the Nurses' Health Study found that coronary heart disease was associated with incident weekly UI (OR 1.46), and incident severe UI (OR 1.79) [135]. If ischaemic heart disease is a risk factor for incident UI, its effects might be mediated by cardiac failure [280], or polypharmacy [283-284].

Several cross-sectional studies have documented an association between depression and incontinence [128,185,224,229,240,285]. It seems plausible both that the stigma of UI leads to depression (for example by reducing a woman's social network), and depression is likely to increase the bother of UI symptoms. In the SWAN study, depression was not associated with incident UI, but in the UAB Study of Aging, in a sample of 490 women aged 65+, baseline depression was weakly associated with incident UI (OR 1.2) over 3 years of follow-up [130]. Similarly in the Health and Retirement Study confounders (n=5,820), major depression was a modest predictor of incident UI (OR 1.46) over six years of follow-up, and including extensive adjustment for confounder. Baseline incontinence did not predict incident depression in the same study. Follow up of women aged 65+ enrolled in an HMO, diagnosed depression was also associated with incident diagnosed UI over 9 years (OR 1.6) [280].

Functional impairments, particularly mobility limitations, a history of falls, arthritis, dizziness, need to use walking aids, and poor lower extremity strength, have been correlated with UI in many community-based and nursing home studies [97,224,229.230,278]. In the Nurse's Health Study osteoarthritis and functional limitations were plausibly associated only with incident urgency UI (RR 1.86 and 2.10), not with incident stress UI or mixed UI [135]. In a study of 2,025 older women improvement in ADLs was associated with remission of urge UI at 3 year follow up [224]. Other longitudinal studies have shown similar findings [130,279]. It remains unclear whether UI is a direct consequence of difficulties in getting to the bathroom and/or removing clothing, or whether mobility limitations and UI may both be consequences of general frailty in older age or of an underlying systemic illness.

V. SUMMARY POINTS

1. The estimated prevalence of UI in middle-aged and older women in the general population appears to be in the range of 30% to 60% (increasing with age); while the prevalence of daily UI ranges from 5% to 15%, rising to over 15% in women over age 70 who are institutionalised. Some studies have found prevalences outside theses ranges, demonstrating that there remains a large variation in the estimated prevalence of

urinary incontinence in women, even after taking into account differences in definitions, ascertainment, and demographic characteristics. At least part of this variation is likely to be due to the sensitivity of the subject and subtle differences in the conduct of studies. (LE 1)

2. Multiple observational studies have confirmed that White, non-Hispanic women have a substantially higher prevalence of stress UI than Black or Asian women that is not explained by differences in known risk factors for UI. (LE 1)

3. Pregnancy, labour and vaginal delivery (vs Caesarean section) are significant risk factors for later UI, but the strength of this association diminishes substantially with age. (LE 1)

4. While several specific parturition factors such as instrumental delivery and birth weight are risk factors for UI in the post-partum period, their association with UI in later life is weak or non-existent, suggesting that changes in birthing practices in developed countries are unlikely to affect UI in older age. (LE 2)

5. Additional evidence has now established body mass as an important, modifiable risk factors for UI. (LE 1)

6. Physical function also appears to be an independent risk factor for UI in older women. Whether improvement in physical function leads to a reduction in UI remains to be established. (LE 2)

7. Evidence from 2 blinded, randomised controlled trials indicate that oral oestrogen, with or without progestogen, is a significant risk factor for UI in women age 55 and older (LE 1).

8. Diabetes is a risk factor for UI in most studies. While diabetic neuropathy and/or vasculopathy are possible mechanisms by which diabetes could lead to UI, no mechanism has been established, nor is it clear whether prevention or treatment of diabetes, separate from weight reduction, will reduce the risk of UI. (LE 2)

9. Menopause, as generally defined, does not appear to be an independent risk factor for stress UI. (LE 2)

10. Hysterectomy remains a possible risk factor for later UI, but the evidence is inconsistent. (LE 2)

11. Moderate to severe dementia in older women is a moderate to strong independent risk factor for UI (LE 2). Whether interventions to maintain or improve cognitive functioning also reduce UI has not been evaluated.

12. Mild loss of cognitive function in community-dwelling women, separated from physical function and other factors, increases the risk of UI slightly if at all, but may increase the impact of UI. (LE 2)

13. Data from twin studies suggests that there is a substantial genetic component to UI. (LE 1)

14. Other potential risk factors, including smoking, diet, depression, constipation, UTIs, and exercise, while associated with UI, have not been established as aetiological risk factors and are in fact difficult to study with observational data because of the potential for unmeasured confounding and questions of direction of the association. (LE 3).

VI. FUTURE DIRECTIONS

Since the 4th ICI in 2009, the quantity and quality of epidemiological studies of UI has continued to increase. Most notable are the availability of prospective data from several studies that can examine risk factors for incident incontinence and a growing number of studies comparing the prevalence and incidence of UI among Caucasian, Black, Asian and Hispanic women using population-based samples and multivariate analysis. Below are several suggestions for research over the next 5 years.

- Obesity is now an established, modifiable risk factor for UI. Investigation and dissemination of strategies to reduce the risk of UI through weight control or reduction should be a priority.

- Poor physical function is a consistent risk factor for incontinence, particularly in the elderly. Whether or not it is modifiable is not clear. Intervention studies are needed to assess the impact of improvement of physical function on prevention or reduction of UI in frail elderly.

- Moderate to severe dementia is also a consistent risk factor for incontinence. Studies aimed to maintain or improve cognitive functioning should assess change in UI as an outcome variable.

- The higher prevalence and incidence of UI, particularly stress UI, among Caucasian women, compared to Black or Asian women remains unexplained. Further studies are needed to identify additional exposures or biological factors that could explain these differences.

- Determining the role of genes and identifying specific genes that increase the risk of UI is a daunting challenge. Nonetheless, laboratory and epidemiological studies are needed to investigate this area.

- While the role of oestrogen in the aetiology of UI has been rendered largely moot due to the move away from estrogen use because of concerns about increased risk of breast cancer and cardiovascular disease, the use of other medications for control of menopausal symptoms and the introduction of selective oestrogen receptor modulators (SERMs) is growing. Their impact on UI

needs to be studied. Add something about the role of vaginal oestrogens.

- More is now understood about the prevalence of and factors affecting treatment seeking among women with UI. However, more work needs to be done to identify women who would benefit from treatment, but who do not seek, or who do not receive, treatment and to develop interventions to help these women.

E. EPIDEMIOLOGY OF UI IN MEN

I. GENERAL COMMENTS

The epidemiology of UI in men has not been investigated to the same extent as women. However, progress has been made during recent years, particularly in the reporting of population-based studies of urinary incontinence among men and more specifically, of urinary incontinence associated with prostatectomy. In addition, more reports have been published on the risk factors for the development of UI in men.

In almost all community based studies, the prevalence rates of UI continue to be reported to be less in men than in women by a 1:2 ratio. The type and age distribution of UI appear to be different between the sexes, and risk factors, although less investigated in men, seem to be different from women. It is also important not to consider UI as an isolated problem in men, but rather as a component of a multifactorial problem. Often other urogenital symptoms (LUTS) such as weak stream, hesitancy, and dribbling, or erectile dysfunction, coexist.

Post-prostatectomy incontinence has been studied and reported with increasing regularity in the last few years. Since radical prostatectomy is being performed with increased frequency, and incontinence is one of the main complications of the procedure, a specific review of UI in the postprostatectomy patient population is presented in this section. In addition to epidemiological studies, we included clinical trial data on postprostectomy incontinence.

II. PREVALENCE

Several surveys from the general population have been conducted to determine the prevalence of UI in men (**Table 12**). Prevalences ranging from 1 – 39% have been published. The wide span of results may be explained by the variation in the population studied, the definition of incontinence used and the methods used in the surveys. A systematic review of 21 studies reported a prevalence of UI in older men ranging from 11-34% (median = 17, pooled mean = 22%), while that among middle-aged and younger men was from 3% to 5% (median = 4% , pooled mean = 5%). In the same review, the prevalence of daily UI in men ranged from 2-11% (median = 4%, pooled mean = 5%) [286]. A more recent systematic review of 69 prevalence studies on UI in community-dwelling men showed pooled overall prevalence rates from 4.81% to 32.17%, with prevalence increasing with age. [333]. A wide definition of UI, older age, inclusion of institutionalised men, and the use of self-reporting methods tend to result in higher prevalence rates [286-287].

For any definition of UI, there is a steady increase in prevalence with increasing age (**Table 13**).

1. TYPES OF INCONTINENCE

Due to differences in anatomy and pathophysiology of UI in men and women, there is a different distribution in incontinence subtypes. Recent studies confirmed our previous reports of the predominance of urgency incontinence (40-80%), followed by mixed forms of UI (10-30%), and stress incontinence (<10%) [322]. The pooled prevalence rates in a systematic review confirmed that such distribution pattern across the different types of UI is consistent across the different age groups [333]. (**Table 14**).

The higher percentages of urgency and mixed types of incontinence are more significant in studies involving older people. In fact, the increasing prevalence of any UI by age in men is largely due to the contribution of urgency incontinence rather than stress incontinence. One study demonstrated an increasing rate of urge UI from 0.7% between age 50-59, 2.7% between 60-69 and 3.4% for 70 years and older respondents. Stress UI was steady at 0.5%, 0.5% and 0.1% for the above groups respectively [295]. A similar trend of increasing proportions of urgency and UI with increasing age is demonstrated in a large population-based study in the US [313], and a smaller population-based Canadian study [336]. On the other hand, Maral and coworkers [292] reported increasing prevalence also of SUI with age, from 0.9% between age 35-44, to 1.2% between 45-54, 3.8% between 55-64, and 4.9% at age 65 and older [292].

Most studies report a significant fraction of other/unclassified types of urinary incontinence. One study reported that a majority of men with UI had overflow and functional types of incontinence [293], while another found constant dribbling in 7% of their respondents [319]. Terminal dribbling or postvoid dribbling is another type of leakage in men that is difficult to assign to the conventional subtypes of UI. In an Australian survey, 12% of respondents reported frequent terminal dribbling [337].

Table 12. Examples of prevalence studies of UI among men
A. General Population Sampling, all adult age groups

Author and year [ref]	N	Response rate (%)	Country	Population (age)	Definition of UI used	Method of assessment	Prevalence (%)
Boyle 2003 [288]	4 979	28-72%	France, Netherlands, UK, Korea	40-79	Lack of control over bladder function which caused urine leakage at times	Self-administered questionnaire	7 (France), 16 (The Netherlands), 14 (UK), 4 (Korea)
Engstrom 2003 [289]	?	86		40-80		Self-administered questionnaire	2 (SUI)
Van Oyen 2002 [290]	7 266	-		> =15			1.4
Schmidbauer 2001 [291]	1 236	-		Mean 49			5
Maral 2001 [292]	1 000	90		> = 15			1 (SUI), 3 (UUI)
Bortolotti 2000 [293]	2 721	-		≥ 50	Any urine loss in the last year	Telephone interview	32 (last year), 14 (weekly)
Smoger 2000 [294]	840	85		25-93, VA clinic	Incontinence in the past 12 months	Self administered questionnaire	32.3
Ueda 2000 [295]	3 500	52.5	Japan	> 40		Mailed self-administered questionnaire	10.5 (UUI)
Roberts 1999 [296]	778	-		≥ 50			25.6 (95CI 22.5-28.8)
Roberts 1998 [297]	2 150	-		≥ 40	Urinary leakage in the previous 12 months	self	18
Schulman 1997 [298]	2 499	-		≥ 30			5.2
Malmsten 1997 [299]	10 458	74		≥ 45			9
Brocklehurst 2003 [300]	1883	-		>=30	Ever suffered from bladder problems such as leaking, wet pants, damp pants	Interview	6.6% overall, 3.8% incontinent in the previous year, 2.8% in the previous 2 months
Irwin 2006 [301]	19165	33%		>=18	ICS 2002 definition	Telephone interview	5.4 (1.9-5.9)
Legace 1993 [302]	2830	86%		>-20	Any urine loss in the past 12 months	Self-administered questionnaire	11 (9-13)
McGrother 2004 [303]	92491	60.2		>=40	In the last year, did you ever leak urine when you don't mean to?	Postal questionnaire	14.2
Obrien 1991 [304]	2496	79				Self administered questionnaire	7.4 (95CI 6.4 – 8.4)
Parrazzini 2002 [305]	9613	97.5		>=50	Involuntarily leaked in the past 3 months		8.3 (7.7-8.9)
Roe 1999 [306]	12529	53	US				5.3
Markland 2011 [307]	9071	-	US	>=20	Positive response to SUI/UUI/Other	Personal interview	13.9% SUI = UUI = 8.3% (7.6-9.0)
Markland 2010 [308]	5297	-	US	>=20	Score of 3 or greater on a validated incontinence severity index (moderate to severe leakage)	interview	4.5 (3.8-5.4)
De Souza 2010 [309]	?		Brazil	>=18			6.2%
Malmsten 2010 [344]	4072	80	Sweden	45-103			
Finkelstei2002 [310]	25400	88.7	Canada	>=30	urinary incontinence diagnosed by a health professional	interview	1.4 (per 100 population)
Diokno 2007 [311]	21,590	66.5	US	>=18	Involuntary leakage or loss of urine in the past 30 days	Postal questionnaire	12.7%
Lee 2011 [312]	888	22.%	Korea	>=18	Involuntary urinary leakage	Telephone interview using a questionnaire	2.9% (other UI = 1.3, SUI = 0,9)
Espuna-Pons 2009 [313]	15,929		Spain	>=15		questionnaire	3.6%

Table 12. Examples of prevalence studies of UI among men (continued)

B. General Population Sampling, Older Group

Author and year [ref]	N	Response rate (%)	Country	Population (age)	Definition of UI used	Method of assessment	Prevalence (%)
Dios-Diz 2003 [315]	350	-		> 64	-	-	? (95CI: 15-28)
Stoddart 2001 [316]	1 000	79		> 65	Incontinence in the previous month		23
Aggazzotti 2000 [317]	893	90		> 65, Community and residential homes	Involuntary loss of urine at least 2x/month	Questionnaire, review of clinical record	39.2
Gavira-Iglesias 2000 [318]	827	-		≥ 65	-	-	29 (25-38 95CI)
Smoger 2000 [294]	840	85		25-93, VA clinic	Incontinence in the past 12 months	Self administered questionnaire	32.3
Damian 1998 [319]	589 (iincluding women)	78		> 65	Current experience of difficulty in controlling urine or urine escaping involuntarily	Interview	15
Umlauf 1996 [320]	1 490	53		Elderly	Uncontrolled urinary leakage of any amount the month before	Mailed self administered questionnaire	29
Nuotio 2003 [321]	171	-		≥ 70			24 (UUI)
Herzog 1990 (MESA study) [322]		66% - 72%		>=60	In the past 12 months about on how many days have you lost any urine, even a small amount beyond control	Interview	18.9%
Janssen 2007 [323]		57%		>= 65	Leaked or lost control of urine in the past year	Interview	13.1%
Landi 2003 [324]	5372			>= 85	MDS urinary incontinence scale of >=1	Health care professional assessment	49%
Thom 1997 [325]	1420	NA		>=65		Review of database	5.3
Diokno 1986 [314]	805	65.1	US	60 older			
Kwong 2010 [326]	1705	47	Australia	>=70	Urinary leakage at least 2x/week over the past 4 weeks	Self administered questionnaire	14.8%
Smith 2010 [327]	572		US (Latino)	older			26.9%
Yu 2009 [328]	743		China (rural)	>=60		Face to face interview	33.38%

2. SEVERITY OF INCONTINENCE

When it comes to severity, the distribution in men follows that of the women. Estimates for severe UI in older women tend to be about twice as high as for older men [322].

3. RACE/ETHNICITY

Very few studies have included the impact of race or ethnicity on the prevalence of UI among men. A four-country study presented lower prevalences of reported UI among men from Korea (4%) and France (7%) than in men from Britain (14%) and Denmark (16%) [288]. On the other hand, unpublished data from the MESA study did not indicate differences in prevalence among white male respondents compared to African American respondents. Similarly, the National Health and Nutrition Examination Survey did not find any difference in prevalence of UI by racial/ethnic group [308].

4. INCIDENCE AND REMISSION

Literature on the incidence of male UI is very scarce. The MESA study [322] found a one-year incidence rate for men older than 60 years of 9-10%. In a population-based survey in the UK among men over 40 years of age, the one-year incidence of UI was noted to be 3.8% [303]. A review of a health organisation database of males at least 65 years old revealed an UI incidence of 23.8 per 1000 person years. Malmsten [299] analysed the age of onset of UI for each age cohort. Mean debut age for all men was 63 years. The mean duration was about 8-10 years in the cohorts. A longitudinal population based study in Sweden showed that 8.6% [212/2471] of those without UI at the initial survey were found to have UI at the survey done 11 years later [344].

Substantial remission rates for UI in males were noted by the MESA study, higher among men (27-32%) than women (11-13%) [322]. A similarly high one-year remission rate of 39.6% was noted among British males [303]. In the Swedish longitudinal study, 47.8% (55/115) of those found to have UI at the initial survey did not present with the problem at the time of the follow up survey 11 years later [344].

One possible explanation for the difference in the published incidence and remission rates in men compared to women, is the predominance of urgency type incontinence among men, and its close relation to overactive bladder with and without incontinence. Another factor is the close association between urgency UI and prostate gland disease, infections, or bowel dysfunction, all of which are relatively amenable to treatment or may improve even without treatment.

III. POTENTIAL RISK FACTORS FOR UI

There is relatively little research concerning conditions and factors that may be associated with UI in men, and clear risk factors are more seldom scientifically documented. However, a few available studies have identified potential risk factors, which are described below.

1. AGE

As in women, increasing age is correlated with increasing prevalence of UI. Multivariate analysis in several studies has shown that age

Table 13. Examples of prevalence of UI across age spectrum in men

Author and year [ref]	N	Distribution by age	Prevalence [1] (%) (95%CI)
Yarnell, 1979 [329]	169	65 70 – 80 80+	9 8 22
Thomas, 1980 [330]	?	45 – 54 55 – 64 65 – 74 75+	5 9 15 18
Diokno,1986 [314]	805	60+	19
Malmsten, 1997 [299]	10458	45 50 55 60 65 70 75 80 85 90+	3.6 4.1 3.3 5.1 6.1 7.3 9.6 19.7 21.8 28.2
Schulman, 1997 [298]	2499	50 – 54 60 – 64 70+	5 6 14
Bortolotti, 2000 [293]	2721	51 – 60 61 – 70 70+	2 3 7
Ueda, 2000 [295]	3500	40 – 59 60 – 69 70+	2 4 4
Aggazzotti, 2000 [317]	839	<65 65 – 74 75 – 84 85+ >= 95	19 23 52 53 57
Temml, 2000 [331]	1236	20 – 39 40 – 59 60 – 69 70+	2 4 8 12
Smoger, 2000 [294]	840	≤40 41 – 50 51 – 60 61 – 70 71 – 80 >80	25.4 30.9 31.4 36.3 33.2 20.0
Mariappan 2006 [332]	353	40-49 50-59 60-69 >=70	6.6 7.9 10.6 10.3
McGrother 2004 [303]	92491	40-49 50-59 60-69 70-79 >=80	7.4 11.1 16.8 23.2 30.5
O Brien 1991 [304]	2496	35-44 45-54 55-64 65-74 >=75	2.4 5.5 5.7 12.1 15.4
Thom 1997 [325]	1420	65-74 75-79 >=80	2.8 5.6 7.6
Shamliyan 2009 [333]		19-44 45-64 65+ 80+	4.81 (3.69-5.94) 11.2 (10.14-12.26) 21.13 (19.9-22.35) 32.17 (29.62-34.73)
Finkelstein 2002 [310]	25400	30-39 40-49 50-59 60-69 70-79 80+	0.2 0.4 1.1 2.7 5.7 6.4
Diokno 2007 [311]	21590	18-34 35-44 45-54 55-64 65-74 75+	7.25 7.17 10.98 15.58 23.82 30.19
Kwong 2010 [326]	1,705	70-74 >=90	12.0 16.3
Espuna-Pons 2009 [313]	15929 (men and women)	45-64 65-74 >=75	2.8% [2] 10.2% [2] 22.7%[2]

1 – Crude prevalence, unless otherwise specified
2 – prevalence estimated using survey sampling weights

Table 14. Relative proportion of types of urinary incontinence in men.

CITATION	Population	Age group	UUI	SUI	MUI	Others
Diokno 1986 [314]		>= 60 y	34.9	7.9	28.9	28.3
Damian 1998 [319]	589	>=65 y	52.2	10.6	16.1	21.1
Chaojie 2002 [334]	2087 (total)	>=70 y	17.4	11.9		
			30.4	20.7		
Nuotio 2003 [285]	171	>70	70.8	8.3	25.0	
Irwin 2006 [301]	19,165	>=18 y	22.2	11.1	11.1	53.7
Herschorn 2007 [336]	482	>=18 y	58	27	15	-
Shamliyan 2009 [333]	*	19-44 y 45-64 65+ 80+	68.2 59.3 54.2 65.9	16.3 28.9 8.0 0	15.5 11.7 17.9 34.1	-
Diokno 2007 [311]	21,590	>=18 18-34 35-44 45-54 55-64 65-74 75+	44.6 30.0 35.4 38.9 46.8 53.8 56.3	24.5 38.1 35.8 30.8 19.3 16.7 13.2	18.8 14.8 12.6 16.5 21.0 22.6 22.4	12.1 17.1 16.2 13.8 13.0 6.9 8.1

is an independent risk factor for incontinence [288,311,324,338-339] Compared to women, however, there seems to be a more steady increase in prevalence in men with increasing age. The National Health and Nutrition Examination Survey in the US reported an odds ratio for moderate to severe UI of 1.8 (95%CI 1.6-2.0) for every 10-year increase in age in a cohort of 5,297 men 20 years or older [308].

2. LOWER URINARY TRACT SYMPTOMS (LUTS) AND INFECTIONS

In postal and telephone surveys of community-living incontinent men, a majority had experienced a variety of other medical conditions, many of which may cause or aggravate UI. LUTS like urgency, nocturia, feeling of incomplete voiding and reduced flow are typically associated with UI [291,314,320, 343]. In one study, UI was reported by 15% of men without voiding symptoms, frequency or urgency and by 34% of those with such symptoms [314].

Studies have also reported that urinary tract infections and cystitis are strongly associated with male UI [295,319], with an odds ratio of 3.7 for UI in men reporting cystitis [295] and an odds ratio of 12.5 among men with recurrent infections [293]. The metaanalysis of 5 studies including the previously mentioned studies showed a significantly higher risk of UI among men with UTI, with a pooled odds ratio of 3.6 (95% CI 2.17-6.00) [333]. It should be noted that most reports indicating a positive association between UTI and incontinence involved men aged older than 60 years.

3. FUNCTIONAL AND COGNITIVE IMPAIRMENT, PHYSICAL ACTIVITY

Mobility problems such as use of a wheelchair or aids to walking, as well as diagnosed arthritis or rheumatism or having a fall the last year, were

significantly greater among incontinent than continent men [319,345]. The Canadian National Population Health Study involving 25,400 men found that those afflicted with arthritis were more likely to have UI with an odds ratio of 1.59 (95% CI 1.07-2.38) [310]. The same study demonstrated that men with back problems were 2x more likely to have UI (OR 2.1, 95%CI 1.50-2.93). A Japanese study on community dwelling men noted that UI is more likely among men whose activities of daily living (ADL) are impaired, specifically those who are unable to change clothes and unable to walk outside, with odds ratio of 17.4 and 4.36 respectively [295]. A Canadian study found odds ratios of 1.8 and 6.4 for partially and totally immobile men aged 65+, respectively, for daily UI compared to those with normal ambulatory function [343]. Similarly, the Silver Network Home Care project among the frail older persons in Italy showed that those with higher ADL scores (i.e., greater functional impairment) had 2-4x higher odds of having UI. A survey of nursing home residents in Wisconsin identified dementia and poor ADL as risk factors for the occurrence of UI [339]. In general, most studies find similarities between men and women (see subsection on women) for functional and cognitive impairment as risk factors for UI.

Corollary to this, the association between physical activity and UI has been studied by Kikuchi and co workers among the elderly, community-based population in Japan [340]. They found that middle level physical activity in men was associated with a lower UI prevalence compared to those with low level physical activity, with as odds ratio of 0.38 (0.17-0.78). High level physical activity showed similar relations but was not statistically significant.

4. NEUROLOGICAL DISORDERS

Many specific neurological diseases may lead to UI [341]. Detrusor hyper-reflexia is seen commonly in mengingo-myelocele patients and in spinal injuries, Parkinson's disease and multiple sclerosis. Areflexic bladder dysfunction due to a cauda equina lesion or diabetes might cause overflow or a paralysed pelvic floor and hence stress incontinence. A meta-analysis of 5 studies showed that men who suffered stroke were at an increased risk for UI with a pooled odds ratio of 2.68 (95% CI 1.31-5.45) [333]. Men who had suffered a stroke were at increased risk for incontinence with an odds ratio of 7.1 [295]. The Canadian National Population Health Survey showed that stroke in men increased their odds of having UI by 8x (OR = 8.26, 95%CI 3.63-18.8) [310]. In a study of 235 stroke patients, the occurrence of UI correlated with motor weakness (OR 5.4), visual defects (OR 4.8, and dysphagia (OR 4.0) [342].

5. DIABETES

Several reports have not found diabetes to be a factor significantly associated with UI in men. This includes the Canadian population-based study involving more than 25,000 men showing no increased risk for UI among men with diabetes [310]. However the pooled analysis of 6 studies showed that diabetic men were significantly more likely to have UI with an odds ratio of 1.36 (95%CI 1.14-1.61) [333].

IV. FACTORS OF UNCLEAR ASSOCIATION WITH UI IN MEN

A 9 year study of Janssen [323] showed increasing rates of UI with increasing BMI among the older men and women. However, multivariate analysis failed to show increased BMI (overweight and obese levels) as an independent risk factor for the development of UI.

In a study including a younger population in Australia, obesity was noted to be associated with UI with an odds ratio of 3.2 (1.2-9.0) [338]. In this study, however, being merely overweight was not associated with UI.

Several studies in older persons have shown an association between physical activity and UI among women that is not seen among men [288,340].

V. SUMMARY POINTS:

- The epidemiology of UI in men has not been investigated to the same extent as for women. But it appears that UI is at least twice as prevalent in women as compared to men. There seems to be a more steady increase in prevalence with increasing age than for women.
- Most studies find a predominance of urgency incontinence, followed by mixed forms of UI and stress incontinence the least. Most studies have a large fraction of other/unclassified types.
- Literature on incidence and remission of male UI is still very scarce.
- Clear risk factors are more seldom scientifically documented, but several medical correlates have been reported. Established risk factors predisposing men to UI include increasing age, presence of lower urinary tract symptoms (LUTS), urinary tract infections, functional and cognitive impairment, diabetes, neurological disorders, and prostatectomy.
- Substantial gains have been achieved on the study of the epidemiology of UI in men compared to the previous years. The conduct of more population-based prevalence studies permitted a better understanding of the problem of UI among men.

F. EPIDEMIOLOGY OF OVERACTIVE BLADDER AND NOCTURIA

I. OVERACTIVE BLADDER

1. GENERAL COMMENTS AND DEFINITIONS

Overactive bladder (OAB) and nocturia have been neglected topics in the medical literature [392-394], with early epidemiological research on urinary symptoms focused either on lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) in men or on urinary incontinence in women [4]. However, there has been increased research interest in OAB and nocturia during the last decade [393-396].

OAB can be bothersome [397-399], and is associated with increased comorbidity [400], impaired quality of life [8], and reduced emotional well-being and work productivity [401]. Nocturia is a common cause of sleep maintenance insomnia [402-404]. Nocturia can be bothersome [405-412] and is associated with impaired mental and physical health [413] and impaired quality of life [412, 414]. Both OAB and nocturia have been reported to be associated with increased risk of falls and fractures [415-422] and nocturia also with mortality [421,423-425].

Generally, the definition of any condition is a critical factor in evaluating its epidemiology, and OAB and nocturia are no exception to this rule [394, 426]. To facilitate discussion and research related to LUTS, the International Continence Society (ICS) has produced standardisation reports The ICS revised and re-revised its Standardisation Report of lower urinary tract function terminology in 2002 [427] and 2009 [428]. We will use the ICS definitions as basis of this chapter. However, we acknowledge that these definitions are not perfect and we encourage further discussion [396,428-431].

OAB is a term to describe the clinical problem of urgency and urgency incontinence from a symptomatic rather than from a urodynamic perspective. Previously various terms, such as 'irritable bladder' or 'unstable bladder' have been used. According to the ICS, OAB is a symptom-defined condition characterised by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia [427,428]. The ICS defines *urinary urgency* as sudden compelling desire to pass urine, and the term OAB is appropriate if there is no proven infection or other obvious pathology [427].

For a long time, it has been known that among healthy people urine production is lower during the night than during the day [432]. Urologists have traditionally defined nocturia as frequency of urination at night without reference to urine amount, while internists have assumed that nocturia results from an increased amount of urine produced with less focus on other urinary symptoms [433]. By the ICS definitions, *nocturia* refers to waking at night one or more times to void, and nocturnal polyuria (NP) to the production of an abnormally large volume of urine during sleep [434]. *Nocturnal urinary* incontinence or nighttime bed wetting (enuresis) differs from nocturia.

According to the ICS, as stated earlier, nocturia is also a component of OAB. However, there is an ongoing debate on the definitions, especially regarding urinary urgency and OAB [396, 430-431, 435-445].

Sometimes OAB has been divided into 'OAB wet' (OAB with urgency urinary incontinence) and 'OAB dry' (OAB without urgency urinary incontinence). In this part of the chapter we focus on the epidemiology of OAB – without distinction between OAB 'wet' and 'dry' – and nocturia. 'OAB wet' (i.e., urgency urinary incontinence) is covered separately in urinary incontinence sections (Epidemiology of UI in Women and Epidemiology of UI in men).

2. PREVALENCE OF OVERACTIVE BLADDER

Prevalence estimates from as low as 2% [446] up to 53%[447] have been reported. Most studies on OAB have reported prevalence estimates between 10% and 20% [448-455], and the most cited articles estimate a prevalence of between 12% and 17% %,[448,450, 455].

In **Table 15**, we have reviewed all population-based studies assessing prevalence of OAB in adults of both sexes. To identify these studies [398, 448, 450, 452, 455-465], a Medline search [English-language articles published before January 2012] was carried out on with the search strategy (((Overactive bladder.mp) or (OAB$.mp)) and ((prevalence.mp). Non-population-based (i.e. based on doctor attendances or similar) studies or studies not conducted among both sexes are not included in **Table 15**.

Among these population-based studies identified, different populations, different sample selection and different data collection methods were often used (**Table 15**). Sample size varied between 913 and 162,906, median being 2,005 individuals. Three (20%) out of 15 studies did not report any response proportion. Among those which reported, as many as seven (58%) studies had response proportion less than 50%. There was significant heterogeneity in symptom assessment, exclusion criteria, case definitions (some studies used grading of symptom severity whereas others did not), and in the time period during which the occurrence of symptoms was asked (**Table 15**). Hence, dissimilarities in study

Table 15. Overview of published population-based studies assessing prevalence of OAB in both sexes (PubMed indexed English-language articles before January 2012 in chronological order).

Origin	Data collection method	Sample source	Respondents (response proportion, %)	Age range (years)	2002 ICS Consensus Definition of OAB	Definition of normal - abnormal occurrence	Time period	Prevalence, %: Men/women
European [448]	Telephone interview / in person interview	Telephone registry / electoral census	16,776 (unreported)	40 – 75+	N/A	N/A	Undefined	16 / 17
USA [450]	Telephone interview	Telephone registry	5,204 (44.5)	18 – 75+	N/A	N/A	Past 4 weeks	16 / 17
Canada [456]	Telephone interview	Telephone registry	3,249 (43.4)	35 – 75+	N/A	N/A	Past month	15 / 21
Japan [452]	Mailed questionnaire	Not reported	4,570 (45.3)	40 – 100	N/A	N/A	Past month	14 / 11
Brazil [457]	Unreported	Not reported	913 (unreported)	15 – 55	Yes	Unreported	Undefined	14 / 23
Taiwan [458]	Questionnaire administered by nurse	Population registry	1,921 (67.0)	30 – 79	No	N/A	Past 4 weeks	16 / 18
International [455]	Telephone interview	Telephone registry	19,165 (33.0)	18 – 70+	Yes	No – Yes	Undefined	11 / 13
Finland [459]	Mailed questionnaire	Population registry	3,727 (62.4)	18 – 79	Yes	Rarely – often	Past 2 weeks	7 / 9
Korea [460]	Telephone interview	Telephone registry	2,005 (13.8)	40 – 89	No	N/A	Past 4 weeks	21 / 31
Canada [461]	Telephone interview	Telephone registry	1,000 (unreported)	18 – 90	No	N/A	Undefined	13 / 15
USA [462]	Mailed questionnaire / Telephone interview	Consumer panel	162,906 (62.7)	18 – 85+	No	N/A	Undefined	24 / 29
Portugal [463]	Telephone interview	Telephone registry	1,934 (59.6)	40 – 80+	No	N/A	Past 4 weeks	35 / 29
International [398]	Web-based interview	Consumer/ voter panel	30,000 (49.5)	40 – 99	Yes	Rarely – sometimes (Sometimes – often)	Past 4 weeks	22 / 36 (5 / 11)
Korea [464]	Telephone interview	Telephone registry	2,000 (22.1)	18 – 96	Yes	Unreported	Undefined	10 / 14
China [465]	Interviewer assisted	Unreported	14,844 (69.0)	18 – 70+	Yes	<1 a week – ≥1 a week	Past week	6 / 6

a In the European study, in five out of six countries, telephone interview was used (excluding Spain, where direct interviews were conducted due to lower proportion of households with telephone). Study sample was obtained from telephone number listings (except Spain, where electoral census data was used).

b Out of 11,740 participants (of 17,231 households contacted), 5,539 were considered ineligible. To calculate response rate, the number of respondents was divided by eligible participants (the former response rate). If same proportion of non-participants, as there were ineligible among participants (47%), were also considered ineligible, response rate was greater (the latter response rate).

c Out of 7487 individuals, 3239 completed the questionnaire (response proportion 43.4%).

d Invitation to complete email survey was sent to 88,150 members of the Internet-based panel. Of the members, 51,546 responded but 7,947 were excluded due to high rates of missing or inconsistent data, or discontinuation of the survey. Finally, 30,000 participants were randomly selected from the pool of respondents with completed surveys.

e ICS, International Continence Society; OAB, overactive bladder; UTI, urinary tract infection.

f Cut-off point (threshold) used for normal vs. abnormal symptom occurrence. Reviewed only for studies using current ICS definition of OAB.1

g Time period during which the occurrence of symptoms was asked.

procedures likely explain the differences in prevalence estimates. Overall, prevalence rates varied between 6% and 32% (Table 15). However, estimates of the prevalence of OAB have actually been smaller in many recent studies compared to earlier estimates (**Table 15**).

Only very few population-based studies have evaluated OAB prevalence using the ICS definition *and* reported bother. Assessing perceived bother associated with OAB drastically decreases the prevalence estimates. In the FINNO Study (conducted in Finland among people aged 18-79) [399], as many as 54% of men and 57% reported *any* (at least rarely) urinary urgency. However, prevalence of at least moderate bother from urgency was 7% for men and 9% for women. Overall, more than 96% of individuals with rare urgency reported no or small bother from it whereas 65% of individuals with urgency *often* and more than 70% with urgency *always* reported moderate or major bother (scale: none-small-moderate-major) [399]. These results are in concordance with two international studies [397-398]. In the EpiLUTS study (conducted in the US, UK and Sweden among people aged 40–99) [398], 22.4% of men and 35.7% of women reported urinary urgency at least sometimes (in scale: never - rarely - sometimes - often - almost - always). However, prevalence estimates were substantially lower when bother was taken into account. Only 6% of men and 12% of women reported “quite a bit” or more bother from urgency (in scale: not at all-a little bit-somewhat-quite a bit-a great deal) [398]. Bother analysis from the EPIC Study [397] showed also that infrequent urinary urgency is not considered as very bothersome by most individuals. Out of OAB cases, 46% did not report symptom bother from it [397]. All these results suggest that bother measurement is essential in estimating the clinically relevant prevalence of OAB [396-398].

3. INCIDENCE OF OVERACTIVE BLADDER

The natural history of OAB has been systematically reviewed quite recently [English articles published between January 1, 1990, and September 20, 2009] [466]. Authors identified 7 longitudinal studies

of OAB. OAB incidence varied between 3.7% and 8.8%; and included studies provided evidence for dynamic nature of OAB [466]. The authors also noted that the variations in symptom definitions and methods used across studies prevent statistical determinations of overall incidence rates. Overall, longitudinal studies have confirmed that OAB prevalence increases with age but also that OAB is a dynamic condition [467-471]. In a population-based study (conducted between 1991 and 2007 in Gothenburg, Sweden) [469], the number of women with OAB with urgency incontinence ("OAB wet") increased from 6% to 16%, however, the proportion of women with OAB without UUI (OAB dry) did not differ significantly (11% vs. 10%). Among women with OAB dry in 1991, 23% remained OAB dry, 28% reported symptom progression to OAB wet and approximately half reported remission of OAB by 2007, supporting the concept of the dynamic nature of OAB. The rate of remission OAB symptoms was greater for women who were OAB dry (49%) compared with those who were OAB wet (26%). Similar findings were recently reported in an Austrian study. The authors concluded that "OAB is a dynamic disease with long-lasting stable disease courses as well as remissions and progressions" [471].

4. RISK FACTORS FOR OVERACTIVE BLADDER

The causes and risk factors of urinary urgency and/or OAB are not well studied. Available studies, that have identified potential risk factors, are summarised below.

a) Age

In numerous cross-sectional studies older individuals reported more OAB than younger ones [448, 450, 452, 455-456, 458-462, 464]. Furthermore, longitudinal studies have confirmed that OAB increases with age [466]. However, while OAB is age-related, it may not be age-dependent. In some studies, OAB was not associated with age after adjustment for other factors/ confounders [400, 472-473]. Besides increasing age, also having urgency in childhood predicts having urgency in later life [474-475].

b) Gender

In **Table 15**, we summarised population-based studies assessing prevalence of OAB among both sexes. In most studies OAB was more common among women [398, 448, 450,455-462, 464-465]. In only two (13%) out of 15 studies, men reported more OAB than women. However, these two studies [452, 463] did not include younger age groups, and typically OAB is more common among women especially in younger ages [448, 455-456, 458-462, 464].

c) Obesity

In a British, prospective study, obesity was a risk factor for the onset of OAB (OR 1.5, 1.0-2.1) in women [400] but not among men [468]). In a Kaiser Permanente study among women aged 25-84, obesity was associated with three-fold risk of OAB [476]. In a population-based study conducted among women in Southern Sweden [477] and in a Japanese study among elderly people [478], OAB was associated obesity. Similarly, among obese women, increasing obesity was associated with OAB after adjustment for age, mode of delivery, and parity [479]. Furthermore, among type 2 diabetic patients, increased waist circumference was associated with prevalence of OAB [480]. Among non-care seeking women (enrolled at one site in a randomised trial) [481], obesity was associated with increased OAB in univariate analysis, but the association did not remain significant after adjustment for confounders. Although OAB seems obesity-related, in many studies, incomplete adjustment for all relevant confounders was possible.

d) Life style

In a prospective study among British women, neither alcohol, coffee nor tea consumption were risk factors for the onset of OAB (defined as having either urgency, UUI, or a combination of these) but drinking carbonated drinks was [400]. Among men, neither tea, coffee nor wine consumption were associated with onset of OAB onset, but a negative association between beer intake at baseline and subsequent OAB onset was found [468]. However, this may be explained by a *systematic misclassification error* (individuals decrease or cease alcohol consumption due to ill health) [482-483], *residual confounding* (moderate drinkers have many other favouring lifestyle factors) [484-485], or direct biological effects. In a Swedish population-based study in young female twins [486], tea (but not coffee) drinking was associated with an increased risk for both OAB and nocturia. However, after controlling for confounders (including zygosity of twins) these associations did not remain significant. Concurring with these studies, among non-care seeking women [481], coffee or alcohol consumption was not associated with OAB. In a population-based study among women in Southern Sweden [477], OAB was not associated with alcohol consumption.

In a prospective British study, smoking was a risk factor for the onset of OAB (defined as having either urgency, UUI, or a combination of these) in women [468] but not in men [468]. In a population-based study among Finnish women aged 18-79 [487], urgency was approximately three times more common among current and twice as common among former than never smokers. Parallel associations for urgency with smoking intensity suggested a dose–response relationship [487]. Other supporting findings have also been reported [473, 488-490]. However, some other studies did not find smoking to be a risk factor for urgency [463, 478, 486].

A prospective study among British men did not provide evidence of any specific dietary patterns as

a risk factor for onset of OAB [468]. Furthermore, physical activity was not significantly associated with OAB onset in men [468]. Contradictory results were found among non-care seeking women [481] where physical activity was associated with decreased OAB.

e) Race/ethnicity and socioeconomic status

Evidence regarding the role of race/ethnicity on OAB prevalence is limited. In a small Taiwanese study [491], higher prevalence of urgency (7.7% vs. 4.3%, p=0.02), was found in indigenous woman than in non-indigenous women. In the US part of the EpiLUTS study [473], OAB was reported by 26% of White, 33% of Black, 27% of Asian and 28% of Hispanic men. In the multivariate analysis, OAB was significantly more common among African-American (OR 2.0, p<.001) and Hispanic (OR 1.7, p<.001) male participants. The authors reported no statistically significant differences among women after multivariate analysis, despite wide variation in crude prevalence (27% for Asian women, 43% for White, 46% for African-American and 42% for Hispanic) [473]. Hospital-based studies have reported no difference in the prevalence of OAB by race/ethnicity [492-493].

f) Reproductive factors and pelvic surgery

Urinary urgency is a common symptom during pregnancy [494]. In a Taiwanese study [495], only 1% of women reported having urgency before pregnancy, whereas corresponding estimates were 16% in the first, 25% in the second, and 31% in the third trimester. Other studies have also found increasing prevalence of urgency with advanced gestational age [496-497]. However, in a Nigerian study, women in 3rd trimester did not report more urgency than women in 2nd trimester [498]. Although one quarter of pregnant women reported urgency, it was associated with moderate or severe bother for only 5% of symptomatic women [498].

The association between parity and urinary urgency is controversial. Some studies reported no association for parity with urgency or OAB [400, 481, 499-500], whereas others found increased prevalence of urgency among parous women [472, 491, 501-503]. However, there were substantial differences in methods between these studies. Regarding delivery mode, most studies demonstrated no effect on prevalence of urgency, urgency incontinence or OAB [463, 499 502-505]. On the other hand, contrary findings have also been reported [506-507]. In a Swedish prospective study, weekly urgency was reported in late pregnancy by 2.6% of women in the elected vaginal delivery and by 2.7% of the women in the elected cesarean section group [506]. Corresponding figures were 7.9% for vaginal delivery and 2.7% for cesarean section groups at 9 months postpartum [506] concurring with the results of a cross-sectional US study [507]. In a recent US study [99], for women with a history of at least one operative vaginal birth, the adjusted odds of OAB was more than quadrupled (OR 4.9, 95% CI 2.2-11; women who had delivered all their children by pre-labor cesarean as reference).

The association of the postmenopausal years with increased urgency or OAB has been reported in several studies [465, 472, 502-503, 508-509]. The impact of hormone therapy on OAB is unclear. The Cochrane Incontinence Group review of urinary incontinence and oestrogens (urgency or nocturia not as the primary objective of the study) found that there were less nocturnal voids and urgency episodes among women treated with local (but not systemic) oestrogen [510]. There were no significant differences in OAB prevalence among women using either oral contraceptives or a levonorgestrel-releasing intrauterine device, in comparison to non-contraceptive users in a population-based study among young, Swedish women [511].

Radical hysterectomy is related to increased prevalence of pelvic floor problems [512]. For instance, patients treated for cervical cancer reported urgency 2-3 times more commonly than the matched controls: 36% of those with history of radical hysterectomy and pelvic lymph node dissection, 49% of those with surgery and adjuvant radiotherapy, and 48% of those with primary radiotherapy reported experiencing urgency [513]. However, the relationship between urgency and hysterectomy for benign indications is less clear. Many studies did not find a significant association between hysterectomy and urgency [499-500, 514-519] . However, some studies reported less [509, 520-523] and some more [463, 472, 501, 524] urinary urgency after hysterectomy. No differences according to the route of hysterectomy on urgency have been found [509, 523, 525-526]. Both prolapse surgery and stress incontinence surgery are associated with a risk of (de novo) urgency or urgency incontinence in both hospital based, and population based studies [489, 500, 527-528].

g) Specific conditions

There is a paucity of studies concerning conditions and co-morbidities that may be associated with OAB, and clear causal risk factors are even more seldom documented. Few available studies have identified potential risk factors, which are described below.

1. *Benign prostatic hyperplasia.* Instead of OAB/urgency, observational, clinic-based studies have assessed the relationship between detrusor overactivity and benign prostatic hyperplasia/obstruction. Although patients with detrusor overactivity are less likely to get symptom improvement after BPH surgery than those without detrusor overactivity, many patients report less urgency after BPH surgery [529]. Similar findings were reported following a prostatectomy study among men aged 47-85,

32% (n=49) reported urgency pre-operatively and 13% post-operatively (n=20) [530]. In another study, detrusor overactivity was present in 68% of patients (n=21) at baseline and in 31% (n=10) at follow-up (mean 2 years) in the prostatectomy group [531]. However, many patients remain symptomatic after prostate surgery, and prognostic factors for success remain largely unknown [532].

2. Pelvic organ prolapse. In community-based studies [476, 533-535], pelvic organ prolapse was associated with 2-6 times higher risk of having urgency incontinence. Concurrent with this finding, hospital based studies have also found pelvic organ prolapse to be a risk factor for urgency incontinence, and in interventional studies urgency incontinence is often (but not always) relieved [536].

3. Mental health. In the BACH survey [537], urinary frequency, urgency, and nocturia were associated with previously experienced sexual, physical, and emotional abuse for both genders and for all ethnic groups in the study (White, Black, Hispanic). Concurring results were found in a German, clinic-based study where 31% of women with OAB reported almost twice as often earlier physical or sexual abuse as did the women with stress urinary incontinence (18%) or women without urinary symptoms (18%) [538]. In an Iranian study, individuals with OAB had a higher prevalence of anxiety (28.2 vs. 8.8%; p=0.001) and depression (38.2 vs. 18.2%; P = 0.02) [453] concurring with finding from multinational EpiLUTS study where increased depression and anxiety scores were found among individuals with OAB [148]. Furthermore, postpartum depression has also been reported to be associated with urgency incontinence [540].

4. Other conditions. In the BACH survey [541], urgency was associated with almost double the risk of hypertension and heart disease in women and with more than double the risk of diabetes in men. However, In a Japanese study among the elderly, OAB was not associated with diabetes or kidney disease but was associated with depression, alcohol use, and increasing BMI [478]. In a UK prospective cohort study within a random sample of 19,241 women aged 40 or more identified from Health Authority lists of 108 general practices [400], predictors of OAB included faecal urgency, imbalance, osteoporosis, ankle swelling, diabetes, DVT and cystitis [9]. Urgency/OAB has also been reported to be common among patients with diabetes [542], stroke [543] and asthma [463].

II. NOCTURIA

1. PREVALENCE OF NOCTURIA

Most earlier studies assessing the prevalence of nocturia have been conducted among elderly men [544-552]. They consistently found that nocturia 1) is a very common symptom and 2) increases with age. These finding have recently been confirmed in comparative studies conducted in both sexes [405-406, 411, 424, 455, 461, 553-558] (**Figure 8**).

We have reviewed all population-based studies assessing prevalence of nocturia in adults of both sexes. To identify these studies, a Medline search [English-language articles published before January 2012] was carried out on with the strategy ((nocturia.mp) and ((prevalence.mp)). Non-population-based (i.e. not based on doctor attendances or similar) studies, studies not conducted among both sexes of adults, studies with narrow age range (less than 40 years), or studies with percentage data unavailable are not shown in **Figure 8**.

In the FINNO Study (individuals aged 18 to 79), approximately one out of eight men and women reported at least two voids per night, in addition one third reported one void per night [557]. Young women reported more nocturia than young men, prevalence of nocturia in men and women equalized only in the sixth to seventh decade of life, and in older age groups men had more nocturia than women. Many other recent studies have supported these findings: higher prevalence of nocturia among young women than young men, and an equalisation of prevalence in middle age [411, 414, 455, 461, 561-562]. As the gender difference has been found across different continents (Europe, Asia, Australia and North America) it probably is not due to the specific country, lifestyle or cultural factors (**Figure 1**) [394, 411, 414, 455, 461, 557,559-562]. The reasons for the excess of nocturia among older men remain unknown, but prostatic enlargement is likely to be the predominant factor.

The Krimpen study (conducted in the Netherlands among elderly men) [563] is one of the few studies where nocturia was assessed by frequency-volume charts). One and a half or more voids/night (average of information on two to three nights) was present in 60% of men aged 70-78 years, whereas at least 2.5 voids per night was present in 20%, respectively. These estimations are comparable to questionnaire studies: most elderly people void at least once per night [564] (**Figure 8**).

2. INCIDENCE OF NOCTURIA

There remains a paucity of studies on the incidence and natural history of nocturia [565]. This is not only due to the fact that longitudinal studies are more difficult to perform than cross-sectional studies but also due to the youth of “nocturia research” [434], uncertainty not only about “incidental nocturia” definition [566-569] but also about the appropriate time interval for repeated sampling [570].

In a US community-based study among adults over 60 [571], nocturia was ascertained during the baseline and

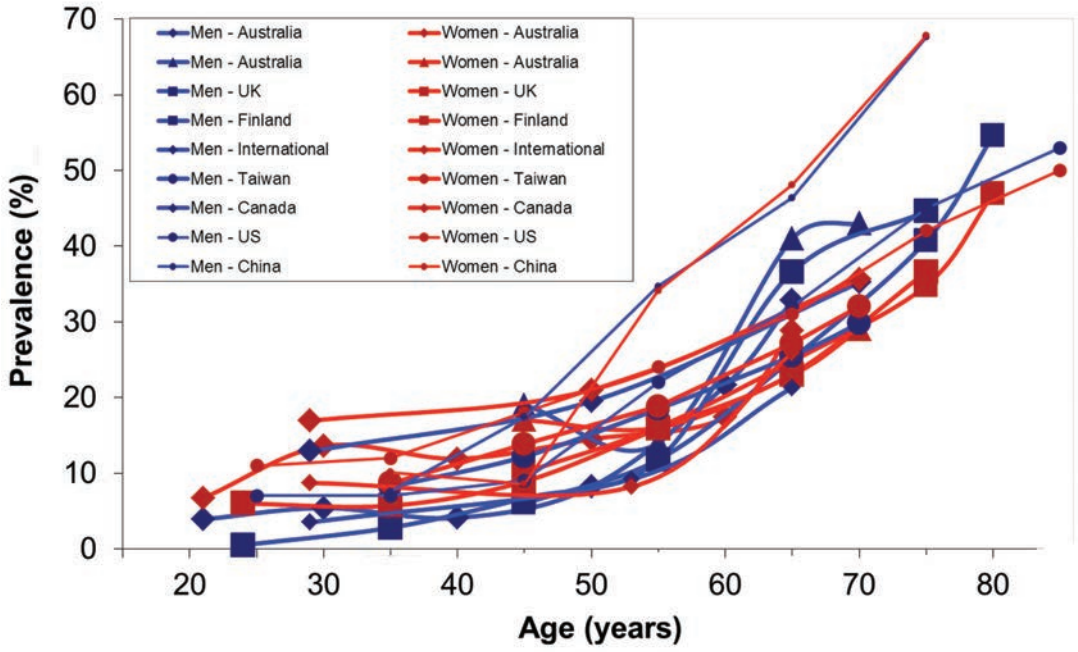


Figure 8. Prevalence of at least two voids per night across age groups by sex in population-based studies conducted among both sexes with wide age-range [411, 414, 455, 461, 557-561].

first and second year follow-ups. Of the 738 individuals with no nocturia at baseline, 34.6% reported having nocturia (*2 or more*) at follow-up, or an incidence rate of 213/1,000 person-years. Of the 357 individuals who had 2 or more episodes at baseline, 66.3% reported 1 or fewer at follow-up, for a remittance rate of 497/1,000 person years. These estimates were not calculated with adjustment for age- or gender, and the exact number of days between date at baseline and date at follow-up were not determined [568].

In a study conducted among elderly men in a Finnish county, questionnaires were mailed in 1994, 1999 and 2004 [572]. The crude incidence of nocturia for men from zero to one or more was 75 new cases per 1000 person-years during the first 5-year period and 126 during the second period. The younger cohort had a lower incidence than the two older cohorts (50-, 60-, 70-year old: 61, 91, 93 cases/1000 person-years, respectively). Interestingly, for all age cohorts the rate of incidence during the second five year period (102, 168, and 167 per 1000 person-years) was higher than during the first. The incidence of nocturia to 3 or more times (from 0 or 1-2 times) was less across all age groups (3, 12 and 16/1000 person-years, respectively for the age cohorts). However, this study is difficult to compare to other studies as no information on incidence of nocturia from <1 episode to >2 or more is available [572].

In a study conducted in the city of Gothenburg, Sweden questionnaires were mailed in 1992 to 10,456 men (aged 45-99) [470]. Follow-up was performed in 2003 when 3,257 men replied (3,000 men had died and 691 had emigrated or were no longer available in the register). The authors presented prevalence data at two time points. Nocturia prevalence increased from 12.8% to 50.1% (2 or more voids/night) among this study [470].

In the Krimpen study [563]. The overall incidence and remission rates (nocturia defined as ≥2 voids/night) were 23.9% and 36.7% after 2.1 years [563]. The incidence was highest among the oldest and lowest among the youngest men. As the absolute number of men with incident nocturia was higher, the prevalence rate increased over time. The authors concluded that "due to this fluctuation it is almost impossible to provide reliable incidence rates for nocturia in community dwelling older men" [563]. Overall, these longitudinal studies have shown that although nocturia increases with age it also has fluctuating character. However, the extent to which lack of reliability of the questionnaires has obscured true incidence or remission estimates remains unknown.

3. RISK FACTORS FOR NOCTURIA

The causes and risk factors of nocturia are not well understood [426, 565]. Available studies, that aimed to identify potential risk factors, are summarised below.

a) Age

There have been numerous studies showing that elderly subjects have more nocturia than younger

people (**Figure 8**) - age is one, if not the most important correlates of nocturia. For instance, in a community-based US study, less than 5% of those aged 18-24 reported two voids per night while the corresponding figures were approximately 15% and 25% for those aged 45-54 and 65-74 respectively [406]. Besides increasing age, also childhood nocturia predicts nocturia in later life [474]

b) Gender

Although there is no remarkable difference in overall prevalence of nocturia between genders, in more detailed age specific analyses differences have emerged between the genders (**Figure 1**). Many studies found higher prevalence of nocturia among young women than young men, and an equalisation of prevalence in middle age [411, 426, 455, 461, 557, 561-562]. Prostatic enlargement has been suggested as a predominant factor for potential excess of nocturia among elderly men [564].

c) Obesity

Several studies have shown the relation between overweight/obesity and nocturia. Obesity was associated with more than three-fold risk of nocturia in a Swedish study among middle-aged women [573], and with more than two fold-risk in the FINNO Study [557]. Confirmatory findings have been reported in numerous studies [574-577]. In the longitudinal TAMUS study among men aged 50 or more [578], obese men had double the risk for nocturia compared with normal weight men. The frequency of nocturia at baseline did not increase the incidence of obesity at follow-up [578].

d) Life-style

Most studies have not found an association between nocturia and either alcohol [405, 556, 568, 576, 579-580] or coffee/caffeine [552, 573, 578, 580-581] consumption. In some studies moderate alcohol consumers had less nocturia than abstainers [578, 582, 583]. However (as discussed earlier in 'Risk factors of overactive bladder'), these findings may be due to systematic misclassification error or residual confounding [482-485].

Most studies have not found an association between nocturia and smoking [424, 552, 576, 578-581, 584]. Some conflicting results have also been reported: in a Swedish study [573] smoking was associated with increased nocturia but in Austrian [405] and Japanese [556] studies, with decreased nocturia.

Physical activity has been reported as being protective against LUTS in men [585-587], and against nocturia in women [573]. In an Austrian study [405], no relation was found between nocturia and physical activity. However, exercise programme has been shown to improve nocturia in a non-randomised trial [588].

e) Race/Ethnicity and socioeconomic status

In several US studies, African Americans were approximately twice as likely to report nocturia as other groups [574, 577, 589-591]. This effect was attenuated, although remained significant [577, 590], with adjustment for socioeconomic status and comorbidity. Furthermore, care-seeking black women also reported nocturia more commonly than other groups [592-593]. Conflicting results were found in a Kaiser Permanente study [594]. Less is known about the relationship between ethnicity and nocturia outside the US. In small studies in Taiwan [491, 595] and Scotland [596], associations between nocturia and ethnicity have been found. In the Scottish study, nocturnal polyuria was more common in Caucasian men compared to Asian men.

f) Reproductive factors and pelvic surgery

Nocturia is a very common symptom during pregnancy. In all studies most pregnant women report nocturia at least weekly, in many studies most women report having nocturia every night [494-498, 503, 597-598]. Typically the occurrence of nocturia increases during pregnancy. In an Indian study [598], nocturia (defined as more than one void per week) was reported by 50.6% of women before pregnancy (retrospective information), by 58.6% of those in the first, 71.9% in the second and 77.0% in the third trimester. In a Finnish study among women aged 18-79 [500], parous women reported slightly more nocturia than nulliparous women, contradicting earlier reports (conducted among perimenopausal women) of no association [501, 599]. The relationship of nocturia between parity has been suggested to be more likely to be due to pregnancy itself than trauma to the urinary tract during delivery [600] supported by the finding of no difference in nocturia between primi- and multiparous women in the same Finnish study [500] and by a finding of no difference between vaginal delivery and caesarean section in a Swedish prospective study [506]. In these studies, the postpartum period was also associated with increased nocturia [500, 506].

In a population-based Swedish study among young women, no difference in nocturia was found among oral contraceptive users and non-users, however, levonorgestrel-releasing intrauterine device (compared with non-contraceptive users), reported less nocturia (OR 0.53, 95% CI 0.32-0.89) [511].

Danish and Finnish population-based studies have reported more than double the risk of nocturia after the menopause [500, 501], consistent with other studies [508, 599]. One study attributed this to aging rather than to menopausal transition [601]. In these Finnish and Swedish studies, there were indications of increased nocturia among women using menopausal hormone therapy, but the findings were statistically insignificant [500, 599]. In a small randomised trial [602], there was

no difference in nocturia among those with menopausal hormone therapy or placebo. Similar findings were reported in a randomised trial of vaginal oestradiol and placebo after sling surgery [603].

The relationship between nocturia and hysterectomy is unclear, with hysterectomy being protective factor [515, 520, 522], risk factor [501], or not associated with nocturia [500, 509, 516]. Surgery for stress urinary incontinence was not associated with nocturia in a population-based study [500].

g) Specific conditions

1. *Benign Prostatic Hyperplasia And Prostate Cancer*. Benign prostatic hyperplasia (BPH) constitutes a well-recognised risk factor for nocturia [563, 580, 604]. In the FINNO Study [580], half of the subjects with physician-diagnosed BPH reported at least two voids per night; however, only a third of the men with nocturia reported BPH. However, nocturia is the least specific LUTS associated with BPO and medical treatment to relieve BPO has less effect on nocturia than on other LUTS [605-606]. Furthermore, nocturia has been reported as one of the most persistent LUTS following prostate surgery [530, 607], and in a study of men with bothersome LUTS, those receiving finasteride had an effect indistinguishable from placebo [608]. Many men with LUTS express a fear of prostate cancer [609], however, whether LUTS (including nocturia) are suggestive of prostate cancer is not clearly established [610]. In the large HUNT-2 study [611], LUTS severity was positively associated with the subsequent diagnosis of localised prostate cancer but not with advanced or fatal disease. More than 70% of men with physician-diagnosed prostate cancer reported at least two voids/night, while 7% of men with nocturia reported prostate cancer in the FINNO Study [580]. Whether men with nocturia are more likely to be diagnosed with prostate cancer (due to use of prostate-specific antigen), prostate cancer causes nocturia, or nocturia is a side-effect of various prostate cancer treatments remains unclear [412, 612]. Impact of radical prostatectomy on nocturia has been neutral or negative (i.e. increased nocturia) [613-615].

2. *Nocturnal polyuria.* The ICS defines nocturnal polyuria as an increased proportion of the 24-hour output of urine volume occurring at night [427]. However, there is a paucity of studies providing reference values. The Krimpen study authors suggested that nocturnal urine production exceeding 90 ml/hr is abnormal [563, 584] but concluded that “nocturnal urine production as an explanatory variable for nocturnal voiding frequency is of little value.” [584]. The fundamental pathogenesis of nocturnal polyuria remains largely unknown.

3. *Overactive bladder.* Urinary urgency was a clear risk factor for nocturia in the FINNO Study (OR 7.4, 95% CI 4.5-12 for men, and OR 4.9, 95% CI 3.2-7.7 for women) [580]. However, while half of subjects with urgency also reported at least two voids per night, only one in three with nocturia reported urgency [459]. The finding that most people with nocturia do not report frequent urinary urgency (**Figure 9)**, has also been reported in the EPIC and EpiLUTS studies [398, 455].

4. *Diabetes.* An association between diabetes and nocturia has been noted in most [556, 574, 576, 580, 583, 604, 616-619], but not all reports [555, 563, 568]. In the BACH Survey [574] and in a Danish study at ages 60-80 years [576], nocturia was associated with double the risk of diabetes. In these surveys [574, 576], it remained unreported whether there were gender differences. In the FINNO Study [580], diabetes was associated with nocturia after adjustment for other factors only in women.

5. *Hypertension.* It has been suggested that essential hypertension and nocturnal polyuria are part of the same pathophysiological process [620]. In Japanese [556] and US [568, 577] studies, hypertension was associated with nocturia, although effect sizes were modest (ORs between 1.5 and 1.6). However, in studies conducted in Europe [555, 563, 580], neither nocturnal polyuria nor nocturia were associated with hypertension. In a secondary analysis from the BACH survey [621], monotherapy with calcium channel blockers in women, and combination therapy with loop diuretics in men was associated with nocturia but no other associations for nocturia with any other antihypertensive was found [621]. While the treatment for hypertension may cause [395, 621-622] or alleviate nocturia [623] in some cases, appropriate methods are of particular importance when trying to assess the relationship between hypertension and nocturia.

6. *Coronary disease.* Earlier (male) studies [164, 165, 172] did not find a relationship between nocturia and cardiac disease. However, in these studies [555-556, 563], an association between cardiac symptoms/disease and nocturia was found in the preliminary analyses before multivariate modelling. In more recent studies [424, 574, 580, 583] coronary disease has been shown to be associated with nocturia.

7. *Depression.* In Swedish and US population-based studies [414, 624], depression and antidepressant use were both associated with increased prevalence of nocturia whereas in a Finnish study a relationship was found only among men using antidepressants after adjustment for other factors [580]. In another Finnish study (among men aged 50 or more), those with depressive symptoms at study entry were at almost triple risk for moderate or severe nocturia than those without depressive symptoms but nocturia had no effect on depressive symptoms during 5-year follow-up [625].

8. *Sleep apnoea and snoring.* In clinic-based studies [618, 626-628], nocturia was associated with sleep apnoea. In US studies conducted among community-dwelling older adults, subjects with increased apnoea-hypopnoea index had greater mean nocturia episodes, nighttime urine production and atrial natriutretic peptide excretion [629-630]. Snoring was one of the three most important nocturia population-level risk factors for both sexes in the FINNO Study [580] concurrent with a Swedish urology clinic study [631].

9. *Neurological diseases.* Most patients with multiple sclerosis have bladder dysfunction, which may also lead to nocturia [632-633]. Nocturia was also associated with stroke and cerebrovascular disease [583, 616]. Moreover, in a study among Parkinson´s patients, severity of disease was also associated with increased nocturia [634]. Furthermore, a relationship between nocturia with restless legs syndrome was recently reported [580].

4. SUMMARY POINTS

- Overactive bladder (syndrome) (OAB) has been defined as urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia (in the absence of infection or other obvious pathology).
- Prevalence of OAB has been estimated from as low as 2% up to 53%.
- Recent population-based studies have shown that less than 10% of people have OAB with at least moderate bother suggesting that bother measurement is essential in estimating the clinically relevant prevalence of OAB.
- Longitudinal studies have shown that OAB increases with age, and that OAB is a dynamic condition, with not only substantial progression but also remission rates.
- OAB has been suggested to be associated with an increased risk of falls, fractures, and impaired quality of life.
- While age is a clear risk factor for urinary urgency and/or OAB, other risk factors have not been that well studied.
- Individuals with benign prostatic hyperplasia, pelvic

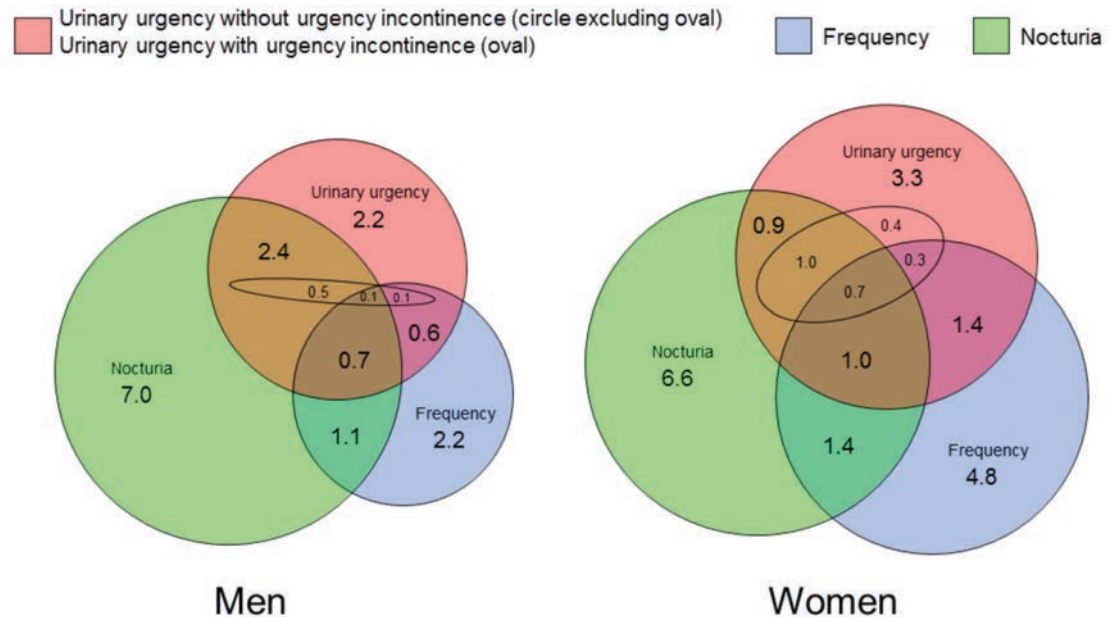


Figure 9. Age-standardised prevalence of nocturia, urinary urgency (with or without urgency incontinence) and urinary frequency among Finnish people aged 18–79 years.

The red circle represents individuals with urinary urgency (often or always in scale: never-rarely-often-always) without urgency incontinence (often or always in scale: never-rarely-often-always) excluding the area of the red oval representing individuals with urinary urgency with urgency incontinence. The blue circle represents individuals with urinary frequency (defined as more than eight voids/day) and the green circle nocturia (defined as at least two voids/night). Age-standardization performed using the age structure of Finland. Modified from 124 which is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

organ prolapse and mental health problems typically report urinary urgency more often than those without.

- Nocturia is one of – if not the - most common lower urinary tract symptom with similar overall prevalence in both genders.
- The prevalence of nocturia is higher among young women than young men, but prevalence increases more strongly with age in men.
- The literature on the incidence of nocturia remains relatively sparse. Incidence of nocturia has been shown to increase with age but also remarkable fluctuation has been identified.
- Two episodes of nocturia constitute meaningful nocturia, affecting quality of life and perceived health, while a single episode does not.
- Nocturia has been associated with an increased risk of falls, fractures, and death.
- Risk factors for nocturia include conditions of the lower urinary tract, but also a range of systemic conditions, including but not limited to prostatic hyperplasia, urinary urgency/overactive bladder, obesity, sleep apnoea, parity, and postmenopausal periods.

5. FUTURE NEEDS

- Due to the relative youth of research in OAB and nocturia, most data currently available are cross-sectional, hence, more prospective studies are needed.
- Natural history of OAB and nocturia needs more research – progression and remission of these symptoms is not yet well understood.
- Better understanding of relationship of different 'overactive bladder symptoms' would be beneficial.
- With prospective studies examining risk factors for incident OAB and nocturia will be possible, however, definition of incident OAB and nocturia may be challenging due to fluctuating character of these symptoms.
- Overall, further studies should be conducted with proper study designs and population-based samplings in order to decrease risk of bias.

G. EPIDEMIOLOGY OF POP

I. GENERAL COMMENTS AND DEFINITIONS

Pelvic organ prolapse (POP) refers to loss of support for the uterus, bladder, colon or rectum leading to prolapse of one or more of these organs into the vagina. Prolapse is thus a continuous condition when measured by visual inspection of the vaginal wall during valsalva. For clinical purposes, the degree of POP is commonly described as above the introitus, at the introitus, or beyond the introitus with or without valsalva. The International Continence Society first developed a standardised definition for the condition of POP in 1996 [635]. The ICS Pelvic Organ Prolapse Quantification (POPQ) examination defines prolapse by measuring the descent of specific segments of the reproductive tract during valsalva strain relative to a fixed point, the hymen. The POPQ system describes the anatomic findings of pelvic organ prolapse without consideration for symptoms and bother perceived by the woman. Validation of this system has shown it to be highly reliable [636]. The stages of prolapse severity are arbitrarily defined, and there is no clear differentiation between normal anatomic variation and mild POP. For research purposes there is consensus for use of the POPQ system until further evidence might clarify the distinction between normal variation and mild prolapse [637].

Determining POP based on self-reported symptoms is difficult because of the lack of specificity and sensitivity of most symptoms attributed to pelvic organ prolapse [638] and the fact that prolapse above the level of the hymeneal ring is usually asymptomatic [639]. The only exception appears to be a sensation of bulging into the vagina [640]. which is most strongly associated with prolapse at or below the hymeneal ring [641-642]. A recent study of 110 women found that a question asking about a feeling of something bulging in or dropping out of their vagina had a sensitivity of 84% and a specificity of 94% for POP at or beyond the hymeneal ring on examination [639]. Seeing prolapse would presumably be even more specific, but is too uncommon to be useful as a definition.

II. PREVALENCE OF POP

Since the 4th ICI several additional studies have reported the prevalence of POP in a general population [643-648]. Reports from the Women's Health initiative (WHI) Oestrogen Plus Progestin Trial, and randomised controlled trial, have been included [643,645-646]. While not actually population-based, the women in the trial were recruited from the community rather then from women seeking gynaecological care, and provide important information on the prevalence of POP based on pelvic examination.

The prevalence of POP based on a sensation of a mass bulging into the vagina was remarkably consistent, ranging between 5 and 10 percent (**Table 16**). The study by Eva et al., which reported a substantially higher prevalence included in the definition of POP, pelvic heaviness or digital pressure on the perineum or in the vagina to aid with defaecation [649]. The prevalence of observed prolapse in women enrolled in the WHI trial is similar to the

Table 16. Prevalence of pelvic organ prolapse (POP) defined by symptoms or observed on pelvic examination in the general population .

First author	Country	Definition of POP	Ages (years)	N	Prevalence Subgroup: %
Kumari [651]	India	"a mass of flesh in the vagina" or equivalent using local terminology	15+	2990	15-24: 5 25-34: 10 35-44: 8 45-54: 6 55-64: 9 65+: 3
McLennan (652)	Australia	A feeling of something coming down in the vagina	15-97	1546	8
Tegerstedt (647)	Sweden	Validated 5 item quetionnaire	30-79	5489	8
Eva [649]	Sweden	Any symptom of pelvic heaviness, genital bulge, or use of fingers in vagina or on perineum for defecation	40 60	641 663	23 28
Samuelsson [650]	Sweden	Standardized pelvic examination	20-59 (mean=39)	487	Any prolapse: 31 To introitus: 2 Cystocele: 16 Rectocele: 14 Uterocele*: 5
Rortveit [648]	USA	Feeling of bulging, pressure or protrusion or visible bulge or protrusion	40-73 (mean=56)	2109	6
Lawrence [644]	USA	Sensation of bulge in vagina or something falling out of vagina with a degree of bother of at least 33 on a 1-100 visual analogue scale (validated)	25-84 (mean= 57)	4103	6
Hendrix [642]	USA	Standardized pelvic examination	50-79 (mean=63)	27,3 42	Any prolapse: 40 Cystocele: 34 Rectocele: 19 Uterocele*: 14
Handa [643]	USA	Standardized pelvic examination	50-79 (mean=63)	412	Any prolapse: 32 Cystocele any: 25 Cystocele grade 1: 14 Cystocele grade 2: 10 Rectocele any: 13 Rectocele grade 1: 8 Rectocele grade 2: 5 Uterocele any: 4 Uterocele grade 1: 3 Uterocele grade 2: 1
Nygaard [646]	USA	POP-Q**	50-79 (mean=68)	270	Stage 0: 2 Stage 1: 33 Stage 2: 63 Stage 3: 2 Stage 4: 0 ≥ hymeneal ring: 26
Bradley [645]	USA	POP-Q	50-79 (mean=68)	270	≥ hymeneal ring: 24

** Denominator is women with a uterus*

*** Stages defined as 0: no prolapse, 1: prolapse to 1 cm above hymen, 2: prolapse to between 1 cm above and 1 cm below hymen, 3: prolapse between 1 cm below hymen and 2 cm above introitus, 4: prolapse beyond 2 cm above introitus.*

Note: Studies reported by Handa, Nygaard and Bradley are all subsets from study reported by Hendrix.

prevalence found in the one population-based study that also used pelvic examination [650], although the prevalence of each type of prolapse was higher in the WHI study [642]. In both studies, prolapse occurs most frequently in the anterior compartment, next most frequently in the posterior compartment, and least in the apical compartment.

Two studies that examined prolapse by race found the that Black women had the lowest prevalence and Hispanic women the highest after controlling for multiple other factors in multivariate analysis [642,648]. The study reported by Rortveit et al based on symptoms found adjusted odds ratios of 0.4 (95% CI=0.2-0.8) for Black and 1.3 (95% CI=0.8-2.2) for Hispanic women, with White women as the referent group [556].14 Hendrix et al reported adjusted odds ratios of 0.6 (95% CI=0.5-0.8) for Black and 1.2 (95% CI=1.0-1.5) for Hispanic women compared to White women for POP based on genital examination [643].

III. INCIDENCE

Only two studies could be located that reported the incidence of new POP. Both studies were done on sub-groups of women enrolled in the WHI Oestrogen Plus Progestin Trial. The first study of 412 women enrolled at the University of California, Davis site, used a standardised pelvic examination repeated every 2 years over 8 years [643]. The incidence of new cystocele, rectocele and uterine prolapse was 9%, 6% and 2%, respectively. Annual rates of remission from grade 1 (prolapse to above introitus) was relatively common for each type of POP (24%, 22% and 48%, respectively) but less common from grade 2 or 3 (prolapse to or beyond the introitus) (9%, 3% and 0%, respectively). In a second study of 259 postmenopausal women with a uterus who were examined using the POP-Q at baseline and annually for 3 years. POP was defined as prolapse to or beyond the hymeneal ring. The incidence of new POP was 26% at 1 year and 40% at 3 years, with remission rates of 21% at 1 year and 19% at 3 years [645].

Several studies have reported the annual incidence of surgery for POP in the US and at least one in the UK. A longitudinal study of over 17,000 women in the U K, age 25 to 39 at baseline, reported an annual rate of prolapse surgery of 0.16% [653]. This rate is consistent with the rate of approximately 0.2% per year reported in the US [654-655]. One US study reported an annual incidence rising with age from 0.05% in women age 30-39 to 0.5% in women age 70-79 with an estimated lifetime cumulative risk of surgery from prolapse of 7% to 11% [656]. A recent US study reported similar surgical rates: 0.07% for women 18-39, 0.24% for women age 40-59, and 0.31% for women age 60-79 [657]. Surgical rates drop substantially after age 80 [656-657]. Estimating rates of prolapse surgery has the advantage of use of hospital discharge data on procedures, which is highly accurate for the procedure performed, but less accurate for the indications for the procedures, particularly when a procedure may have more then one indication.

IV. POTENTIAL RISK FACTORS

1. BOWEL DYSFUNCTION AND PELVIC ORGAN PROLAPSE

Women who seek urogynecological care report a high prevalence of bowel symptoms [658]. However, bowel dysfunction is highly prevalent among women in general and it has been estimated that up to 27% of the female population in industrialised countries is affected by constipation [659]. The overall prevalence of constipation and associated symptoms in women with pelvic organ prolapse ranges between 20-53% depending on the definition of disorders [660-662]. Although definitions of disease differ between studies it is widely acknowledged that bowel dysfunction is a complex condition with a multifactorial aethiology. Bowel dysfunction comprises a wide variety of symptoms including constipation, rectal emptying difficulties, incomplete defaecation, manually assisted defaecation, faecal urgency and irritable bowel syndrome (IBS). Neurophysiological assessments have shown that damage to the pelvic floor musculature and nerve supply can occur as a result of chronic constipation [663]. Other predisposing factors comprise low socio-economic status, pelvic floor surgery, depressive disorders, thyroid dysfunction, physical disability and inactivity, and food habits [664].

Current epidemiological evidence on the association between bowel dysfunction and pelvic organ prolapse are at odds. A number of studies suggest that women with pelvic organ prolapse are significantly more likely to experience constipation and other symptoms of bowel dysfunction, [662,665-668] whereas others show a weak or non-existent association [661,669-671]. In a case-control study, manually assisted defaecation was present in 19.7% of women with prolapse compared to 4.4% of control subjects ($p<0.001$) [662]. In a randomly selected population based study, irritable bowel syndrome and constipation were both strongly associated with pelvic organ prolapse (OR 2.8 95% CI 1.7-4.6, and OR 2.5 95% CI 1.7-3.7 respectively) [667]. Varma et al., [668] suggested that among randomly selected women, having symptomatic pelvic organ prolapse more than doubled the risk for obstructed defaecation (OR 2.3 95% CI 1.5-3.7). A retrospective questionnaire based survey of women with and without prolapse concluded that constipation as a young adult was an important factor in the development of uterovaginal prolapse[665]. In a case-control study, women with prolapse were at increased risk for constipation also after adjustment

for dietary fibre intake (OR 2.9, 95% CI 1.1-13.5). when compared to women without prolapse[666].

In the cross-sectional Women´s Health Initiative (WHI), cysto- and rectocele was only weakly associated with constipation (OR 1.1 95% CI 1.0-1.2) [669]. Similar weak associations between prolapse and bowel dysfunction have been observed in other large cross-sectional studies [661,670-671]. Overall severity and prevalence of bowel dysfunction has shown poor correlation with findings of pelvic organ prolapse at radiological imaging [672-674]. Also at clinical examination, increasing vaginal descent and prolapse severity, show a generally weak (or absent) association with symptoms related to bowel dysfunction [660,675-678]. In a substudy to the WHI, no specific bowel symptom was associated with increasing loss of pelvic organ support in any vaginal compartment [671]. When considering compartment-specific pelvic floor defects, most studies suggest that increasing posterior vaginal wall prolapse and perineal descent are correlated to more symptoms of obstructive defaecation [661,674,676]. In a cross-sectional study of 260 women with pelvic organ prolapse, women with posterior vaginal wall prolapse were more likely to incomplete emptying (41% vs 21%, P=0.003), straining at defaecation (39% vs 19%, P=0.002), and splinting with defecation (36% vs 14%, P<0.001) compared with women without posterior vaginal wall prolapse. But there was no significant association between bowel symptoms and increasing severity of prolapse [679].

The association between bowel dysfunction other than specifically obstructive symptoms and pelvic organ prolapse has been poorly investigated. In a random population-based study of 2109 racially diverse women women with IBS (prevalence =9.7%) had higher odds of reporting symptomatic pelvic organ prolapse (OR 2.4; 95% CI, 1.4-4.1) compared to those without IBS [680]. It has also between suggested that anal sphincter dysfunction such as paradoxical anal sphincter reaction is more common in patients with rectocele as compared to women without rectocele at defaecography [681].

2. PELVIC SURGERY AND POP

Even though the notion that hysterectomy increases the risk for pelvic organ prolapse has wide acceptance, longitudinal studies confirming a temporal association are few and previous studies do not often differentiate between various types of hysterectomy. A number of cross-sectional and retrospective studies implicate hysterectomy as an independent risk factor for pelvic organ prolapse. However, due to a delay of onset, large population samples and a sufficiently long duration of follow-up are required to determine an association with adequate certainty.

In a nationwide cohort study, Altman et al. [682]. reported that 3.2% of women with hysterectomy had pelvic organ prolapse surgery, compared with 2.0% in non-hysterectomized controls, corresponding to a risk of 1.7 (95% CI, 1.6-1.7). In this Swedish study, vaginal hysterectomy had the highest risk for subsequent prolapse surgery (HR 3.8, 95% CI, 3.1 to 4.8) in comparison to non-hysterectomised controls. These results were corroborated by Cooper et al. in a large study from Scotland showing an increased risk for prolapse surgery among women after hysterectomy, compared to endometrial ablation [683]. These register-based data are largely in agreement with the longitudinal Oxford Family Planning Association study by Mant et al. [684] reporting increased overall incidence rates for prolapse surgery following hysterectomy. Although not separating various hysterectomy techniques, Mant el al. determined that the risk of prolapse following hysterectomy was 5.5 times higher (95% CI 3.1-9.7) in women whose hysterectomy was performed for prolapse as opposed to other benign conditions. A history of hysterectomy has also been identified to increase the risk for prolapse in several cross-sectional and retrospective studies [685-686].

Specific risk factors for posthysterectomy prolapse have been assessed in two case-control studies. Both Dällenbach et al. [687]. and Forsgren et al. [688]. reported that pelvic floor surgery before hysterectomy was the strongest risk factor for developing posthysterectomy pelvic organ prolapse (OR 7.9, 95% CI 1.3-48.2 and OR 2.8, 95% CI 1.0-7.7 respectively). The risk of prolapse repair was 4.7 times higher in women whose initial hysterectomy was indicated by prolapse [687]. Vaginal vault prolapse involves the loss of vaginal apical support and may per definition only occur after hysterectomy [689]. Marchionni et al. reported a 4.4% overall incidence of vaginal vault prolapse after hysterectomy but in women where uterine prolapse was the indication for hysterectomy the incidence was 11.6% [690]. In a register-based study Forsgren et al. showed that the greatest risks for prolapse surgery (HR 4.9, 95% CI 3.4-6.9) were observed subsequent to vaginal hysterectomy for pelvic organ prolapse but having a vaginal hysterectomy also for other indications significantly increased the risk for subsequent pelvic organ prolapse surgery compared to other modes of hysterectomy [691]. Similar observational results were shown by Cooper et al. [683].

It has also been suggested that pelvic surgery other than hysterectomy may predispose women to subsequent genital prolapse including: rectopexy for rectal prolapse (OR 3.1; 95% CI 1.4-6.9) [692].; gynaecological surgery in general (OR = 3.9, 95% CI 1.8-8.8) [693]; and retropubic colposuspension procedures are associated with a near 30% risk of subsequent vaginal vault and posterior vaginal prolapse at long-term evaluations [694-695]. In a prospective cohort study of 374 women, the 10-year re-operation rate was 17% after traditional prolapse or incontinence surgery[696]. Having undergone pelvic organ prolapse or incontinence surgery prior

to the index operation increased the risk of re-operation to 17% compared with 12% for women who underwent a first procedure (p=.04) [696].

3. OBSTETRIC FACTORS AND POP

For ethical and practical reasons, randomised controlled trials to study the causal effects of vaginal and caesarean delivery on the pelvic floor will never be performed. Observational studies will therefore most likely remain the main source of knowledge on this subject. Nonetheless it is widely accepted that childbirth is a significant risk factor for pelvic organ prolapse, presumably due to overt or occult pelvic floor tissue trauma. Controversy does, however, remain with regard to the protective effect of caesarean section and if specific obstetric events should be considered as risk modifiers. Due to a delayed onset of pelvic organ prolapse in relation to giving birth, studies on the subject need a long duration of follow-up as well as large study populations to be able to elucidate the possible causative events. Therefore, the majority of studies on the subject are typically designed as cross-sectional surveys or retrospective cohort or case-control studies. It is, however, encouraging that long term longitudinal data are starting to emerge.

Pregnancy itself has been identified as a risk factor for stress urinary incontinence. With regard to pelvic organ prolapse, the association is less substantiated. In a clinical case-control study, all 21 nulliparous non-pregnant women had POP-Q stage 0 or 1, whereas 47.6% of 21 nulliparous pregnant women had pelvic organ descent corresponding to stage II (p<0.001) [697]. Overall POP-Q stage was higher in the third trimester than in the first (p=0.001). Also Sze et al.[698] found that in 94 nulliparous women evaluated at the 36 with antepartum visit and six weeks postpartum, POP-Q staging increased.

A large number of studies identify childbirth as one of the strongest predictors for developing pelvic organ prolapse later in life [667,669,684-685,699-704]. It is also a recurrent observation that the number of deliveries is associated with the risk of prolapse although there are data to suggest the contrary [705]. In the prospective Oxford Family Planning Association study, [684] childbirth was the single strongest risk factor for developing prolapse in women under 59 years of age and the risk increased by every delivery. Similar findings derived from the WHI, [669] where a parity of one conveyed an overall two-fold risk increase for prolapse compared to having no children, after which each additional childbirth added a 10-20% risk increase. In a case-control study, Tegerstedt et al. [703] found that the risk for symptomatic pelvic organ prolapse increased with the number of deliveries and were 3.3-times higher among mothers of four than among mothers of one. Similarly, Rortveit et al. [667] found that the risk of prolapse increased in women with one (OR 2.8 95% CI 1.1-7.2), two (OR 4.1, 95% CI 1.8-9.5), and three or more (OR 5.3, 95% CI 2.3-12.3) vaginal deliveries compared with nulliparous women. In a questionnaire based cross-sectional study among 2,640 middle-aged women the number of vaginal deliveries was a risk factor for past or present symptomatic prolapse [704].

Whether or not caesarean section provides sufficient protection to the pelvic floor, thereby preventing loss of pelvic organ support, is controversial. Several studies suggest that elective cesarean does indeed protect women from developing pelvic organ prolapse later in life [699,700-703]. In 4,458 randomly selected women, vaginal childbirth increased the risk of prolapse by 1.82 (95% CI 1.04-3.19) [701] In a nested case-control study, Uma et al. [702] found that caesarean section was associated with a significantly reduced risk of pelvic floor surgery compared with spontaneous vaginal delivery (OR 0.16, 95% CI 0.05-0.55). In a case-control study, Chiaffarino et al. [706] found that women who were delivered by caesarean section were at significantly lower risk of prolapse (OR 0.3 95% CI 0.1-1.0). Other investigators suggest that in the long term, caesarean delivery does not provide a significant risk reduction in pelvic floor morbidity compared with vaginal delivery [707-708]. In a cohort study of women having their first and all subsequent deliveries by cesarean (n = 33,167), and an age-matched sample of women only having vaginal deliveries (n = 63,229) between 1973 and 1983, Leijonhufvud et al. found that women only having vaginal deliveries had increased overall risk of subsequent prolapse surgery (hazard ratio, 9.2; 95% CI 7.0-12.1) compared with women only having cesarean deliveries [709] Among women with vaginal deliveries only the incidence rate for prolapse surgery increased steadily, reaching its peak close to three decades after first delivery. In women with cesarean deliveries only the incidence rate for POP surgery showed very little variation over time and being notably lower compared to the vaginal delivery cohort 10 years after first birth for the duration of the observational period. These observational data suggest that cesarean section conveys a long-term protective effect with regard to the development of pelvic organ prolapse (**Figure 10**).

A number of specific obstetric events and interventions have been implicated as risk factors for the development of pelvic organ prolapse. In one study, maternal age and use of epidural analgesia was associated with an increased need for pelvic organ prolapse surgery [700]. A case-control study found no significant association with maternal age, instrumental delivery (forceps or vacuum), or length of delivery when comparing women with prolapse to randomly selected controls [703] However, Handa et al. [710] found that operative vaginal birth significantly increased the risk for all pelvic floor disorders and pelvic organ prolapse in particular (OR 7.5, 95% CI 2.7-20.9). In a case-control study, Chiaffarino et al.

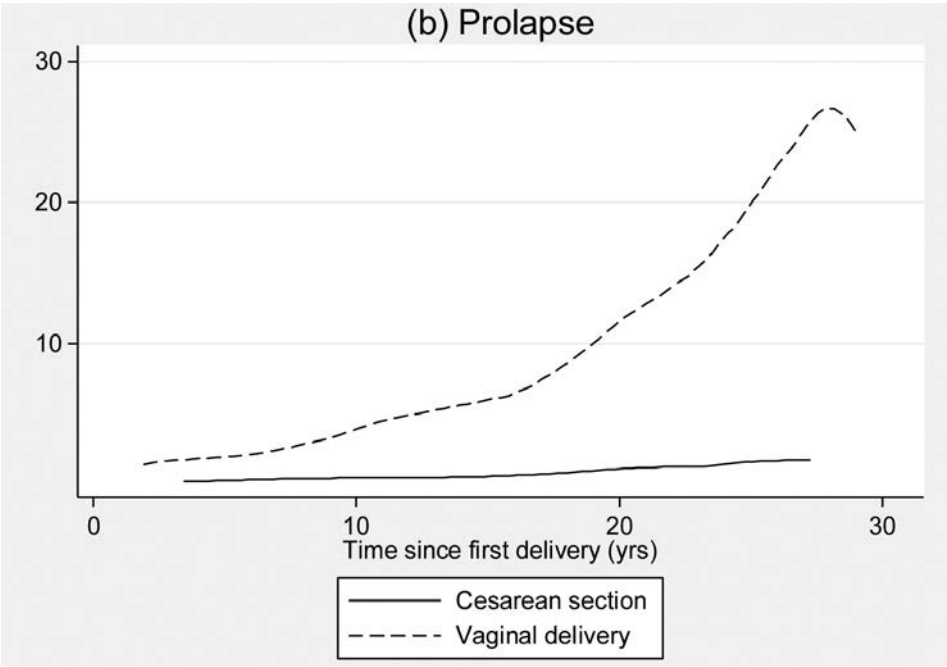


Figure 10. Rate of pelvic organ prolapse surgery in relation to mode of delivery and time from first childbirth[709].

[706] found that after forceps delivery women had an OR of 3.6 (95% CI 1.0-13.5) for developing pelvic organ prolapse, but after adjustment for vaginal delivery the odds were no longer significant (OR 1.3 95% CI 0.6-3.1). Also Moalli et al. [693] concluded that forceps delivery posed a risk for prolapse. On the othr hand, Uma et al. [702] found no significant association between pelvic organ prolapse and forceps delivery (OR 0.9, 95% CI 0.7-1.2); infant birthweight >4.0 kg (OR 0.9, 95% CI 0.5-1.7); episiotomy (OR 1.46, 95% CI 1.0-2.10); and labour prolonged >12 hours (OR 1.51, 95% CI 1.00, 2.27). The inconsistency and wide variety in the magnitude of the risk estimates suggest that most studies so far lack sufficient statistical power for valid conclusions.

4. MISCELLANEOUS RISK FACTORS AND POP

A wide variety of risk factors for pelvic organ prolapse, others than those addressed above, have been identified in the literature. Most of these have been investigated as part of larger multivariate analyses based on cross-sectional surveys or retrospective case-control studies. Overall, these associations are largely of level III-IV evidence and further research is needed to disentangle the effects and interactions of environmental risk factors for prolapse.

Several somatic risk factors for pelvic organ prolapse have been identified. Generalised connective tissue disorders such as Ehlers-Danhlos disease and Marfans syndrome [711-712] have been linked to an increased risk for pelvic organ prolapse. In a community-based study of prolapse in rural West Africa, chronic anaemia was the strongest risk factor for prolapse after parity and age (OR 2.1 95% CI 1.1-3.4). [713] and chronic obstructive pulmonary disorders. Skeletal abnormalities such as thoracic kyphosis, lumbar lordosis and pelvic dimension changes have been associated with an increased risk for prolapse [713-715]. Women with joint hypermobility have a significantly higher prevalence of genital (and rectal) prolapse in comparison to women with normal mobility[716-717] Weak associations have also been shown for osteoporosis and rheumatoid arthritis [707] Obesity may be associated with increased pelvic floor symptoms and more severe symptomatic prolapse [704,718-719] yet increasing body mass index and obesity have not consistently been identified as risk factors for prolapse as compared to stress urinary incontinence [720-721] Other factors that has not convincingly demonstrated any significant linkage to prolapse include the presence of chronic obstructive pulmonary disease and diabetes mellitus [685,721] Pulmonary impairment has been shown to more common in women with loss of pelvic organ support compared to those without [722].

A low educational level (OR 2.16, 95% CI 1.10-4.24) [723] and low annual income, [724] are socio-economic factors which have been associated with an increased risk for pelvic organ prolapse. In 21,449 non-hysterectomised Italian women, higher education was associated was a protective factor for uterine prolapse [708]. However, despite significant differences in educational level, smoking habits, alcohol consumption, and socio-economic indices, the prevalence of pelvic organ prolapse did not differ between

Kroatian urban and rural women [725] Interestingly, risk factors for pelvic floor disorders including pelvic organ prolapse among women in developing countries were similar to those in industrialised countries (increased age and parity). In a review study across 16 low-income and lower middle-income countries the mean prevalence for pelvic organ prolapse was 19.7% (range 3.4-56.4%) but risk factors were similar to those described in studies from more affluent countries but additionally pelvic organ prolapse and other pelvic floor disorders were associated with other factors including poor nutrition and heavy physical work [726].

A physically strenuous occupation has also been shown to influence the risk for pelvic organ prolapse. In a register based study of 28,000 Danish assistant nurses exposed to repetitive heavy lifting, the risk for prolapse was higher among the nurses compared to controls (OR 1.6 95% CI 1.2-2.2) [727]. Women who were labourers/factory workers had significantly more severe prolapse than other job categories ($p < 0.001$) in a cross-sectional study of women presenting for routine gynecological care [724]. Also, hard physical training may increase the risk for prolapse as women attending paratrooper training, were more likely to present stage II prolapse compared to controls (RR=2.7 95% CI 1.4-5.4) [728].

V. SUMMARY POINTS

- Most studies have used a cross-sectional design and there are limited longitudinal data to suggest a causal relationship between symptoms of obstructed defaecation and pelvic organ prolapse or vice versa. Posterior vaginal wall prolapse and perineal descent are the specific pelvic defects most frequently associated with symptoms of obstructive defaecation.
- Current evidence suggest that hysterectomy increases the risk for subsequent pelvic organ prolapse in general.
- Vaginal hysterectomy and hysterectomy performed for pelvic organ prolapse are the strongest risk factors for having secondary pelvic floor surgery.
- Childbirth is associated with an increased risk for pelvic organ prolapse later in life and increasing number of deliveries is positively associated with the risk.
- Longitudinal long-term data suggest that caesarean section decreases the risk for surgically managed pelvic organ prolapse and most studies indicate that caesarean is associated with a decreased risk for subsequent pelvic floor morbidity in comparison to giving vaginal birth.
- There is a dearth in the understanding of how specific obstetric events and the process of labour and delivery affect the risk for pelvic organ prolapse yet instrumental delivery may increase the risk for development of pelvic organ prolapse.
- Life style factors and socio-economic indices may be associated with the risk of pelvic organ prolapse in both industrialised and non-industrialised countries.
- A number of somatic diseases and conditions have been linked to the occurrence of prolapse but the cause-effect relationship is undetermined.

H. THE GENETIC EPIDEMIOLOGY OF UI AND POP IN ADULT WOMEN

The existence of both acquired and inherited risk factors for incontinence has been recognised for more than 150 years [729]. Although recent advances in formal genetics have quantified the relative contribution of environmental and genetic variation, we still have very limited understanding of the molecular genetics of these conditions. In this section we consider the evidence for genetic predisposition from family studies, twin studies and segregation analyses, and then consider in detail efforts to identify causal variants from linkage studies, candidate gene association studies, and the first reported genome wide association study for pelvic organ prolapse.

I. FAMILY STUDIES

Family studies have classically been considered the first step in establishing the genetic basis of any disease. However, familial aggregation provides limited evidence of heritability, since it fails to control for the effects of shared environmental factors. For pelvic floor disorders, exposures to all major lifestyle risk factors are likely to be at least partly determined by socio-cultural values that are shared within families. Such effects are at least plausible for family size, smoking, socio-economic status, care seeking behaviour, physical exercise, dietary and drinking habits, and toilet training. Both incontinence and prolapse are considered stigmatising in many populations, which places family studies at high risk of differential misclassification bias. This might be expected to have particular impact on the validity of estimates obtained from studies employing the family history method, and any study with non-random sampling of families, for example those relying on probands recruited in secondary care, or those recruiting volunteers via advertisement. Finally, while age correction of risks is possible to account for increasing disease prevalence with age, this has typically not been employed in family studies of pelvic floor disorders.

Although family studies may not provide robust evidence, there have been many studies that

examined prevalence of incontinence (**Table 17**) among relatives of women with incontinence [730-735]. Despite considerable variation in case ascertainment and sampling methods, all studies demonstrate increased risks for urinary incontinence among first degree relatives of probands. This appears to apply for all subtypes of urinary incontinence, and to have a plausible biological gradient, with higher risks among relatives of women with severe incontinence.

In the only study to attempt adjustment [732], it appears that these familial risks are attenuated but not eliminated by classic risk factors for incontinence including age, parity, and BMI. At least three studies have also assessed family history as a risk factor for incident post-partum incontinence, with conflicting findings [737-739].

There is also a large body of evidence regarding familial transmission of pelvic organ prolapse. With wide variation in prolapse rates with different cases definitions?, uncontrolled studies have produced disparate estimates of the proportion of prolapse patients with a family history of prolapse [740-742]. Reports from controlled studies (**Table 18**) have however consistently demonstrated increased risks [743-746], with unadjusted OR of 2-3 for prolapse among first-degree relatives of prolapse sufferers. These risks are attenuated but not eliminated by adjustment for other risk factors [743-745]. As for

Table 17. Family studies investigating the prevalence of urinary incontinence amongst relatives of women with incontinence

Study	Setting	Design	Age range	n (♀ probands and controls)	Proband phenotype	Family member outcomes	OR or RR (95%CI)
Diokno 1990[730]	Population Based	Controlled – Family History Method	>60	1,154	Any UI	Either parent with UI as adult	2.04 (1.55-2.68)
						Any sibling with UI as adult	1.85 (1.32-2.60)
					Urge UI	Either parent with UI as adult	1.89 (0.93-3.82)
						Any sibling with UI as adult	0.68 (0.20-2.28)
					Stress UI	Either parent with UI as adult	1.74 (1.12-2.70)
						Any sibling with UI as adult	1.59 (0.92-2.75)
					Mixed UI	Either parent with UI as adult	2.63 (1.91-3.61)
						Any sibling with UI as adult	2.32 (1.58-3.40)
					Other UI	Either parent with UI as adult	0.23 (0.06-0.99)
						Any sibling with UI as adult	0.70 (0.21-2.34)
Mushkat 1995[731]	Secondary Care	Controlled – Direct ascertainment	>18	424	Urodynamic Stress UI	SUI among all first degree ♀ relatives	3.00 (2.06-4.38)
						SUI among mothers	3.68 (2.10-6.45)
						SUI among sisters	3.39 (1.89-6.08)
						SUI among daughters	2.43(0.68-8.65)
Hannestad 2004[732]	Population based	Controlled – Direct ascertainment	>18	8,771 (mothers) 2,866 (older sisters)	Any UI	Any UI among daughters	1.31(1.19-1.44)* 1.94(1.26 3.00)**
						Any UI among younger sisters	1.59(1.34-1.89)*
*RR adjusted for age, BMI, and parity **RR adjusted for age, BMI, and parity and restricted to subgroup of daughters of mothers with severe UI Note: unadjusted risks generally higher across all outcomes, indicative of substantial concordance/correlation in age, BMI, and parity between family pairs.					Stress UI	Stress UI among daughters	1.52(1.28-1.81)* 2.98(1.11-8.03)**
						Stress UI among younger sisters	1.77(1.34-2.33)*
					Urge UI	Urge UI among daughters	1.80(0.83-3.92)*
					Mixed UI	Mixed UI among daughters	1.55(1.21-1.99)* 2.07(0.92-4.64)**
						Mixed UI among younger sisters	1.74(1.08-2.82)*
Elia et al 2002[733]	Secondary Care	Family history method	>18	667	Any UI	Any UI among any relatives	4.51(2.833-7.20)
Ertunc et al 2004[734]	Secondary Care	Direct ascertainment	>18	513	Surgically treated SUI	SUI among mothers	3.71(1.84-7.47)
						SUI among sisters	2.49(1.49-4.16)
Buchsbamet al 2005 [735]	Community Based	Direct ascertainment	Post menopause	143	Nulliparous with any UI	Any UI among parous sisters	2.89(1.46-5.70)
Lapitan et al, 2001[736]	Secondary Care	Family history	>18	5502	OAB	Any family history	1.62(1.42-1.83)

Table 18. Familial transmission of pelvic organ prolapse.

Study	Setting	Design	Age range	n (♀ probands and controls)	Proband phenotype	Family member outcomes	Unadjusted OR (95%CI) (Unless specified)
Chiaffarino 1999 [743]	Secondary Care	Controlled – Family History Method	<75	208	Stage II-IV Baden-Walker	History of mother with prolapse	3.2 (1.1-7.6)*
						History of sister with prolapse	2.4 (1.0-5.6)*
McLennan 2008 [744]	Secondary Care	Controlled – Family History Method	>18	624	Stage I-IV Baden-Walker	Family history of any relative with hernia or prolapse	RR 1.81(1.41-2.32) RR 1.4 (1.2-1.8)** 2.71(1.83-4.01)
					Stage I-II Baden-Walker	Family history of any relative with hernia or prolapse	RR 1.69 (1.19-2.41) 2.37(1.27-4.39)
					Stage III-IV Baden-Walker	Family history of any relative with hernia or prolapse	RR 2.69 (2.13-3.41) 8.72 (5.26-14.42)
Sleiker-ten Hove 2009 [745]	Population based	Controlled - Family History Method	45-85	1397	Symptom of vaginal bulge	Mother with prolapse	1.99 (1.31-3.04) 1.67 (1.10-2.54)***
Mathlouthi 2011 [746]	Secondary Care	Controlled - Family History Method	<45	66	Surgically treated POP	Any family history POP	4.41 (0.47-41.8)

**Adjusted for age*
***Adjusted for vaginal deliveries, incontinence status, and family history of incontinence*
****Adjusted for age, current heavy physical work, and prolapse symptoms during pregnancy*

incontinence, there again seems to be a plausible biological gradient [744], with anatomically more severe cases of prolapse being more likely to have a positive family history. This is consistent with the suggestion of an earlier onset of prolapse among familial cases [742].Only one study has used direct anatomic ascertainment, in a study based on sib-pairs discordant for parity [747].There familial concordance was observed not only for overall prolapse stage, but also by compartment. Where it has been tested, there also appears to be shared familial risk between prolapse and incontinence [744-745], although this overlapping propensity may be explained by known shared environmental risk factors, rather than common genetic predisposition.

In summary, family studies have consistently demonstrated familial aggregation of both incontinence and prolapse. A family history of incontinence or prolapse is associated with approximately double the risk of developing either condition. Such an effect appears to hold for all subtypes of incontinence, and prolapse in all compartments. There is plausible evidence that family history is associated with both earlier onset, and more severe phenotype. These effects are partly explained by known environmental risk factors, and family studies cannot exclude the risk of further unmeasured confounding from shared environmental risks. For this we should consider evidence from classical twin studies.

II. TWIN STUDIES

Twin studies compare the concordance in a trait or condition between monozygotic (MZ) twins and same-sex dizygotic (DZ) twins, to estimate heritability. For genetically determined traits higher concordance is observed in MZ twins compared to DZ twins, while for entirely environmentally determined traits, concordance should be the same in both types of twin pair. This simple idea is illustrated by consideration of a fully penetrant autosomal single gene disorder, which will display 100% concordance in MZ twins, while in DZ twins will have only 50% concordance for a gene with dominant mode of inheritance, or 25% concordance for a gene with recessive mode of inheritance. A fundamental assumption of these analyses is that both types of twin pair share equal environment. This assumption is clearly violated both pre-natally, and in later life. This bias can be partially compensated for either in studies of twins reared apart, or in adoption studies, but these designs have not been applied to the study of incontinence or prolapse.

Three major twin resources have been used to assess genetic influences on incontinence or prolapse: the US Twins Days festival, the Danish Twin Registry, and the Swedish Twin Registry. The Twins Days festival relies on volunteers, and the resulting recruitment bias is likely to overestimate concordance for many traits for both MZ and DZ twins. In the sample of 1,764, predominantly MZ, middle-aged twins from Twins Days, concordance of symptomatic stress urinary incontinence was 79.5% for MZ and 78.6% for DZ twins [748]. Such a result suggests no significant genetic contribution to stress urinary incontinence at all.

Among a sample of 2,336 twins surveyed as part of four surveys from the Danish Twin Register, concordances for both MZ and DZ twins were much lower

not only for stress urinary incontinence, but also for urgency and mixed incontinence [749].With separate cohorts for middle-aged and elderly women, heritability was calculated separately in each age group. As in the Twins Day sample, genetic factors were not significant for stress incontinence in middle-aged women, but rose to a heritability of 39% in the elderly women. Similarly heritability increased with age for urgency incontinence (42% rising to 49%), and mixed incontinence (27% to 55%).

Women participating in the Swedish Twin Register have provided relevant data as part of two separate analyses [750-751].Treatment codes corresponding to stress incontinence and prolapse surgery from a nationwide surgical register were used to estimate heritability for a sample of 16,886 twins aged >50. As might be expected for such a strict phenotype definition, concordances for surgical treatment were low, but produced heritability estimates of 41% for stress incontinence surgery, and 43% for prolapse surgery. Similarly for female twins aged 20-46 from the same register (evaluable sample 4,550), using questionnaire based phenotyping, produced an estimate of 34% heritability for stress incontinence. From the same survey heritability was estimated for urgency incontinence (37%), mixed incontinence (18%), “any” incontinence (51%), nocturia (48%), and urinary frequency (40%). It should be noted that because of sample size limitations, an absence of genetic effects cannot be entirely precluded for stress, urgency, or mixed incontinence.

The mechanism of these probable genetic effects has been explored in analyses of joint hypermobility and pelvic floor mobility in twins [752-753].These data suggest heritability of 59% for oblique bladder neck descent on Valsalva in nulliparous twins aged 18-24, with a shared genetic component to both pelvic floor and elbow mobility.

In summary, twin studies to date have suggested significant heritability for stress incontinence, urgency incontinence, and pelvic organ prolapse, with genetic variation potentially contributing up to half of population phenotypic variation. Heritability appears to be highest for urgency incontinence, with apparent heritability increasing with age as environmental factors reduce in importance. This is consistent with our understanding of childbirth as a major environmental determinant of both incontinence and prolapse. Genetic predisposition to incontinence and prolapse may manifest at a preclinical stage in pelvic floor hypermobility. Together with data from family studies this provides strong evidence of genetic risk factors for incontinence and prolapse.

III. SEGREGATION ANALYSES

Despite the large number of family studies for incontinence and prolapse in adults, there have been few studies to examine segregation among extended pedigrees. Studies of families affected by nocturnal enuresis [754], have however included some adults affected by urgency incontinence. Analysis of different enuretic families has usually suggested autosomal dominant inheritance with high penetrance, but low penetrance and autosomal recessive modes have also been reported. In the only segregation analysis reported to date of 10 families affected by prolapse [742], a dominant mode of inheritance was again proposed. These findings could be a consequence of selection or ascertainment bias. In contrast results from more recent association studies strongly suggest that polygenic inheritance is most likely across the population as a whole.

IV. LINKAGE STUDIES

Again, many linkage studies have been conducted using families of children affected by nocturnal enuresis [754], but only two studies have considered uniquely adult symptoms. In a family including 6 women with early onset prolapse across three generations, 10 putative loci were suggested, but none approached genome wide significance [755]. Allen-Brady and colleagues [785] genotyped women from 32 families, including 70 patients needing surgical treatment for prolapse. There was strong overlap with other pelvic floor disorders including a high prevalence of treatment for both stress and urgency incontinence. Using a set of 27,157 markers from a larger Illumina array, they observed a genome wide significant peak at 9q21, and further suggestive peaks at 9q31 and 1q42.

V. GENE ASSOCIATED STUDIES

Currently reported candidate gene studies have assessed polymorphisms of 10 different genes for incontinence (**Table 19**), and 15 genes for prolapse (**Table 20**). To allow comparisons across all studies, we extracted all genotype counts, and recalculated the allelic test. As a check on study quality we also recalculated the power of the study for an OR of 2.0 between cases and controls based on observed minor allele frequencies, and finally rechecked Hardy-Weinberg Equilibrium for cases, controls, and the overall population. We assessed the credibility of associations using the interim Venice criteria [756].

Polymorphisms in COLIA1, ADRB3, HTR2A, LOXL1, MMP1, MMP3, CYP17, CYP19, ESR, and AR, have been tested for an association with incontinence, or one of its subtypes. There is little uniformity in case definitions, with a mixture of urodynamic, clinical, and questionnaire based inclusion criteria used, and frequently inadequate matching between cases and controls for age, parity, or prolapse stage. In most cases we found significant

Table 19. Candidate gene association studies for urinary incontinence

Gene	refSNP ID	Phenotyping	Authors	Population	n cases	n controls	Allelic Test OR(95% CI)	Power for OR>=2	Hardy-Weinberg	Notes
COLIA1	rs1800012	SUI confirmed using cough test and cystometry	Skorupski et al 2006 [757]	White Polish	50	50	2 (1.12-3.6)	38.8%	Deviation from HWE for controls p<0.01	Likely genotyping errors
COLIA1	rs1800012	SUI confirmed using cough test and cystometry	Sioutis et al 2011 [758]	White Greek	45	45	2.19 (1.15-4.17)	35.6%	In HWE	Inadequate matching for parity
ADRB3	rs4994	OAB (with and without UUI) determined using questionnaire and bladder diary	Ferreira et al 2011 [759]	Unselected Brazilian	49	169	2.41 (1.38-4.21)	68.2%	Deviation from HWE for cases p<0.05	High risk population stratification
ADRB3	rs4994	Idiopathic OAB (with and without UUI) confirmed with questionnaire	Honda et al 2006 [760]	Unselected Japanese	100	101	2.48 (1.47-4.20)	71.8%	In HWE	
HTR2A	rs6313	Self reported incontinence	Schwanke et al 2007 [761]	Unselected Brazilian	102	196	1.12 (0.69-1.82)	62.5%	Deviation from HWE for cases p<0.05	High risk population stratification
HTR2A	rs6313	Self reported incontinence confirmed with cystometry	Noronha et al 2010 [762]	Unselected Brazilian	68	162	1.61 (1.08-2.42)	54.4%	Deviation from HWE for controls p<0.05	Inadequate matching for ethnicity
LOX-L1	rs1048661	Self reported SUI	Ozbek et al 2011 [763]	Unselected Turkish	87	87	1.22(0.74-2.01)	<37.8% after correction for multiple comparisons	Massive deviation from HWE for cases p<0.0001	Low genotyping rate
	rs3825942						1.29(0.72-2.31)		In HWE	
	rs2165241						2.80(1.74-4.5))		Massive deviation from HWE for cases and controls p<0.0001	
MMP3	rs3025058	Self reported SUI	Skorupski et al 2010 [764]	Unselected Polish	149	109	1.01(0.72-1.44)	<53.8% after correction for multiple comparisons	Deviation from HWE for both controls (<0.05) and cases (<0.0001)	
MMP 1	rs1799750				155	111	0.83(0.59-1.18)		Deviation from HWE for cases (<0.05)	
MMP1	rs1799750	SUI confirmed by questionnaire	Vishwajit et al 2009 [765]	Unselected USA	12	8	1.66(0.46-6.00)	10.5%	Deviation from HWE for cases (<0.05)	
CYP17	rs743572	UUI or SUI confirmed by questionnaire and cough test	Cornu et al 2011[766]	Unselected French	121	66	ns	<41.2% after correction for multiple comparisons	Not calculable from published data	
CYP19	rs2414096									
ESR1	rs2234693									
AR	Exon1 CAG STR						Not calculable			

Table 20. Candidate gene association studies for pelvic organ prolapse.

Gene	refSNP ID	Pheno-typing	Authors	Population	n cases	n controls	Allelic Test OR(95% CI)	Power OR>=2	Hardy-Weinberg	Other Notes
COLIA1	rs1800012	POPQ	Skorupski et al 2006 [767]	White Polish	37	40	1.39(0.61-3.15)	42.7%	Deviation from HWE for controls p<0.05	
	rs1800012	POPQ	Rodrigues et al 2008 [769]	Brazilian	107	209	1.38(0.89-21.5)	92.5%	In HWE	High risk population stratification
	rs1800012	POPQ	Feiner et al 2009 [770]	White Israeli or Ashkenazi	36	36	1.4(0.55-3.56)	31.6%	In HWE	High risk population stratification
	rs1800012	POPQ	Cho et al 2009 [771]	Korean	15	15	1(Not calculable)	0%	In HWE	MAF=0% among popn
COL3A1	rs1800255	POPQ	Martins et al 2011 [772]	Brazilian	107	209	0.91(0.61-1.36)	91.6%	In HWE	High risk population stratification
	rs1800255	POPQ	Jeon et al 2009 [773]	Korean	36	36	3.24(1.51-6.94)	26.6%	In HWE	
	rs1800255	POPQ	Kluivers et al 2009 [774]	Dutch	202	102	1.46(1.00-2.13)	86.7%	In HWE	High risk population stratification
	rs1800255	POPQ	Chen et al 2008 [775]	Taiwanese	84	147	1.22(0.77-1.93)	50.3%	Deviation for cases (p<0.05)	Likely genotyping error
	rs1801184						0.47(0.19-1.10)		Deviation for controls (p<0.005) cases (p<0.05), and population (p<0.001)	
LOX-L1	rs1048661	POPQ	Ferrell et al 2009 [776]	Caucasian and African American US	137	141	1.34(0.94 -1.90)	82.3%	Not calculable	High risk population stratification
LAMC1	rs10911193	POPQ	Fu et al 2009 [777]	Unselected US	61	32	1.18(0.53-2.59)	40.4%	Not calculable	High risk population stratification
	rs10911193	POPQ	Chen et al 2010 [778]	Caucasian US	102	163	1.12(0.65-1.96)	74.8%	Not calculable	
	rs20563						0.85(0.60-1.21)			
							0.75(0.53-1.07)			
				African American US	63	83	0.55(0.19-1.64)	32.5%		
	rs20558						1.28(0.79-2.06)			
							1.29(0.80-2.09)			
MMP1	rs2071230	POPQ	Romero et al 2008 [779]	White US	36	36	0.78(0.28-2.0)	12.2%	Deviation only for controls at rs738789 p<0.001	
MMP2	rs7201						1.26(0.64-2.45)			
MMP3	rs679620						0.57(0.29-1.11)			
MMP8	rs35866072						0.27(0.05-1.32)			

Table 20. Candidate gene association studies for pelvic organ prolapse (continued)

Gene	refSNP ID	Pheno-typing	Authors	Population	n cases	n controls	Allelic Test OR(95% CI)	Power OR>=2	Hardy-Weinberg	Other Notes
MMP9	rs17576						0.94(0.46-1.89)			
MMP10	rs17435959						<0.74(0-0.74)			
MMP11	rs738789						0.58(0.13-2.53)			
TIMP1	rs4898						0.76(0.39-1.45)			
TIMP3	rs2016293						0.60(0.31-1.17)			
MMP3	rs3025058	POPQ	Skorupski et al 2010[763]	Polish	126	132	1.04(0.73-1.47)	32.8%	Deviation <0.05 for controls and <0.001 for cases and popn	Likely genotyping errors
MMP 1	rs1799750				149	109	0.94(0.67-1.33)	33.1%	Deviation <0.05 for cases controls and <0.005 for popn	
MMP1	rs1144393	POPQ	Campeau et al 2011 [780]	US	23	18	0.27(0.08-0.97)	6.7%	Not calculable but stated as in HWE	8 SNPs tested in total but negative results not reported
	rs498186				19	16	6.61(1.13-38.7)	3.1%		
	rs473509				20	21	0.24(0.07-0.85)	6.4%		
MMP1	rs1799750	POPQ	Vishwajit et al 2009 [765]	Unselected US	12	8	1.66(0.46-6.00)	10.5%	Deviation from HWE for cases (<0.05)	No distinction between SUI and POP
MMP9	rs3918242	POPQ	Chen et al 2010 [781]	Taiwanese	92	152	0.80(0.43-1.47)	71.1%	In HWE	Likely genotyping errors
	rs17576						0.62(0.40-0.98)	75.7%	Deviation for controls <0.001	
	rs2250889						1.56(0.98-2.49)	72.6%	Deviation for controls <0.05	
ESR1	rs17847075	POPQ	Chen et al 2008 [782]	Taiwanese	88	153	1.11(0.75-1.63)	67.4%	Deviation for cases alone at rs2228480 (p<0.05)	
	rs2207647						1.02(0.69-1.50)			
	rs2234693						0.97(0.66-1.42)			
	rs3798577						0.90(0.62-1.31)			
	rs2228480						1.47(0.94-2.29)			
ESR2	rs2987983	POPQ	Chen et al 2008 [783]	Taiwanese	69	141	1.20(0.77-1.85)	19.4%	In HWE	
	rs1271572						1.32(0.84-2.08)			
	rs944459						1.25(0.82-1.90)			
	rs1256049						1.28(0.84-1.94)			
	rs1255998						1.31(0.86-1.99)			
PGR	rs500760	POPQ	Chen et al 2009 [784]	Taiwanese	87	150	0.96(0.61-1.52)	53.7%	In HWE	Likely genotyping error
	rs484389						2.02(1.15-3.54)		Deviation for controls (p<0.0001) and cases (p<0.05) and population (p<0.05)	

deviation from Hardy-Weinberg Equilibrium for controls, or both cases and controls, highly suggestive either of genotyping error, or problems with population stratification. In addition to the high risk of bias introduced, these studies are all underpowered other than for extremely large genetic effects, and in most cases fail to account for multiple comparisons in their primary analyses.

Despite this multiplicity of methodological problems, there remains tentative evidence of replicated effects for two different polymorphisms. The rs1800012 polymorphism of collagen type I alpha1 (COLIA1), has been associated with a two-fold increased prevalence of stress incontinence in separate European populations [758,767]. The rs4994 polymorphism of the beta 3 adrenoceptor (ADRB3) has been associated with almost 2.5 fold increased risk of overactive bladder in separate studies of Japanese and Brazilian samples [30,31]. Other polymorphisms tested in more than one study include rs6313 in the 5-HT2A receptor, and rs1799750 in matrix metalloproteinase-1. In each case there are however inconsistent findings, with a high risk of genotyping error, and or population stratification.

Candidate gene studies for prolapse are at an equally nascent stage. Here polymorphisms have been tested in COLIA1, COL3A1, LOX-L1, LAMC, MMPs 1, 2, 3, 8, 9, 10, 11, TIMP1, TIMP3, ESR, and PGR. In comparison to incontinence, investigators have used the POPQ system as standard. However, other methodological problems are common. We again found many underpowered studies, frequent significant deviation from Hardy-Weinberg Equilibrium, and many instances of failure to consider the impact of population stratification in samples. Although many of the primary studies report significant results, our reanalysis suggests that there are no consistently replicated associations in any populations.

With these disappointing results in mind we can consider findings from the first reported genome wide association study in this area. The discovery cohort comprised 115 familial cases of prolapse identified as having had surgical treatment (and frequently also stress or urgency incontinence treatment) with 2,976 controls. In the discovery cohort 6 individual SNPs approached or exceeded genome wide significance ($p<=5x10-8$), but in Manhattan and Regional Association Plots no evidence was seen to support a wider associated locus. Correspondingly, after correction for multiple comparisons none of the 6 SNPs (rs1455311 rs1036819 rs430794 rs8027714 rs1810636 rs2236479) were successfully replicated in a sample of 76 Dutch familial cases. Given the failure of the candidate gene approach, genome-wide association studies are urgently needed, but will require much larger samples of cases for reliable identification of significant loci.

VI. SUMMARY POINTS

Family studies and twin studies have provided convincing evidence of genetic predisposition to incontinence and prolapse, with genetic variation contributing up to half of population phenotypic variability in elderly women. Despite a large research effort, the candidate gene approach has not produced consistent results. Only the rs1800012 polymorphism of collagen type I alpha1 (COLIA1), and the rs4994 polymorphism of the beta 3 adrenoceptor (ADRB3) have been replicated. Despite an urgent need for genome-wide association studies to discover susceptibility genes for these conditions, initial results from the genome-wide approach have been fruitless. Future progress will likely be made through collaboration between large scale population based cohorts phenotyped for these conditions.

I. EPIDEMIOLOGY OF ANAL INCONTINENCE

I. GENERAL COMMENTS AND DEFINITIONS

Faecal Incontinence (FI) is the involuntary loss of faeces – solid or liquid. Anal Incontinence (AI) includes these events as well as the involuntary loss of flatus, which is felt by many patients to be an equally disabling disorder.

The discussion below will therefore focus on the broader definition: AI. A third cause of soiling or embarrassment is anal mucoid seepage, a troubling condition that cannot be deferred by an able sphincter and intact cognition, most often caused by an organic colonic disease or dietary sensitivity, and more rarely by faecal impaction. This is the loss of fluid, sometimes faeculent, often following a normal continent defaecation. This is an important condition to distinguish from other manifestations of incontinence because most authors that report very high prevalence rates of AI include leakage in their questionnaires and thus may include these individuals with this very common symptom. However in these individuals there is often no detectable sphincter abnormality [786]. It is not treatable by any of the standard therapies for incontinence of faeces: such as sphincter repair, neuromuscular re-education or even faecal diversion. It is in fact why we wear underclothes. Not really true for women.

1. ASCERTAINMENT OF ANAL INCONTINENCE

Older reports of AI prevalence have come from single institutions, and the patients described therein have been subject to referral bias when demographics and aetiology are discussed. The accuracy of AI

prevalence estimates may also be diminished by difficulty in ascertaining those figures due to the common underreporting of AI and patients' reluctance to report symptoms or to seek treatment [787-788]. It has been shown that women are more willing to report AI than men [789] In addition, the character (incontinence of solid faeces, diarrhoea, or flatus, or merely anal seepage) and frequency (daily versus episodic) of reported AI varies greatly in each report, and indeed between individuals. So, prevalence depends heavily on the definition of AI.

The variation in prevalence of AI seen in a sampling of surveys in **Table 21** further demonstrates how difficult the ascertainment of AI is. The border between occasional dyschezia which may be associated with minor illness, travel or diet and a disabling disease that requires intervention to return a patient to acceptable function is not clearly drawn. Many questionnaires have been developed and "validated" for the detection of AI, at least three published since the last update of this book. No systematic review of these many questionnaires has yet to be published. The most insightful of prevalence studies has recently been published from New Zealand [790]. The authors studied adults, not excluding those in custodial care. Acknowledging the difficulty in prevalence estimation, they used three different questionnaires: the first simply asking if the participant had incontinence and if they were troubled by it, the second a well known quantitative instrument and the third a quality of life instrument specific to faecal incontinence. In the cohort examined there were those who were totally continent, those that exceeded thresholds in all three instruments and were incontinent and those who had positive responses on only one or two of the questionnaires (**Figure 11**). The authors surmised the two out of three positive responses constituted clinical AI, though the threshold for the quality of life instrument was very high (i.e. perhaps too sensitive). From **Figure 11** it can be seen that the prevalence of AI varied from 12.6% to 26.8% for each individual instrument, 4.6% were positive for all three and 13.2% were positive for two of three, which was the authors' definition of AI.

2. DATA SOURCES AND LEVEL OF EVIDENCE

Since ICI 4 new studies were sought using Medline and EMBASE using the search terms faecal, faecal, anal, incontinence, epidemiology. In addition systematic reviews were specifically sought in Medline, EMBASE and the Cochrane Library.

II. PREVALENCE

Because therapeutic interventions are not the subject of this chapter, and so the epidemiology is descriptive and not derived from randomised clinical trials (aside from the antenatal intervention described below), the level of evidence will be at best 2, and the strongest evidence will come from systematic reviews in which there was a predefined search strategy and application of quality assessment tools that were designed specifically to minimize bias in referral or ascertainment.

Table 21. Population-based Surveys of Prevalence of Anal Incontinence

COUNTRY (ref)	POPULATION	N	PREVALENCE
U.K. [788]	Community Service	4 844	1.9%
France [808]	All >45 years	1 100	11%, 6% to faeces, 60% are women
U.S.A. [806]	Market mailing	5 430	7% soiling, 0.7% to faeces
U.S.A. [789]	Wisconsin households	6 959	2.2%, 63% women
Australia [805]	Household survey	3 010	6.8% in men, 10.9% in women, >age 15
Germany [811]	>18 years	500	4.4%-6.7% (by health)
Australia [810]	>18 years	618	11-20% (gender M>F)
Australia [482]	>18 years	651	11.3%
New Zealand [814]	>18 years old	717	8.1% for solid and higher for gas
U.K. [815]	>40 years	10 116	1.4%
U.K. [816]	Postpartum women	549	5.5%
Canada [817]	Postpartum women	949	3.1% solid, 25.5% flatus
Denmark [818]	Postpartum women	1 726	8.6% in past year, 0.6% to solid stool
Nigeria [819]	Gynecology patients	3 963	6.9%, 2.3% to solid stool
United Arab Emirates [820]	Women multips	450	11.3%, 5.5% to solid stool
Canada [821]	Teenage females	228	3.5% flatus, 3% FI
Czech Republic [822]	Gynecology patients	2 212	5.6%, 4.4% in the community
Japan [823]	Cystectomy patients	28	60.7% post ureterosigmoidostomy
Sweden [824]	Prostate cancer	864	RR 1.3-4.5
Australia [825]	Diabetics	8 657	Increased risk
Holland [826]	Women >60 years	719	4.2% to 16.9% with rising age
U.S.A. [827]	>65 years at home	328	3.7% (M >F)
Japan [828]	>65 years at home	1 405	6.6-8.7% (by age).
U.S.A. [829]	>50 years	1 440	11.1 – 15.2% (F > M)
U.K. [830]	>65 years at home	2 818	3%
Holland [831]	>60 years	3 345	6%, (M = F)
Czech Republic [832]	Nursing homes	1 162	54.4%
U.S.A. [833]	Nursing homes	18 170	47% FI
Canada [834]	Nursing homes	447	46% FI, 44% both UI and FI
France [835]	>18 years	713	30% response rate. 11% gas,0.4% feces, Women>men.
U.S.A. [836]	Women >20 years	2 800	53% response rate. Median age onset 55 years.
France [837]	Women >50 years	2 640	85% response rate. 9.5% FI, but includes leakage.
USA [838]	Women >25 years	4 10	337% response rate. 25% AI. Obesity.

1. ADULTS

In an effort to resolve the widely varying reported prevalence figures (**Table 21**) two systematic reviews of the published frequencies have been reported of community dwelling adults (above age 15 in the second). A summary frequency was not calculated in the first because of the marked clinical heterogeneity between reports. The three reports that the authors judged most free of potential biases had frequencies between 11% and 15%, although only one of these three used a validated assessment instrument [791]. The degree of disability present in these 11%-15% is not known, nor even if a portion of them had only anal seepage. These high prevalences were obtained in surveys that employed anonymous self-administered questionnaires, which may not allow objective confirmation of AI or assessment of degree of disability associated with AI. The second systematic review found a range of solid and liquid anal incontinence of 0-15.2%, with an average across both genders and all age groups of 4.3% [462]. The prevalence in a more recent and rigorous study is discussed above under Ascertainment [790].

2. CHILDREN

The reported prevalence of AI in children can be broadly divided into two facets: in those children born with congenital anomalies of the anus and rectum – either congenital aganglionosis (Hirschprung's Disease) or imperforate anus – and those children without congenital anomalies. Among those children and adults who were born with defects, despite surgical correction of the defect, life long defaecation difficulties are common, occurring in roughly half of affected children [792-794]. Problems with psychological health and development because of the defaecation disorder is also common in this group, as is a generally depressed quality of life [795]. These disorders are not horribly rare, occurring in 3 to 5 per 10,000 live births [796].

Among children without congenital defects of the anal canal, bowel control has been found to be complete in one Swiss cohort in 33% by age 1 year, 75% by age two and 97% by age three. Nevertheless in this longitudinal study, a quarter of the boys and one tenth of the girls had a major period of incomplete bowel or bladder control between the ages of 6 and 18. At least annual encopresis occurred in 2-3% of these children, boys more frequently than girls [797]. In the Wisconsin Family Health Survey the prevalence of AI in children from the ages of 5 and 16 years was 12/1367 (0.88%) with the gender distribution being 7 boys and 5 girls (Wisconsin Family Health Survey: unpublished data). The common disorder for all children and then adults in this discussion is faecal retention with overflow.

III. INCIDENCE

Clinical trials have provided incidence data after a therapeutic intervention, but usually without a preliminary continence assessment. This is best seen in two Cochrane reviews of therapy for anal fissure

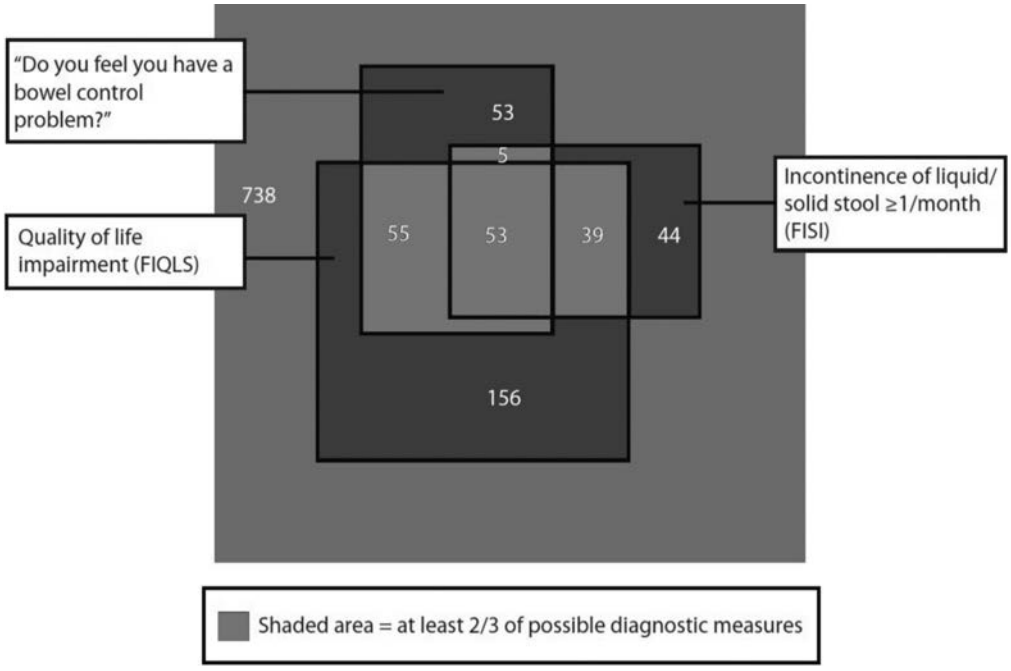


Figure 11. Co-occurrence of fecal incontinence in each of 3 diagnostic measures. FISI = Fecal Incontinence Severirty Index; FIQLS = Fecal Incontinence Quality of Life Scale

[798-799]. AI incidence rates varied widely from 0% to 30%, to flatus only, and the duration was unspecified in the trials. Medical therapy was less likely than surgery to cause AI (0.23, 0.02-2.1), and certain operations (anal stretch) were more likely to cause AI than others (sphincterotomy) (4.2, 1.9-9.4). None of these trials reported rigorous ascertainment of continence before the onset of disease or therapy.

IV. RISK FACTORS

1. AGE

Two systematic reviews have analyses of the association of age and anal incontinence and found age to be the most significant of all assessed associations [800-801].

2. GENDER

Most discussions of the aetiology of AI have been based upon the assumption that women, particularly for individuals under the age of 65 years, are far more at risk for AI than men. Injury to the pudendal nerve or sphincter muscle from prior obstetric trauma is described as the primary risk factor [802-804], followed by irritable bowel syndrome (a disease thought to be more prevalent in women) [805], and other aetiologies such as diabetes a distant third [806]. Yet each population based-survey of the prevalence of AI has shown a surprisingly high prevalence in males (**Table 21**) [788-789, 807-838].

Of the two systematic reviews that looked specifically at prevalence, only one assessed the role gender played and in that review gender was not associated with incontinence in any age group [800]. In the search for this updated review, 26 publications assessed prevalence of AI, two in both genders and 24 only in women. Clearly, aetiologies other than childbirth must be sought. This represents a rather gross imbalance in research on this topic.

3. OBESITY

Four reports have demonstrated an increased risk of AI in obese women, a Kaiser cohort, a cross sectional survey in a specialty clinic and two case control studies [839-842]. One longitudinal study found a reduction in anal leakage (again not necessarily a direct correlate with incontinence) in women after bariatric surgery and weight loss, though other factors including diet and activity change may have been responsible for the improvement [843].

4. CHILDBIRTH AND MODE OF DELIVERY

A meta-analysis of published reports that assessed anal sphincter integrity after vaginal delivery and correlated this with continence stated that 77%-83% (depending on parity) of anal incontinence in parous women was due to sphincter disruption [844]. Another systematic review that looked only at post partum factors in prospective cohorts found that the only predictor of AI was 3rd-4th degree sphincter rupture during birth [845]. Three things are implied by the conclusion or the first review: first, that incontinence in men, children, of elderly onset (or even in middle aged women) and in nulliparous

women, or women having Caesarean section has a completely different cause than in women who have ever delivered vaginally. There is scant epidemiological evidence that this is the case [846]. Second, it is implied that sphincter repair would be effective

treatment for anal incontinence in almost all parous women. Yet repair of disrupted sphincter has less than a perfect track record. Even more importantly, there is a reported rapid decay in function after repair that is far too great to be explained by age alone [847-854]. Third, if direct trauma to the anal sphincter (and not intra-pelvic nerves) were the major cause of anal incontinence, then Caesarean section should beeffective in preventing incontinence. However a systematic review has shown that this is not the case [801] (**Figure 12**). Twenty-one reports have been found eligible for inclusion in the review, encompassing 31,198 women having had 6,028 Caesarean deliveries and 25,170 vaginal births as index events prior to anal continence assessment. Only one of these reports demonstrated a significant benefit of Caesarean section in the preservation of anal continence. In that report AI rates exceeded 39% in both groups, suggesting a problem with ascertainment. The greater the quality of the report, the closer its Odds ration approached 1.0. Among the seven reports that passed all quality criteria (age adjustment, parity adjustment, no previous vaginal delivery in the Caesarean section group, continence assessment more than 4 months post partum) the odds ratio for faecal incontinence was 0.98 (0.79-1.21. **Figure 12**). In reports that allowed comparison of vaginal delivery with elective Caesarean section there was also no significant difference in AI risk (OR=0.73; 0.52-1.03. **Figure 13**) There was no difference incontinence preservation in women have emergency versus elective Caesarean section (OR= 1.09; 0.89-1.34. **Figure 14**). Among the seven best studies, the NNT is 339, i.e. 339 Caesarean sections would have to be performed to prevent a single case of faecal incontinence. Pregnancy with delivery of any kind was found to be only a marginal risk factor for faecal incontinence (OR= 0.86; 0.73-1.01. **Figure 15**) though there is significant statistical heterogeneity in this analysis (p=0.05, I2=62%). In another publication increasing parity as an isolated risk factor does increase risk of AI [838].

But why doesn't Caesarean section prevent anal incontinence, especially when associating perineal trauma with loss of bowel control is not just intuitive, but sometimes visibly obvious? Certain aspects of vaginal delivery are clearly causally related to anal

incontinence: significant laceration, forceps, and some episiotomies [855-856]. However this review demonstrates that other factors need to be explored. So one must look to pregnancy and not just labour and delivery as an initiating factor. Further evidence in favour of this comes from the sphincter repair literature cited above. The rapid decay in function suggests that another defect is present besides a gap in the sphincter that remains after the early effects of sphincter repair wear off. What this is, is not yet known, doesn't make sense although trauma at the pelvic inlet during pregnancy or in early labour [857] seems likely. Sphincter dysfunction has been demonstrated in women who have had Caesarean section [858]. Further indirect evidence for the possibility that injury higher in the pelvis may be related to AI in pregnant women can be found in the association between hysterectomy and AI, an association seen more prominently with abdominal hysterectomy (TAH) than vaginal hysterectomy (VH), and for flatus only [859] (Odds Ratio of TAH vs. VH for faeces: 1.2, 0.3-4.7, Odds Ratio for gas: 18.9, 1.1-327). Pelvic nerve injury during surgery is the postulated reason for this difference.

5. NURSING HOME RESIDENCE

The most prominent association with AI by far is nursing home residence. Whereas the prevalence of AI is probably around 2% to 5% for community-dwelling persons, and may rise with increasing age to greater than 10%, among nursing home residents the prevalence approaches 50% [832-834]. This is partly explained by FI being one of the most common reasons for nursing home admission. In a large survey of 18,000 Wisconsin nursing home residents, risk factors for faecal incontinence (FI) were directly observed by nursing home personnel [833]. Urinary incontinence (UI) was the greatest association with FI (OR = 12.6, 11.5-13.7), followed by the loss of ability to perform daily living activities (6.0, 4.7-7.7), tube feeding (7.6, 5.6-10.4), physical restraints (3.2, 4.7-7.7), diarrhoea (3.3, 2.7-4.2), dementia (1.5, 1.4-1.7), impaired vision (1.5, 1.4-1.7), constipation (1.4, 1.3- 1.6), faecal impaction (1.5, 1.1-2.1), stroke (1.3, 1.2- 1.5) male gender (1.2, 1.1-1.3), age and body mass index. Inverse associations were noted with heart disease, arthritis and depression.

6. DIARRHOEA

The importance of diarrhoea of liquid stool in FI cannot be overemphasised [842]. One case series noted that 51% of individuals with chronic diarrhoea were incontinent [787]. In the Wisconsin Family Health Survey of AI [789], 10 of the 25 subjects with FI lived in Milwaukee when the city experienced an outbreak of waterborne disease [860]. Non-infectious causes of diarrhoea must also be considered, such as inflammatory bowel disease [861] and those initiated by sports activities such as running [862-863].

7. SURGERY

AI originating from surgery would seem fairly insignificant in the general population, since previous anal surgery has not been an apparent risk factor in the larger surveys. Several operations nonetheless can frequently result in AI. Examples are midline internal sphincterotomy, lateral internal sphincterotomy, fistulectomy, fistulotomy, ileo-anal reservoir reconstruction, low anterior rectal resection, total abdominal colectomy, and

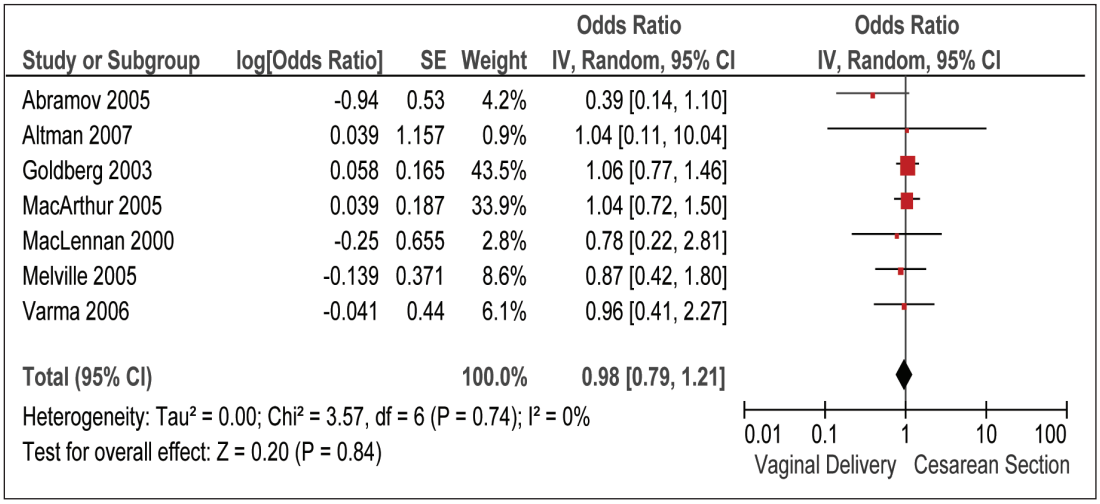


Figure 12. Systematic review of Efficacy of Cesarean Section in Preventing Faecal Incontinence: 7 Studies fulfilling all quality criteria

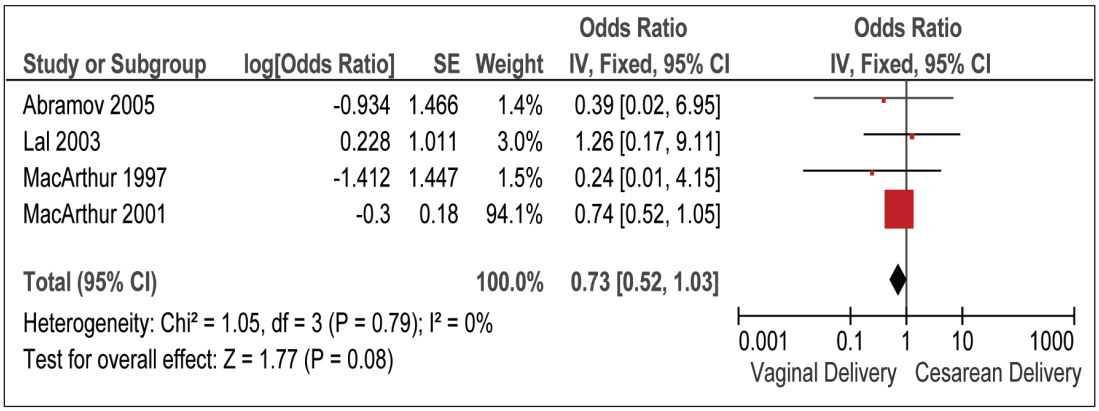


Figure 13. Systematic review of Efficacy of Cesarean Section in Preventing Faecal Incontinence: Vaginal Delivery versus Elective Cesarean Section

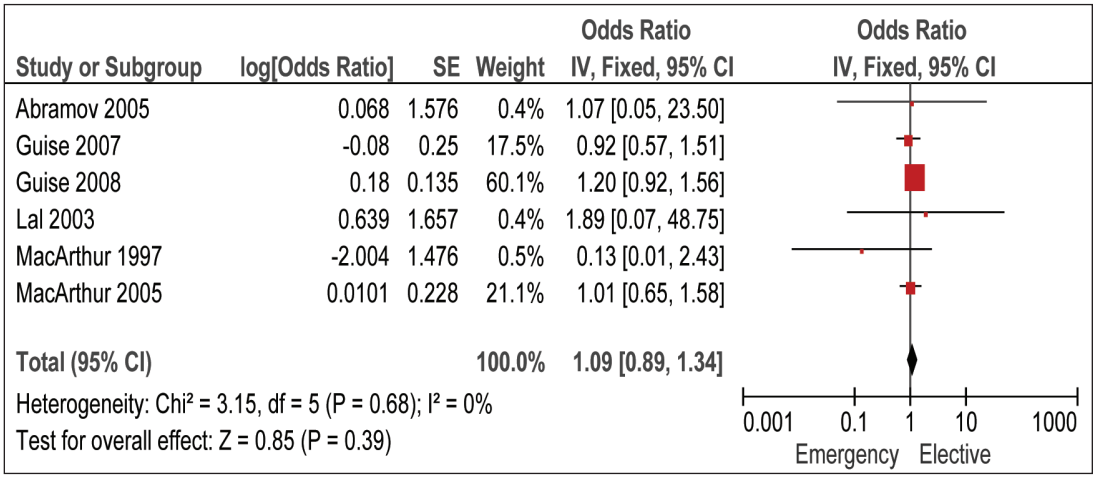


Figure 14. Systematic review of Efficacy of Cesarean Section in Preventing Faecal Incontinence: Elective vs. Emergency Cesarean Section

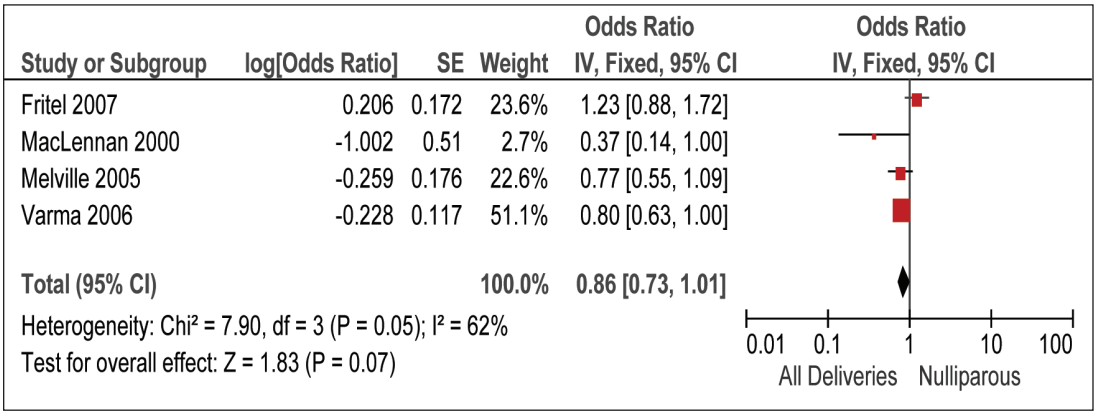


Figure 15. Systematic review of Efficacy of Cesarean Section in Preventing Faecal Incontinence: Nulliparous women versus Any Form of Delivery

ureterosigmoidostomy. The risk of lateral internal sphincterotomy for anal fissure causing AI was previously thought to be insignificant when compared to midline sphincterotomy, but a recent reappraisal of this operation has shown an AI risk may be 8% [864]. The risk of AI after fistulotomy has been reported to be as high as 18% to 52% [865]. New approaches to fissure and fistula have recently been developed specifically to lower this risk [865-866]. However incontinence after haemorrhoidectomy has also been reported to be as high as 33%, an operation in which no sphincter is divided [867]. This suggests either that division of the anoderm, not the sphincter may be affecting continence, or that the method of ascertainment used in published surveys is not accurate. Mixing urine and stool has been found to have a predictable effect on anal sphincter control, as does diarrhoea, in patients having uretero-sigmoidostomy after urinary bladder resection [823]. Patients with rectal cancer form a special group in whom cancer issues often mute the continence disturbance that may result from rectal resection [868] or radiotherapy [869].

8. SPECIFIC NEUROLOGICAL AND OTHER DISEASES

Several specific diseases have been anecdotally associated with AI in case series, and mechanisms to explain the associations have been investigated [870]. Examples are diabetes [825], stroke [871-872], multiple sclerosis, Parkinson's disease, systemic sclerosis, myotonic dystrophy, amyloidosis, spinal cord injury, imperforate anus, Hirschsprung's disease, retarded or interrupted toilet training, procidentia, and any illness causing diarrhoea (HIV, IBD, radiation, infection). Many of these conditions directly affect patient mobility and ability to perform daily living activities or they cause diarrhoea or faecal impaction.

9. CONSTIPATION

Constipation may alternate with diarrhoea in irritable bowel syndrome making defaecation chaotic and often very urgent. Just as often retained faeces lead to anal seepage that cannot be held. In the New Zealand survey [790], the 2 of 3 rule for categorising an individual as incontinent excluded constipated patients, which was also assessed in their survey, the positive rate fell from 13.2% to just over 9%. This further demonstrates the frequent co-existence of constipation and AI, similar to the frequent coexistence of urinary incontinence and AI.

10. COHORTS INITIATED BEFORE CLINICAL AI ASSESSED FOR SUBSEQUENT DEVELOPOMENT OF AI

Because of a paucity of clinical trials that specifically address risk factors and prevention of AI, the strongest available data to identify risk come from cohorts that collected data on potential risk factors prior to the onset of incontinence. Prospectively collected risk assessments for FI have occurred in three nursing home cohorts. Porell combined UI and FI into a single outcome variable and found many positive associations in a cohort of 60,000 nursing home residents in Massachusetts [873]. Age, African American race, cognitive and ADL impairments, predicted the outcome, although specific relative risks for incidence are not presented. Chassange followed 234 previously non-FI residents in France for 10 months, during which 20% had FI episodes, but only 7.5% developed long lasting FI [874]. The others had acute episodes due to diarrhoea or impaction. The factors associated with the development of long lasting FI were urinary incontinence (UI) (2.9, 1.8-4.6), decreased mobility (1.8, 1.1-3.0), and cognitive defects: either as seen in an MMSE score <15 (2.5,1.4-4.4) on history of dementia (2.1, 1.2-3.5). Neither gender nor age were risk factors. Nelson reported, in a cohort of 18,000 nursing home residents in Wisconsin, a subgroup of 3,850 continent of both urine and faeces in 1992 who were assessed one year later [875]. 15% developed FI. Positive associations were seen for ADL loss (3.4, 2.4-4.5), trunk restraints (2.5, 1.7-3.6), dementia (1.7, 1.4-2.0), African American race (2.1, 1.3-3.4) and age (1.02, 1.0-1.0). UI was not investigated as a risk factor because it was felt to be a co-morbid condition. In a broadly based cross sectional survey, it was apparent that factors that affect an individual's general health or physical capabilities, independent of age and gender, place that individual at greatest risk for AI [805], though all four are significantly associated with AI [789]. Among obstetric patients age has also been a consistent association, with less consistent associations noted for chronic bronchitis (OR =6.5, 1.1-38), symptoms of pelvic organ prolapse (5.0, 3.0-8.7) and obesity (3.0, 1.0-3.4) [876]. Defaecatory dysfunction has also been assessed in antenatal women [877-879], found to be prevalent which has led to an important preventive strategy for post partum AI described below.

V. PREVENTION

This discussion is by necessity descriptive, so preventive measures are only relevant insofar as they provide insight into the aetiology of incontinence. By far the most frequently applied preventive measure is Caesarean delivery, discussed above. Its lack of effectiveness in preventing anal incontinence provides a valuable insight into the relationship between pregnancy and AI – that the focus may need to be more on the pregnancy rather than the delivery and how it

affects defaecation afterwards. A decision analysis study suggests specific obstetric indication for elective C. section that may be cost effective [880]. Another study related to birth trauma randomised mothers to immediate post-partum anal ultrasound with repair of occult defects in the sphincter and continence assessed in follow-up, demonstrating an improved outcome with this intervention [881]. Antenatal intervention with pelvic floor exercises has been assessed in a number of randomised trials [882-883] for the purpose of diminishing post partum AI. One Cochrane review found this strategy effective [882]. Sixteen studies were included in the analysis in which 6,181 women participated. Those without prior urinary incontinence were randomised to either pelvic floor training or standard care. At 12 months postpartum the intervention group were half as likely to have AI (RR= 0.52; 0.31-0.87). A subsequent report has not shown this benefit, and has yet to be included in the Cochrane review [883].

The AHRQ recently published a monograph on the prevention of incontinence, although the strategies listed for AI were therapies for existing AI, such as pelvic floor exercises and retraining, rather than stablished mechanisms for prevention [884].

VI. SUMMARY POINTS

- Anal and urinary incontinence commonly coexist, particularly in the elderly and in nursing home residents (LE 1).
- The prevalence of anal incontinence increases with age, but is present in all age groups and both genders varying from 1.5% in children to more than 50% in nursing home residents (LE1).
- AI is almost as common in men as in women (LE 2).
- Mode of delivery does not seem to be a significant factor in the development of obstetric anal incontinence, i.e., AI develops after Caesarean delivery as often as after vaginal delivery (LE 2).
- Obesity is perhaps the most modifiable risk factor for AI (LE 2). Intrapartum pelvic floor education can decrease the risk of subsequent development of post partum AI (LE 1).
- As populations age, co-morbid disease becomes a significant component of faecal incontinence risk. Surgery, neurological diseases, and stroke are examples.
- Cognitive and ADL impairment are associated with faecal incontinence.
- More population based prevalence surveys have been published.
- More analyses comparing AI after Caesarean section and vaginal delivery have been published.
- Systematic reviews of prevalence, including the role of age and gender, Caesarean delivery and decision analyses for the application of Caesarean delivery in macrosomia have been published, providing needed aggregation of data with quality assessment of existing literature.

VII. FUTURE NEEDS

- Risk factors for AI in each age group are still poorly defined.
- Prevention research, much less policy, are therefore still a great distance away.
- Randomised trials are needed of AI (and UI) in average risk women comparing vaginal delivery and Cesarean section.

J. WHY DO PREVALENCE ESTIMATES DIFFER?

The discussion here relates to UI only, as data and literature for FI and POP are very scarce. However, many of the principal arguments will be relevant to these conditions as well.

I. GENERAL PROBLEMS IN SURVEY RESEARCH

The well documented variation in prevalence estimates is thought to result at least in part from several confounders common to survey and epidemiological research. Herzog and Fultz, [74] in a review of the prevalence and incidence of UI in community-dwelling populations, proposed that past investigations were plagued by sampling and non-response issues, by self selection and attrition, by definitional, conceptual, and measurement issues. It is clear that there are large methodological challenges to rigorous research in this field. In general, the quality of recent large studies has undoubtedly improved, but the scientific community must continue to deal with methodological challenges in order to achieve progress.

II. DIFFERENT DEFINITIONS AND MEASUREMENT

A major problem in research on UI has been the use of different definitions and measurements,

and this might contribute to the wide range of reported prevalence estimates. The former ICS definition of UI – as a condition in which involuntary loss of urine is a social or hygienic problem and is objectively demonstrable - included objective demonstration of urine loss as one critical component. This aspect limited the ICS definition for community based epidemiological investigations, because objective demonstration of UI is difficult to achieve outside of the clinical setting, and studies which were able to include this aspect in their assessment might have produced different prevalences. In addition, a social or hygienic aspect of the definition was problematic in epidemiologic studies because it added a subjective aspect to an objectively defined condition and therefore confounded the investigation of prevalence, incidence, and risk factors. In our previous report we argued for reconsideration of the definition of UI, and we emphasized that the core of the definition should be "any involuntary loss of urine". In accordance with this view, ICS changed its definition in 2003 to UI being "the complaint of any involuntary leakage of urine".[1]

The new definition makes epidemiological research easier. But three consequences should be addressed:

1. Epidemiological studies should not be based on this definition alone, and all studies should include a minimal additional data set, standard confounders, and questions specific to the aim of the study. This is discussed in the Section on Recommendations for further research.

2. The number of persons fulfilling the definition will increase. This should not be interpreted as an increase in the number potential of patients.

3. Public awareness, case finding of health care personnel, and help seeking behaviour may be affected of a new and more extensive definition.

Studies have used different severity levels and time frames for defining UI. A further factor complicating the conceptualisation and measurement of UI in epidemiological studies lies in the nature of the condition. UI is a chronic condition (or set of conditions) that often starts slowly and comes and goes for a considerable time period before it become fully established. If people get used to their UI or notice it less, this can interfere with valid assessment.

Ideally self-report measures are validated by clinical evaluations. However, clinical and even urodynamic investigations should be regarded as other measures, not necessarily as gold standards, because it is known to be difficult to demonstrate all urinary symptoms in the clinical setting.

Holtedahl calculated prevalence estimates using different definitions of UI for the same sample of 50 to 70 year old women. The prevalence of any self-reported leakage was 47%. Self-reported regular UI with or without objective demonstration was found for 31% of women, regular incontinence according to the former full ICS definition for 19%. Another study found prevalences of 69% and 30% for any UI and the former ICS definition, respectively. The results indicate that the former ICS definition was rather restrictive.

Low response rates may further bias prevalence estimates. Known differences between responders and non-responders can be compensated during the analysis. The major problems is unknown differences in response rates and other characteristics. Incontinent women may not answer (or deny UI) because of embarrassment or related handicaps. But incontinent women may also find the subject particularly relevant and therefore respond to a greater extent than continent women. At present, we do not know much about how these factors may affect the comparison between incontinent and continent women.

One paper explored the problem of underreporting incontinence and how it can be altered with the use of an introduction to the incontinence questions and probing. Another paper explored the issue of selection bias in mailed surveys. The first wave had higher prevalence of incontinence than follow-up mailings, and thus individuals with UI tended to respond on the first wave. In an English mailed survey on incontinence and other urinary symptoms, a sample of non-responders were traced, and those eligible were asked questions from the survey. Compared with the responders, the non-responders overall showed little differences in reporting of urinary symptoms. However, non-responders >70 tended to be of poorer general health, and they reported certain urinary symptoms more frequently.

III. SUMMARY POINTS:

- The lack of epidemiological data from populations underrepresented in research limits the world wide application of the present information.
- Many investigations are plagued by sampling and non response issues, by self selection and attrition. Many early studies were obtained from sampling patients seeking care.
- A major problem is the use of different definitions of incontinence. The new ICS definition makes epidemiological research easier.
- There are large methodological challenges to research in the field of UI. Unless the scientific community deals with these issues, progress will be difficult to make.

K. HELP SEEKING BEHAVIOUR

I. URINARY INCONTINENCE

A majority of people with UI have not sought help, and this is confirmed also in recent publications. [454-455, 469-470] Reasons given by people for not seeking help include: not regarding incontinence as abnormal or serious, considering incontinence to be a normal part of ageing, having low expectations of treatment and thinking they should cope on their own. Some studies also confirm the notion that embarrassment may be an important reason for not seeking help [332-334] There is an association between help seeking and condition-specific factors like duration, frequency and amount, and people's perceptions of the impact of incontinence, but other more personal characteristics like individual health care behaviour and attitudes may also play a role.

In a Norwegian study 4.4 % of all women >20 years old in a community consulted their general practitioner for UI during a 3 year period. But mentioning the symptoms to a physician may not be enough. There are reports of doctors not responding, either by ignoring the statement of symptoms or by providing a dismissive explanation, and people interpreting a lack of response from the doctor as an indication that no treatment is available. In a study of management of incontinence in general practice, 30% of the women who had told their doctor about their symptoms perceived that they were offered no help. It is probable that many primary health care providers lack confidence in managing UI, and that this contributes to under treatment in those seeking help [338].

Only a small proportion of incontinent community-residing women have had surgery, medication, or exercise regimens. In addition to seeking help from the formal health care system, common responses to symptoms of illness are self-management and self-treatment behaviour. The major method of actively managing UI among community residents is the use of absorbent products.

It is obvious that millions of men and women suffer from their UI, and that for many of them good treatment options are available. However, for many persons with very mild or occasional UI it is probably adequate not to seek help from the health care system. Others are satisfied with just information and understanding about the causes and in many cases self care may be quite appropriate. A Danish study has shown that simple information and advice was adequate " treatment" for 23% of the women attending an open access incontinence clinic. A Swedish study found that among 136 women with UI, 36% wanted clinical evaluation, and only 24% subsequently started treatment.

Both epidemiological and qualitative research in this field should be encouraged in order to understand cultural, religious, and personal factors for help seeking behaviour world wide. Specifically, other than condition-specific factors should be further explored, e.g. persons' health care behaviour, perceptions and attitudes.

II. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE

There are indications of underreporting also of FI and patients' reluctance to report symptoms or to seek treatment.[787-788, 820] It has been shown that women are more willing to report FI than men. For POP we have no information.

III. SUMMARY POINTS:

- Recent publications confirm that a majority of people with FI, UI, and POP have not sought help.
- Only a small proportion of urinary incontinent community-residing people have had surgery, medication, or exercise regimens.
- Increasing severity, increasing duration, and urgency/mixed type of UI are related to consulting a health care provider.
- Associations other than condition-specific factors should be further explored in future research, e.g. persons' health care behaviour, perceptions and attitudes.
- Health care personnel should be encouraged to approach those at risk for FI, UI and POP. People with such symptoms should be assessed so services and treatment can be offered and targeted. The patient's view of management, even denial, should be respected.

L. EPIDEMIOLOGY AND CLINICAL WORK: FROM RESPONDENT TO PATIENT

We have emphasised some major and important differences between epidemiology and clinical work. These differences may have several implications. A selection process is most often accomplished first by self-selection (help seeking), then a referral system, which provides specialist physicians to a patient population with higher prevalence of disease, more severe disease, and often skewed type distribution, thus obtaining

test results with fewer false positives, better diagnostic accuracy, and more efficient use of resources. However, such intended and purposeful selection bias has its drawbacks. There is growing evidence that this selection process introduces bias into research and hampers our ability to generalise hospital based research back to general or primary care populations. Furthermore, it may result in recommendations and guidelines for diagnosis or therapy derived from tertiary care centres that are inappropriate at the primary care level. Often guidelines, review articles or teaching material do not take into account the varying prevalence and variation in clinical picture between community and hospital. They may also emphasise use of tests or equipment that are not appropriate or relevant for primary health care, thus leading to over utilisation of referrals. Data from hospitals or specialist level may also overestimate level of burden, costs and number of persons in need of treatment if such data are used for extrapolation back to community level. Therefore it is important that this Consultation uses different algorithms for initial and specialised care (see other relevant chapters).

One study provides substantial empirical evidence to support the existence of selection bias for UI. The analyses were based on three populations of incontinent women: Community level (epidemiological survey), primary care level (prospective study), and secondary care level (university hospital, prospective study). The general practice patients were older and the hospital patients younger than those in the community. From community via general practice to hospital, there was an increase in duration, frequency of leakage, amount of leakage, severity and perceived impact of incontinence. Help-seeking at the primary care level was associated with increasing age and severity, and with urgency symptoms and impact. Referral from general practice to hospital was only associated with (lower) age and urgency symptoms.

Under the subtitle Severity and impact we have given examples of how the prevalence estimates for women change dramatically when bothersomeness and severity are considered. Taken together with selection bias, this emphasises caution when epidemiological data are used in a clinical context. It concerns " level of care" in several ways; there is a large transitional zone from healthy to diseased, there is a danger of medicalisation, and there is a danger of treating patients at a higher level than necessary. Risk factors, predictors and correlates discovered in epidemiological studies are probabilistic of nature and may not be decisive in the clinical assessment of an individual patient. In addition, the attributable risk due to some known risk factors may be statistically but not clinically significant.

I. WORLDWIDE ESTIMATES OF CURRENT AND FUTURE INDIVIDUALS (≥20 YEARS) WITH LOWER URINARY TRACT SYMPTOMS INCLUDING URINARY INCONTINENCE AND OVERACTIVE BLADDER

In order to effectively plan health care resources it is necessary to estimate the prevalence and incidence of illnesses to know to what extent resources require to be allocated to a specific illness health care condition. This chapter has dealt with three major global problems, urinary and faecal incontinence as well as pelvic organ prolapse, that affect women and men throughout the world. Irwin and coworkers [885] have published data estimating the current and future worldwide prevalence of lower urinary tract symtoms.

The objective of the study was to estimate the current and future number of people with LUTS, including overactive bladder (OAB) and Urinary Incontinence (UI) utilising the current ICS definitions. Age- and gender-specific prevalence rates from the EPIC study[455] were applied to the worldwide over 20 year old population (4.2 billion) with males and females stratified into five-year age groups (20-24 to 80+). Projected population estimates for all worldwide regions were based on the United States Census Bureau International Database (IDB).

Estimates were presented for 2008, 2013 and 2018 and are summarised in **Tables 22 and 23**. **Table 22** summarises the estimated number of individuals with certain LUTS symptoms by year and sex in the world population and **Table 23** describes the estimated number of individuals of LUTS and OAB over 10 years across the world regions.

Estimates and projections featured in this analysis were based on prevalence rates of LUTS described in the EPIC study – based primarily on a European population. The prevalence rates featured in the EPIC study are similar to other prevalence rates of LUTS that were found in others studies across other countries [452,461]

The projections in this report assume the prevalence rates of LUTS will remain throughout the year 2018 for all age and sex groups

Prevalence of LUTS will also increase as other factors related to LUTS, such as obesity, increases (**Figures 16 & 17**). The estimated number for present and future years are not true numbers but are based on a projected population configured by the International Database (IDB). The IDB's estimates and projections are drawn by Census Bureau demographers and are based on reviewed censuses, surveys, and vital statistics provided by

Table 22. Estimated Number of Individuals with Certain LUTS By Year & Sex- World Population (In Millions)

LUTS Symptoms Incontinence	Male 2008	Male 2013	Male 2018	Female 2008	Female 2013	Female 2018
Any Incontinence	98	109	120	250	275	301
UUI	22	25	27	27	30	33
MUI	11	12	14	43	47	52
SUI	10	12	13	127	140	153
Other**1**	55	61	66	53	58	64
Storage						
Any Storage Symptom (Noct**2** ≥1)	1,050	1,151	1,250	1,249	1,363	1,474
Any Storage Symptom (Noct ≥2)	597	655	713	760	831	901
Noct ≥1	942	1,035	1,127	1,098	1,200	1,301
Noct ≥2	388	427	467	464	509	555
Urgency	205	226	247	249	273	297
Frequency	127	139	152	161	174	186
Voiding Symptoms						
Voiding Symptoms	515	563	610	402	511	473
Intermittency	164	181	198	148	176	175
Slow Stream	156	173	193	122	161	146
Straining	132	145	157	83	120	98
Term Dribble	289	315	340	210	276	245
Post Micturition Symptoms						
Post Mic**3** Symptoms	332	365	396	297	350	348
Incomplete Emptying	263	288	314	257	290	302
Other Post Mic Incontinence	108	118	129	64	96	76
Any LUTS (Noct ≥1)						
Any LUTS (Noct ≥1)	1,260	1,377	1,490	1,379	1,460	1,623
Storage + Voiding Symptoms (Noct ≥1)	350	386	422	309	373	367
Storage + Post Mic Symptoms (Noct ≥1)	247	273	299	238	274	282
Voiding + Post Mic Symptoms (Noct ≥1)	205	226	247	158	205	187
Storage + Voiding + Post Mic Symptoms (Noct ≥1)	166	183	202	137	173	163
Any LUTS (Noct ≥2)						
Any LUTS (Noct ≥2)	933	1,020	1,104	994	1,068	1,170
Storage + Voiding Symptoms (Noct ≥2)	247	273	299	237	275	283
Storage + Post Mic Symptoms (Noct ≥2)	188	207	227	190	214	226
Voiding + Post Mic Symptoms (Noct ≥2)	205	226	247	158	205	187
Storage + Voiding + Post Mic Symptoms (Noct ≥2)	130	144	158	119	142	142

Table 23. Estimated Worldwide Number of Individuals with LUTS including OAB and Incontinence by Region (In Millions)

	Estimated Number of individuals with any LUTS			Estimated Number of Individuals with OAB			Estimated Number of Individuals with Incontinence		
Region	**2008**	**2013**	**2018**	**2008**	**2013**	**2018**	**2008**	**2013**	**2018**
World	1,930	2,106	2,277	455	500	545	346	383	420
Africa	203	231	263	46	53	60	33	38	43
North America	167	180	193	40	44	48	32	34	37
South America	111	122	133	26	29	32	20	22	24
Asia	1,166	1,284	1,396	272	302	332	206	231	256
Europe	273	278	280	68	70	71	54	56	57

Table 24. Summary of major findings

46% of the 4.2 billion of the adult world population (≥ 20 and over) experience any LUTS

455 million individuals or 11% of the world population estimated to experience OAB symptoms

346 million individuals or 8% of the world population estimated to experience some type of UI

SUI is the most common type of incontinence in 2008 and 2018 (Figure 1)

136 (3%) and 164 (4%) million individuals are estimated to experience SUI in 2008 and in 2018 respectively

49 (1%) and 60 (1%) million individuals are estimated to experience UUI in 2008 and in 2018 respectively

53(1%) and 65 (1%) million individuals are estimated to experience MUI in 2008 and in 2018 respectively

108 (3%) and 131 (3%) million individuals are estimated to experience Other Incontinence in 2008 and in 2018 respectively

Assuming LUTS prevalence rates remain stable for the next ten years, 2.3 billion individuals are estimated to experience LUTS by the year 2018
An increase of 18% from 2008

Storage symptoms has the highest burden in both the male and female population than other LUTS (Figure 2)

Male: estimated 597 million in 2008, 713 million in 2018

Female: estimated 760 million in 2008, 901 million in 2018

Asia region is estimated to carry the highest burden of LUTS. Estimated 1.2 billion individuals in Asia regions may experience any LUTS

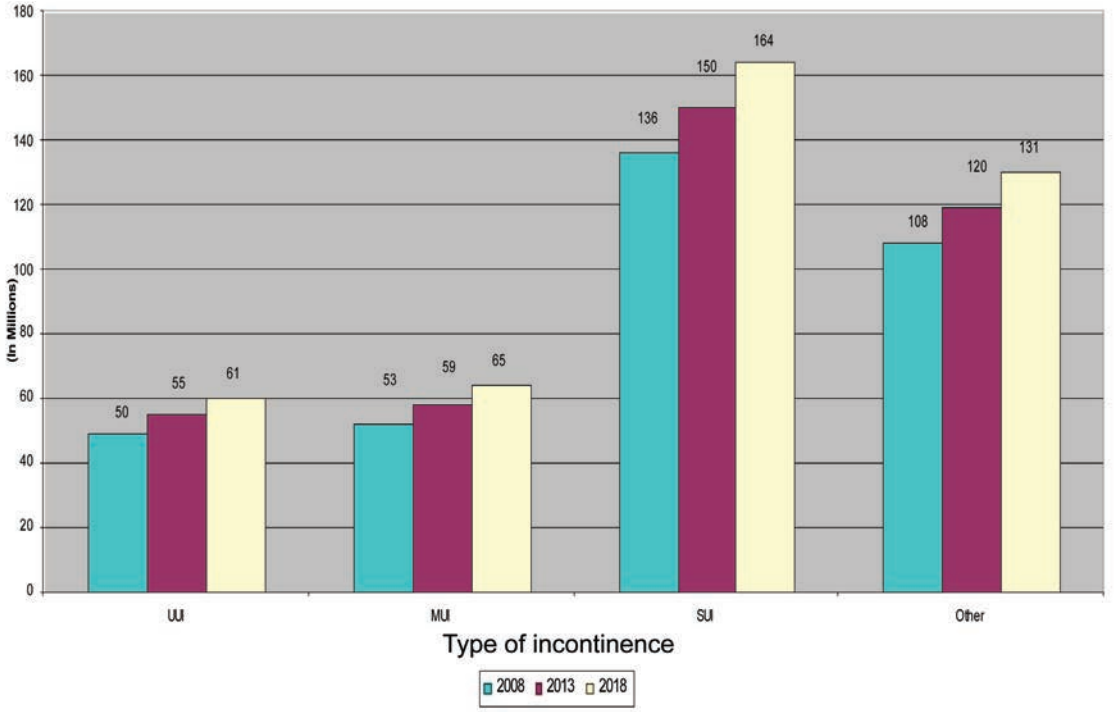


figure 16. Estimated number of individuals with UI 2008, 2013 and 2018 grouped according to type of incontinence

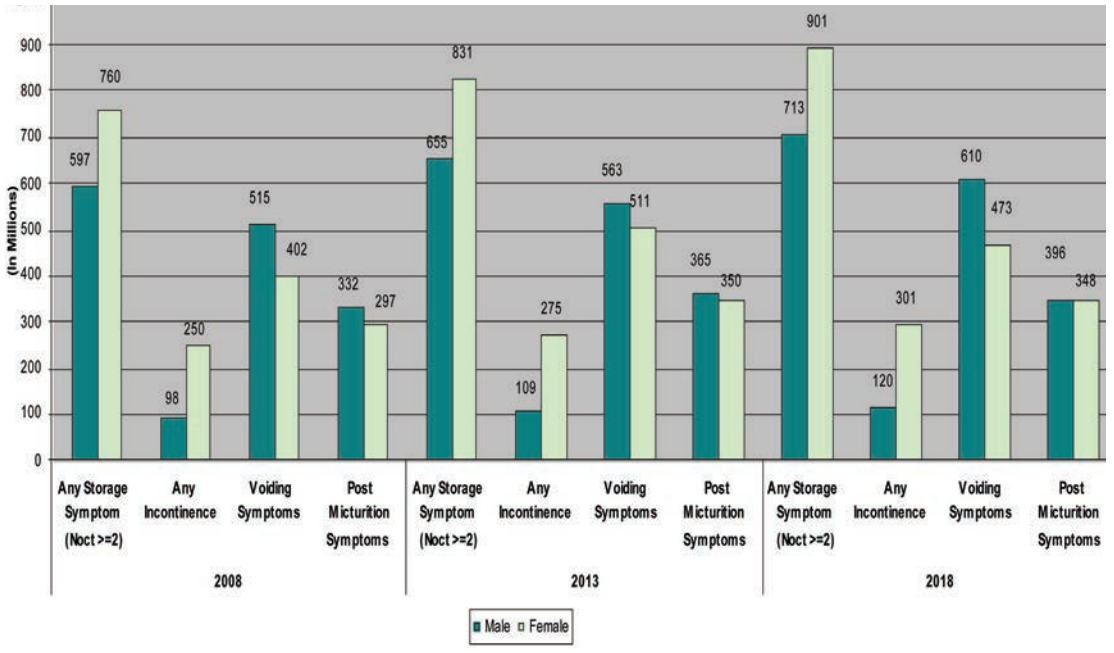


figure 17. Estimated number of individuals with LUTS 2008, 2013 and 2018 grouped according to gender.

National Statistics Offices9. Data on international migration and refugee movements, public health efforts, socio-political circumstances, and historical events such as natural disasters and conflict are all considered when the IDB calculates the estimates and projections.

It is anticipated that with the overall aging of the population the prevalence of LUTS will also increase.

It has been shown that LUTS are burdensome to individuals [397,539] and the likely increase in the number of individuals experiencing. LUTS has implications on healthcare resources and overall health burden. This analysis is an estimate of the number of individuals with LUTS based on a conservative prevalence rate, and so the future number of those with certain LUTS may surpass those of this report.

II. SUMMARY POINTS

- The spectrum of severity of anal and urinary incontinence, as well as pelvic organ prolapse, and the symptom profile of patients referred to specialist centres do not necessarily reflect the spectrum of disease seen in the community.
- The selection and referral process may introduce bias into research and hamper the ability to generalise hospital-based research back to primary care populations.
- One should be very careful with calculating numbers of patients in need of therapy based on epidemiological data.

M. RECOMMENDATIONS FOR FURTHER RESEARCH

Much biomedical research is observational and the reporting of such research is often inadequate which hampers the assessment of its strengths and weaknesses and of a study´s generalisability. The STROBE (Strengthening of the Reporting of OBservational studies in Epidemiology) statement was introduced [661]. It is a a checklist of items that should be addressed in articles reporting on the three main study designs of analytical epidemiology: cohort, case-control, and cross sectional studies. The use of this checklist is highly recommended.

I. URINARY INCONTINENCE

It is recommended that more sustained research on measurement of UI should be performed including, its types and severity to move the research ahead. Longitudinal study designs are needed to estimate incidence of UI and describe the course of the condition and its different forms and to investigate its risk factors and possible protective factors.

There is still little knowledge with regard to prevalence, incidence, and other epidemiological data in developing countries. It is recommended that fundamental research regarding prevalence, incidence and other epidemiological data in developing countries should be encouraged, and tailored to the cultural, economic and social environment of the population under study.

Crude prevalence studies (descriptive epidemiology) from USA and Europe are abundant, and further studies should be done only with recommended and validated questionnaires or in order to combine data from the prevalence study with studies of co-factors and predictors (analytical epidemiology). Control for confounders, stratification, and multivariate techniques should be increasingly used because of the need for more advanced epidemiological analyses of risk factors and comorbidity. Strength of associations should be determined by relative risks and odds ratios, and confidence limits should be given. We still have very little knowledge of the absolute and relative importance of several risk factors, and almost no information about the attributable risk of the factors in the society.

Some potential risk and protective factors deserve more attention. For example, the role of pregnancy and childbirth in the development of UI must be studied in a fashion that links population-based methods to clinical assessment of pregnancy, delivery and the birth trauma and follows women over many years. Such a design is necessary because the effect of pregnancy and childbirth may become clear only years later when the woman is older and because the woman will not be able to report the exact nature of the tear or episiotomy, etc. There should be more emphasis on the associations between UI and specific diseases like stroke, diabetes, psychiatric disease and genital prolapse. Genetic components should be investigated.

Primary prevention is the main goal in the management of human disease. An important strategy would thus be to identify the individuals at risk, and then take measures to reduce the risk among those individuals or in certain risk groups. Based on current knowledge there are no well documented efforts that can be done in order to avoid the occurrence of UI in large populations. Primary prevention studies should be encouraged, but the epidemiological basis for choosing appropriate interventions is weak.

In surveys based on questionnaires or interviews symptoms can be registered. There are convincing data suggesting that the different types may reflect quite different pathologies and risk factors. Differentiating the types in future research might therefore prove very fruitful. Methodological work has still to be done in this area, but typical type descriptions should be included in new studies. Likewise, studies of risk factors should include important and known confounders such as age, parity, and weight.

Variations in definitions and measurement issues are fundamental and lead to problems with assessing the findings in epidemiological studies. We need to improve epidemiological studies by including variables that better characterise UI, so that more advanced and informative analyses may be conducted. It is therefore recommended that all epidemiological studies include a minimum data set (**Table 25**), including elements of screening question, frequency measure, quantity of urine loss, duration, type, and severity. In addition, it is recommended that validated measures of bother/quality of life and urinary symptoms other than UI should be included. We here also refer to the chapter from the committee on symptom and quality of life assessment.

In addition, it is recommended that validated measures of bother/quality of life and urinary symptoms other than UI should be included.

II. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE

In these areas there is a need for more epidemiological research in all areas; prevalence, incidence, and risk factors. Many of the fundamental methodological issues relevant to UI discussed above are highly relevant to the fields of FI and POP.

The committee emphasises that uniform definitions of FI and POP should be used in studies, and there should be a move towards a standardisation of measurement instruments in community surveys that can be used worldwide. Developing definitions is a scientific process requiring careful conceptualisation of the condition in light of its many clinical presentations and underlying mechanisms. This will require a multi-method approach and consideration of issues such a reliability and validity.

Table 25. Elements in a minimum data set recommended for all epidemiological studies

- Screening question for any involuntary urine loss.
- Frequency measure. For example, classification into categories of none, less than once a month, one/several times a month, one/several times a week, every day/nigth, all the time.
- Quantity of urine loss for a typical episode. For example, classification into categories of none, drops, small amounts, moderate amounts, much/a great deal.
- Duration. For example months, years.
- Type. Based on typical description; stress, urge, mixed and other.
- Severity. Either by combining excisting questions or by a validated index.

REFERENCES

1. Abrams, P., Cardozo, L., Fall, M., Griffits, D. Rosier, P., Ulmsten, U. et al. : The standardisation of terminology in lower urinary tract function : report from the standardisation sub-committee of the International Continence Society. Urology, 61: 37m 2003.
2. Haylen BT, De Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol. Urodyn. 2010. p. 4–20.
3. Stroup, D. F., Berlin, J.A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D. et al. : Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observtional Studies in Epidemiology (MOOSE) group. JAMA 283: 2008, 2002.
4. Nevéus, T., et al., The Standardization of Terminology of Lower Urinary Function in Children and Adolcents: Report from standardisation Committee of International Children´s Continence Society. J Urol, 2006. 176: p. 314 - 324.
5. Rittig, S., et al., Abdorminal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. Am J Physiol, 1989. 25: p. 664-666.
6. Yeung, C.K., Chiu, H.N., Sit, F.K., Bladder dysfunction in children with refractory monosymptomatic primary nocturnak enuresis. J Urol, 1999. 162: p. 1049-55.
7. Holmdahl, G., et al., Four-hours voiding observation in healthy infants. Scan J Urol Nephrol, 1996. 156: p. 1808-1812.
8. Jansson, U.-B., et al., Voiding pattern and acquisition of bladder control from birth to age 6 years - a longitudinal study. J Urol, 2005. 174: p. 298 - 293.
9. Kranz, I., et al., On the Epidemiology of Nocturnal Enuresis - A Critical Rewiew of Methods used in descriptive Epidemiological studies on Nocturnal Enuresis. 1994: p. 75-81.
10. McGree, R., et al., A longitudinal study of enuresis from five to nine years. Aust. Paediatr. J., 1984. 20: p. 39-42.
11. Forsythe, W.I. and A. Redmond, Enuresis and spontaneous cure rate - study of 1129 enuretics. Arch Dis Child, 1974. 49: p. 259-263.
12. Fergusson, D.M., L.J. Horwood, and F.T. Shannon, Factors Related to the Age of Attainment of Nocturnal Bladder Control: An 8-Year Longitudinal Study. Pediatrics, 1986. 87(5): p. 884-890.
13. Fergusson, D.M. and L.J. Horwood. Nocturnal enuresis and behavioral problems in adolescence: a 15-year longitudinal study. Pediatrics, 1994. 94(5): p. 662-668.
14. Feehan, M., et al., A 6 year follow-up of childhood enuresis: Prevalence in adolescence and consequences for mental health. J. Paediatr. Child Health, 1990. 26: p. 75-79.
15. Butler, R.J. and J. Heron, The prevalence of infrequent bedwetting and nocturnal enuresis in childhood. A large British cohort. Scandinavian journal of urology and nephrology, 2008. 42(3): p. 257-64.
16. Chiozza, M., L, et al., An Italian epidemiological multicentre study of nocturnal enuresis. BJU, 1998. 81.suppl.3: p. 86-89.
17. Yeung, C.K., Nocturnal Enuresis in Hong Kong: Different Chinese Phenotypes. Scan J Urol Nephrol, 1996. suppl.31: p. 17-21.
18. Spee- van der Wekke, J., et al., Childhood nocturnal enuresis in the Netherlands. Urology, 1998. 51: p. 1022.
19. Cher, T.-W., G.-J. Lin, and K.-H. Hsu, Prevalence of nocturnal enuresis and associated familiar factors in primary school children in Taiwan. J Urol, 2002. 168: p. 1142-1146.
20. Serel, T.K., et al., epidemiology of enuresis in Turkish children. Scan J Urol Nephrol, 1997. 31: p. 537.
21. Lee, S.D., et al., An epidemiological study of enuresis in Korean children. BJU Int., 2000. 85: p. 869-873.
22. Kajiwara, M., et al., Nocturnal enuresis and overactive bladder in children: An epidemiological study. Int J Urol, 2006. 13: p. 36-41.
23. Söderstrom, U., et al., Urinary and faecal incontinence: A population-based study. Acta Paediatr, 2004. 93: p. 386-89.
24. Yeung, C.K., et al., differences in characteristics of nocturnal enuresis between children and adolescents: A critical appraisal from a large epidemiological study. BJU Int., 2006. 97(5): p. 1069-73.
25. Kanaheswari, Y., Epidemiology of childhood nocturnal enuresis in Malaysia. J Paediatr Child Health, 2003. 39(2): p. 118-123.
26. Su, M.S., et al., Nocturnal enuresis in children: prevalence, correlates, and relationship with obstructive sleep apnea. The Journal of pediatrics, 2011. 159(2): p. 238-42 e1.
27. Hellström, A.-L., et al., Micturition habits and incontinence in 7-year-ola Swedish school entrants. Eur J Pediatr, 1990. 149(6): p. 434-437.
28. Järvelin, M.R., et al., Enuresis in Seven-Year-Old Children. Acta Paediatr Scan, 1988. 77: p. 148-153.
29. Hellström, A.-L., et al., Micturition habits and incontinence at age 17 - reinvestigation of a cohort studied at age 7. BJU, 1995. 76: p. 231-234.
30. Swithinbank, L.V., J.C. Carr, and P.H. Abrams, Longitudinal Study of Urinary Symptoms in Children. Scan J Urol Nephrol, 1994. Suppl 163: p. 163-167.
31. Swithinbank, L.V., et al., The natural history of urinary symtoms during adolescence. BJU, 1998. 81, Suppl 3: p. 90-93.
32. Hirasing, R.A., et al., Enuresis Nocturna in Adults. Scan J Urol Nephrol, 1997. 31: p. 533-536.
33. Nevéus, T., et al., Deepth of sleep and sleep habits among enuretic and incontinence children. Acta Paediatr, 1999. 88: p. 748.
34. Bower, W.F., et al., The epidemiology of childhood enuresis in Australia. British Journal of Urology, 1996. 78: p. 602-606.
35. Gümüs, B., et al., Prevalence of nocturnal enuresis and accompanying factors in children aged 7-11 years in Turkey. Acta Paediatr, 1999. 88: p. 1369.
36. Watanabe, H. and A. Kawauchi, Nocturnal Enuresis: Social Aspects and Traetment in Japan. Scan J Urol Nephrol, 1994. suppl. 163: p. 29-38.
37. Liu, X., et al., Attaining Nocturnal Urinary Control, Nocturnal Enuresis, and Behavioral Problems in Chinese Children Aged 6 Through 16 Years. J Am Acard Child Adolesc Phychiatry, 2000. 39(12): p. 1557-1564.
38. Sureshkumar, P., et al., Risk factors for nocturnal enuresis in school-age children. The Journal of urology, 2009. 182(6): p. 2893-9.
39. Järvelin, M.R., et al., Aetiological and Percipitating Factors for Childhood Enuresis. Acta Paediatr Scan, 1991. 80: p. 361-369.
40. von Gontard, A., J. Heron, and C. Joinson, Family history of nocturnal enuresis and urinary incontinence: results from a large epidemiological study. The Journal of urology, 2011. 185(6): p. 2303-6.
41. Eiberg, H., Nocturnal enuresis is linked to a specific gene. Scan J Urol Nephrol, 1995. Suppl.173: p. 15.
42. Arnell, H., et al., The genetics of primary nocturnal enuresis: inheritance and suggestion of a second major gene on chromosome 12q. J Med Genet, 1997. 34: p. 360.
43. von Gontard, A., et al., Molecular genetics of nocturnal enuresis: clinical and genetic heterogeneity. Acta Paediatr, 1997. 87: p. 571.
44. Moilanen, I., et al., A follow-up of enuresis from childhood to adolescence. BJU, 1998. 81,suppl.3: p. 94-97.
45. Schulpen, T., The burden of nocturnal enuresis. Acta Paediatr, 1997. 86(9): p. 981-984.
46. van Hoecke, E., et al., Socioeconomic Status as a Common Factor Underlaying the Association Between Enure-

sis and Psychopathology. J Dev Behav Pediatrics, 2003. 24(2): p. 109-114.

47. Coppola, G., et al., Psychological correlates of enuresis: a case-control study on an Italian sample. Pediatric nephrology, 2011. 26(10): p. 1829-36.

48. Kawauchi, A., et al., Follow-up study of bedwetting from 3 to 5 years of age. Urology, 2001. 58(5): p. 772-776.

49. Lunsing, R.J., et al., Nocturnal enuresis and minor Neurological dysfunction at 12 years: A follow-up study. Dev Medicine and Child Neurology, 1991. 33: p. 439-445.

50. Duel, B.P., et al., A survey of voiding dysfunction in children with attention deficit-hyperactivity disorder. J Urol, 2003. 170: p. 1521-1524.

51. Robson, W.L.M., et al., Enuresis in childraen with attention deficit hyperactivity disorder. Southern Medical Journal, 1997. 90: p. 503.

52. Elia, J., et al., Nocturnal enuresis: a suggestive endophenotype marker for a subgroup of inattentive attention-deficit/hyperactivity disorder. The Journal of pediatrics, 2009. 155(2): p. 239-44 e5.

53. Wolfish, N.M., R.T. Pivik, and K.A. Busby, Elevated sleep arousal thresholds in enuretic boys: clinical implications. Acta Paediatr, 1997. 86: p. 381-384.

54. Kawauchi, A., et al., Changes in the structure of sleep spindles and delta waves on electroencephalography in patients with nocturnal enuresis. BJU, 1998. 81, suppl. 3: p. 72-75.

55. Hunsballe, J.M., Increased delta component in computerized sleep electroencephalographic analysis suggest abnormally deep sleep in primary monosymptomatic nocturnal enuresis. Scan J Urol Nephrol, 2000. 34: p. 294.

56. Chandra, M., et al., Prevalence of diurnal voiding symptoms and difficult arousal from sleep in children with nocturnal enuresis. J Urol, 2004. 172: p. 311-16.

57. Osungbade, K.O. and F.O. Oshiname, Prevalence and perception of nocturnal enuresis in children of a rural community in southwestern Nigeria. Trop Doc, 2003. 33(4): p. 243-236.

58. Baruzzi, A., et al., Atrial natriuretic peptide and catecholamines in obstructive sleep apnoea. Sleep, 1991. 14: p. 83.

59. Barone, J.G., et al., Nocturnal enuresis and overweight are associated with obstructive sleep apnea. Pediatrics, 2009. 124(1): p. e53-9.

60. Weider, D.J., M.j. Sateia, and R.p. West, Nocturnal enuresis in children with upper airway obstruction. Otolaryngol Head Neck Surg, 1991. 105: p. 427-432.

61. Loening-Baucke, V., Urinary Incontinence and Urinary Tract Infection and Their Resolution With Treatment of Chronic Constipation of Childhood. Pediatrics, 1997. 100(2): p. 228-232.

62. Forbes, F.C., Children with enuresis. Nowdays, a strong suspicion of sexualabuse would prompt full investigation. BMJ, 1998. 316: p. 777.

63. Ferrara, P., et al., Preliminary data on monosymptomatic nocturnal enuresis in children and adolescents with type 1 diabetes. Scan J Urol Nephrol, 2006. 40: p. 238-40.

64. Hoebeke, P., et al., One thousend video-urodynamic studies in children with non-neurogenic bladder sphincter dysfunction. BJU Int., 2001. 87: p. 575-580.

65. Hellerstein, S., Voiding Dysfunction in Pediatric Patients. Clin Pediatr (Phila), 2003. 42(1): p. 43-49.

66. Kajiwara, M., et al., The micturition habits and prevalence of daytime urinary incontinence in Japanese primary school children. J Urol, 2004. 171: p. 403-7.

67. Joinson, C., et al., Psychological problems in children with daytime wetting. Pediatric, 2006. 118(5): p. 1985-93.

68. Swithinbank, L.V., et al., The natural history of daytime urinary incontinence in children: a large British cohort. Acta paediatrica, 2010. 99(7): p. 1031-6.

69. Sureshkumar, P., et al., A population based study of 2,856 school-age children with urinary incontinence. The Journal of urology, 2009. 181(2): p. 808-15; discussion 815-6.

70. von Gontard, A., Hollmann,E., Comorbidity of functional urinary incontinence and enkopresis: Somatic and behavioural associations. J Urol, 2004. 171: p. 2644-47.

71. Sureshkumer P., C.P., Roy L.P, Knight J.F.,, et al., Daytime urinary incontinence in primary school children: A population-based survey. The Journal of Pediatrics, 2001. 137(6): p. 814-818.

72. Lettgren, B., et al., Urge incontinence and voiding postponement in children : somatic and phsychosocial factors. Acta Paediatr, 2002. 91: p. 978-984.

73. Zink, S., C.M. Freitag, and A. von Gontard, Behavioral comorbidity differs in subtypes of enuresis and urinary incontinence. J Urol, 2008. 179: p. 295-8.

74. Fultz NH, Herzog AR. Prevalence of urinary incontinence in middle-aged and older women: a survey-based methodological experiment. J Aging Health. 2000 Nov.;12(4):459–469.

75. van Leijsen SAL, Evert JSH-V, Mol BWJ, Vierhout ME, Milani AL, Heesakkers JPFA, et al. The correlation between clinical and urodynamic diagnosis in classifying the type of urinary incontinence in women. A systematic review of the literature. Neurourol. Urodyn. 2011 Feb. 4;30(4):495–502.

76. Bosch JLHR, Cardozo L, Hashim H, Hilton P, Oelke M, Robinson D. Constructing trials to show whether urodynamic studies are necessary in lower urinary tract dysfunction. Neurourol. Urodyn. 2011 Jun.;30(5):735–740.

77. Minassian VA, Stewart WF, Hirsch AG. Why do stress and urge incontinence co-occur much more often than expected? Int Urogynecol J Pelvic Floor Dysfunct. 2008 Oct.;19(10):1429–1440.

78. Sandvik H, Hunskaar S, Vanvik A, Bratt H, Seim A, Hermstad R. Diagnostic classification of female urinary incontinence: an epidemiological survey corrected for validity. J Clin Epidemiol. 1995 Mar.;48(3):339–343.

79. Digesu GA, Salvatore S, Fernando R, Khullar V. Mixed urinary symptoms: What are the urodynamic findings? Neurourol. Urodyn. 2008;27(5):372–375.

80. Stach-Lempinen B, Kirkinen P, Laippala P, Metsänoja R, Kujansuu E. Do objective urodynamic or clinical findings determine impact of urinary incontinence or its treatment on quality of life? Urology. 2004 Jan.;63(1):67–71; discussion 71–2.

81. Lowenstein L, Dooley Y, Kenton K, Rickey L, FitzGerald MP, Mueller E, et al. The volume at which women leak first on urodynamic testing is not associated with quality of life, measures of urethral integrity or surgical failure. JURO. 2007 Jul.;178(1):193–196.

82. Elstad EA, Taubenberger SP, Botelho EM, Tennstedt SL. Beyond incontinence: the stigma of other urinary symptoms. J Adv Nurs. 2010 Nov.;66(11):2460–2470.

83. Thom DH, Van Den Eeden SK, Ragins AI, Wassel-Fyr C, Vittinghof E, Subak LL, et al. Differences in prevalence of urinary incontinence by race/ethnicity. JURO. 2006 Jan.;175(1):259–264.

84. Klovning A, Sandvik H, Hunskaar S. Web-based survey attracted age-biased sample with more severe illness than paper-based survey. J Clin Epidemiol. 2009 Oct.;62(10):1068–1074.

85. Walker GJA, Gunasekera P. Pelvic organ prolapse and incontinence in developing countries: review of prevalence and risk factors. Int Urogynecol J. 2011 Feb.;22(2):127–135.

86. Botlero R, Urquhart DM, Davis SR, Bell RJ. Prevalence and incidence of urinary incontinence in women: review of the literature and investigation of methodological issues. Int J Urol. 2008 Mar.;15(3):230–234.

87. Thom D. Variation in estimates of urinary incontinence prevalence in the community: effects of differences in definition, population characteristics, and study type. J Am Geriatr Soc. 1998 Apr.;46(4):473–480.

88. Minassian VA, Stewart WF, Wood GC. Urinary incontinence in women: variation in prevalence estimates and risk factors. Obstet Gynecol. 2008 Feb.;111(2 Pt 1):324–331.

89. Hunskaar S, Lose G, Sykes D, Voss S. The prevalence of urinary incontinence in women in four European countries. BJU Int. 2004 Feb.;93(3):324–330.

90. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur. Urol. 2006 Dec.;50(6):1306–14; discussion 1314–5.

91. Coyne KS, Sexton CC, Kopp ZS, Luks S, Gross A, Irwin D, et al. Rationale for the study methods and design of the epidemiology of lower urinary tract symptoms (EpiLUTS) study. BJU Int. 2009 Aug.;104(3):348–351.

92. Niang L, Kane R, Ndoye M, Jalloh M, Labou I, Diaw JJ, et al. [Urinary incontinence in woman: epidemiologic profile in Sub Saharian countries]. Prog. Urol. 2010 Dec.;20(13):1213–1216.

93. Coyne KS, Margolis MK, Kopp ZS, Kaplan SA. Racial Differences in the Prevalence of Overactive Bladder in the United States From the Epidemiology of LUTS (EpiLUTS) Study. Urology. 2012 Jan.;79(1):95–101.

94. Espuña-Pons M, Brugulat Guiteras P, Costa Sampere D, Medina Bustos A, Mompart Penina A. [Prevalence of urinary incontinence in Catalonia, Spain]. Med Clin (Barc). 2009 Nov. 14;133(18):702–705.

95. Herschorn S, Gajewski J, Schulz J, Corcos J. A population-based study of urinary symptoms and incontinence: the Canadian Urinary Bladder Survey. BJU Int. 2007 Oct.;0(0):071003001542002–???

96. Tähtinen RM, Auvinen A, Cartwright R, Johnson TM, Tammela TLJ, Tikkinen KAO. Smoking and bladder symptoms in women. Obstet Gynecol. 2011 Sep.;118(3):643–648.

97. Tennstedt SL, Link CL, Steers WD, McKinlay JB. Prevalence of and risk factors for urine leakage in a racially and ethnically diverse population of adults: the Boston Area Community Health (BACH) Survey. Am. J. Epidemiol. 2008 Feb. 15;167(4):390–399.

98. Lee K-S, Sung HH, Na S, Choo M-S. Prevalence of urinary incontinence in Korean women: results of a National Health Interview Survey. World J Urol. 2008 Apr.;26(2):179–185.

99. Zhu L, Lang J, Wang H, Han S, Huang J. The prevalence of and potential risk factors for female urinary incontinence in Beijing, China. Menopause. 2008 Apr.;15(3):566–569.

100. Nygaard I, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, et al. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008 Sep. 17;300(11):1311–1316.

101. Martínez Agulló E, Ruiz Cerdá JL, Gómez Pérez L, Ramírez Backhaus M, Delgado Oliva F, Rebollo P, et al. [Prevalence of urinary incontinence and hyperactive bladder in the Spanish population: results of the EPICC study]. Actas Urol Esp. 2009 Feb.;33(2):159–166.

102. Bodhare TN, Valsangkar S, Bele SD. An epidemiological study of urinary incontinence and its impact on quality of life among women aged 35 years and above in a rural area. Indian J Urol. 2010 Jul.;26(3):353–358.

103. Ojengbede OA, Morhason-Bello IO, Adedokun BO, Okonkwo NS, Kolade CO. Prevalence and the associated trigger factors of urinary incontinence among 5000 black women in sub-Saharan Africa: findings from a community survey. BJU Int. 2011 Mar. 25;107(11):1793–1800.

104. Ahmadi B, Alimohammadian M, Golestan B, Mahjubi B, Janani L, Mirzaei R. The hidden epidemic of urinary incontinence in women: a population-based study with emphasis on preventive strategies. Int Urogynecol J. 2010 Apr.;21(4):453–459.

105. Liapis A, Bakas P, Liapi S, Sioutis D, Creatsas G. Epidemiology of female urinary incontinence in the Greek population: EURIG study. Int Urogynecol J. 2010 Feb.;21(2):217–222.

106. Amaro JL, Macharelli CA, Yamamoto H, Kawano PR, Padovani CV, Agostinho AD. Prevalence and risk factors for urinary and fecal incontinence in Brazilian women. Int Braz J Urol. 2009 Aug.;35(5):592–7; discussion 598.

107. López M, Ortiz AP, Vargas R. Prevalence of urinary incontinence and its association with body mass index among women in Puerto Rico. J Womens Health (Larchmt). 2009 Oct.;18(10):1607–1614.

108. Correia S, Dinis P, Rolo F, Lunet N. Prevalence, treatment and known risk factors of urinary incontinence and overactive bladder in the non-institutionalized Portuguese population. Int Urogynecol J. 2009 Aug. 14;20(12):1481–1489.

109. Slieker-ten Hove MCP, Pool-Goudzwaard AL, Eijkemans MJC, Steegers-Theunissen RPM, Burger CW, Vierhout ME. Prevalence of double incontinence, risks and influence on quality of life in a general female population. Neurourol. Urodyn. 2010 Apr.;29(4):545–550.

110. Ge J, Yang P, Zhang Y, Li X, Wang Q, Lu Y. Prevalence and Risk Factors of Urinary Incontinence in Chinese Women: A Population-Based Study. Asia Pac J Public Health. 2011 Dec. 20.

111. Wennberg A-L, Molander U, Fall M, Edlund C, Peeker R, Milsom I. Lower urinary tract symptoms: lack of change in prevalence and help-seeking behaviour in two population-based surveys of women in 1991 and 2007. BJU Int. 2009 Oct.;104(7):954–959.

112. Franzén K, Johansson J-E, Andersson G, Pettersson N, Nilsson K. Urinary incontinence in women is not exclusively a medical problem: a population-based study on urinary incontinence and general living conditions. Scand. J. Urol. Nephrol. 2009;43(3):226–232.

113. Zhu L, Lang J, Liu C, Han S, Huang J, Li X. The epidemiological study of women with urinary incontinence and risk factors for stress urinary incontinence in China. Menopause. 2009 Jun.;16(4):831–836.

114. Lasserre A, Pelat C, Guéroult V, Hanslik T, Chartier-Kastler E, Blanchon T, et al. Urinary Incontinence in French Women: Prevalence, Risk Factors, and Impact on Quality of Life. Eur. Urol. 2009 Jul.;56(1):177–183.

115. Onur R, Deveci SE, Rahman S, Sevindik F, Acik Y. Prevalence and risk factors of female urinary incontinence in eastern Turkey. Int J Urol. 2009 Jun.;16(6):566–569.

116. Jackson S, Donovan J, Brookes S et al. The Bristol female lower urinary tract symptoms questionnaire: development and psychometric testing. Br J Urol. 1996 Jun;77(6):805-12.

117. Flyger H, Brasso K, Schou J et al. Validation of the self□ administered Danish Prostatic Symptom Score (DAN□ PSS□1) system for use in benign prostatic hyperplasia. Br J Urol. 1995 Oct;76(4):451-8.

118. Wyman JF, Harkins SW, Choi SC, Taylor JR, Fantl JA. Psychosocial impact of urinary incontinence in women. Obstet Gynecol. 1987 Sep.;70(3 Pt 1):378–381.

119. Pekkanen J, Sunyer J, Chinn S. Nondifferential disease misclassification may bias incidence risk ratios away from the null. J Clin Epidemiol. 2006 Mar.;59(3):281–289.

120. Wennberg A-L, Molander U, Fall M, Edlund C, Peeker R, Milsom I. A longitudinal population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in women. Eur. Urol. 2009 Apr.;55(4):783–791.

121. Samuelsson EC, Victor FT, Svärdsudd KF. Five-year incidence and remission rates of female urinary incontinence in a Swedish population less than 65 years old. Am. J. Obstet. Gynecol. 2000 Sep.;183(3):568–574.

122. Hägglund D, Walker-Engström M-L, Larsson G, Leppert J. Changes in urinary incontinence and quality of life after four years. A population-based study of women aged 22-50 years. Scand J Prim Health Care. 2004 Jun.;22(2):112–117.

123. Wehrberger C, Temml C, Ponholzer A, Madersbacher S. Incidence and remission of female urinary incontinence over 6.5 years: analysis of a health screening project. Eur. Urol. 2006 Aug.;50(2):327–332.

124. Townsend MK, Danforth KN, Lifford KL, Rosner B, Curhan GC, Resnick NM, et al. Incidence and remission of urinary incontinence in middle-aged women. Am. J. Obstet. Gynecol. 2007 Aug.;197(2):167.e1–5.

125. Dallosso HM, McGrother CW, Matthews RJ, Donaldson MMK, Leicestershire MRC Incontinence Study Group. The association of diet and other lifestyle factors with overactive bladder and stress incontinence: a longitudinal study in women. BJU Int. 2003 Jul.;92(1):69–77.

126. McGrother CW, Donaldson MMK, Shaw C, Matthews RJ, Hayward TA, Dallosso HM, et al. Storage symptoms of the bladder: prevalence, incidence and need for services in the UK. BJU Int. 2004 Apr.;93(6):763–769.

127. Donaldson MMK, Thompson JR, Matthews RJ, Dallosso HM, McGrother CW, Leicestershire MRC Incontinence Study Group. The natural history of overactive bladder and stress urinary incontinence in older women in the community: a 3-year prospective cohort study. Neurourol. Urodyn. 2006;25(7):709–716.

128. Waetjen LE, Liao S, Johnson WO, Sampselle CM, Sternfield B, Harlow SD, et al. Factors associated with prevalent and incident urinary incontinence in a cohort of midlife women: a longitudinal analysis of data: study of women's health across the nation. Am. J. Epidemiol. 2007 Feb. 1;165(3):309–318.

129. Liu C, Andrews GR. Prevalence and incidence of urinary incontinence in the elderly: a longitudinal study in South Australia. Chin. Med. J. 2002 Jan.;115(1):119–122.

130. Goode PS, Burgio KL, Redden DT, Markland A, Richter HE, Sawyer P, et al. Population based study of incidence and predictors of urinary incontinence in black and white older adults. J. Urol. 2008 Apr.;179(4):1449–53; discussion 1453–4.

131. Østbye T, Seim A, Krause KM, Feightner J, Hachinski V, Sykes E, et al. A 10-year follow-up of urinary and fecal incontinence among the oldest old in the community: the Canadian Study of Health and Aging. Can J Aging. 2004;23(4):319–331.

132. Møller LA, Lose G, Jørgensen T. Incidence and remission rates of lower urinary tract symptoms at one year in women aged 40-60: longitudinal study. BMJ. 2000 May 27;320(7247):1429–1432.

133. Holtedahl K, Hunskaar S. Prevalence, 1-year incidence and factors associated with urinary incontinence: a population based study of women 50-74 years of age in primary care. Maturitas. 1998 Jan. 12;28(3):205–211.

134. Byles J, Millar CJ, Sibbritt DW, Chiarelli P. Living with urinary incontinence: a longitudinal study of older women. Age Ageing. 2009 May;38(3):333–8; discussion 251.

135. Lifford KL, Townsend MK, Curhan GC, Resnick NM, Grodstein F. The epidemiology of urinary incontinence in older women: incidence, progression, and remission. J Am Geriatr Soc. 2008 Jul.;56(7):1191–1198.

136. Jackson SL, Scholes D, Boyko EJ, Abraham L, Fihn SD. Predictors of urinary incontinence in a prospective cohort of postmenopausal women. Obstet Gynecol. 2006 Oct.;108(4):855–862.

137. Nygaard IE, Lemke JH. Urinary incontinence in rural older women: prevalence, incidence and remission. J Am Geriatr Soc. 1996 Sep.;44(9):1049–1054.

138. Gavira Iglesias F, Caridad Y Ocerín JM, Guerrero Muñoz JB, López Pérez M, Romero López M, Pavón Aranguren MV. [Five-year follow-up of urinary incontinence in older people in a Spanish rural population]. Aten Primaria. 2005 Feb. 15;35(2):67–74.

139. Herzog AR, Diokno AC, Brown MB, Normolle DP, Brock BM. Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. J Gerontol. 1990 Mar.;45(2):M67–74.

140. Burgio KL, Matthews KA, Engel BT. Prevalence, incidence and correlates of urinary incontinence in healthy, middle-aged women. JURO. 1991 Nov.;146(5):1255–1259.

141. Melville JL, Fan M-Y, Rau H, Nygaard IE, Katon WJ. Major depression and urinary incontinence in women: temporal associations in an epidemiologic sample. Am. J. Obstet. Gynecol. 2009 Nov.;201(5):490.e1–7.

142. Jahanlu D, Hunskaar S. The Hordaland women's cohort: prevalence, incidence, and remission of urinary incontinence in middle-aged women. Int Urogynecol J. 2010 May 7;21(10):1223–1229.

143. Botlero R, Davis SR, Urquhart DM, Bell RJ. Incidence and resolution rates of different types of urinary incontinence in women: findings from a cohort study. J. Urol. 2011 Apr.;185(4):1331–1337.

144. Hannestad Y, Rortveit G, Sandvik H. ScienceDirect - Journal of Clinical Epidemiology : A community-based epidemiological survey of female urinary incontinence:: The Norwegian EPINCONT Study. Journal of Clinical …. 2000.

145. Grodstein F, Fretts R, Lifford K, Resnick N, Curhan G. Association of age, race, and obstetric history with urinary symptoms among women in the Nurses' Health Study. Am. J. Obstet. Gynecol. 2003 Aug.;189(2):428–434.

146. Mishra GD, Cardozo L, Kuh D. Menopausal transition and the risk of urinary incontinence: results from a British prospective cohort. BJU Int. 2010 Oct.;106(8):1170–1175.

147. Simeonova Z, Milsom I, Kullendorff AM, Molander U, Bengtsson C. The prevalence of urinary incontinence and its influence on the quality of life in women from an urban Swedish population. Acta Obstet Gynecol Scand. 1999 Jul.;78(6):546–551.

148. Sgadari A, Topinková E, Bjørnson J, Bernabei R. Urinary incontinence in nursing home residents: a cross-national comparison. Age Ageing. 1997 Sep.;26 Suppl 2:49–54.

149. Offermans MPW, Moulin Du MFMT, Hamers JPH, Dassen T, Halfens RJG. Prevalence of urinary incontinence and associated risk factors in nursing home residents: a systematic review. Neurourol. Urodyn. 2009;28(4):288–294.

150. Adelmann PK. Prevalence and detection of urinary incontinence among older Medicaid recipients. J Health Care Poor Underserved. 2004 Feb.;15(1):99–112.

151. Holroyd-Leduc JM, Mehta KM, Covinsky KE. Urinary incontinence and its association with death, nursing home admission, and functional decline. J Am Geriatr Soc. 2004 May;52(5):712–718.

152. Waetjen LE, Ye J, Feng W-Y, Johnson WO, Greendale GA, Sampselle CM, et al. Association between menopausal transition stages and developing urinary incontinence. Obstet Gynecol. 2009 Nov.;114(5):989–998.

153. Jahanlu D, Hunskaar S. Type and severity of new-onset urinary incontinence in middle-aged women: the Hordaland Women's Cohort. Neurourol. Urodyn. 2011 Jan.;30(1):87–92.

154. Hunskaar S. A systematic review of overweight and obesity as risk factors and targets for clinical intervention for urinary incontinence in women. Neurourol. Urodyn. 2008;27(8):749–757.

155. Subak LL, Richter HE, Hunskaar S. Obesity and urinary incontinence: epidemiology and clinical research update. J. Urol. 2009 Dec.;182(6 Suppl):S2–7.

156. Danforth KN, Townsend MK, Lifford K, Curhan GC, Resnick NM, Grodstein F. Risk factors for urinary incontinence among middle-aged women. Am. J. Obstet. Gynecol. 2006 Feb.;194(2):339–345.

157. Chiarelli P, Brown W, McElduff P. Leaking urine: prevalence and associated factors in Australian women. Neurourol. Urodyn. 1999;18(6):567–577.

158. Brown JS, Grady D, Ouslander JG, Herzog AR, Varner RE, Posner SF. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estrogen/Progestin Replacement Study (HERS) Research Group. Obstet Gynecol. 1999 Jul.;94(1):66–70.

159. Kuh D, Cardozo L, Hardy R. Urinary incontinence in middle aged women: childhood enuresis and other lifetime risk factors in a British prospective cohort. J Epidemiol Community Health. 1999 Aug.;53(8):453–458.

160. Hannestad YS, Rortveit G, Daltveit AK, Hunskaar S. Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. BJOG: An International Journal of Obstetrics & Gynaecology. 2003 Mar.;110(3):247–254.

161. Mishra GD, Hardy R, Cardozo L, Kuh D. Body weight through adult life and risk of urinary incontinence in middle-aged women: results from a British prospective cohort. Int J Obes (Lond). 2008 Sep.;32(9):1415–1422.

162. Townsend MK, Danforth KN, Rosner B, Curhan GC, Resnick NM, Grodstein F. Body mass index, weight gain, and incident urinary incontinence in middle-aged women. Obstet Gynecol. 2007 Aug.;110(2 Pt 1):346–353.

163. Bump RC, Sugerman HJ, Fantl JA, McClish DK. Obesity and lower urinary tract function in women: effect of surgically induced weight loss. Am. J. Obstet. Gynecol. 1992 Aug.;167(2):392–7; discussion 397–9.

164. Richter HE, Creasman JM, Myers DL, Wheeler TL, Burgio KL, Subak LL, et al. Urodynamic characterization of obese women with urinary incontinence undergoing a weight loss program: the Program to Reduce Incontinence by Diet and Exercise (PRIDE) trial. Int Urogynecol J. 2008 Aug. 5;19(12):1653–1658.

165. Tai H-C, Chung S-D, Ho C-H, Tai T-Y, Yang W-S, Tseng C-H, et al. Metabolic syndrome components worsen lower urinary tract symptoms in women with type 2 diabetes. J. Clin. Endocrinol. Metab. 2010 Mar.;95(3):1143–1150.

166. Uzun H, Zorba OU. Metabolic Syndrome in Female Patients With Overactive Bladder. Urology. 2011 Oct. 17.

167. Kirby MG, Wagg A, Cardozo L, Chapple C, Castro-Diaz D, De Ridder D, et al. Overactive bladder: Is there a link to the metabolic syndrome in men? Neurourol. Urodyn. 2010;29(8):1360–1364.

168. Kupelian V, McVary KT, Barry MJ, Link CL, Rosen RC, Aiyer, L. P., et al. Association of C-reactive Protein and Lower Urinary Tract Symptoms in Men and Women: Results From Boston Area Community Health Survey. Urology. 2009;73(5):950–957.

169. Link CL, Steers WD, Kusek JW, McKinlay JB. The association of adiposity and overactive bladder appears to differ by gender: results from the Boston Area Community Health survey. J. Urol. 2011 Mar.;185(3):955–963.

170. Kim I-H, Chun H, Kwon J-W. Gender differences in the effect of obesity on chronic diseases among the elderly Koreans. J. Korean Med. Sci. 2011 Feb.;26(2):250–257.

171. Subak LL, Whitcomb E, Shen H, Saxton J, Vittinghoff E, Brown JS. Weight loss: a novel and effective treatment for urinary incontinence. JURO. 2005 Jul.;174(1):190–195.

172. Subak LL, Wing R, West DS, Franklin F, Vittinghoff E, Creasman JM, et al. Weight loss to treat urinary incontinence in overweight and obese women. N. Engl. J. Med. 2009 Jan. 29;360(5):481–490.

173. Wing RR, West DS, Grady D, Creasman JM, Richter HE, Myers D, et al. Effect of weight loss on urinary incontinence in overweight and obese women: results at 12 and 18 months. J. Urol. 2010 Sep.;184(3):1005–1010.

174. Auwad W, Steggles P, Bombieri L, Waterfield M, Wilkin T, Freeman R. Moderate weight loss in obese women with urinary incontinence: a prospective longitudinal study. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Sep.;19(9):1251–1259.

175. Thomas TM, Plymat KR, Blannin J, Meade TW. Prevalence of urinary incontinence. Br Med J. 1980 Nov. 8;281(6250):1243–1245.

176. Holst K, Wilson PD. The prevalence of female urinary incontinence and reasons for not seeking treatment. N. Z. Med. J. 1988 Nov. 9;101(857):756–758.

177. Højberg KE, Salvig JD, Winsløw NA, Lose G, Secher NJ. Urinary incontinence: prevalence and risk factors at 16 weeks of gestation. Br J Obstet Gynaecol. 1999 Aug.;106(8):842–850.

178. Rortveit G, Hannestad YS, Daltveit AK, Hunskaar S. Age- and type-dependent effects of parity on urinary incontinence: the Norwegian EPINCONT study. Obstet Gynecol. 2001 Dec.;98(6):1004–1010.

179. Connolly TJ, Litman HJ, Tennstedt SL, Link CL, McKinlay JB. The effect of mode of delivery, parity, and birth weight on risk of urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Sep.;18(9):1033–1042.

180. Miller YD, Brown WJ, Russell A, Chiarelli P. Urinary incontinence across the lifespan. Neurourol. Urodyn. 2003;22(6):550–557.

181. Lukacz ES, Lawrence JM, Contreras R, Nager CW, Luber KM. Parity, mode of delivery, and pelvic floor disorders. Obstet Gynecol. 2006 Jun.;107(6):1253–1260.

182. Hirsch AG, Minassian VA, Dilley A, Sartorius J, Stewart WF. Parity is not associated with urgency with or without urinary incontinence. Int Urogynecol J. 2010 Sep.;21(9):1095–1102.

183. Press JZ, Klein MC, Kaczorowski J, Liston RM, Dadelszen von P. Does cesarean section reduce postpartum urinary incontinence? A systematic review. Birth. 2007 Sep.;34(3):228–237.

184. MacLennan AH, Taylor AW, Wilson DH, Wilson D. The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery. BJOG: An International Journal of Obstetrics & Gynaecology. 2000 Dec.;107(12):1460–1470.

185. Melville JL, Katon W, Delaney K, Newton K. Urinary incontinence in US women: a population-based study. Arch. Intern. Med. 2005 Mar. 14;165(5):537–542.

186. Rortveit G, Daltveit AK, Hannestad YS, Hunskaar S, Norwegian EPINCONT Study. Urinary incontinence after vaginal delivery or cesarean section. N. Engl. J. Med. 2003 Mar. 6;348(10):900–907.

187. Peyrat L, Haillot O, Bruyere F, Boutin JM, Bertrand P, Lanson Y. Prevalence and risk factors of urinary incontinence in young and middle-aged women. BJU Int. 2002 Jan.;89(1):61–66.

188. MacArthur C, Glazener C, Lancashire R, Herbison P, Wilson D, ProLong study group. Exclusive caesarean section delivery and subsequent urinary and faecal incontinence: a 12-year longitudinal study. BJOG: An International Journal of Obstetrics & Gynaecology. 2011 Jul.;118(8):1001–1007.

189. Viktrup L, Rortveit G, Lose G. Risk of stress urinary incontinence twelve years after the first pregnancy and delivery. Obstet Gynecol. 2006 Aug.;108(2):248–254.

190. Altman D, Ekström A, Gustafsson C, López A, Falconer C, Zetterström J. Risk of urinary incontinence after childbirth: a 10-year prospective cohort study. Obstet Gynecol. 2006 Oct.;108(4):873–878.

191. Gyhagen M, Bullarbo M, Nielsen TF, Milsom I. The prevalence of urinary incontinence 20 years after child birth: a national cohort study in singleton primiparae after vaginal or caesarean delivery. BJOG. 2012 Mar 14. doi: 10.1111/j.1471-0528.2012.03301.x. [Epub ahead of print].

192. Hannah ME, Whyte H, Hannah WJ, Hewson S, Amankwah K, Cheng M, et al. Maternal outcomes at 2 years after planned cesarean section versus planned vaginal birth for breech presentation at term: the international randomized Term Breech Trial. Am. J. Obstet. Gynecol. 2004 Sep.;191(3):917–927.

193. Thom DH, Rortveit G. Prevalence of postpartum urinary incontinence: a systematic review. Acta Obstet Gynecol Scand. 2010 Dec.;89(12):1511–1522.

194. Chaliha C, Kalia V, Stanton SL, Monga A, Sultan AH. Antenatal prediction of postpartum urinary and fecal incontinence. Obstet Gynecol. 1999 Nov.;94(5 Pt 1):689–694.

195. Eason E, Labrecque M, Marcoux S, Mondor M. Effects of carrying a pregnancy and of method of delivery on urinary incontinence: a prospective cohort study. BMC Pregnancy Childbirth. 2004 Feb. 19;4(1):4.

196. Eftekhar T, Hajibaratali B, Ramezanzadeh F, Shariat M. Postpartum evaluation of stress urinary inconti-

nence among primiparas. Int J Gynaecol Obstet. 2006 Aug.;94(2):114–118.

197. Ekström A, Altman D, Wiklund I, Larsson C, Andolf E. Planned cesarean section versus planned vaginal delivery: comparison of lower urinary tract symptoms. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Apr.;19(4):459–465.

198. Pregazzi R, Sartore A, Troiano L, Grimaldi E, Bortoli P, Siracusano S, et al. Postpartum urinary symptoms: prevalence and risk factors. Eur. J. Obstet. Gynecol. Reprod. Biol. 2002 Jul. 10;103(2):179–182.

199. Farrell SA, Allen VM, Baskett TF. Parturition and urinary incontinence in primiparas. Obstet Gynecol. 2001 Mar.;97(3):350–356.

200. Groutz A, Rimon E, Peled S, Gold R, Pauzner D, Lessing JB, et al. Cesarean section: does it really prevent the development of postpartum stress urinary incontinence? A prospective study of 363 women one year after their first delivery. Neurourol. Urodyn. 2004;23(1):2–6.

201. Glazener CMA, Herbison GP, MacArthur C, Lancashire R, McGee MA, Grant AM, et al. New postnatal urinary incontinence: obstetric and other risk factors in primiparae. BJOG: An International Journal of Obstetrics & Gynaecology. 2006 Feb.;113(2):208–217.

202. Schytt E, Lindmark G, Waldenström U. Physical symptoms after childbirth: prevalence and associations with self-rated health. BJOG: An International Journal of Obstetrics & Gynaecology. 2005 Feb.;112(2):210–217.

203. Borello-France D, Burgio KL, Richter HE, Zyczynski H, FitzGerald MP, Whitehead W, et al. Fecal and urinary incontinence in primiparous women. Obstet Gynecol. 2006 Oct.;108(4):863–872.

204. Marshall K, Thompson KA, Walsh DM, Baxter GD. Incidence of urinary incontinence and constipation during pregnancy and postpartum: survey of current findings at the Rotunda Lying-In Hospital. Br J Obstet Gynaecol. 1998 Apr.;105(4):400–402.

205. Mørkved S, Bø K. Prevalence of urinary incontinence during pregnancy and postpartum. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(6):394–398.

206. Foldspang A, Hvidman L, Mommsen S, Nielsen JB. Risk of postpartum urinary incontinence associated with pregnancy and mode of delivery. Acta Obstet Gynecol Scand. 2004 Oct.;83(10):923–927.

207. Hvidman L, Foldspang A, Mommsen S, Nielsen JB. Postpartum urinary incontinence. Acta Obstet Gynecol Scand. 2003 Jun.;82(6):556–563.

208. Aslan E, Beji NK, Erkan HA, Yalcin O, Gungor F. The prevalence of and the related factors for urinary and fecal incontinence among older residing in nursing homes. J Clin Nurs. 2009 Dec.;18(23):3290–3298.

209. Yang X, Zhang HX, Yu HY, Gao XL, Yang HX, Dong Y. The prevalence of fecal incontinence and urinary incontinence in primiparous postpartum Chinese women. Eur. J. Obstet. Gynecol. Reprod. Biol. 2010 Oct.;152(2):214–217.

210. Carroli G, Mignini L. Episiotomy for vaginal birth. Cochrane Database Syst Rev. 2009;(1):CD000081.

211. MacArthur C, Glazener CMA, Wilson PD, Lancashire RJ, Herbison GP, Grant AM. Persistent urinary incontinence and delivery mode history: a six-year longitudinal study. BJOG: An International Journal of Obstetrics & Gynaecology. 2006 Feb.;113(2):218–224.

212. Brown SJ, Gartland D, Donath S, MacArthur C. Effects of prolonged second stage, method of birth, timing of caesarean section and other obstetric risk factors on postnatal urinary incontinence: an Australian nulliparous cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2011 Jul.;118(8):991–1000.

213. O'Mahony F, Hofmeyr GJ, Menon V. Choice of instruments for assisted vaginal delivery. Cochrane Database Syst Rev. 2010;(11):CD005455.

214. Rortveit G, Daltveit AK, Hannestad YS, Hunskaar S. Vaginal delivery parameters and urinary incontinence: the Norwegian EPINCONT study. Am. J. Obstet. Gynecol. 2003 Nov.;189(5):1268–1274.

215. Thom DH, van den Eeden SK, Brown JS. Evaluation of parturition and other reproductive variables as risk factors for urinary incontinence in later life. Obstet Gynecol. 1997 Dec.;90(6):983–989.

216. Thom DH, Brown JS, Schembri M, Ragins AI, Creasman JM, Van Den Eeden SK. Parturition events and risk of urinary incontinence in later life. Neurourol. Urodyn. 2011 Nov.;30(8):1456–1461.

217. Foldspang A, Mommsen S, Djurhuus JC. Prevalent urinary incontinence as a correlate of pregnancy, vaginal childbirth, and obstetric techniques. Am J Public Health. 1999 Feb.;89(2):209–212.

218. Persson J, Wolner-Hanssen P, Rydhstroem H. Obstetric risk factors for stress urinary incontinence: a population-based study. Obstet Gynecol. 2000 Sep.;96(3):440–445.

219. Rortveit G, Hunskaar S. Urinary incontinence and age at the first and last delivery: the Norwegian HUNT/EPINCONT study. Am. J. Obstet. Gynecol. 2006 Aug.;195(2):433–438.

220. Roe B, Doll H. Lifestyle factors and continence status: comparison of self-report data from a postal survey in England. J Wound Ostomy Continence Nurs. 1999 Nov.;26(6):312–3, 315–9.

221. Fenner DE, Trowbridge ER, Patel DA, Patel DL, Fultz NH, Miller JM, et al. Establishing the prevalence of incontinence study: racial differences in women's patterns of urinary incontinence. J. Urol. 2008 Apr.;179(4):1455–1460.

222. Townsend MK, Curhan GC, Resnick NM, Grodstein F. The incidence of urinary incontinence across Asian, black, and white women in the United States. Am. J. Obstet. Gynecol. 2010 Apr.;202(4):378.e1–7.

223. Fultz NH, Herzog AR, Raghunathan TE, Wallace RB, Diokno AC. Prevalence and severity of urinary incontinence in older African American and Caucasian women. J. Gerontol. A Biol. Sci. Med. Sci. 1999 Jun.;54(6):M299–303.

224. Nygaard I, Turvey C, Burns TL, Crischilles E, Wallace R. Urinary incontinence and depression in middle-aged United States women. Obstet Gynecol. 2003 Jan.;101(1):149–156.

225. Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. Obstet Gynecol. 2002 Dec.;100(6):1230–1238.

226. Anger JT, Saigal CS, Litwin MS, Urologic Diseases of America Project. The prevalence of urinary incontinence among community dwelling adult women: results from the National Health and Nutrition Examination Survey. JURO. 2006 Feb.;175(2):601–604.

227. Jackson RA, Vittinghoff E, Kanaya AM, Miles TP, Resnick HE, Kritchevsky SB, et al. Urinary incontinence in elderly women: findings from the Health, Aging, and Body Composition Study. Obstet Gynecol. 2004 Aug.;104(2):301–307.

228. Dooley Y, Kenton K, Cao G, Luke A, Durazo-Arvizu R, Kramer H, et al. Urinary incontinence prevalence: results from the National Health and Nutrition Examination Survey. J. Urol. 2008 Feb.;179(2):656–661.

229. Markland AD, Gerety MB, Goode PS, Kraus SR, Cornell J, Hazuda HP. Urinary incontinence in community-dwelling older Mexican American and European American women. Arch Gerontol Geriatr. 2009 Feb.;48(2):232–237.

230. Markland AD, Goode PS, Burgio KL, Redden DT, Richter HE, Sawyer P, et al. Correlates of urinary, fecal, and dual incontinence in older African-American and white men and women. J Am Geriatr Soc. 2008 Feb.;56(2):285–290.

231. Fantl JA, Cardozo L, McClish DK. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. First report of the Hormones and Urogenital Therapy Committee. Obstet Gynecol. 1994 Jan.;83(1):12–18.

232. Diokno AC, Brock BM, Herzog AR, Bromberg J. Medical correlates of urinary incontinence in the elderly. URL. 1990 Aug.;36(2):129–138.

233. Cody JD, Richardson K, Moehrer B, Hextall A, Glazener CM. Oestrogen therapy for urinary incontinence in postmenopausal women. Cochrane Database Syst Rev. 2009;(4):CD001405.

234. Grodstein F, Lifford K, Resnick NM, Curhan GC. Postmenopausal hormone therapy and risk of developing urinary incontinence. Obstet Gynecol. 2004 Feb.;103(2):254–260.

235. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T, et al. Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. Obstet Gynecol. 2001 Jan.;97(1):116–120.

236. Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesia C, et al. Effects of estrogen with and without progestin on urinary incontinence. JAMA. 2005 Feb. 23;293(8):935–948.

237. Goldstein SR, Johnson S, Watts NB, Ciaccia AV, Elmerick D, Muram D. Incidence of urinary incontinence in postmenopausal women treated with raloxifene or estrogen. Menopause. 2005 Mar.;12(2):160–164.

238. Albertazzi P, Sharma S. Urogenital effects of selective estrogen receptor modulators: a systematic review. Climacteric. 2005 Sep.;8(3):214–220.

239. Hsieh C-H, Chang W-C, Lin T-Y, Su T-H, Li Y-T, Kuo T-C, et al. Long-term effect of hysterectomy on urinary incontinence in Taiwan. Taiwanese Journal of Obstetrics & Gynecology. Elsevier Taiwan LLC; 2011 Sep. 1;50(3):326–330.

240. Moghaddas F, Lidfeldt J, Nerbrand C, Jernström H, Samsioe G. Prevalence of urinary incontinence in relation to self-reported depression, intake of serotonergic antidepressants, and hormone therapy in middle-aged women: a report from the Women's Health in the Lund Area study. Menopause. 2005 Apr.;12(3):318–324.

241. Forsgren C, Lundholm C, Johansson ALV, Cnattingius S, Zetterström J, Altman D. Vaginal hysterectomy and risk of pelvic organ prolapse and stress urinary incontinence surgery. Int Urogynecol J. 2011 Aug. 18.

242. Bhattacharya S, Middleton LJ, Tsourapas A, Lee AJ, Champaneria R, Daniels JP, et al. Hysterectomy, endometrial ablation and Mirena® for heavy menstrual bleeding: a systematic review of clinical effectiveness and cost-effectiveness analysis. Health Technol Assess. 2011 Apr.;15(19):iii–xvi, 1–252.

243. Heliövaara-Peippo S, Halmesmäki K, Hurskainen R, Teperi J, Grenman S, Kivelä A, et al. The effect of hysterectomy or levonorgestrel-releasing intrauterine system on lower urinary tract symptoms: a 10-year follow-up study of a randomised trial. BJOG: An International Journal of Obstetrics & Gynaecology. 2010 Apr.;117(5):602–609.

244. Arya LA, Myers DL, Jackson ND. Dietary caffeine intake and the risk for detrusor instability: a case-control study. Obstet Gynecol. 2000 Jul.;96(1):85–89.

245. Martins G, Soler ZASG, Cordeiro JA, Amaro JL, Moore KN. Prevalence and risk factors for urinary incontinence in healthy pregnant Brazilian women. Int Urogynecol J. 2010 Oct.;21(10):1271–1277.

246. Bortolotti A, Bernardini B, Colli E, Di Benedetto P, Giocoli Nacci G, Landoni M, et al. Prevalence and risk factors for urinary incontinence in Italy. Eur. Urol. 2000 Jan.;37(1):30–35.

247. Tettamanti G, Altman D, Pedersen NL, Bellocco R, Milsom I, Iliadou AN. Effects of coffee and tea consumption on urinary incontinence in female twins. BJOG: An International Journal of Obstetrics & Gynaecology. 2011 Jun.;118(7):806–813.

248. Jura YH, Townsend MK, Curhan GC, Resnick NM, Grodstein F. Caffeine intake, and the risk of stress, urgency and mixed urinary incontinence. J. Urol. 2011 May;185(5):1775–1780.

249. Schmidbauer J, Temml C, Schatzl G, Haidinger G, Madersbacher S. Risk factors for urinary incontinence in both sexes. Analysis of a health screening project. Eur. Urol. 2001 May;39(5):565–570.

250. Teleman PM, Lidfeldt J, Nerbrand C, Samsioe G, Mattiasson A, WHILA study group. Overactive bladder: prevalence, risk factors and relation to stress incontinence in middle-aged women. BJOG: An International Journal of Obstetrics & Gynaecology. 2004 Jun.;111(6):600–604.

251. Huang AJ, Brown JS, Kanaya AM, Creasman JM, Ragins AI, Van Den Eeden SK, et al. Quality-of-life impact and treatment of urinary incontinence in ethnically diverse older women. Arch. Intern. Med. 2006 Oct. 9;166(18):2000–2006.

252. Kraus SR, Markland A, Chai TC, Stoddard A, FitzGerald MP, Leng W, et al. Race and ethnicity do not contribute to differences in preoperative urinary incontinence severity or symptom bother in women who undergo stress incontinence surgery. Am. J. Obstet. Gynecol. 2007 Jul.;197(1):92.e1–6.

253. Saadoun K, Ringa V, Fritel X, Varnoux N, Zins M, Bréart G. Negative impact of urinary incontinence on quality of life, a cross-sectional study among women aged 49-61 years enrolled in the GAZEL cohort. Neurourol. Urodyn. 2006;25(7):696–702.

254. Roe B, Doll H. Prevalence of urinary incontinence and its relationship with health status. J Clin Nurs. 2000 Mar.;9(2):178–187.

255. Coyne KS, Kaplan SA, Chapple CR, Sexton CC, Kopp ZS, Bush EN, et al. Risk factors and comorbid conditions associated with lower urinary tract symptoms: EpiLUTS. BJU Int. 2009 Apr.;103 Suppl 3:24–32.

256. Kim H, Yoshida H, Hu X, Yukawa H, Shinkai S, Kumagai S, et al. [Risk factors associated with onset of urinary incontinence in a community-dwelling elderly population: a 4-year follow-up study]. Nihon Koshu Eisei Zasshi. 2004 Aug.;51(8):612–622.

257. Waetjen LE, Feng W-Y, Ye J, Johnson WO, Greendale GA, Sampselle CM, et al. Factors associated with worsening and improving urinary incontinence across the menopausal transition. Obstet Gynecol. 2008 Mar.;111(3):667–677.

258. Nygaard IE, Thompson FL, Svengalis SL, Albright JP. Urinary incontinence in elite nulliparous athletes. Obstet Gynecol. 1994 Aug.;84(2):183–187.

259. Simeone C, Moroni A, Pettenò A, Antonelli A, Zani D, Orizio C, et al. Occurrence rates and predictors of lower urinary tract symptoms and incontinence in female athletes. Urologia. 2010 Mar.;77(2):139–146.

260. Eliasson K, Larsson T, Mattsson E. Prevalence of stress incontinence in nulliparous elite trampolinists. Scand J Med Sci Sports. 2002 Apr.;12(2):106–110.

261. Eliasson K, Edner A, Mattsson E. Urinary incontinence in very young and mostly nulliparous women with a history of regular organised high-impact trampoline training: occurrence and risk factors. Int Urogynecol J Pelvic Floor Dysfunct. 2008 May;19(5):687–696.

262. Nygaard I, Girts T, Fultz NH, Kinchen K, Pohl G, Sternfeld B. Is urinary incontinence a barrier to exercise in women? Obstet Gynecol. 2005 Aug.;106(2):307–314.

263. Bø K, Mørkved S, Frawley H, Sherburn M. Evidence for benefit of transversus abdominis training alone or in combination with pelvic floor muscle training to treat female urinary incontinence: A systematic review. Neurourol. Urodyn. 2009;28(5):368–373.

264. Van Oyen H, Van Oyen P. Urinary incontinence in Belgium; prevalence, correlates and psychosocial consequences. Acta Clin Belg. 2002 Jun.;57(4):207–218.

265. Zhu L, Lang J, Wang H, Han S, Huang J. The prevalence of and potential risk factors for female urinary incontinence in Beijing, China. Menopause. 2008 May;15(3):566–569.

266. Eliasson K, Nordlander I, Larson B, Hammarström M, Mattsson E. Influence of physical activity on urinary leakage in primiparous women. Scand J Med Sci Sports. 2005 Apr.;15(2):87–94.

267. Danforth KN, Shah AD, Townsend MK, Lifford KL, Curhan GC, Resnick NM, et al. Physical activity and urinary incontinence among healthy, older women. Obstet Gynecol. 2007 Mar.;109(3):721–727.

268. McGrother CW, Donaldson MMK, Hayward T, Matthews R, Dallosso HM, Hyde C, et al. Urinary storage symptoms and comorbidities: a prospective population cohort study in middle-aged and older women. Age Ageing. 2006 Jan.;35(1):16–24.

269. Ebbesen MH, Hannestad YS, Midthjell K, Hunskaar S. Diabetes and urinary incontinence - prevalence data from Norway. Acta Obstet Gynecol Scand. 2007 Sep. 4;:1–7.

270. Ebbesen MH, Hannestad YS, Midthjell K, Hunskaar S. Diabetes related risk factors did not explain the increased risk for urinary incontinence among women with diabetes. The Norwegian HUNT/EPINCONT study. BMC Urol. 2009;9:11.

271. Sarma AV, Kanaya AM, Nyberg LM, Kusek JW, Vittinghoff E, Rutledge B, et al. Urinary incontinence among women with type 1 diabetes--how common is it? J. Urol. 2009 Mar.;181(3):1224–30; discussion 1230.

272. Brown JS, Vittinghoff E, Lin F, Nyberg LM, Kusek JW, Kanaya AM. Prevalence and risk factors for urinary incontinence in women with type 2 diabetes and impaired fasting glucose: findings from the National Health and Nutrition Examination Survey (NHANES) 2001-2002. Diabetes Care. 2006 Jun.;29(6):1307–1312.

273. Moore EE, Jackson SL, Boyko EJ, Scholes D, Fihn SD. Urinary incontinence and urinary tract infection: temporal relationships in postmenopausal women. Obstet Gynecol. 2008 Feb.;111(2 Pt 1):317–323.

274. Herzog AR, Fultz NH. Prevalence and incidence of urinary incontinence in community-dwelling populations. J Am Geriatr Soc. 1990 Mar.;38(3):273–281.

275. Brown J, Grady D, Ouslander J. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estyrogen/Progestin Replacement Study (HERS) Research group. Obstet Gynecol 1999;94:66-70.

276. Caljouw MAA, Elzen den WPJ, Cools HJM, Gussekloo J. Predictive factors of urinary tract infections among the oldest old in the general population. A population-based prospective follow-up study. BMC Med. 2011;9:57.

277. Ouslander JG, Uman GC, Urman HN, Rubenstein LZ. Incontinence among nursing home patients: clinical and functional correlates. J Am Geriatr Soc. 1987 Apr.;35(4):324–330.

278. Østbye T, Borrie MJ, Hunskaar S. The prevalence of urinary incontinence in elderly Canadians and its association with dementia, ambulatory function, and institutionalization. Norsk epidemiologi. 2009;8(2).

279. Huang AJ, Brown JS, Thom DH, Fink HA, Yaffe K, Study of Osteoporotic Fractures Research Group. Urinary incontinence in older community-dwelling women: the role of cognitive and physical function decline. Obstet Gynecol. 2007 Apr.;109(4):909–916.

280. Thom D, Haan M, van den Eeden S. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. Age Ageing. 1997;26:367–374.

281. Pinner G, Johnson H, Bouman WP, Isaacs J. Psychiatric manifestations of normal-pressure hydrocephalus: a short review and unusual case. Int Psychogeriatr. 1997 Dec.;9(4):465–470.

282. Akiguchi I, Ishii M, Watanabe Y, Watanabe T, Kawasaki T, Yagi H, et al. Shunt-responsive parkinsonism and reversible white matter lesions in patients with idiopathic NPH. J. Neurol. 2008 Sep.;255(9):1392–1399.

283. Palmer MH, Hardin SR, Behrend C, Collins SK-R, Madigan CK, Carlson JR. Urinary incontinence and overactive bladder in patients with heart failure. J. Urol. 2009 Jul.;182(1):196–202.

284. Ekundayo OJ, Markland A, Lefante C, Sui X, Goode PS, Allman RM, et al. Association of diuretic use and overactive bladder syndrome in older adults: a propensity score analysis. Arch Gerontol Geriatr. 2009 Jun.;49(1):64–68.

285. Nuotio M, Jylhä M, Luukkaala T, Tammela TLJ. Urinary incontinence in a Finnish population aged 70 and over. Prevalence of types, associated factors and self-reported treatments. Scand J Prim Health Care. 2003 Sep.;21(3):182–187.

286. Thom D. : Variations in estimated of urinary incontinence prevalence in the community: Effects of Differences in Definitions, Population Characteristics, and Study Type. J. Amer Geriatrics Society, 46: 473, 1998.

287. Koyama W, Koyanagi A, Mihara S, Kawazu S, Uemura T, Nakano H et al. : Prevalence and conditions or urinary incontinenc among the elderly. Methods Inf Med, 37: 151, 1998.

288. Boyle P, Boyle P, Robertson C, Mazzetta C, Keech M, Hobbs FD, Fourcade R, Kiemeney L, Lee C; The UrEpik Study Group. : The prevalence of male urinary incontinence in four centres: the UREPIK study. BJU Int., 92 : 943, 2003.

289. Engstrom G, Walker-Engstrom ML, Loof L, Leppert J. : Prevalence of three lower urinary tract symptoms in men - a population-based study. Fam Pract, 20 : 7, 2003 .

290. Van Oyen H, Van Oyen P.: Urinary incontinence in Belgium; prevalence, correlates and psychosocial consequences. Acta Clin Belg., 57: 207, 2002.

291. Schmidbauer J, Temml C, Schatzl G, Haidinger G, Madersbacher S.: Risk factors for urinary incontinence in both sexes. Analysis of a health screening project. Eur Urol., 39: 565, 2001.

292. Maral I, Ozkardes H, Peskircioglu L, and Bumin MA. : Prevalence of stress urinary incontinence in both sexes at or after age 15 years: a cross-sectional study. J Urol., 165: 408, 2001.

293. Bortolotti A., Bernardini B., Colli, E., Dibendetto, P., Nacci, G.G., Landoni, M. et al : Prevalence and risk factors for urinary incontinence in Italy. Eur. Urol., 37: 30, 2000.

294. Smoger SH, Felice TL, and Kloecker GH. : Urinary incontinence among male veterans receiving care in primary care clinics. Ann Intern Med., 132: 547, 2000.

295. Ueda T, Tamaki M, Kageyama S, Yoshimura N, and Yoshida O. : Urinary incontinence among community-dwelling people aged 40 years or older in Japan: prevalence, risk factors, knowledge and self-perception. Int J Urol., 7: 95, 2000.

296. Roberts RO, Jacobsen SJ, Reilly WT, Pemberton JH, Lieber MM, and Talley NJ.: Prevalence of combined fecal and urinary incontinence: a community-based study. J Am Geriatr Soc., 47: 837, 1999.

297. Roberts RO, Jacobsen SJ, Rhodes T, Reilly WT, Girman CJ, Talley NJ, and Lieber MM. : Urinary incontinence in a community-based cohort: prevalence and healthcare-seeking. J Am Geriatr Soc., 46: 467,1998.

298. Schulman C, Claesm H, and Mattijs J: Urinary incontience in Belgium: a population-based epidemiological survey. Eur. Urol., 32: 315, 1997.

299. Malmsten UG, Milsom I, Molander U, and Norlen LJ.: Urinary incontinence and lower urinary tract symptoms: an epidemiological study of men aged 45-99 years. J Urol., 158: 1733, 1997.

300. Brocklehurst JC. Urinary incontinence in the community – analysis of a MORI poll. BMJ 306: 832-4, 1993.

301. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al., Population-based survey of urinary incontinence, overactive bladder and other lower urinary tract symptoms in five countries : Results of the EPIC study. Eur Urol 50m 1306-15, 2006.

302. Lagace EA, Hansen W, and Hickner JM. Prevalence and severity of urinary incontinence in ambulatory adults : an UPRNet study. J fam Pract 36(6): 610-5, 1993.

303. McGrother CW, Donaldson MMK, Shaw C, Matthews RJ, Hayward TA, Dallosso HM, Jagger c, et al. Storage symptoms of the bladder : prevalence, incidence and need for services in the UK. BJU Int 93: 763-69, 2004.

304. O Brien J, Austin M, Sethi P, and O'Boyle P : Urinary incontinence : prevalence , need for treatment, and effectiveness of intervention by nurse. BMJ, 303: 1308-12, 1991.

305. Parrazzini F, Lavezzari M, and Artibani W. Prevalence of overactive bladder and urinary incontinence. J Fam Pract 5:1072-4, 2002.

306. Roe B. Prevalence of urinary incontinence and its relationship with health status. J Clin Nursing 9: 178-88, 2000.

307. Markland AD, Richter HE, Fwu CW, Eggers P, Kusek JW. Prevalence and trends of urinary incontinence in adults in the United States,2001 to 2008.J urol 2011 Aug; 186(2): 589-93

308. Markland AD, Goode PS, Redden DT, Borrud LG, Burgio KL. Prevalence of urinary incontinence in men: results from the national health and nutrition examination survey. J Urol 2010 Sep; 184(3):1022-7

309. de Souza Santos CR, Santos VL. Prevalence of urinary incontinence in a random sample of the urban population of Pouso Alegre, Minas Gerais, Brazil.Rev Lat Am Enfermagem. 2010 Sep-Oct;18(5):903-10

310. Finkelstein MM. Medical conditions, medications and urinary incontinence. Analysis of a population-based survey. Can Fam Physician 2001; 48:96-101

311. Diokno AC, Estanol MVC, Ibrahim IA, and Balasubamanian M. Prevalence of urinary incontiennce in community dwelling men : a cross sectional nationwide epidemiology survey. Int Urol Nephrol 39: 129-36, 2007.

312. Lee YS, Lee KS, Jung JH, Han DH, Oh SJ, Seo JT, Lee JG, Park HS, Choo MS Prevalence of overactive bladder, urinary incontinence, and lower urinary tract symptoms: results of Korean EPIC study.World J Urol 2011 Apr; 29(2): 185-90

313. Espuña-Pons M, Brugulat Guiteras P, Costa Sampere D, Medina Bustos A, Mompar. Prevalence of urinary incontinence in Catalonia, Spain. Penina A. Med Clin (Barc). 2009 Nov 14;133(18):702-5

314. Diokno, A.C., Brock, B.M., Brown, M.B., and Herzog, R. : Prevalence of urinary incontinence and other urological symptoms in the non-institutionalized elderly. J. Urol., 136: 1022, 1986.

315. Dios-Diz JM, Rodriguez-Lama M, Martinez-Calvo JR, Rodriguez-Perez C, Melero-Brezo M, Garcia-Cepeda JR. : [Prevalence of urinary incontinence in the population aged more than 64 years in Galicia, Spain]. Gac Sanit, 17 : 409, 2003.

316. Stoddart H, Donovan J, Whitley E, Sharp D, and Harvey I. : Urinary incontinence in older people in the community: a neglected problem? Br J Gen Pract., 51: 548, 2001.

317. Aggazzotti G, Pesce F, Grassi D, Fantuzzi G, Righi E, De Vita D, Santacroce S., and Artibani W.: Prevalence of urinary incontinence among institutionalized patients: a cross-sectional epidemiologic study in a midsized city in northern Italy. Urology, 56: 245, 2000.

318. Gavira Iglesias FJ, Caridad y Ocerin JM, Perez del Molino Martin J, Valderrama Gama E, Lopez Perez M, Romero Lopez M, et al. : Prevalence and psychosocial impact of urinary incontinence in older people of a Spanish rural population. J Gerontol A Biol Sci Med Sci., 55 : M207, 2000.

319. Damian J., Martin-Moreno, J.M., Lobo F., Bonache J., Cervino J., Redondo-Marquez, L., et al.: Prevalence of urinary incontinence among Spanish older people living at home. Eur. Urol., 34: 333, 1998.

320. Umlauf MG, AND Sherman SM.: Symptoms of urinary incontinence among older community-dwelling men.J Wound Ostomy Continence Nurs., 23: 314, 1996.

321. Nuotio M, Jylha M, Luukkaala T, and Tammela TL. : Urinary incontinence in a Finnish population aged 70 and over. Prevalence of types, associated factors and self-reported treatments. Scand J Prim Health Care., 21: 182, 2003.

322. Herzog, AR and Fultz NH.: Epidemiology of urinary incontinence: prevalence, incidence and correlates in community populations. Urology Suppl., 36: 2, 1990.

323. Janssen I. Morbidity and mortality risk associated with an overweight BMI in older women and women. Obesity 17: 1827-80, 2007.

324. Landi F, Cesari M, Russo A, Onder G, Lattansio F, Bernabe R, Silvernet-HC Study group. Potentially reversible risk factors and urinary incontinence in frail older people living in community. Age and Ageing 32: 194-9, 2003.

325. Thom C, Haan MN, and Van Den Eeden SK. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. Age and Ageing 26(5) : 367-9,1997.

326. Kwong PW, Cumming RG, Chan L, Seibel MJ, Naganathan V, Creasey H, Le Couteur D, Waite LM, Sambrook PN, Handelsman D. Urinary incontinence and quality of life among older community-dwelling Australian men: the CHAMP study.Age Ageing. 2010 May;39(3):349-54

327. Smith AL, Wang PC, Anger JT, Mangione CM, Trejo L, Rodríguez LV, Sarkisian CA. Correlates of urinary incontinence in community-dwelling older Latinos. J Am Geriatr Soc 2010 Jun; 58(6):1170-6

328. Yu PL. Shi J, Liu XR, Xia CW, Liu DF, Wu ZL, Sun ZQ. Zhonghua Liu Xing Bing Xue Za Zhi. 2009 Aug;30(8):766-71

329. Yarnell JW, and St Lege AS.: The prevalence, severity and factors associated with urinary incontinence in a random sample of the elderly. Age Ageing, 8: 81, 1979.

330. Thomas TM, Plymat KR, Blannin J and Meade TW: Prevalence of urinary incontinence. BMJ., 281:1243, 1980.

331. Temml, C., Haidinger, G., Schmidbauer, J., Schatzl, G., and Madershbacher, S.: Urinary incontinence in both sexes: Prevalence rates and impact on quality of life and sexual life. Nuerourol. Urodyn., 19: 259, 2000.

332. Marriapan P and Chong WL. Prevalence and correlations of lower urinary tract symptoms, erectile dysfunction and incontinence in men from a multiethnic Asian population : results of a regional population-based survey and comparison with industrialized nations. BJU Int 98: 1264-8, 2006.

333. Shamliyan TA, Wyman JF, Ping R, Wilt TJ, Kane RL. Male urinary incontinence: prevalence, risk factors, and preventive interventions. Rev Urol 2009 Summer ; 11(3): 145-65

334. Chaojie L, and Andrews GR. Prevalence and incidence of urinary incontinence in the elderly : a longitudinal study in South Australia. Chinese Med J 115(1) : 119-22, 2002.

335. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, Coyne K, Kelleher C, Hampel C, Artibani W, Abrams P. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 50 (6), 1306-14, Dec 2006.

336. Herschorn A, Gajewski J, Schulz J, and Corcos J : A population-based study of urinary symptoms and incontninence : the Canadian urinary bladder survey. BJU Int 101: 52-8, 2007.

337. Sladden MJ, Hughes AM, Hirst GH, and Ward JE.: A community study of lower urinary tract symptoms in older men in Sydney, Australia. Aust N.Z. J. Surg, 70: 322, 2000.

338. Muscatello DJ, Rissel C, and Szonyi G. Urinary symptoms and incontinence in an urban community prevalence and associated factors in older men and women. Int Med J 31:151-160, 2001.

339. Nelson RL, and Furner SE. Risk factors for the development of fecal and urinary incontinence in Winconsin nursing home residents. Maturitas 52: 26-31, 2005.

340. Kikuchi A, Niu K, Ikeda Y, Hozawa A, Nakagawa H, Guo H, Ohmori-Marsuda K, et al. Association between physical activity and urinary incontinence in a community-based elderly population aged 70 years and over. Eur Urol 52: 868-75, 2007.

341. Resnick NM and Yalla SV.: Detrusor hyperactivity with impaired contractile function : an unrecognized but common cause of incontinence in elderly patients. JAMA., 257: 3076, 1987.

342. Patel M, Coshall C, Rudd AG, and Wolfe CD.: Natural history and effects on 2-year outcomes of urinary incontinence after stroke. Stroke, 32 (1): 122-7, 2001.

343. Hunskaar S.: One hundred and fifty men with urinary incontinence. I. Demography and medical history. Scan. J. Prim. Health Care, 10: 21, 1992.

344. Malmsten UG, Molander U, Peeker R, Irwin DE, Milsom I. Urinary incontinence, overactive bladder, and other lower urinary tract symptoms: a longitudinal population-based survey in men aged 45-103 years.Eur Urol 2010 Jul 58(1): 149-56

345. Diokno A, Brock B, Hersog A, and Bromberg J: Medical correlates of urinary incontinence in the elderly. Urology, 36: 129, 1990.

346. van Melick HH, van Venrooij GE, Eckhardt MD, and Boon TA.: A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: analysis of subjective changes, morbidity and mortality. J Urol., 169: 1411, 2003.

347. Demirkesen O, Onal B, Tunc B, Alici B, Onder AU, Ozalp AU, Cetinel B.. Assessment of the continence status and patients' satisfaction after retropubic radical prostatectomy: a questionnaire based study. Int Urol Nephrol. 39(2):531-6, 2007.

348. Kundu SD, Roehl KA, Eggender SE, Antenor JV, Han M and Catalona WJ. Potency, continence and complications in 3477 consecutive radical retropubic prostatectomies. J Urol 172: 2227-2231, dec 2004.

349. Salomon L, Saint F, Anastasiadis AG, Sebe P, Chopin D, Abbou CC.: Combined reporting of cancer control and functional results of radical prostatectomy. Eur Urol., 44: 656, 2003

350. Moinzadeh A, Shunaigat AN, and Libertino JA.: Urinary incontinence after radical retropubic prostatectomy: the outcome of a surgical technique. BJU Int., 92: 355, 2003.

351. Maffezzini M, Seveso M, Taverna G, Giusti G, Benetti A, and Graziotti P.: Evaluation of complications and results in a contemporary series of 300 consecutive radical retropubic prostatectomies with the anatomic approach at a single institution. Urology, 61: 982, 2003.

352. Deliveliotis C, Protogerou V, Alargof E, and Varkarakis J.: Radical prostatectomy: bladder neck preservation and puboprostatic ligament sparing--effects on continence and positive margins. Urology, 60: 855, 2002.

353. Benoit RM, Naslund MJ, and Cohen JK.: Complications after radical retropubic prostatectomy in the medicare population. Urology, 56: 116, 2000.

354. Walsh PC, Marschke P, Ricker D and Burnett AL.: Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology, 55: 58, 2000.

355. Poon M, Ruckle H, Bamshad DBR, Rsai C, Webster R, and Lui P.: Radical retropubic prostatectomy : bladder neck preservation versus reconstruction. J. Urol., 163: 194, 2000.

356. Catalona WJ, Carvalhal GF, Mager DE, and Smith DS.: Potency, continence and complication rates in 19870 consecutive radical retropubic prostatectomies. J. Urol., 162: 433, 1999.

357. Horie S, Tobisu KI, Fujimoto H, Doi N. and Kakizoe T.: Urinary incontinence after non-nervesparing radical prostatectomy with neoadjuvant androgen deprivation. Urology, 53: 561, 1999.

358. Goluboff ET, Saidi JA, Mazer S, Bagiella E, Heitjan DF, Benson MC. Et. Al.: Urinary continence after radical prostatectomy: The Columbia experience. J. Urol., 159: 1276, 1998.

359. Weldon VE, Tavel FR, and Neuwirth H. : Continence, potency and morbidity after radical perineal prostatectomy. J Urol., 158: 1470, 1997.

360. Lowe BA. : Comparison of bladder neck preservation to bladder neck resection in maintaining postprostatectomy urinary incontinence. Urology, 48: 889, 1996.

361. Hu JC, Gold KF, Pashos CL, Mehta SS, and Litwin MS.: Temporal trends in radical prostatectomy complications from 1991 to 1998. J Urol, 169: 1443, 2003.

362. Augustin H, Pummer K, Daghofer F, Habermann H, Primus G, and Hubmer G. : Patient self-reporting questionnaire on urological morbidity and bother after radical retropubic prostatectomy. Eur Urol., 42: 112, 2002.

363. Sebesta M, Cespedes RD, Luhman E, Optenberg S, and Thompson IM.: Questionnaire-based outcomes of urinary incontinence and satisfaction rates after radical prostatectomy in a national study population. Urology, 60: 1055, 2002.

364. Potosky, A.L., Legler, J., Albertsen, P.C., Stanford, J.L., Gilliland, F.D., Hamilton, A.S., Eley, J.W., Stephenson, R.A., Harlan, L.C.: Health outcomes after prostatectomy or radiotherapy for prostate cancer : results from the Prostate Cancer Outcomes Study. J Natl Cancer Inst, 92: 1582, 2000.

365. Arai Y, Okubo K, Aoki Y, Maekawa S, Okada T, Maeda H, Ogawa O, and Kato T. : Patient-reported quality of life after radical prostatectomy for prostate cancer. Int J Urol., 6: 78, 1999.

366. Bishoff JT, Motley G., Optenberg SA, Stein CR, Moon KA, Browning SM. Et al.: Incidence of fecal and urinary incontinence following radical perineal and retropubic prostatectomy in a national population. J. Urol., 160: 454, 1998.

367. Egawa S, Minei S, Iwamura M, Uchida T, and Koshiba K. : Urinary continence following radical prostatectomy. Jpn J Clin Oncol., 27: 71, 1997.

368. Gray M, Petroni GR, and Theodorescu D.: Urinary function after radical prostatectomy: a comparison of the retropubic and perineal approaches. Urology, 53: 881, 1999.

369. Olsson LE, Salomon L, Nadu A, Hoznek A, Cicco A, Saint F, Chopin D, and Abbou CC. : Prospective patient-reported continence after laparoscopic radical prostatectomy. Urology, 58: 570, 2001.

370. LaFontaine P, Chan D, Partin AW, Gurganus R, Hortopan SC, and Marshall FF. : Minilaparotomy radical retropubic prostatectomy: updated technique and results. Semin Urol Oncol., 18: 19, 2000.

371. Galli S, Simonato A, Bozzola A, Gregori A, Lissiani A, Scaburri A, Gabardi F. Oncologic outcome and continence revcovery after laparoscopic radical prostatectomy: 3 years' follow-up in a "second generation center'. Eur Urol 49 : 859-865, 2006.

372. McKammon KA, Kolm P, Main B, and Schellhammer PF: Comparative quality of life analysis after radical retropubic prostatectomy: objective and subjective analysis. Urology, 49: 225, 1997.

373. Donnellan SM, Duncan HJ., MacGregor RJ., and Russel, JM. : Prospectiveassessment of incontinence after radical retropubic prostatectomy: objective and subjective analysis. Urology 49: 225, 1997.

374. Ojdeby G, Claezon A, Brekkan E, Haggman M, and Norlen BJ: Urinary incontinence and sexual impotence after radical prostatectomy. Scand. J. Urol. Nephrol., 30: 473, 1996.

375. Saranchuk JW, Kattan MW, Elkin E, Taurier K, Scardino PT, and Eastham, JA. Achieving optimal outcomes after radical prostatectomy. J Clin Oncol 23 (18) : 4146-51, June 2005.

376. Harris MJ. The anatomic radical perineal prostatectomy : An outcomes-based evolution. Eur Urol 52 : 81-88, 2007.

377. Jaconsen NB, Moore KN, Estey E, and Voaklander D. Open versus laparoscopic radical prostatectomy : A prostective comparison of postoperative urinary incontinence rates. J Urol, 177 : 615-619, Feb 2007.

378. Link RE, Su LM, Sullivan W, Bhayani S, and Pavlovich CP. Health related quality of life before and after laparoscopic radical prostatectomy. J Urol 173 : 173-9, January 2005.

379. Jonler M, Madsen FA, Rhodes PR, Sall M, Messing EM, Brusketwitz RB. A prospective study of quantification of urinary incontinence and quality of life in patients undergoing radical retropubic prostatectomy. Urology 48 : 433-40, 1996.

380. Penson DF, McLerran D, Feng Z, Li L, Albertsen PC, Gilland FD et al. 5-year urinary and sexual outcomes after radical prostatectomy : Results from the prostate cancer outcomes study. J Urol 173:1701-5, May 2005.

381. Wei JT, Dunn RL, Marcovich R, Montie JE, and Sanda MG.: Prospective assessment of patient reported urinary continence after radical prostatectomy. J Urol., 164: 744, 2000.

382. Eastham JA, Kattan MW, Rogers E, Goan JR, Ohori M, Boone TB, and Scardino PT.: Risk factors for urinary incontinence after radical prostatectomy. J Urol., 156: 1707, 1996.

383. Van Kampen M, De Weerdt W, Van Poppel H, Castell Campesino A., Stragier J. and Baert, L.: Prediction of urinary continence following radical prostatectomy. Urol. Int., 60: 80, 1998.

384. Srougi M, Nesrallah LJ, Kauffmann JR, Nesrallah A, and Leite KR.: Urinary continence and pathological outcome after bladder neck preservation during radical retropubic prostatectomy: a randomized prospective trial. J Urol., 165: 815, 2001.

385. Noh C, Kshirsagar A, and Mohler JL.: Outcomes after radical retropubic prostatectomy. Urology, 61: 412, 2003.

386. Kao TC., Garner D., Foley J., Seay T., Friedrichs P., Thrasher JB., et al : Multicenter patient self-reporting questionnaire on impotence, incontinence and stricture after radical prostatectomy. J. Urol., 163: 858, 2000.

387. Moul JW, Mooneyhan RM, Kao TC, McLeod DG, and Cruess DF.: Preoperative and operative factors to predict incontinence, impotence and stricture after radical prostatectomy. Prostate Cancer Prostatic Dis., 1: 242, 1998.

388. Lee SE, Byun SS, Lee HJ, Song SH, Chang IH, Kim YJ, Gill MC, and Hong SK. Impact of variations in prostatic apex shape on early recovery on urinary continence after radical retropubic prostatectomy. Urology 68 : 137-41, 2006.

389. Johnson TK, Gilliland FD, Hoffman RM, Deapen D, Penson DF, Stanforn J>, e tal. Racial/ethnic differences in functional outcomes in the 5 years after diagnosis of localized prostate concer. J Clin Onco 22(20) : 4193-4201, Oct 2004.

390. Formenti SC, Lieskovsky G, Skinner D, Tsao-Wei DD, Groshen S, and Petrovich Z.: Update on impact of moderate dose of adjuvant radiation on urinary continence and sexual potency in prostate cancer patients treated with nerve-sparing prostatectomy. Urology, 56: 453, 2000.

391. Hofmann T, Gaensheimer S, Buchner A, Rohloff R, and Schilling A. An unrandomized prospective comparison of urinary continence, bowel symptoms and the need for further procedures in patients with and with no adjuvant radiation after radical prostatectomy. BJU Int 92 : 360-4, 2003.

392. Barker JC, Mitteness LS. Nocturia in the elderly. Gerontologist 1988; Feb;28(1):99-104.

393. Cartwright R, Renganathan A, Cardozo L. Current management of overactive bladder. Curr Opin Obstet Gynecol 2008; Oct;20(5):489-95.

394. Tikkinen KAO. Epidemiology of Nocturia - Results from the FINNO Study [dissertation]. Tampere, Finland: Tampere University Press; 2010. Available at: http://acta.uta.fi/pdf/978-951-44-8020-1.pdf

395. Weiss JP, Blaivas JG. Nocturia. J Urol 2000; Jan;163(1):5-12.

396. Tikkinen KA, Auvinen A. Does the Imprecise Definition of Overactive Bladder Serve Commercial Rather than Patient Interests? Eur Urol. 2012 Apr;61(4):746-8; discussion 749-50. Epub 2012 Jan 5.

397. Irwin DE, Milsom I, Kopp Z, Abrams P, EPIC Study Group. Symptom bother and health care-seeking behavior among individuals with overactive bladder. Eur Urol 2008; May;53(5):1029-37.

398. Coyne KS, Sexton CC, Thompson CL, Milsom I, Irwin D, Kopp ZS, et al. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. BJU Int 2009; Aug;104(3):352-60.

399. Vaughan CP, Johnson TM,2nd, Ala-Lipasti MA, Cartwright R, Tammela TL, Taari K, et al. The Prevalence of Clinically Meaningful Overactive Bladder: Bother and Quality of Life Results from the Population-Based FINNO Study. Eur Urol 2011; Jan 25;.

400. McGrother CW, Donaldson MM, Hayward T, Matthews R, Dallosso HM, Hyde C, et al. Urinary storage symptoms and comorbidities: a prospective population cohort study in middle-aged and older women. Age Ageing 2006; Jan;35(1):16-24.

401. Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int 2008; Jun;101(11):1388-95.

402. Middelkoop HA, Smilde-van den Doel DA, Neven AK, Kamphuisen HA, Springer CP. Subjective sleep characteristics of 1,485 males and females aged 50-93: effects of sex and age, and factors related to self-evaluated quality of sleep. J Gerontol A Biol Sci Med Sci 1996; May;51(3):M108-15.

403. Bing MH, Moller LA, Jennum P, Mortensen S, Skovgaard LT, Lose G. Prevalence and bother of nocturia, and causes of sleep interruption in a Danish population of men and women aged 60-80 years. BJU Int 2006; Sep;98(3):599-604.

404. Bliwise DL, Foley DJ, Vitiello MV, Ansari FP, Ancoli-Israel S, Walsh JK. Nocturia and disturbed sleep in the elderly. Sleep Med 2009; May;10(5):540-8.

405. Schatzl G, Temml C, Schmidbauer J, Dolezal B, Haidinger G, Madersbacher S. Cross-sectional study of nocturia in both sexes: analysis of a voluntary health screening project. Urology 2000; Jul;56(1):71-5.

406. Coyne KS, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int 2003; Dec;92(9):948-54.

407. Fiske J, Scarpero HM, Xue X, Nitti VW. Degree of bother caused by nocturia in women. Neurourol Urodyn 2004;23(2):130-3.

408. Liew LC, Tiong HY, Wong ML, Png DC, Tan JK. A population study of nocturia in Singapore. BJU Int 2006; Jan;97(1):109-12.

409. Yu HJ, Chen FY, Huang PC, Chen TH, Chie WC, Liu CY. Impact of nocturia on symptom-specific quality of life among community-dwelling adults aged 40 years and older. Urology 2006; Apr;67(4):713-8.

410. Lowenstein L, Brubaker L, Kenton K, Kramer H, Shott S, FitzGerald MP. Prevalence and impact of nocturia in a urogynecologic population. Int Urogynecol J Pelvic Floor Dysfunct 2007; Sep;18(9):1049-52.

411. Choo MS, Ku JH, Park CH, Lee YS, Lee KS, Lee JG, et al. Prevalence of nocturia in a Korean population aged 40 to 89 years. Neurourol Urodyn 2008;27(1):60-4.

412. Tikkinen KA, Johnson TM,2nd, Tammela TL, Sintonen H, Haukka J, Huhtala H, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2010; Mar;57(3):488-96.

413. Asplund R, Marnetoft SU, Selander J, Akerstrom B. Nocturia in relation to somatic health, mental health and pain in adult men and women. BJU Int 2005; Apr;95(6):816-9.

414. Kupelian V, Wei JT, O'Leary MP, Norgaard JP, Rosen RC, McKinlay JB. Nocturia and quality of life: results from the Boston area community health survey. Eur Urol 2012; Jan;61(1):78-84.

415. Stewart RB, Moore MT, May FE, Marks RG, Hale WE. Nocturia: a risk factor for falls in the elderly. J Am Geriatr Soc 1992; Dec;40(12):1217-20.

416. Brown JS, Vittinghoff E, Wyman JF, Stone KL, Nevitt MC, Ensrud KE, et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc 2000; Jul;48(7):721-5.

417. Temml C, Ponholzer A, Gutjahr G, Berger I, Marszalek M, Madersbacher S. Nocturia is an age-independent risk factor for hip-fractures in men. Neurourol Urodyn 2009;28(8):949-52.

418. Asplund R. Hip fractures, nocturia, and nocturnal polyuria in the elderly. Arch Gerontol Geriatr 2006; Nov-Dec;43(3):319-26.

419. Parsons JK, Mougey J, Lambert L, Wilt TJ, Fink HA, Garzotto M, et al. Lower urinary tract symptoms increase the risk of falls in older men. BJU Int 2009; Jul;104(1):63-8.

420. Vaughan CP, Brown CJ, Goode PS, Burgio KL, Allman RM, Johnson TM,2nd. The association of nocturia with incident falls in an elderly community-dwelling cohort. Int J Clin Pract 2010; Apr;64(5):577-83.

421. Nakagawa H, Niu K, Hozawa A, Ikeda Y, Kaiho Y, Ohmori-Matsuda K, et al. Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. J Urol 2010; Oct;184(4):1413-8.

422. Moon SJ, Kim YT, Lee TY, Moon H, Kim MJ, Kim SA, et al. The influence of an overactive bladder on falling: a study of females aged 40 and older in the community. Int Neurourol J 2011; Mar;15(1):41-7.

423. Asplund R. Mortality in the elderly in relation to nocturnal micturition. BJU Int 1999; Aug;84(3):297-301.

424. Bursztyn M, Jacob J, Stessman J. Usefulness of nocturia as a mortality risk factor for coronary heart disease among persons born in 1920 or 1921. Am J Cardiol 2006; Nov 15;98(10):1311-5.

425. Kupelian V, Fitzgerald MP, Kaplan SA, Norgaard JP, Chiu GR, Rosen RC. Association of Nocturia and Mortality: Results From the Third National Health and Nutrition Examination Survey. J Urol 2010; Dec 17;.

426. Hunskaar S. Epidemiology of nocturia. BJU Int 2005; Sep;96 Suppl 1:4-7.

427. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. Neurourol Urodyn 2002;21(2):167-78.

428. Abrams P, Artibani W, Cardozo L, Dmochowski R, van Kerrebroeck P, Sand P, et al. Reviewing the ICS 2002 terminology report: the ongoing debate. Neurourol Urodyn 2009;28(4):287.

429. Weiss JP, Wein AJ, van Kerrebroeck P, Dmochowski R, Fitzgerald MP, Tikkinen KAO, et al. Nocturia: New Directions ICI-RS Think Tank 2010 2010;(in press).

430. Wein A. Symptom-based diagnosis of overactive bladder: an overview. Can Urol Assoc J 2011; Oct;5(5 Suppl 2):S135-6.

431. Abrams P, Wein A. Re: Kari A.O. Tikkinen, Anssi Auvinen. Does the Imprecise Definition of Overactive Bladder Serve Commercial Rather than Patient Interests? Eur Urol 2012 (in press).

432. Roberts W. Observations on some of the daily changes of the urine 1860;5:817-825,906-923.

433. Rubin SW, Nagel H. Nocturia in the aged. J Am Med Assoc 1951; Oct 27;147(9):840-1.

434. van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, et al. The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21(2):179-83.

435. Madersbacher H. Overactive bladder: a clinical entity or a marketing hype?. Eur Urol 2005; Mar;47(3):273-6.

436. Blaivas JG. Overactive bladder and the definition of urgency. Neurourol Urodyn 2007;26(6):757,8; discussion 759-60.

437. Yamaguchi O, Honda K, Nomiya M, Shishido K, Kakizaki H, Tanaka H, et al. Defining overactive bladder as hypersensitivity. Neurourol Urodyn 2007; Oct;26(6 Suppl):904-7.

438. Homma Y. Lower urinary tract symptomatology: Its definition and confusion. Int J Urol 2008; Jan;15(1):35-43.

439. Dmochowski RR, FitzGerald MP, Wyndaele JJ. Measuring urgency in clinical practice. World J Urol 2009; Dec;27(6):739-45.

440. De Wachter S, Hanno P. Urgency: all or none phenomenon?. Neurourol Urodyn 2010; Apr;29(4):616-7.

441. Shah JR. Should we treat lower urinary tract symptoms without a definitive diagnosis? No. BMJ 2011; Dec 1;343:d6058.

442. Abrams P. Should we treat lower urinary tract symptoms without a definitive diagnosis? Yes. BMJ 2011; Dec 1;343:d6038.

443. Zinner NR. OAB. Are we barking up the wrong tree? A lesson from my dog. Neurourol Urodyn 2011; Nov;30(8):1410-1.

444. Abrams P. Response to OAB, are we barking up the wrong tree? A lesson from my dog. Neurourol Urodyn 2011; Nov;30(8):1409; discussion 1412-4.

445. Herschorn S. Overactive bladder: Symptom complex or separate entity?. Can Urol Assoc J 2011; Oct;5(5 Suppl 2):S152-4.

446. Parazzini F, Lavezzari M, Arbitani W. Prevalence of overactive bladder and urinary incontinence. J Fam Pract 2002; Dec;51(12):1072-5.

447. Lapitan MC, Chye PL, Asia-Pacific Continence Advisory Board. The epidemiology of overactive bladder among females in Asia: a questionnaire survey. Int Urogynecol J Pelvic Floor Dysfunct 2001;12(4):226-31.

448. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001; Jun;87(9):760-6.

449. Chen GD, Lin TL, Hu SW, Chen YC, Lin LY. Prevalence and correlation of urinary incontinence and overactive bladder in Taiwanese women. Neurourol Urodyn 2003;22(2):109-17.

450. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003; May;20(6):327-36.

451. Temml C, Heidler S, Ponholzer A, Madersbacher S. Prevalence of the overactive bladder syndrome by applying the International Continence Society definition. Eur Urol 2005; Oct;48(4):622-7.

452. Homma Y, Yamaguchi O, Hayashi K, Neurogenic Bladder Society Committee. An epidemiological survey of overactive bladder symptoms in Japan. BJU Int 2005; Dec;96(9):1314-8.

453. Safarinejad MR. Prevalence of the overactive bladder among Iranian women based on the International Continence Society definition: a population-based study. Int Urol Nephrol 2009;41(1):35-45.

454. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int 2011; Oct;108(7):1132-8.

455. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-Based Survey of Urinary Incontinence, Overactive Bladder, and Other Lower Urinary Tract Symptoms in Five Countries: Results of the EPIC Study. Eur Urol 2006; Dec;50(6):1306-15.

456. Corcos J, Schick E. Prevalence of overactive bladder and incontinence in Canada. Can J Urol 2004; Jun;11(3):2278-84.

457. Teloken C, Caraver F, Weber FA, Teloken PE, Moraes JF, Sogari PR, et al. Overactive bladder: prevalence and implications in Brazil. Eur Urol 2006; Jun;49(6):1087-92.

458. Yu HJ, Liu CY, Lee KL, Lee WC, Chen TH. Overactive bladder syndrome among community-dwelling adults in Taiwan: prevalence, correlates, perception, and treatment seeking. Urol Int 2006;77(4):327-33.

459. Tikkinen KA, Tammela TL, Rissanen AM, Valpas A, Huhtala H, Auvinen A. Is the prevalence of overactive bladder overestimated? A population-based study in Finland. PLoS ONE 2007; Feb 7;2:e195.

460. Choo MS, Ku JH, Lee JB, Lee DH, Kim JC, Kim HJ, et al. Cross-cultural differences for adapting overactive bladder symptoms: results of an epidemiologic survey in Korea. World J Urol 2007; Oct;25(5):505-11.

461. Herschorn S, Gajewski J, Schulz J, Corcos J. A population-based study of urinary symptoms and incontinence: the Canadian Urinary Bladder Survey. BJU Int 2008; Jan;101(1):52-8.

462. Benner JS, Becker R, Fanning K, Jumadilova Z, Bavendam T, Brubaker L, et al. Bother related to bladder control and health care seeking behavior in adults in the United States. J Urol 2009; Jun;181(6):2591-8.

463. Correia S, Dinis P, Rolo F, Lunet N. Prevalence, treatment and known risk factors of urinary incontinence and overactive bladder in the non-institutionalized Portuguese population. Int Urogynecol J Pelvic Floor Dysfunct 2009; Aug 14;.

464. Lee YS, Lee KS, Jung JH, Han DH, Oh SJ, Seo JT, et al. Prevalence of overactive bladder, urinary incontinence, and lower urinary tract symptoms: results of Korean EPIC study. World J Urol 2011; Apr;29(2):185-90.

465. Wang Y, Xu K, Hu H, Zhang X, Wang X, Na Y, et al. Prevalence, risk factors, and impact on health related quality of life of overactive bladder in China. Neurourol Urodyn 2011; Nov;30(8):1448-55.

466. Irwin DE, Milsom I, Chancellor MB, Kopp Z, Guan Z. Dynamic progression of overactive bladder and urinary incontinence symptoms: a systematic review. Eur Urol 2010; Oct;58(4):532-43.

467. Dallosso HM, McGrother CW, Matthews RJ, Donaldson MM, Leicestershire MRC Incontinence Study Group. Nutrient composition of the diet and the development of overactive bladder: a longitudinal study in women. Neurourol Urodyn 2004;23(3):204-10.

468. Dallosso HM, Matthews RJ, McGrother CW, Donaldson MM, Shaw C, Leicestershire MRC Incontinence Study Group. The association of diet and other lifestyle factors with the onset of overactive bladder: a longitudinal study in men. Public Health Nutr 2004; Oct;7(7):885-91.

469. Wennberg AL, Molander U, Fall M, Edlund C, Peeker R, Milsom I. A longitudinal population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in women. Eur Urol 2009; Apr;55(4):783-91.

470. Malmsten UG, Molander U, Peeker R, Irwin DE, Milsom I. Urinary incontinence, overactive bladder, and other lower urinary tract symptoms: a longitudinal population-based survey in men aged 45-103 years. Eur Urol 2010; Jul;58(1):149-56.

471. Heidler S, Mert C, Temml C, Madersbacher S. The natural history of the overactive bladder syndrome in females: a long-term analysis of a health screening project. Neurourol Urodyn 2011; Nov;30(8):1437-41.

472. Lawrence JM, Lukacz ES, Nager CW, Hsu JW, Luber KM. Prevalence and co-occurrence of pelvic floor disorders in community-dwelling women. Obstet Gynecol 2008; Mar;111(3):678-85.

473. Coyne KS, Margolis MK, Kopp ZS, Kaplan SA. Racial Differences in the Prevalence of Overactive Bladder in the United States From the Epidemiology of LUTS (EpiLUTS) Study. Urology 2012; Jan;79(1):95-101.

474. Fitzgerald MP, Thom DH, Wassel-Fyr C, Subak L, Brubaker L, Van Den Eeden SK, et al. Childhood urinary symptoms predict adult overactive bladder symptoms. J Urol 2006; Mar;175(3 Pt 1):989-93.

475. Labrie J, de Jong TP, Nieuwhof-Leppink A, van der Deure J, Vijverberg MA, van der Vaart CH. The relationship between children with voiding problems and their parents. J Urol 2010; May;183(5):1887-91.

476. Lawrence JM, Lukacz ES, Liu IL, Nager CW, Luber KM. Pelvic floor disorders, diabetes, and obesity in women: findings from the Kaiser Permanente Continence Associated Risk Epidemiology Study. Diabetes Care 2007; Oct;30(10):2536-41.

477. Teleman PM, Lidfeldt J, Nerbrand C, Samsioe G, Mattiasson A, WHILA study group. Overactive bladder: prevalence, risk factors and relation to stress incontinence in middle-aged women. BJOG 2004; Jun;111(6):600-4.

478. Ikeda Y, Nakagawa H, Ohmori-Matsuda K, Hozawa A, Masamune Y, Nishino Y, et al. Risk factors for overactive bladder in the elderly population: a community-based study with face-to-face interview. Int J Urol 2011; Mar;18(3):212-8.

479. Whitcomb EL, Lukacz ES, Lawrence JM, Nager CW, Luber KM. Prevalence and degree of bother from pelvic floor disorders in obese women. Int Urogynecol J Pelvic Floor Dysfunct 2009; Mar;20(3):289-94.

480. Liu RT, Chung MS, Lee WC, Chang SW, Huang ST, Yang KD, et al. Prevalence of overactive bladder and associated risk factors in 1359 patients with type 2 diabetes. Urology 2011; Nov;78(5):1040-5.

481. Bradley CS, Kennedy CM, Nygaard IE. Pelvic floor symptoms and lifestyle factors in older women. J Womens Health (Larchmt) 2005; Mar;14(2):128-36.

482. Shaper AG, Wannamethee G, Walker M. Alcohol and mortality in British men: explaining the U-shaped curve. Lancet 1988; Dec 3;2(8623):1267-73.

483. Fillmore KM, Stockwell T, Chikritzhs T, Bostrom A, Kerr W. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies and new hypotheses. Ann Epidemiol 2007; May;17(5 Suppl):S16-23.

484. Naimi TS, Brown DW, Brewer RD, Giles WH, Mensah G, Serdula MK, et al. Cardiovascular risk factors and confounders among nondrinking and moderate-drinking U.S. adults. Am J Prev Med 2005; May;28(4):369-73.

485. Jackson R, Broad J, Connor J, Wells S. Alcohol and ischaemic heart disease: probably no free lunch. Lancet 2005; Dec 3;366(9501):1911-2.

486. Tettamanti G, Altman D, Pedersen NL, Bellocco R, Milsom I, Iliadou AN. Effects of coffee and tea consumption on urinary incontinence in female twins. BJOG 2011; Jun;118(7):806-13.

487. Tahtinen RM, Auvinen A, Cartwright R, Johnson TM, Tammela TL, Tikkinen KA. Smoking and bladder symptoms in women. Obstet Gynecol 2011; Sep;118(3):643-8.

488. Nuotio M, Jylha M, Koivisto AM, Tammela TL. Association of smoking with urgency in older people. Eur Urol 2001; Aug;40(2):206-12.

489. de Boer TA, Slieker-ten Hove MC, Burger CW, Vierhout ME. The prevalence and risk factors of overactive bladder symptoms and its relation to pelvic organ prolapse symptoms in a general female population. Int Urogynecol J 2011; May;22(5):569-75.

490. Handa VL, Blomquist JL, Knoepp LR, Hoskey KA, McDermott KC, Munoz A. Pelvic floor disorders 5-10 years after vaginal or cesarean childbirth. Obstet Gynecol 2011; Oct;118(4):777-84.

491. Chuang FC, Kuo HC. Prevalence of lower urinary tract symptoms in indigenous and non-indigenous women in Eastern Taiwan. J Formos Med Assoc 2010; Mar;109(3):228-36.

492. Finkelstein K, Glosner S, Sanchez RJ, Uddin N. Prevalence of probable overactive bladder in a private obstetrics and gynecology group practice. Curr Med Res Opin 2008; Apr;24(4):1083-90.

493. Cheung WW, Blank W, Borawski D, Tran W, Bluth MH. Prevalence of overactive bladder, its under-diagnosis, and risk factors in a male urologic veterans population. Int J Med Sci 2010; Nov 12;7(6):391-4.

494. Viktrup L. The risk of lower urinary tract symptoms five years after the first delivery. Neurourol Urodyn 2002;21(1):2-29.

495. Liang CC, Chang SD, Lin SJ, Lin YJ. Lower urinary tract symptoms in primiparous women before and during pregnancy. Arch Gynecol Obstet 2011; Nov 1;.

496. Aslan D, Aslan G, Yamazhan M, Ispahi C, Tinar S. Voiding symptoms in pregnancy: an assessment with international prostate symptom score. Gynecol Obstet Invest 2003;55(1):46-9.

497. Sun MJ, Chen GD, Chang SY, Lin KC, Chen SY. Prevalence of lower urinary tract symptoms during pregnancy in Taiwan. J Formos Med Assoc 2005; Mar;104(3):185-9.

498. Adaji S, Shittu O, Bature S, Nasir S, Olatunji O. Bothersome lower urinary symptoms during pregnancy: a preliminary study using the International Consultation on Incontinence Questionnaire. Afr Health Sci 2011; Aug;11 Suppl 1:S46-52.

499. Parazzini F, Chiaffarino F, Lavezzari M, Giambanco V, VIVA Study Group. Risk factors for stress, urge or mixed urinary incontinence in Italy. BJOG 2003; Oct;110(10):927-33.

500. Tikkinen KA, Auvinen A, Tiitinen A, Valpas A, Johnson TM,2nd, Tammela TL. Reproductive factors associated with nocturia and urinary urgency in women – a population-based study in Finland 2008;(in press).

501. Alling Moller L, Lose G, Jorgensen T. Risk factors for lower urinary tract symptoms in women 40 to 60 years of age. Obstet Gynecol 2000; Sep;96(3):446-51.

502. Handa VL, Harvey L, Fox HE, Kjerulff KH. Parity and route of delivery: does cesarean delivery reduce bladder symptoms later in life?. Am J Obstet Gynecol 2004; Aug;191(2):463-9.

503. Zhang W, Song Y, He X, Huang H, Xu B, Song J. Prevalence and risk factors of overactive bladder syndrome in Fuzhou Chinese women. Neurourol Urodyn 2006;25(7):717-21.

504. Scarpa KP, Herrmann V, Palma PC, Ricetto CL, Morais S. Prevalence of urinary symptoms in the third trimester of pregnancy. Rev Assoc Med Bras 2006; May-Jun;52(3):153-6.

505. van Brummen HJ, Bruinse HW, van de Pol G, Heintz AP, van der Vaart CH. The effect of vaginal and cesarean delivery on lower urinary tract symptoms: what makes the difference?. Int Urogynecol J Pelvic Floor Dysfunct 2007; Feb;18(2):133-9.

506. Ekstrom A, Altman D, Wiklund I, Larsson C, Andolf E. Planned cesarean section versus planned vaginal delivery: comparison of lower urinary tract symptoms. Int Urogynecol J Pelvic Floor Dysfunct 2008; Apr;19(4):459-65.

507. Lukacz ES, Lawrence JM, Contreras R, Nager CW, Luber KM. Parity, mode of delivery, and pelvic floor disorders. Obstet Gynecol 2006; Jun;107(6):1253-60.

508. Rekers H, Drogendijk AC, Valkenburg HA, Riphagen F. The menopause, urinary incontinence and other symptoms of the genito-urinary tract. Maturitas 1992; Oct;15(2):101-11.

509. Prasad M, Sadhukhan M, Tom B, Al-Taher H. The effect of hysterectomy on urinary symptoms and residual bladder volume. J Obstet Gynaecol 2002; Sep;22(5):544-7.

510. Cody JD, Richardson K, Moehrer B, Hextall A, Glazener CM. Oestrogen therapy for urinary incontinence in postmenopausal women. Cochrane Database Syst Rev 2009; Oct 7;(4)(4):CD001405.

511. Iliadou A, Milsom I, Pedersen NL, Altman D. Risk of urinary incontinence symptoms in oral contraceptive users: a national cohort study from the Swedish Twin Register. Fertil Steril 2009; Aug;92(2):428-33.

512. Plotti F, Angioli R, Zullo MA, Sansone M, Altavilla T, Antonelli E, et al. Update on urodynamic bladder dysfunctions after radical hysterectomy for cervical cancer. Crit Rev Oncol Hematol 2011; Nov;80(2):323-9.

513. Hazewinkel MH, Sprangers MA, van der Velden J, van der Vaart CH, Stalpers LJ, Burger MP, et al. Long-term cervical cancer survivors suffer from pelvic floor symptoms: a cross-sectional matched cohort study. Gynecol Oncol 2010; May;117(2):281-6.

514. Stanton SL, Hilton P, Norton C, Cardozo L. Clinical and urodynamic effects of anterior colporrhaphy and vaginal hysterectomy for prolapse with and without incontinence. Br J Obstet Gynaecol 1982; Jun;89(6):459-63.

515. Virtanen H, Makinen J, Tenho T, Kiilholma P, Pitkanen Y, Hirvonen T. Effects of abdominal hysterectomy on urinary and sexual symptoms. Br J Urol 1993; Dec;72(6):868-72.

516. Altman D, Lopez A, Falconer C, Zetterstrom J. The impact of hysterectomy on lower urinary tract symptoms. Int Urogynecol J Pelvic Floor Dysfunct 2003; Dec;14(6):418-23.

517. Weber AM, Walters MD, Schover LR, Church JM, Piedmonte MR. Functional outcomes and satisfaction after abdominal hysterectomy. Am J Obstet Gynecol 1999; Sep;181(3):530-5.

518. de Tayrac R, Chevalier N, Chauveaud-Lambling A, Gervaise A, Fernandez H. Is vaginal hysterectomy a risk factor for urinary incontinence at long-term follow-up?. Eur J Obstet Gynecol Reprod Biol 2007; Feb;130(2):258-61.

519. Krogh RA, Neumann GA, Lauszus FF, Guttorm E, Rasmussen KL. Hysterectomy is associated with stress incontinence in women who previously had a transcervical endometrial resection. Gynecol Obstet Invest 2007;63(3):121-5.

520. Vervest HA, Kiewiet de Jonge M, Vervest TM, Barents JW, Haspels AA. Micturition symptoms and urinary incontinence after non-radical hysterectomy. Acta Obstet Gynecol Scand 1988;67(2):141-6.

521. Carlson KJ, Miller BA, Fowler FJ,Jr. The Maine Women's Health Study: I. Outcomes of hysterectomy. Obstet Gynecol 1994; Apr;83(4):556-65.

522. Thakar R, Ayers S, Clarkson P, Stanton S, Manyonda I. Outcomes after total versus subtotal abdominal hysterectomy. N Engl J Med 2002; Oct 24;347(17):1318-25.

523. Learman LA, Summitt RL,Jr, Varner RE, McNeeley SG, Goodman-Gruen D, Richter HE, et al. A randomized comparison of total or supracervical hysterectomy: surgical complications and clinical outcomes. Obstet Gynecol 2003; Sep;102(3):453-62.

524. Phelan S, Kanaya AM, Subak LL, Hogan PE, Espeland MA, Wing RR, et al. Prevalence and risk factors for urinary incontinence in overweight and obese diabetic women: action for health in diabetes (look ahead) study. Diabetes Care 2009; Aug;32(8):1391-7.

525. El-Toukhy TA, Hefni M, Davies A, Mahadevan S. The effect of different types of hysterectomy on urinary and sexual functions: a prospective study. J Obstet Gynaecol 2004; Jun;24(4):420-5.

526. Link CL, Pulliam SJ, McKinlay JB. Hysterectomies and Urologic Symptoms: Results from the Boston Area Community Health (BACH) Survey. Female Pelvic Med Reconstr Surg 2010; Jan;16(1):37-47.

527. Kershen RT, Appell RA. De novo urge syndrome and detrusor instability after anti-incontinence surgery: current concepts, evaluation, and treatment. Curr Urol Rep 2002; Oct;3(5):345-53.

528. Holmgren C, Nilsson S, Lanner L, Hellberg D. Frequency of de novo urgency in 463 women who had undergone the tension-free vaginal tape (TVT) procedure for genuine stress urinary incontinence--a long-term follow-up. Eur J Obstet Gynecol Reprod Biol 2007; May;132(1):121-5.

529. Van Venrooij GE, Van Melick HH, Eckhardt MD, Boon TA. Correlations of urodynamic changes with changes in symptoms and well-being after transurethral resection of the prostate. J Urol 2002; Aug;168(2):605-9.

530. Abrams PH, Farrar DJ, Turner-Warwick RT, Whiteside CG, Feneley RC. The results of prostatectomy: a symptomatic and urodynamic analysis of 152 patients. J Urol 1979; May;121(5):640-2.

531. de Nunzio C, Franco G, Rocchegiani A, Iori F, Leonardo C, Laurenti C. The evolution of detrusor overactivity after watchful waiting, medical therapy and surgery in patients with bladder outlet obstruction. J Urol 2003; Feb;169(2):535-9.

532. Housami F, Abrams P. Persistent detrusor overactivity after transurethral resection of the prostate. Curr Urol Rep 2008; Jul;9(4):284-90.

533. Miedel A, Tegerstedt G, Maehle-Schmidt M, Nyren O, Hammarstrom M. Symptoms and pelvic support defects in specific compartments. Obstet Gynecol 2008; Oct;112(4):851-8.

534. Tegerstedt G, Maehle-Schmidt M, Nyren O, Hammarstrom M. Prevalence of symptomatic pelvic organ prolapse in a Swedish population. Int Urogynecol J Pelvic Floor Dysfunct 2005; Nov-Dec;16(6):497-503.

535. Fritel X, Varnoux N, Zins M, Breart G, Ringa V. Symptomatic pelvic organ prolapse at midlife, quality of life, and risk factors. Obstet Gynecol 2009; Mar;113(3):609-16.

536. de Boer TA, Salvatore S, Cardozo L, Chapple C, Kelleher C, van Kerrebroeck P, et al. Pelvic organ prolapse and overactive bladder. Neurourol Urodyn 2010;29(1):30-9.

537. Link CL, Lutfey KE, Steers WD, McKinlay JB. Is abuse causally related to urologic symptoms? Results from the Boston Area Community Health (BACH) Survey. Eur Urol 2007; Aug;52(2):397-406.

538. Jundt K, Scheer I, Schiessl B, Pohl K, Haertl K, Peschers UM. Physical and sexual abuse in patients with overactive bladder: is there an association?. Int Urogynecol J Pelvic Floor Dysfunct 2007; Apr;18(4):449-53.

539. Coyne KS, Sexton CC, Kopp ZS, Ebel-Bitoun C, Milsom I, Chapple C. The impact of overactive bladder on mental health, work productivity and health-related quality of life in the UK and Sweden: results from EpiLUTS. BJU Int 2011; Nov;108(9):1459-71.

540. Hullfish KL, Fenner DE, Sorser SA, Visger J, Clayton A, Steers WD. Postpartum depression, urge urinary incontinence, and overactive bladder syndrome: is there an association?. Int Urogynecol J Pelvic Floor Dysfunct 2007; Oct;18(10):1121-6.

541. Kupelian V, Rosen RC, Link CL, McVary KT, Aiyer LP, Mollon P, et al. Association of urological symptoms and chronic illness in men and women: contributions of symptom severity and duration--results from the BACH Survey. J Urol 2009; Feb;181(2):694-700.

542. Fayyad AM, Hill SR, Jones G. Prevalence and risk factors for bothersome lower urinary tract symptoms in women with diabetes mellitus from hospital-based diabetes clinic. Int Urogynecol J Pelvic Floor Dysfunct 2009; Nov;20(11):1339-44.

543. Tibaek S, Gard G, Klarskov P, Iversen HK, Dehlendorff C, Jensen R. Prevalence of lower urinary tract symptoms (LUTS) in stroke patients: a cross-sectional, clinical survey. Neurourol Urodyn 2008;27(8):763-71.

544. Britton JP, Dowell AC, Whelan P. Prevalence of urinary symptoms in men aged over 60. Br J Urol 1990; Aug;66(2):175-6.

545. Garraway WM, Collins GN, Lee RJ. High prevalence of benign prostatic hypertrophy in the community. Lancet 1991; Aug 24;338(8765):469-71.

546. Chute CG, Panser LA, Girman CJ, Oesterling JE, Guess HA, Jacobsen SJ, et al. The prevalence of prostatism: a population-based survey of urinary symptoms. J Urol 1993; Jul;150(1):85-9.

547. Sagnier PP, MacFarlane G, Richard F, Botto H, Teillac P, Boyle P. Results of an epidemiological survey using a modified American Urological Association symptom index for benign prostatic hyperplasia in France. J Urol 1994; May;151(5):1266-70.

548. Homma Y, Imajo C, Takahashi S, Kawabe K, Aso Y. Urinary symptoms and urodynamics in a normal elderly population. Scand J Urol Nephrol Suppl 1994;157:27-30.

549. Malmsten UG, Milsom I, Molander U, Norlen LJ. Urinary incontinence and lower urinary tract symptoms: an epidemiological study of men aged 45 to 99 years. J Urol 1997; Nov;158(5):1733-7.

550. Sommer P, Nielsen KK, Bauer T, Kristensen ES, Hermann GG, Steven K, et al. Voiding patterns in men evaluated by a questionnaire survey. Br J Urol 1990; Feb;65(2):155-60.

551. Brieger GM, Yip SK, Hin LY, Chung TK. The prevalence of urinary dysfunction in Hong Kong Chinese women. Obstet Gynecol 1996; Dec;88(6):1041-4.

552. Samuelsson E, Victor A, Tibblin G. A population study of urinary incontinence and nocturia among women aged 20-59 years. Prevalence, well-being and wish for treatment. Acta Obstet Gynecol Scand 1997; Jan;76(1):74-80.

553. Pinnock C, Marshall VR. Troublesome lower urinary tract symptoms in the community: a prevalence study. Med J Aust 1997; Jul 21;167(2):72-5.

554. van Dijk L, Kooij DG, Schellevis FG. Nocturia in the Dutch adult population. BJU Int 2002; Nov;90(7):644-8.

555. Rembratt A, Norgaard JP, Andersson KE. Nocturia and associated morbidity in a community-dwelling elderly population. BJU Int 2003; Nov;92(7):726-30.

556. Yoshimura K, Terada N, Matsui Y, Terai A, Kinukawa N, Arai Y. Prevalence of and risk factors for nocturia: Analysis of a health screening program. Int J Urol 2004; May;11(5):282-7.

557. Tikkinen KA, Tammela TL, Huhtala H, Auvinen A. Is nocturia equally common among men and women? A population based study in Finland. J Urol 2006; Feb;175(2):596-600.

558. Zhang X, Zhang J, Chen J, Zhang C, Li Q, Xu T, et al. Prevalence and Risk Factors of Nocturia and Nocturia-Related Quality of Life in the Chinese Population. Urol Int 2011; Jan 5;.

559. Pinnock C, Marshall VR. Troublesome lower urinary tract symptoms in the community: a prevalence study. Med J Aust 1997; Jul 21;167(2):72-5.

560. Muscatello DJ, Rissel C, Szonyi G. Urinary symptoms and incontinence in an urban community: prevalence and associated factors in older men and women. Intern Med J 2001; Apr;31(3):151-60.

561. McGrother CW, Donaldson MM, Shaw C, Matthews RJ, Hayward TA, Dallosso HM, et al. Storage symptoms of the bladder: prevalence, incidence and need for services in the UK. BJU Int 2004; Apr;93(6):763-9.

562. Parsons M, Tissot W, Cardozo L, Diokno A, Amundsen CL, Coats AC, et al. Normative bladder diary measurements: night versus day. Neurourol Urodyn 2007;26(4):465-73.

563. Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A, Ruud Bosch JL. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 2000; Oct;164(4):1201-5.

564. Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol 2010; Aug;184(2):440-6.

565. Tikkinen KAO, Johnson TM 2nd, Cartwright R. Epidemiology of Nocturia. In: Weiss JP, Blaivas J, van Kerrebroeck P, Wein AJ, eds. Nocturia: Causes, Consequences and Clinical Approaches, 1st edition. New York: Springer-Verlag, 2011.

566. Hunskaar S. Fluctuations in lower urinary tract symptoms in women. Reassurance and watchful waiting can prevent overtreatment. BMJ 2000; May 27;320(7247):1418-9.

567. Moller LA, Lose G, Jorgensen T. Incidence and remission rates of lower urinary tract symptoms at one year in women aged 40-60: longitudinal study. BMJ 2000; May 27;320(7247):1429-32.

568. Johnson TM,2nd, Sattin RW, Parmelee P, Fultz NH, Ouslander JG. Evaluating potentially modifiable risk factors for prevalent and incident nocturia in older adults. J Am Geriatr Soc 2005; Jun;53(6):1011-6.

569. van Doorn B, Blanker MH, Kok ET, Westers P, Bosch JL. Once nocturia, always nocturia? Natural history of nocturia in older men based on frequency-volume charts: the Krimpen study. J Urol 2011; Nov;186(5):1956-61.

570. Yoshimura K, Kamoto T, Tsukamoto T, Oshiro K, Kinukawa N, Ogawa O. Seasonal alterations in nocturia and other storage symptoms in three Japanese communities. Urology 2007; May;69(5):864-70.

571. Herzog AR, Fultz NH. Prevalence and incidence of urinary incontinence in community-dwelling populations. J Am Geriatr Soc 1990; Mar;38(3):273-81.

572. Hakkinen JT, Hakama M, Shiri R, Auvinen A, Tammela TL, Koskimaki J. Incidence of nocturia in 50 to 80-year-old Finnish men. J Urol 2006; Dec;176(6 Pt 1):2541,5; discussion 2545.

573. Asplund R, Aberg HE. Nocturia in relation to body mass index, smoking and some other life-style factors in women. Climacteric 2004; Sep;7(3):267-73.

574. Fitzgerald MP, Litman HJ, Link CL, McKinlay JB, BACH Survey Investigators. The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey. J Urol 2007; Apr;177(4):1385-9.

575. Laven BA, Orsini N, Andersson SO, Johansson JE, Gerber GS, Wolk A. Birth weight, abdominal obesity and the risk of lower urinary tract symptoms in a population based study of Swedish men. J Urol 2008; May;179(5):1891,5; discussion 1895-6.

576. Bing MH, Moller LA, Jennum P, Mortensen S, Lose G. Nocturia and associated morbidity in a Danish population of men and women aged 60-80 years. BJU Int 2008 Sep;102(7):808-14; discussion 814-5.

577. Burgio KL, Johnson TM,2nd, Goode PS, Markland AD, Richter HE, Roth DL, et al. Prevalence and correlates of nocturia in community-dwelling older adults. J Am Geriatr Soc 2010; May;58(5):861-6.

578. Shiri R, Hakama M, Hakkinen J, Auvinen A, Huhtala H, Tammela TL, et al. The effects of lifestyle factors on the incidence of nocturia. J Urol 2008; Nov;180(5):2059-62.

579. Hsieh CH, Chen HY, Hsu CS, Chang ST, Chiang CD. Risk factors for nocturia in Taiwanese women aged 20-59 years. Taiwan J Obstet Gynecol 2007; Jun;46(2):166-70.

580. Tikkinen KA, Auvinen A, Johnson TM,2nd, Weiss JP, Keranen T, Tiitinen A, et al. A systematic evaluation of factors associated with nocturia--the population-based FINNO study. Am J Epidemiol 2009; Aug 1;170(3):361-8.

581. Klein BE, Klein R, Lee KE, Bruskewitz RC. Correlates of urinary symptom scores in men. Am J Public Health 1999; Nov;89(11):1745-8.

582. Kang D, Andriole GL, Van De Vooren RC, Crawford D, Chia D, Urban DA, et al. Risk behaviours and benign prostatic hyperplasia. BJU Int 2004; Jun;93(9):1241-5.

583. Gourova LW, van de Beek C, Spigt MG, Nieman FH, van Kerrebroeck PE. Predictive factors for nocturia in elderly men: a cross-sectional study in 21 general practices. BJU Int 2006; Mar;97(3):528-32.

584. Blanker MH, Bernsen RM, Ruud Bosch JL, Thomas S, Groeneveld FP, Prins A, et al. Normal values and determinants of circadian urine production in older men: a population based study. J Urol 2002; Oct;168(4 Pt 1):1453-7.

585. Platz EA, Kawachi I, Rimm EB, Colditz GA, Stampfer MJ, Willett WC, et al. Physical activity and benign prostatic hyperplasia. Arch Intern Med 1998; Nov 23;158(21):2349-56.

586. Prezioso D, Catuogno C, Galassi P, D'Andrea G, Castello G, Pirritano D. Life-style in patients with LUTS suggestive of BPH. Eur Urol 2001;40 Suppl 1:9-12.

587. Rohrmann S, Crespo CJ, Weber JR, Smit E, Giovannucci E, Platz EA. Association of cigarette smoking, alcohol consumption and physical activity with lower urinary tract symptoms in older American men: findings from the third National Health And Nutrition Examination Survey. BJU Int 2005; Jul;96(1):77-82.

588. Soda T, Masui K, Okuno H, Terai A, Ogawa O, Yoshimura K. Efficacy of nondrug lifestyle measures for the treatment of nocturia. J Urol 2010; Sep;184(3):1000-4.

589. Gopal M, Sammel MD, Pien G, Gracia C, Freeman EW, Lin H, et al. Investigating the associations between nocturia and sleep disorders in perimenopausal women. J Urol 2008; Nov;180(5):2063-7.

590. Kupelian V, Link CL, Hall SA, McKinlay JB. Are Racial/Ethnic Disparities in the Prevalence of Nocturia Due to Socioeconomic Status? Results of the BACH Survey. J Urol 2009; Feb 20;.

591. Markland AD, Vaughan CP, Johnson TM,2nd, Goode PS, Redden DT, Burgio KL. Prevalence of Nocturia in United States Men: Results from the National Health and Nutrition Examination Survey. J Urol 2011; Jan 18;.

592. Munro-Faure AD, Beilin LJ, Bulpitt CJ, Coles EC, Dollery CT, Gear JS, et al. Comparison of black and white patients attending hypertension clinics in England. Br Med J 1979; Apr 21;1(6170):1044-7.

593. Sze EH, Jones WP, Ferguson JL, Barker CD, Dolezal JM. Prevalence of urinary incontinence symptoms among black, white, and Hispanic women. Obstet Gynecol 2002; Apr;99(4):572-5.

594. Lukacz ES, Whitcomb EL, Lawrence JM, Nager CW, Luber KM. Urinary frequency in community-dwelling women: what is normal?. Am J Obstet Gynecol 2009; May;200(5):552.e1,552.e7.

595. Kuo HC. Prevalence of lower urinary tract symptoms in male aborigines and non-aborigines in eastern Taiwan. J Formos Med Assoc 2008; Sep;107(9):728-35.

596. Mariappan P, Turner KJ, Sothilingam S, Rajan P, Sundram M, Stewart LH. Nocturia, nocturia indices and variables from frequency-volume charts are significantly different in Asian and Caucasian men with lower urinary tract symptoms: a prospective comparison study. BJU Int 2007; Aug;100(2):332-6.

597. Parboosingh J, Doig A. Studies of nocturia in normal pregnancy. J Obstet Gynaecol Br Commonw 1973; Oct;80(10):888-95.

598. Sharma JB, Aggarwal S, Singhal S, Kumar S, Roy KK. Prevalence of urinary incontinence and other urological problems during pregnancy: a questionnaire based study. Arch Gynecol Obstet 2009; Jun;279(6):845-51.

599. Asplund R, Aberg HE. Development of nocturia in relation to health, age and the menopause. Maturitas 2005; Aug 16;51(4):358-62.

600. Lose G, Alling-Moller L, Jennum P. Nocturia in women. Am J Obstet Gynecol 2001; Aug;185(2):514-21.

601. Lin TL, Ng SC, Chen YC, Hu SW, Chen GD. What affects the occurrence of nocturia more: menopause or age?. Maturitas 2005; Feb 14;50(2):71-7.

602. Cardozo L, Rekers H, Tapp A, Barnick C, Shepherd A, Schussler B, et al. Oestriol in the treatment of postmenopausal urgency: a multicentre study. Maturitas 1993; Dec;18(1):47-53.

603. Liapis A, Bakas P, Georgantopoulou C, Creatsas G. The use of oestradiol therapy in postmenopausal women after TVT-O anti-incontinence surgery. Maturitas 2010; May;66(1):101-6.

604. Yu HJ, Chen TH, Chie WC, Liu CY, Tung TH, Huang SW. Prevalence and associated factors of nocturia among adult residents of the Matsu area of Taiwan. J Formos Med Assoc 2005; Jun;104(6):444-7.

605. Homma Y, Yamaguchi T, Kondo Y, Horie S, Takahashi S, Kitamura T. Significance of nocturia in the International Prostate Symptom Score for benign prostatic hyperplasia. J Urol 2002; Jan;167(1):172-6.

606. Yoshimura K, Ohara H, Ichioka K, Terada N, Matsui Y, Terai A, et al. Nocturia and benign prostatic hyperplasia. Urology 2003; Apr;61(4):786-90.

607. Bruskewitz RC, Larsen EH, Madsen PO, Dorflinger T. 3-Year Followup of Urinary Symptoms After Transurethral Resection of the Prostate. J Urol 1986; Sep;136(3):613-5.

608. Johnson TM, Burrows PK, Kusek JW, Nyberg LM, Tenover JL, Lepor H, et al. The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia. J Urol 2007; Nov;178(5):2045,50; discussion 2050-1.

609. Brown CT, O'Flynn E, Van Der Meulen J, Newman S, Mundy AR, Emberton M. The fear of prostate cancer in men with lower urinary tract symptoms: should symptomatic men be screened?. BJU Int 2003; Jan;91(1):30-2.

610. Young JM, Muscatello DJ, Ward JE. Are men with lower urinary tract symptoms at increased risk of prostate cancer? A systematic review and critique of the available evidence. BJU Int 2000; Jun;85(9):1037-48.

611. Martin RM, Vatten L, Gunnell D, Romundstad P, Nilsen TI. Lower urinary tract symptoms and risk of prostate cancer: the HUNT 2 Cohort, Norway. Int J Cancer 2008; Oct 15;123(8):1924-8.

612. Damber JE, Aus G. Prostate cancer. Lancet 2008; May 17;371(9625):1710-21.

613. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008; Mar 20;358(12):1250-61.

614. Namiki S, Saito S, Ishidoya S, Tochigi T, Ioritani N, Yoshimura K, et al. Adverse effect of radical prostatectomy on nocturia and voiding frequency symptoms. Urology 2005; Jul;66(1):147-51.

615. Namiki S, Ishidoya S, Saito S, Satoh M, Tochigi T, Ioritani N, et al. Natural history of voiding function after radical retropubic prostatectomy. Urology 2006; Jul;68(1):142-7.

616. Asplund R. Nocturia in relation to sleep, somatic diseases and medical treatment in the elderly. BJU Int 2002; Oct;90(6):533-6.

617. Lee WC, Wu HP, Tai TY, Liu SP, Chen J, Yu HJ. Effects of diabetes on female voiding behavior. J Urol 2004; Sep;172(3):989-92.

618. Fitzgerald MP, Mulligan M, Parthasarathy S. Nocturic frequency is related to severity of obstructive sleep apnea, improves with continuous positive airways treatment. Am J Obstet Gynecol 2006; May;194(5):1399-403.

619. Sarma AV, Burke JP, Jacobson DJ, McGree ME, St Sauver J, Girman CJ, et al. Associations between diabetes and clinical markers of benign prostatic hyperplasia among community-dwelling Black and White men. Diabetes Care 2008; Mar;31(3):476-82.

620. McKeigue PM, Reynard JM. Relation of nocturnal polyuria of the elderly to essential hypertension. Lancet 2000; Feb 5;355(9202):486-8.

621. Hall SA, Chiu GR, Kaufman DW, Wittert GA, Link CL, McKinlay JB. Commonly used antihypertensives and lower urinary tract symptoms: results from the Boston Area Community Health (BACH) Survey. BJU Int 2011; Sep 27;.

622. Bulpitt CJ, Connor M, Schulte M, Fletcher AE. Bisoprolol and nifedipine retard in elderly hypertensive patients: effect on quality of life. J Hum Hypertens 2000; Mar;14(3):205-12.

623. Reynard JM, Cannon A, Yang Q, Abrams P. A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. Br J Urol 1998; Feb;81(2):215-8.

624. Asplund R, Johansson S, Henriksson S, Isacsson G. Nocturia, depression and antidepressant medication. BJU Int 2005; Apr;95(6):820-3.

625. Hakkinen JT, Shiri R, Koskimaki J, Tammela TL, Auvinen A, Hakama M. Depressive symptoms increase the incidence of nocturia: Tampere Aging Male Urologic Study (TAMUS). J Urol 2008; May;179(5):1897-901.

626. Krieger J, Petiau C, Sforza E, Delanoe C, Hecht MT, Chamouard V. Nocturnal pollakiuria is a symptom of obstructive sleep apnea. Urol Int 1993;50(2):93-7.

627. Pressman MR, Figueroa WG, Kendrick-Mohamed J, Greenspon LW, Peterson DD. Nocturia. A rarely recognized symptom of sleep apnea and other occult sleep disorders. Arch Intern Med 1996; Mar 11;156(5):545-50.

628. Lowenstein L, Kenton K, Brubaker L, Pillar G, Undevia N, Mueller ER, et al. The relationship between obstructive sleep apnea, nocturia, and daytime overactive bladder syndrome in women. Am J Obstet Gynecol 2008; May;198(5):598.e1,598.e5.

629. Endeshaw Y. Correlates of self-reported nocturia among community-dwelling older adults. J Gerontol A Biol Sci Med Sci 2009; Jan;64(1):142-8.

630. Umlauf MG, Chasens ER, Greevy RA, Arnold J, Burgio KL, Pillion DJ. Obstructive sleep apnea, nocturia and polyuria in older adults. Sleep 2004; Feb 1;27(1):139-44.

631. Kinn AC, Harlid R. Snoring as a cause of nocturia in men with lower urinary tract symptoms. Eur Urol 2003; Jun;43(6):696-701.

632. Compston A, Coles A. Multiple sclerosis. Lancet 2002; Apr 6;359(9313):1221-31.

633. DasGupta R, Fowler CJ. Bladder, bowel and sexual dysfunction in multiple sclerosis: management strategies. Drugs 2003;63(2):153-66.

634. Young A, Home M, Churchward T, Freezer N, Holmes P, Ho M. Comparison of sleep disturbance in mild versus severe Parkinson's disease. Sleep 2002; Aug 1;25(5):573-7.

635. Bump, R. C., Mattiasson, A., Bo, K. et al.: The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol, 175: 10, 1996.

636. Hall, A. F., Theofrastous, J. P., Cundiff, G. W. et al.: Interobserver and intraobserver reliability of the proposed International Continence Society, Society of Gynecologic Surgeons, and American Urogynecologic Society pelvic organ prolapse classification system. Am J Obstet Gynecol, 175: 1467, 1996.

637. Weber, A. M., Abrams, P., Brubaker, L. et al.: The standardization of terminology for researchers in female pelvic floor disorders. Int Urogynecol J Pelvic Floor Dysfunct, 12: 178, 2001.

638. Ellerkmann, R. M., Cundiff, G. W., Melick, C. F. et al.: Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol, 185: 1332, 2001.

639. Lukacz, E. S., Lawrence, J. M., Buckwalter, J. G. et al.: Epidemiology of prolapse and incontinence questionnaire: validation of a new epidemiologic survey. Int Urogynecol J Pelvic Floor Dysfunct, 16: 272, 2005.

640. Ghetti, C., Gregory, W. T., Edwards, S. R. et al.: Pelvic organ descent and symptoms of pelvic floor disorders. Am J Obstet Gynecol, 193: 53, 2005.

641. Swift, S. E.: The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care. Am J Obstet Gynecol, 183: 277, 2000.

642. Hendrix, S. L., Clark, A., Nygaard, I. et al.: Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J Obstet Gynecol, 186: 1160, 2002.

643. Handa, V. L., Garrett, E., Hendrix, S. et al.: Progression and remission of pelvic organ prolapse: a longitudinal study of menopausal women. Am J Obstet Gynecol, 190: 27, 2004.

644. Lawrence, J. M., Lukacz, E. S., Nager, C. W. et al.: Prevalence and co-occurrence of pelvic floor disorders in community-dwelling women. Obstet Gynecol, 111: 678, 2008.

645. Bradley, C. S., Zimmerman, M. B., Qi, Y. et al.: Natural history of pelvic organ prolapse in postmenopausal women. Obstet Gynecol, 109: 848, 2007.

646. Nygaard, I., Bradley, C., Brandt, D.: Pelvic organ prolapse in older women: prevalence and risk factors. Obstet Gynecol, 104: 489, 2004.

647. Tegerstedt, G., Hammarstrom, M.: Operation for pelvic organ prolapse: a follow-up study. Acta Obstet Gynecol Scand, 83: 758, 2004.

648. Rortveit, G., Brown, J. S., Thom, D. H. et al.: Symptomatic pelvic organ prolapse: prevalence and risk factors in a population-based, racially diverse cohort. Obstet Gynecol, 109: 1396, 2007.

649. Eva, U. F., Gun, W., Preben, K.: Prevalence of urinary and fecal incontinence and symptoms of genital prolapse in women. Acta Obstet Gynecol Scand, 82: 280, 2003.

650. Samuelsson, E. C., Victor, F. T., Tibblin, G. et al.: Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors. Am J Obstet Gynecol, 180: 299, 1999.

651. Kumari, S., Walia, I., Singh, A.: Self-reported uterine prolapse in a resettlement colony of north India. J Midwifery Womens Health, 45: 343, 2000.

652. MacLennan, A. H., Taylor, A. W., Wilson, D. H. et al.: The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery. BJOG, 107: 1460, 2000.

653. Mant, J., Painter, R., Vessey, M.: Epidemiology of genital prolapse: observations from the Oxford Family Planning Association Study. Br J Obstet Gynaecol, 104: 579, 1997.

654. Boyles, S. H., Weber, A. M., Meyn, L.: Procedures for pelvic organ prolapse in the United States, 1979-1997. Am J Obstet Gynecol, 188: 108, 2003.

655. Brown, J. S., Waetjen, L. E., Subak, L. L. et al.: Pelvic organ prolapse surgery in the United States, 1997. Am J Obstet Gynecol, 186: 712, 2002.

656. Olsen, A. L., Smith, V. J., Bergstrom, J. O. et al.: Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol, 89: 501, 1997.

657. Shah, A. D., Kohli, N., Rajan, S. S. et al.: The age distribution, rates, and types of surgery for pelvic organ prolapse in the USA. Int Urogynecol J Pelvic Floor Dysfunct, 19: 421, 2008.

658. Raza-Khan F, Cunkelman J, Lowenstein L, Shott S, Kenton K. Prevalence of bowel symptoms in women with pelvic floor disorders. Int J Urogynecol 2010 Aug;21(8):933-8. Epub 2010 May 7.

659. Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: a systematic review. BMC Gastroenterol. 2008 Feb 12;8:5. Review.

660. Jelovsek JE, Barber MD, Paraiso MF, Walters MD. Functional bowel and anorectal disorders in patients with pelvic organ prolapse and incontinence. Am J Obstet Gynecol 2005;193:2105-11.

661. Kahn MA, Breitkopf CR, Valley MT, Woodman PJ, O'Boyle AL, Bland DI, Schaffer JI, Grady JJ, Swift SE. Pelvic Organ Support Study (POSST) and bowel symptoms: straining at stool is associated with perineal and anterior vaginal descent in a general gynecologic population. Am J Obstet Gynecol 2005;192:1516-22.

662. Morgan DM, DeLancey JO, Guire KE, Fenner DE. Symptoms of anal incontinence and difficult defecation among women with prolapse and a matched control cohort. Am J Obstet Gynecol 2007;197:509 e1-6.

663. Snooks SJ, Barnes PR, Swash M, Henry MM. Damage to the innervation of the pelvic floor musculature in chronic constipation. Gastroenterology. 1985;89:977-81.

664. Lembo A, Camilleri M. Chronic constipation. N Engl J Med 2003;349:1360-8.

665. Spence-Jones C, Kamm MA, Henry MM, Hudson CN. Bowel dysfunction: a pathogenic factor in uterovaginal prolapse and urinary stress incontinence. Br J Obstet Gynaecol 1994;101:147-52.

666. Arya LA, Novi JM, Shaunik A, Morgan MA, Bradley CS. Pelvic organ prolapse, constipation, and dietary fiber intake in women: a case-control study. Am J Obstet Gynecol 2005;192:1687-91.

667. Rortveit G, Brown JS, Thom DH, Van Den Eeden SK, Creasman JM, Subak LL. Symptomatic pelvic organ prolapse: prevalence and risk factors in a population-based, racially diverse cohort. Obstet Gynecol 2007;109:1396-403.

668. Varma MG, Hart SL, Brown JS, Creasman JM, Van Den Eeden SK, Thom DH. Obstructive Defecation in Middle-aged Women. Dig Dis Sci 2008.

669. Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J Obstet Gynecol 2002;186:1160-6.

670. Tegerstedt G, Maehle-Schmidt M, Nyren O, Hammarstrom M. Prevalence of symptomatic pelvic organ prolapse in a Swedish population. Int Urogynecol J Pelvic Floor Dysfunct 2005;16:497-503.

671. Bradley CS, Kennedy CM, Nygaard IE. Pelvic floor symptoms and lifestyle factors in older women. J Womens Health (Larchmt) 2005;14:128-36.

672. Yoshioka K, Matsui Y, Yamada O, Sakaguchi M, Takada H, Hioki K, Yamamoto M, Kitada M, Sawaragi I. Physiologic and anatomic assessment of patients with rectocele. Diseases of the Colon & Rectum. 1991;34:704-8.

673. Kelvin FM, Maglinte DD, Hornback JA, Benson JT. Pelvic prolapse: assessment with evacuation proctography (defecography)[comment]. Radiology. 1992;184:547-51.

674. Altman D, Lopez A, Kierkegaard J, Zetterstrom J, Falconer C, Pollack J, Mellgren A. Assessment of posterior vaginal wall prolapse: comparison of physical findings to cystodefecoperitoneography. Int Urogynecol J Pelvic Floor Dysfunct 2005;16:96-103; discussion 103.

675. Weber AM, Walters MD, Ballard LA, Booher DL, Piedmonte MR. Posterior vaginal prolapse and bowel function. American Journal of Obstetrics & Gynecology. 1998;179:1446-9; discussion 1449-50.

676. Ellerkmann RM, Cundiff GW, Melick CF, Nihira MA, Leffler K, Bent AE. Correlation of symptoms with location and severity of pelvic organ prolapse. American Journal of Obstetrics & Gynecology. 2001;185:1332-7.

677. Bradley CS, Brown MB, Cundiff GW, Goode PS, Kenton KS, Nygaard IE, Whitehead WE, Wren PA, Weber AM. Bowel symptoms in women planning surgery for pelvic organ prolapse. Am J Obstet Gynecol 2006.

678. Klingele CJ, Bharucha AE, Fletcher JG, Gebhart JB, Riederer SG, Zinsmeister AR. Pelvic organ prolapse in defecatory disorders. Obstet Gynecol 2005;106:315-20.

679. Saks EK, Harvie HS, Asfaw TS, Arya LA. Clinical significance of obstructive defecatory symptoms in women with pelvic organ prolapse. Int J Gynaecol Obstet. 2010 Dec;111(3):237-40.

680. Wang J, Varma MG, Creasman JM, Subak LL, Brown JS, Thom DH, van den Eeden SK. Pelvic floor disorders and quality of life in women with self-reported irritable bowel syndrome. Aliment Pharmacol Ther. 2010 Feb 1;31(3):424-31. Epub 2009 Oct 23.

681. Mellgren A, López A, Schultz I, Anzén B. Rectocele is associated with paradoxical anal sphincter reaction. Int J Colorectal Dis. 1998;13(1):13-6.

682. Altman D, Falconer C, Cnattingius S, Granath F. Pelvic organ prolapse surgery following hysterectomy on benign indications. Am J Obstet Gynecol 2008.

683. Cooper K, Lee A, Chien P, Raja E, Timmaraju V, Bhattacharya S. Outcomes following hysterectomy or endometrial ablation for heavy menstrual bleeding: retrospective analysis of hospital episode statistics in Scotland. BJOG. 2011 Sep;118(10):1171-9. doi: 10.1111/j.1471-0528.2011.03011.x. Epub 2011 May 31.

684. Mant J, Painter R, Vessey M. Epidemiology of genital prolapse: observations from the Oxford Family Planning Association Study. British Journal of Obstetrics & Gynaecology. 1997;104:579-85.

685. Swift SE, Pound T, Dias JK. Case-control study of etiologic factors in the development of severe pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2001;12:187-92.

686. Swift SE. The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care. Am J Obstet Gynecol 2000;183:277-85.

687. Dallenbach P, Kaelin-Gambirasio I, Dubuisson JB, Boulvain M. Risk factors for pelvic organ prolapse repair after hysterectomy. Obstet Gynecol 2007;110:625-32.

688. Forsgren C, Zetterstrom J, Lopez A, Nordenstam J, Anzen B, Altman D. Effects of hysterectomy on bowel function: a three-year, prospective cohort study. Dis Colon Rectum 2007;50:1139-45.

689. DeLancey JO. Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol 1992;166:1717-28.

690. Marchionni M, Bracco GL, Checcucci V, Carabaneanu A, Coccia EM, Mecacci F, Scarselli G. True incidence of vaginal vault prolapse. Thirteen years of experience. J Reprod Med 1999;44:679-84.

691. Forsgren C, Lundholm C, Johansson AL, Cnattingius S, Zetterström J, Altman D.Vaginal hysterectomy and risk of pelvic organ prolapse and stress urinary incontinence surgery. Int Urogynecol J. 2012 Jan;23(1):43-8. Epub 2011 Aug 18.

692. Altman D, Zetterstrom J, Schultz I, Nordenstam J, Hjern F, Lopez A, Mellgren A. Pelvic organ prolapse and urinary incontinence in women with surgically managed rectal prolapse: a population-based case-control study. Dis Colon Rectum 2006;49:28-35.

693. Moalli PA, Jones Ivy S, Meyn LA, Zyczynski HM. Risk factors associated with pelvic floor disorders in women undergoing surgical repair. Obstet Gynecol 2003;101:869-74.

694. Wiskind AK, Creighton SM, Stanton SL. The incidence of genital prolapse after the Burch colposuspension. Am J Obstet Gynecol 1992;167:399-404; discussion 404-5.

695. Kjölhede P. Genital prolapse in women treated successfully and unsuccessfully by the Burch colposuspension. Acta Obstet Gynecol Scand 1998;77:444-50.

696. Denman M, Gregory W, Boyles S, Smith V, Edwards S, Clark A. Reoperation 10 years after surgically managed pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol 2008;198:555.e1-5.

697. O'Boyle AL, Woodman PJ, O'Boyle JD, Davis GD, Swift SE. Pelvic organ support in nulliparous pregnant and nonpregnant women: a case control study. Am J Obstet Gynecol 2002;187:99-102.

698. Sze EH, Sherard GB, 3rd, Dolezal JM. Pregnancy, labor, delivery, and pelvic organ prolapse. Obstet Gynecol 2002;100:981-6.

699. Sze EH, Jones WP, Ferguson JL, Barker CD, Dolezal JM. Prevalence of urinary incontinence symptoms among black, white, and Hispanic women. Obstet Gynecol 2002;99:572-5.

700. Carley ME, Turner RJ, Scott DE, Alexander JM. Obstetric history in women with surgically corrected adult urinary incontinence or pelvic organ prolapse. Journal of the American Association of Gynecologic Laparoscopists 1999;6:85-9.

701. Lukacz ES, Lawrence JM, Contreras R, Nager CW, Luber KM. Parity, mode of delivery, and pelvic floor disorders. Obstet Gynecol 2006;107:1253-60.

702. Uma R, Libby G, Murphy DJ. Obstetric management of a woman's first delivery and the implications for pelvic floor surgery in later life. Bjog 2005;112:1043-6.

703. Tegerstedt G, Miedel A, Maehle-Schmidt M, Nyren O, Hammarstrom M. Obstetric risk factors for symptomatic prolapse: a population-based approach. Am J Obstet Gynecol 2006;194:75-81.

704. Fritel X, Varnoux N, Zins M, Breart G, Ringa V. Symptomatic pelvic organ prolapse at midlife, quality of life, and risk factors. Obstet Gynecol. 2009 Mar;113(3):609-16.

705. Quiroz LH, Muñoz A, Shippey SH, Gutman RE, Handa VL. Vaginal parity and pelvic organ prolapse. J Reprod Med. 2010 Mar-Apr;55(3-4):93-8.

706. Chiaffarino F, Chatenoud L, Dindelli M, Meschia M, Buonaguidi A, Amicarelli F, Surace M, Bertola E, Di Cintio E, Parazzini F. Reproductive factors, family history, occupation and risk of urogenital prolapse. European Journal of Obstetrics, Gynecology, & Reproductive Biology 1999;82:63-7.

707. MacLennan AH, Taylor AW, Wilson DH, Wilson D. The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery. BJOG: an International Journal of Obstetrics & Gynaecology 2000;107:1460-70.

708. Risk factors for genital prolapse in non-hysterectomized women around menopause. Results from a large cross-sectional study in menopausal clinics in Italy. Progetto Menopausa Italia Study Group. Eur J Obstet Gynecol Reprod Biol 2000;93:135-40.

709. Leijonhufvud A, Lundholm C, Cnattingius S, Granath F, Andolf E, Altman D. Risks of stress uriunary incontinence and pelvic organ prolapse surgewry in relation to mode of childbirth. Am J Obstet Gynecol. 2011 Jan;204(1):70.e1-7.

710. Handa VL, Blomquist JL, Knoepp LR, Hoskey KA, McDermott KC, Muñoz A. Pelvic floor disorders 5-10 years 5-10 years after vaginal or cesarean birth. Obstet Gynecol. 2011 Oct;118(4):777-84.

711. Carley ME, Schaffer J. Urinary incontinence and pelvic organ prolapse in women with Marfan or Ehlers Danlos syndrome. American Journal of Obstetrics & Gynecology. 2000;182:1021-3.

712. McIntosh LJ, Mallett VT, Frahm JD, Richardson DA, Evans MI. Gynecologic disorders in women with Ehlers-Danlos syndrome. J Soc Gynecol Investig 1995;2:559-64.

713. Scherf C, Morison L, Fiander A, Ekpo G, Walraven G. Epidemiology of pelvic organ prolapse in rural Gambia, West Africa. BJOG: an International Journal of Obstetrics & Gynaecology 2002;109:431-6.

714. Lind LR, Lucente V, Kohn N. Thoracic kyphosis and the prevalence of advanced uterine prolapse. Obstet Gynecol 1996;87:605-9.

715. Nguyen JK, Lind LR, Choe JY, McKindsey F, Sinow R, Bhatia NN. Lumbosacral spine and pelvic inlet changes associated with pelvic organ prolapse. Obstet Gynecol 2000;95:332-6.

716. Marshman D, Percy J, Fielding I, Delbridge L. Rectal prolapse: relationship with joint mobility. Australian & New Zealand Journal of Surgery 1987;57:827-9.

717. Norton PA, Baker JE, Sharp HC, Warenski JC. Genitourinary prolapse and joint hypermobility in women. Obstetrics & Gynecology. 1995;85:225-8.

718. Pandey S, Bhattacharya S. Impact of obesity on gynecology. Womens Health (Lond Engl). 2010 Jan;6(1):107-17. Review.

719. Washington BB, Erekson EA, Kassis NC, Myers DL. The association between obesity and stage II or greater prolapse. Am J Obstet Gynecol. 2010 May;202(5):503.e1-4. Epub 2010 Feb 20.

720. Samuelsson EC, Arne Victor FT, Tibblin G, Svardsudd KF. Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors. American Journal of Obstetrics & Gynecology 1999;180:299-305.

721. Forsman M, Iliadou A, Magnusson P, Falconer C, Altman D. Diabetes and obesity-related risks for pelvic reconstructive surgery in a cohort of Swedish twins. Diabetes Care. 2008 Oct;31(10):1997-9. Epub 2008 Jul 15.

722. Strinic T, Eterovic D, Dujic Z, Markovic V, Tocilj J. Spirometric disorders in women with genital descensus. Acta Obstet Gynecol Scand 1997;76:879-83.

723. Nygaard I, Bradley C, Brandt D. Pelvic organ prolapse in older women: prevalence and risk factors. Obstet Gynecol 2004;104:489-97.

724. Woodman PJ, Swift SE, O'Boyle AL, Valley MT, Bland DR, Kahn MA, Schaffer JI. Prevalence of severe pelvic organ prolapse in relation to job description and socioeconomic status: a multicenter cross-sectional study. Int Urogynecol J Pelvic Floor Dysfunct 2006;17:340-5.

725. Strinic T, Bukovic D, Roje D, Milic N, Pavic M, Turcic P. Epidemiology of pelvic floor disorders between urban and rural female inhabitants. Coll Antropol 2007;31:483-7.

726. Walker GJ, Gunasekera P. Pelvic organ prolapse and incontinence in developing countries: review of prevalence and risk factors. Int Urogynecol J. 2011 Feb;22(2):127-35. Epub 2010 Jul 9. Review.

727. Jorgensen S, Hein HO, Gyntelberg F. Heavy lifting at work and risk of genital prolapse and herniated lumbar disc in assistant nurses. Occup Med (Lond) 1994;44:47-9.

728. Larsen WI, Yavorek T. Pelvic prolapse and urinary incontinence in nulliparous college women in relation to paratrooper training. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:769-71.

729. Thompson H. On irritability of the bladder. The Lancet. 1854;63(1607):637–638.

730. Diokno AC, Brock BM, Herzog AR, Bromberg J. Medical correlates of urinary incontinence in the elderly. URL. 1990 Aug.;36(2):129–138.

731. Mushkat Y, Bukovsky I, Langer R. Female urinary stress incontinence--does it have familial prevalence? Am J Obstet Gynecol 1996;174:617-9.

732. Hannestad YS, Lie RT, Rortveit G, Hunskaar S. Familial risk of urinary incontinence in women: population based cross sectional study. BMJ 2004;329:889-91.

733. Elia G, Bergman J. Familial incidence of urinary incontinence. Am. J. Obstet. Gynecol. 2002;187:53–55.

734. Ertunc D, Tok E, Pata O, Dilek U. Is stress urinary incontinence a familial condition? Acta Obstet Gynecol Scand 2004;83:912-6.

735. Buchsbaum GM, Duecy EE, Kerr LA, Huang L-S, Guzick DS. Urinary incontinence in nulliparous women and their parous sisters. Obstet Gynecol. 2005 Dec.;106(6):1253–1258.

736. Lapitan MC, Chye PL; Asia-Pacific Continence Advisory Board. The epidemiology of overactive bladder among females in Asia: a questionnaire survey. Int Uroggynecol J Pelvic Floor Dysfunct 2001;12(4):226-31.

737. Torrisi G, Sampugnaro EG, Pappalardo EM, D'Urso E, Vecchio M, Mazza A. Postpartum urinary stress incontinence: analysis of the associated risk factors and neurophysiological tests. Minerva Ginecol. 2007 Oct.;59(5):491–498.

738. Chaliha C, Kalia V, Stanton SL, Monga A, Sultan AH. Antenatal prediction of postpartum urinary and fecal incontinence. Obstet Gynecol. 1999 Nov.;94(5 Pt 1):689–694.

739. Torrisi G, Minini G, Bernasconi F, Perrone A, Trezza G, Guardabasso V, et al. A prospective study of pelvic floor dysfunctions related to delivery. Eur. J. Obstet. Gynecol. Reprod. Biol. 2011 Nov. 15;

740. Rinne K. What predisposes young women to genital prolapse? European Journal of Obstetrics, Gynecology, & Reproductive Biology. 1999;84:23-5.

741. Rechberger T, Miotła P, Futyma K, Bartuzi A, Basta A, Opławski M, et al. [Risk factors of pelvic organ prolapsed in women qualified to reconstructive surgery--the Polish multicenter study]. Ginekol. Pol. 2010 Nov.;81(11):821–827.

742. Jack GS, Nikolova G, Vilain E, Raz S, Rodríguez LV. Familial tranmission of genitovaginal prolapse. Int Urogynecol J. 2005 Dec. 20;17(5):498–501.

743. Chiaffarino F, Chatenoud L, Dindelli M, Meschia M, Buonaguidi A, Amicarelli F, Surace M, Bertola E, Di Cintio E, Parazzini F. Reproductive factors, family history, occupation and risk of urogenital prolapse. European Journal of Obstetrics, Gynecology, & Reproductive Biology 1999;82:63-7.

744. McLennan MT, Harris JK, Kariuki B, Meyer S. Family history as a risk factor for pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2008.

745. Slieker-ten Hove MC, Pool-Goudzwaard AL, Eijkemans MJ, Steegers-Theunissen RP, Burger CW, Vierhout ME. Symptomatic pelvic organ prolapse and possible risk factors in a general population. Am J Obstet Gynecol. 2009 Feb;200(2):184.e1-7. Epub 2008 Dec 25.

746. Mathlouthi N, Ben Ayed B, Dhouib M, Chaabene K, Trabelsi K, Amouri H, et al. Genital prolapse in young women: a study of risk factors. Tunis Med. 2011 Jul.;89(7):627–631.

747. Buchsbaum GM, Duecy EE. Incontinence and pelvic organ prolapse in parous/nulliparous pairs of identical twins. Neurourol. Urodyn. 2008;27(6):496–498.

748. Nguyen A, Aschkenazi SO, Sand PK, Du H, Botros SM, Gamble TL, et al. Nongenetic factors associated with stress urinary incontinence. Obstet Gynecol. 2011 Feb.;117(2 Pt 1):251–255.

749. Rohr G, Kragstrup J, Gaist D, Christensen K. Genetic and environmental influences on urinary incontinence: a Danish population-based twin study of middle-aged and elderly women. Acta Obstet Gynecol Scand. 2004 Oct.;83(10):978–982.

750. Altman D, Forsman M, Falconer C, Lichtenstein P. Genetic influence on stress urinary incontinence and pelvic organ prolapse. Eur. Urol. 2008 Oct.;54(4):918–922.

751. Wennberg A-L, Altman D, Lundholm C, Klint A, Iliadou A, Peeker R, et al. Genetic influences are important for most but not all lower urinary tract symptoms: a population-based survey in a cohort of adult Swedish twins. Eur. Urol. 2011 Jun.;59(6):1032–1038.

752. Hansell NK, Dietz HP, Treloar SA, Clarke B, Martin NG. Genetic covariation of pelvic organ and elbow mobility in twins and their sisters. Twin Res. 2004 Jun.;7(3):254–260.

753. Dietz HP, Hansell NK, Grace ME, Eldridge AM, Clarke B, Martin NG. Bladder neck mobility is a heritable trait. BJOG: An International Journal of Obstetrics & Gynaecology. 2005 Mar.;112(3):334–339.

754. Gontard von A, Schaumburg H, Hollmann E, Eiberg H, Rittig S. The genetics of enuresis: a review. J. Urol. 2001 Dec.;166(6):2438–2443.

755. Nikolova G, Lee H, Berkovitz S, Nelson S, Sinsheimer J, Vilain E, et al. Sequence variant in the laminin gamma1 (LAMC1) gene associated with familial pelvic organ prolapse. Hum. Genet. 2007 Feb.;120(6):847–856.

756. Ioannidis JP, Boffetta P, Little J, O'Brien TR, Uitterlinden AG, Vineis P, et al. Assessment of cumulative evidence on genetic associations: interim guidelines. International Journal of Epidemiology. 2007 Dec. 3;37(1):120–132.

757. Skorupski P, Król J, Starega J, Adamiak A. An [alpha]-1 chain of type I collagen Sp1-binding site polymorphism in women suffering from stress urinary incontinence. Am J Obstet Gynecol. 2006 Feb;194(2):346-50.

758. Sioutis D, Economou E, Lambrinoudaki I, Tsamadias V, Creatsa M, Liapis A. Sp1 collagen I A1 polymorphism in women with stress urinary incontinence. Int Urogynecol J. 2011 Jul.;22(7):835–839.

759. Ferreira CE, Fonseca AM, Silva ID, Girão MJ, Sartori MG, Castro RA. The relationship between the Trp 64 Arg polymorphism of the beta 3-adrenoceptor gene and idiopathic overactive bladder. Am J Obstet Gynecol. 2011 Jul;205(1):82.e10-4. Epub 2011 Feb 23.

760. Honda et al. Mutation of B3-Adrenoceptor gene: a genetic marker for overactive bladder. Neurourol. Urodyn. 2006 Jul. 26;25:652.

761. Schwanke CHA, Bittencourt L, Noronha JAP, Augustin SAJ, Jung IE, Cruz IBM. Is there an association between T102C polymorphism of the serotonin receptor 2A gene and urinary incontinence? Braz. J. Med. Biol. Res. 2007 Oct.;40(10):1315–1322.

762. Noronha JAP, Schwanke CHA, Machado DC, Braga R, Lubianca JM, Sesti FL, et al. Association between T102C polymorphism of serotonin 2A receptor gene and urinary incontinence in older women. J. Investig. Med. 2010 Jan.;58(1):32–37.

763. Ozbek et al. Tt polymorphism in rs 2165241 region and cc polymorphism in rs 3825942 region in lysyl oxidase like-1 (lox-l1) gene may play a role in stress urinary incontinence pathophysiology. European Urology, Supplements. 2011;10(2):291.

764. Skorupski P, Miotła P, Jankiewicz K, Rechberger T. [MMP-1 and MMP-3 gene encoding polymorphism and the risk of the development of pelvic organ prolapse and stress urinary incontinence]. Ginekol. Pol. 2010 Aug.;81(8):594–599.

765. Vishwajit S et al. Association of MMP1 promoter variant with stress urinary incontinence and pelvic organ prolapse in women. J. Urol. 2009 Apr. 28;191(4):481.

766. Cornu JN, Merlet B, Cussenot O, Cancel-Tassin G, Ciofu C, Amarenco G, et al. Genetic susceptibility to urinary incontinence: implication of polymorphisms of androgen and oestrogen pathways. World J Urol. 2011 Apr.;29(2):239–242.

767. Skorupski P, Król J, Starega J, Adamiak A, Jankiewicz K, Rechberger T. An alpha-1 chain of type I collagen Sp1-binding site polymorphism in women suffering from stress urinary incontinence. Am. J. Obstet. Gynecol. 2006 Feb.;194(2):346–350.

768. Skorupski P, Miotła P, Jankiewicz K, Rechberger T. Polymorphism of the gene encoding alpha-1 chain of collagen type I and a risk of pelvic organ prolapse--a preliminary study. Ginekol. Pol. 2007 Nov.;78(11):852–855.

769. Rodrigues AM, Girão MJBC, da Silva IDCG, Sartori MGF, Martins K de F, Castro R de A. COL1A1 Sp1-binding site polymorphism as a risk factor for genital prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Nov.;19(11):1471–1475.

770. Feiner B, Fares F, Azam N, Auslender R, David M, Abramov Y. Does COLIA1 SP1-binding site polymorphism predispose women to pelvic organ prolapse? Int Urogynecol J Pelvic Floor Dysfunct. 2009 Sep.;20(9):1061–1065.

771. Cho HJ, Jung HJ, Kim SK, Choi JR, Cho NH, Bai SW. Polymorphism of a COLIA1 gene Sp1 binding site in Korean women with pelvic organ prolapse. Yonsei Med. J. 2009 Aug. 31;50(4):564–568.

772. Martins K de F, de Jármy-DiBella ZIK, da Fonseca AMRM, Castro RA, da Silva IDCG, Girão MJBC, et al. Evaluation of demographic, clinical characteristics, and genetic polymorphism as risk factors for pelvic organ prolapse in Brazilian women. Neurourol. Urodyn. 2011 Sep.;30(7):1325–1328.

773. Jeon MJ, Chung SM, Choi JR, Jung HJ, Kim SK, Bai SW. The relationship between COL3A1 exon 31 polymorphism and pelvic organ prolapse. J. Urol. 2009 Mar.;181(3):1213–1216.

774. Kluivers KB, Dijkstra JR, Hendriks JCM, Lince SL, Vierhout ME, van Kempen LCL. COL3A1 2209G>A is a predictor of pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Sep.;20(9):1113–1118.

775. Chen H-Y, Chung Y-W, Lin W-Y, Wang J-C, Tsai F-J, Tsai C-H. Collagen type 3 alpha 1 polymorphism and risk of pelvic organ prolapse. Int J Gynaecol Obstet. 2008 Oct.;103(1):55–58.

776. Ferrell G, Lu M, Stoddard P, Sammel MD, Romero R, Strauss JF, et al. A single nucleotide polymorphism in the promoter of the LOXL1 gene and its relationship to pelvic organ prolapse and preterm premature rupture of membranes. Reprod Sci. 2009 May;16(5):438–446.

777. Fu R, Hagstrom S. Mutation screen of lysyl oxidase-like -1 and laminin. gamma 1 variant in patients with advanced female pelvic organ prolapse. J. Urol. 2009;181(4):481.

778. Chen C, Hill LD, Schubert CM, Strauss JF, Matthews CA. Is laminin gamma-1 a candidate gene for advanced pelvic organ prolapse? Am. J. Obstet. Gynecol. 2010 May;202(5):505.e1–5.

779. Romero A, Jamison M. Are Single Nucleotide Polymorphisms Associated With Pelvic Organ Prolapse? Female Pelvic Medicine & …. 2008

780. Campeau L et al. Characterization of SNPS within the MMP-1 promotor region in women with and without POP. Neurourol. Urodyn. 2011 Jun. 15;:1–1.

781. Chen H-Y, Lin W-Y, Chen Y-H, Chen W-C, Tsai F-J, Tsai C-H. Matrix metalloproteinase-9 polymorphism and risk of pelvic organ prolapse in Taiwanese women. Eur. J. Obstet. Gynecol. Reprod. Biol. 2010 Apr.;149(2):222–224.

782. Chen H-Y, Chung Y-W, Lin W-Y, Chen W-C, Tsai F-J, Tsai C-H. Estrogen receptor alpha polymorphism is associated with pelvic organ prolapse risk. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Aug.;19(8):1159–1163.

783. Chen H-Y, Wan L, Chung Y-W, Chen W-C, Tsai F-J, Tsai C-H. Estrogen receptor beta gene haplotype is associated with pelvic organ prolapse. Eur. J. Obstet. Gynecol. Reprod. Biol. 2008 May;138(1):105–109.

784. Chen H-Y, Chung Y-W, Lin W-Y, Chen W-C, Tsai F-J, Tsai C-H. Progesterone receptor polymorphism is associated with pelvic organ prolapse risk. Acta Obstet Gynecol Scand. 2009;88(7):835–838.

785. Allen-Brady K, Cannon-Albright L, Farnham JM, Teerlink C, Vierhout ME, van Kempen LC, Kluivers KB, Norton PA. Identification of six loci associated with pelvic organ prolapse using genome-wide association analysis. Obstet Gynecol. 2011 Dec;118(6):1345-53.

786. Titi M, Jenkins JT, Urie A, Molloy RG. Prospective study of the diagnostic evaluation of faecal incontinence and leakage in male patients. Colorectal Dis. 2007;9:647-52.

787. Leigh RJ, Turnberg LA. Faecal incontinence: the unvoiced symptom. Lancet. 1982;1:1349-1351.

788. Thomas TM, Egan M, Walgrove A, Meade TW. The prevalence of faecal and double incontinence. Comm Med.1984;6:216-220.

789. Nelson RL, Norton N, Cautley E, Furner S. Community based prevalence of AI. JAMA. 1995;274:559-562.

790. Sharma A, Marshjall RJ, MacMillan AK, Merrie AEH, Reid P, Bissett IP. Determining levels of fecal incontinence in the community: a New Zealand cross-sectional study. Dis. Colon Rectum. 2011;54:1381-7.

791. Macmillan AK, Merrie AEH, Marshall RJ, Parry BR. The prevalence of faecal incontinence in community dwelling adults: a systematic review. Dis. Colon & Rectum.2004.47.1341-49.

792. Bai Y, Chen H, Hao J, Huang Y, Wang W. Long term outcome and quality of life after the Swenson procedure for Hirschprung's disease. J Pediatric Surg. 2002;37:639-42.

793. Javid PJ, Barnhart DC, Hirschi RB, Coran AG, Harmon CM. Immediate and long term results of surgical management of low imperforate anus in girls. J Pediatric Surg. 1998;33:198-203.

794. Rintala RJ, Lindahl H. Is normal bowel function possible after repair of intermediate and high anorectal malformations? J Pediatric Surg. 1995;30:491-4.

795. Hartman EE, Oort FJ, Aronson DC, Hanneman JG, van der Zee DC, et al. Critical factors affecting the quality of life of adult patients with anorectal malformations or Hirschprung's Disease. Am J Gastroent.2004;xx:907-13.

796. Forrester MB, Merz RD. Descriptive epidemiology of anal atresia in Hawaii, 1986-1999. Teratology.2002;66supp.:S12-6.

797. Largo RH, Gianciaruso M, Prader A. Development of intestinal and bladder control from birth until the 18th year of age. Longitudinal Study. Schweiz Med Wochenschr. 1978;108:155-60.

798. Nelson RL, Chattopadhyay A, Brooks W, Platt I, Paavana T, Earl S. Operative procedures for fissure in ano. Cochrane Database Syst Rev. 2011 Nov 9;11: CD002199.

799. Nelson R. Anal fissure (chronic). Clin Evid (Online). 2010 Mar 24;2010. pii: 0407. PubMed PMID: 21718564.

800. Pretlove SJ, Thompson PJ, Toozs-Hobson PM, Radley S, Khan KS. Does the mode of delivery predispose women to anal incontinence in the first year postpartum? A comparative systematic review. BJOG. 2008 Mar;115(4):421-34. Review. Erratum in: BJOG. 2010 Sep;117(10):1307-8.

801. Nelson RL, Furner SE, Westercamp M, Farquhar C. Cesarean delivery for the

prevention of anal incontinence. Cochrane Database Syst Rev. 2010 Feb 17;(2) :CD006756. Review.

802. Small KA, Wynne JM. Evaluating the pelvic floor in obstetric patients. Aust New Zeal Obstet Gynecol. 1990;30:41-45.

803. Madoff RD, Williams JG, Caushaj PF. Current concepts: Fecal incontinence. N Engl J Med. 1992;326:1002-1007.

804. Abou-Zahr C. Obstructed labour. In: Murray CJL, Lopez AD, eds. Health dimensions of sex and reproduction: the global burden of sexually transmitted diseases, HIV, maternal conditions, perinatal disorders and congenital anomalies. Cambridge, Mass. Harvard University Press, 1996.

805. Drossman DA. What can be done to control incontinence associated with the irritable bowel syndrome? Am J Gastroenterol. 1989;84:355-357.

806. Schiller LR, Santa Ana CA, Schmulen AC, Hendler RS, Harford WV, Fordtran JS. Pathogenesis of fecal incontinence in diabetes mellitus. N Engl J Med. 1982;307:1666-1671.

807. Campbell AJ, Reinken J, McCosh L. Incontinence in the elderly: prevalence and prognosis. Age Ageing. 1985;14:65-70.

808. Denis P, Bercoff E, Bizien MF, Brocker P, Chassagne P, Lamouliatte H et al. Etude de la prevalence de l'incontinence anale chez l'adulte. Gastroent Clin Biol. 1992;16:344-350.

809. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG et al. U.S. householder survey of functional gastrointestinal disorders: Prevalence, sociodemography, and health impact. Dig Dis Sci. 1993;38:1569-1580. 2001;114:474-477.

810. MacLennan AH, Taylor AW, Wilson DH, Wilson D. The prevalence of pelvic floor disorders and their relationship to gender, age, parity, and mode of delivery. BJOG 2000;107:1460-1470.

811. Giebel GD, Lefering R, Troidl H, Blochl H. Prevalence of fecal incontinence: what can be expected? Int J Colorectal Dis. 1998;13:73-77.

812. Lam L, Kennedy M, Chen F. Prevalence of faecal incontinence: obstetric and constipation risk factors: a population based study. Colorectal Dis. 1999;1:197-203.

813. Kalantar JS, Howell S, Talley NJ. Prevalence of faecal incontinence and associated risk factors. Med J Aust. 2002;176:54-57.

814. Lynch AJ, Dobbs BR, Keating J, Frizelle FA. The prevalence of faecal incontinence and constipation in a general New Zealand population: a postal survey. NZ Med J 2001;114:474-477.

815. Perry S, Shaw C, McGrother C, Mathews RJ, Assassa RP, Dallosso H et al. Prevalence of faecal incontinence in adults aged 40 years or more living in the community. Gut. 2002;50: 480-484.

816. Chaliha C, Kalia V, Stanton SL, Monga A, Sultan AH. Antenatal prediction of postpartum urinary and fecal incontinence. Obstet Gynecol. 1999;94:689-694.

817. Eason E, Labrecque M, Marcoux S, Mondor M. AI after childbirth. CMAJ. 2002;166:326-330.

818. Sangalli MR, Floris L, Faltin D, Weil A. AI in women with third or fourth degree perineal tears and subsequent vaginal deliveries. Aust NZ J Obstet Gynaecol. 2000;40:244-248.

819. Okonkwo JE, Obionu CN, Okonkwo CV, Obiechina NJ. AI among Igbo women. Int J Clin Pract. 2002;56:178-180.

820. Rizk DE, Hassan MY, Shaheen H, Chervian JV, Micallef R, Dunn E. The prevalence and determinants of health care seeking behavior for fecal incontinence in multiparous United Arab Emirates females. Dis Colon Rectum. 2001;44:1850-1856.

821. Alnaif B, Drutz HP.The prevalence of urinary and fecal incontinence in Canadian secondary school teenage girls: questionnaire study and review of the literature. Int J Urogynecol/J Pelvic Floor Dysfunct. 2001;12:134-137.

822. Faltin DL, Sangalli MR, Curtin F, Morabia A, Weil A. Prevalence of AI and other anorectal symptoms in women. Int J Urogynecol/J Pelvic Floor Dysfunct. 2001;121: 117-120.

823. Ishigooka M, Hashimoto T, Izumiya K, Sasagawa I, Nakada T. Incidence of AI after long term follow up of patients treated by ureterosigmoidostomy. Int Urol Nephrol. 1993;25:455-460.

824. Adolfsson J, Helgason AR, Dickman P, Steineck G. Urinary and bowel symptoms in men with and without prostate cancer: results from an observational study in the Stockholm area. Eur Urol. 1998;33:11-16.

825. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population bases survey of 15000 adults. Arch Intern Med. 2001;161:1989-1996.

826. Kok ALM, Voorhorst FJ, Burger CW, van Houten P, Kenemans P, Jansens J. Urinary and faecal incontinence in community-residing elderly women. Age Ageing. 1992;21:211-215.

827. Talley NJ, O'Keefe EA, Zinsmeister AR, Melton LJ. Prevalence of gastrointestinal symptoms in the elderly: a population based study. Gastroenterol. 1992;102:895-901.

828. Nakanishi N, Tatara K, Nakajima K, Takabayashi H, Takahashi S, Naramura H et al. Urinary and fecal incontinence in a community-residing elderly population: prevalence, correlates and prognosis. Nippon Koshu Eisei Zasshi. 1997;44:192-200.

829. Roberts RO, Jacobsen SJ, Reilly WT, Pemberton JH, Lieber MM, Talley NJ. Prevalence of combined fecal and urinary incontinence: a community-based study. J Am Geriatr Soc. 1999;47:837-841.

830. Edwards NI, Jones D. The prevalence of faecal incontinence in older people living at home. Age Ageing. 2001;30:503-507.

831. Verhagen TE, Lagro-Janssen AL. Fecal incontinence in community dwelling elderly: findings from a study of prevalence, consultation of physicians, psychosocial aspects and treatment. Ned Tijdschr Geneeskd. 2001;145:741-745.

832. Tpokinova E, Neuwirth J, Stankova M, Mellanova A, Haas T. Urinary and fecal incontinence in geriatric facilities in the Czech Republic. Cas Lek Cesk. 1997;136:573-577.

833. Nelson RL, Furner S, Jesudason V. Fecal incontinence in Wisconsin nursing homes. Dis Colon Rectum. 1998;41:1226-1229.

834. Borrie MJ, Davidson HA. Incontinence in institutions: costs and contributing factors. CMAJ. 1992;147:322-328.

835. Damon H, Guye O, Seigneurin A,Long F, Faucheron AL, Grandjean JP, Mellier G, Vallancogne G, FayardO, Henry L, Guyot P, Barth X, Mion F. Prevalence of anal incontinence in adults impact on quality of life. Gastroenterologie. 2006;30:37-43.

836. Bharucha AE, Zinsmeister AR, Locke GR, Seide BM,,McKeon K, Schleck CD, Melton III J. Rick factors for fecal incontinence: a population-based study in women. Am J mGastro.2006;101:1305-12.

837. Fritel X, Ringa V, Varnoux N, Zins M, Breart G. Mode of delivery and fecal incontinence at midlife; a study of 2640 women in the Gazel cohort. Obstet Gynecol 2007;110:31-8.

838. Lawrence JM, Lukasz ES, Nager CW, Hsu JWY, Luber KM. Prevalence and co-occurence of pelvic floor disorders in community-dwelling women. Obstet Gynecol. 2008; 111:678-85.

839. Borello-France D, Burgio KL, Richter HE, Zyczynski H, Fitzgerald MP, Whitehead W, Fine P, Nygaard I, Handa VL, Visco AG, Weber AM, Brown MB. Fecal and urinary incontinence in primiparous women. Obstet Gynecol 2006;108:863-72.

840. Erekson EA, Sung VW, Myers DL. Effect of body mass index on the risk of anal incontinence and defecatory dysfunction in women. Am J Obstet Gyencol. 2008;198:596-99.

841. Altman D, Falconer C, Rossner S, Melin I. The risk of anal incontinence in obese women. Int. Urogynecol. J. 2007;18:1283-9.

842. Bharucha AE, Zinsmeister AR, Schleck CD, Melton LJ 3rd. Bowel disturbances are the most important risk factors for late onset fecal incontinence: a population-based case-control study in women. Gastroenterology. 2010 Nov;139(5):1559-66. Epub 2010 Aug 10.

843. Burgio KL, Richter HE, Clements RH, Redden DT, Goode PS. Changes in urinary and fecal incontinence symptoms with weight loss surgery in morbidly obese women. Obstet Gynecol. 2007;110:1034-40.

844. Oberwalder M, Connor J, Wexner SD. Meta-analysis to determine the incidence of obstetric anal sphincter damage. Brit. J Surg. 2003;90:1333-7.

845. Bols EM, Hendriks EJ, Berghmans BC, Baeten CG, Nijhuis JG, de Bie RA. A systematic review of etiological factors for postpartum fecal incontinence. Acta Obstet Gynecol Scand. 2010 Mar;89(3):302-14. Review.

846. Nelson RL. Epidemiology of fecal Incontinence. Gastroenterology.2004;126 (Suppl. 1): s3-7.

847. Goffeng AR, Andersch B, Andersson M, Berndtsson I, Hulten L, Oreslan T. Objective methods cannot predict anal incontinence after primary repair of extensive anal tears. Acta Obstet Gynecol Scand. 1998;77:439-43.

848. Guttierz AB, Madoff RD, Lowry AC, Parker SC,Buie WD, Baxter NN. Long term results of anterior sphincteroplasty. Dis Colon & Rectum. 2004;47:727-32.

849. Halverson AN, Hull TL. Long-term outcome of overlapping anal sphincter repair. Dis Colon & Rectum. 2002;45:345-8

850. Karoui S, Leroi AM, Koning E, Menar JF, Michot F, Dens P. Results of sphincteroplast in 86 patients with anal incontinence. Dis Colon & Rectum. 2000;43:813-20.

851. Malouf AJ, Norton CS, Engel AF, Nicholls RJ, Kamm MA. Long-term resuls of overlapping anterior anal sphincter repair for obstetrical trauma. Lancet. 2000;355:260-5.

852. Pinta T, Kyaanpaa ML, Salmi T, Jaarvinen HJ, Luukkonen P. Delayed sphincter repair for obstetric ruptures: analysis of failure. Colorectal Dis. 2003;5:73-8.

853. Rothbart J, Bemelman WA, Meijerink WJ. Long term results of anterior anal sphincter repair for rectal incontinence due to obstetric injury. Dig. Surg. 2000;17:390-4.

854. Vaizey CJ, Norton C, Thornton MJ, Nicholls RJ, Kamm MA. Long term results of repeat anterior anal sphincter repair. Dis Colon & Rectum.2004;47:858-63.

855. MacArthur C, Glazener CMA, Lancashire R, Herbison P, et al. Faecal incontinence and mode of first and subsequent deliveries: a six year longitudinal study. Br J Obstet Gynecol.2005;112:1075-82.

856. Zetterstrom J, Lopez A, Anzen B, Dolk A, Norman M, Mellgren A. Analincontinence after vaginal delivery: a prospective study in pimiparous women. Obstet Gynecol.1999;106:324-30.

857. Devine JB, Ostergard DR, Noblett KL. Long tern complications of the second stage of labor. Contemp. Obstet Gynecol.1999:119-26.

858. Fynes M, Donnelly VS, O'Connell PR, O'Herlihy C. Cesarean section and anal sphincter injury. Obstet Gynec.1998;92:496-500.

859. Altman D, Zetterestrom J, Lopez A, Pollack J, Nordenstam J, Mellgren A. Effect of hysterectomy on bowel function. Dis. Colon & Rectum 2004;47 :502-9.

860. MacKenzie WR, Hoxie NJ, Proctor ME, Gradus MS, Blair KA, Petersen DE et al. A massive outbreak in Milwaukee of cryptosporidium infection transmitted through the public water supply. N Eng J Med. 1994;331:161-167.

861. Papathanasopoulos AA, Katsanos KH, Tatsioni A, Christodoulou DK, Tsianos EV. Increased fatigability of external anal sphincter in inflammatory bowel disease: significance in fecal urgency and incontinence. J Crohns Colitis. 2010 Nov;4(5):553-60. Epub 2010 Jun 11.

862. Sullivan SN, Wong C. Runner's diarrhea. Different patterns and associated factors. J Clin Gastroenterol. 1992;14:101-104.

863. Vitton V, Baumstarck-Barrau K, Brardjanian S, Caballe I, Bouvier M, Grimaud JC. Impact of high-level sport practice on anal incontinence in a healthy young female population. J Womens Health (Larchmt). 2011 May;20(5):757-63. Epub 2011 Apr 18.

864. Pernikoff BJ, Eisenstat TE, Rubin RJ, Oliver GC, Salvati EP. Reappraisal of partial lateral internal sphincterotomy. Dis Colon Rectum. 1994;37:1291-1295.

865. del Pino A, Nelson RL, Pearl RK, Abcarian H. Island flap anoplasty for treatment of transsphincteric fistula-in-ano. Dis Colon Rectum. 1996;39:224-226.

866. Gorfine SR. Treatment of benign anal disease with topical nitroglycerin. Dis Colon & Rectum. 1995;38:453-457.

867. Johannsson HO, Graf W, Pahlman L. Long term results of hemorrhoidectomy. Eur J Surg.2002;168:485-9.

868. Denost Q, Laurent C, Capdepont M, Zerbib F, Rullier E. Risk factors for fecal incontinence after intersphincteric resection for rectal cancer. Dis Colon Rectum. 2011 Aug;54(8):963-8.

869. Maeda Y, Høyer M, Lundby L, Norton C. Faecal incontinence following radiotherapy for prostate cancer: a systematic review. Radiother Oncol. 2011 Feb;98(2):145-53. Epub 2011 Jan 21.

870. Wald A. Systemic diseases causing disorders of defecation and continence. Sem Gastrointest. Dis. 1995;6:194-202.

871. Bliss DZ, Johnson S, Savik K, Clabots CR, Gerding DN. Fecal incontinence in hospitalized patients who are acutely ill. Nursing Res. 2000;49:101-108.

872. Nakayama H, Jorgensen HS, Pedersen PM, Raaschou HO, Olsen TS. Prevelance and risk factors of incontinence after stroke: The Copenhagen Stroke Study. Stroke. 1997;28:58-62.

873. Porell F, Caro FG, Silva A, Monane M. A longitudinal analysis of nursing home outcomes. Health Svc.s Rsch. 1998;33:835-65.

874. Chassange P, Landrin I, Neveu C, Czernichow M, Doucet J, Denis P, Bercoff E. Fecal incontinence in the institutionalized elderly: incidence, risk factors and prognosis. Am J Med.1999;106:185-190.

875. Nelson RL, Furner SE. Prospective cohort study or risk factors for incontinence in Wisconsin Nursing Homes. Maturitas. 2005 Sep 16;52(1):26-31. Epub 2005 Jan 19.

876. Fornell EU, Wingren G, Kjoelhede P. Factors associated with pelvic floor dysfunction with emphasis on urinary and fecal incontinence and genital prolapse: an epidemiological study. Act. Obstet. Gynecol. Scand. 2004;83:383-389.

877. Lewicky-Gaupp C, Cao DC, Culbertson S. Urinary and anal incontinence in African American teenaged gravidas during prgnancy and in the puerperium. J Ped Adolsc Gynec. 2008;21:21-6.

878. von Brummen HJ, Bruinse HW, van de Pol G, Heintz APM, van der Vaart CH. Defecatory symnptoms during and after the first pregnancy: prevalences and associated factors. Int. Urogynec. J. 2006;17:224-30.

879. Solans-Demenech M, Sanchez E, Espuna-Pons M. Urinary and anal incontinence during pregnancy and the post-partum: incidence, severity and risk factors. Obstet Gynec. 2010;115:618-28.

880. Culligan PJ, Myers JA, Goldberg RP, Blackwell L,Gohmann SF, Abell TD. Elective cesarean section to prevent anal incontinence and brachial plexus injuries associated with macrosomia – a decision analysis. Int Urogyencol J. 2005;16:19-28.

881. Faltin DL, Boulvain M, Floris LA, Irion O. Diagnosis of anal sphincter tears to prevent fecal incontinence; a randomized controlled trial. Obstet & Gynecol. 2005;106:6-13.

882. Hay-Smith J, Mørkved S, Fairbrother KA, Herbison GP. Pelvic floor muscle training for prevention and treatment of urinary and faecal incontinence in antenatal and postnatal women. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD007471. Review.

883. Bø K., Haakstad LA. Is pelvic floor muscle training effective when taught in a general fitness class in pregnancy? A randomised controlled trial. Physiotherapy. 2011 Sep;97(3):190-5. Epub 2011 Feb 4.

884. Shamliyan T, Wyman J, Bliss DZ, Kane RL, Wilt TJ. Prevention of urinary and fecal incontinence in adults. Evid Rep Technol Assess (Full Rep). 2007 Dec;(161):1-379.

885. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int. 2011 Oct;108(7):1132-8. doi: 10.1111/j.1464-410X.2010.09993.x. Epub 2011 Jan 13.

Committee 2

Cell Biology

Chair

CH Fry (U.K)

Members

S Chacko (USA),

S de Wachter (Belguim),

AJ Kanai (USA),

M Takeda (Japan),

JS Young (UK),

CONTENTS

I. INTRODUCTION

II. INTERSTITIAL CELLS: THEIR ROLES IN MUSCLE AND SUBUROTHELIAL LAYERS

1. IMMUNOHISTOCHEMICAL MARKERS USED TO CHARACTERIZE BLADDER INTERSTITIAL CELLS
2. STRUCZTURAL IMMUNOHISTOCHEMICAL MARKERS USED TO IDENTIFY INTERSTITIAL CELLS
3. FUNCTIONAL CHARACTERISTICS OF INTERSTITIAL CELLS

III. THE UROTHELIUM – STRUCTURE AND FUNCTION

1. RELEASE OF TRANSMITTERS
2. UROTHELIAL ION TRANSPORT AND PERMEABILITY
3. FUNCTIONAL INTERACTIONS WITH THE DETRUSOR LAYER

IV. DETRUSOR SMOOTH MUSCLE CONTRACTILE ACTIVATION

1. SMOOTH MUSCLE CELLS
2. CONTRACTILE PROTEIN ISOFORMS AND THE CONTRACTILE MACHINERY
3. CONTRACTILE ACTIVATION OF SMOOTH MUSCLE
4. SPONTANEOUS ACTIVITY
5. ELECTRICAL ACTIVITY AND ION CHANNELS

V. THE OUTFLOW TRACT

1. TRIGONE
2. THE URETHRA AND SPHINCTER MECHANISMS
3. PROSTATE

VI. NOVEL MOLECULAR TARGETS FOR OAB AND DETRUSOR OVERACTIVITY

1. INTRODUCTION
2. SEVEN TRANSMEMBRANE SPANNING RECEPTORS (7-TM, METABOTROPIC RECEPTORS)
3. LIGAND-GATED ION-CHANNELS
4. ION-CHANNELS

VII. BIOMARKERS FOR OAB AND DO

1. INTRODUCTION
2. URODYNAMIC FINDINGS
3. URINARY BIOMARKERS
4. SERUM BIOMARKERS
5. BLADDER WALL IMAGING BIOMARKERS
6. CONCLUSION

VIII. THE LOWER GASTROINTESTINAL TRACT (ANUS AND RECTUM) AS RELEVANT TO FAECAL INCONTINENCE

1. INTRODUCTION
2. BASIC PHYSIOLOGY OF THE RECTUM AND ANUS.
3. INNERVATION OF THE RECTUM AND ANUS
4. SMOOTH MUSCLE AND INTERSTITIAL CELLS
5. FUTURE DIRECTIONS FOR RESEARCH

IX. RECOMMENDATIONS FOR RESEARCH CONCERNING LOWER URINARY TRACT (LUT) AND LOWER GASTROINTESTINAL TRACT RESEARCH (LGIT)

X. ABBREVIATIONS AND NOMENCLATURE

REFERENCES

Cell Biology

CH Fry

S Chacko, S de Wachter, AJ Kanai, M Takeda, JS Young

I. INTRODUCTION

The four years between this and the 4th report* on Cell Biology as part of the International Consultation on Incontinence has seen enormous advances in our understanding of the physiology and pathophysiology of the urinary tract. In addition, different aspects of lower urinary tract physiology have come to the forefront of research, which offers new and exciting avenues to understand and manage LUT dysfunctions such as overactive bladder syndrome (OAB) and detrusor overactivity (DO). This is reflected in the major topics chosen for this report. An understanding of the pathophysiology of detrusor smooth muscle remains essential to understand OAB and DO and a significant portion of the report is devoted to spontaneous contractile activity. However, the key role exerted by the mucosal layer of the bladder (the urothelium and suburothelium) is becoming recognised and the myogenic basis of spontaneous activity, although still important, is more complex than initially recognised. The urothelium is also appreciated not just as a relatively inert lining of the inner wall of the bladder, but as an active metabolising structure that releases transmitter molecules due to chemical and mechanical stresses that in turn influence adjacent nerves and smooth muscle. Another important cellular structure is the interstitial cell, a ubiquitous structure throughput the lower urinary tract whose functions are likely to be various, and about which we are only now becoming familiar. This is not a homogeneous cell type but a series of related cells that probably serve different functions within various regions. In addition, our knowledge of other regions of the lower urinary tract, in particular the complex outflow tract, is also increasing and a separate section is devoted to this region. The lower gastro-intestinal tract remains important in this report. Less attention through research is devoted to this tract but the clinical and social problems are no less important and probably no less prevalent. Finally, consideration is given to the search for potential new targets to manage lower urinary and gastro-intestinal tract disorders, as our knowledge of the basic science concerned with these regions increases so does our opportunity to identify new drug targets. Allied with this search, is one for better biomarkers of LUT dysfunction, ranging from physical methods to chemical markers. In all a series of relatively new topics that reflects the flux of research in this key area of academic medicine.

* Incontinence. 4th International Consultation on Incontinence, ed P Abrams, L Cardozo, S Khoury, A Wein 2009. ISBN 0-9546956-8-2.

II. INTERSTITIAL CELLS: THEIR ROLES IN MUSCLE AND SUBUROTHELIAL LAYERS

Cells resembling the Interstitial Cells of Cajal (ICC) in the G-I tract have been described in several other organs. In the bladder they have been termed Interstitial Cells (IC), ICC, ICC-like cells and myofibroblasts. Although a recent international meeting on Interstitial Cells advocated the use of the term “Interstitial Cell of Cajal-like Cells” [1], the less contentious term IC will be used to describe these cells in the bladder: this does not imply that they have similar functional properties as the ICC in the G-I tract. The IC represent a family of cells that demonstrate specific electron microscopic features: numerous mitochondria, a prominent endoplasmic reticulum, a Golgi apparatus producing secretion granules, thin and intermediate filaments and a basal membrane which may be discontinuous [2,3]. Electron microscopy permits detailed studies of cell structures and cell interactions, and is considered the gold standard for identifying IC [4]. However most studies aiming at the identification and characterization of interstitial cells have been performed by fluorescence microscopy using antibodies against specific epitopes. By combining different antibodies IC have been characterized in the bladder of a number of species. It should be pointed out that immunohistochemical proof for one or another receptor does not imply they exert any function within the cell. Given the problem of histochemical specificity, concepts or hypothesis based on histochemical findings will have to be verified with functional experiments.

1. IMMUNOHISTOCHEMICAL MARKERS USED TO CHARACTERIZE BLADDER INTERSTITIAL CELLS

c-Kit is a proto-oncogene that encodes a membrane tyrosine kinase receptor Kit, or CD117, which is expressed on the surface membrane of haematopoietic stem cells, mast cells, skin melanocytes, and IC [5]. Antibodies against c-Kit are considered the most reliable marker to identify IC in smooth muscle preparations as Kit receptors are not found on smooth muscle cells (SMC), nerves or fibroblasts [6]. c-Kit positive cells have been described in the bladder by many authors [7-11], but others have been unable to reproduce these observations. Whilst c-Kit positive cells were not found in the urinary bladder of the mouse they have been in the upper urinary tract [12]. Furthermore, c-Kit immunoreactivity (IR) has not been found in the mouse urinary bladder although cells were described that showed a rise in cGMP after NO stimulation, which was considered to be an identifier of IC [13]. Davidson & McCloskey identified a network of vimentin positive cells below the urothelium, of which many, but not all, cells were c-Kit positive. The reasons for these discrepancies remain unknown, but difficulties have been reported using anti-Kit consistently to label bladder cryosections [6]. Furthermore c-Kit has a role in the maturation of IC [3] and it is unknown whether Kit receptor expression remains stable during cell maturation. It has been suggested that it might be that some cells that have fully differentiated from mesenchymal cells lose their reactivity to c-Kit [14], which could explain why part of the vimentin positive cells show negative Kit immunofluorescence.

Vimentin is a member of the intermediate filament family of proteins, which is a general marker for mesenchymal stem cells. Vimentin is found in IC and other cells of mesenchymal origin like fibroblasts, but not in smooth muscle [2]. Vimentin antibodies can therefore be used to visualize potential IC, although fibroblasts cannot be excluded. However the expression of prostaglandin receptors EP1-IR, EP2-IR [15,16], the muscarinic receptor M3-IR [17], and COX I-IR [18] suggest that these vimentin positive cells are not merely fibroblasts, but may have a role in a complex communication system. **Figure 1** shows vimentin labelling in various ICs.

The **CD34 molecule** is a cluster of differentiation molecules present on certain cells within the human body. It is a cell surface glycoprotein and functions as a cell-cell adhesion factor. Cells expressing CD34 are found in the umbilical cord and bone marrow as haematopoietic cells, endothelial progenitor cells, endothelial cells of blood vessels, mast cells, a sub-population of dendritic cells. A subtype of IC's located between muscle bundles in the bladder that show immunoreactivity for the CD34 molecule have been identified [19,20].

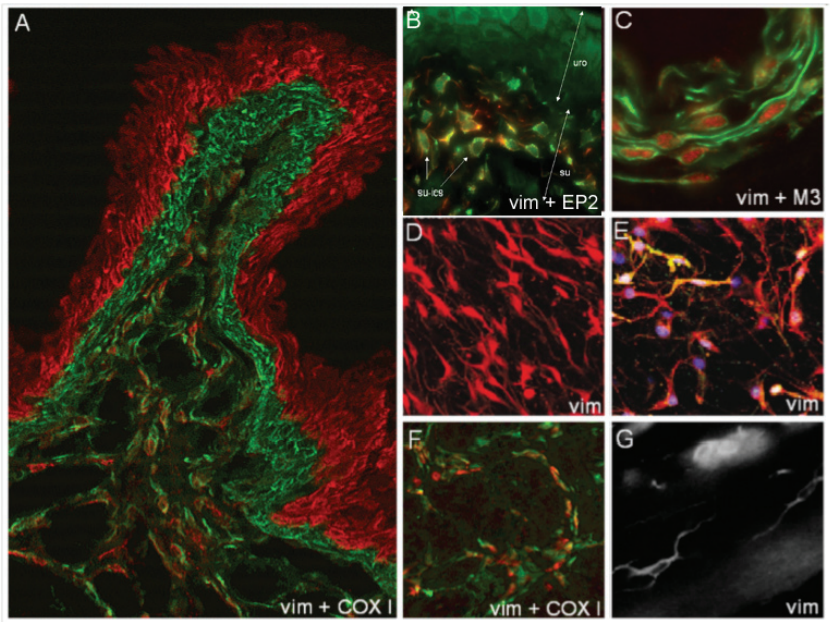


Figure 1. Vimentin immunoreactivity in interstitial cells. A: Vimentin positive sub-urothelial interstitial cells (SU-ICs) directly below the urothelium (green). Below this layer are vimentin-positive lamina propria interstitial cells (LP-ICs; green). COX-I immunoreactivity (IR) is visible in red. The basal urothelial layer shows strong COX I IR. A subset of the LP-ICs show IR for COX I. B: SU-ICs vimentin (red) and EP2 IR (green). Colocalization of vimentin and EP2 is seen in SU-ICs (yellow). Note also the strong labelling of the urothelium (uro) for EP2. Vimentin IR in the SU-ICs is visible in green. C: Co-labelling of SU-ICs for vimentin (green) and the M3 receptor (red). D: vimentin IR in LP-ICs (red). E: shows vimentin IR in muscle ICs (red). A subset of these cells also label for c-Kit (yellow). Nuclei are visible in purple. F: vimentin, COX-1 IR in muscle ICs G: vimentin IR visible in surface muscle ICs cells in muscle bundles, after S de Wachter

CD44 is a cell-surface glycoprotein involved in cell-cell interactions, cell adhesion and migration and is a receptor for hyaluronic acid. CD44 participates in a wide variety of cellular functions including lymphocyte activation, recirculation and homing, haematopoiesis, and tumour metastasis. Transcripts for this gene undergo complex alternative splicing that results in many functionally distinct isoforms; however, the full-length nature of some of these variants has not been determined. CD44 is expressed on cells in the interstitial space, and are possibly interstitial cells [21]; however the function of CD44 in these cells is not known.

PDGFRα (PDGF receptor-α) is a marker located on fibroblast-like and interstitial cells at many locations and has been proposed as mediator of normal and pathological cellular remodelling [22,23]. In the G-I tract, like c-Kit, PDGFRα as mutations are associated with most gastrointestinal stromal tumours [24,25]. PDGFRα on G-I tract interstitial cells has also been proposed to have a physiological function by transducing inputs from enteric motor neurons [26]. PDGFRα labelling has also been identified on mouse bladder interstitial cells in both the muscle and suburothelial layers and found to be associated closely with nerve fibres [27]. This implies that, as in the GI-tract, they may have a neuromodulatory function.

An overview of the immunohistochemical reactivity with respect to the location of the ICs is presented in **table 1**.

2. STRUCTURAL IMMUNOHISTOCHEMICAL MARKERS USED TO IDENTIFY INTERSTITIAL CELLS

a) Suburothelial interstitial cells

Suburothelial-ICs (SU-IC) are described as a distinctive zone directly below the urothelium [28-30]. All layers consist of long spindle-shaped cells with branches that apparently form a network [6,8,12,31-33]. Depending upon the region, this zone varies from two cell layers in the dome up to five cell layers in the lateral wall. SU-ICs contain bundles of fine cytoplasmic filaments, dense bodies, linear arrays of subsurface vacuoles, and an interrupted basal lamina, **Figure 2**.

c-Kit-IR on SU-ICs has been reported positive [6,9,14,32,34] and negative [6,14]; suggesting the existence of different subpopulations and or variability in the effectiveness of different antibodies to bind to the surface antigen. A further subdivision of SU-ICs can be made on a functional basis. Below the urothelium there are cells that show an increase of intracellular cGMP upon NO stimulation. Immediately below the urothelium there is a single layer of cells with long linking processes that do not show cGMP-IR upon NO stimulation, although they do express the cGMP-dependent protein kinase I [35]. Underneath these cGMP-IR negative cells, cGMP-IR positive cells, one or two cells thick, can be visualized after NO stimulation [6,29,31,35-38], which resemble the vimentin positive cells initially described by Smet et al. [39]. As the urothelium releases substances such as NO [40], these SU-IC's would be ideally situated to respond to and transmit signals from the urothelium either to underlying smooth muscle cells or adjacent nerve fibres.

Furthermore, acetylcholine [41,42] and prostaglandins [44-47] are also released by the urothelium, endogenously and augmented after different stresses. Both M2 and M3 muscarinic acetylcholine receptors have been reported on SU-IC's [17,48,49], which suggests that these cells can respond to muscarinic stimulation. Although muscarinic receptors play an important role in the mediation of bladder contractions, their role on SU-IC's is unknown. Electron microscopy shows close interaction between SU-IC and unmyelinated axonal varicosities of presumably cholinergic sensory nerves, containing a mixture of clear and large dense-core vesicles, or clear vesicles alone [50]. The identification of these vesicles indicates the release of acetylcholine alone (clear vesicles) or acetylcholine and ATP (dense-core vesicles) [50]. Purinoceptors have also been identified

Table 1. Immunohistochemical reactivity to different types of ICC. SU-ICC: sub urothelial ICC; SM-ICC: surface muscle ICC; IM-ICC: intra-muscle ICC; MC-ICC: muscle coat ICC

Label	SU-ICC	SM-ICC	IM-ICC	MC-ICC
c-Kit	some +	some +	some +	
Vimentin	+	+	+	+
cGKI	+			
cGMP	+	Outer muscle + Inner muscle -	Outer muscle+ Inner muscle -	+
Connexin 43	+	+		
E-cadherin	+			
CD44	+			
Alpha-SMA	+	-	-	
ChAT			some +	
nNOS	+	some +		
$P2X_3$, $P2Y_2$, $P2Y_4$ $P2Y_6$	weakly+			
M2 receptor	+			
M3 receptor	+			
Vanilloid receptor-1	+	some +		
PDGFRα	+	+	+	

on SU-ICs. The most readily-labelled purinoceptor is P2Y6, with weak labelling of P2X3, P2Y2 and P2Y4 [30,51]. Activation of a P2Y receptor by ATP results in an intracellular Ca^{2+} transient and generates transient depolarisations. This suggests that purinoceptors on SU-ICs may play a role in regulating the excitability of the SU-IC, which may then modulate the non-voiding bladder activity.

To increase the complexity of this suburothelial cell layer, prostaglandin EP1 and EP2 receptor immunoreactivity has also been shown on vimentin positive SU-IC [16]. Furthermore some of these SU-ICs were also immunopositive for COX 1 [37]. Additionally, some of the SU-IC's show immunoreactivity for the vanilloid receptor-1 [52]. Vanilloids are thought to block selectively C-fibres by desensitization, decreasing bladder activity, although the relationship between the vanilloid receptors on the SU-IC's and C-fibre desensitization is unclear. Further research is necessary in order to understand the role of the vanilloid receptor on the SU-ICs.

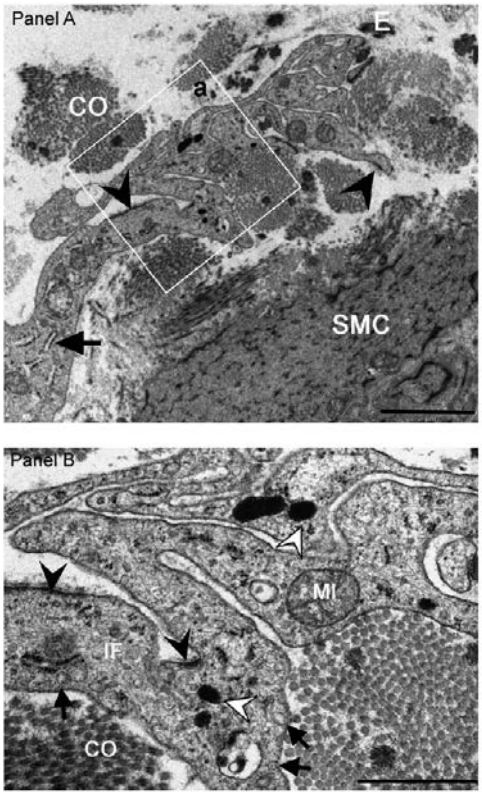


Figure 2: Ultrastructural characteristics of interstitial cells. A: convoluted processes of an IC with a patchy basal lamina (arrowheads) and cisternae of rough endoplasmic reticulum (arrow). Bar 2 µm; CO, collagen; E, elastic fibrils; SMC, smooth muscle cell. B: a higher magnification view of the boxed area in A, showing intermediate filaments (IF), primary lysosomes (white arrowheads), caveolae (arrows), dense bands (black arrowheads), collagen (CO) and mitochondria (M) (Bar 1 µm), after S de Wachter.

The SU-ICs appear to be inter-connected through connexin-43 containing gap junctions [8,9,14,30,33,53]. The role of the connexin-43 positive SU-ICs is unknown but their coupling by gap junctions implies that they have the capacity to form a functional syncytium in the suburothelial space. Double labelling with the nerve marker PGP 9.5, showed that the SU-ICs are in close contact to each other, but also to nerves [6,50]. E-cadherins are located on SU-ICs, at areas where SU-ICs come in close contact with each other [21,54]. Cadherin-11 most probably plays an important role in the intercellular physical coupling of SU-ICs [54]. SU-ICs also label for CD44, a cell-surface glycoprotein which is also involved in cell-cell interactions [21]. CD44 participates in a wide variety of cellular functions including lymphocyte activation, recirculation and homing, haematopoiesis, and tumour metastasis. The function of CD44 on the SU-ICs is not known.

b) Surface muscle interstitial cells

Surface muscle (SM) ICs are described as cells located on the edge of smooth muscle bundles. A sub-population of the SM-ICs are c-Kit positive [6,7,9,12,19,34,55,56]. They contain lateral branches that run in parallel with the muscle bundles [6,7,8,12,55,57]. Contrary to the SU-ICs the elongated SM ICs appear not be interconnected [1], but connect adjacent muscle bundles and also connect to the muscle coat interstitial cells (MC-ICs) [31]. A close association between enteric nerves and SM-ICs has been described [6-8]. The SM-ICs contain nuclei, with clumped peripheral heterochromatin, and a dilated rough endoplasmic reticulum with a moderately electron dense amorphous content and prominent Golgi complexes [55]. EP1 receptor expression was found on SM-IC's, of which some also showed COX I-IR in different parts of their processes. Furthermore, processes expressing the EP1 receptor lay very close to processes of other IM-SCC showing the presence of COX I [15]. This could suggest the presence of a signal propagation network. The outer muscle SM-ICs react to NO with a rise in cGMP [13,31,36,58,59], while this was not the case for the inner muscle SM-ICs. This suggests further heterogeneity in these cells. A subset of SM-ICs showed immunoreactivity to the vanilloid receptor 1 and nNOS [52,60]. Also positive staining for CD34 has been reported [19]. These CD34 positive cells showed no c-Kit immunoreactivity.

c) Intramuscular interstitial cells

IM-ICs are located throughout the smooth muscle bundles [55]. They have a stellate-like morphology [6,53,55] and are in close contact with cholinergic nerve fibres [58]. Ultrastructurally the IM-ICs are comparable to the SM-ICs as they have nuclei with clumped peripheral heterochromatin, a dilated rough endoplasmic reticulum with a moderately electron dense amorphous content, and prominent Golgi complexes [55].

c-Kit immunoreactivity has been described in IM-ICs [19,34,55,56], although c-Kit negative IM-ICS in mice have been described [13]. Another study reported that a subset of IM-ICs stained for c-Kit while another subset was c-Kit negative [6]. Similar to SM-IC, IM-IC also express EP1 receptor immunoreactivity, with a similar distribution [15]. The IM-ICs of the outer muscle show an increased cGMP-IR after NO stimulation, a feature not shown by the inner muscle IM-ICs [6,31,58,59]. Surprisingly, immunohistochemical staining for choline acetyltransferase (ChAT) showed immunoreactivity in a subset of the IM-ICs [58]. Currently little data are available on other neurotransmitter receptors on this subtype of IC's. Labelling done with an antibody to CD34 showed positive results in a subset of these cells [19].

d) Muscle coat interstitial cells

Muscle coat (MC)-ICs are located on the boundary of the outer muscle layer. It has been reported that, in a number of species, these cells react to NO with a rise in cGMP [31], which was also found also after incubation of tissue with atrial or brain natriuretic peptide, but not to C-type natriuretic peptide [38].

3. FUNCTIONAL CHARACTERISTICS OF INTERSTITIAL CELLS

a) Suburothelial interstitial cells

Similar to the gut, the bladder exhibits rhythmic small transient contractions during the filling phase. The origin of this "autonomous" or "non-voiding" activity is still unknown. It is contentious if detrusor myocytes initiate this activity as there are different reports about their ability to generate spontaneous action potentials, despite the fact that they are electrically excitable [61,62]. SU-ICs are also electrically active and at least a fraction of them show spontaneous transient inward currents with increases in intracellular Ca^{2+} concentration and spontaneous depolarization [63,64]. They also respond to exogenous ATP and low pH, a response that is augmented when SU-ICs make physical intercellular contact [65]. The observation that SU-IC may be electrically activated by exogenous agents or physiological interventions known to influence bladder activity suggests that these cells could participate in a sensing network between urothelium and afferent nerves. The immunohistochemistrical observation of the expression of muscarinic [17,48], purinergic [30,51] and prostanoid [16] receptors on the SU-IC would make them ideal substrates to process and converge signalling from physiological pathways or mechanisms. **Figure 3** shows electrical responses from isolated SU-IC, the first panel shows spontaneous electrical activity from a relatively negative resting potential. The depolarisations never overshoot the zero potential consistent with the observation that the major charge-carrying conductance mechanism is by Cl-, who have a reversal potential around -20 t0 -30 mV [64]. The remaining panels show responses to different interventions that could represent stimuli associated with increased bladder filling and exposure to urine itself; low pH, high osmolality and exogenous ATP. Each generated a large inward ionic current that would generate significant transient depolarisations.

In dysfunctional bladders, morphological and/or functional changes in the SU-IC population occur. In the initial stages following spinal cord injury in rats the bladder develops an overactive phenotype and is associated with an increase of SU-IC number [66], **figure 4**. At longer times after injury the bladder develops a high compliance state, demonstrating only small rises of intravesical pressure. At this time the SU-IC network is markedly reduced and cell processes appear retracted or lost [67]. Following outflow obstruction in the guinea pig, there is not necessarily an increase of SU-IC number, but cells were more uniformly distributed across the lamina propria compared to the control bladders [48,68]. Bladder dysfunctional states were associated with an increase of M2 and M3-receptor immunoreactivity [49]. A further consideration of how SU-IC number correlate with pathological bladder function is described in section 3.

b) Interstitial cells in the detrusor layer

Muscle IC that lie at the boundary of muscle bundles are spontaneously active and respond electrically to cholinergic stimulation by generating electrical activity and Ca^{2+} transients [7,11] the latter observation is absent in SU-IC . This has led to the speculation that they might function as pacemaker or modulator cells initiating or regulating "non-voiding" activity. However, spontaneous Ca^{2+} transients appear to be independent of those of smooth muscle even when synchronous Ca^{2+} waves sweep across muscle bundles [56]. These findings have formed basis for the hypothesis that the muscle IC have more a role in mediating the propagation of action potentials along the bundles rather than generating them [56,61,69]. Similar to SU-IC, after the generation of a hyper-compliant bladder after spinal cord injury in rats, the IC network is similarly damaged and connections with nerves also impaired [66]. Following outflow obstruction in the guinea pig, there is an up-regulation of muscle IC number, with an altered distribution into clusters and formation of type-3 muscarinic immunoreactivity [48]. In men with overactive detrusor, IC are also more numerous than in the normal bladder [10]. The functional impact of these changes is still unknown as there are currently no cellular studies that have evaluated any changes to IC spontaneous activity or response to exogenous agents that may elucidate their role in altered bladder behaviour associate with lower urinary tract dysfunction.

Studies using Glivec (imatinib mesylate), a specific c-Kit receptor inhibitor, have suggested a possible role for the IC in pathophysiology. In guinea pigs,

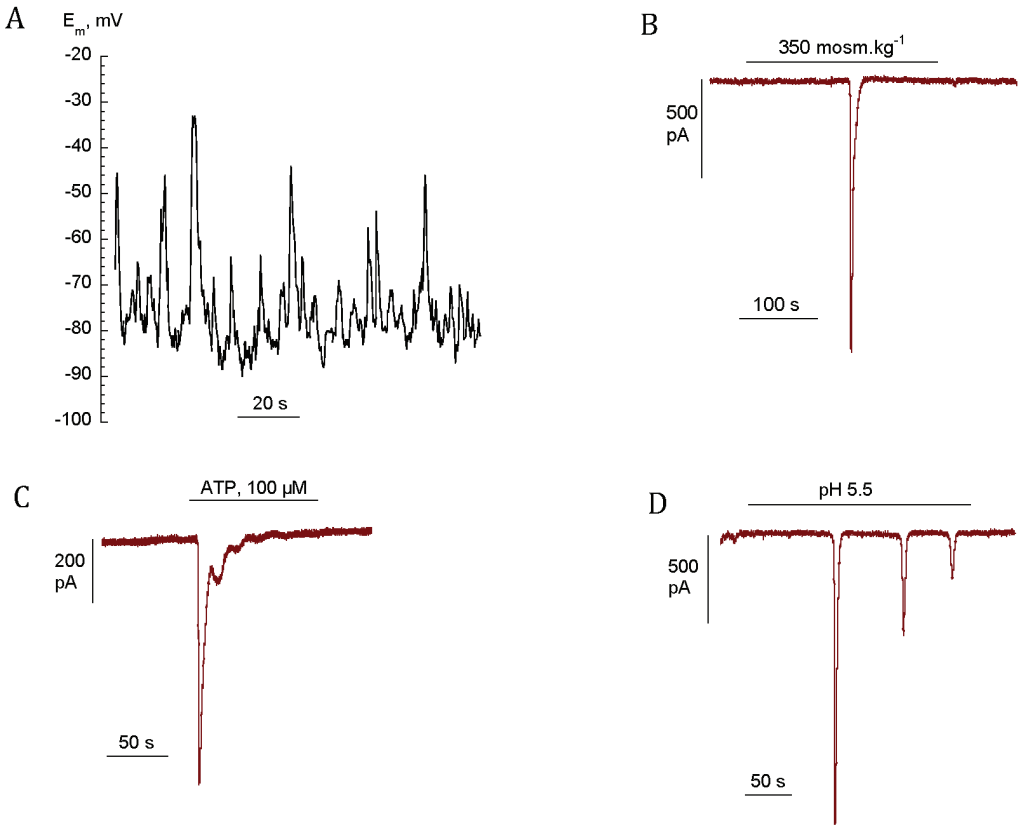


Figure 3. Electrical recordings from isolated guinea-pig suburothelial interstitial cells. A: Spontaneous variations of membrane potential. The spontaneous depolarisations never overshoot (i.e. become greater than 0 mV) but tend to limit near the Cl- equilibrium potential for the cell. B-D: inward currents from isolated suburothelial interstitial cells held under voltage-clamp at -60 mV. Responses are shown on exposure to: B, hyper-osmotic solutions; C, 100 µM ATP; D, low pH (CH Fry, C Wu, GP Sui, unpublished data).

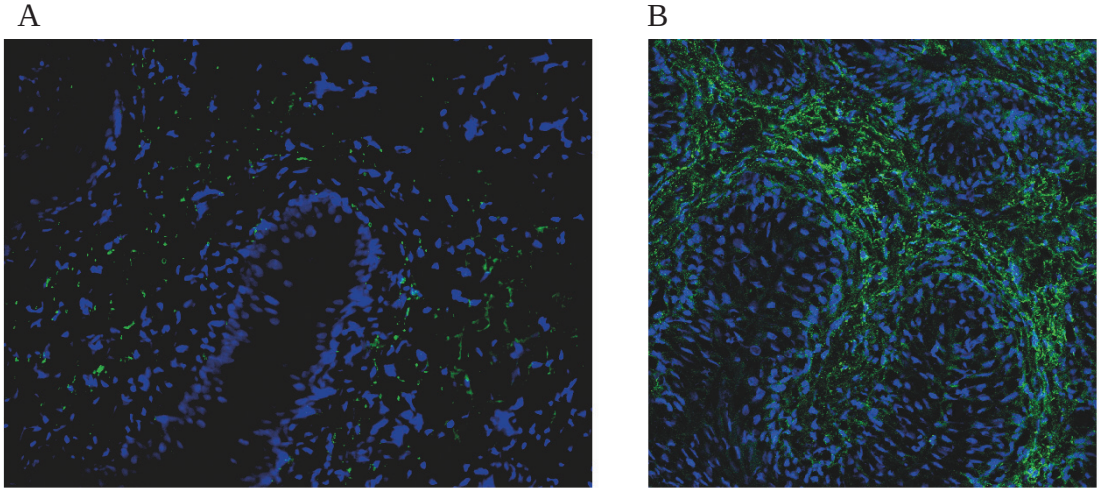


Figure 4. Connexin43 labelling in rat bladder suburothelium. A: Normal bladder. B: Bladder from a spinal cord injured animals. Connexin43 (green), DAPI (nuclei, blue). Connexin43 labelling is prominent below the urothelium layer, observed as the invaginated, dense nuclear density regions. x200 magnification (CH Fry, AJ Kanai, unpublished data).

administration of Glivec reduced spontaneous electrical and mechanical activity in isolated bladder tissues [10,70]. It also reduced spontaneous bladder activity, improved bladder capacity and compliance in cystometric studies in guinea pigs, and inhibited detrusor contractions in biopsy samples from human overactive bladders [10]. Current data point to a more prominent role for IC in dysfunctional bladders than in normal bladders. Their role in normal bladders is unclear. Do they merely fine-tune smooth muscle activity or do they have a role as primary relay or processing stations between urothelial cells, nerves and muscle cells [4]?

III. THE UROTHELIUM – STRUCTURE AND FUNCTION

The outer layer of the bladder facing the urine is a composite of the urothelium and an underlying suburothelium. The whole structure is termed the mucosa by some authors and will be used in this report: however this does not imply a vigorous secretion of mucus as with the gastro-intestinal tract for example. Different terminologies have been employed for its two faces. When using preparations of whole bladder wall the terms mucosal and serosal faces have been used to refer to the sides facing the lumen of the urinary tract and the underlying tissues of the body, respectively. When preparations of isolated mucosa and urothelium are used these terms become more confusing and their faces may be termed apical and basolateral respectively, by analogy to polarised epithelium membranes. In this report the terms apical and basolateral will be used.

Interest in the functional properties of the mucosa has increased recently as its different physiological functions are increasingly characterised. The barrier properties have been described in detail in previous reports [71] and more recent aspects will be included in the Committee 3 report. Moreover, the mucosa has a sensory function, responding to several external stresses generally associated with bladder filling, to influence the activity of mucosal afferent fibres as well as underlying smooth muscle. Different aspects of these functions will be considered in this and Committee 3 reports; here the release of ATP and acetylcholine; mucosal electrophysiological properties and the functional interaction between mucosa and smooth muscle will be discussed. A summary of the important relationship between different cellular layers and factors that have been shown to influence the release of important transmitters is shown in **Figure 5**.

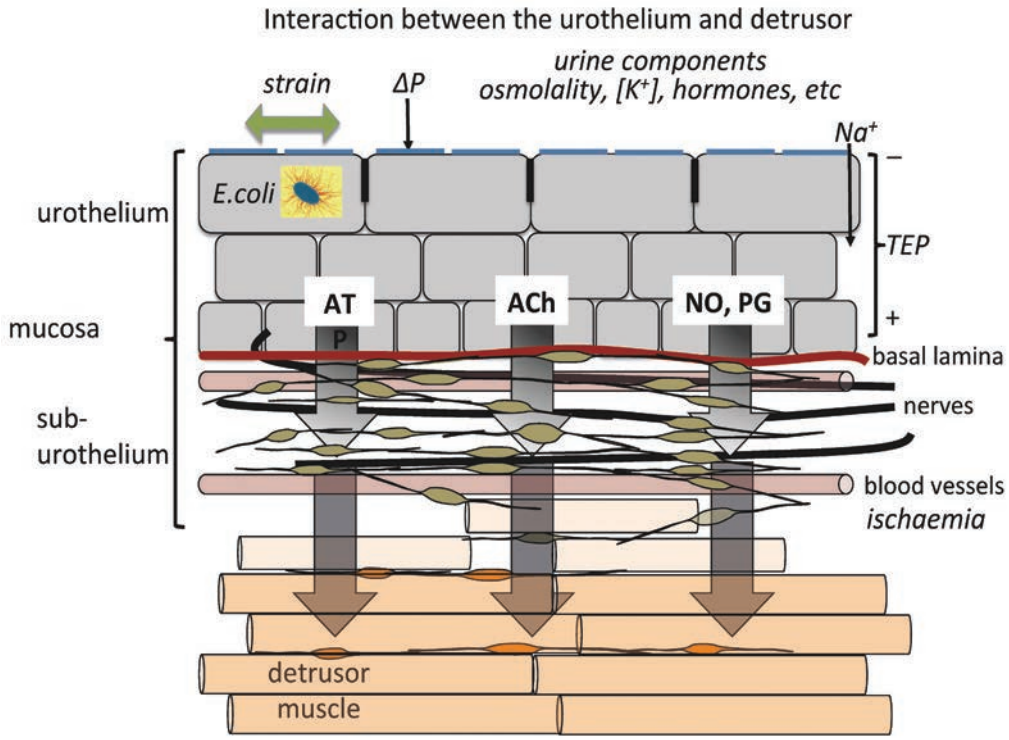


Figure 5. A schematic diagram of transmitter release by the urothelium. Urothelial cells are shown in grey, above which are examples of physical and chemical stresses that may cause transmitter (e.g. ATP, acetylcholine (ACh), nitric oxide (NO) or prostaglandin (PG) release. Deformation of the bladder wall, as in bladder filling, can also limit blood flow and generate a local ischaemia with accompanying acidosis and hypoxia. Transmitters may act on suburothelial cells, interstitial cells or afferent nerves and/or influence directly underlying detrusor smooth muscle.

1. RELEASE OF TRANSMITTERS

The epithelial lining of the urinary tract releases a number of agents into the extracellular space when subjected to many alterations of the physical and chemical external environment. These agents may be released across either the apical or basolateral surfaces [43,71-73]. This phenomenon is common [74-78], but not ubiquitous [79], to epithelia of many tissues, such as the G-I tract and airways, as well as the endothelium of blood vessels and is considered to be a sensory process that allows external stimuli to be transduced to a chemical signal. The fate of these signalling molecules and factors that regulate their release will be considered below.

a) Stimuli for release

Different experimental paradigms have been used to generate release of chemicals from the mucosa including: lateral stretch [80-82]; changes to trans-mucosal pressure [43,83], although responses are reported to be different if pressure is raised on the apical or basolateral face [84]; stroking with hairs [79]; electrical stimulation to increase tension (stress) within the bladder wall [80,81]; hypotonic solutions to cause cell swelling [41,85]; and application of chemical agents such as acid solutions, prostaglandins or ATP itself [80,86-88]. Whether these interventions are equivalent on transmitter release is unclear and data derived from these different paradigms will be combined. In particular, changes to transmural pressure are analogous to equivalent alterations in the intact bladder during filling with urine and experimentally cause lateral strain to the mucosal membrane. Application of hypotonic extracellular solutions causes cell swelling as water enters the cell under osmotic forces. Although easy to use in an in vitro setting, care must be taken that any subsequent effects are not due to changes of the ionic composition of the extracellular and intracellular spaces, per se.

b) Transmitter chemicals, ATP

ATP has been the transmitter most extensively studied in response to stretch. It has been measured, in preparations ranging from intact bladders to cultures of urothelial cells, in the bladder lumen and in the basolateral compartment. The function of ATP release into the bladder lumen is unclear. It may have a direct effect on bladder function as ATP infused into the bladder causes contraction [89]. In addition, it can represent a useful biomarker for different bladder conditions where the amount of ATP that is released is variable [90]. ATP released across the basolateral face can have several functions: it may excite (depolarize) afferent nerve endings in the suburothelium through ionotropic P2X2/P2X2/3 receptors, thus providing a direct link between bladder filling and afferent activation [91]. Evidence in support of this hypothesis was gained from P2X2/P2X2/3 knock-out mice in which the micturition reflex attenuated, with lower frequency of afferent firing on filling and a greater intravesical volume before voiding was initiated [71,92,93]. Alternatively, ATP may first excite, via P2Y receptors, a network of interstitial cells that have been observed in the suburothelium [14,63,64]. These cells in turn may excite afferent nerve fibres with which they make intimate connections [50]. Finally, ATP may diffuse directly to the smooth muscle layer and thus depolarise the myocytes, via P2X1 receptors, cells leading to their contraction [94].

Several important questions pertain to ATP release from the urothelium: the cellular routes that mediate release; factors that control release; and alteration to ATP release associated with lower urinary tract dysfunction. Several lines of evidence indicate that ATP release requires a rise of intracellular [Ca^{2+}] as a result of Ca^{2+} release from intracellular stores, i.e caffeine, acetylcholine and prostaglandin E2 increase ATP release and heparin, acting as an IP3 receptor inhibitor, reduced release [95,96]. However, extracellular Ca reduces ATP release and this occurs also by agents believed to reduce store-operated Ca^{2+} entry, although others have contradicted this effect of extracellular Ca using cultured urothelial cells [97]. The opposing effects of these Ca^{2+} sources may be related to their occupation of different microdomains within the cell and hence the activation of different cellular pathways, but does provide a negative feedback control to prevent excessive ATP release. Several routes for Ca^{2+} entry into urothelial cells including: TRPV4 channels [97]; TRPV1 channels [98]; TRPV2 channels [99]; and Gd3+-sensitive stretch activated channels [100]. The routes for ATP efflux from urothelial cells is less clear, although there is evidence for ATP accumulation in vesicles and release by exocytosis [101]. However, other routes are possible, such as through anion channels [102] that have been characterised in urothelium [103].

Several factors provide a physiological regulation of ATP release. Purinergic regulation provides positive and negative feedback as extracellular ATP itself generates further ATP release [88] whilst its breakdown product, adenosine, attenuates stretch-induced release [104]. Acetylcholine receptor antagonists also reduce stretch-induced release [105], suggesting a positive feedback effect by acetylcholine, as well as an explanation for how clinical antimuscarinic agents may reduce lower urinary tract symptoms associated with filling. In addition transmitter release is dependent on the magnitude of the potential difference across the urothelium (the transepithelial potential, TEP), such that abolishing TEP prevents stress-induced ATP release and increasing TEP in the absence of other external interventions increases ATP release.

Several lower urinary tract disorders are associated with augmented stretch-activated ATP release and this has been used to hypothesise that there is a causal link between the two phenomena. Urothelial tissue from animals and patients with interstitial cystitis or painful bladder syndrome and inflammatory conditions exhibits greater release [85,88,106,107]. This enhanced release was normalised by botulinum toxin-A suggesting a therapeutic mode of action for the neurotoxin [107]. A potential mediator of enhanced release of ATP is pituitary adenylate cyclase activating polypeptide (PACAP) that exhibits upregulation in dorsal root ganglia and the urothelium with inflammation induced by cyclophosphamide and acts to enhance ATP release from cultured urothelial cells [108].

Enhanced ATP release has also been measured using mucosa samples from patients with idiopathic and neuropathic bladder overactivity, or in animals with bladder obstruction following spinal cord injury [80,90,109]. Of interest was that with the human specimens from patients with neuropathic bladder overactivity most of the enhanced increase was abolished with the neurotoxin, tetrodotoxin [80], suggesting it had a neuronal origin. **Table 2** summarises factors that have been shown to alter the extent of ATP from urothelium.

c) Transmitter chemicals, acetylcholine

Stretch also generates acetylcholine (ACh) release from bladder wall preparations that is greater with an intact mucosa. Release is independent of tetrodotoxin and increases with the age of the patient from whom biopsies were obtained [110-111]: however a positive feedback control, as with ATP release, seems to be absent for ACh release [41]. Cultured urothelial cells contain the machinery to synthesise ACh, with positive expression of a high affinity choline transporter (CHT1) and the synthetic enzymes choline acetyltransferase and carnitine acetyltransferase. Release may be via a cation transporter, but not by vesicular exocytosis as it is independent of brefeldin [41].

2. UROTHELIAL ION TRANSPORT AND PERMEABILITY

a) Urothelial ion transport

The urothelium is a tight epithelium with a high specific resistance [112,113] due mainly to uroplakin [114] proteins on apical umbrella cells limiting membrane transport and effective tight junctions between cells [115,116]. Because of the high resistance ion transport that does occur can generate a significant transepithelial potential that is linked to other urothelial functions, such as transmitter release. Therefore an understanding of those factors that regulate ion transport and urothelial resistance will provide insight into the regulation of transmitter release.

Na^+ transport across the urothelium is similar to that across many epithelia with an apical route that allows Na^+ to enter the cell down a concentration gradient, accompanied by basolateral expulsion through a Na^+-K^+ ATPase. In the case of the urothelium a significant fraction of Na^+ influx is by an amiloride-sensitive epithelial Na^+ channel (ENaC),

Table 2. Factors affecting urothelium-mediated ATP release

Factor or associated conditions	Increase	Decrease
Lateral strain	+	
Apical hydrostatic pressure	+	
Transepithelial potential	+	
Extracellular Ca		+
Hypo-osmotic solutions	+	
Low pH	+	
ATP	+	
Adenosine		+
Acetylcholine	+	
Muscarinic antagonists		+
Caffeine	+	
Prostaglandins	+	
Capsaicin (abolished by capsazepine)	+	
Heparin		+
$TRPC_4$ receptor activation	+	
PACAP	+	
Painful bladder syndrome/interstitial cystitis	+	
Inflammation	+	
Painful bladder syndrome/interstitial cystitis	+	
NDO, IDO	+	
Botulinum toxin		+
Antiproliferative factor, epidermal growth factor	+	

which is increased when the apical hydrostatic pressure is raised as in bladder filling [117,118]. Na^+ transport is modulated by a number of hormones including aldosterone [119], arginine vasopressin [120] and atrial natriuretic peptide [121].

ATP release from urothelium is itself dependent on ENaC activity providing a direct linkage between transmitter release and ion transport [43]. What remains unclear is whether the TEP itself, generated by Na^+ transport, or the transported ions themselves regulate ATP release. One hypothesis is that an increase of intracellular Na^+, when ENaC activity is raised, increases intracellular Ca^{2+} through Na^+-Ca^{2+} exchange [100] that leads to release of the transmitter. K^+ transport across the urothelium is also modulated by stretch and several K^+ channels have been identified including: an amiloride-sensitive non-specific cation channel [122]; Ca^{2+}-activated K^+ channels sensitive to charybdotoxin and apamin; and an inward rectifying channel (Kir2.1) [123]. Their particular roles remain to be identified.

In addition, channels of the TRP family have been identified on urothelium including: TRPV1, TRPV2, TRPV4, TRPM8, TRPA1 [124-128] and may be involved in transduction of stimuli as diverse as stretch, acidosis, altered local osmolality and temperature [129]. Their mode of action is also unclear but their characteristic to act as non-specific cation channels means that their activation will result in an increase of intracellular Na^+ and Ca^{2+}.

b) Urinary tract infections

A significant component of the clinical morbidity associated with urinary tract infections, in particular by Escherichia coli, is believed to be due to a reduction of the barrier properties of the urothelium. This would allow fractions in urine to interact more easily with underlying tissues and generate inflammatory responses associated with such infections. Acute exposure of mucosal membranes to E. coli reduced the transepithelial resistance. This effect was attributed to a degradation of tight junction integrity with a consequent increase of paracellular permeability and associated with a loss of the tight junction protein ZO-1 [130]. Flagellin in the bacterial wall most likely interacts with Toll-like receptors to mediate the host response [131]. The causative agents remain unclear but E coli infection is associated with generation of several cytokines such as IL-6, IL-8, IL-15 and TNF-α [130,132,133]. These have not just a pro-inflammatory action but also modulate urothelial permeability, in the case of IL-6 and IL-15 urothelial integrity can be restored [130,134].

3. FUNCTIONAL INTERACTIONS WITH THE DETRUSOR LAYER

The urothelium exerts direct control over the contractile function of the bladder wall in several different ways: it may release chemical agents that diffuse to the detrusor layer and influence the contractility of muscle; it increases spontaneous contractile activity; and it may itself have intrinsic contractile activity. All of these modalities will influence the overall contractile output of the bladder and could represent targets for the modulation of such function.

a) Urothelium-derived relaxing factors

The in vitro contractile responses of bladder wall preparations from the dome and trigone to electrical field stimulation and agonists is reduced if the mucosa is left intact on the smooth muscle [135-139]. However, not all agonist responses are equally affected: those to carbachol, histamine and electrical field stimulation are depressed, but those to phenylephrine and raised KCl are not; the response to neurokinins has been reported as being reduced or unaffected [135,138]. A similar depressant response has been reported in the ureter where the presence of the mucosa attenuated spontaneous contractions and those evoked by high-KCl, neurokinin-A, vasopressin, carbachol, bradykinin and angiotensin-II [140]. This has led to the concept of a urothelium-derived inhibitory factor generated by the mucosa. However, if only the urothelium was removed from bladder preparations, leaving an intact suburothelium, smaller contractions evoked by carbachol, ABMA (a P2X1 agonist) or electrical field stimulation are also measured. One explanation is that the urothelium has a potentiating action on detrusor contractility, whilst the suburothelial layer has an inhibitory effect [141].

The nature of these agents is unknown, but they are probably diffusible and do not rely on cell-to-cell contact, as the contractility of a mucosa-denuded detrusor preparation is reduced if a second mucosa-intact preparation is placed in its vicinity [136]. Thus, these agents may be produced constitutively or in response to agonists and directly modulate muscle contractility, alternatively they may inactivate contractile the contractile agonists. The latter possibility is unlikely as presence of mucosa modifies responses to several different agonists, as well as contractions to electrical field stimulation. Control of their release may be mediated by purinergic receptor agonists, as ATP mimicked the effect of the urothelium in modulating carbachol contractions [142].

The inhibitory agent, at least, is unlikely to be nitric oxide, a cyclo-oxygenase product, a catecholamine, adenosine, GABA or a mediator of TEA- or apamin-blocked K^+ channels [135,136]. However, one study did show that in mucosa-intact preparations carbachol responses were increased by L-NAME (to limit NO production) and the cyclo-oxygenase inhibitor indomethacin [143], although their direct effect on muscle function cannot be excluded.

b) Contractile activity of the mucosa.

In vitro preparations of mucosa dissected from the detrusor layer generate small spontaneous contractions and responses to agonists such as carbachol and neurokinin-A [144] as well as to electrical field

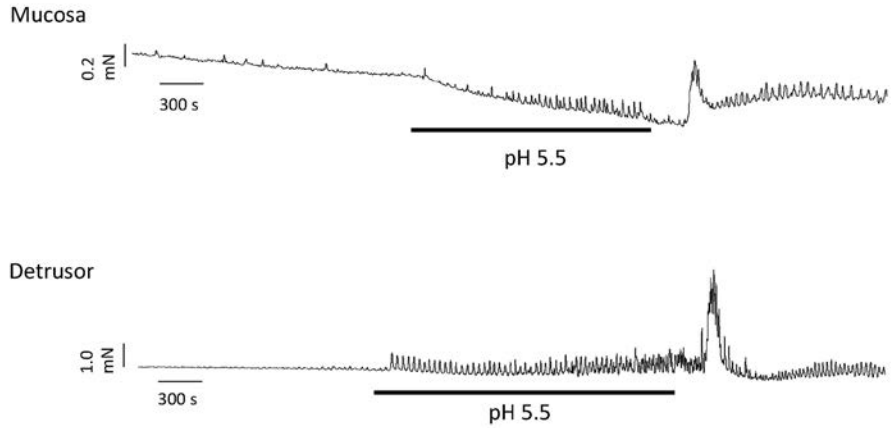


Figure 6. Spontaneous contractions generated by preparations of isolated mucosa and detrusor (guinea-pig). Upper trace: spontaneous contractions from isolated mucosa, the preparation was exposed to a low-pH solution when shown. Lower trace: spontaneous contractions from isolated detrusor preparations, a similar exposure to a low-pH solution is also indicated.

stimulation [145]. The frequency of spontaneous contractions are similar to that generated by detrusor muscle preparations – see **figure 6**.

These contractions may originate from small smooth muscle bundles, muscularis mucosa, at the base of the suburothelial layer or from contractions of interstital cells that are abundant throughout the suburothelium and which form a network of cells connected by gap junctions formed from connexin43 (Cx43) [14]. Evidence for contractions arising from the muscularis mucosa is poor as the magnitude of contractions is independent of the amount of smooth muscle in isolated preparations from which experiments were made [144]. Moreover, as seen below, the profile of contractile responses to many agonists is differs in several respects from bladder smooth muscle. The spontaneous activity is independent of tetrodotoxin and NO-synthase or cyclooxygenase inhibitors and carbachol responses are mediated by M3 receptors [146]. Of interest was that NO-donors did depress contractile function suggesting that there is no endogenous production of NO by the tissue under resting conditions.

The other possibility that contractions may be generated by the interstitial cells remains to be fully investigated. In the bladder suburothelium, interstitial cells have a phenotype typical of myofibroblasts [147], which have a contractile phenotype, contain smooth muscle actin and label for vimentin [14,144,148,149]. Their ability to form norm a functional syncitium through gap junctions means that chemical and electrical signals can propagate to a significant extent over several millimetres and produce a co-ordinated contractile response [33]. Sub-urothelial interstitial cells generate large intracellular Ca^{2+} transients and inward currents to ATP, through P2Y receptors, and to a reduction of pH [64,65]. The ability of such agents to increase spontaneous activity in preparations of mucosa will lend support to a role for suburothelial cells in generating significant contractile responses.

c) Interaction between mucosa and detrusor

When the mucosa is left attached to in vitro detrusor preparations there is an increased prevalence of spontaneous contractile activity and the magnitude of prevailing contractions is greatly enhanced [65,150]. Thus, the character of such activity changes from small amplitude, high frequency contractions to larger, more prolonged and less frequent phenomena. This is especially the case in bladders showing an overactive phenotype resulting from, say, spinal cord injury [66]. This augmented activity may result from: i) spontaneous contractions within the mucosa itself, as discussed above; ii) the mucosa, through either cell-to-cell interaction or release of diffusible agents, influences detrusor function.

It is unlikely that mucosal contractions are the sole explanation as they are of relatively low amplitude. They are however of similar frequency and it is possible that they may influence additional activity in the detrusor. Propagating waves of depolarisation and intracellular Ca^{2+} have been demonstrated that originate in the suburothelium, propagate initially throughout this layer and to the urothelium, and then after a delay of several hundred milliseconds to the detrusor [151]. This extent and propagation speed of this interaction between mucosa and detrusor is increased by: exogenous agents such as P2Y agonists (**Figure 7**); small (50 nM) concentrations of carbachol; and mechanical distension. Such interaction is similarly augmented in the bladder wall from spinal cord injured rats, in which there is a large increase of suburothelial IC number and Cx26 expression in the urothelium [152], as well as the enhanced spontaneous contractile activity, described above. Several lines of evidence suggest that ICC contribute to increased spontaneous contractile activity with an intact mucosa:

ICC form an electrical syncitium in the suburothelium as observed from their expression of the gap junction

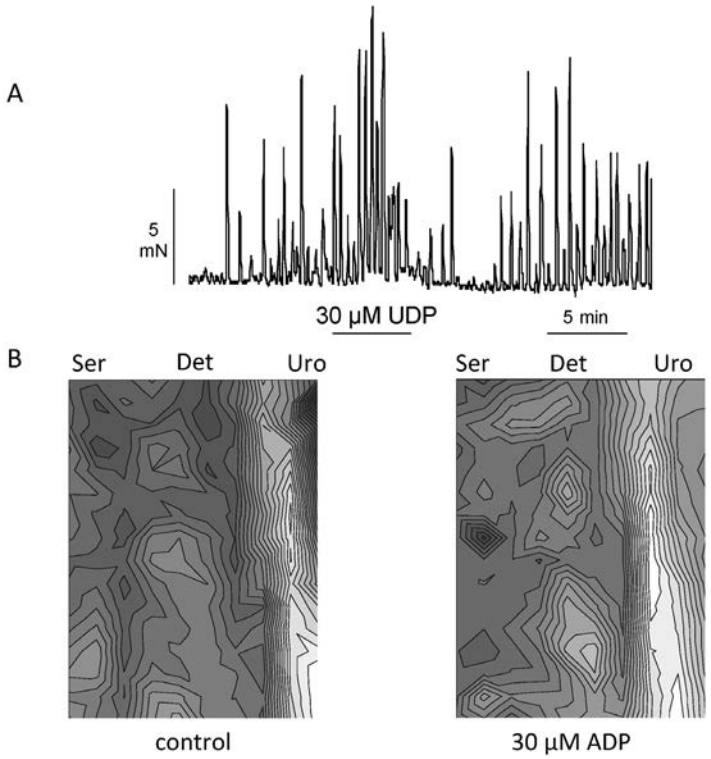


Figure 7. Spontaneous contractions and propagating Ca2+ waves. A: Spontaneous contractions arising from a rat bladder sheet, with an intact mucosa, from a spinal cord-injured rat – the bladder displays an overactive phenotype. At the time shown the preparation was exposed to a P2Y-receptor agonist (UDP). B: Ca2+ waves (shown as isochrones of equal delay for a Ca2+ transient) in a transverse rat bladder preparation from a spinal cord-injured animal: urothelium (right) through to the serosal (ser) surface (left). Under control conditions a focus of activity (light area) originates from the suburothelium and propagates initially throughout the suburothelium and into the urothelium. At later times, activity progresses to the detrusor layer. In the presence of the P2Y-receptor agonist ADP, the pattern of activity remains similar except that transmission is quicker: shown as wider-spaced isochrones – isochronal intervals 50 ms.

protein Cx43 and cable calculations based on their electrical properties [14,63,64]; from their A role for interstitial cells in signalling is suggested by several observations:

ICC number; the intensity of Cx43 labelling; and Ca^{2+}/depolarisation wave propagation speed are all increased in overactive bladders [152].

P2Y agonists generate excitatory responses in ICC and increase spontaneous contractile activity [64,65,153], whereas they reduce the contractility of detrusor muscle itself [154,155].

The first two of these arguments are consistent with a cell-to-cell interaction, however, it is unknown if there is a significant diffusion of excitatory agents between the mucosa and detrusor. Certainly the increase of stretch-induced mucosal ATP release, coupled with reduced extracellular ectoATPase activity in idiopathic detrusor overactivity [80,156] would provide such a substrate, but definitive experiments remain to be done.

IV. DETRUSOR SMOOTH MUSCLE CONTRACTILE ACTIVATION

1. SMOOTH MUSCLE CELLS

Smooth muscle (SM) cells are the major component cells of the walls of visceral organs and the vascular wall, and their ability to contract and relax is the hallmark of the physiological function of these organs. These mesoderm-derived (mesenchymal) cells have common characteristics, although cells in various regions of the body are heterogeneous in regard to their ability to express contractile proteins, contract spontaneously, and their responses to hormonal/neuronal stimulation. SM cells are elongated with tapering ends, and their length varies from 20 µm in certain small blood vessels to 500 µm or more in the gestational uterus [157]. There are three layers of SM aligned in a complex orientation in the bladder wall. The middle layer is the most prominent, but the other layers, a muscularis mucosa below the suburothelium and a thin layer below the serosa, may not

always be identified in a random histological section. In the trigone, the SM cells orient around the opening of the urethra.

The arrangement of the SM cells in the muscle bundle or sheet is staggered, with the broad nuclear region of one cell lying opposite to the narrow tapered end of an adjacent cell. At various points, adjacent cells form an intimate association, called a nexus or gap junction, where electrical coupling is facilitated. The cytoplasmic organelles of the myocytes, which include mitochondria, Golgi apparatus, rough endoplasmic reticulum, and free ribosomes, are abundant in the conical perinuclear region. The remainder of the cytoplasm is occupied by contractile filaments, which form the contractile machinery, and cytoskeletal filaments, which help maintain the cellular shape. The contractile apparatus of the SM cell is composed of thick (15 nm) myosin filaments and thin (7 nm) actin filaments [158,159]. Thin filaments, although composed mainly of actin, also contain actin-binding proteins, such as tropomyosin (Tm), caldesmon (CaD), and calponin, all of which are arranged in a specific manner and molar concentration. These proteins are also thought to be involved in regulation of the actin-myosin interaction that occurs during force generation. The filaments that form the cytoskeletal structure consist of intermediate filaments with a diameter of 10 nm. These filaments, which are connected to the dense bodies, are composed of desmin and vimentin. In addition, microtubules composed of tubulin and actin-containing thin (7 nm) microfilaments that are not part of the contractile apparatus also contribute to the cytoskeletal structure.

2. CONTRACTILE PROTEIN ISOFORMS AND THE CONTRACTILE MACHINERY

a) Myosin

Myosin in SM is mostly class II (myosin II) and contains two heavy chains (MHC, 200-204 kDa) that constitute the globular head (NH2-terminal) and the tail (carboxyl-terminal) domain. Thus, myosin II has two heads and a rod portion that is composed of a coiled-coil region. The ATPase and actin-binding sites reside in the head portion, whereas the ability of myosin to form filaments is due to properties that arise from the rod portion of the molecule. Myosin II also contains four light chains (i.e. two per head) that weigh 20 (MLC20) and 17 (MLC17) kDa. These bind to the heavy chains in the “neck” region between the head and the tail. MLC20 is also known as the regulatory light chain and actively participates in muscle contraction. Two MLC20 isoforms are found in SM. and encoded by different genes [160], but only one isoform participates in contractility [161]. MLC17 is known as the essential light chain. Its exact function is unclear, but it is believed that it, along with MLC20, contributes to the structural stability of the myosin head. Two variants of MLC17 (MLC17a/b) exist due to the alternative splicing of the MLC17 gene [162].

Alternative splicing of the MHC pre-mRNA at the 5’-end produces SM-A and SM-B isoforms, whereas splicing at the 3’ end of this mRNA produces SM1 and SM2 heavy chain isoforms that differ in molecular size (204 kDa for SM1 vs. 200 kDa for SM2) [163,164]. The SM-B isoform includes a 21-nucleotide exon that encodes a seven-amino acid insert in the N-terminal region near the ATP-binding site. This is the major isoform found in visceral SM and small muscular arteries. On the other hand, large arteries, such as the aorta and pulmonary artery, mainly express the SM-A isoform [165]. Compared to the SM-A isoform, the SM-B isoform has higher ATPase activity and moves actin filaments faster in an in vitro motility assay [166]. Detrusor smooth muscle (DSM) contains nearly 100% SM-B myosin isoform, which hydrolyzes ATP faster than the SM-A isoform. DSM is a phasic SM with a maximum velocity of contraction (Vmax) higher than that of tonic smooth muscles that are composed primarily of the of SM-A isoform [165]. DSM from obstructed bladders with severe dysfunction shows an upregulation of the SM-A isoform [167,168] and exhibits tonic-type contractions, characterized by slow force generation and high force maintenance. These results suggest that bladder outlet obstruction produces a muscle that develops higher levels of force but greatly reduced cross bridge cycling rates [169]. Along with these changes in myosin heavy chain isoforms, hypertrophied tissue also showed a doubling in the relative expression of the basic isoform of the 17 kDa (MLC17b) myosin light chain. A relative increase of the MLC17b isoform is associated with a lowered ATPase activity [170]. Comparative studies have shown that muscles with a high MLC17b content have a lower shortening velocity [171] and a higher affinity for ADP-analogues [172,173].

The ratio of the C-terminal isoforms SM2 and SM1 in the DSM switches from ≈1.7:1 in a normal rabbit bladder to ≈1:1 in a decompensated bladder [174,175]. Increasing the SM1/SM2 ratio in the bladder has a significant effect on contractile function [176], possibly by the stabilization of the thick filament through the tail region interaction with the head of an adjacent myosin molecule [177]. SM2 homozygous knockout (SM2−/−) mice die within 30 days of birth and show pathologies that include segmental distention of the alimentary tract, retention of urine, distension of the bladder, and development of end-stage hydronephrosis [178]. In contrast, heterozygous (SM2+/−) mice appeared normal and reproduced well. In SM2−/− bladder SM, loss of SM2 myosin was accompanied by a concomitant down-regulation of SM1 and a reduced number of thick filaments.

Virtually nothing is known about the transcriptional regulation of myosin isoform expression in both normal and pathological SM. A better understanding would help target mechanistic steps that regulate the alternative splicing of the pre-mRNA that generates

the SM-B and SM-A mRNAs and could shed light on the differences between SM in normal and obstructed bladders. The recently established human bladder SM cell line that expresses the SM-B isoform should be helpful in gaining insight into the factors that regulate the expression of the various myosin isoforms [179].

SM cells also express non-muscle myosin. In humans, non-muscle myosin heavy chain (NMMHC) isoforms NMMHC-A and NMMHC-B are expressed. The mRNAs encoding NMMHC-A and NMMHC-B are products of different genes, localized to chromosome 22q11.2 and chromosome 17q13, respectively [180]. Obstruction-induced hypertrophy is associated with an increase in NMMHC-B, primarily in interstitial fibroblasts [181].

b) Actin isoforms

Vertebrates express at least six different actin isoforms in a tissue-specific manner and multiple actin isoforms are found even in the same cell [182,183]. Differentiated SM cells typically contain a mixture of muscle (α,γ) and cytoplasmic (β,γ) actin isoforms. The muscle isoforms are associated with contractile filaments, whereas the cytoplasmic isoforms form the non-contractile cytoskeleton. The amount of different isoforms in a muscle cell varies according to the source of tissue. The dominant type of actin in SM of mammalian visceral organs (chicken gizzard, uterus, intestine, urinary bladder) is γ-SM actin, whereas the major actin type in vascular SM is α-SM actin [182].

Bladders from SM α-actin-/- mice tended to generate less force than those from wild-type mice in response to electrical field stimulation (EFS) with or without prior treatment with carbachol and atropine. However, their bladders appeared to function normally with no gross or histological abnormalities [184]. DSM SM α-actin protein and mRNA are not altered in response to obstruction-induced bladder hypertrophy [185]. In addition there was a decrease in β-cytoplasmic actin and a small increase of SM γ-actin. Hence, the composition of the actin isoforms in bladder SM is altered in response to obstruction-induced hypertrophy.

c) Actin-associated proteins in the thin filaments

Caldesmon (CaD) is a Ca^{2+}/calmodulin-binding protein thought to play a role in the Ca^{2+}-dependent regulation of both SM and non-muscle contraction [186]. Two CaD isoforms have been identified, h-CaD (high Mr form), expressed predominantly in differentiated SM cells, and l-CaD (low Mr form), widely distributed in non-muscle cells [187,188]. The expression of CaD is tightly associated with the phenotypic modulation of SM cells, as the CaD isoform switches from the l- to h-form during differentiation [189]. Therefore, CaD is a useful molecular marker for the study of the phenotypic modulation of SM cells. Whether the h- or l-CaD isoform is expressed depends on the unique selection of two 5′-splice sites within exon 3 [190]. Another important molecular event is the upregulation of CaD expression during SM cell differentiation [189]. DSM cells from obstructed bladders over-expressed l-CaD; in the compensated phase h-CaD was also increased [191].

Tropomyosin (Tm) is a rod-like helical protein that dimerizes and binds to actin and stabilizes actin contractile filaments. The four Tm genes produce many isoforms (>40) as a result of alternative exon usage. Most isoforms are found in non-muscle cells, but there are some specific to either striated or SM. Only two isoforms appear to be specific to mammalian SM, one from the β-Tm gene, and the other from the α-Tm gene. α-SM Tm contains the unique exon 2a, whereas β-SM Tm uses exon 2b, the exon used in the other muscle isoforms [192]. There is no specific antibody against either of the two SM isoforms of Tm. Antibodies that detect both isoforms also detect non-muscle and/or striated muscle isoforms and thus SM cannot be labelled specifically. Thus, Tm in SM has not been widely studied, especially in comparison to actin and myosin. Tm cooperatively turns on actin-activated ATP hydrolysis by myosin ATPase [193-195], thus it is considered to be important for thin filament-mediated regulation of smooth muscle.

3. CONTRACTILE ACTIVATION OF SMOOTH MUSCLE

The previous consultation [196] considered in more detail the signalling pathways that generate contraction or relaxation through muscarinic, nicotinic, adrenergic, purinergic, nitrergic and neuropeptide-mediated mechanisms. This report will provide a brief overview of receptor-mediated activation (4.3.1) and updates on electrical activity in detrusor smooth muscle (section 4.4) and the cellular and tissue basis of spontaneous contractile activity in detrusor (section 4.5).

a) Receptor-mediated activation of detrusor smooth muscle

The relaxed state of the bladder in filling and the generation or wall tension to effect emptying are regulated by external neuronal, hormonal, and central systems. Neurotransmitters released from nerves act on receptors located in the DSM, the functionally most important of which are muscarinic, M3, and purinergic, P2X1, receptors. However, the contributions of these receptors and their subtypes differ between species, age and bladder pathologies. With the stable bladder the predominant contractile regulator are muscarinic receptors. The main route for detrusor relaxation is the adenyl cyclase-cyclic adenosine monophosphate (cAMP) pathway, activated by the β3-receptor in humans [197].

Muscarinic receptors are coupled to G-proteins. The M1, M3, and M5 receptors are considered to preferentially couple to Gq/11, which leads to phos-

phoinositide hydrolysis through activation of phospholipase C and the subsequent mobilization of intracellular Ca^{2+} by generation of inositol trisphosphate (IP3) [198]. M2 and M4 receptors couple to pertussis toxin-sensitive Gi/o, which results in the inhibition of adenylyl cyclase activity thereby blocking Ca^{2+} channels in the SR or cell membrane as well as activating K^{+} channels and modulating rho-kinase pathways [199]. Acetylcholine-induced contraction is mediated by stimulation of M3 receptors and finally IP3 release [200]. However, other signalling pathways are probably also involved in muscarinic stimulation of detrusor contraction. Contractions elicited by the muscarinic agonist bethanechol were abolished by inhibition of rho-activated kinase (ROK) in combination with a non-selective cation channel inhibitor [201]. Carbachol-induced contractions in human bladder SM are mediated by M3 receptors and largely dependent on Ca^{2+} entry through nifedipine-sensitive channels and activation of the ROK pathway [202]. Thus, it has been proposed that the main intracellular pathways for detrusor activation by M3 receptors are Ca2+`influx via L-type Ca^{2+} channels and increased Ca^{2+} sensitivity to the contractile machinery via inhibition of myosin light chain phosphatase (MLCP), thus maintaining myosin light chain (MLC20) in a phosphorylated state [203]. The latter is achieved by ROK-mediated phosphorylation and binding of a 17 kDa protein kinase C-potentiated myosin phosphatase inhibitor, CPI-17. The calcium sensitization pathway is described in more detail below.

b) Molecular mechanisms for activation of the contractile machinery.

Contraction of DSM is initiated by an increase of the free [Ca^{2+}] [204]. Free Ca^{2+} bind to calmodulin (CaM) and the Ca^{2+} CaM complex activates myosin light chain kinase (MLCK) [205], which catalyzes phosphorylation of at serine-19 [206]. MLC20 phosphorylation is a prerequisite for actin-induced activation of myosin Mg ATPase activity of myosin [207,208] and the development of force [209,210]. During force maintenance, utilization of ATP is very low, and myosin cross-bridges cycle slowly, if at all [209,210] – the "latch" mechanism. In addition to MLCK, other kinases (PKC, ZIP kinase and integrin-linked kinase) can phosphorylate MLC20 under certain conditions [211].

c) Role of the Ca^{2+}-sensitization pathway in the regulation of the myosin-mediated pathway for smooth muscle contraction.

MLCP activity is also regulated by ROK, which in turn is activated by the small GTPase RhoA. ROK phosphorylates the regulatory subunit (MYPT1) of MLCP at Thr697 and Thr855 [212]. The phosphatase activity of MLCP is decreased by this phosphorylation, thereby increasing the level of

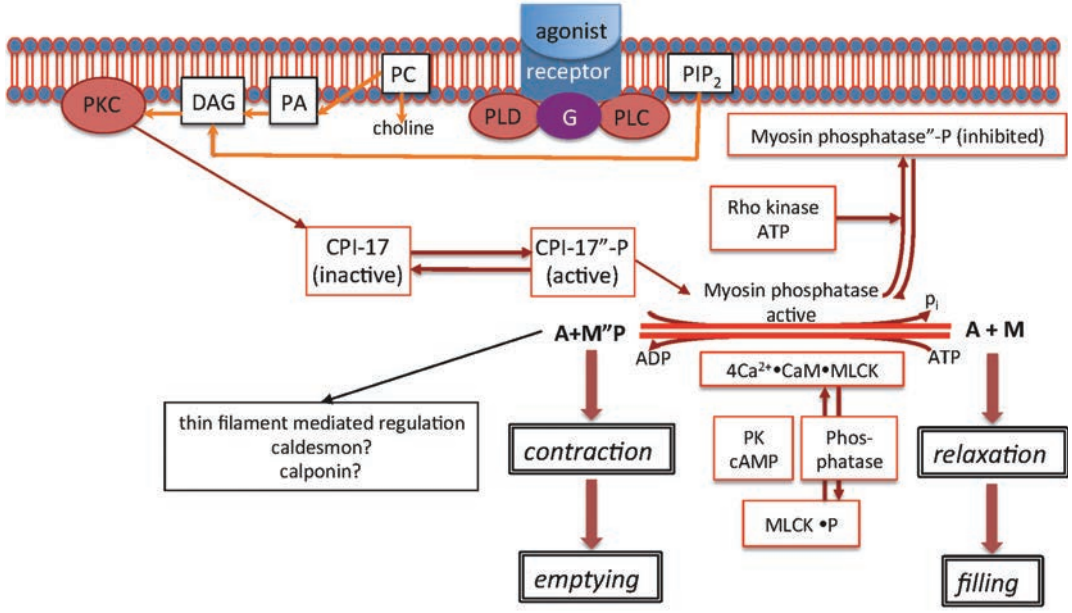


Figure 8. Schematic of signal transduction mechanism that activates the Ca2+- sensitization pathway in smooth muscle. Cross-bridge cycling and force development in smooth muscle require phosphorylation of the myosin regulatory light chain (MLC20). The level of MLC20 phosphorylation is determined by MLCK and myosin phosphatase activities. At low Ca2+ concentration, MLCK is not activated, but the myosin phosphatase is inactivated by Rho-kinase-mediated phosphorylation of the MYPT1 subunit of myosin phosphatase. The CPI-17, when phosphorylated by PKC, binds to myosin phosphatase and this also lowers the phosphatase activity. Thus, PKC signaling through CPI-17 phosphorylation and Rho-kinase-mediated phosphorylation of myosin phosphatase maintains the myosin in the phosphorylated form, which helps to maintain muscle tone at the basal Ca2+ concentration.

MLC20 phosphorylation. This causes the muscle to contract at low (basal) [Ca^{2+}] (Ca^{2+} sensitization). This mechanism plays an important role in maintaining and modulating normal tone of SM [212,213]. A second signalling pathway regulates calcium sensitization, particularly in tonic SM and involves CPI-17, which is phosphorylated at Thr38 by protein kinase C (PKC) [214,215]. The phosphorylated CPI-17 binds strongly to MLCP and inhibits the catalytic subunit of MLCP [216]. Cross-talk between these two mechanisms in the regulation of phosphatase activity has been proposed [217]. The Ca^{2+} sensitization mechanism is important for the retention of resting tone in viscous organs, including the bladder during filling. ROK expression is enhanced in DSM from obstructed bladders that are dysfunctional [218]. Furthermore, MLCP activity is decreased, and the maintenance of force by the detrusor of a decompensated bladder is inhibited by a ROK inhibitor. Thus, the RhoA/ROK cascade appears to regulate the force maintenance (tone) of DSM in a decompensated bladder.

d) The role of thin filament-mediated regulation of contraction.

Although myosin-mediated (via MLC20 phosphorylation) regulation is the major mechanism that activates myosin ATPase and generates force, there is sufficient evidence that a thin filament-mediated regulatory mechanism modulates the MLC20 phosphorylation-dependent regulation. One likely candidate is the thin filament-associated protein caldesmon (CaD).

The CaD molecule has two irregular domains in the C- and N-terminal regions and an elongated central space region that consists of a highly charged repeat sequence of 150 amino acids. The isoform l-CaD lacks this space region. The C-terminal region is rich in aromatic amino acids, whereas the N-terminal and central regions contain relatively high proportions of acidic amino acids [219]. SM CaD is elongated (75 nm in length) and interactions between CaD and Tm when both are bound to actin filaments induce changes in Tm [220], although it is not known if these conformational changes are caused by direct contact between CaD and Tm or are indirectly mediated through actin. If a labelled antibody specific for CaD is incubated with SM, it binds along the actin filaments in register with Tm, as labelling is repeated every 40 nm along a thin filament. This indicates that the CaD molecules bound to each actin strand are staggered by the length of one tropomyosin molecule [220-221]. There is general agreement that actin-activated ATP hydrolysis mediated by myosin is inhibited by CaD [222-224]. Tm enhances CaD-induced inhibition of actin-activated ATP hydrolysis [222] and CaD inhibits the cooperative induction of SM heavy meromyosin by tropomyosin and actin [194,222,225]. CaD tethers myosin to actin by through binding of the N-terminal region of CaD to the S-2 region of myosin and the CaD C-terminal region to actin. This is thought to be important for the stability of SM myosin filaments in the presence Mg^{2+}ATP and has been suggested as a plausible mechanism for force maintenance [226-227].

The “tethering” of CaD to actin decreases the in vitro motility of actin filaments and requires both the myosin-binding and the actin-binding domains of CaD [228]. When myosin is fully phosphorylated tethering is negligible, i.e. when actin-activated ATPase activity is high as in force generation when cytosolic Ca^{2+} is also raised. Thus, “tethering” is believed to play a role in maintaining muscle tone with very low ATP hydrolysis, useful for force maintenance in tonic muscle, e.g. aorta and sphincter muscles. The biochemical basis of basal SM tone and force maintenance (the “latch” phenomenon) is not understood but may involve some variation in Ca^{2+}-dependent phosphorylation in which force is maintained at very low levels of ATP utilization and slow myosin cross-bridge cycling. Thus, the thin filament-associated protein CaD is thought to play a role in the maintenance of force at low levels of phosphorylation and cross-bridge cycling. The phosphorylation of CaD itself might also be important as a regulatory mechanism, although evidence is weak. Nonetheless, CaD phosphorylation, catalysed by extracellular signal-regulated kinase (ERK), is involved in non-muscle cell migration [229]. Other data supporting a role for CaD in the regulation of contraction has come from studies of conformational changes induced by CaD on the actin filaments in “ghost fibres,” which contain actin filaments in their native organization but lack all other muscle proteins [230]. The binding of CaD to actin filaments changes the conformation of actin to the weak-binding (“off”) state and prevents the transition of actin filaments in muscle fibres to the strong-binding (“on”) state, which occurs when myosin heads bind to actin. Indeed binding of actin and CaD leads to a change in the conformation of actin filaments from the “on” to the “off” state [195]. The removal of CaD from chemically “skinned” SM increases the Ca^{2+} sensitivity of force development, and the addition of the C-terminal fragment of CaD to a skinned fibre inhibits contraction, indicating that CaD suppresses the force [231]. The use of antisense oligodeoxynucleotides designed to bind CaD mRNA decreased CaD expression and increased basal cross-bridge cycling rates [232].

e) Smooth muscle relaxation.

During urine storage, the bladder outlet is closed and DSM is relaxed and the increase of intravesical pressure is small over a wide range of bladder volumes. During voiding, DSM contracts, and the smooth and skeletal muscles in the urethra and internal sphincter relax, which raises the intravesical pressure. This is followed by relaxation of DSM due to either removal of the contractile stimulus or the direct effect of a substance that stimulates inhibition of the contractile mechanism

(e.g. β-adrenergic stimulation). Regardless of the relaxation mechanism, there is a decrease of the intracellular [Ca^{2+}] which leads to a subsequent decrease in MLC activity and increase in MLCP activity (**Figure 8**) [233]. The removal of cytosolic Ca^{2+} involves the sarcoplasmic reticulum (SR) and plasma membrane ATPases and a membrane Na^{+}-Ca^{2+} exchanger. There are several pharmacological agents that disrupt the Mg^{2+}-dependent SR Ca^{2+}-ATPase (SERCA), such as vanadate ions and thapsigargin [234]. The SR also plays important roles in buffering Ca^{2+} influx and the phasic component of DSM contraction [235]. Phosphorylation of phospholamban by multifunctional Ca^{2+}/CaM-stimulated protein kinase (CaMK II) activates SERCA, increasing both the Ca^{2+} clearance from the myoplasm and the frequency of localized Ca^{2+} release from intracellular stores [236]. SR function changes during bladder development and in bladder hypertrophy and hence will modify the magnitude and duration of the contraction [237,238].

The intracellular [Ca^{2+}] is also controlled by a plasma membrane Ca,Mg-ATPase (PMCA) [239]. This enzyme is regulated by phosphorylation through a membrane-bound CaM kinase, which stimulates Ca^{2+} sequestration and muscle relaxation [240]. In addition, the plasma membrane contains a Na^{+}-Ca^{2+} exchanger (NCX), which decreases intracellular Ca^{2+}. These low-affinity antiporters are closely coupled to intracellular Ca^{2+} levels and play a role in the regulation of DSM [Ca^{2+}] [241]. Further evidence for a role of NCX in regulating intracellular [Ca^{2+}] in DSM comes from transgenic mice over-expressed with the exchanger when contractions elicited by a number of processes were reduced compared to DSM from control bladders [242].

f) Alterations to contractile and regulatory proteins in lower urinary tract dysfunction.

The precise molecular mechanisms underlying the pathophysiology of the bladder dysfunction associated with bladder outflow obstruction (BOO) is not understood. However, outlet obstruction induces molecular, cellular and structural alterations in the SM cells in the bladder wall, leading to an impaired ability of the bladder to store and empty urine. Although the initial events that lead to detrusor SM remodeling are not understood, evidence from recent studies clearly shows that BOO induces molecular events that cause bladder wall SM to undergo hypertrophy, a compensatory response to increase detrusor pressure and maintain flow in the face of increased outflow resistance [243]. Despite detrusor hypertrophy, some obstructed bladders continue to remain dysfunctional (decompensated bladders) and show increased frequency of voiding, low void volume, and decreased intravesical (micturition) pressure [244]. The DSM from decompensated bladders over-express the non-muscle isoform of caldesmon [191,245]. The role that the overabundance of l-CaD in DSM cells has in contractile dysfunction of a decompensated bladder is unknown. However, the reversal of outlet obstruction and the regression of hypertrophy lead to decreased l-CaD expression and the return of bladder function to a near-normal state. Downregulation of CaD has been shown to affect the cytoskeletal structure of cultured cells [246].

In addition to the changes in thin filament-associated proteins, studies from several laboratories18;108 have demonstrated that overexpression of the C-terminal myosin isoform SM1 is associated with the detrusor hypertrophy induced by BOO [175,247]. In a rabbit model of BOO, although DSM from normal bladders expressed the SM myosin heavy chain isoform SM-B and LC17a almost exclusively, detrusor muscle from severely dysfunctional bladders expressed as much as 75% SM-A and 40% LC17b (both are associated with a decreased maximum velocity of shortening) [167].

DSM from dysfunctional bladders also exhibited tonic-type contractions, characterized by slow force generation and high force maintenance. Immunofluorescence microscopy showed that the decreased SM-B expression found in dysfunctional bladders was not due to the generation of a new cell population that lacked SM-B. Metabolic cage monitoring revealed that decreased void volume and increased voiding frequency were correlated with overexpression of SM-A and LC17b [167]. The upregulation of the low ATPase-activity myosin isoform in the remodelled DSM caused the detrusor to develop force slowly but with low utilization of ATP and a more economical generation of force. Myosin isoform expression and bladder function returned close to normal upon removal of the obstruction, indicating that the level of expression of these isoforms is a marker of BOO-induced bladder dysfunction.

4. SPONTANEOUS ACTIVITY

Spontaneous contractions are observed in whole bladders, bladder strips and isolated detrusor myocytes [62,248,249] from animal models and man, **Figure 9A**. Such spontaneous activity is, however, not common to all strips [249,250] or all areas of the bladder [251] at any given time. Likewise, only a proportion of smooth muscle cells sampled by intracellular recording exhibit spontaneous action potentials [252] and the basis of such heterogeneity is yet to be established. The function of spontaneous contractions is likely to be in maintaining bladder tone during filling and enabling rapid elevation in intravesical pressure when micturition is required [250]. Pathologies such as OAB and BOO are characterised by increased spontaneous activity and fused tetanic contractions [250,253,254], making its study pertinent.

a) The origin of spontaneous activity

Spontaneous contractions in physiology and pathophysiology are resistant to TTX, atropine and α,β-methylene ATP suggesting they are not due to acti-

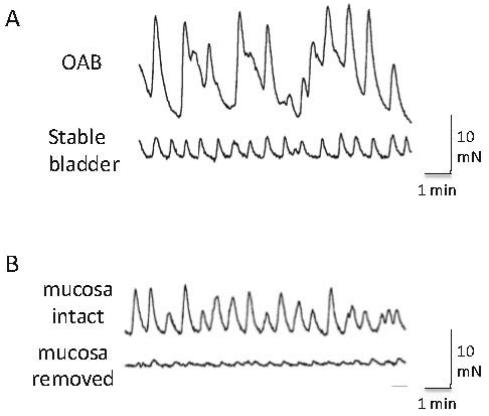


Figure 9. Spontaneous activity contractile activity. A: Spontaneous contractile activity from isolated strips of human detrusor smooth muscle from a patient with OAB (upper trace) and a stable bladder (lower trace). B: Spontaneous contractile activity from isolated strips of human detrusor smooth muscle with the mucosa intact (upper trace) and with the mucosa removed (lower trace).

vation of parasympathetic fibres [249,250]. Activity is, however, abolished by agents that limit transmembrane Ca^{2+} influx, such as L-type Ca^{2+}-channel blockers, and by a reduction of extracellular Ca^{2+} [255], suggesting an origin within the bladder itself. Several hypotheses have been put forward to account for the origins of spontaneous activity but those most often described – the myogenic hypothesis [250] and neurogenic hypothesis [256] – concern origins in pathology, not physiology. This review will give a brief overview of these hypotheses but will aim to focus mainly on hypotheses bridging physiology and pathophysiology.

Prostanoids. In the rabbit, at least, spontaneous contractions are likely to result from prostanoids binding to EP receptors on detrusor smooth muscle. Spontaneous contractions can be abolished by inhibiting the production of prostaglandins (PGs) through non-selective or receptor-specific antagonism. Likewise, spontaneous contraction amplitude is increased by PGs or their mimics [257,258]. The origin of the PGs that cause spontaneous contractility is yet to be established as detrusor smooth muscle [45] and the urothelium [259] can produce PGs; and ICs show cyclo-oxygenase (COX) immunoreactivity [18,257]. Given an up-regulation of COX1 and COX2 expression and PG synthesis in disease states such as BOO and chronic ischemic bladder, [260-262], the possibility of NSAID treatment seems attractive. The few published studies are, however, equivocal in their findings [263-265]. Further studies are required to describe the role of PGs in the spontaneous contractions of human detrusor.

Nitric oxide. Nitric oxide (NO), derived from neuronal nitric oxide synthase (nNOS), contributes to spontaneous activity in mice [266] and guinea-pig [267]. The frequency of spontaneous action potentials was lower in nNOS-/- mice than their wild-type (nNOS+/+) siblings and their frequency could be restored by the addition of the NO donor, NONOate [266]. As with the role of PGs underlying spontaneous activity in rabbit detrusor, it remains to be established what role NO plays in other species. Furthermore, it is yet to be established whether the role of NO is up- or down-regulated in pathology.

Acetylcholine. In rat and guinea-pig there is a spontaneous TTX-resistant release of acetylcholine (ACh) from autonomic nerves which at least partly underlies bladder spontaneous contractions [268]. It is not known, however, whether such spontaneous release of ACh occurs and contributes to spontaneous contractions in man; an inhibition of ACh breakdown, resulting in increased resting tone and inducing spontaneous contractions was only observed in OAB patients – not in asymptomatic patients [269], implying the origins of spontaneous contractions in man may differ between physiology and pathophysiology.

Unknown agent(s) released by the mucosa. In many species, spontaneous activity is increased if the mucosa (comprising urothelium and suburothelium/interstitium/propria lamina) is left intact, **Figure 9B**.

Optical imaging experiments of bladder cross-sections show that spontaneous activity often arises in the suburothelium and spreads to the detrusor layer [151]. Using bladder sheets with the urothelial surface uppermost, optical imaging measurements show propagating Ca^{2+} waves over the sheets, but only in those sections where the mucosa had not been removed [65]. This aspect of spontaneous activity was considered above in more detail (section 3.3.3) but overall it consistent with the hypothesis that spontaneous activity can originate in the suburothelial layer of interstitial cells and then propagate to the detrusor where spontaneous contractions are generated. The increase of suburothelial interstitial cells in overactive bladders is consistent with their greater incidence of spontaneous activity.

b) The myogenic hypothesis

Central to the theory of a myogenic basis for OAB is: denervation and/or reduction of parasympathetic activation causing an increase in smooth muscle cell excitability and coupling [250]. There is evidence for increased smooth muscle cell excitability in isolated cells from overactive bladder samples [62]. The origin of this activity may reside in altered Ca^{2+} channel populations. Both L-type and T-type Ca^{2+} current can be recorded from detrusor muscle. However, the proportion of T-type current is increased in cells from overactive bladders [270], as T-type channels are opened at more negative membrane potentials, an increase in density would increase spontaneous electrical activity [271]. Evidence for increased coupling is compelling in animal models of disease; with consistent increases

in the gap junction proteins connexin43 [66,272-276] and connexin26 [152,272] associated with BOO and spinal cord injury. By contrast, evidence from human tissue is equivocal for connexin45 [e.g. 14,277] and connexin43 [14,278].

c) The neurogenic hypothesis

The neurogenic hypothesis [256] concerns how damage to the neural circuits in the brain and spinal cord that regulate storage and periodical voiding might result in OAB through: a reduction in the suppression or enhancement of the parasympathetic excitatory outflow; sensitisation of peripheral afferent terminals; emergence of bladder reflexes that are resistant to central inhibition. This aspect will be considered in the report of Committee 3.

5. ELECTRICAL ACTIVITY AND ION CHANNELS

How the electrical activity of detrusor smooth muscle is regulated by the movement of ions, and how receptor modulators affect excitability is the subject of the previous consultation [196] and other reviews [279-281]. The focus shall therefore be on channels that influence spontaneous activity and therapeutics; other channels, such as TRP and ligand-gated channels are included in Section 6.4.

K^+ channels. Detrusor myocytes possess several types of K^+ channel, including large (BK) and small (SK) Ca^{2+}-activated channels as well as voltage-sensitive K^+ (Kv) and ATP-sensitive (KATP) channels. The spontaneous contractility of human detrusor strips is dependent on both BK and SK channels, as blockade increases activity [282,283]. Openers of Ca^{2+}-activated K^+ channels (e.g. NS-9541) reduce spontaneous contractility in tissue from asymptomatic patients [284], making them potential candidates for the treatment of pathologies in which spontaneous contractility is elevated, such as OAB. But there is a reduced role for BK channels in contributing to spontaneous contractions in NDO patients; whilst a BK opener (NS-1619) reduced spontaneous contractions and a BK antagonist (iberiotoxin) increased activity in control patients, neither agent had an effect in strips from NDO patients. SK channels were unaffected in NDO patients, as apamin increased spontaneous contracture, in both groups [285]. Clearly there is a great need for experiments on pathological human tissue; animal studies are poor models in this case [286,287]. KATP openers offer some promise as pinacidil and ZD0947, for example, relax carbachol-contracted human detrusor [288]. KNCQ (Kv7) channels contribute to the resting membrane potential and excitability of several cell types and mutations in genes encoding for the channel have been implicated in contributing to abnormal activity in several tissues [289]. Their recent identification in detrusor interstitial cells [290] implies they may contribute a similar role. The KNCQ channel opener retigabine increased micturition volume and voiding intervals and reduced overactive bladder behaviour from capsaicin installation when the agents was infused into the bladder [291]. Recent understanding of many of the functions regulated by K^+ channels has been recently summarised [292].

Isolated detrusor myocytes display an ability to generate spontaneous action potentials, especially in cells isolated from overactive bladders [62]. The more frequent spontaneous activity is associated with an increase of T-type Ca^{2+} channel activity, which is activated at more negative membrane potentials [270,293]. Ca^{2+} influx through T-type channels has been proposed to have a dual role: to contribute to action potential generation and also to stabilise the resting membrane potential through its close association with SK channels [294]. Mibefradil is a Ca-antagonist with a more selective action on T-type Ca^{2+} channels than other antagonists and one suggested use has been for the management of atrial fibrillation [295]. However, its ability to reduce contractions elicited by electrical field stimulation and high-KCl solutions was less than that achieved by more selective L-type Ca^{2+} channel antagonists [296,297]. It would be of interest to characterise the action of this agent on tissue from overactive bladders.

Cl- are not at thermodynamic equilibrium across the cell membrane of most smooth muscles [298] and thus opening a Cl--selective channel will result in membrane depolarisation. The role of Ca^{2+}-activated K^+ currents in the regulation of normal and overactive detrusor function has been well-reviewed (section 6.4, 196). The contribution of Ca^{2+}-activated Cl- channels is less clear but has been identified in both detrusor and urethral smooth muscle [299,300]. The expression of Ca^{2+}-activated Cl- channels is increased in tissue from overactive bladders and hence may contribute to transient inward currents and an increase of cell excitability [299,301]. Ca^{2+}-activated Cl- current is blocked by agents such as niflumic acid and DIDS [302], but the true contribution of the current to spontaneous activity, especially in the overactive bladder, remains to be evaluated.

V. THE OUTFLOW TRACT

1. TRIGONE

The trigone consists of the triangular region between the ureteral orifices and the bladder outlet that aids bladder emptying and helps prevents ureteral reflux. Along with the bladder neck, it forms the base of the bladder that provides support for the bladder dome and transition to the urethra. The trigone contracts during bladder filling to help keep the ureteral orifices open and the bladder neck closed, and relaxes during micturition to help funnel urine into the outlet and prevent ureteric reflux [303]. The tone of the trigone muscle is predominately under adrenergic control [304] and as such this regions exhibits higher frequency spontaneous activity in comparison to detrusor smooth muscle [249]. This is believed to be mediated by L-type Ca^{2+} currents and Ca^{2+}-activated Cl^- fluxes, the propagation and

coordination of which is mediated by gap junction coupling [303]. It has been suggested that trigone spontaneous activity is initiated by peristaltic waves originating in the ureters but this has not yet been experimentally confirmed. The trigone is also heavily innervated and is the region where the majority of the fibres from the pelvic and hypogastric nerves enter the bladder wall [305,306]. This has made the trigone a target for the treatment of detrusor overactivity using botulinum neurotoxin type A (BoNT/A), as it is believed that it will be more effective due to the greater nerve density [307]. **Figure 10** shows a diagram of the male lower urinary tract, i.e. with the additional presence of the prostate gland.

a) Developmental origins of the trigone and insertion of the vesicoureteral junctions

Trigone smooth muscle was originally believed to be formed from the mesodermal tissue of the ureters that project into the developing bladder, while the urothelium is formed from endodermal tissue [308]. Recent evidence, however, suggests that the trigone is mostly derived from bladder smooth muscle and that there are very few projections from the ureters [309].

The 'ureteric bud theory' of Mackie and Stephens suggests that the trigone develops from the ureters and the common mesonephric (Wolffian) ducts, independent of any contribution from the bladder [310,311]. This is reported to occur when the independently developing upper and lower urinary tracts connect at mid-gestation, when the ureters migrate from their initiation sites in the Wolffian ducts to form the trigone. The mechanism responsible for the precise location and angle of insertion of the ureters in the trigone is poorly understood but crucial for the proper functioning of the ureteric valves in preventing urine reflux and renal obstruction. Thus, this theory implies a common mesodermal origin for the trigone and ureterovesical junctions but it has not been tested experimentally [312-314].

An alternative 'smooth muscle theory' for the development of the trigone is based on recent studies utilizing cre-lox mice with fluorescently labelled epithelial cells in the ureters and Wolffian ducts. These studies confirmed the insertion of the common me-

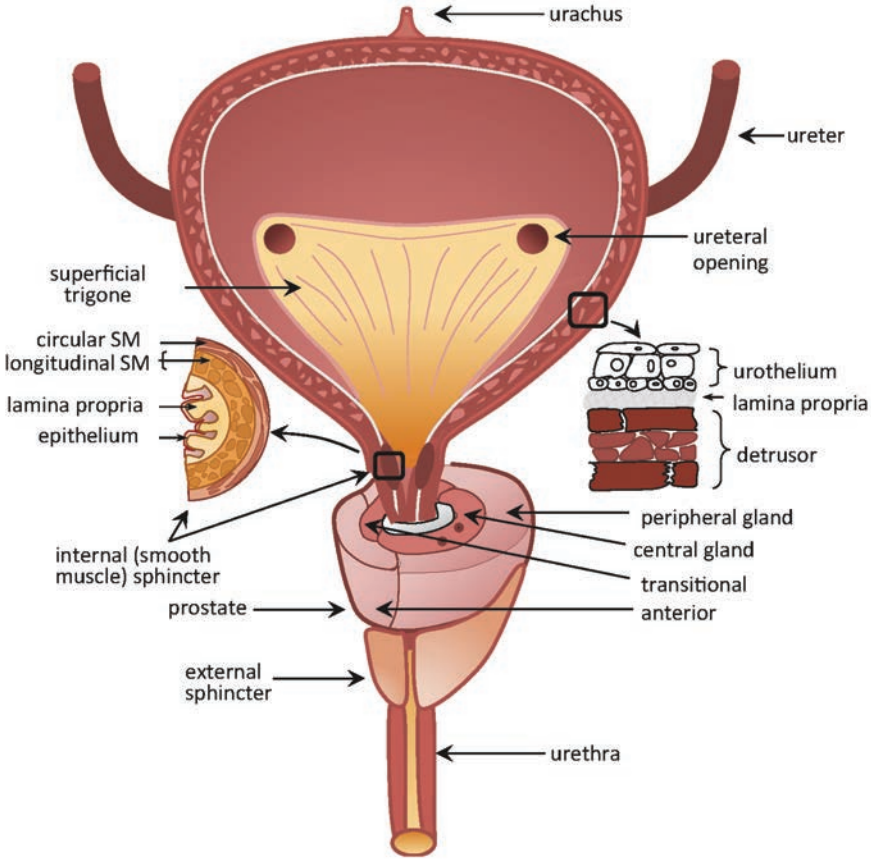


Figure 10. The male lower urinary tract. Depicted are the ureters, the bladder and a cross-section of its wall, the trigone, and the urethra with a cross-section of its longitudinal and transverse smooth muscle sphincters. Also shown is the prostate, its different regions, as well as the striated external urethral sphincter.

sonephric ducts in the bladder wall. However, they also suggested that after insertion this tissue undergoes apoptosis and regresses and that the growth of the bladder smooth muscle moves the ureteral orifices to their final positions in the trigone [309,315]. This implies that the trigone is formed mostly from bladder smooth muscle with only a minor contribution from the ureters [308,309,316-318]. However, a role for both theories is suggested by findings from a recent transgenic mouse model with a primary defect in bladder smooth muscle differentiation that develops a megabladder and obstructive uropathy [319,320]. Although these mice completely lack detrusor smooth muscle they still develop a trigone, however the ureteric orifices insert incorrectly.

b) Superficial and deep trigone.

Superficial and deep trigone layers have been distinguished based on histological studies [321,322] where the former appears to function separately from the detrusor [323] but the origins of the different layers remain controversial. It has been suggested that the deep trigone is derived from the detrusor and the superficial layer from the ureters [324]. Recent studies, using optical mapping and mouse bladder sheets stained with a voltage-sensitive dye have demonstrated that the superficial trigone is electrically discrete from the underlying detrusor. Focal electrical stimulation of the superficial trigone in bladders from control mice resulted in membrane depolarization that did not spread beyond this region (**figure 11A,B**). However, in bladders from mice two weeks following T8-T9 spinal cord transection, stimulation of the superficial trigone initiated activity that spread to the detrusor (**figure 11C**). This enhanced spread of activity was reduced following desensitization of TRPV1 containing afferent nerves using capsaicin (**figure 11D,E**), suggesting that this is mediated by the morphological expansion of sensory nerves from the superficial trigone to the detrusor (i.e., sprouting). This enhanced afferent activity may be responsible, in part, for the neurogenic detrusor overactivity that occurs following thoracic level spinal cord injury and may help explain the therapeutic benefit of focal trigone injections of BoNT/A [307]. Note that capsaicin at 1 μM was able to activate transiently contractile activity before the preparation became desenstised (**figure 11F**).

2. THE URETHRA AND SPHINCTER MECHANISMS

a) Bladder-urethral coordination

There is neural regulation between the bladder and the outflow tract that facilitates the coordinated relaxation of the urethral sphincters and contraction of the detrusor smooth muscle. This allows for complete emptying of the bladder during micturition with a minimal increase in intravesical pressure.

The bladder base is a region of dual sympathetic-adrenergic and parasympathetic-muscarinic innervation [199,325] similar to that of the urethra. There is a higher expression of α1-adenoreceptors in the trigone and the bladder neck in comparison to the detrusor [199] with muscarinic receptor expression found predominantly in the superficial trigone [325,326]. Animal studies have shown that adrenergic stimulation via sympathetic nerves is active during the storage phase and induces contraction of the bladder base. Together with similar actions in the urethra it results in closure of the bladder base preventing incontinence [327]. Thus, the bladder neck

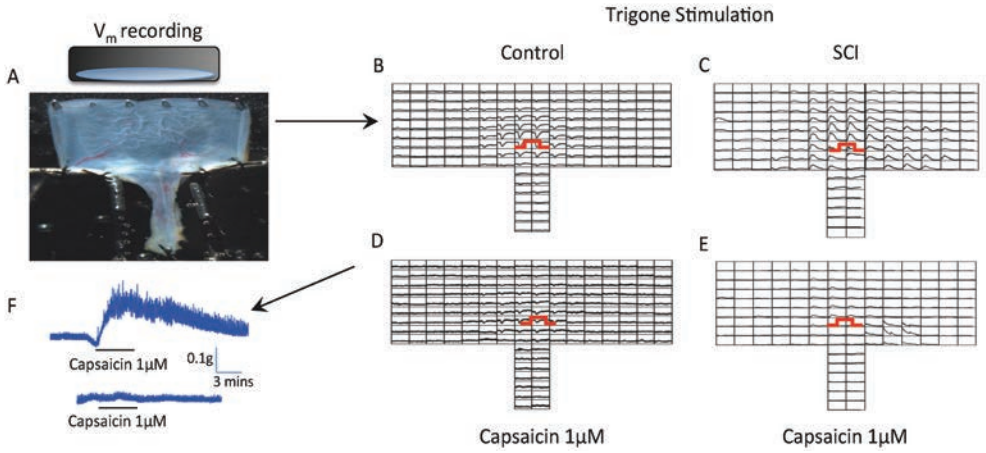


Figure 11. Optical mapping of membrane potential activity after electrical stimulation of the trigone: bladder-urethral sheets from control mice and mice with an upper spinal cord injury (SCI). A: Image of a preparation in the recording chamber to measure simultaneously tension and electrical activity. B: Electrical stimulation in control bladders resulted in a limited propagation of membrane activity within the region. C: Similar stimulation of bladders from mice with SCI – there is enhanced spread of activity beyond the trigone. D: desensitization of TRPV1 receptors with capsaicin (1 μM) reduced the spread of activity in normal bladders. E: desensitization with capsaicin (1 μM) in an SCI preparation also reduced the spread of activity in the preparation. F: Tension recordings demonstrating decreased force generation by the trigone following desensitization with capsaicin.

may represent a transitional region with functional characteristics of both the urethra and the bladder. In addition, parasympathetic innervation may act synergistically with sympathetic nerves as simultaneous activation of both systems produce a gain of function not seen if the two are activated independently [325]. This synergism may contribute to the prevention of reflux and increase in outflow closing pressure, and may explain the particular effectiveness of combination therapies utilizing both antimuscarinic and α1-adrenergic receptor antagonists.

Recent findings suggest that there is also intrinsic coordination between the bladder and the urethra mediated through intramural ganglia. Using optical mapping of bladder-urethral sheets propagation of action potentials were recorded in control and spinal cord injured mouse bladders (**figure 12**). In bladders from control and thoracic level injured animals (upper motoneurone lesion, UMN), focal electrical stimulation of the bladder dome caused signals to spread into the urethra (**figure 12A,C**). This spread was inhibited in the presence of a hexamethonium; a ganglion blocker (**figure 12B,D**). In bladders of mice with a lumbar-sacral level lesion (lower motoneurone lesion, LMN), signals were limited to the bladder (**figure 12E,F**). These finding suggest that pre-ganglionic parasympathetic nerves may innervate both bladder and urethral intramural ganglia to facilitate coordinated activation of the two structures (**figure 13**).

b) The internal sphincter

The presence of a single sphincter at the bladder base and proximal part of the urethra is a contentious subject. Several tissues of this region combine to generate a region that controls the flow of urine from the bladder and is often called the internal urethral sphincter. Because of the complex form and function of this region and the fact that an effective sphincter function is not due entirely to contraction of urethral smooth muscle, this mechanism will be termed 'the internal sphincter'. By contrast, the incomplete ring of skeletal muscle that surrounds the more distal urethra forms a more recognisable sphincter mechanism, and will be described as an external urethral sphincter (section 5.2.3)

Urinary continence is maintained through the tonic contraction of the internal sphincter, which is further supported by the voluntarily controlled striated external urethral sphincter (EUS). The internal sphincter has two distinct longitudinal and circular muscular layers, a lamina propria and an epithelial lining (**figure 14**). During the storage phase, the circular smooth muscle contracts to maintain a high fluid resistance in this region and the longitudinal smooth muscle relaxes to facilitate closure. This occurs through the release of noradrenaline from sympathetic terminals and activation of α1-adrenoceptors on the circular muscle and β3-adrenergic receptors on the longitudinal fibres. Alternatively, during the emptying phase, the circular fibres relax and the longitudinal ones contract to lower fluid resistance and facilitate voiding [328]. This is believed to occur in response to nitric oxide and acetylcholine released from parasympathetic nerve terminals that activate guanylyl cyclase [329] and stimulate M2/3 cholinergic receptors, respectively [330]. Urethral smooth muscle cells from both layers also display intrinsic contractile activity that promotes urethral tone [328] and this is contributed by similar activity in smooth muscle cells of the bladder base. Mucus secreted from goblet cells on the luminal surface is believed to facilitate the passage of urine. Urethral closure may

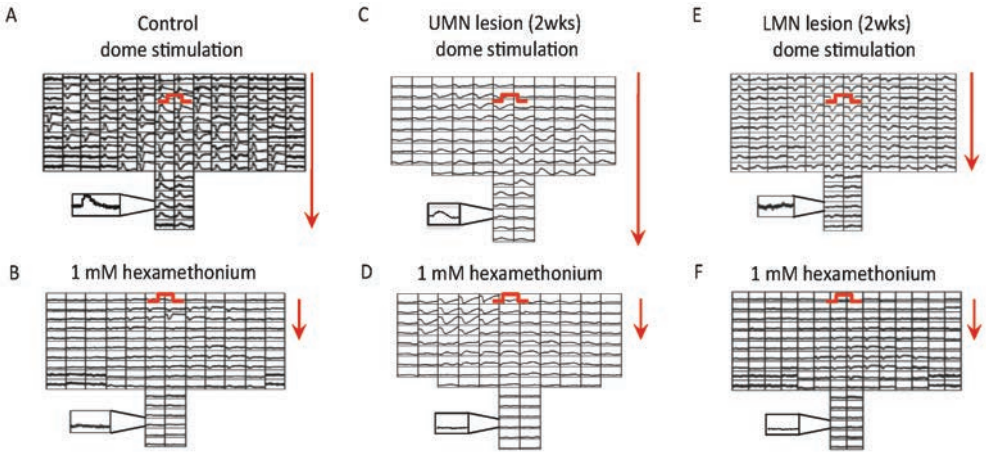


Figure 12. Optical mapping of bladder-urethra sheets from control, upper motor neuron (UMN; T8-T9) and lower motor neuron (LMN; L4-L5) lesioned mice. Electrical activity maps show that in both control (part A) and UMN lesioned (part C) mice electrical stimulation of the dome resulted in activity that spread throughout the bladder and into the urethra. In LMN lesioned mice, there was disco-ordination, as electrical stimulation of the bladder evoked activity that did not spread into the urethra (part E). Hexamethonium inhibited propagation of signals from the bladder into the urethra in control (part B) and UMN lesioned (part D) mice, the blocker did not alter the signals from LMN-lesioned bladders (part F). These data suggest that bladder urethral coordination is mediated through intramural ganglia.

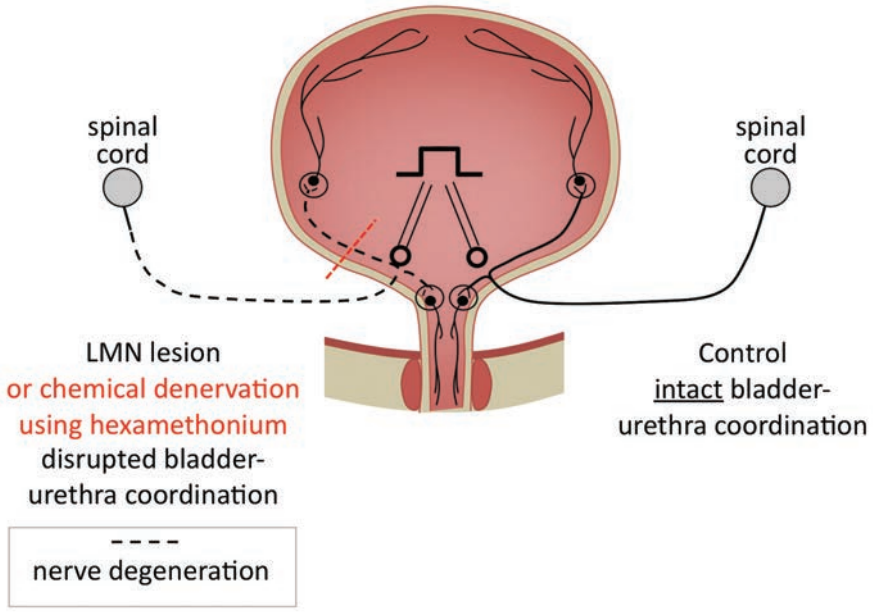


Figure 13. Hypothesis for the involvement of intramural ganglia in bladder-urethra coordination. Focally evoked electrical activity (O) spreads from the bladder to the urethra via intramural post-ganglionic parasympathetic axons (right side). Following a lower motor neuron (LMN) lesion, pre-ganglionic fibres degenerate (left side) resulting in disruption of coordination. Alternatively, coordination could be disrupted via chemical denervation using the ganglion blocker, hexamethonium.

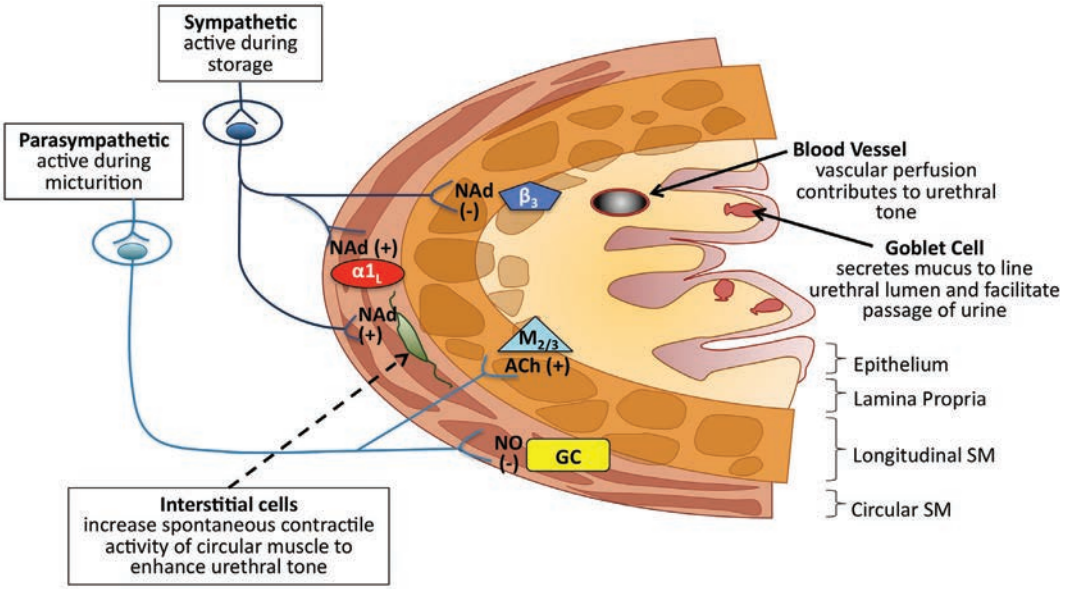


Figure 14: Innervation of the internal sphincter. The circular and longitudinal smooth muscle layers are innervated by sympathetic, parasympathetic and nitrergic nerves. During the storage phase, sympathetic activity relaxes the longitudinal and contracts the circular muscles to close the urethra and maintain continence. During micturition, parasympathetic and nitrergic activity relaxes the circular and contracts the longitudinal muscles to open the urethra and promote voiding. NAd, noradrenaline; Ach, acetylcholine; GC, guanylyl cyclase.

be enhanced by the well-vascularized mucosa and submucosa that reduce the open space in the lumen.

Interstitial cells have been identified in the smooth muscle layers of the proximal urethra and show physiological characteristics similar to interstitial cells of Cajal found in the intestine [331-333]. It has been suggested that these cells may communicate with the smooth muscle cells to promote intrinsic contractile activity. However, this mechanism has not been elucidate and urethral smooth muscle appears to maintain intrinsic activity in the absence of interstitial cells [334]. Another cell type that may modulate contractility of smooth muscle in the internal sphincter is neuroendocrine cells or paraneurons. These are found on the luminal surface of the urethra scattered between epithelial cells. Neuroendocrine cells have microvilli that project into the lumen that can sense mechanical or chemical changes [335]. Urethral neuroendocrine cells also express transmitters such as chromogranin A, somatostatin and serotonin, which may be released in response to stimuli to regulate urethral tone [336].

c) External urethral sphincter (EUS)

The EUS or rhabdosphincter consists of striated muscle innervated by motoneurons through the pudendal nerves. The EUS facilitates voluntary regulation of micturition by maintaining outlet pressure during the storage phase and coordinating its relaxation with detrusor contraction for efficient voiding [337]. Prior to bladder contraction and EUS relaxation, there is a gradual rise of sphincter tone, as measured by electromyographic activity, referred to as the guarding reflex.

The EUS in both males and females forms a horseshoe shape surrounding the urethra. It covers the dorsal, lateral and a majority of the anterior urethra. In males the EUS surrounds a greater portion of the urethra; in females the uterus prevents further coverage of the urethra during development [338]. The less complete coverage in the female EUS may be a contributing factor to the higher incidence of stress urinary incontinence in women. In addition, women are more likely to experience damage to the EUS as a result of vaginal delivery. However, stress urinary incontinence also occurs frequently in men, where damage can result from radical prostatectomy, age-related degeneration of EUS muscle or neurodegenerative conditions. Sex hormones may also play a role in regulation of EUS function. Urinary dysfunction occurs more frequently in postmenopausal women and there has been evidence to suggest that decreased oestrogen levels can affect EUS function [339]. Fowler's syndrome, an obstructive condition in women that occurs as a result of overactive urethral sphincters, is also believed to be influenced by hormones [340].

d) Consequences of EUS dysfunction and treatments

Disruption of neural regulation of the lower urinary tract can lead to severe impairment of EUS function. Thoracic level spinal cord injury can cause bladder-sphincter dyssynergia; a discoordination between contraction of the bladder and relaxation of the urethral sphincters during micturition. This can lead to further complications such as vesicoureteral reflux, hydronephrosis and potentially renal failure. There are a number of treatments for EUS dysfunction including, catheterization, BoNT/A injections, sacral neuromodulation, or in the most severe cases external sphincterotomy [341-343]. In the case of EUS damage (e.g., due to child birth or radical prostatectomy) a current treatment under investigation is the use of bone marrow derived mesenchymal stem cells to promote regeneration of the striated muscle. Several studies have indicated that this treatment improves sphincter function in rat models of stress urinary incontinence [344,345] and in clinical trials using autologous stem cell [346,347].

3. PROSTATE

a) Prostatic lobes and their cellular components

The human prostate consists of four lobes (**figures 10 and 15**). The anatomy varies between different species, and in particular between the human gland and that of small laboratory animals (**Figure 15**). The anterior lobe is mostly smooth muscle and constitutes approximately 10% of the prostate. The peripheral lobe, which is the site of most cancers, is mostly glandular cells and makes up about 60% of the organ. The central lobe is also mostly glandular cells and accounts for another 25% of the gland. The transitional lobe, which surrounds the urethra and is the site where benign prostatic hyperplasia (BPH) develops, constitutes the remaining 5% of the prostate.

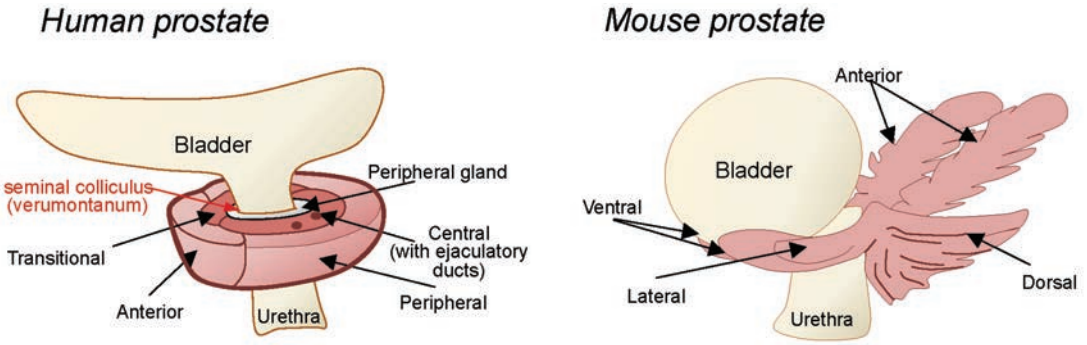
The mammalian prostate is a fibromuscular (anterior lobe) and glandular (peripheral, central and transitional lobes) organ where the glandular lobes are composed of prostatic ducts that include an epithelial layer of basal, columnar secretory and neuroendocrine APUD (Amine Precursor Uptake and Decarboxylase) cells, and an underlying stromal layer made up of fibroblasts and smooth muscle, bound to one another by an extracellular matrix [348,349]. Together with the seminal vesicles and the bulbourethral (Cowper's) gland it produces the bulk of the seminal fluid or ejaculate that is released during emission. Its secretions include acid phosphatase, citric acid, fructose, prostaglandins, proteolytic enzymes and zinc [348,350,351]. These factors provide nutrients and enhance sperm motility, viability and transport as they traverse the male and female reproductive tracts optimizing conditions for fertilization [352]. Emission results when the stromal smooth muscle contracts to propel these secretions from storage in the acini into the seminal fluid and the prostatic urethra to become part of the ejaculate.

b) Prostatic innervation and its role in seminal fluid secretion and emission

The growth, development and regulation of the mammalian prostate are under endocrine (androgen) and autonomic control and is densely innervated by hypogastric (sympathetic) and pelvic (parasympathetic) nerves. The distribution of nerves and pre- and post-synaptic receptor expression suggest that seminal fluid secretion is under cholinergic control with acetylcholine acting on postsynaptic M1-muscarinic receptors on the epithelium (**figure 16**). Emission is mediated by adrenergic control with noradrenaline stimulating postsynaptic α1-adrenergic receptors on stromal smooth muscle cells. Noradrenaline is also believed to contract the prostatic capsule [353]. ß-adrenergic receptors on smooth muscle and epithelial cells are believed to be involved in stromal relaxation and epithelial protein synthesis, respectively. Presynaptic M1-muscarinic receptors on adrenergic terminals in the stroma suggest that acetylcholine may play a role in smooth muscle contractility [354]. Moreover, the co-localization of ATP [355], excitatory neuropeptides (e.g., vasoactive intestinal peptide, neuropeptide Y) [356-360] and nitric oxide [358] in cholinergic terminals also suggest that these transmitters play a role in prostate secretion and emission (**figure 16**). After castration, there is a marked loss of epithelial cells and atrophy that can be restored by exogenous administration of androgens demonstrating their importance in prostate growth and development [361]. This is the basis for the use of anti-androgenic 5α-reductase inhibitors (5ARIs) to shrink the prostate in patients with BPH [362].

Animal studies suggest that prostatic secretion is mediated mainly through parasympathic nerves [306,363-365], but this has not been verified in humans. Dense cholinergic innervation has been demonstrated in both the prostate epithelium and stroma with M1-muscarinic receptor density exceeding that of α1-adrenergic receptors. However, these receptors are localized mainly to the epithelium and cholinergic agonists evoke only a small contractile response in the prostate [366], which may be mediated by activation of presynaptic M1-muscarinic receptors on sympathetic nerve terminals (**figure 16**).

Emission occurs when the testis/epididymis form and release sperm (~5% of the semen) into the vas deferens which contract peristaltically to propel the sperm into the ejaculatory duct. The seminal vesicles also release seminal vesicle fluid (~60% of the semen) into this duct, which passes through the prostate gland to enter the urethra at the seminal colliculus or verumontanum. The bulbourethral or Cowper's gland also adds fluid (~5% of the semen) just below the prostate. Ejaculation, on the other hand, is driven by the somatic system and involves the rhythmic contractions of the periurethral striated muscle. The pre-prostatic urethral sphincter contracts during ejaculation to keep semen from entering the bladder. This is under adrenergic sympathetic control and the therapeutic use of α1-adrenergic receptor antagonists to treat BPH can allow semen to enter the bladder resulting in 'retrograde' ejaculations.



Human prostate regions	Corresponding regions in mouse prostate	% Volume of prostate	Major tissue composition	Commonly associated pathology
Anterior	-	10%	Fibromuscular	Prostadynia
Peripheral	Anterior	60%	Glandular	Cancer
Central	Dorsal / Lateral	25%	Glandular / Ejaculatory ducts	Prostatitis
Transitional	Lateral / Ventral	5%	Glandular	BPH

Figure 15: Comparison of the human and mouse prostate gland. The table shows correspondences between different regions in the human and mouse prostate gland.

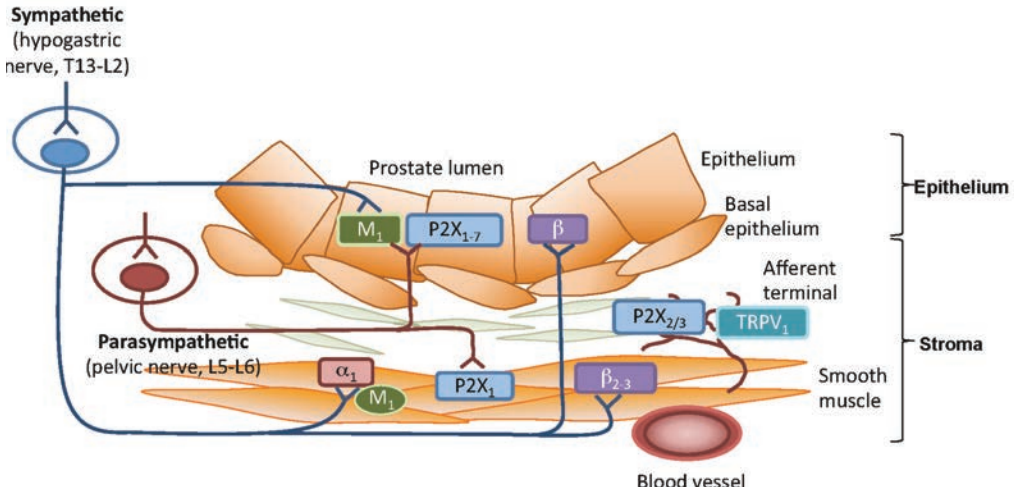


Figure 16: Hypothesis for the autonomic nerves and their receptors involved in prostatic seminal fluid secretion and emission. The growth, development and regulation of the mammalian prostate are under endocrine (androgen) and autonomic control. Synthesis of seminal fluid is principally mediated by parasympathetic innervation with acetylcholine acting on M1-muscarinic receptors on the epithelium. Emission is principally mediated by sympathetic innervation with noradrenaline stimulating postsynaptic α1-adrenergic receptors on stromal smooth muscle cells. Noradrenaline is also believed to contract the prostatic capsule. Purinergic, β-adrenergic and TRPV1 receptors are also shown.

c) Benign prostatic hyperplasia (BPH), prostatitis and therapeutic approaches

As the prostate anatomically surrounds the urethra, inflammation and hyperplasia can lead to irritative and obstructive lower urinary tract symptoms. Although surgery is the gold-standard for alleviating these symptoms, there is considerable interest in three classes of drugs: α1-adrenergic receptor antagonists which reduce stromal smooth muscle tone by antagonizing the action of noradrenaline [367,368]; 5ARIs which are anti-androgenic and reduce the mass of the prostate [369]; and BoNT/A which inhibits neurotransmitter release at sympathetic, parasympathetic and sensory nerve terminals [370].

The prostate is the only accessory genital organ that often undergoes abnormal growth during later life. At puberty, the human prostate gland increases in weight from about 5 to 20 grams but sustains growth throughout life, which may contribute to its benign and malignant pathologies. BPH afflicts approximately 50% of men by their 5th decade and 95% of men by their 8th decade. African-American males develop BPH earlier in life than Caucasian men, often in their 4th decade, and Asian-Americans are less likely to develop it. While not known to be linked to BPH, prostate cancer develops in approximately 16% men during their lifetime with nearly 3% succumbing to the disease. As such, it is the second leading cause of cancer deaths in males in the United States next to lung carcinoma [371].

BPH is readily treated by excision or drug therapy. However, many men die with undiagnosed BPH and may have become impotent, experienced decreased sexual drive and developed urinary incontinence needlessly. The most common therapy is transurethral resection of the prostate (TURP). While TURP has long been the “gold standard” for the surgical treatment of BPH, intra-operative and postoperative side effects have led to the emergence of new surgical and pharmacological therapies. The complications of this therapy include excessive bleeding, urinary sepsis, transurethral resection syndrome and the development of long-term effects such as incontinence, urethral strictures, bladder neck contractures, and sexual dysfunction (retrograde ejaculation and erectile dysfunction). There are several different methods that are reported to be less invasive treatments for BPH, including transurethral laser ablation, transurethral microwave therapy (TUMT) [372], transurethral needle ablation, high intensity focused ultrasound, transurethral needle ablation and trans-rectal high intensity focused ultrasound. They are useful in certain groups of patients, but the evidence to justify the replacement of TURP is still insufficient [373].

Current guidelines recommend α-adrenoreceptor antagonists, to “relax” the prostate by reducing smooth muscle tone, and anti-androgenic 5ARIs, to reduce prostatic volume, either alone or in combination [374] as the preferred pharmacological treatments for BPH. However, these therapies can cause adverse sexual effects: α-blockers are associated with retrograde ejaculation and 5ARIs can cause reduced libido, erectile dysfunction and ejaculatory disorders. Prostatic injections of BoNT/A have also been proposed as a minimally invasive treatment for BPH and this approach is currently undergoing phase 2 clinical trials [375]. Preclinical animal studies have proposed several mechanisms of action for BoNT/A, with evidence of significant glandular apoptosis and pros-

tatic atrophy. It also may induce relaxation of smooth muscle tone through a reduction in the release of noradrenaline and stimulation of α1-adrenergic receptors, and decrease gland size by inhibiting the trophic effect of the autonomic nervous system. Other possible treatments include; phosphodiesterase type-5 inhibitors, luteinizing hormone-releasing hormone antagonists, vitamin D analogues and a proprietary protein with selective pro-apoptotic properties (e.g., NX-1207) [370].

Reliable animal models for studying the lower urinary tract symptoms due to BPH are limited to the chimpanzee [376,377], as unlike humans and chimps, dogs, rabbits, cats and rodents lack a prostatic capsule. Thus, prostatic hyperplasia does not compress the urethra to cause outflow obstruction [378-380]. Like humans and chimps, the dog spontaneously develops BPH but requires encapsulating the prostate in mesh to cause obstruction [379,380]. Transgenic mice that overexpress prolactin can undergo a 20-fold enlargement of the prostate [381], but outlet obstruction does not develop. Partial bladder outlet obstruction (PBOO) can be implemented in rabbits and rodents by tying a partially obstructing ligature around the urethra. However, this is an acute rather than a slowly developing obstruction and female animals are often used.

While BPH and prostatic cancer are more prevalent in older adults and aged men, prostatitis is the most common pathology during young adulthood (20 to 40 years of age). There are four classifications: acute and chronic bacterial prostatitis, which are usually caused by gram-negative bacilli; chronic prostatitis/chronic pelvic pain syndrome; and asymptomatic prostatitis. Acute bacterial prostatitis is an acute bacterial infection of the prostate gland and is typically treated with parenteral or oral antibiotics, depending on the severity of the disease. Chronic bacterial prostatitis is a persistent bacterial infection of the prostate lasting longer than three months. Antibiotics with good tissue penetration are usually recommended for treatment. Chronic nonbacterial prostatitis can be inflammatory or noninflammatory and may involve afferent nerve sensitization. The main symptomology is pain localized to the prostate without evidence of infection. Treatment options include α-adrenoreceptor antagonists and anti-inflammatory and antimicrobial medications. Other pharmacotherapies include 5ARIs, steroids and glycosaminoglycans. Asymptomatic prostatitis is diagnosed when inflammatory cells or leukocytes are noticed upon prostate or semen analysis, respectively, during the examination for other urological conditions. Treatment depends on the primary reason for evaluation. As prostatitis is multifactorial, there are a number of different animal models developed by exogenously administering α-adrenoreceptor agonists to male rodents to increase prostate size and promote inflammation [382], or by injecting inflammatory agents (capsaicin, Freund's adjuvant, lipopolysaccharide, or Zymosan) directly into the prostate. The prostate can also be irritated through afferent cross-sensitization induced by irradiating the bladder. Different treatment paradigms that may be used to investigate prostatis are shown in **Table 3**.

VI. NOVEL MOLECULAR TARGETS FOR OAB AND DETRUSOR OVERACTIVITY

The importance of the urothelium and underlying suburothelium of the urinary bladder in mechanosensory control, and the role of afferent pathways including urothelium/ suburothelium/interstitial cell function in the pathophysiology for OAB is increasingly recognized [383-385]. This has revealed a greater variety of targets to manage OAB other than those concerned with smooth muscle contraction. This section will be concerned with identification of potential novel targets and the identification of biomarkers that can objectively measure the extent and progression of OAB.

Table 3: Animal models for prostatitis

Model	Dosage/Treatment	Pathology	Response
Cross Sensitization			
Bladder irradiation	10 Gray (Gy)	Prostatitis	Cross-sensitization of prostate afferents
Direct Sensitization			
Capsaicin	direct injection into prostate 10-100 mM in 10 ml	Prostatitis	Neurogenic inflammation
Freund's adjuvant Lipopolysaccharide Zymosan	direct injection into prostate Freund's adjuvant, 10 ml LPS: 1 mg/ml, 10 ml Zymosan: 20 mg/ml, 10 ml	Prostatitis	Immune response/ inflammation
Phenylephrine	Subcutaneous, once-a-day for 14 days; 1–10 mg/kg	BPH Prostatitis	Enlargement/ inflammation

1. INTRODUCTION

Signal transduction mechanisms are subclassified into seven different categories (G-protein coupled receptors, ligand-gated ion channels, ion channels, nuclear receptors, catalytic receptors, transporters, and enzymes [386]. This report will focus on the first three of these categories from where most evidence has been derived, **Table 4**.

2. SEVEN TRANSMEMBRANE SPANNING RECEPTORS (7-TM, METABOTROPIC RECEPTORS)

a) Acetylcholine (ACh)-muscarinic receptors

The urinary bladder is profusely supplied with autonomic nerve fibres, which form a dense plexus among the detrusor smooth muscle cells. The majority of these nerves contain acetyl cholinesterase, and while they occur in profusion throughout the muscle coat of the bladder, some muscle bundles are more richly innervated than others. The majority of the autonomic nerves innervating the detrusor muscle is considered to be excitatory cholinergic [387], and contraction of the normal human detrusor is mediated almost exclusively through muscarinic receptor stimulation by released acetylcholine. Detrusor strips from normal human bladders produce little response to single stimuli and require repetitive activation of intrinsic nerves to induce a response that is completely abolished by atropine [249], suggesting that it is purely cholinergic. Molecular cloning studies have revealed five distinct genes for muscarinic ACh receptors in rats and humans, and it is now generally accepted that five receptor subtypes correspond to these gene products [388]. Muscarinic receptors are coupled to G-proteins; M2 and M4 are inhibitory (Gi); M1, M3 and M5 are facilitatory (Gq). The signal transduction systems of M1, M3 and M5 preferentially couple to phosphoinositide hydrolysis leading to mobilization of intracellular Ca^{2+}, whereas activation of M2 and M4 receptors inhibits adenylate cyclase activity. Hence, activation of either M2 or M3 subtypes elicits bladder contraction. Evidence suggests that the detrusor possesses both M2 and M3 receptors [389,390]. Although M2 receptors predominate in receptor binding studies, it is the M3 receptor that is thought to mediate contraction.

Desensitization of muscarinic ACh receptors is one mechanism to reduce the sensitivity of detrusor smooth muscle to incoming stimuli, and is mediated by phosphorylation of the receptor by guanosine phosphate binding protein-coupled receptor kinase (GRK) [391-393]. Protein expression of the GRK2 subtype was significantly decreased in obstructed bladder detrusor from patients with benign prostatic hyperplasia compared to that from normal bladders [393]. Failure of the desensitizing mechanism could contribute to detrusor overactivity with bladder outlet obstruction.

In addition to ACh released from peripheral nerve endings, non-neuronal ACh may also be present when released from bladder urothelium or suburothelium. This ACh fraction is increased by stretch of the bladder wall, and is increased with patient age [111]. At present its function is unknown but may contribute to the pathogenesis of OAB.

The principal treatment for overactive bladder (OAB) is the use of anticholinergic drugs that were initially believed to inhibit the effect of parasympathetic ACh on the detrusor. However, there is now evidence to suggest that anticholinergic drugs could interact with sensory pathways. Stimulation of muscarinic receptor pathways can depress sensory transduction by a mechanism independent of changes in bladder tone, suggesting that muscarinic receptor pathways and ACh could contribute to normal or pathological bladder sensations [394], however, there is no apparent evidence in the clinical setting. Recent studies have described muscarinic receptors on the mucosa as

Table 4. Future potential target molecules for treatment of OAB

Signal transduction mechanisms	Receptor
7TM(transmembrane) receptors	Muscarinic receptors
	β-adrenoceptors
	Cannabinoid (CB) receptors, GPR18/55/119
	$GABA_B$
	mGlu (Metabotropic glutamate receptor)
	Prostanoid receptors
	Tachykinin receptors
Ligand-gated ion channels	P2X
Ion channels	ASICs
	Epithelial Na^+ channels
	K^+ channels
	TRP channels

well as the detrusor. The density and binding affinity profile of the muscarinic receptor population in the human bladder mucosa is similar to that of the detrusor muscle; mucosal M3 subtype density is similar to that in detrusor muscle but lower than in the parotid gland [395]. Furthermore, commonly-used and clinically-effective muscarinic receptor antagonists bind to receptors located on both the bladder mucosa and the detrusor, providing support for the hypothesis that muscarinic receptors in the mucosa may represent an important site of action for these agents in OAB [396].

b) Adrenergic β-receptors

With many animals, sympathetic nerve activity to the bladder increases during the urine storage phase, although this remains to be definitively shown in humans. In addition, there is both relaxation of bladder smooth muscle via an adrenergic β-receptor and contraction of urethral smooth muscle via adrenergic α1-receptors [397]. However, solabegron and other β-adrenoceptor agonists, such as isoprenaline, evoke potent concentration-dependent relaxation of isolated human bladder strips. There are three adrenergic β-receptor subtypes (β1, β2, β3) and relaxation of bladder smooth muscle has been regarded as mediated by the adrenergic β2-receptor [397,398] and the β3-receptor was thought to be related only to fat metabolism. In human bladder tissue it is regarded that the β3-adrenoceptor (β3-AR) is the most significant functional subtype with gene expression of the β3-adrenoceptor (β3-AR) and relaxation of human detrusor via this receptor have been reported [399-402]. In the near future, the role of the β3-AR will be important and several β3-agonists (KUC-7483, YM-178, FK-175) have been developed: YM-178 was launched in Japan in September 2011.

The β-AR is Gs-protein-coupled and its activation elevates intracellular cAMP; the pathway believed to be a key mediator in relaxation of smooth muscle. Downstream effectors activated via cAMP include plasma membrane K^+ channels, such as the large-conductance, Ca^{2+}-activated K^+ (BK, Maxi-K) channel. β-AR-mediated relaxant mechanisms also include cAMP-independent signalling pathways, supported by numerous pharmacological and electrophysiological lines of evidence. In airway smooth muscle, direct activation of the Maxi-K channel by stimulation of β2-AR and Gsα is such a mechanism [403]. The β3-AR is recognized as an attractive target for drug discovery. On the other hand, activation of the β1- or β2-AR can cause undesirable side effects such as increased heart rate or muscle tremors. Consequently, a number of recent efforts in this field have been directed toward the design of selective agonists for the β3-AR [404]. GW427353, a novel β3 AR agonist, evokes bladder relaxation and facilitates bladder storage mechanisms in the dog [405]. The β3-AR agonist CL-316243 has also been shown to act on detrusor muscle and increase urine storage in spontaneously hypertensive rats [406].

The role of the urothelium in bladder responses to β-AR agonists is not yet clear. Masunaga et al. revealed that β3-ARs are involved in mediating inhibitory effects of β-AR agonists on detrusor contractions via the urothelium in pig bladder dome [407]. β3-AR mRNA has been found in the urothelium as well as the detrusor muscle and suggests multiple site of actions in the lower urinary tract [408].

c) Cannabinoids, GPR18, GPR55, GPR119

In recent years cannabinoids, the active components of Cannabis sativa linnaeus (marijuana) and their derivatives, are drawing renewed attention because of their diverse pharmacological activities such as cell growth inhibition, anti-inflammatory effects, and tumour regression [409-414]. The cannabinoid receptor has two subtypes, CB1 and CB2, which are both G-protein-coupled receptors [415]. Cannabinoid receptors are activated by endogenous ligands that include N-arachidonoylethanolamine (anandamide) and N-homo-g-linolenoylethanolamine, N-docosatetra-7,10,13,16-enoylethanolamine and 2-arachidonoyl-glycerol [386].

CB1 was initially characterized in rat brains [416], and later cloned from rat cerebral cortex [417] and human testis [418]. CB1 is distributed mainly in the central nervous system, i.e. cerebellum, hippocampus, and cerebral cortex [419], as well as on peripheral neurons and in non-neuronal tissues including pituitary gland, adrenal gland, lung, testis, ovary, uterus, prostate, eye, and vascular tissue [419-423]. CB2 was cloned from rat spleen macrophages [424], and has also been found in the peripheral immune system tissues, such as spleen and tonsils, and particularly expressed on B-cells and natural killer cells [419].

CB1 is found expressed in human urinary bladder tissue from patients with hypersensitivity and overactivity disorders, and the amount correlates with changes of symptoms. CB1-immunoreative nerve fibres were significantly increased in the suburothelium of patients with bladder pain symptoms (BPS) and idiopathic detrusor overactivity (IDO), and in detrusor layer in IDO patients, as compared with control. CB1-immunoreactive suburothelial nerve fibre density correlated significantly with pain scores on a visual analogue scale in PBS and urgency scores in IDO. Neurofilament-immunoreactive suburothelial nerve fibres were significantly increased in PBS and IDO. The results suggest that increased expression of CB1 on nerve fibres may be related to bladder pain in PBS and urgency in IDO and support clinical trials of CB1 agonists in bladder disorders [425]. A Cannabis sativa extract enriched in cannabidiol (CBD) and pure CBD reduced cholinergic-mediated contractility. This effect was modulated by transient receptor potential vanilloid type-1 (TRPV1) in rats but not in humans. If confirmed in vivo, such results

could provide a pharmacological basis to explain, at least in part, the efficacy of cannabis products in reducing incontinence episodes in patients with multiple sclerosis [426,427].

Agents named GPR18, GPR55 and GPR119 (a provisional nomenclature), although showing little structural similarity to CB1 and CB2 receptors, respond to endogenous agents analogous to the endogenous cannabinoid ligands, as well as some natural/synthetic cannabinoid receptor ligands [386]. The expression of fatty acid amide hydrolase (FAAH), the endocannabinoid-degrading enzyme, was measured in human, rat and mouse bladders, as well as the effects of inhibition of FAAH. These data were compared to urodynamic measurements in awake rats using the FAAH inhibitor oleoyl ethyl amide (OEtA), rimonabant (CB1 antagonist) and SR144528 (CB2 antagonist). Bladder mucosa of all species expressed FAAH. Rat and human urothelium coexpressed FAAH and CB2. The FAAH inhibitor OEtA altered urodynamic parameters that reflect a sensory function for cannabinoids during the rat micturition cycle. This suggests a role for the endocannabinoid system in bladder mechanoafferent function of rats [428].

d) GABAB

Functional GABAB receptors are formed from the heterodimerization of two similar 7-TM subunits termed GABAB1 ENSG00000168760 and GABAB2 ENSG00000136928. Stimulation of spinal GABAergic mechanisms by intrathecal application of GABAA and GABAB receptor agonists could be effective for the treatment of detrusor overactivity in spinal cord injured rats [429]. Fourteen of 31 patients with refractory OAB and nocturia improved with oral gabapentin. Gabapentin was generally well tolerated and can be considered in selective patients when conventional modalities have failed [430]. Gabapentin has also revealed efficacy in the treatment of DO of neurogenic origin. Preliminary results have shown significant modifications of urodynamic indexes, particularly of the DO, whereas the symptomatic score evaluation and the voiding diary data have demonstrated a significant lowering of the irritative symptoms [431]. These data support the rationale that DO may be controlled by modulating the afferent input from the bladder and the excitability of the sacral reflex centre and suggest a novel method with oral gabapentin to treat OAB patients.

e) Glutamate metabotropic receptors

Glutamate receptors consist of two major classes, the ionotropic receptors which form ligand-gated cation channels [432] and the metabotropic receptors (mGluRs) which are a family of G-protein coupled receptors activating distinct signal transduction pathways in neurons [433]. The former includes N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-lisoxazole-4-propionic acid (AMPA), and kainite receptors, and have an essential role in the control of micturition reflexes [434,435]. Less is known about the functional roles of mGluRs in the lower urinary tract. They comprise eight subtypes (mGluR1 to mGluR8), which are placed into three groups on the basis of sequence homology, transduction mechanism and agonist pharmacology: group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7, mGluR8).

Glutamate is involved in many CNS functions, and drugs acting on the different glutamate receptors may affect not only micturition [436]. Most previous work with lower urinary tract function has used ionotropic glutamate receptors, however the mGluRs should be of value to study further. The involvement of group I mGluRs in the micturition reflex of mice has been investigated. Wild-type female C57BL/6 mice and mGluR1 knockout mice under decerebrate, unanesthetized conditions were used for in vivo cystometry with 6-methyl-2-(phenylethynyl)pyridine (MPEP, 0.3-30 mg/kg i.p.), a selective mGluR5 antagonist. Inter-micturition interval was measured during continuous infusion cystometrograms. Blockade of mGluR1, mGluR5 or both increased bladder capacity and mGluR1 and mGluR5 additively interacted to transmit afferent signals from the bladder. Thus, a group I mGluR antagonist, which blocks both mGluR1 and mGluR5, would have a more beneficial effect than a drug targeting either mGluR1 or mGluR5 alone. This provides a further promising target to treat storage dysfunctions including OAB and urgency urinary incontinence [437]. Similar data has also indicated that glutamic acid has a transmitter function in bladder and somato-bladder reflex mechanisms and raises the possibility that mGluR5 may be a target for pharmacological treatment of lower urinary tract disorders [438,439].

f) Prostanoid receptors

Prostanoid receptors are activated by the endogenous ligands prostaglandin PGD2 (D), PGE2 (E), PGF2α (F), PGH2 (H), prostacyclin PGI2 (I) and thromboxane A2 (T). Prostanoid actions are mediated by specific receptors on cell membranes, which include the DP, EP, FP, IP, and TP receptors that preferentially respond to PGD2, PGE2, PGF2, PGI2, and TXA2, respectively. In turn, EPs are subdivided into four subtypes: EP2, EP2, EP2 and EP2 (**Table 5**) [440,441].

The signalling pathways vary. TP receptors signal via the Gq protein, activating Ca^{2+}/diacylglycerol pathways, but also other G-proteins may be involved; EP1 receptors signal via IP3 generation and increase intracellular Ca^{2+}; activation of EP2 and EP4 leads to an increase of cAMP; and EP3 activation inhibits cAMP generation via a pertussis toxin-sensitive Gi-coupled mechanism and may also signal via the small G-protein Rho. Prostanoids may affect excitation- contraction coupling in detrusor smooth muscle in two ways, directly by

effects on the smooth muscle, and/or indirectly via effects on neurotransmission.

The prostanoid receptor most important for detrusor function has not been established. Mice lacking EP1 receptors had normal cystometry, but did not react to intravesical PGE2 instillation, which caused detrusor overactivity in wild-type controls. Bladder outlet obstruction of EP1 receptor-knockout mice did not prevent the resulting gain of bladder weight, but prevented the increase of spontaneous non-voiding contractions [442]. PGE2 enhances the micturition reflex through C-fibre afferents via EP1; thereby an EP1-selective antagonist may improve bladder storage function [443]. However, the prostaglandin EP1 receptor antagonist ONO-8359 failed to distinguish itself from placebo and was inferior to tolterodine, as reported at a late-breaking science session at the AUA 2011 meeting (http://www.medpagetoday.com/Meeting Coverage /AUA / 26716). The urodynamic effects of an EP4 receptor antagonist (AH23848) in cyclophosphamide-induced OAB was evaluated in rats, and the results were favorable. Antagonists to the EP4 receptor may be a new target for treatment of patients with OAB [444].

The change in expression of each EP receptor subtype and the functional role of the EP4 receptor in bladder outlet obstruction was studied using a selective EP4 antagonist, EP4ONO-AE1-329. EP4 receptor mRNA and proteins have been detected in obstructed bladder detrusor smooth muscle and epithelium, as well as EP1-3 receptor mRNA in normal and obstructed bladders (**Figure 17**). ONO-AE1-329 (100 nM) significantly relaxed KCl-induced contractions of detrusor strips from rat bladder with outlet obstruction. A significant correlation was found between the relaxant effect of ONO-AE1-329 and bladder weight. Activation of EP4 receptors expressed in bladders with outlet obstruction may thus suppress detrusor muscle contraction and afferent activity (**Figure 18, Table 6**). This might be a compensatory mechanism to counteract the deterioration of storage function in bladders with outlet obstruction [445]. However, EP receptor distribution, and its implication, on human urinary bladder mucosa are not fully understood. EP2 and EP4 mRNA are over-expressed in the urothelium of obstructed human urinary bladder compared to non-obstructed bladder and significantly correlated with IPSS, especially storage scores. Hence, in contrast to previous mouse data, EP2 and EP4 may be promising receptor subtypes to treat OAB [446].

g) Tachykinins

Tachykinin receptors are activated by the endogenous peptides: substance P (SP), neurokinin A (NKA), neurokinin B, neuropeptide K and neuropeptide g (N-terminally extended forms of neurokinin A). The neurokinins (A and B) are mammalian members of the tachykinin family, which includes peptides of mammalian and nonmammalian origin containing the consensus sequence: Phe-x-Gly-Leu-Met. Marked species differences in pharmacology exist for all three receptors, in particular with nonpeptide ligands.

Table 5. Classification of prostanoid receptors, EP1-EP4. The pKi values for antagonists are given in parenthesis

Nomenclature	EP1	EP2	EP3	EP4
Ensembl ID	ENSG00000160951	ENSG00000125384	ENSG00000050628	ENSG00000171522
Principal transduction	Gq/11	Gs	Gi/o	Gs
Rank order of potency	E > F,I > D,T	E > F,I > D,T	E > F,I > D,T	E > F,I > D,T
Selective agonists	17-Phenyl-PGE_2 ONO-AE1–329	Butaprost-free acid ONO-AE1–259-01 CP533536	Sulprostone SC46275 ONO-AE-248	ONO-AE1–329 L902688 CP734432
Selective antagonists	ONO-8711 (9.2) GW848687X (9.1) SC51322 (8.8)		L798106 (7.7 ONO-AE3-240 (8.8)	GW627368 (9.2) ONO-AE3208 (8.5) L161982 (8.5) BGC201531 (7.8) CJ042794 (8.6) ER819762 MK2894
Probes	[^{3}H]-PGE2 (1–25 nM)	[^{3}H]-PGE2 (5–22 nM)	[^{3}H]-PGE2 (0.3–7 nM)	[^{3}H]-PGE2 (0.6–24 nM)

See also IUPHAR database:
http://www.iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=34

Table 6. Effect of the EP4 agonist ONO-AE1-329 on detrusor contractility Contractions elicited with 50 mM KCl. Mean data±SEM; *p<0.01 BOO vs sham

Animal model	10 μM	30 μM	100 μM
Sham-operation	3.3±2.2	3.7±2.3	1.2±1.2
Bladder outflow obstruction (BOO)	4.1±2.3	4.6±1.4	15.4±3.7 *

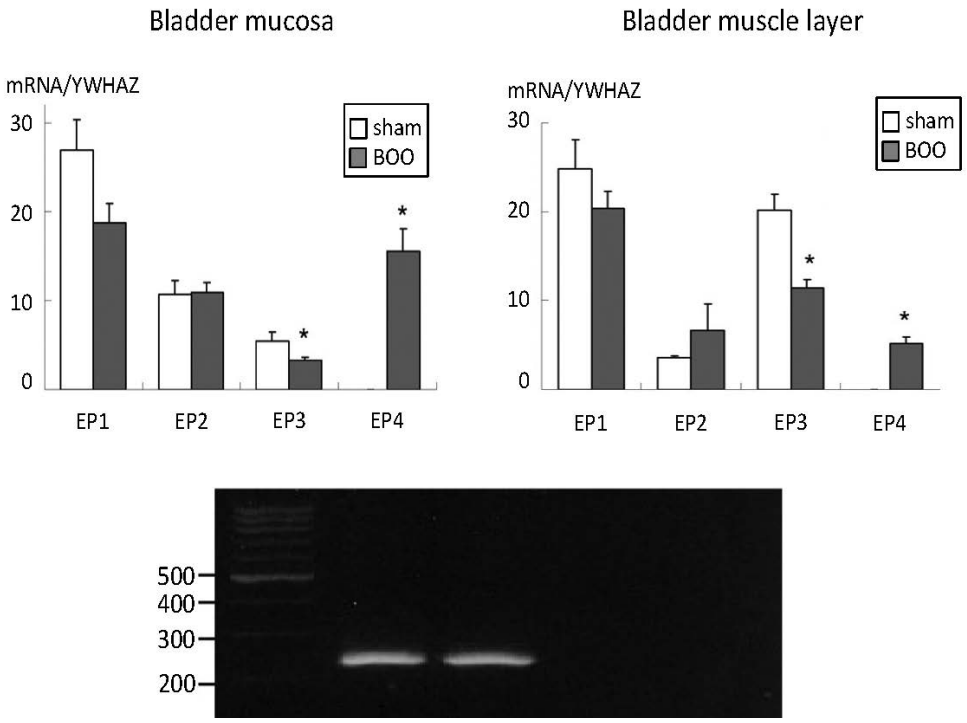


Figure 17. Quantitative analysis of PGE receptor subtypes gene expression in sham operated and bladders subjected to outflow obstruction (BOO). A: Quantitative data of EP1-4 mRNA in the mucosa and detrusor layers vs a house-keeping gene (WYHAZ). Mean ±SEM (n=5, 10 respectively), *p<0.05 vs sham-operated control. B: Representative PCR result of EP4 receptor cDNA in agarose gel electrophoresis; Muc, mucosa. SM, smooth muscle.

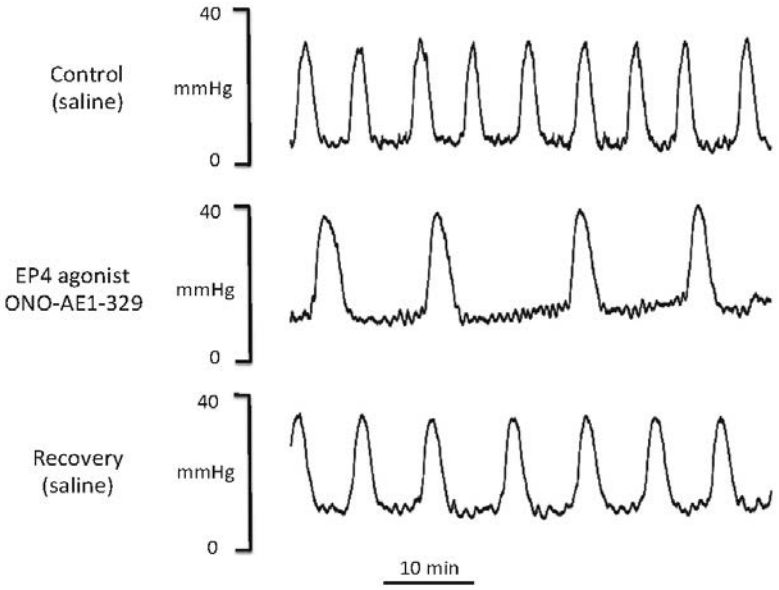


Figure 18. Representative traces to show the effect of the intravesically-infused EP4 selective agonist on the micturition reflex in a urethane-anesthetized BOO rat. Reflex voiding contractions were induced by continuous infusion of normal saline in control, saline with 10μM ONO-AE1-329 and normal saline recovery after ONO-AE1-329 washout at 2 ml per hour. Inter-contraction interval and peak pressure were reversibly increased by intravesical infusion of ONO-AE1-329.

The enogenous receptor for substance P is the G-protein coupled NK1 receptor. The hexapeptide agonist septide appears to bind to an overlapping but non-identical site to SP on the NK1 receptor [386].

Initial clinical trials revealed that Aprepitant, a NK1 receptor antagonist, may show efficacy for the treatment of OAB, suggesting that receptor antagonism may represent a novel therapeutic approach to treating OAB [447]. Cizolirtine citrate (cizolirtine) exerts an inhibitory influence on calcitonin gene-related peptide (CGRP) and substance P release by primary afferent fibres and/or dorsal horn interneurons at the spinal level, mediated through presynaptic serotonin and α2-ARs that are partly related to an increase of the descending noradrenaline pain inhibitory system [448-452]. A dose-finding study was performed as the first step in the clinical development of cizolirtine citrate. Its therapeutic potential at 400mg bid in OAB has been evidenced [453] and has provided further clinical evidence that modulation of tachykinins could be an effective way to treat OAB.

3. LIGAND-GATED ION-CHANNELS

Ligand-gated ion channels (LGICs) are integral membrane proteins containing a pore that allows the regulated flow of selected ions across the plasma membrane. Ion flux is passive and driven by the electrochemical gradient for permeant ions. The channels are opened, or gated, by a neurotransmitter binding to an orthosteric site(s) that triggers a conformational change that results in a different conducting state. Among eight ligand-gated ion channels (5-HT3, nicotinic-ACh, GABAA, glutamate-ionotropic, glycine, P2X, and Zn2+-activated channel), only P2X channels will be discussed. P2X receptors have a trimeric topology with two putative transmembrane domains, where the endogenous ligand is ATP and gate primarily Na^+, K^+ and Ca^{2+}, exceptionally Cl-. The native receptors may occur as either homopolymers (e.g. P2X1 in smooth muscle) or heteropolymers (e.g. P2X2:P2X3 in the nodose ganglion or peripheral afferents and P2X1:P2X5 in mouse cortical astrocytes). P2X2, P2X4 and P2X7 receptors form functional homopolymers which, in turn, activate pores permeable to low molecular weight solutes. The hemi-channel pannexin-1 has been implicated in the pore formation induced by P2X7, but not P2X2 receptor activation [386].

AF-792(5-(5-ethynyl-2-isopropyl-4-methoxy-phenoxy) -pyrimidine-2,4-diamine, a novel selective P2X3 and P2X2/3 antagonist, 300 nM), inhibits micturition reflex activity significantly by increasing baseline contraction intervals. Afferent signals originating from the bladder are regulated by spinal P2X3 and P2X2/3 receptors and establish directly an endogenous central presynaptic purinergic mechanism to regulate visceral sensory transmission. P2X3 and P2X2/3 antagonists may therefore may be promising to treat lower urinary tract dysfunction, such as OAB, and possibly other debilitating sensory disorders, including chronic pain states [454].

After bladder outlet obstruction with overactivity the expression of M2, M3 and P2X3 receptors is increased in rat urothelium, suggesting that changes in urothelium P2X3 receptor expression may mediating afferent sensory responses in the urinary bladder [455]. The P2X3 and P2X2/3 receptor antagonist A-317491 is effective at improving the signs of cyclophosphamide-induced cystitis in the rat, suggesting that the P2X3 or P2X2/3 receptor pathway is involved in the resultant bladder overactivity [456]. The exact mechanisms that underline mechanosensory transduction in bladder afferent terminals remain ambiguous; however, a wide range of ion channels (e.g. TTX-resistant Na^+ channels, Kv channels and hyperpolarization-activated cyclic nucleotide-gated cation channels) and receptors (e.g. TRPV1, TRPM8, TRPA1, P2X2/3) have been identified at bladder afferent terminals and implicated in the generation and modulation of afferent signals. The expression and/or function of these ion channels and receptors may be altered in animal models and patients with overactive and painful bladder disorders. Some of these ion channels and receptors may be potential therapeutic targets for bladder diseases [457]. However, it has also been shown that with detrusor from idiopathic DO patients there was a selective absence of P2X3 and P2X5 that may impair control of detrusor contractility and contribute to the pathophysiology of urge incontinence [458].

4. ION-CHANNELS

Ion channels are pore-forming proteins that allow the flow of ions across either plasma membranes or those of intracellular organelles. Many ion channels (i.e most Na^+, K^+, Ca^{2+} and some Cl- channels) are voltage-gated, but others (i.e. certain K^+ and Cl- channels, TRP channels, ryanodine receptors and IP3 receptors) are relatively voltage-insensitive and are gated by second messengers and other intracellular and/or extracellular mediators. Many ion channels, such as K^+, Na^+, Ca^{2+}, HCN and TRP channels, share several structural similarities. Others, such as Cl- channels, aquaporins and connexins, have completely different structural properties. At present, ion channels (including ligand-gated ion channels) represent the second largest target for existing drugs after G protein-coupled receptors. However, the advent of novel, faster screening techniques for compounds acting on ion channels suggests that these proteins represent promising targets for the development of additional, novel therapeutic agents [386]. The recent demonstration that the urothelium is sensitive to both mechanical and other stimuli, and responds by releasing signalling molecules (NO, ATP) makes this tissue an attractive additional target to detrusor smooth muscle. One or multiple mechanosensitive ion channels play a role in transduction of hydrostatic pressure changes, which supports the view that not only tissue stretch or tension, but also pressure is an important parameter for mechanosensing bladder fullness [459]. A survey of interesting potential targets follows.

a) Acid-sensing (proton-gated) ion channels (ASICs)

Acid-sensing ion channels (ASICs) are members of a Na^+ channel superfamily that includes the epithelial Na^+ channel (ENaC), the FMRF-amide activated channel (FaNaC) of invertebrates, the degenerins (DEG) of Caenorhabitis elegans, channels in Drosophila melanogaster and 'orphan' channels. ASIC subunits contain two transmembrane domains and assemble as homo- or hetero-trimers to form proton-gated, voltage-insensitive, Na^+ permeable, channels. (**Table 7**) ASIC1 is the dominant subunit expressed in bladder epithelium, whereas both ASIC1 and ASIC2 are expressed in detrusor smooth muscle. ASIC3 expression was much less abundant, but localized in the subepithelial region. In the mucosa, the ASIC1 gene is more highly expressed in male than in female mice, whereas the expression level of ASIC2 in the bladder muscle is higher in female than in male mice [460] (**Figure 19**).

Urothelial cells express multiple TRP and ASIC channels, whose activation elicits ionic currents and Ca^{2+} influx. These "neuron-like" properties might be involved in transmitter release, such as ATP, that can act on afferent nerves or smooth muscle to modulate their responses to different stimuli [461]. Indeed, capsaicin (acting on TRPV1) and acid (acting on TRPV1 and ASIC) induce ATP release from the rat bladder urothelium and highlights the importance of both ATP and H+ as signalling molecules in modulating bladder function [81]. Intravesical administration of 100 uM capsazepine (TRPV1 antagonist) showed no effect on bladder irritation by acetic acid (**Table 8**) and implies the two systems are independent. Urinary bladder inflammation induced by cyclophosphamide alters ASIC2a and ASIC3 expression in the rat urinary bladder; ASIC1 transcript expression is not altered [462]. Several ASIC subunits are expressed in human bladder and urothelial cells, in which levels are regulated during urothelial differentiation. Up-regulation of ASIC2a and ASIC3 in patients with bladder pain syndrome suggests involvement in increased pain and hyperalgesia. Down-regulation of TRPV1 mRNA might indicate that a different regulatory mechanism controls its expression in the human bladder [463].

Table 7. Classification of acid-sensing ion channels (ASICs)

Nomenclature	ASIC1	ASIC2	ASIC3
Other names	ASIC; BNaC2	BNC1; BNaC1; MDEG	DRASIC, TNaC1
Ensembl ID	ENSG00000110881	ENSG00000108684	ENSG00000213199
Endogenous activators	Extracellular H^+ ASIC1a pEC_{50} ~ 6.2-6.8 ASIC1b pEC_{50} ~ 5.1-6.2	Extracellular H^+ pEC_{50} ~ 4.1-5.0	Extracellular H^+ transient component pEC_{50} ~ 6.2-6.7 sustained component pEC_{50} ~ 3.5-4.3, agmatine EC_{50} ~9.8 mM aracaine EC_{50} ~1.2 mM both at pH 7.4
Blockers	Psalmotoxin-1, 0.9 nM; amiloride 10 μM; EIPA/benzamil 10μM; nafamostat ~13 μM.	amiloride; 28 μM; A-317567, ~30 μM; nafamostat, ~70 μM.	transient component only APETx2, 63 nM; nafamostat, ~2.5 μM; amiloride 16–63 μM sustained component A-317567 ~10 μM; diclofenac, 92 μM; salicylic acid 260 μM

Table 8. Effects of intravesical acid on bladder function. Acetic acid (pH 3.0 installation) in the absence or presence of capsazepine (100 μM). Mean±SE *p<0.05, **p<0.01, ***p<0.001 acetic acid vs saline

	MVP (mmHg)	PT (mmHg)	ICI (s)	BCP (ml/mmHg)
Control group (n=5)				
Saline (baseline)	25.2 ± 1.7	7.3 ± 0.7	302 ± 39	36.9 ± 3.3
Acetic acid + vehicle	18.9 ± 1.5**	5.0 ± 0.4*	100 ± 18**	19.9 ± 3.4*
Treatment group (n=5)				
Saline (baseline)	27.7 ± 0.9	7.3 ± 1.0	321 ± 19	41.2 ± 5.7
Acetic acid + capsazepine	18.9 ± 1.0***	5.4 ± 0.3	110 ± 11***	24.2 ± 1.7*

Key: MVP, maximal voiding pressure; PT, pressure threshold for inducing voiding contraction; ICI, inter-contraction interval; BCP, bladder compliance

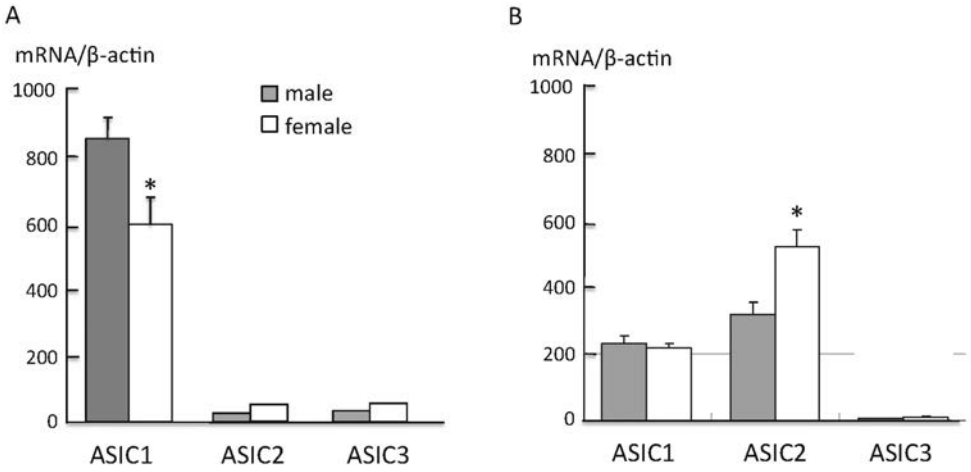


Figure 19. Gender-specific expression of ASIC subunits genes by RT-PCR. A: Expression in bladder mucosa. B: Expression in smooth muscle layer. *p<0.05 male (n=14) vs female (n=10).

b) Epithelial sodium channels (ENaC)

ENaCs are responsible for Na^+ reabsorption by the epithelia lining the distal part of the kidney tubule, and fulfil similar functional roles in some other tissues such as the alveolar epithelium and the distal colon. This reabsorption of Na^+ is regulated by aldosterone, vasopressin and glucocorticoids, and is one of the essential mechanisms in the regulation of Na^+ balance, blood volume and blood pressure. The degenerin ENaC family has been proposed as a transducer of sensory stimuli in several species [464-467] and seem to be mechanosensitive. In the rabbit urinary bladder, ENaC can change Na^+ transporter properties after alterations to hydrostatic pressure [465]. The ENaC in the renal pelvic epithelium of rats participates in the activation of afferent renal mechanosensitive neurons by increased renal pelvic pressure [468]. Thus, ENaCs are likely to be involved in mechanotransduction in the bladder, and may be related to the pathophysiology of changes to sensory nerve function by ENaC upregulation in the bladder urothelium or afferent nerve terminals. cAMP stimulates the insertion of ENaC channel into the apical membrane of the rabbit bladder epithelium [469]. ENaC is expressed in the mammalian bladder urothelium and is the main route of amiloride-sensitive Na^+ transport [470].

In human tissue the α-, β- and γ -subunits ENaC proteins and mRNA are well-expressed in urothelium from patients with and without BOO and the amounts are positively associated with the storage symptom score [471]. In rat bladder the intravesical infusion of 1 mM amiloride (to block ENaC) significantly reduced the frequency of reflex voiding during bladder filling and increased bladder capacity, without any effect on the amplitude of micturition pressure. Stretch (50%) induced significant increase in the ATP release from whole layer bladder strips, but only a slight increase in muscular layer strips without epithelium. Amiloride suppressed stretch-evoked ATP release from rat urinary bladder epithelium [472].

c) K^+ channels

K^+ channels are fundamental regulators of excitability; they control the frequency and shape of the action potential waveform, the secretion of hormones and neurotransmitters and the cell membrane potential. Their activity may be regulated by transmembrane voltage, intracellular Ca^{2+} and neurotransmitters. They consist of a primary pore-forming α-subunit often associated with auxiliary regulatory subunits. The three main families are the 2TM (two transmembrane domains), 4TM and 6TM families [386].

1. The 2TM family of K^+ channels

The 2TM domain family of K^+ channels are also known as the inward-rectifier K^+ channels. This family includes the strong inward-rectifier K^+ channels (Kir2.x), the G-protein-activated inward-rectifier K^+ channels (Kir3.x) and the ATP-sensitive K^+ channels (Kir6.x, which combine with sulphonylurea receptors (SUR)). The pore-forming α-subunits form tetramers, and heteromeric channels may be formed within subfamilies (e.g.Kir3.2 with Kir3.3).

2. The 6TM family of K^+ channels

The 6TM family of K^+ channels comprises the voltage-gated KV subfamilies, the KCNQ subfamily, the EAG subfamily (which includes herg channels), the Ca^{2+}-activated Slo subfamily (actually with 7TM) and the Ca^{2+}-activated SK subfamily. The pore-forming α-subunits also form tetramers and heteromeric channels may be formed within subfamilies (e.g. KV1.1 with KV1.2; KCNQ2 with KCNQ3). Large-conductance, voltage- and Ca^{2+}-activated K^+ (Maxi-K or BK) channels regulate the resting potential and repolarisation of the action potential and play a critical role in modulating contractile tone of smooth muscle and neuronal processes.

BKCa channels play an important role in controlling membrane potential and contractility of urinary bladder smooth muscle [473,474]; SKCa channels are

regulators of excitability in detrusor smooth muscle. Ca^{2+} entry through voltage-dependent Ca^{2+} channels activates both BKCa and SKCa channels, but Ca^{2+} release through ryanodine receptors (Ca^{2+} sparks) activates only BKCa channels. BKCa channels are able to counteract enhanced spontaneous mechanical activity with urinary bladder smooth muscle stretch [475,476]. However, the ability of BKCa channels to regulate spontaneous contractility in tissue from neuropathic DO patients appears more limited [477,478]. NS-8, a selective antagonist for BKCa channels, decreased afferent pelvic nerve firing rate during bladder filling. Thus NS-8 might have the potential for treating patients with urinary frequency and incontinence [479]. A further demonstration of the importance of the BKCa channel is that local injection of hSlo cDNA (i.e. the BKCa channel) ameliorated detrusor overactivity in a rat model of partial urinary outlet obstruction [480]. Consistent with increased bladder contractility caused by absence of BKCa currents, Slo(-/-) mice show a marked elevation in urination frequency [481]. Phasic contractions of human detrusor are dependent on Ca^{2+} entry through L-type Ca^{2+} channels and BKCa and SKCa channels play a key role in the modulation of this activity and supports the concept that increasing conductance through BKCa, SKCa and even KATP channels may represent attractive pharmacological targets to decrease phasic contractions in OAB [482,483]. BKCa channel activity also reduces significantly both cholinergic- and purinergic-induced contractions and suggests that alterations to BKCa channel expression or function could contribute to pathologies such as OAB [484].

A novel BKCa channel blocker, A-272651, represents one of the first small molecules that could serve as a useful tool for their further characterization in physiological and pathological states [485]. No other K^+ channel opener has passed the proof-of-concept stage, and there is at present no convincing evidence showing that K^+ channel opening is a useful principle for treatment of detrusor overactivity [486]. The safety and tolerability of escalating doses of hMaxi-K, a gene transfer product of human Maxi-K^+ channel, were confirmed by clinical evaluations and laboratory tests in 11 patients with moderate to severe erectile dysfunction. It was proposed that hMaxi-K gene transfer is a viable approach to treat erectile dysfunction and other smooth muscle diseases with targeted access [487].

d) Transient receptor potential (TRP) cation channels

The TRP superfamily of cation channels, whose founder member is the Drosophila Trp channel, can be divided, in mammals, into six families; TRPC, TRPM, TRPV, TRPA, TRPP and TRPML based on amino acid homologies. TRP subunits contain six putative transmembrane domains and assemble as homo- or hetero-tetramers to form cation selective channels with varied permeation properties. The TRPC ('Canonical') and TRPM ('Melastatin') subfamilies consist of seven and eight different channels, respectively (i.e. TRPC1-TRPC7 and TRPM1-TRPM8). The TRPV ('Vanilloid') subfamily comprises six members (TRPV1-TRPV6), whereas the TRPA (Ankyrin) subfamily has only one mammalian member (TRPA1). Established, or potential, physiological functions of the individual members of the TRP families are discussed in detail in the recommended reviews and are only briefly mentioned here (**Figure 20**). The established, or potential, involvement of TRP channels in disease has been reviewed [488,489]. In the bladder, afferent nerves have been identified not

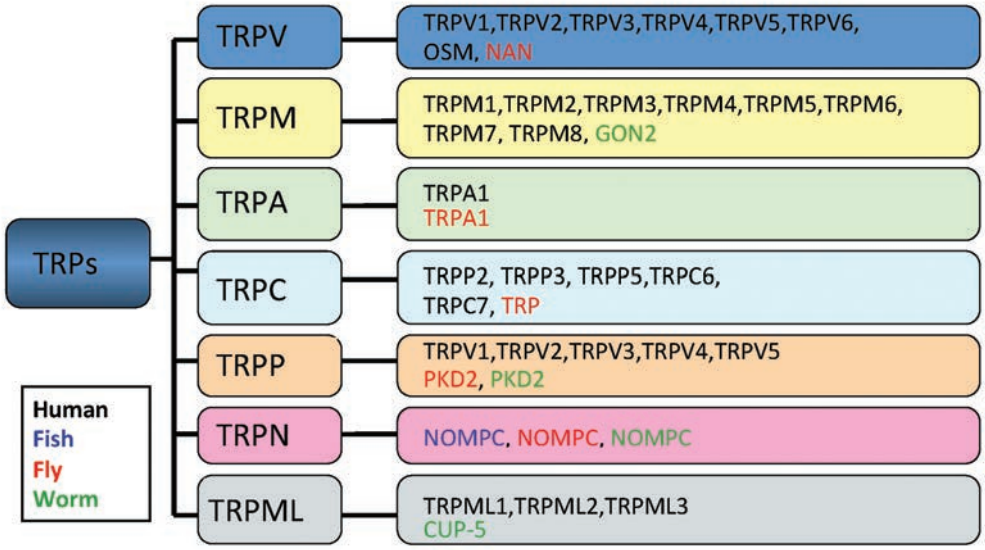


Figure 20. Phylogenetic relationships between members of the human transient receptor potential (TRP) channel superfamily. TRPC2 is a pseudogene in primates and TRPN channels have not been identified in mammals.

only in the detrusor, but also in the suburothelium, where they form a plexus immediately beneath the urothelium. The bladder epithelium plays important roles in mechanosensory transduction [490], bladder distention causes release of ATP which excites small-diameter sensory neurons via P2X3 receptors [491].

Mechanosensitive molecules in the epithelial cells are responsible for stretch-evoked ATP release [492] and include ENaC (above) and TRP(transient receptor potential) ion channels. TRP are subclassified into seven superfamilies, and many of them are mechano- and thermo-sensing [454]. Among several thermosensing TRP channels, TRPA1, TRPM8, TRPV1, and TRPV4 are candidates of molecular targets of the novel treatments for OAB (**Figure 21**) [493-495]. An understanding of the physiological function of these different channels will provide insight into how they control bladder function and if they may be exploited to control dysfunction in the lower urinary tract.

1. Distribution and function of the TRP channel family in urogenital organs

The potential roles of TRP channels have been explored in the bladder. Thus far, expression of TRPV1, TRPV2, TRPV4, TRPA1 and TRPM8 has been reported in different regions of urogenital tracts [493] (**Table 9**). TRPs are not only mechanosensitive but also thermosensitive (**Figure 21**).

Table 9. Overview of possible mechanosensing and thermosensing TRP channels: expression and function in the urogenital organs

Families	Activator	Blocker	Possible function	Location
$TRPV_1$	heat (43°C), low pH, anandamide vanilloids voltage, OEA, AA eicosanoids,	capsazepin, BCTC	detection of chemical irritants, intravesical pressure, diuresis, natriuresis	urothelium, nerve ending, DRG, prostate, seminiferous tubules, corpus cavernosum
$TRPV_2$	noxious heat (53°C), mechanical, growth factors		intravesical pressure	urothelium, nerve endings, myofibroblasts
$TRPV_4$	moderate heat (24°C), cell swelling, shear stress, anandamide, AA, 4α-PDD, 52,62EET		intravesical pressure urethrovesical reflex	urothelium, DRG, prostate, testicle
$TRPA_1$	noxious cold (17°C), mechanical, garlic cinnamaldehyde, isothiocyanate, marijuana, bradykinin		bladder contractions	urothelium, nerve ending, detrusor
$TRPM_8$	cold (8–28°C), menthol, icilin		reflex micturition, prostate secretion, sperm motility, homeostasis of testicular temperature	prostate, urothelium, nerve ending, detrusor

Key: OEA, oleoylethanolamide: AA, arachidonic acid; BCTC, N-(4- tertiary butylphenyl)-4-(3-chloropyridin-2-yl) tetrahydropyrazine-1(2H)-2-carboxamide; 4α-PDD, 4α-phorbol 12,13-didecanoate; 52,62EET, 52,62-epoxyeicosatrienoic acid; DRG, dorsal root ganglion

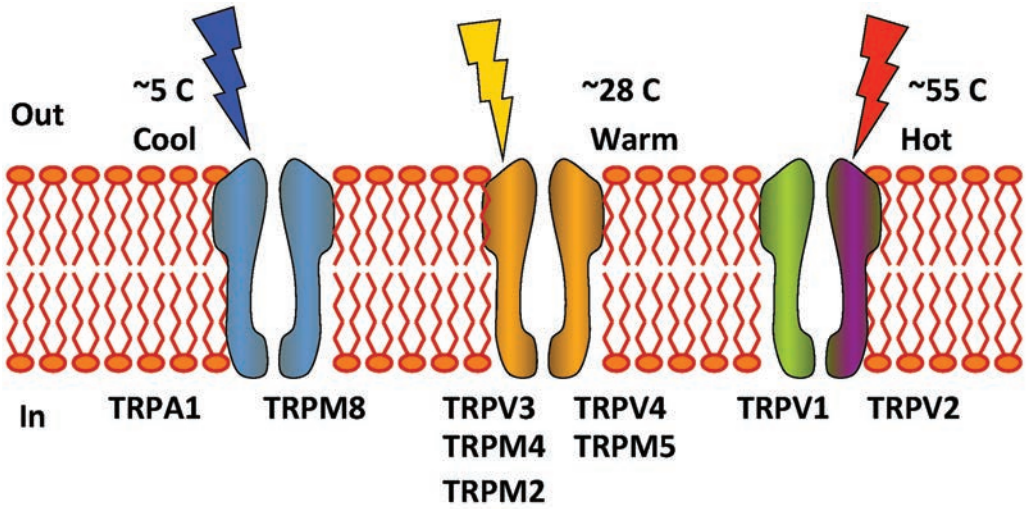


Figure 21. Thermo-sensing transient receptor potential (TRP) channels

Expression of other TRP channels, e.g. TRPM8 and TRPA1, has been found in sensory C-fibres in the bladder [493,496-499]. The diagnostic ice water test is utilized to determine whether disturbance of bladder function involves neurogenic components, one of which could be related to TRPM8 function, in patients with spinal cord lesion [500].

The neurochemical phenotypes of TRP melastatin-8 (TRPM8)-immunoreactive afferent neurons innervating the rat urinary bladder were examined by using a highly-sensitive tyramide signal amplification method, combined with wheat-germ agglutinin-horseradish peroxidase (WGA-HRP) retrograde tracing. It was suggested that the TRPM8-expressing bladder afferents should be classified as Aδ-fibres and C-fibres, whilst some of these afferents may be involved in nociceptive sensations [501]. TRPA1 in sensory afferents is activated by several known ligands (allyl isothiocyanate and cinnamaldehyde), thereby inducing bladder overactivity [502].

The TRPV ("vaniloid") family, on the basis of structure and function, comprises four groups of mammalian TRPVs: TRPV1/2, TRPV3, TRPV4 and TRPV5/6; reviews [502,503]. TRPV1-4 are non-selective cation channels that are thermosensitive, although TRPV1 and TRPV4 can also be activated by numerous other stimuli [502,504,505]. TRPV3, and to a lesser extend also TRPV2 and TRPV1, but not TRPV4, can be activated by 2-aminoethoxydiphenyl borate (2-APB), which, in contrast, blocks some TRPC and TRPM channels [506,507]. All channels of the TRPV family contain 3-5 NH2-terminal ankyrin repeats.

2. TRPV1

TRPV1 is an ion channel activated by capsaicin, heat, H+ and endogenous ligands such as anandamide. It is largely expressed in the urinary tract of mammals, especially in sensory fibres and urothelial cells. As in other systems, pain perception was the first role attributed to TRPV1 in the urinary tract. However, it is now increasingly clear that TRPV1 also regulates the frequency of bladder reflex contractions, either through direct excitation of sensory fibres, or through urothelial-sensory fibre cross-talk involving the release of neuromediators from urothelial cells. Capsaisin and resiniferatoxin (RTX) are agonists for TRPV1, and their desensitization of the receptor has been investigated for therapeutic purposes for painful bladder syndrome of neurogenic and non-neurogenic OAB. However, desensitization may become obsolete when non-toxic, potent TRPV1 antagonists become available [508]. TRPV1 channel blockers are used to ameliorate chronic pain, whereas TRPV1 agonists that induce desensitization are used to treat diseases in which channel over-expression occurs [509]. A splice variant of TRPV1, TRPV1b, in which 60 amino acids are deleted in the intracellular N-terminal region, forms capsaicin-insensitive and stretch-inhibited cation channels [510]. This channel is activated by hypertonic cell shrinkage and mediates osmosensitivity in the supraoptic nucleus [511]. Such TRPV1 variants might explain why some reports have suggested a mechanosensory function of TRPV1 in the bladder [511,512], although expression of these variants in the bladder or dorsal root ganglion has not been studied. In bladder strips excised from mice lacking TRPV1, hypoosmolality-evoked ATP and NO release are diminished [511].

Patients with neurogenic DO (NDO) have an increased immunoreactivity of PGP 9.5 and TRPV1 in the suburothelium and an increased TRPV1 reactivity in basal layers of the urothelium. In addition, patients with NDO clinically responding to intravesical instillations of RTX show a significant decrease of TRPV1 immunoreactivity in both the suburothelium and the basal urothelial layers compared to non-responders, suggesting a role for TRPV1 in the pathophysiology of NDO [385,513]. However, no data from clinical trials in this patient group are available thus far.

TRPV1 is expressed in the urothelium, in interstitial cells, and in sensory nerve terminals. TRPV1-deficient mice displayed a higher frequency of low-amplitude nonvoiding bladder contractions in comparison with wild-type (WT) [511]. It suggested that TRPV1 is required for detection of bladder stretch involving stretch-evoked release of ATP and nitric oxide, as release of both mediators was reduced in the bladders of TRPV1-deficient mice. In a clinical setting, capsaicin or RTX reduces bladder overactivity through desensitization of bladder afferents by acting on TRPV1 [508]. The specific effect of RTX on TRPV1 receptors suggests that urothelium and sub-urothelial C-fibres are important in the generation of urgency sensations [514].

Capsaicin (6 μM) evoked intracellular [Ca^{2+}] changes in human bladder urothelial cells from non-neurogenic OAB patients and controls. Augmented TRPV1 signalling in OAB cells allows the hypothesis that urothelial cells are involved in sensory signalling [515]. GRC-6211, an orally active TRPV1 antagonist, counteracted hyperactivity and noxious inputs of inflamed bladders induced by cystitis in rats. At high doses it also suppressed normal bladder activity by a TRPV1-dependent mechanism [516]. XEN-D0501, a novel TRPV1 antagonist, is being developed to treat overactive bladder and appears safe and well-tolerated at doses up to 5 mg twice daily for 14 days in healthy subjects [517].

Botulinum toxin A (BoNT/A) injection into the bladder wall is being increasingly used to treat persistent OAB. The first large, randomized, placebo-controlled trial evaluating OAB for the treatment of urgency urinary incontinence secondary to OAB has been performed. Although all doses of onabotulinumtoxinA were more effective than placebo, doses higher than 150 U appeared to place the patient at higher risk for urinary retention. In the phase-III trial, patients will be injected with placebo or 100 U initially and, if a higher

dose is requested with a second injection, a 150 U dose will be used; no doses higher than 150 U will be used [518]. The effects of BoNT/A on the expression of nerve growth factor (NGF) and TRPV1 in the urothelium and detrusor muscle of rats with partial bladder outlet obstruction-induced detrusor overactivity is being investigated. Detrusor wall injection of BoNT/A modulates the expression of NGF, which is greater in BOO, in both urothelium and detrusor muscle. However, TRPV1 expression particularly in the urothelium was not changed [519]. In 2011, Botox has received FDA approval for use in neurogenic DO in the treatment of urinary incontinence that results from neurological impairments such as spinal cord injury or multiple sclerosis.

3. TRPV4

TRPV4 was originally postulated to serve as a mechano- or osmosensor [520]. Recent studies using mice lacking TRPV4 revealed its involvement in sensing mechanical pressure, osmolality and warmth in vivo [521,522]. TRPV4 is abundantly expressed in rodent bladder epithelium [523]. TRPV4 knockout mice manifest an incontinence phenotype in spontaneous voiding pattern with a lower frequency of voiding contractions and increased bladder volume in continuous filling cystometry [524]. In cultured rat bladder urothelial cells, TRPV4 agonists promote Ca^{2+} influx and enhances ATP release [523]. The role of TRPV4 channels in a stretch sensing mechanism in mouse primary urothelial cell cultures using both wild-type (WT) and TRPV4-deficient mice was investigated. The results showed that TRPV4 senses distension of the urothelium, which is converted to an ATP signal in the micturition reflex pathway during urine storage (**Figure 22**) [525]. Thus, TRPV4 may contribute to physiological bladder function, especially mediating bladder distension signals to primary afferent nerves during urine storage. These findings indicate that modulation (inhibition) of TRPV4 channels could represent a novel therapy for OAB and storage dysfunction. Only the effects of TRPV4 channel agonists on bladder function have been described to date. Compounds endowed with antagonistic activity are being developed and it is anticipated that their effects on different models of bladder overactivity will be evaluated [526]. The development of cystitis-induced bladder dysfunction is strongly impaired in TRPV4(-/-) mice, and that HC-067047, a previously uncharacterized, potent, and selective TRPV4 antagonist increases functional bladder capacity and reduces micturition frequency in normal mice and rats with cystitis. HC-067047 did not affect bladder function in TRPV4(-/-) mice. These results also indicate that TRPV4 antagonists may provide a promising means of treating bladder dysfunction [527-529].

4. TRPA1

TRPA1 is the only mammalian member of the Ankyrin TRP subfamily and is a potential candidate for mechanosensor and/or nociceptor responding to chemicals: allyl isothiocyanate (the pungent compound in mustard oil); allicin (garlic); cinnamaldehyde (in cinnamon) [530,531] and thermal stimuli [524]. TRPA1 is probably activated by noxious cold (<17°C) [532]. TRPA1 is expressed in rodent and human bladders [526,533] and sensory C-fibres beneath the bladder mucosa. TRPA1 activation induces bladder contractions, mediated by sensory afferent stimulation and release of neuropeptides and prostanoids.

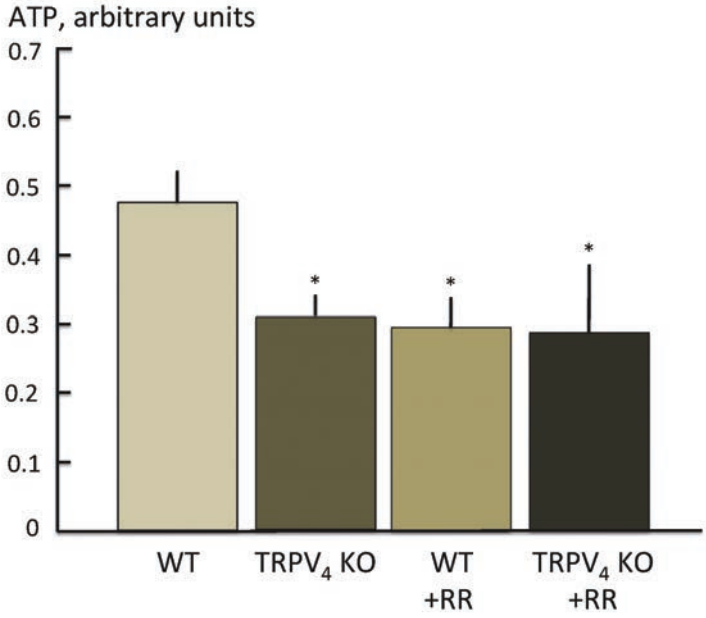


Figure 22. Measurement of stretch-evoked ATP released from primary cultured urothelial cells. WT, Wild type mice; TRPV4 KO, knock-out mice of TRPV4 receptor; RR: ruthenium red, a non-specific TRP channel blocker, *p<0.05 vs WT

The expression levels of TRPA1 mRNA in the bladder mucosa and muscular layers as well as prostate were in the ratio of 639:1:16. TRPA1 mRNA in the bladder mucosa of obstructed bladders was significantly upregulated to more than twice control. The expression of TRPM8 mRNA (below) in the prostate was much higher than that in the bladder mucosa (3024:1), but was not found in the bladder muscle layer. BPH or bladder obstruction did not significantly affect the expression of TRPM8. TRPA1 in the bladder epithelium might be involved in bladder sensory transduction and the induction process of OAB by bladder obstruction [496].

The relevance of TRPA1 in OAB induced by spinal cord injury (SCI) was evaluated using a rat SCI model, HC-030031 (a TRPA1 antagonist), and the TRPA1 antisense oligodeoxy- nucleotide (AS-ODN). TRPA1 activation and upregulation exerted an important effect in OAB following SCI [534]. TRPA1 distribution and the effects of hydrogen sulphide, as a TRPA1 activator, on micturition in conscious rats were examined. The expression of TRPA1 on C-fibre bladder afferents and urothelial cells, together with the finding that intravesical hydrogen sulphide initiates detrusor overactivity indicates that TRPA1 may have a role in sensory transduction in the rat urinary bladder. Hydrogen sulphide as a TRPA1 activator potentially is involved in inflammatory bladder disease [535].

5. TRPM8

TRPM8 is not only mechanosensitive, but also cold-sensitive. The bladder-cooling reflex is observed in guinea pigs if animals were pretreated with menthol, as a TRPM8 agonist. This reflex was sensitive to ganglion blockade or capsaicin-sensitive C-fibre deafferentation and might be mediated by C-fibre activation through TRPM8 [499]. TRPM8 in nerve fibres of overactive and painful bladders, and its relationship with clinical symptoms have been demonstrated. TRPM8 may play a role in the symptomatology and pathophysiology of these disorders, and may provide an additional target for future overactive and painful bladder pharmacotherapy [500].

A TRPM8 channel blocker, N-(3-aminopropyl)-2-(159)-N-(2-thienylmethyl)benzamide hydrochloride salt (AMTB), can act on the bladder afferent pathway to attenuate the bladder micturition and nociceptive reflex responses. Targeting TRPM8 channel may provide a new therapeutic opportunity for OAB and painful bladder syndrome [536]. Intravesical infusion of menthol facilitated the micturition reflex and capsaicin pretreatment had no effect on this response. Menthol inhibited carbachol-induced contraction of the detrusor smooth muscle. This suggests that intravesically infused menthol cannot relax detrusor muscle, and acts on capsaicin-resistant afferents (probably through TRPM8 on urothelium or sensory nerve endings) to facilitate the micturition reflex [537]. The TRPM8 -expressing bladder afferents in rat should be classified as Aδ-fibres and C-fibres, while some of these afferents may be involved in nociceptive sensations [538]. The function and expression pattern of TRPM8 in urinary bladder afferent neurons from control and bladder outlet obstruction rats has been investigated. The neuronal input through TRPM8-positive bladder afferent neurons are augmented after bladder outlet obstruction, however, the neurochemical phenotype of the up-regulated TRPM8-positive bladder afferent neurons is not changed [538]. There is no explanation for the mechanism of urinary urgency evoked by cold sensation. Cold and menthol stimuli to the skin generate bladder nerve responses conducted through dichotomizing axons, which significantly decreased in the presence of the TRPM8 blocker [N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide] (BCTC). Sensory neurons expressing TRPM8, with dichotomizing axons projecting to the skin and bladder, may be responsible for the urinary urgency evoked by cold sensation [539].

Overall, many lines of evidence suggest that TRP ion channels are candidates for mechano-sensors in the urinary bladder as summarized in **Figure 23**.

VII. BIOMARKERS FOR OAB AND DO

1. INTRODUCTION

A biomarker is “a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.” It may be objectively measured and evaluated as an indication of normal biological and pathogenic processes, or pharmacological responses to a particular treatment or condition [540]. Biomarkers are widely used as analytical tools to assess biological parameters for a rapid and comprehensive therapeutic analysis. In addition, biomarker measures can further the development and evaluation of new therapies [541]. An ideal biomarker should be quick, consistent, economical, and quantifiable in an accessible biological fluid or clinical sample (e.g., plasma, urine, or prostatic fluid) that is readily interpretable by a clinician [542,543]. In the search for reliable, non-invasive biomarkers, interest has focused on urinary factors, imaging and genetic markers.

Along with other cytokines detectable in urine, prostaglandin E2 and nerve growth factor are indicators of low-grade inflammation. Although they correlate with OAB symptom severity, they have not been shown to have independent prognostic benefit.

Imaging biomarkers have been investigated since the earliest days of video urodynamics. Despite extensive research on the ultrasonographic estimation of bladder wall thickness, further standardization of the technique is required before conclusions can be reached regarding diagnostic accuracy.

Genetic factors contribute about half of the total risk for urgency incontinence. Functional polymor-

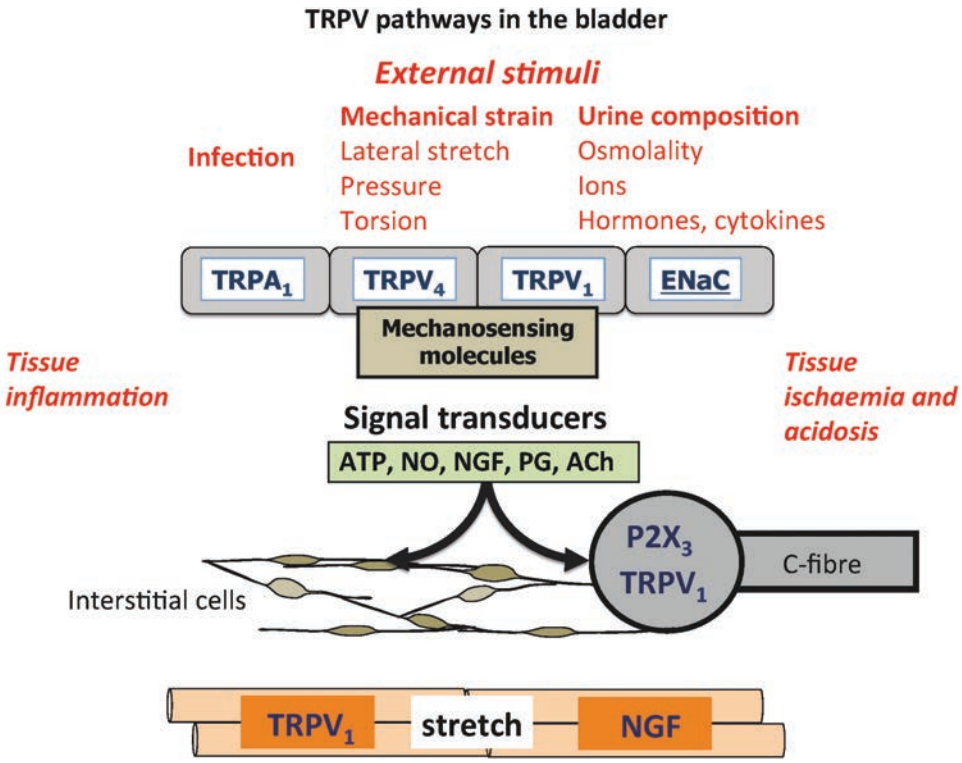


Figure 23. Interactions between receptors, chemical mediators released from bladder urothelial cells and afferent nerve endings in the bladder. Different receptors (bradykinin, trkA, trkB, adrenergic, cholinergic, and TRP) are expressed on urothelial cells. ATP, NO, acetylcholine (ACh), nerve growth factor (NGF), and prostaglandins (PG) can be released from the urothelium via activation of urothelially expressed ligand receptors and/or mechanoceptive receptors such as the epithelial Na+ channel.

phisms of the cytochrome P450 IID6 gene significantly alter the metabolism of some commonly used anticholinergic drugs, but no genetic loci that influence the risk of OAB have been definitively identified. The first genome-wide association studies for OAB are in progress, and should identify new susceptibility genes. Although current putative biomarkers correlate with OAB severity, much future work is required to assess their prognostic value, and establish their role in clinical practice [544].

Urodynamic assessment of DO may be associated with a diagnosis of overactive bladder (OAB), but there is not always a one-to-one correspondence and OAB is detected by a history of exclusion of obvious pathological causes. In addition, by the definition used above urodynamic measurements would not be considered as a biomarker. However, a short section on urodynamics will be included to place this method in context.

2. URODYNAMIC FINDINGS

A study of urodynamic results in OAB women with and without urodynamic DO found that patients with DO were more likely to have abnormal sensations, lower volume for strong desire and urgency and more urinary urge incontinence (UUI) episodes. In patients with persistent urinary frequency, urgency and/or UUI, involuntary detrusor contractions were observed in 100% of neurologically-impaired patients, compared with 76% of control patients [540]. Urgency associated with increased sensation is common and may presage DO [546]. Interestingly, the efficacy of a combination of anti-cholinergics and bladder training for OAB symptoms was not different in groups with or without DO [547]. Therefore, a less invasive method to diagnose OAB and assess therapeutic outcomes, especially for female patients, is still required.

The gender difference in the measrement of urodynamic DO of OAB patients could result from anatomical differences, causing increased urge sensation in women during their daily life and mimicking OAB symptoms [548]. Pelvic organ prolapse (POP) frequently presents with urinary incontinence, either urge (UUI), stress (SUI), or mixed (MUI).

OAB symptoms in men could result from bladder outflow obstruction (BOO) or idiopathic DO (IDO), as LUTS suggestive of DO are commonly associated with these conditions [549]. The incidence of DO after TURP for BPH, and the influence of lower urinary tract perfusion on postoperative outcomes were prospectively evaluated in 50 men. Before and

one year after TURP, IPSS and QoL scores were recorded and perfusion of the lower urinary tract was measured with transrectal colour Doppler ultrasonography. Persistent DO in men after TURP was associated with increased vascular resistance, with subsequent reduced perfusion and hypoxia [550].

3. URINARY BIOMARKERS

Recent studies in patients with lower urinary tract disorders, particularly OAB, indicate that changes to the concentration of several urinary molecules, such as neurotrophins, prostaglandins, cytokines and several smaller molecules, are altered. Therefore, such changes could be used as potential biomarkers of OAB.

a) Cytokines and chemokines

Chemokines constitute a large family of secretory proteins that are expressed by leucocytes as well as bladder tissue. The detection of bladder inflammation associated with OAB through altered urine levels of cytokines, chemokines, and growth factors has been attempted. Elevated urinary levels of markers involved in inflammation and tissue repair are raised in OAB patients. This suggests an association between inflammation and OAB, and could also provide suitable diagnostic tests for OAB [551].

Alternatively OAB could produce inflammatory cytokines due to afferent neural plasticity or urothelial dysfunction. An analysis of urinary proteins using an antibody-based array chip for 120 human cytokines found that the majority were expressed at similar levels in control and OAB patients. However, some cytokines were upregulated, such as monocyte chemo-attractant protein, MCP1; TARC; PARC and Fas/TNFRSF6. Others were also increased in urinary tract infections and included: MCP2; MCP3; tumour necrosis factor-β, GCSF and eotaxin3. In addition, some were down-regulated in OAB, including IL5, IL6, IL7, and GM-CSF [552]. Pre-clinical studies have shown that increased urine levels of MCP1 and CXCL1 are evidence of bladder inflammation [553].

b) Prostaglandins in OAB

In the urinary bladder, prostaglandin E2 (PGE2) is a cytoprotective eicosanoid that inhibits apoptosis of epithelial cells. Intravesical instillation of PGE2 induces detrusor contraction while topical application of PGE2 to the urethra causes relaxation [554].

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in animal models of disease, by suppressing prostaglandin synthesis. Aspirin, in contrast to ketoprofen or indomethacin, does not cause significant gastrointestinal lesions and has been proposed as an NSAID treatment of choice for overactive bladder [555]. The association between OAB symptoms in patients with suprapontine brain diseases and the urinary levels of prostaglandins (PGE2 and PGF2α), nerve growth factor (NGF) and substance P were measured. PGE2 levels were raised in this cohort, compared to control, and were positively associated with the OAB symptom score [556]. In young boys with lower urinary tract obstruction due to urethral stricture higher levels of PGE2 were also associated with the incidence of OAB. [557].

Several studies have demonstrated the in vivo efficacy of PGE2 receptor 1 (EP1) antagonists in preclinical models of inflammatory pain and overactive bladder [558,559]. Others studies have also showed the possible efficacy of EP4 receptor antagonists for treatment of patients with OAB [444,445].

c) Urine ATP and nitric oxide (NO)

ATP and NO are released from the bladder urothelium during several physical and chemical stresses, and the amount released is increased in tissue from NDO and IDO patients and analogous animal models (section 3.1). Thus, a quantifiable relationship between their levels and the presence of DO may be available.

The relationship between ATP and NO release in 1) early diabetic bladders - an overactive bladder model; and 2) in “diuretic” bladders - an underactive bladder model were measured. ATP release positively correlated, whilst NO release negatively correlated with bladder contraction frequency. The relation between the improvement of LUTS and urinary ATP level has also been measured. Improvement of LUTS with α1 receptor antagonists or anti-muscarinic agent was associated with a decrease of the urinary ATP/creatinine ratio in patients with BPH or OAB. The urinary ATP/NO ratio or urinary ATP concentration itself may be a clinically relevant biomarker to characterize the extent of bladder dysfunction [90,560].

d) Urinary nerve growth factor (NGF) in OAB

NGF is a small, secreted protein that induces the differentiation and survival of particular target neurones and is produced by urothelium and smooth muscle [561]. NGF levels in the urinary bladder can be affected by its pathology and this change can be measured in urine. Urinary levels of NGF, and PGE2, were significantly increased in male patients with OAB compared with control. Urodynamic measurements on patients in this study showed that more than half had DO and BOO. Also of interest, was that several patients demonstrated bladder underactivity where PGE2 were lowered compared to control [562]. Urinary NGF levels in patients with BOO, with or without OAB have been compared. NGF/creatinine ratios were low in the control group and in BOO patients without OAB. However, ratios were higher in the BOO/OAB and BOO/DO groups. Moreover, urinary NGF/Cr levels returned to normal after successful relief of OAB symptoms [563]. Together, data such as these provide the possibility that measurement of urinary NGF and prostaglandin levels may be useful in detecting OAB/DO in male patients.

The effect of botulinum toxin A (BoNT/A) treatment on NGF levels in DO patients has also been evaluated. Participants included patients with idiopathic and neurogenic DO (IDO, NDO) who were untreated, well-treated, and failed-treated with antimuscarinic agents. BoNT/A treatment significantly reduced urinary the NGF/Cr ratio in responders within the IDO and NDO groups. In patients who failed to respond to BoNT/A treatment NGF levels remained significantly higher after three months [564].

Urinary NGF levels in women with stress urinary incontinence (SUI) and OAB have also been measured and indicated that it could be a potential biomarker of DO in women with mixed UI [565]. The effect of bladder volume on urinary NGF production in normal controls and patients with OAB has been measured. Urinary NGF increases physiologically in normal subjects at urge to void, but is pathologically elevated in OAB patients at small bladder volumes and does not significantly increase at urgency sensation [566]. The effect of antimuscarinics (tolterodine, 4 mg once daily) on urinary NGF levels in patients with OAB has also been measured. Changes to urinary NGF levels correlated with alteration of the urgency severity score (USS) after antimuscarinic treatment and discontinued medication [567].

A comparison between urinary NGF and other biomarkers has been evaluated. Urinary NGF and PGE2 levels among patients with DO, increased bladder sensation (IBS), interstitial cystitis/bladder pain syndrome (IC/BPS) and controls have been compared. Urinary NGF/Cr levels were elevated in women with IC/BPS or DO, but not in those with IBS. The differential diagnosis of women with IC/BPS from those with frequency-urgency syndrome may possibly be based on the urinary NGF/Cr levels but not the urinary PGE2/Cr level [568]. Differences in urinary NGF and detrusor wall thickness (DWT) measured by transabdominal ultrasound between OAB and control patients were also examined. Urinary NGF level in natural-filling urine samples was a better biomarker for assessment of OAB-wet compared to DWT. Patients with OAB-dry or hypersensitive bladder did not have an elevated urinary NGF level [569,570].

However, the relationship between urinary NGF levels and lower urinary tract pathology is not always evident. About 30% of patients with OAB symptoms do not have elevated urinary NGF levels [571]. Stress-related events may also result in increased plasma NGF levels that can involve the neuroendocrine system. Patients with OAB may have symptoms that wax-and-wane without definite treatment and this may contribute to fluctuations of NGF in the urine. Thus before other confounding factors that cause urinary NGF levels to alter, its use as a biomarker must be treated with caution.

4. SERUM BIOMARKERS

a) C-reactive protein (CRP)

Chronic inflammation has been implicated in the development of OAB and IC/BPS. An elevation of CRP has been associated with chronic inflammation and LUTS. In one study serum CRP levels were significantly higher in subjects with OAB than in controls. No significant difference in CRP level was noted between patients with OAB and IC/BPS. There was no significant correlation between serum CRP and urinary NGF levels in the controls or patients with OAB or IC/BPS, except in the OAB patients with CRP >3 mg/l. These data may confirm the association between chronic inflammation of the urinary bladder in patients with OAB or IC/BPS [572].

5. BLADDER WALL IMAGING BIOMARKERS

a) Ultrasonography

Because patients with OAB may have frequent detrusor contractions during the storage phase, sustained isometric detrusor contractions could result in increased muscle bulk and hence, increased detrusor wall thickness (DWT) or bladder wall thickness (BWT). It has therefore been hypothesized that DWT increases in patients with DO [573]. The thickened bladder wall might decrease in response to antimuscarinic treatment, and measurement of DWT might also be a potentially useful biomarker for evaluation of disease progression and effectiveness of treatment for OAB. Consequently, ultrasound measurement of BWT has been proposed as a diagnostic variable in patients with BOO and other voiding dysfunctions. BWT measurement was assessed as a non-invasive test in control and test patients with BOO, DO or increased bladder sensation [574]. However, values were similar in all test groups, including those in the control and bladder dysfunction groups, and it was therefore concluded that it was unreliable predictor of BOO or DO.

In more definitive groups some predictive value has been suggested. DWT is increased in men with BOO and children with bladder-induced enuresis [575-577]. In men with BOO measurement of DWT was proposed as a useful diagnostic parameter, although there was not a consensus that it could replace conventional urodynamics as a predictor of DO [577-579]. However, further confirmation of the extent of the difference in DWT between patient groups is needed.

The diagnostic value of DWT in predicting DO in women has also been investigated. There was a statistically significant association between DWT and DO, however further analysis demonstrated that DWT as measured by translabial ultrasound was of limited use as a diagnostic test for DO [580]. Women with OAB might also have a greater DWT, suggestive of detrusor DO. DWT was measured by transabdominal and transvaginal ultrasonography

in controls and women with OAB-dry and OAB-wet. A greater DWT at bladder capacity measured by transabdominal ultrasound was observed for women with OAB and DO [581,582].

The clinical usefulness of measuring DWT as a non-invasive test in women with OAB was evaluated in sub-groups with no OAB symptoms, OAB-dry and OAB-wet. Women with OAB-wet had significantly greater DWTs than controls at maximal bladder volume. The maximal bladder capacity was significantly greater in controls than in those with OAB. DWT measured by transabdominal ultrasound in women with OAB and without OAB was not different and did not differ with urodynamic status and was not recommended as a useful diagnostic test for DO in women with OAB [583].

The ultrasound measurement of BWT in women was compared with different urodynamic diagnoses and data were compared with different urodynamic findings of DO. Women with DO had a significantly greater BWT and a cut-off of 6.5 mm had a positive predictive value of 100% for all DO. The ultrasound BWT showed a highly significant association with DO. However, it was considered that the performance of this test could not replace urodynamic testing [584].

However, the relationship between ultrasound estimation of bladder weight (UEBW) and variation of age, height, body-mass index (BMI) and body surface area (BSA) of individuals in the general population might confound the use of the method to identify bladder pathologies. A significant correlation between UEBW and both height and BSA for healthy volunteers (30 men and 40 women) has been measured [585]. Therefore, caution should be taken when extrapolating ultrasound data to patients with pathological function until the dependence of normal demographic factors on ultrasound variables has been fully-accounted for.

Methodological factors can also impact on the interpretation of data obtained from ultarsound measuemets of bladder structure. A low echogenic zone between two layers of bladder wall has been used in the assessment of DWT, with a reported very low inter-observer and intra-observer variability in its measurement [586]. Discrepant data in measurement of DWT in patients with DO might include inconsistent bladder filling conditions or differences in resolution of the ultrasound probe. Total measured bladder volume is greater than that determined by transabdominal ultrasound or infused volume, and DWT decreased rapidly during the first 250 ml volume of filling, followed by a slower decrease during the second 250 ml [581,583] and represents the relative geometrical change of bladder shape during progressive filling. In addition, DWT measurements obtained using a low frequency probe (2-5 MHz) were greater than those obtained using a high frequency probe (7.5-10 MHz) [574,577-579,581,583,586].

Transvaginal ultrasound assessment of mean BWT has been postulated as a sensitive screening tool to detect DO in women with equivocal laboratory urodynamics. Measurement of BWT using transvaginal ultrasound has been claimed to discriminate between women with confirmed DO and those with urodynamic stress incontinence. Bladder wall thickness showed a positive correlation with pdet/Qmax and to urodynamic diagnoses of stress incontinence, DO and obstruction [587].

How then should bladder wall thickness be measured? A comparison of vaginal, perineal and abdominal ultrasound has been made to determine if abdominal, perineal and vaginal ultrasound measurements of bladder wall thickness are comparable. Vaginal ultrasound of BWT showed the smallest values, abdominal ultrasound the largest. At the trigone, differences were significant between vaginal and perineal ultrasound but not between abdominal and the perineal approach [588].

Ultrasonographic measurement for diagnosis and characterisation of LUTS is relatively new, but shows a promising future. Measurements of BWT, DWT and UEBW are potentially noninvasive clinical tools for assessing the lower urinary tract. Quantification of bladder wall hypertrophy seems to be useful for the assessment of diseases, prediction of treatment outcomes, and longitudinal studies investigating disease development and progression. However, lack of data in healthy asymptomatic subjects currently may account for some of the disparity between studies and hampers the use of ultrasound in routine practice. If methodological discrepancies can be resolved, BWT, DWT and UEBW should be valuable in assessing LUTS.

b) Near-infrared spectroscopy (NIRS) and DO

NIRS is an optical technology and detects the haemodynamic changes in tissues via non-invasive measurement of changes to the concentration of tissue chromophores such as oxyhemoglobin and deoxyhemoglobin. Involuntary bladder contractions may cause changes detectable by NIRS. A prospective cohort study was carried out on 41 patients with OAB symptoms to address the accuracy and reproducibility of NIRS and to detect the haemodynamic effects of DO. Those patients underwent one or more filling cystometries with simultaneous NIRS of the bladder as a successful proof-of-principle [589].

6. CONCLUSION

OAB is not a single clinical entity. Hence, it is difficult to develop a satisfactory biomarker for all kinds of OAB, but recent research has identified several potential biomarkers. In the near future, with further trials of urine, serum and bladder tissue biomarkers from patients with OAB, potential molecules which give rise to the urgency sensation might be isolated and serve as ideal biomarkers for OAB assessment.

VIII. THE LOWER GASTROINTESTINAL TRACT (ANUS AND RECTUM) AS RELEVANT TO FAECAL INCONTINENCE

1. INTRODUCTION

The rectum and anus serve as a reservoir for faecal contents and regulator of continence respectively. A number of mechanisms are involved in the maintenance of faecal continence and include a resting internal anal sphincter (IAS) tone, which is the main contributor to the development of a resting anal intraluminal pressure and the external anal sphincter that enhances sphincter tone during voluntary squeeze. In addition, the endovascular cushions and the anal mucosal folds aid continence by maintaining an effective seal. A number of recto-anal reflexes involving all three arms of the autonomic nervous system (parasympathetic, sympathetic, enteric) act to regulate faecal storage and provide efficient evacuation of contents during defecation.

Faecal incontinence is a common condition defined as the uncontrolled passing of material or gas. The condition affects more than 10% of the population and that number may approach 20% in the elderly [590]. The most common cause of faecal incontinence is obstetric trauma to the internal or external sphincters, or the pudendal nerves. Often the injuries to younger women do not result in faecal incontinence until middle age when increasing general muscle weakness related to ageing also impacts, thus reflecting the common multi-factoral nature of this condition [591]. Other causes include damage to the endovascular cushions or mucosa resulting in a poor anal seal, pudendal neuropathy which interfere with sensory mechanisms leading to stool accumulation and then faecal overflow and systemic sclerosis where the main cause is usually impaired function of the internal anal sphincter [592].

2. BASIC PHYSIOLOGY OF THE RECTUM AND ANUS

For the maintenance of faecal continence and timely defecation, coordination of rectal and anal activities are essential; there are two main recto-anal reflex pathways regulating activity in these regions. The first involves an excitatory pathway that is triggered by low volume rectal distension and elicits a desire to defecate and produces contraction of the puborectalis muscle and the IAS [593]. The second reflex is the recto-anal inhibitory reflex (RAIR), which is triggered by higher volume rectal distension and produces the urge to defecate and a transient relaxation of the IAS [593-596]. Thus the IAS receives both excitatory and inhibitory pathways from the rectum and both are important for normal continence.

Defecation requires the reflex activation of peristalsis in the rectum and the simultaneous relaxation of the internal anal sphincter (IAS). Excitatory motor responses in the rectum involve acetylcholine and substance P, while noradrenaline and ATP are the predominant transmitters operating in the IAS. The inhibitory motor reflexes are mediated predominantly via nitric oxide (NO) and vasoactive intestinal peptide (VIP) in both regions.

a) The internal anal sphincter (IAS)

The IAS is a ring of involuntary muscle formed by the thickening of the circular smooth muscle of the intestine (**Figure 24**). The sphincter develops spontaneous tone and contributes 50-85% of normal resting anal pressure [597,598]. This tone is predominantly

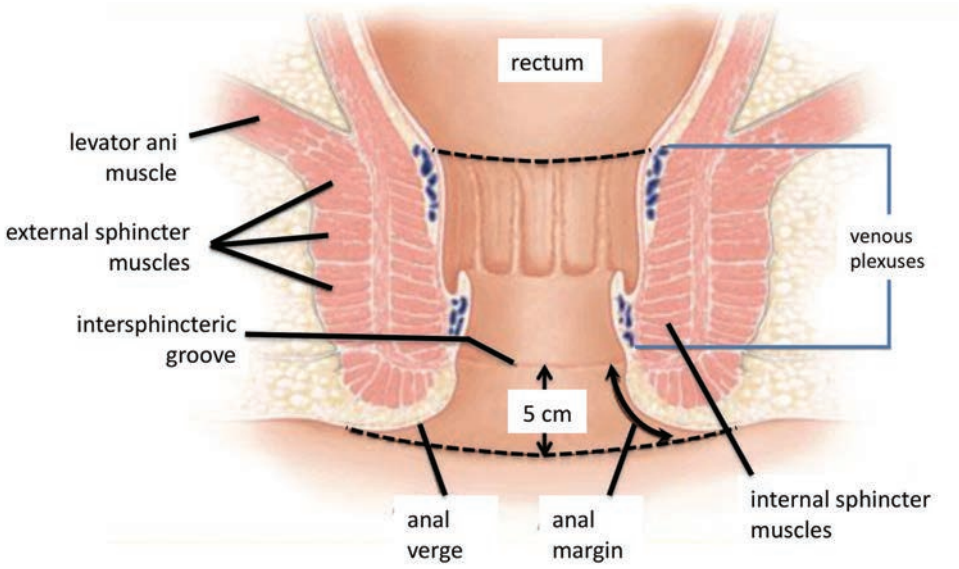


Figure 24. Structure of the human anus

myogenic in nature, but neuronal (mainly sympathetic) and hormonal (eg angiotensin II) influences may also contribute to the maintenance of sphincter tone and the relatively high resting luminal anal pressure required to maintain continence. The resting anal pressure in humans decreases with age and is linked to the increased prevalence of faecal incontinence (FI) with age [599]. Also, it has been reported that sphincter relaxation is enhanced in patients with incontinence [600], again highlighting the important role played by this tissue.

3. INNERVATION OF THE RECTUM AND ANUS

Studies of muscle contraction suggest that the sympathetic innervation mediates contraction in the internal anal sphincter but not rectum, while nitrergic nerves mediate relaxation responses in both tissues (see [601]). Thus in the rat, the myenteric ganglia of the rectum and anus appear to receive cholinergic and nitrergic innervations and this would agree with studies showing that atropine inhibits both ascending and descending contractile pathways, while NO synthase inhibition increases contractile responses in both pathways [602].

a) Parasympathetic innervation

The parasympathetic nervous system innervates the IAS and will be involved in defecation reflexes, but the parasympathetic nerves do not significantly contribute to the resting anal sphincter tone in vivo [603]. Early studies of IAS function in vitro reported that the IAS contracted in response to muscarinic receptor stimulation [604]. However this could not be confirmed in later studies where acetylcholine appeared to act on muscarinic receptors to induce a relaxation of the IAS [605]. These confusing results were later explained when it was shown that the relaxation responses were mediated indirectly via the release of nitric oxide [606]. The muscarinic receptor subtypes involved in these direct contractile and indirect inhibitory responses are unknown, but would represent novel drug targets for influencing IAS tone.

In the rectum the predominant innervation is parasympathetic and atropine depresses ascending and descending excitatory reflex pathways in this region [602]. The innervation however runs to the myenteric ganglion, and the influence on smooth muscle activity is indirect and mediated via interstitial cells with which the nerves are closely associated.

b) Sympathetic innervation

The sympathetic system also has a dual role in the IAS and has the ability to cause both contraction and relaxation. Contraction of the IAS in response to noradrenaline is attributed to the stimulation of α adrenoceptors and relaxation is attributed to stimulation of β adrenoceptors. It has been shown in several species that there is a high density of α1 and α2-adrenoceptors in the IAS and synthetic mixed agonists such as clonidine induce IAS contraction via both receptors [607]. The α2-adrenocptors of this tissue have been classified as the α2D-adrenoceptor subtype [607]. However the overwhelming response to nerve stimulation (see **Figure 25**) and the predominant mechanism maintaining tone of the IAS is noradrenaline acting on α1-adrenoceptors. It

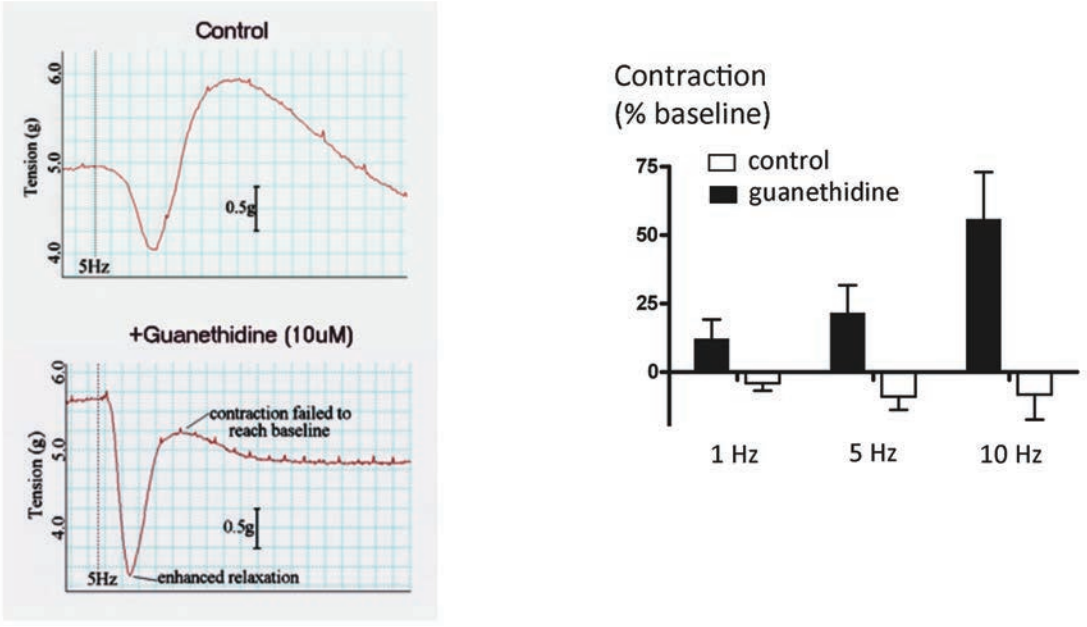


Figure 25. Effects of guanethidine on IAS responses to electrical field stimulation. In the presence of guanethidine (10μM) contractile responses to EFS (5 Hz stimulation) were abolished, while relaxation responses were enhanced. (from [619]).

has been reported that the IAS also possesses β3-adrenoceptors that cause relaxation. Non-selective β-adrenoceptor agonists such as isoprenaline induce relaxation by a direct action on the smooth muscle, but β3-adrenoceptor selective agonists exert a direct relaxation action on the smooth muscle and also activate smooth muscle eNOS to induce nitric oxide release; both actions being antagonised by selective β-antagonists [608,609]. These sphincter inhibitory responses are totally masked by the α1-adrenoceptor contractile responses and the role of β-adrenoceptors in normal continence mechanisms is unclear.

Beta3-adrenoceptors are also generally expressed in the human enteric nervous system where they may release somatostatin and reduce neuronal activity [610,611]. Whether these sympathetic influences are involved in ano-rectal function is currently unknown.

c) Non-adrenergic, non-cholinergic (NANC) innervation

Vasoactive intestinal peptide (VIP) and the gaseous transmitters nitric oxide (NO) and carbon monoxide (CO) have been implicated in the relaxation of the IAS during defecation. The presence of VIP and the enzymes responsible for the synthesis of NO (NO synthase) and CO (haem oxygenase, HO-1 and HO-2) have been demonstrated in the myenteric plexus of the mouse IAS (Rattan et al., 2005), while Western blot studies have shown the presence of nNOS, HO-1 and HO-2 in the smooth muscle of the IAS [612]. Functional studies using electrical field stimulation suggest that NO is the major transmitter mediating 80% of relaxation response, while VIP mediates the remainder. Evidence linking CO to relaxant responses of the IAS is lacking. CO and CO-releasing agents such as CORM-2 induce relaxation of the IAS [612,613], but inhibitors of CO (e.g. tin protoporphyrin IX) do not affect responses to field stimulation. Furthermore, in HO-2 knockout mice IAS responses to field stimulation are normal. Thus NO, VIP and CO can all cause relaxation of the IAS, but only NO and VIP appear to be involved in mediating nerve induced effects. This conclusion is supported by studies with nNOS deficient mice where relaxation of the IAS to rectal distension was significantly diminished [614].

d) Sensory innervation

The sensory innervations to the rectum and anus are very different. The anal canal is densely supplied with sensory nerves that respond to many modalities including touch, pain, temperature and friction. The sensory mechanisms in the rectum in contrast are limited and mainly respond to distension [615], low levels of distension stimulating the desire to defaecate, greater distension stimulating the urge to defecate and activate the RAIR [593,596]. At least in the mouse, this sensitivity to a wide range of distension appears to be mediated via individual sensory fibres and nearly all of the rectal fibres sensitive to stretch respond from low levels of stretch right up to noxious distension [616]. Furthermore, the sensitivity of rectal mechanoreceptors increases during chemically-induced inflammation and is also augmented by inflammatory mediators such as bradykinin [617].

4. SMOOTH MUSCLE AND INTERSTITIAL CELLS

a) Smooth muscle

Rectal and anal smooth muscle differ in their functions: rectal muscle producing transient phasic contractions resulting in peristalsis; anal muscle developing spontaneous myogenic tone to maintain continence. To enable different functions, the muscles have different morphology, innervation and cell biology. In the rectum the circular muscle layer is composed of large muscle bundles spanning the whole muscle layer, whereas the muscle bundles of the IAS are subdivided into many smaller bundles separated by connective tissue layers [601]. The innervations (see above) and ICC distribution and function (see below) also differ between the rectum and IAS. Unlike the rectum, the smooth muscle of the IAS receives direct sympathetic and nitrergic innervations and the tissue possess receptors for a range of transmitters and hormones including noradrenaline, acetylcholine, VIP, 5-HT, ATP, angiotensin II [618].

Contractile responses of the IAS are dominated by the sympathetic rather than the parasympathetic system and IAS smooth muscle contraction is mediated predominantly via α1-arenoceptors. Three subtypes of α1-adrenoceptor exist (α1A, α1B, α1D) and an isoform of the α1A-adrenoceptor (the α1A/L) with a low affinity for prazosin has been identified in functional experiments [386]. The receptors of the IAS have been pharmacologically characterised as belonging to the α1A/L subtype [619]. Thus selective agonists at this receptor are a potential treatment for faecal incontinence and a few small-scale clinical trials with topical phenylephrine have been undertaken. These studies reported increases in anal pressure with 10% phenylephrine gel [620,621] and greater improvements with 40% gel [622]. Patients also reported subjective benefit but further clinical studies with α1-adrenoceptor agonist are required (for review see [623]).

As previously discussed, β-adrenoceptors are also located on IAS smooth muscle where they mediate relaxation. Using Western blotting, all three β-adrenoceptor subtypes have been shown to be present at the protein level (β2≥ β1≥ β3) in the human IAS [609]. In some species (eg. rat) the β3-adrenoceptors predominate, but in human tissues β3-agonists induce maximum responses only one third the magnitude of those to non-specific β-adrenoceptor stimulation. Activation of the recep-

tors elevates intracellular cAMP levels without affects cGMP levels, and inhibits intracellular calcium signalling in response to histamine. However, these effects have been found to have no influence on IAS basal tone [609] demonstrating the receptors inhibit cellular responses to agonist without affecting the essential basal tone that protects against incontinence. In some species the relaxation response to β-adrenoceptor stimulation may be partly mediated indirectly via the release of NO, but in the human IAS NO synthase inhibitors fail to affect responses to BRL37344 a β3-selective agonist [609].

Two intracellular mechanisms are involved in the development of smooth muscle contraction/tone. The first is direct contractile mechanisms whereby receptor-induced increases in intracellular calcium activates calmodulin resulting in the activation of myosin light chain (MLC) kinase, phophorylation of MLC and hence contraction. The stimulation of G-protein linked receptors eg muscarinic receptors in tissues such as the rectum increase intracellular calcium and induce contraction via this mechanism. At the same time, a second mechanism known as calcium sensitisation may also occur whereby dephosphorylation of MLC by MLC-phosphatase is inhibited via a pathway known as the Rho/ROK pathway. Rho A is a small GTP binding protein which can interact with a kinase known as ROK II (Rho activated, coiled coil containing protein kinase 2). Rho A when activated and bound to GTP activates ROK II, which in turn phosphorylates and thereby inhibits MLC-phosphatase resulting in less relaxation and a sensitisation to calcium (see section 4.3 and [624,625]). In phasic muscle such as the rectum, ROK II activity is low and tissues are completely relaxed until activated following receptor stimulation. However in tissues with myogenic tone (eg. IAS), the Rho/ROK pathway is active even in unstimulated pathways and can result in the development of spontaneous basal contraction. Thus RhoA/ROK levels are greater in IAS smooth muscle than rectal smooth muscle [626,627]. Protein kinase C (PKC) may also inhibit MLCK-phosphatase and cause calcium sensitisation. The relationship between RhoA/ROK and PKC is incompletely understood, but in human IAS smooth muscle, phorbol esters which activate RhoA/ROK and PKC, induce contractions of human IAS cells via the Rho/ROK pathway rather than the PKC pathway [628]. Since this pathway controls IAS myogenic tone, drugs that modulate the RhoA/ROK pathway may offer new opportunities for drug development in the treatment of faecal incontinence.

b) Interstitial cells

Interstitial cells of Cajal (ICC) are specialised cells of mesenchymal origin that are found distributed throughout the gastrointestinal tract including the rectum and IAS, where they are involved in the regulation of contractile activity. The cells express a tyrosine kinase (c-Kit) that is not expressed in muscle or nerves, and antibodies against this protein can be used to examine ICC distribution. Using these immunohistological techniques ICC have been identified as dense networks within the IAS in all species so far examined including human [629]. The c-Kit receptor is essential for the development of the ICC phenotype and mice lacking c-Kit (W/Wv mice) or its ligand, stem cell factor (Sl/Sl[d] mice) have drastically reduced numbers of ICC (see [630]).

Several types of ICC exist with different morphology (spindle vs stellar) and function (neurotransmission vs pacemaker). One population which has an intramuscular distribution running along muscle fibres has a spindle appearance and generate slow electrical waves which are thought to be involved in neurotransmission. These cells transduce excitatory signals from the efferent parasympathetic nerves, with which they make synaptic connections, to smooth muscle fibres with which they make close contact via gap junctions [631]. The other population of ICC are located in the myenteric plexus and submucosal plexus. These have a stellate appearance, and are thought to act as pacemakers of contractile activity. In these cells spontaneous phasic slow wave activity passes between ICC and muscle fibres via gap junction and these can summate and initiate phasic contractile activity [632,633].

Contractile functions of the rectum and anus differ, the rectum demonstrating phasic contractile activity and the IAS spontaneous tonic muscular tone. These differences in function are reflected in the characteristics of their respective ICC. Also the density of ICC is higher in the rectum than the IAS [629]. Rectal ICC more closely resemble the spindle-shaped intramuscular ICC found throughout the rest of the gastrointestinal tract [601]. These ICC are involved in neurotransmission, with vagal and nitrergic motor fibres innervating intramuscular ICC. Gastrointestinal ICC possess receptors for acetylcholine (M2 and M3 receptors), tachykinins (NK1 and NK3 receptors) and VIP (VIP-1) [630].

The function of the sphincter is to develop tone rather than phasic contractile activity and the IAS differs from the rectum in having a predominantly sympathetic excitatory input and also a different distribution of ICC. In this tissue, the sympathetic motor fibres do not innervate the ICC of the myenteric plexus as in the rectum and do not appear to be associated with intramuscular ICC. Thus sympathetic nerves are likely to innervate directly the smooth muscle of the IAS [601], while the ICC may contribute to myogenic tone as proposed for these cells in some tissues such as the urethra [634].

As in the rectum the IAS has a nitrergic innerva-

tions, but unlike the rectum, these do not seem to innervate the ICC. The role of ICC has been investigated in mice deficient in c-Kit positive cells (W/Wv mice). These studies have identified a dense network of c-Kit immunoreactive cells in the IAS of normal but not mutated mice, and unlike the sphincters in the upper gastrointestinal tract where these cells are involved in nitrergic neurotransmission, in the IAS they do not appear to be involved in relaxation responses to EFS, since responses were normal in c-Kit knockout animals [635] although inhibitory junction potentials were depressed. Whether c-Kit expressing cells are essential for the RAIR is not yet clear. The reflex has been reported to be intact in c-Kit deficient mice in one study, while another has reported IAS relaxation in response to rectal distension is reduced in c-Kit deficient mice [595,614]. Thus in the sphincter, ICC do not participate in neurotransmission but may be involved in regulating muscle tone, and basal myogenic tone is lower in ICC deficient mice compared with controls [614].

Thus ICC in the rectum and anus differ, reflecting the different functions of these two tissues. There is also growing evidence that ICC play a role in sensory mechanisms in the gastrointestinal tract. Vagal afferent nerve endings are found in close proximity to ICC and it has been suggested that they are involved in stretch perception. In the stomach, mutations resulting in the loss of c-Kit or its ligand result in loss of vagal intramuscular mechanosensitivity (see [636]), Furthermore, in the bladder, interstitial cells release ATP when stretched, a chemical known to sensitise afferent nerves [87].

5. FUTURE DIRECTIONS FOR RESEARCH

Our lack of understanding of the physiology of the IAS and rectum hinder the development of new treatments for faecal incontinence. The distribution, types and regulation of interstitial cells and their activity in the anorectal region requires further investigation and this may yield novel drug targets. Several receptor systems have been identified within the IAS that warrant further attention (α1-adrenoceptor, muscarinic) and regulators of ICC activity may also be potential drug targets.

Drug development should be easier for faecal incontinence than urinary incontinence, since the location of the internal sphincter allows drugs to be administered topically as a gel by the patient. This has the benefit of avoiding any undesirable adverse effects that may be observed with oral administration. Surprisingly few drugs with actions on the IAS are currently in use, but this may reflect the lack of research support anorectal problems attract. The lack of knowledge in this area will make the development of new drug therapies difficult. A few clinical trials have examined α1-adrenoceptor agonists in patients with faecal incontinence but the numbers of patients have been very small.

One problem when using receptor agonist as a treatment option is that tissues may become desensitised to the drug. This is a general phenomenon the importance of which varies depending on the receptor subtype and the tissue in which the receptor is found. Whether the IAS α1-adrenoceptor undergoes desensitisation is unknown and this will be critical information for the development of a clinically useful drug.

The emergence of the RhoA/ROK pathway as an important regulator of myogenic sphincter tone also offers new possibilities for the development of novel treatments. More selective inhibitors of the RhoA/ROK isoforms could be developed. Alternatively, it has been suggested that small interfering RNA (siRNA) may provide a more selective approach to inhibiting this pathway [625].

Two other cellular approaches to treatment include the use of stem cells to improve anal pressure [637] and the bioengineering of new sphincters using the patient's own smooth muscle cells [638]. Both techniques are in the very early stages of development and problems associated with blood supply to developing tissue and the establishment of a functional innervation once transplanted into the patient, pose major obstacles to development.

IX. RECOMMENDATIONS FOR RESEARCH CONCERNING LOWER URINARY TRACT (LUT) AND LOWER GASTROINTESTINAL TRACT RESEARCH (LGIT)

1. Integrate research obtained from isolated cells, tissue and organs to inform data from whole-organism measurements.
2. Increase research activity in poorly-investigated areas; e.g.: LUT outflow tract; lower GIT; nervous regulation of LUT and LGIT function.
3. Use genome-wide bioinformatic surveys to generate testable hypotheses regarding the physiological and pathophysiological functions of the LUT and LGIT
4. Investigate the pathophysiology of the LUT and LGIT by: developing animal models to address specific pathophysiologies; using human tissues from patients with clinically-defined pathologies.
5. Integrate multidisciplinary approaches to investigate LUT and LGIT function through collaborations in areas of e.g.: physical/mathematical modelling of LUT and LGIT function and physiological measurements; bioinformatics, genomics and cellular signalling; protein structure modelling

and generation of novel receptor ligands; tissue engineering.

6. Develop centres of excellence in LUT and LGIT research and integrate expertise from university departments, academic medical units and industry.
7. Encourage translational research to develop alongside basic research units.
8. Develop inter-institutional research-training programmes to allow new researchers the opportunity to better interact and exchange ideas
9. Allow researchers-in-training better access to international meetings through reduced registration charges and travel grants.
10. Lobby research-funding organisations about the medical and social importance of LUT and LGIT disorders.

X. ABBREVIATIONS AND NOMENCLATURE

AA	arachidonic acid
ABMA	α,β-methylene ATP
ACh	acetylcholine
ADP	adenosine diphosphate
AMPA	α-amino-3-hydroxy-5-methyl-lisoxazole-4-propionic acid
2-APB	2-aminoethoxydiphenyl borate
APUD	cells Amine Precursor Uptake and Decarboxylase cells
5ARI	5α-reductase inhibitor
ASIC	acid-sensing (proton-gated) ion channel
ATP	adenosine triphosphate
AUA	American urological association
β-AR	β-adrenoceptor
BCP	bladder compliance
BK	large conductance Ca^{2+}-activated K^+ channel
BoNT/A	botulinum neurotoxin type A
BOO	bladder outflow obstruction
BPH	benign prostatic hyperplasia
BWT	bladder wall thickness
CaD	caldesmon
CaM	calmodulin
cAMP	cyclic adenosine monophosphate
CB	cannabinoid receptor
CBD	cannabidiol
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
ChAT	choline acetyltransferase
CHT1	choline transporter
CNS	central nervous system
CO	carbon monoxide
COX	cyclo-oxygenase
Cr	creatinine
CRP	C-reactive protein
Cx43, Cx26	connexin proteins (numbered subtypes)
CXCL1	Chemokine(C-X-C motif)ligand 1
DIDS	diisothiocyano-2,2'-stilbenedisulphonic acid
DO	detrusor overactivity
DRG	dorsal root ganglion
DSM	detrusor smooth muscle
DWT	detrusor wall thickness
EAG	channel ether-a-go-go K^+ channel
EFS	electrical field stimulation
ENaC	epithelial Na^+ channel
EP	prostaglandin E receptors
ERK	extracellular signal-regulated kinase
EUS	external urethral sphincter
FAAH	fatty acid amide hydrolase
FaNaC	FMRF-amide activated channel
FI	faecal incontinence
GABA	γ-amino butyric acid
GC	guanylyl cyclase
G-I Tract	gastro-intestinal tract
GRK	G protein-coupled receptor kinase
HO-1,HO-2	haem oxygenase,
HCN	channel hyperpolarization-activated cyclic nucleotide-gated channel
HERG	channel human ether-a-go-go family K^+ channels
5-HT	5-hydroxytryptamine
IAS	internal anal sphincter
IBS	increased bladder sensation
IC	interstitial cell
ICC	interstitial cell of Cajal
IC/BPS	interstitial cystitis/bladder pain syndrome
ICI	intercontraction interval
IDO	idiopathic detrusor overactivity
IF	intermediate filaments
IL-6	Interleukin-6 and other numbered subtypes
IP3	inositol trisphosphate
IPSS	international Prostate Symptom Score
IR	immunoreactivity
KCl	potassium chloride
kDa	kiloDalton (unit of molecular weight)
Kir	inward-rectifier K^+ channel
KNCQ	family of delayed rectifier voltage-gated K^+ channels
KO	knock-out
L4-L5	spinal lumbar segments 4,5
LC	light chain
LGIC	ligand-gated ion channel
LMN	lower motoneurone
L-NAME	N (G)-nitro-L- arginine methyl ester
LP	lamina propria
LUT	lower urinary tract

M1,M2,M3	muscarinic receptor (numbered subtypes)
MCP	monocyte chemo-attractant protein
mGluR	metabotropic glutamate receptor
MHC	myosin heavy chain
MHz	megahertz (frequency)
MLC	myosin light chain
MLCK	myosin light chain kinase
MLCP	myosin light chain phosphatase
mRNA	messenger ribonucleic acid
MUI	mixed urinary incontinence
MVP	maximal voiding pressure
NANC	non-adrenergic, non-cholinergic
NMDA	N-methyl-D-aspartate
NSAID	non-steroidal anti-inflammatory drugs
NCX	Na^+-Ca^{2+} exchanger
NDO	neurogenic detrusor overactivity
NGF	nerve growth factor
NIRS	near-infrared spectroscopy
NKA	neurokinin A
nNOS	neuronal nitric oxide synthase
NMMHC	non-muscle myosin heavy chain
NO	nitric oxide
OAB	overactive bladder
OEtA	oleoyl ethyl amide
P2X	ionotropic family of purinergic receptors
P2Y	metabotropic family of purinergic receptors
PACAP	pituitary adenylate cyclase activating polypeptide
PARC	pulmonary and activation-regulated chemokine
PBOO	partial bladder outlet obstruction
pdet	detrusor pressure
PDGF	platelet-derived growth factor
PG	prostaglandin
PGP 9.5	protein gene product 9.5
PKC	protein kinase C
PMCA	plasma membrane Ca,Mg-ATPase
PT	pressure threshold for voiding
Qmax	maximum flow rate
QoL	quality of life
ROK	rho-activated kinase
RR	ruthenium red
RT-PCR	reverse transcriptase polymerase chain reaction
RTX	resiniferatoxin
SCI	spinal cord injury
SERCA	Mg^{2+}-dependent SR Ca^{2+}-ATPase
siRNA	small interfering RNA
SK	large conductance Ca^{2+}-activated K^+ channel
SMC	smooth muscle cell
SP	substance P
SR	sarcoplasmic reticulum
SUI	stress urinary incontinence
SU-IC	suburothelial-IC
SUR	sulphonylurea receptor
T8-T9	spinal thoracic segments 8,9
TARC	T cell-directed CC chemokine
TEA	tetraethylammonium
TEP	transepithelial potential
Tm	tropomyosin
7-TMR	Seven transmembrane spanning receptor
TNF-α	tumour necrosis factor-α
TRP	transient receptor potential cation channel
TTX	tetrodotoxin
TUMT	transurethral microwave therapy
TURP	transurethral resection of the prostate
UDP	uridine diphosphate
UEBW	ultrasound estimation of bladder weight
UMN	upper motoneurone
USS	urgency severity score
UUI	urinary urge incontinence
VIP	vasoactive intestinal peptide
Vmax	maximum contraction velocity
WT	wild-type
ZIP	kinase a serine/threonine kinase mediating apoptosis
ZO-1	a tight junction protein

Notes on convention of units and symbols

1 SI (Systeme Internationale) units have been used in the report; based on units of length (metre, m); mass (kilogramme, kg); time (second, s); electric current (ampere, A); amount of substance (mol, M):

2 Prefixes are k (10^3), m (10^{-3}), μ (10^{-6}), n (10^{-9}), p (10^{-12}).

3 Derived units are combinations of SI units and include: voltage (V, = $kg.m^2.s^{-3}.A^{-1}$); resistance ($\Omega = V.A^{-1}$); conductance ($S = \Omega^{-1}$); force (Newton, N = $kg.m.s^{-2}$); frequency (Hz, s^{-1}); pressure (Pascal, $Pa=Nm^{-2}$).

4 Some non-SI units, derived from SI units, include gramme (g), minute (min).

5 Some non-SI units without a precise definition are sometimes used: these include litre (l, approximates to dm^3); mmHg and cmH_2O as units of pressure (1 mmHg ≈ 0.133 kPa; 1 cmH_2O ≈ 0.0981 kPa).

6 The molar unit of concentration (moles per dm^3 solvent) is used, denoted by the letter M. Thus, the non-standard form of concentration - mol/L - is avoided, as it is meaningless in the SI system of units.

7 Symbols for ions in solution, eg Ca^{2+}, Na^+, K^+, Mg^{2+} etc, refer to the species that are presumed to take part in chemical reactions. No assumptions are made about the activity coefficient of the species in solution.

REFERENCES

1. McCloskey KD. Interstitial cells in the urinary bladder - localization and function. Neurourol Urodyn 2010; 29: 82-87.
2. Komuro T. Re-evaluation of fibroblasts and fibroblast-like cells. Anat Embryol 1990; 182: 103-112.
3. Komuro T, Seki K, Horiguchi K.. Ultrastructural characterization of the interstitial cells of Cajal. Arch Histol Cytol 1999; 62: 295-316.
4. McCloskey KD. Interstitial cells of Cajal in the urinary tract. Handb Exp Pharmacol 2011; 202: 233-254.
5. Maeda H, Yamagata A, Nishikawa S, Yoshinaga K, Kobayashi S, Nishi K.. Requirement of c-kit for development of intestinal pacemaker system. Development 1992; 116: 369-375.
6. Davidson RA, McCloskey KD. Morphology and localization of interstitial cells in the guinea pig bladder: structural relationships with smooth muscle and neurons. J Urol 2005; 173: 1385-1390.
7. McCloskey KD, Gurney AM. Kit positive cells in the guinea pig bladder. J Urol 2002; 168: 832-836.
8. Blyweert W, Van der Aa F, Ost D, Stagnaro M, De Ridder D. Interstitial cells of the bladder: the missing link? BJOG 2004; 111 Suppl 1: 57-60.
9. van der Aa F, Roskams T, Blyweert W, Ost D, Bogaert G, De Ridder D. Identification of kit positive cells in the human urinary tract. J Urol 2004; 171: 2492-2496.
10. Biers SM, Reynard JM, Doore T, Brading AF. The functional effects of a c-kit tyrosine inhibitor on guinea-pig and human detrusor. BJU Int 2006; 97: 612-616.
11. Johnston L, Carson C, Lyons AD, Davidson RA, McCloskey KD. Cholinergic-induced Ca^{2+} signaling in interstitial cells of Cajal from the guinea pig bladder. Am J Physiol Renal Physiol 2008; 294: F645-655.
12. Pezzone MA, Watkins SC, Alber SM, King WE, de Groat WC, Chancellor MB, Fraser MO. Identification of c-kit-positive cells in the mouse ureter: the interstitial cells of Cajal of the urinary tract. Am J Physiol Renal Physiol 2003; 284: F925-929.
13. Lagou M, De Vente J, Kirkwood TB, Hedlund P, Andersson KE, Gillespie JI, Drake MJ. Location of interstitial cells and neurotransmitters in the mouse bladder. BJU Int 2006; 97: 1332-1337.
14. Sui GP, Rothery S, Dupont E, Fry CH, Severs NJ. Gap junctions and connexin expression in human suburothelial interstitial cells. BJU Int 2002; 90: 118-129.
15. Rahnama'i MS, de Wachter SG, van Koeveringe GA, van Kerrebroeck PE, de Vente J, Gillespie JI. The relationship between prostaglandin E receptor-1 and cyclooxygenase-1 expression in guinea pig bladder interstitial cells: proposition of a signal propagation system. J Urol 2011; 185: 315-322.
16. Rahnama'i MS, van Koeveringe GA, Essers PB, de Wachter SG, de Vente J, van Kerrebroeck PE, Gillespie JI. Prostaglandin receptor EP1 and EP2 site in guinea pig bladder urothelium and lamina propria. J Urol 2010; 183: 1241-1247.
17. Grol S, Essers PB, van Koeveringe GA, Martinez-Martinez P, de Vente J, Gillespie JI. M3 muscarinic receptor expression on suburothelial interstitial cells. BJU Int 2009; 104: 398-405.
18. de Jongh R, Grol S, van Koeveringe GA, van Kerrebroeck PE, de Vente J, Gillespie JI.. The localization of cyclo-oxygenase immuno-reactivity (COX I-IR) to the urothelium and to interstitial cells in the bladder wall. J Cell Mol Med 2009; 13: 3069-3081.
19. Rasmussen H, Hansen A, Smedts F, Rumessen JJ, Horn T. CD34-positive interstitial cells of the human detrusor. APMIS 2007; 115: 1260-1266.
20. Rasmussen H, Rumessen JJ, Hansen A, Smedts F, Horn T. Ultrastructure of Cajal-like interstitial cells in the human detrusor. Cell Tissue Res 2009; 335: 517-527.
21. Ozturk H, Guneli E, Yagmur Y, Buyukbayram H. Expression of CD44 and E-cadherin cell adhesion molecules in hypertrophied bladders during chronic partial urethral obstruction and after release of partial obstruction in rats. Urology 2005; 65: 1013-1018.
22. van Roeyen CR, Ostendorf T, Floege J. The platelet-derived growth factor system in renal disease: An emerging role of endogenous inhibitors. Eur J Cell Biol 2011 Aug 26.
23. Zhao W, Zhao T, Huang V, Chen Y, Ahokas RA, Sun Y. Platelet-derived growth factor involvement in myocardial remodeling following infarction. J Mol Cell Cardiol 2011; 51: 830-838.
24. Pantaleo MA, Astolfi A, Nannini M, Ceccarelli C, Formica S, Santini D, Heinrich MC, Corless C, Dei Tos AP, Paterini P, Catena F, Maleddu A, Saponara M, Di Battista M, Biasco G. Differential expression of neural markers in KIT and PDGFRA wild-type gastrointestinal stromal tumours. Histopathology 2011; 59: 1071–1080.
25. González-Cámpora R, Delgado MD, Amate AH, Gallardo SP, León MS, Beltrán AL. Old and new immunohistochemical markers for the diagnosis of gastrointestinal stromal tumors. Anal Quant Cytol Histol. 2011; 33: 1-11.
26. Kurahashi M, Nakano Y, Hennig GW, Ward SM, Sanders KM. Platelet derived growth factor receptor α-positive cells in the tunica muscularis of human colon. transducing inputs from enteric motor neurons. J Cell Mol Med. 2012 Jan 6. doi: 10.1111/j.1582-4934.2011.01510.x.
27. Koh BH, Roy R, Hollywood MA, Thornbury KD, McHale NG, Sergeant GP, Hatton WJ, Ward SM, Sanders KM, Koh SD. PDGFRα cells in mouse urinary bladder: A new class of interstitial cells. J Cell Mol Med. 2011 Dec 12. doi: 10.1111/j.1582-4934.2011.01506.x.
28. Fry CH, Ikeda Y, Harvey R, Wu C, Sui GP. Control of bladder function by peripheral nerves: avenues for novel drug targets. Urology 2004; 63(3 Suppl 1): 24-31.
29. Gillespie JI, Markerink-van Ittersum M, de Vente J. Expression of neuronal nitric oxide synthase (nNOS) and nitric-oxide-induced changes in cGMP in the urothelial layer of the guinea pig bladder. Cell Tissue Res 2005; 321: 341-351.
30. Fry CH, Sui GP, Kanai AJ, Wu C. The function of suburothelial myofibroblasts in the bladder. Neurourol Urodyn 2007; 26(6 Suppl): 914-919.
31. Gillespie JI, Markerink-van Ittersum M, de Vente J. cGMP-generating cells in the bladder wall: identification of distinct networks of interstitial cells. BJU Int 2004; 94: 1114-1124.
32. Piaseczna Piotrowska A, Rolle U, Solari V, Puri P. Interstitial cells of Cajal in the human normal urinary bladder and in the bladder of patients with megacystis-microcolon intestinal hypoperistalsis syndrome. BJU Int 2004; 94: 143-146.
33. Sui GP, Wu C, Fry CH. 2004. Electrical characteristics of suburothelial cells isolated from the human bladder. J Urol 2004; 171: 938-943.
34. Brading AF, McCloskey KD. 2005. Mechanisms of Disease: specialized interstitial cells of the urinary tract - an assessment of current knowledge. Nat Clin Pract Urol 2005; 2: 546-554.
35. Gillespie JI, Markerink-van Ittersum M, De Vente J. Endogenous nitric oxide/cGMP signalling in the guinea pig bladder: evidence for distinct populations of sub-urothelial interstitial cells. Cell Tissue Res 2006; 325: 325-332.
36. de Jongh R, van Koeveringe GA, van Kerrebroeck PE, Markerink-van Ittersum M, de Vente J, Gillespie JI. Altera-

tions to network of NO/cGMP-responsive interstitial cells induced by outlet obstruction in guinea-pig bladder. Cell Tissue Res 2007; 330: 147-160.

37. de Jongh R, van Koeveringe GA, van Kerrebroeck PE, Markerink-van Ittersum M, de Vente J, Gillespie JI. The effects of exogenous prostaglandins and the identification of constitutive cyclooxygenase I and II immunoreactivity in the normal guinea pig bladder. BJU Int 2007; 100: 419-429.

38. de Vente J, Markerink-van Ittersum M, Gillespie JI. Natriuretic peptide responsive, cyclic guanosine monophosphate producing structures in the guinea pig bladder. J Urol 2007; 177: 1191-1194.

39. Smet PJ, Jonavicius J, Marshall VR, de Vente J. Distribution of nitric oxide synthase-immunoreactive nerves and identification of the cellular targets of nitric oxide in guinea-pig and human urinary bladder by cGMP immunohistochemistry. Neuroscience 1996; 71: 337-348.

40. Birder LA. Urothelial signaling. Auton Neurosci 2010; 153: 33-40.

41. Hanna-Mitchell AT, Beckel JM, Barbadora S, Kanai AJ, de Groat WC, Birder LA. Non-neuronal acetylcholine and urinary bladder urothelium. Life Sci 2007; 80: 2298-2302.

42. Zarghooni S, Wunsch J, Bodenbenner M, Bruggmann D, Grando SA, Schwantes U, Wess J, Kummer W, Lips KS. Expression of muscarinic and nicotinic acetylcholine receptors in the mouse urothelium. Life Sci 2007; 80: 2308-2313.

43. Ferguson DR, Kennedy I, Burton TJ. ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes - a possible sensory mechanism? J Physiol 1997; 505: 503-511.

44. Gilmore NJ, Vane JR. Hormones released into the circulation when the urinary bladder of the anaesthetized dog is distended. Clin Sci 1971; 41: 69-83.

45. Abrams PH, Sykes JA, Rose AJ, Rogers AF. The synthesis and release of prostaglandins by human urinary bladder muscle in vitro. Invest Urol 1979; 16: 346-348.

46. Jeremy JY, Tsang V, Mikhailidis DP, Rogers H, Morgan RJ, Dandona P. Eicosanoid synthesis by human urinary bladder mucosa: pathological implications. Br J Urol 1987; 59: 36-39.

47. Mikhailidis DP, Jeremy JY, Dandona P. Urinary bladder prostanoids - their synthesis, function and possible role in the pathogenesis and treatment of disease. J Urol 1987; 137: 577-582.

48. Grol S, Nile CJ, Martinez-Martinez P, van Koeveringe G, de Wachter S, de Vente J, Gillespie JI. M3 muscarinic receptor-like immunoreactivity in sham operated and obstructed guinea pig bladders. J Urol 2011; 185: 1959-1966.

49. Mukerji G, Yiangou Y, Grogono J, Underwood J, Agarwal SK, Khullar V, Anand P. Localization of M2 and M3 muscarinic receptors in human bladder disorders and their clinical correlations. J Urol 2006; 176: 367-373.

50. Wiseman OJ, Fowler CJ, Landon DN. The role of the human bladder lamina propria myofibroblast. BJU Int 2003; 91: 89-93.

51. Sui GP, Wu C, Fry CH. Characterization of the purinergic receptor subtype on guinea-pig suburothelial myofibroblasts. BJU Int 2006; 97: 1327-1331.

52. Ost D, Roskams T, Van Der Aa F, De Ridder D. Topography of the vanilloid receptor in the human bladder: more than just the nerve fibers. J Urol 2002; 168: 293-297.

53. Gillespie JI, Harvey IJ, Drake MJ. Agonist- and nerve-induced phasic activity in the isolated whole bladder of the guinea pig: evidence for two types of bladder activity. Exp Physiol 2003; 88: 343-357.

54. Kuijpers KA, Heesakkers JP, Jansen CF, Schalken JA. Cadherin-11 is expressed in detrusor smooth muscle cells and myofibroblasts of normal human bladder. Eur Urol 2007; 52: 1213-1221.

55. Drake MJ, Hedlund P, Andersson KE, Brading AF, Hussain I, Fowler C, Landon DN. Morphology, phenotype and ultrastructure of fibroblastic cells from normal and neuropathic human detrusor: absence of myofibroblast characteristics. J Urol 2003; 169: 1573-1576.

56. Hashitani H, Yanai Y, Suzuki H. Role of interstitial cells and gap junctions in the transmission of spontaneous Ca^{2+} signals in detrusor smooth muscles of the guinea-pig urinary bladder. J Physiol 2004; 559: 567-581.

57. McCloskey KD. Characterization of outward currents in interstitial cells from the guinea pig bladder. J Urol 2005; 173: 296-301.

58. Gillespie JI, Markerink-van Ittersum M, De Vente J. Interstitial cells and cholinergic signalling in the outer muscle layers of the guinea-pig bladder. BJU Int 2006; 97: 379-385.

59. Lagou M, Drake MJ, Markerink-van Ittersum M, J DEV, Gillespie JI. Interstitial cells and phasic activity in the isolated mouse bladder. BJU Int 2006; 98: 643-650.

60. De Ridder D, Roskams T, Van Poppel H, Baert L. Nitric oxide synthase expression in neurogenic bladder disease: a pilot study. Acta Neurol Belg 1999; 99: 57-60.

61. Brading AF. Spontaneous activity of lower urinary tract smooth muscles: correlation between ion channels and tissue function. J Physiol 2006; 570: 13-22.

62. Sui G, Fry CH, Malone-Lee J, Wu C. Aberrant Ca^{2+} oscillations in smooth muscle cells from overactive human bladders. Cell Calcium 2009; 45: 456-464.

63. Sui GP, Wu C, Fry CH. Electrical characteristics of suburothelial cells isolated from the human bladder. J Urol 2004; 171: 938-943.

64. Wu C, Sui GP, Fry CH. Purinergic regulation of guinea pig sub-urothelial myofibroblasts. J Physiol 2004; 559: 231-243.

65. Sui GP, Wu C, Roosen A, Ikeda Y, Kanai AJ, Fry CH. Modulation of bladder myofibroblast activity: implications for bladder function. Am J Physiol Renal Physiol 2008; 295: F688-697.

66. Ikeda Y, Kanai A. Urotheliogenic modulation of intrinsic activity in spinal cord-transected rat bladders: role of mucosal muscarinic receptors. Am J Physiol Renal Physiol 2008; 295: F454-461.

67. Johnston L, Cunningham RM, Young JS, Fry CH, McMurray G, Eccles R, McCloskey KD. Altered distribution of interstitial cells and innervation in the rat urinary bladder following spinal cord injury. J Cell Mol Med. 2011 Aug 25. doi: 10.1111/j.1582-4934.2011.01410

68. Kubota Y, Hashitani H, Shirasawa N, Kojima Y, Sasaki S, Mabuchi Y, Soji T, Suzuki H, Kohri K. Altered distribution of interstitial cells in the guinea pig bladder following bladder outlet obstruction. Neurourol Urodyn 2008; 27: 330-340.

69. Kubota Y, Kojima Y, Shibata Y, Imura M, Sasaki S, Kohri K. Role of KIT-Positive Interstitial Cells of Cajal in the Urinary Bladder and Possible Therapeutic Target for Overactive Bladder. Adv Urol 2011; 2011: 816342.

70. Kubota Y, Biers SM, Kohri K, Brading AF. Effects of imatinib mesylate (Glivec) as a c-kit tyrosine kinase inhibitor in the guinea-pig urinary bladder. Neurourol Urodyn 2006; 25: 205-210.

71. Vlaskovska M, Kasakov L, Rong WF, Bodin R, Bardini M, Cockayne DA, Ford AP, Burnstock G. $P2X_3$ knock-out mice reveal a major sensory role for urothelially released ATP. J Neurosci 2001; 21: 5670–5677.

72. Knight GE, Bodin P, De Groat WC, and Burnstock G. ATP is released from guinea pig ureter epithelium on distension. Am J Physiol Renal Physiol 2002; 282: F281–F288.

73. Lewis SA, Lewis JR. Kinetics of urothelial ATP release. Am J Physiol Renal Physiol 2006; 291: F332-340.

74. Mihara H, Boudaka A, Sugiyama T, Moriyama Y, Tominaga M. Transient receptor potential vanilloid 4 (TRPV4)-dependent calcium influx and ATP release in mouse oesophageal keratinocytes. J Physiol 2011; 589: 3471-3482.

75. Davis CW, Lazarowski E. Coupling of airway ciliary activity and mucin secretion to mechanical stresses by purinergic signaling. Respir Physiol Neurobiol 2008; 163: 208-213.

76. Homolya L, Steinberg TH, Boucher RC. Cell to cell communication in response to mechanical stress via bilateral release of ATP and UTP in polarized epithelia. J Cell Biol 2000; 150: 1349-1360.

77. Yamamura H, Ugawa S, Ueda T, Nagao M, Shimada S. Epithelial Na^+ channel delta subunit mediates acid-induced ATP release in the human skin. Biochem Biophys Res Commun 2008; 373: 155-158.

78. Yamamoto K, Shimizu N, Obi S, Kumagaya S, Taketani Y, Kamiya A, Ando J. Involvement of cell surface ATP synthase in flow-induced ATP release by vascular endothelial cells. Am J Physiol Heart Circ Physiol 2007; 293: H1646-1653.

79. Zagorodnyuk VP, Lynn P, Costa M, Brookes SJ. Mechanisms of mechanotransduction by specialized low-threshold mechanoreceptors in the guinea pig rectum. Am J Physiol Gastrointest Liver Physiol 2005; 289: G397-406.

80. Kumar V, Chapple CR, Rosario D, Tophill PR, Chess-Williams R. In vitro release of adenosine triphosphate from the urothelium of human bladders with detrusor overactivity, both neurogenic and idiopathic. Eur Urol 2010; 57: 1087-1092.

81. Sadananda P, Shang F, Liu L, Mansfield KJ, Burcher E. Release of ATP from rat urinary bladder mucosa: role of acid, vanilloids and stretch. Br J Pharmacol 2009; 158; 1655-1662.

82. Wei B, Chen Z, Zhang X, Feldman M, Dong XZ, Doran R, Zhao BL, Yin WX, Kotlikoff MI, Ji G. Nitric oxide mediates stretch-induced Ca^{2+} release via activation of phosphatidyl-inositol 3-kinase-Akt pathway in smooth muscle. PLoS One 2008 Jun 25; 3: e2526.

83. Gevaert T, Vriens J, Segal A, Everaerts W, Roskams T, Talavera K, Owsianik G, Liedtke W, Daelemans D, Dewachter I, Van Leuven F, Voets T, De Ridder D, Nilius B. Deletion of the transient receptor potential cation channel TRPV4 impairs murine bladder voiding. J Clin Invest 2007; 117: 3453-3462.

84. Stiffler DF, Thornburg KL, Swanson RE. Structural and functional responses of eth bull frog urinary bladder to distension caused by hydostatic pressure gradients. Arch Physiol Biochem 2000; 108: 405-414.

85. Birder LA, Barrick SR, Roppolo JR, Kanai AJ, de Groat WC, Kiss S, Buffington CA. Feline interstitial cystitis results in mechanical hypersensitivity and altered ATP release from bladder urothelium. Am J Physiol Renal Physiol 2003; 285: F423-429

86. Tanaka I, Nagase K, Tanase K, Aoki Y, Akino H, Yokoyama O. Modulation of stretch evoked adenosine triphosphate release from bladder epithelium by prostaglandin E_2. J Urol 2011; 185: 341-346.

87. Cheng Y, Mansfield KJ, Sandow SL, Sadananda P, Burcher E, Moore KH. Porcine bladder urothelial, myofibroblast, and detrusor muscle cells: characterization and ATP release. Front Pharmacol 2011; 2: 27.

88. Sun Y, Chai TC. Augmented extracellular ATP signaling in bladder urothelial cells from patients with interstitial cystitis. Am J Physiol Cell Physiol 2006; 290: C27-34.

89. Pandita RK, Andersson KE. Intravesical adenosine triphosphate stimulates the micturition reflex in awake, freely moving rats. J Urol 2002; 168: 1230-1234.

90. Munoz A, Smith CP, Boone TB, Somogyi GT. Overactive and underactive bladder dysfunction is reflected by alterations in urothelial ATP and NO release. Neurochem Int 2011; 58: 295-300.

91. Rong W, Spyer KM, Burnstock G. Activation and sensitisation of low and high threshold afferent fibres mediated by P2X receptors in the mouse urinary bladder. J Physiol 2002; 541: 591-600.

92. Cockayne DA, Hamilton SG, Zhu QM, Dunn PM, Zhong Y, Novakovic S, Malmberg AB, Cain G, Berson A, Kassotakis L, Hedley L, Lachnit WG, Burnstock G, McMahon SB, Ford AP. Urinary bladder hyporeflexia and reduced pain-related behaviour in $P2X_3$-deficient mice. Nature 2000; 407: 1011-1015.

93. Cockayne DA, Dunn PM, Zhong Y, Rong W, Hamilton SG, Knight GE, Ruan HZ, Ma B, Yip P, Nunn P, McMahon SB, Burnstock G, Ford AP. $P2X_2$ knockout mice and $P2X_2/P2X_3$ double knockout mice reveal a role for the $P2X_2$ receptor subunit in mediating multiple sensory effects of ATP. J Physiol 2005; 567: 621-639.

94. Hansen MA, Balcar VJ, Barden JA, Bennett MR. The distribution of single $P2X_1$-receptor clusters on smooth muscle cells in relation to nerve varicosities in the rat urinary bladder. J Neurocytol 1998; 27: 529-539.

95. Matsumoto-Miyai K, Kagase A, Murakawa Y, Momota Y, Kawatani M. Extracellular Ca^{2+} regulates the stimulus-elicited ATP release from urothelium. Auton Neurosci 2009; 150: 94-99.

96. Matsumoto-Miyai K, Kagase A, Yamada E, Yoshizumi M, Murakami M, Ohba T, Kawatani M. Store-operated Ca^{2+} entry suppresses distention-induced ATP release from the urothelium. Am J Physiol Renal Physiol 2011; 300: F716-720.

97. Mochizuki T, Sokabe T, Araki I, Fujishita K, Shibasaki K, Uchida K, Naruse K, Koizumi S, Takeda M, Tominaga M. The TRPV4 cation channel mediates stretch-evoked Ca^{2+} influx and ATP release in primary urothelial cell cultures. J Biol Chem 2009; 284: 21257-21264.

98. Li M, Sun Y, Simard JM, Chai TC. Increased transient receptor potential vanilloid type-1 (TRPV1) signalling in idiopathic overactive bladder urothelial cells. Neurourol Urodyn 2011; 30: 606-611.

99. Everaerts W, Vriens J, Owsianik G, Appendino G, Voets T, De Ridder D, Nilius B. Functional characterization of transient receptor potential channels in mouse urothelial cells. Am J Physiol Renal Physiol 2010; 298: F692-701.

100. Wu C, Gui GP, Fry CH. Intracellular Ca^{2+} regulation and electrophysiolgical properties of bladder urothelium subjected to stretch and exogenous agonists. Cell Calcium 2011; 49: 395-399.

101. Wang EC, Lee JM, Ruiz WG, Balestreire EM, von Bodungen M, Barrick S, Cockayne DA, Birder LA, Apodaca G. ATP and purinergic receptor-dependent membrane traffic in bladder umbrella cells. J Clin Invest 2005; 115: 2412-2422.

102. Kimelberg HK, Macvicar BA, Sontheimer H. Anion channels in astrocytes: biophysics, pharmacology, and function. Glia 2006; 54: 747-757.

103. Wang EC, Lee JM, Johnson JP, Kleyman TR, Bridges R, Apodaca G. Hydrostatic pressure-regulated ion transport in bladder uroepithelium. Am J Physiol Renal Physiol 2003; 285: F651-663.

104. Dunning-Davies BM, Fry CH, Mansour D, Ferguson DR. The regulation of ATP release from the urothelium by adenosine and transepithelial potential. BJU Int 2012 In the Press.

105. Matharu R, Young JS, Carew M, Fry CH. Inhibition of stretch evoked ATP release from bladder mucosa by anticholinergic agents. BJU Int 2012, In the Press.

106. Kumar V, Chapple CR, Surprenant AM, Chess-Williams R. Enhanced adenosine triphosphate release from the urothelium of patients with painful bladder syndrome: a possible pathophysiological explanation. J Urol 2007; 178: 1533-1536.

107. Smith CP, Vemulakonda VM, Kiss S, Boone TB, Somogyi GT. Enhanced ATP release from rat bladder urothelium during chronic bladder inflammation: effect of botulinum toxin A. Neurochem Int 2005; 47: 291-297.

108. Girard BM, Wolf-Johnston A, Braas KM, Birder LA, May V, Vizzard MA. PACAP-mediated ATP release from rat urothelium and regulation of PACAP/VIP and receptor mRNA in

micturition pathways after cyclophosphamide (CYP)-induced cystitis. J Mol Neurosci 2008; 36: 310-320.

109. Smith CP, Gangitano DA, Munoz A, Salas NA, Boone TB, Aoki KR, Francis J, Somogyi GT. Botulinum toxin type A normalizes alterations in urothelial ATP and NO release induced by chronic spinal cord injury. Neurochem Int 2008; 52: 1068-1075.

110. Yoshida M, Miyamae K, Iwashita H, Otani M, Inadome A. Management of detrusor dysfunction in the elderly: changes in acetylcholine and adenosine triphosphate release during aging. Urology 2004; 63 (3 Suppl 1): 17-23.

111. Yoshida M, Inadome A, Maeda Y, Satoji Y, Masunaga K, Sugiyama Y, Murakami S. Non-neuronal cholinergic system in human bladder urothelium. Urology 2006; 67: 425-430.

112. Lewis SA, Diamond JM. Na^+ transport by rabbit urinary bladder, a tight epithelium. J Membr Biol 1976; 28: 1–40.

113. Hu P, Meyers S, Liang FX, Deng FM, Kachar B, Zeidel ML, Sun TT. Role of membrane proteins in permeability barrier function: uroplakin ablation elevates urothelial permeability. Am J Physiol Renal Physiol 2002; 283: F1200-1207.

114. Khandelwal P, Abraham SN, Apodaca G. Cell biology and physiology of the uroepithelium. Am J Physiol Renal Physiol 2009; 297: F1477-1501.

115. Acharya P, Beckel J, Wang E, Ruiz W, Rojas R, Apodaca G. Distribution of the tight junction proteins ZO-1, occludin, and claudin-4, -8, and -12 in bladder epithelium. Am J Physiol Renal Physiol 2004; 287: F305–F318.

116. Varley CL, Garthwaite AE, Cross WR, Hinley J, Trejdosie. wicz LK, Southgate J. PPARγ-regulated tight junction development during human urothelial cytodifferentiation. J Cell Physiol 2006; 208: 407–417.

117. Lewis SA, Eaton DC, Diamond JM. The mechanism of Na^+ transport by rabbit urinary bladder. J Membr Biol 1976; 28: 41-70.

118. Wang EC, Lee JM, Johnson JP, Kleyman TR, Bridges R, Apodaca G. Hydrostatic pressure-regulated ion transport in bladder uroepithelium. Am J Physiol Renal Physiol 2003; 285: F651-663.

119. Stockand JD, Zeltwanger S, Bao HF, Becchetti A, Worrell RT, Eaton DC. S-adenosyl-L-homocysteine hydrolase is necessary for aldosterone-induced activity of epithelial Na^+ channels. Am J Physiol Cell Physiol 2001; 281: C773-785.

120. Bugaj V, Pochynyuk O, Stockand JD. Activation of the epithelial Na^+ channel in the collecting duct by vasopressin contributes to water reabsorption. Am J Physiol Renal Physiol 2009; 297: F1411-1418.

121. Yamada T. Matsuda K, Uchiyama M. Atrial natriuretic peptide and cGMP activate sodium transport through PKA-dependent pathway in the urinary bladder of the Japanese tree frog. J Comp Physiol B 2006; 176: 203-212.

122. Yu W, Khandelwal P, Apodaca G. Distinct apical and basolateral membrane requirements for stretch-induced membrane traffic at the apical surface of bladder umbrella cells. Mol Biol Cell 2009; 20: 282-295.

123. Sun Y, Chen M, Lowentritt BH, Van Zijl PS, Koch KR, Keay S, Simard JM, Chai TC. EGF and HB-EGF modulate inward potassium current in human bladder urothelial cells from normal and interstitial cystitis patients. Am J Physiol Cell Physiol 2007; 292: C106-114.

124. Birder LA, Kanai A, de Groat WC et al. Vanilloid receptor expression suggests a sensory role for urinary bladder epithelial cells. Proc Natl Acad Sci 2001; 98: 13396-13401.

125. Birder LA, Nakamura Y, Kiss S, et al. Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci 2002; 5: 856-860.

126. Birder LA, Kullmann F, Lee H et al. Activation of urothelial transient receptor potential vanilloid 4 by 4-alpha-phorbol 12,13-didecanote contributes to altered bladder reflexes in the rat. J Pharmacol Exp Ther 2007; 323: 227-335.

127. Stein RJ, Nagatomi J, Hayashi Y et al. Cool (TRPM8) and hot (TRPV1) receptors in the bladder and male genital tract. J Urol 2004; 172: 1175-1178.

128. Streng T, Axelsson HE, Hedlund P et al. Distribution and function of the hydrogen sulfide-sensitive TRPA1 ion channel in rat urinary bladder. Eur Urol 2008; 53: 391-399.

129. Birder LA, Ruggieri M, Takeda M, van Koeveringe G, Veltkamp S, Korstanje C, Parsons B, Fry CH. How does the urothelium affect bladder function in health and disease? Neurourol Urodyn 2012; In the Press.

130. Wood MW, Breitschwerdt EB, Nordone SK, Linder KE, Gookin JL. Uropathogenic E. coli promote a paracellular urothelial barrier defect characterized by altered tight junction integrity, epithelial cell sloughing and cytokine release. J Comp Pathol 2011; Oct 18: 1-9

131. Smith NJ, Varley CL, Eardley I, Feather S, Trejdosiewicz LK, Southgate J. Toll-like receptor responses of normal human urothelial cells to bacterial flagellin and lipopolysaccharide. J Urol 2011; 186: 1084-1092.

132. Rodhe N, Löfgren S, Strindhall J, Matussek A, Mölstad S. Cytokines in urine in elderly subjects with acute cystitis and asymptomatic bacteriuria. Scand J Prim Health Care 2009; 27: 74-79.

133. Ko YC, Mukaida N, Ishiyama S et al. Elevated interleukin-8 levels in the urine of patients with urinary tract infections. Infect Immun 1993; 61; 1307-1314.

134. Wood MW, Breitschwerdt EB, Gookin JL. Autocrine effects of interleukin-6 mediate acute-phase proinflammatory and tissue-reparative transcriptional responses of canine bladder mucosa. Infect Immun 2011; 79: 708–715.

135. Saban R, Keith IM, Nielsen KT, Christensen MM, Rhodes PR, Bruskewitz RC. In vitro effects of bladder mucosa and an enkephalinase inhibitor on tachykinin induced contractility of the dog bladder. J Urol 1992; 147: 750-755.

136. Hawthorn MH, Chapple C, Cock M, Chess-Williams R. Urothelium-derived inhibitory factor(s) influences on detrusor muscle contractility in vitro. Br J Pharmacol 2000; 129: 416-419.

137. Templeman L, Chapple CR, Chess-Williams R. Urothelium derived inhibitory factor and cross-talk among receptors in the trigone of the bladder of the pig. J Urol 2002; 167: 742-745.

138. Chaiyaprasithi B, Mang C, Kilbinger H, Hohenfellner M. Inhibition of human detrusor contraction by a urothelium derived factor. J Urol 2003; 170: 1897-1900.

139. Kosan M, Hafez G, Ozturk B, Ozgünes O, Gür S, Cetinkaya M. Effect of urothelium on bladder contractility in diabetic rats. Int J Urol 2005; 12: 677-682.

140. Mastrangelo D, Iselin CE. Urothelium dependent inhibition of rat ureter contractile activity. J Urol 2007; 178: 702-709.

141. Munoz A, Gangitano DA, Smith CP, Boone TB, Somogyi GT. Removal of urothelium affects bladder contractility and release of ATP but not release of NO in rat urinary bladder. BMC Urol 2010; 10: 10.

142. Santoso AG, Sonarno IA, Arsa, Liang W. The role of the urothelium and ATP in mediating detrusor smooth muscle contractility. Urology 2010; 76: 1267.e7-e12.

143. Santoso AG, Lo WN, Liang W. Urothelium-dependent and urothelium-independent detrusor contractility mediated by nitric oxide synthase and cyclooxygenase inhibition. Neurourol Urodyn 2011; 30: 619-625.

144. Sadananda P, Chess-Williams R, Burcher E. Contractile properties of the pig bladder mucosa in response to neurokinin A: a role for myofibroblasts? Br J Pharmacol 2008; 153: 1465-1473.

145. Moro C, Leeds C, Chess-Williams R. Contractile activity of the bladder urothelium/ lamina propria and its regulation by nitric oxide. Eur J Pharmacol 2011 Nov 19.

146. Moro C, Uchiyama J, Chess-Williams R. Urothelial/lamina propria spontaneous activity and the role of m3 muscarinic receptors in mediating rate responses to stretch and carbachol. Urology 2011; 78: 1442.e9-1442.e15.

147. Drake MJ, Fry CH, Eyden B. Structural characterization of myofibroblasts in the bladder. BJU Int 2006; 97: 29-32.

148. Thompson SA, Copeland CR, Reich DH, Tung L. Mechanical coupling between myofibroblasts and cardiomyocytes slows electric conduction in fibrotic cell monolayers. Circulation 2011; 123: 2083-2093.

149. Faggian L, Pampinella F, Roelofs M Paulon T, Franch R, Chiavegato A, Sartore S. Phenotypic changes in the regenerating rabbit bladder muscle. Role of interstitial cells and innervation on smooth muscle cell differentiation. Histochem Cell Biol 1998; 109: 25-39.

150. Akino H, Chapple CR, McKay N et al. Spontaneous contractions of the pig urinary bladder: the effect of ATP-sensitive potassium channels and the role of the mucosa. BJU Int 2008; 102: 1168-1174.

151. Kanai A, Roppolo J, Ikeda Y et al. Origin of spontaneous activity in neonatal and adult rat bladders and its enhancement by stretch and muscarinic agonists. Am J Physiol Renal Physiol 2007; 292: F1065-1072.

152. Ikeda Y, Fry CH, Hayashi F et al. Role of gap junctions in spontaneous activity of the rat bladder. Am J Physiol Renal Physiol 2007; 293: F1018-1025.

153. Fry CH, Young JS, Jabr RI, McCarthy C, Ikeda Y, Kanai AJ Modulation of spontaneous activity in the overactive bladder – the role of P2Y agonists. Am J Physiol

154. McMurray G, Dass N, Brading AF. Purinoceptor subtypes mediating contraction and relaxation of marmoset urinary bladder smooth muscle. Br J Pharmacol 1998; 123: 1579-1586.

155. Young JS, Johnston L, Soubrane C, McCloskey KD, McMurray G, Eccles R, Fry CH The passive and active contractile properties of the underactive bladder. BJU Int 2012

156. Harvey RA, Skennerton DE, Newgreen D, Fry CH. The contractile potency of adenosine triphosphate and ecto-adenosine triphosphatase activity in guinea pig detrusor and detrusor from patients with a stable, unstable or obstructed bladder. J Urol 2002; 168: 1235-1239.

157. Weiss l. Cell and Tissue Biology. Sixth Edition 1983;Urban and Schwarzenberg, Baltimore, MD.

158. Somlyo AP, Somlyo AV. Vascular smooth muscle. I. Normal structure, pathology, biochemistry, and biophysics. Pharmacol Rev 1968; 20: 197-272.

159. Somlyo AP, Somlyo AV, Kitazawa T, Bond M, Shuman H, Kowarski D. Ultrastructure, function and composition of smooth muscle. Ann Biomed Eng 1983; 11: 579-588.

160. Higashihara M, Watanabe M, Usuda S, Miyazaki K. Smooth muscle type isoform of 20 kDa myosin light chain is expressed in monocyte/macrophage cell lineage. J.Smooth Muscle Res 2008; 44: 29-40.

161. Adelstein RS, Eisenberg E. Regulation and kinetics of the actin-myosin-ATP interaction. Ann Rev Biochem 1980; 49: 921-956.

162. Helper DJ, Lash JA, Hathaway DR. Distribution of isoelectric variants of the 17,000-dalton myosin light chain in mammalian smooth muscle. J Biol Chem 1988; 263:1 5748-5753.

163. Babij P, Periasamy M. Myosin heavy chain isoform diversity in smooth muscle is produced by differential RNA processing. J Mol Biol 1989 ;210 : 673-679.

164. Babij P, Kelly C, Periasamy M. Characterization of a mammalian smooth muscle myosin heavy-chain gene: complete nucleotide and protein coding sequence and analysis of the 5' end of the gene. Proc Natl Acad Sci U.S.A 1991; 88: 10676-10680.

165. DiSanto ME, Cox RH, Wang Z, Chacko S. NH_2-terminal-inserted myosin II heavy chain is expressed in smooth muscle of small muscular arteries. Am J Physiol Cell Physiol 1997; 272: C1532-1542.

166. Rovner AS, Freyzon Y, Trybus KM. An insert in the motor domain determines the functional properties of expressed smooth muscle myosin isoforms. J Muscle Res Cell Motil 1997; 18: 103-10.

167. DiSanto ME, Stein R, Chang S, Hypolite JA, Zheng Y, Zderic S, Wein AJ, Chacko S. Alteration in expression of myosin isoforms in detrusor smooth muscle following bladder outlet obstruction. Am.J.Physiol Cell Physiol 2003; 285: C1397-1410.

168. Hypolite JA, Chang S, LaBelle E, Babu GJ, Periasamy M, Wein AJ, Chacko S. Deletion of SM-B, the high ATPase isoform of myosin, upregulates the PKC-mediated signal transduction pathway in murine urinary bladder smooth muscle. Am J Physiol Renal Physiol 2009; 296: F658-665.

169. Su X, Stein R, Stanton MC, Zderic S, Moreland RS. Effect of partial outlet obstruction on rabbit urinary bladder smooth muscle function. Am J Physiol Renal Physiol 2003; 284: F644-652.

170. Sjuve R, Haase H, Morano I, Uvelius B, Arner A. Contraction kinetics and myosin isoform composition in smooth muscle from hypertrophied rat urinary bladder. J Cell Biochem 1996; 63: 86-93.

171. Malmqvist U, Arner A. Correlation between isoform composition of the 17 kDa myosin light chain and maximal shortening velocity in smooth muscle. Pflugers Arch. 1991; 418: 523-530.

172. Fuglsang A, Khromov A, Torok K, Somlyo AV, Somlyo AP. Flash photolysis studies of relaxation and cross-bridge detachment: higher sensitivity of tonic than phasic smooth muscle to MgADP. J Muscle Res Cell Motil 1993; 14: 666-677.

173. Hasegawa Y, Morita F. Role of 17-kDa essential light chain isoforms of aorta smooth muscle myosin. J.Biochem. 1992;111(6):804-9.

174. Cher ML, Abernathy BB, McConnell JD, Zimmern PE, Lin VK. Smooth-muscle myosin heavy-chain isoform expression in bladder-outlet obstruction. World J Urol 1996; 14: 295-300.

175. Wang ZE, Gopalakurup SK, Levin RM, Chacko S. Expression of smooth muscle myosin isoforms in urinary bladder smooth muscle during hypertrophy and regression. Lab Invest 1995; 73: 244-251.

176. Martin AF, Bhatti S, Paul RJ. C-terminal isoforms of the myosin heavy chain and smooth muscle function. Comp Biochem Physiol B 1997; 117: 3-11.

177. Rovner AS, Fagnant PM, Lowey S, Trybus KM. The carboxyl-terminal isoforms of smooth muscle myosin heavy chain determine thick filament assembly properties. J.Cell Biol. 2002; 156: 113-23.

178. Chi M, Zhou Y, Vedamoorthyrao S, Babu GJ, Periasamy M. Ablation of smooth muscle myosin heavy chain SM2 increases smooth muscle contraction and results in postnatal death in mice. Proc Natl Acad Sci U.S.A 2008; 105: 18614-18618.

179. Zheng Y, Chang S, Boopathi E et al. Generation of a human urinary bladder smooth muscle cell line. In Vitro Cell Dev Biol Anim 2012.

180. Simons M, Wang M, McBride OW, Kawamoto S, Yamakawa K, Gdula D, Adelstein RS, Weir L. Human nonmuscle myosin heavy chains are encoded by two genes located on different chromosomes. Circ Res 1991; 69: 530-539.

181. Sjuve R, Haase H, Ekblad E, Malmqvist U, Morano I, Arner A. Increased expression of non-muscle myosin heavy chain-B in connective tissue cells of hypertrophic rat urinary bladder. Cell Tissue Res 2001; 304: 271-278.

182. Vandekerckhove J, Weber K. At least six different actins are expressed in a higher mammal: an analysis based on the amino acid sequence of the amino-terminal tryptic peptide. J Mol Biol 1978; 126: 783-802.

183. North AJ, Gimona M, Lando Z, Small JV. Actin isoform compartments in chicken gizzard smooth muscle cells. J Cell Sci 1994; 107: 445-455.

184. Zimmerman RA, Tomasek JJ, McRae J et al. Decreased expression of smooth muscle alpha-actin results in decreased contractile function of the mouse bladder. J Urol 2004; 172: 1667-1672.

185. Kim YS, Wang Z, Levin RM, Chacko S. Alterations in the expression of the beta-cytoplasmic and the gamma-smooth muscle actins in hypertrophied urinary bladder smooth muscle. Mol Cell Biochem 1994; 131: 115-124.

186. Sobue K, Muramoto Y, Fujita M, Kakiuchi S. Purification of a calmodulin-binding protein from chicken gizzard that interacts with F-actin. Proc Natl Acad Sci U.S.A 1981; 78: 5652-5655.

187. Dingus J, Hwo S, Bryan J. Identification by monoclonal antibodies and characterization of human platelet caldesmon. J Cell Biol 1986; 102: 1748-1757.

188. Sobue K, Tanaka T, Kanda K, Ashino N, Kakiuchi S. Purification and characterization of caldesmon77: a calmodulin-binding protein that interacts with actin filaments from bovine adrenal medulla. Proc Natl Acad Sci U.S.A 1985; 82: 5025-5029.

189. Ueki N, Sobue K, Kanda K, Hada T, Higashino K. Expression of high and low molecular weight caldesmons during phenotypic modulation of smooth muscle cells. Proc Natl Acad Sci U.S.A 1987; 84: 9049-9053.

190. Hayashi K, Yano H, Hashida T, Takeuchi R, Takeda O, Asada K, Takahashi E, Kato I, Sobue K. Genomic structure of the human caldesmon gene. Proc Natl Acad Sci U.S.A 1992; 89: 12122-12126.

191. Zhang EY, Stein R, Chang S, Zheng Y, Zderic SA, Wein AJ, Chacko S. Smooth muscle hypertrophy following partial bladder outlet obstruction is associated with overexpression of non-muscle caldesmon. Am J Pathol 2004; 164: 601-612.

192. Vrhovski B, McKay K, Schevzov G, Gunning PW, Weinberger RP. Smooth muscle-specific alpha tropomyosin is a marker of fully differentiated smooth muscle in lung. J Histochem Cytochem 2005; 53: 875-883.

193. Chacko S, Eisenberg E. Cooperativity of actin-activated ATPase of gizzard heavy meromyosin in the presence of gizzard tropomyosin. J Biol Chem. 1990; 265 : 2105-2110.

194. Horiuchi KY, Chacko S. Caldesmon inhibits the cooperative turning-on of the smooth muscle heavy meromyosin by tropomyosin-actin. Biochemistry 1989; 28: 9111-9116.

195. Borovikov YS, Avrova SV, Vikhoreva NN, Vikhorev PG, Ermakov VS, Copeland O, Marston SB. C-terminal actin-binding sites of smooth muscle caldesmon switch actin between conformational states. Int J Biochem Cell Biol 2001; 33: 1151-1159.

196. Fry CH, Kanai AJ, Roosen A, Takeda M, Wood DN. Cell Biology. In *Incontinence* 4th International Consultation on Incontinence, ed P Abrams, L Cardozo, S Khoury, A Wein 2009. ISBN 0-9546956-8-2.

197. Andersson KE, Wein AJ. Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence. Pharmacol Rev 2004; 56: 581-631.

198. Harriss DR, Marsh KA, Birmingham AT, Hill SJ. Expression of muscarinic M3-receptors coupled to inositol phospholipid hydrolysis in human detrusor cultured smooth muscle cells. J Urol 1995; 154: 1241-1245.

199. Michel MC, Vrydag W. Adrenoreceptors in the lower urinary tract. Br J Pharmacol 2006; 147: S88-S119.

200. An JY, Yun HS, Lee YP, Yang SJ, Shim JO, Jeong JH, Shin CY, Kim JH, Kim DS, Sohn UD. The intracellular pathway of the acetylcholine-induced contraction in cat detrusor muscle cells. Br J Pharmacol 2002; 137: 1001-1010.

201. Jezior JR, Brady JD, Rosenstein DI, McCammon KA, Miner AS, Ratz PH. Dependency of detrusor contractions on calcium sensitization and calcium entry through LOE-908-sensitive channels. Br J Pharmacol 2001; 134: 78-87.

202. Fleichman M, Schneider T, Fetscher C, Michel MC. Signal transduction underlying carbachol-induced contraction of rat urinary bladder. II. Protein kinases. J Pharmacol Exp Ther 2004; 308: 54-58.

203. Chang S, Hypolite JA, Mohanan S, Zderic SA, Wein AJ, Chacko S. Alteration of the PKC-mediated signaling pathway for smooth muscle contraction in obstruction-induced hypertrophy of the urinary bladder. Lab Invest 2009; 89: 823-832.

204. Moore ED, Voigt T, Kobayashi YM, Isenberg G, Fay FS, Gallitelli MF, Franzini-Armstrong C. Organization of Ca^{2+} release units in excitable smooth muscle of the guinea-pig urinary bladder. Biophys J 2004; 87: 1836-1847.

205. Kamm KE, Stull JT. Dedicated myosin light chain kinases with diverse cellular functions. J Biol Chem 2001; 276: 45274530.

206. Ikebe M, Hartshorne DJ. Effects of Ca^{2+} on the conformation and enzymatic activity of smooth muscle myosin. J Biol Chem 1985; 260: 13146-13153.

207. Aksoy MO, Williams D, Sharkey EM, Hartshorne DJ. A relationship between Ca^{2+} sensitivity and phosphorylation of gizzard actomyosin. Biochem Biophys Res Comm 1976; 69: 35-41.

208. Chacko S, Conti MA, Adelstein RS. Effect of phosphorylation of smooth muscle myosin on actin activation and Ca^{2+} regulation. Proc Natl Acad Sci U.S.A 1977; 74: 129-133.

209. Butler TM, Siegman MJ. Chemical energetics of contraction in mammalian smooth muscle. Fed Proc 1982; 41: 204-208.

210. Dillon PF, Aksoy MO, Driska SP, Murphy RA. Myosin phosphorylation and the cross-bridge cycle in arterial smooth muscle. Science 1981; 211: 495-497.

211. Ihara E, MacDonald JA. The regulation of smooth muscle contractility by zipper-interacting protein kinase. Can J Physiol Pharmacol 2007; 85: 79-87.

212. Somlyo AP, Somlyo AV. Ca^{2+} sensitivity of smooth muscle and nonmuscle myosin II: modulated by G proteins, kinases, and myosin phosphatase. Physiol Rev 2003; 83: 1325-1358.

213. Kimura K, Ito M, Amano M, Chihara K, Fukata Y, Nakafuku M, Yamamori B, Feng J, Nakano T, Okawa K, Iwamatsu A, Kaibuchi K. Regulation of myosin phosphatase by Rho and Rho-associated kinase (Rho-kinase). Science 1996; 273: 245-248.

214. Eto M, Ohmori T, Suzuki M, Furuya K, Morita F. A novel protein phosphatase-1 inhibitory protein potentiated by protein kinase C. Isolation from porcine aorta media and characterization. J Biochem 1995; 118: 1104-1107.

215. Eto M, Senba S, Morita F, Yazawa M. Molecular cloning of a novel phosphorylation-dependent inhibitory protein of protein phosphatase-1 (CPI17) in smooth muscle: its specific localization in smooth muscle. FEBS Lett 1997; 410: 356-360.

216. Kitazawa T, Eto M, Woodsome TP, Khalequzzaman M. Phosphorylation of the myosin phosphatase targeting subunit and CPI-17 during Ca^{2+} sensitization in rabbit smooth muscle. J.Physiol 2003; 546: 879-889.

217. Dimopoulos GJ, Semba S, Kitazawa K, Eto M, Kitazawa T. Ca^{2+}-dependent rapid Ca^{2+} sensitization of contraction in arterial smooth muscle. Circ Res 2007; 100:121-129.

218. Bing W, Chang S, Hypolite JA, DiSanto ME, Zderic SA, Rolf L, Wein AJ, Chacko S. Obstruction-induced changes in urinary bladder smooth muscle contractility: a role for Rho kinase. Am J Physiol Renal Physiol 2003; 285: F990-997.

219. Martin F, Harricane MC, Audemard E, Pons F, Mornet D. Conformational change of turkey-gizzard caldesmon induced by specific chemical modification with carbodiimide. Eur J Biochem 1991; 195: 335-342.

220. Marston S, Burton D, Copeland O, Fraser I, Gao Y, Hodgkinson J, Huber P, Levine B, el-Mezgueldi M, Notarianni G. Structural interactions between actin, tropomyosin, caldesmon and calcium binding protein and the regulation of smooth muscle thin filaments. Acta Physiol Scand 1998; 164: 401-414.

221. Moody C, Lehman W, Craig R. Caldesmon and the structure of smooth muscle thin filaments: electron microscopy of isolated thin filaments. J Muscle Res Cell Motil 1990; 11: 176-185.

222. Horiuchi KY, Miyata H, Chacko S. Modulation of smooth muscle actomyosin ATPase by thin filament associated proteins. Biochem Biophys Res Comm 1986; 136: 962-968.

223. Lash JA, Sellers JR, Hathaway DR. The effects of caldesmon on smooth muscle heavy actomeromyosin ATPase activity and binding of heavy meromyosin to actin. J Biol Chem 1986; 261: 16155-16160.

224. Velaz L, Hemric ME, Benson CE, Chalovich JM. The binding of caldesmon to actin and its effect on the ATPase activity of soluble myosin subfragments in the presence and absence of tropomyosin. J Biol Chem 1989; 264: 9602-9610.

225. Marston SB, Fraser ID, Huber PA. Smooth muscle caldesmon controls the strong binding interaction between actin-tropomyosin and myosin. J Biol Chem 1994; 269: 32104-32109.

226. Katayama E, Scott-Woo G, Ikebe M. Effect of caldesmon on the assembly of smooth muscle myosin. J Biol Chem 1995; 270: 3919-3925.

227. Hemric ME, Chalovich JM. Characterization of caldesmon binding to myosin. J Biol Chem 1990; 265: 19672-19678.

228. Wang Z, Jiang H, Yang ZQ, Chacko S. Both N-terminal myosin-binding and C-terminal actin-binding sites on smooth muscle caldesmon are required for caldesmon-mediated inhibition of actin filament velocity. Proc Natl Acad Sci U.S.A 1997; 94: 11899-118904.

229. Yamboliev IA, Gerthoffer WT. Modulatory role of ERK MAPK-caldesmon pathway in PDGF-stimulated migration of cultured pulmonary artery SMCs. Am J Physiol Cell Physiol 2001; 280: C1680-1688.

230. Borovikov YS, Khoroshev MI, Chacko S. Comparison of the effects of calponin and a 38-kDa caldesmon fragment on formation of the “strong-binding” state in ghost muscle fibers. Biochem Biophys Res Comm 1996; 223: 240-244.

231. Pfitzer G, Strauss JD, Ruegg JC. Modulation of myosin phosphorylation-contraction coupling in skinned smooth muscle. Jap J Pharmacol 1992; 58 Suppl 2: 23P-28P.

232. Earley JJ, Su X, Moreland RS. Caldesmon inhibits active crossbridges in unstimulated vascular smooth muscle: an antisense oligodeoxynucleotide approach. Circ Res 1998; 83: 661-667.

233. Webb RC. Smooth muscle contraction and relaxation. Adv Physiol Educ 2003; 27: 201-206.

234. Rohrmann D, Zderic SA, Wein AJ, Levin RM. Effect of thapsigargin on the contractile response of the normal and obstructed rabbit urinary bladder. Pharmacology 1996; 52: 119-124.

235. Yoshikawa A, van BC, Isenberg G. Buffering of plasmalemmal Ca^{2+} current by sarcoplasmic reticulum of guinea pig urinary bladder myocytes. Am J Physiol 1996; 271: C833-841.

236. Perrino BA. Regulation of gastrointestinal motility by Ca^{2+}/calmodulin-stimulated protein kinase II. Arch Biochem Biophys. 2011; 510:174-181.

237. Zderic SA, Gong C, Hypolite J, Levin RM. Developmental aspects of excitation contraction coupling in urinary bladder smooth muscle. Adv Exp Med Biol 1995; 385: 105-115.

238. Levin RM, Levin SS, Zhao Y, Buttyan R. Cellular and molecular aspects of bladder hypertrophy. Eur Urol 1997; 32 Suppl 1: 15-21.

239. Liu L, Ishida Y, Okunade G, Shull GE, Paul RJ. Role of plasma membrane Ca^{2+}-ATPase in contraction-relaxation processes of the bladder: evidence from PMCA gene-ablated mice. Am J Physiol Cell Physiol 2006; 290: C1239-1247.

240. Narayanan N, Xu A. Phosphorylation and regulation of the Ca^{2+}-pumping ATPase in cardiac sarcoplasmic reticulum by calcium/calmodulin-dependent protein kinase. Basic Res Cardiol 1997; 92 Suppl 1: 25-35.

241. Wu C, Fry CH. Na^{+}/Ca^{2+} exchange and its role in intracellular Ca^{2+} regulation in guinea pig detrusor smooth muscle. Am J Physiol Cell Physiol 2001; 280: C1090-1096.

242. Cellular Ca^{2+} dynamics in urinary bladder smooth muscle from transgenic mice overexpressing Na^{+}-Ca^{2+} exchanger. J Pharmacol Sci 2010; 112: 373-377.

243. Wein AJ. Bladder outlet obstruction - an overview. Adv Exp Med Biol 1995; 385: 3-5.

244. Stein R, Hutcheson JC, Krasnopolsky L, Canning DA, Carr MC, Zderic SA. The decompensated detrusor V: molecular correlates of bladder function after reversal of experimental outlet obstruction. J Urol 2001; 166: 651-657.

245. Burkhard FC, Lemack GE, Zimmern PE, Lin VK, McConnell JD. Contractile protein expression in bladder smooth muscle is a marker of phenotypic modulation after outlet obstruction in the rabbit model. J Urol 2001; 165: 963-967.

246. Deng M, Mohanan S, Polyak E, Chacko S. Caldesmon is necessary for maintaining the actin and intermediate filaments in cultured bladder smooth muscle cells. Cell Motil. Cytoskeleton 2007; 64: 951-965.

247. Lin VK, McConnell JD. Effects of obstruction on bladder contractile proteins. Prog Clin Biol Res 1994; 386: 263-269.

248. Sherrington CS. Notes on the arrangement of some motor fibres in the lumbo-sacral plexus. J Physiol 1892;13: 621-772.

249. Sibley GN 1984. A comparison of spontaneous and nerve-mediated activity in bladder muscle from man, pig and rabbit. J Physiol. 354: 431-343.

250. Brading AF. A myogenic basis for the overactive bladder. Urology 1997; 50: 57-67

251. Drake MJ, Harvey IJ, Gillespie JI. Autonomous activity in the isolated guinea pig bladder. Exp Physiol 2003; 88: 19-30.

252. Meng E, Young JS and Brading AF. Spontaneous activity of mouse detrusor smooth muscle. Neurourol Urodyn 2008; 27: 79-87.

253. Kinder RB and Mundy AR. Pathophysiology of idiopathic detrusor instability and detrusor hyper-reflexia. An in vitro study of human detrusor muscle. Br J Urol 1987; 60: 509-515.

254. German K, Bedwani J, Davies J, Brading AF, Stephenson TP. Physiological and morphometric studies into the pathophysiology of detrusor hyperreflexia in neuropathic patients. J Urol 1995; 153:1678-1683.

255. Maggi CA, Manzini S, Parlani M, Conte B, Giuliani S, Meli A. The effect of nifedipine on spontaneous, drug-induced and reflexly-activated contractions of the rat urinary bladder: evidence for the participation of an intracellular calcium store to micturition contraction. Gen Pharmacol 1988; 19: 73-81.

256. de Groat WC. A neurologic basis for the overactive bladder. Urology 1997; 50: 36-52.

257. Collins C, Klausner AP, Herrick B, Koo HP, Miner AS, Henderson SC, Ratz PH. Potential for control of detrusor smooth muscle spontaneous rhythmic contraction by cyclooxygenase products released by interstitial cells of Cajal. J Cell Mol Med 2009; 13: 3236-3250.

258. Klausner AP, Johnson CM, Stike AB, Speich JE, Sabarwal V, Miner AS, Cleary M, Koo HP, Ratz PH. Prostaglandin E_2 mediates spontaneous rhythmic contraction in rabbit detrusor muscle. Can J Urol 2011; 18: 5608-5614.

259. Brown WW, Zenser TV, Davis BB. Prostaglandin E2 production by rabbit urinary bladder. Am J Physiol Renal Physiol 1980; 239: F452-458.

260. Gilmore NJ, Vane JR. Hormones released into the circulation when the urinary bladder of the anaesthetized dog is distended. Clin Sci 1971; 41: 69-83.

261. Park JM, Yang T, Arend LJ, Schnermann JB, Peters CA, Freeman MR, Briggs JP. Obstruction stimulates COX-2 expression in bladder smooth muscle cells via increased mechanical stretch. Am J Physiol Renal Physiol 1999; 276: F129-136

262. Azadzoi KM, Shinde VM, Tarcan T, Kozlowski R, Siroky MB. Increased leukotriene and prostaglandin release, and overactivity in the chronically ischemic bladder. J Urol 2003; 169: 1885-1891

263. Cardozo LD, Stanton SL, Robinson H, Hole D. Evaluation of flurbiprofen in detrusor instability. Br Med J 1980; 280: 281-282.

264. Park JM, Houck CS, Sethna NF, Sullivan LJ, Atala A, Borer JG, Cilento BG, Diamond DA, Peters CA, Retik AB, Bauer SB. Ketorolac suppresses postoperative bladder spasms after pediatric ureteral reimplantation. Anaesth Analg 2000; 91: 11-15.

265. Delaere KP, Debruyne FM, Moonen WA. The use of indomethacin in the treatment of idiopathic bladder instability Urol Int 1981; 36:124-127.

266. Meng E, Young JS, Cha TL, Sun GH, Yu DS, Brading AF.Neuronal-derived nitric oxide modulates the activity of mouse detrusor smooth muscle. Neurourol Urodyn. 2012; 31: 572-578.

267. Yanai Y, Hashitani H, Hayase M, Sasaki S, Suzuki H, Kohri K.. Role of nitric oxide/cyclic GMP pathway in regulating spontaneous excitations in detrusor smooth muscle of the guinea-pig bladder. Neurourol Urodyn 2008; 27: 446-453.

268. Zagorodnyuk VP, Gregory S, Costa M, Brookes SJ, Tramontana M, Giuliani S, Maggi CA. Spontaneous release of acetylcholine from autonomic nerves in the bladder. Br J Pharmacol 2009; 157:607-619.

269. Yossepowitch O, Gillon G, Baniel J, Engelstein D, Livne PM. The effect of cholinergic enhancement during filling cystometry: can edrophonium chloride be used as a provocative test for overactive bladder? J Urol 2001; 165:1441-1445.

270. Sui GP, Wu C, Fry CH. A description of Ca^{2+} channels in human detrusor smooth muscle. BJU Int 2003; 92: 476-482.

271. Yanai Y, Hashitani H, Kubota Y, Sasaki S, Kohri K, Suzuki H. The role of Ni^{2+}-sensitive T-type Ca^{2+} channels in the regulation of spontaneous excitation in detrusor smooth muscles of the guinea-pig bladder. BJU Int 2006; 97: 182-189.

272. Haefliger JA, Tissières P, Tawadros T, Formenton A, Bény JL, Nicod P, Frey P, Meda P. Connexins 43 and 26 are differentially increased after rat bladder outlet obstruction. Exp Cell Res 2002; 274: 216-225.

273. Mori K, Noguchi M, Matsuo M, Nomata K, Suematsu T, Kanetake H. Decreased cellular membrane expression of gap junctional protein, connexin 43, in rat detrusor muscle with chronic partial bladder outlet obstruction. Urology 2006; 65: 1254-1258.

274. Li L, Jiang C, Hao P, Li W, Song C, Song B. Changes of gap junctional cell-cell communication in overactive detrusor in rats. Am J Physiol Cell Physiol 2007; 293: C1627-1635.

275. Zhang ZB, Zhou DR, Song B. Gap junctional protein connexin 43 in rat detrusor muscle with unstable bladder. Chin Med J 2008; 121: 1698-1701.

276. Miyazato M, Sugaya K, Nishijima S, Kadekawa K, Machida N, Oshiro Y, Saito S. Changes of bladder activity and connexin 43-derived gap junctions after partial bladder-outlet obstruction in rats. Int Urol Nephrol 2009; 41: 815-821.

277. Neuhaus J, Pfeiffer F, Wolburg H, Horn LC, Dorschner W. Alterations in connexin expression in the bladder of patients with urge symptoms. BJU Int 2005; 96: 670-676.

278. Roosen A, Datta SN, Chowdhury RA, Patel PM, Kalsi V, Elneil S, Dasgupta P, Kessler TM, Khan S, Panicker J, Fry CH, Brandner S, Fowler CJ, Apostolidis A. Suburothelial myofibroblasts in the human overactive bladder and the effect of botulinum neurotoxin type A treatment. Eur Urol 2009; 55: 1440-1448.

279. Brading AF. 2006. Spontaneous activity of lower urinary tract smooth muscles: correlation between ion channels and tissue function. J Physiol 2006; 570: 13-22.

280. Fry CH, Meng E, Young JS. The physiological function of lower urinary tract smooth muscle. Auton Neurosci 2010; 154: 3-13.

281. Andersson KE, Chapple CR, Cardozo L, Cruz F, Hashim H, Michel MC, Tannenbaum C, Wein AJ. Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. Curr Opin Urol 2009; 19: 380-394.

282. Darblade B, Behr-Roussel D, Oger S, Hieble JP, Lebret T, Gorny D, Benoit G, Alexandre L, Giuliano F. Effects of potassium channel modulators on human detrusor smooth muscle myogenic phasic contractile activity: potential therapeutic targets for overactive bladder. Urology 2006; 68: 442-448.

283. Hristov KL, Chen M, Kellett WF, Rovner ES, Petkov GV. Large-conductance voltage- and Ca^{2+}-activated K^+ channels regulate human detrusor smooth muscle function. Am J Physiol Cell Physiol 2011; 301: C903-12.

284. Nielsen JS, Rode F, Rahbek M, Andersson KE, Rønn LC, Bouchelouche K, Nordling J, Bouchelouche P. Effect of the SK/IK channel modulator 4,5-dichloro-1,3-diethyl-1,3-dihydro-benzoimidazol-2-one (NS4591) on contractile force in rat, pig and human detrusor smooth muscle. BJU Int 2011; 108: 771-777.

285. Oger S, Behr-Roussel D, Gorny D, Bernabé J, Comperat E, Chartier-Kastler E, Denys P, Giuliano F. Effects of potassium channel modulators on myogenic spontaneous phasic contractile activity in human detrusor from neurogenic patients. BJU Int 2010; 108: 604-611.

286. Hashitani, Brading AF. Electrical properties of detrusor smooth muscles from the pig and human urinary bladder. Br J Pharmacol 2003; 140:146-158.

287. Parajuli SP, Soder RP, Hristov KL, Petkov GV. Pharmacological activation of small conductance calcium-activated potassium channels with naphtho[1,2-d]thiazol-2-ylamine decreases guinea pig detrusor smooth muscle excitability and contractility. J Pharmacol Exp Ther 2012; 340: 114-123.

288. Aishima M, Tomoda T, Yunoki T, Nakano T, Seki N, Yonemitsu Y, Sueishi K, Naito S, Ito Y, Teramoto N. 2006. Actions of ZD0947, a novel ATP-sensitive K^+ channel opener, on membrane currents in human detrusor myocytes. Br J Pharmacol 2006; 149: 542-550.

289. Robbins J. KCNQ potassium channels: physiology, pathophysiology, and pharmacology. Pharmacol Ther 2001; 90: 1-19.

290. Anderson UA, Carson C, McCloskey KD. KCNQ currents and their contribution to resting membrane potential and the excitability of interstitial cells of Cajal from the guinea pig bladder. J Urol 2009; 182: 330-336.

291. Streng T, Christoph T, Andersson KE. Urodynamic effects of the K^+ channel (KCNQ) opener retigabine in freely moving, conscious rats. J Urol 2004; 172: 2054-2058.

292. Petkov GV. Role of potassium ion channels in detrusor smooth muscle function and dysfunction. Nat Rev Urol 2011; 9: 30-40.

293. Li L, Jiang C, Hao P, Li W, Fan L, Zhou Z, Song B. Changes in T-type calcium channel and its subtypes in overactive detrusor of the rats with partial bladder outflow obstruction. Neurourol Urodyn 2007; 26: 870-878.

294. Yanai Y, Hashitani H, Kubota Y, Sasaki S, Kohri K, Suzuki H. The role of Ni^{2+}-sensitive T-type Ca^{2+} channels in the regulation of spontaneous excitation in detrusor smooth muscles of the guinea-pig bladder. BJU Int. 2006; 97: 182-189.

295. Fareh S, Bénardeau A, Thibault B, Nattel S. The T-type Ca^{2+} channel blocker mibefradil prevents the development of a substrate for atrial fibrillation by tachycardia-induced atrial remodeling in dogs. Circulation 1999; 100: 2191-2197.

296. Badawi JK, Li H, Langbein S, Kamp S, Guzman S, Bross S. Inhibitory effects of various L-type and T-type calcium antagonists on electrically generated, potassium- and carbachol-induced contractions of porcine detrusor muscle. J Comp Physiol B 2006; 176: 429-439.

297. Badawi JK, Li H, Langbein S, Kwon ST, Kamp S, Bross S. Inhibitory effects of L- and T-type calcium antagonists on contractions of human detrusor muscle. Eur J Clin Pharmacol 2006; 62: 347-354.

298. Aickin CC, Brading AF. Measurement of intracellular chloride in guinea-pig vas deferens by ion analysis, ^{36}chloride efflux and micro-electrodes. J Physiol 1982; 326: 139-154.

299. Li L, Jiang C, Song B, Yan J, Pan J. Altered expression of calcium-activated K and Cl channels in detrusor overactivity

of rats with partial bladder outlet obstruction. BJU Int 2008; 101: 1588-1594.

300. Sancho M, García-Pascual A, Triguero D. Presence of the Ca^{2+}-activated chloride channel anoctamin 1 in the urethra and its role in excitatory neurotransmission. Am J Physiol Renal Physiol 2012; 302: F390-400.

301. Darblade B, Behr-Roussel D, Oger S, Hieble JP, Lebret T, Gorny D, Benoit G, Alexandre L, Giuliano F. Effects of potassium channel modulators on human detrusor smooth muscle myogenic phasic contractile activity: potential therapeutic targets for overactive bladder. Urology 2006; 68: 442–448.

302. Mitchell C, Syed NI, Gurney AM, Kennedy C. A Ca^{2+}-dependent chloride current and Ca^{2+} influx via $Ca_v1.2$ ion channels play major roles in P2Y receptor-mediated pulmonary vasoconstriction. Br J Pharmacol. 2012 Feb 9. doi: 10.1111/j.1476-5381.2012.01892.x.

303. Roosen A, Wu C, Sui G, Chowdhury RA, Patel PM, Fry CH. Characteristics of spontaneous activity in the bladder trigone. Eur Urol 2009; 56: 346-353.

304. Edyvane KA, Smet PJ, Jonavicius J, Marshall VR. Regional differences in the innervation of the human ureterovesical junction by tyrosine hydroxylase-, vasoactive intestinal peptide- and neuropeptide Y-like immunoreactive nerves. J Urol 1995; 154: 262-268.

305. Kihara K, de Groat WC. Sympathetic efferent pathways projecting to the bladder neck and proximal urethra in the rat. J Auton Nerv Syst 1997; 62: 134-142.

306. Davies MR. Anatomy of the nerve supply of the rectum, bladder, and internal genitalia in anorectal dysgenesis in the male. J Paed Surg 1997; 32: 536-541.

307. Chancellor MB, Ten years single surgeon experience with botulinum toxin in the urinary tract; clinical observations and research discovery. Int Urol Nephrol 2010; 42: 383-391.

308. Tanaka ST, Ishii K, Demarco RT, Pope JC 4th, Brock JW 3rd, Hayward SW. Endodermal origin of bladder trigone inferred from mesenchymal-epithelial interaction. J Urol 2010; 183: 386-391.

309. Viana R, Batourina E, Huang H, Dressler GR, Kobayashi A, Behringer RR, Shapiro E, Hensle T, Lambert S, Mendelsohn C. The development of the bladder trigone, the center of the anti-reflux mechanism. Development 2007; 134: 3763-3769.

310. Mackie GG, Awang H, Stephens FD. The ureteric orifice: the embryologic key to radiologic status of duplex kidneys. J Paed Surg 1975; 10: 473-481.

311. Mackie GG, Stephens FD. Duplex kidneys: a correlation of renal dysplasia with position of the ureteral orifice. J Urol 1975; 114: 274-280.

312. Waldeyer W. Ueber die sogenannte Ureter-scheide. Anat Anz 1892; 6: 259-260.

313. Tanagho EA, Meyers FH, Smith DR. The trigone: anatomical and physiological considerations. I. In relation to the ureterovesical junction. J Urol 1968; 100: 623-632.

314. Tanagho EA, Smith DR, Meyers FH. The trigone: anatomical and physiological considerations. 2. In relation to the bladder neck. J Urol 1968; 100: 633-639.

315. Mendelsohn C. Using mouse models to understand normal and abnormal urogenital tract development. Organogenesis 2009; 5: 306-314.

316. DiSandro MJ, Li Y, Baskin LS, Hayward S, Cunha G. Mesenchymal-epithelial interactions in bladder smooth muscle development: epithelial specificity. J Urol 1998; 160: 1040-1046.

317. Hains DS, Sims-Lucas S, Carpenter A, Saha M, Murawski I, Kish K, Gupta I, McHugh K, Bates CM. High incidence of vesicoureteral reflux in mice with Fgfr2 deletion in kidney mesenchyma. J Urol 2010; 183: 2077-2084.

318. Pradidarcheep W, Wallner C, Dabhoiwala NF, Lamers WH. Anatomy and histology of the lower urinary tract. Handb Exp Pharmacol 2011; 202: 117-148.

319. Singh S, Robinson M, Ismail I, Saha M, Auer H, Kornacker K, Robinson ML, Bates CM, McHugh KM. Transcriptional profiling of the megabladder mouse: a unique model of bladder dysmorphogenesis. Developmental dynamics 2008. 237: 170-186.

320. Singh S, Robinson M, Nahi F, Coley B, Robinson ML, Bates CM, Kornacker K, McHugh KM. Identification of a unique transgenic mouse line that develops megabladder, obstructive uropathy, and renal dysfunction. J Am Soc Nephrol 2007; 18: 461-471.

321. Tanagho EA, Pugh RC. The anatomy and function of the ureterovesical junction. BrJ Urol 1963; 35: 1511-1565.

322. Hutch JA, The mesodermal component: its embryology, anatomy, physiology and role in prevention of vesicoureteral reflux. J Urol 1972; 108: 406-410.

323. Shafik A. Role of the trigone in micturition. J Endourol 1998; 12: 273-277.

324. Roshani H, Dabhoiwala NF, Verbeek FJ, Lamers WH. Functional anatomy of the human ureterovesical junction. Anat Rec 1996; 245: 645-651.

325. Roosen A, Wu C, Sui GP, Fry CH. Synergistic effects in neuromuscular activation and calcium-sensitization in the bladder trigone. BJU Int 2008;101: 610-614.

326. Roosen A, Fry CH, Sui G, Wu C. Adreno-muscarinic synergy in the bladder trigone: calcium-dependent and -independent mechanisms. Cell Calcium 2009; 45: 11-17.

327. Fry CH, Meng E, Young JS. The physiological function of lower urinary tract smooth muscle. Autonom Neurosci 2010; 154: 3-13.

328. Brading AF, The physiology of the mammalian urinary outflow tract. Exp Physiol 1999; 84: 215-221.

329. Kakizaki H, Fraser MO, de Groat WC. Reflex pathways controlling urethral striated and smooth muscle function in the male rat. Am J Physiol. 1997; 272: R1647-1656.

330. Yamanishi T, Chapple CR, Yasuda K, Chess-Williams R. The role of M2 muscarinic receptor subtypes mediating contraction of the circular and longitudinal smooth muscle of the pig proximal urethra. J Urol 2002;167: 397-401.

331. Sergeant GP, Hollywood MA, McHale NG, Thornbury KD. Ca^{2+} signalling in urethral interstitial cells of Cajal. J Physiol 2006; 576: 715-720.

332. Sergeant GP, Johnston L, McHale NG, Thornbury KD, Hollywood MA. Activation of the cGMP/PKG pathway inhibits electrical activity in rabbit urethral interstitial cells of Cajal by reducing the spatial spread of Ca^{2+} waves. J Physiol 2006; 574:167-181.

333. Sergeant GP, Thornbury KD, McHale NG, Hollywood MA. Interstitial cells of Cajal in the urethra. J Cell Mol Med 2006; 10: 280-291.

334. Hashitani H. Suzuki H. Properties of spontaneous Ca^{2+} transients recorded from interstitial cells of Cajal-like cells of the rabbit urethra in situ. J Physiol 2007; 583: 505-519.

335. Hashimoto Y, Ushiki T, Uchida T, Yamada J, Iwanaga T. Scanning electron microscopic observation of apical sites of open-type paraneurons in the stomach, intestine and urethra. Arch Histol Cytol 1999; 62: 181-189.

336. Vittoria A, La Mura E, Cocca T, Cecio A., Serotonin-, somatostatin- and chromogranin A-containing cells of the urethro-prostatic complex in the sheep. An immunocytochemical and immunofluorescent study. J Anat 1990; 171: 169-178.

337. Fowler CJ, Griffiths D de Groat WC The neural control of micturition. Nature Rev, Neurosci, 2008; 9: 453-466.

338. Wallner C, Dabhoiwala NF, DeRuiter MC, Lamers WH. The anatomical components of urinary continence. Eur Urol. 2009; 55: 932-943.

339. Cheng CL, de Groat WC. Effect of ovariectomy on external urethral sphincter activity in anesthetized female rats. J Urol. 2011; 186: 334-340.

340. DasGupta R, Fowler CJ. The management of female void-

ing dysfunction: Fowler's syndrome - a contemporary update. Curr Opin Urol. 2003; 13: 293-299.

341. Kessler TM, Fowler CJ. Sacral neuromodulation for urinary retention. Nat Clin Pract Urol 2008; 5: 657-66.

342. Sadananda P, Vahabi B, Drake MJ. Bladder outlet physiology in the context of lower urinary tract dysfunction. Neurourol Urodyn 2011; 30: 708-713.

343. Mahfouz W, Corcos J. Management of detrusor external sphincter dyssynergia in neurogenic bladder. Eur J Phys Rehabil Med 2011; 47: 639-650.

344. Kinebuchi Y, Aizawa N, Imamura T, Ishizuka O, Igawa Y, Nishizawa O. Autologous bone-marrow-derived mesenchymal stem cell transplantation into injured rat urethral sphincter. Int J Urol 2010; 17: 359-368.

345. Corcos J, Loutochin O, Campeau L, Eliopoulos N, Bouchentouf M, Blok B, Galipeau J. Bone marrow mesenchymal stromal cell therapy for external urethral sphincter restoration in a rat model of stress urinary incontinence. Neurourol Urodyn 2011; 30: 447-455.

346. Surcel C, Savu C, Chibelean C, Iordache A, Mirvald C, Sinescu I. Comparative analysis of different surgical procedures for female stress urinary incontinence. Is stem cell implantation the future? Rom J Morphol Embryol. 2012; 53: 151-154.

347. Carr LK, Steele D, Steele S, Wagner D, Pruchnic R, Jankowski R, Erickson J, Huard J, Chancellor MB. 1-year follow-up of autologous muscle-derived stem cell injection pilot study to treat stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008;19: 881-883.

348. Coffey DS, The molecular biology of a prostate. In: *Prostatic Diseases* 1993; H Lepor, RK Lawson (Eds.): p 28-56. Philadelphia: W.B. Saunders.

349. Farnsworth WE. Prostate stroma: physiology. The Prostate 1999; 38: 60-72.

350. Huggins C. The physiology of a prostate gland. Physiol Rev 1945; 25: 281-295.

351. Brandes D. Prostate gland: embryology, anatomy and histology. In: *Uropathology*, 1989; GS Hill (Ed): p 1165-1180. Churchill Livingstone, New York.

352. Parsons SJ, Lipshultz LI. The effects of prostatic secretions on male fertility. In: T*he Prostate* 1989; JM Fitzpatrick, RJ Krane (Eds): p 53-59. Churchill Livingstone, New York.

353. Caine M, Raz S, Zeigler M. Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. Br J Urol 1975; 47: 193-202.

354. Hedlund H, Andersson KE, Larsson B. Alpha-adrenoceptors and muscarinic receptors in the isolated human prostate. J Urol 1985; 134: 1291-1298.

355. Hedlund P, Ekström P, Larsson B, Alm P, Andersson KE. Heme oxygenase and NO-synthase in the human prostate--relation to adrenergic, cholinergic and peptide-containing nerves. J Auton Nerv Syst 1997 14; 63: 115-126.

356 Crowe R, Milner P, Lincoln J, Burnstock G. Histochemical and biochemical investigation of adrenergic, cholinergic and peptidergic innervation of the rat ventral prostate 8 weeks after streptozotocin-induced diabetes. J Auton Nerv Syst. 1987; 20: 103-112.

357 Gu J, Polak JM, Probert L, Islam KN, Marangos PJ, Mina S, Adrian TE, McGregor GP, O'Shaughnessy DJ, Bloom SR. Peptidergic innervation of the human male genital tract. J Urol 1983; 130 386-391.

358 Hedlund P, Larsson B, Alm P, Andersson KE. Nitric oxide synthase-containing nerves and ganglia in the dog prostate: a comparison with other transmitters. Histochem J 1996; 28: 635-642.

359 Kaleczyc J, Timmermans JP, Majewski M, Lakomy M, Scheuermann DW. Immunohistochemical properties of nerve fibres supplying accessory male genital glands in the pig. A colocalisation study. Histochem Cell Biol 1999; 111: 217-228.

360 Higgins JR, Gosling JA. Studies on the structure and intrinsic innervation of the normal human prostate. Prostate Suppl. 1989; 2: 5-16.

361. Kwan PW, Merk FB, Leav I, Ofner P. Estrogen-mediated exocytosis in the glandular epithelium of prostates in castrated and hypophysectomized dogs. Cell Tissue Res 1982; 226: 689-693.

362. Abbou CC, Salomon L, Chopin D, Ravery V, Haillot O. [The current approach to the management of benign hypertrophy of the prostate]. Ann Urol (Paris) 1996; 30: 294-301

363. Rodrigues AO, Machado MT, Wroclawski ER. Prostate innervation and local anesthesia in prostate procedures. Rev Hosp Clin Fac Med Sao Paulo 2002; 57: 287-292.

364. Pennefather JN, Lau WA, Mitchelson F, Ventura S. The autonomic and sensory innervation of the smooth muscle of the prostate gland: a review of pharmacological and histological studies. J Auton Pharmacol 2000; 20: 193-206.

365. Ventura S, Pennefather J, Mitchelson F. Cholinergic innervation and function in the prostate gland. Pharmacol Ther 2002; 94: 93-112.

366. Witte LP, Chapple CR, de la Rosette JJ, Michel MC. Cholinergic innervation and muscarinic receptors in the human prostate. Eur Urol 2008; 54: 326-334.

367. Lepor H. Alpha blockers for the treatment of benign prostatic hyperplasia. Rev Urol. 2007; 9: 181-190.

368. Ventura S, Oliver V, White CW, Xie JH, Haynes JM, Exintaris B. Novel drug targets for the pharmacotherapy of benign prostatic hyperplasia (BPH). Br J Pharmacol 2011; 163: 891-907.

369. Tarter TH, Vaughan ED Jr. Inhibitors of 5alpha-reductase in the treatment of benign prostatic hyperplasia. Curr Pharm Des 2006; 12: 775-783.

370. Parsons BA, Hashim H. Emerging treatment options for benign prostatic obstruction. Curr Urol Rep 2011; 12: 247-254.

371. American Cancer Society, Cancer facts and figures. 2012. http://www.cancer.org/Research/CancerFactsFigures/

372. Djavan B, Kazzazi A, Bostanci Y. Revival of thermotherapy for benign prostatic hyperplasia. Curr Opin Urol 2012; 22: 16-21.

373. Metcalfe C, Poon KS. Poon, Long-term results of surgical techniques and procedures in men with benign prostatic hyperplasia. Curr Urol Rep 2011; 12: 265-273.

374. Barkin J. Benign prostatic hyperplasia and lower urinary tract symptoms: evidence and approaches for best case management. Can J Urol 2011; 18 Suppl: 14-19.

375. Crawford ED, Hirst K, Kusek JW, Donnell RF, Kaplan SA, McVary KT, Mynderse LA, Roehrborn CG, Smith CP, Bruskewitz R. Effects of 100 and 300 units of onabotulinum toxin A on lower urinary tract symptoms of benign prostatic hyperplasia: a phase II randomized clinical trial. J Urol 2011; 186: 965-970.

376. Lewis RW, Kim JC, Irani D, Roberts JA. The prostate of the nonhuman primate: normal anatomy and pathology. Prostate 1981; 2: 51-70.

377. Steiner MS, Couch RC, Raghow S, Stauffer D. The chimpanzee as a model of human benign prostatic hyperplasia. J Urol 1999; 162: 1454-1461.

378. McConnell JD. The pathophysiology of benign prostatic hyperplasia. J Androl 1991; 12: 356-363.

379. Broderick GA, Longhurst PA, Juniewicz PE, Wein AJ, Levin RM. A novel canine model of partial outlet obstruction secondary to prostatic hypertrophy. World J Urol 1994; 12: 245-248.

380. Mahapokai W, Van Sluijs FJ, Schalken JA. Models for studying benign prostatic hyperplasia. Prostate Cancer Prostatic Dis 2000; 3: 28-33.

381. Wennbo H, Kindblom J, Isaksson OG, Törnell J. Transgenic mice overexpressing the prolactin gene develop dramatic enlargement of the prostate gland. Endocrinology 1997; 138: 4410-4415.

382. Rosenzweig N, Horodniceanu J, Abramovici A. Phenylephrine-induced neurogenic prostatitis facilitates the promotion of PIN-like lesions in rats. Prostate 2004; 59: 107-113.

383. Abrams P, Kelleher CJ, Kerr LA, Rogers RG. Overactive bladder significantly affects quality of life. Am J Manag Care 2000; 6 :S580-590.

384. Temml C, Heidler S, Ponholzer A, Madersbacher S. Prevalence of the overactive bladder syndrome by applying the International Continence Society definition. Eur Urol 2005; 48: 622-627.

385. Apostolidis A, Brady CM, Yiangou Y, Davis J, Fowler CJ, Anand P. Capsaicin receptor TRPV1 in urothelium of neurogenic human bladders and effect of intravesical resiniferatoxin, Urology 2005; 65: 400-405.

386. Alexander S P, Mathie A, Peters JA. Guide to Receptors and Channels, 5th Edition, Br Jf Pharmacol 2011;164: 1-324.

387. Dixon JS, JenPY, Gosling JA. The distribution of vesicular acetylcholine transporter in the human male genitourinary organs and its co-localization with neuropeptide Y and nitric oxide synthase. Neurourol Urodyn 2000; 19: 185-194.

388. Alexander S P, Mathie A, Peters JA. Acetylcholine receptors (muscarinic). Trends Pharmacol Sci 2001; 22: 15-18.

389. Eglen R M, Reddy H, Watson N, Challiss RA. Muscarinic acetylcholine receptor subtypes in smooth muscle. Trends Pharmacol Sci 1994; 15: 114-119.

390. Kondo S, Morita T, Tashima Y. Muscarinic cholinergic receptor subtypes in human detrusor muscle studied by labeled and nonlabeled pirenzepine, AFDX-116 and 4DAMP. Urol Int 1995; 54: 150-153.

391. Pals-Rylaarsdam R, Xu Y, Witt-Enderby P, Benovic JL, Hosey MM. Desensitization and internalization of the m2 muscarinic acetylcholine receptor are directed by independent mechanisms. J Biol Chem 1995; 270: 29004-29011.

392. Hosey MM, DebBurman SK, Pals-Rylaarsdam R, Richardson RM, Benovic JL. The role of G-protein coupled receptor kinases in the regulation of muscarinic cholinergic receptors. Prog Brain Res 1996;109: 169-179.

393. Furuya Y, Araki I, Kamiyama M, Zakoji H, Takihana Y, Takeda M. Decreased expression of G protein-coupled receptor kinases in the detrusor smooth muscle of human urinary bladder with outlet obstruction. Int J Urol 2006; 13, 1226-1232.

394. Daly DM, Chess-Williams R, Chapple C, Grundy D. The inhibitory role of acetylcholine and muscarinic receptors in bladder afferent activity. Eur Urol 2010; 58: 22-28.

395. Yoshida A, Seki M, Nasrin S, Otsuka A, Ozono S, Takeda M, Masuyama K, Araki I, Ehlert FJ, Yamada S. Characterization of muscarinic receptors in the human bladder mucosa: direct quantification of subtypes using 4-DAMP mustard. Urology 2011;78: 721.e7-e12.

396. Mansfield KJ, Chandran JJ, Vaux KJ, Millard RJ, Christopoulos A, Mitchelson FJ, Burcher E. Comparison of receptor binding characteristics of commonly used muscarinic antagonists in human bladder detrusor and mucosa. J Pharmacol Exp Ther 2009; 328: 893-899.

397. Elbadawi A. Comparative neuromorphology in animals, In The physiology of the lower urinary tract 1987; M Torrens, JF Morrison (Eds.) p 23, Springer-Verlag, Berlin.

398. Morita T, Dohkita S, Kondo S, Nishimoto T, Hirano S, Tsuchida S. Cyclic adenosine monophosphate production and contractile response induced by beta-adrenoceptor subtypes in rabbit urinary bladder smooth muscle. Urol Int 1990; 45: 10-15.

399. Takeda M, Obara K, Mizusawa T, Tomita Y, Arai K, Tsutsui T, Hatano A, Takahashi K, Nomura S. Evidence for beta3-adrenoceptor subtypes in relaxation of the human urinary bladder detrusor: analysis by molecular biological and pharmacological methods. J Pharmacol Exp Ther 1999;288: 1367-1373.

400. Fujimura T, Tamura K, Tsutsumi T, Yamamoto T, Nakamura K, Koibuchi Y, Kobayashi M, Yamaguchi O. Expression and possible functional role of the beta3-adrenoceptor in human and rat detrusor muscle. J Urol. 1999; 161: 680-685.

401. Igawa Y, Yamazaki Y, Takeda H, Hayakawa K, Akahane M, Ajisawa Y, Yoneyama T, Nishizawa O, Andersson KE. Functional and molecular biological evidence for a possible beta3-adrenoceptor in the human detrusor muscle. Br J Pharmacol 1999; 126: 819-825.

402. Nomiya M, Yamaguchi O. A quantitative analysis of mRNA expression of alpha 1 and beta-adrenoceptor subtypes and their functional roles in human normal and obstructed bladders, J Urol 2003; 170:: 649-653.

403. Tanaka Y, Horinouchi T, Koike K. New insights into beta-adrenoceptors in smooth muscle: distribution of receptor subtypes and molecular mechanisms triggering muscle relaxation. Clin Exp Pharmacol Physiol 2005; 32: 503-514.

404. Sawa M, Harada H. Recent developments in the design of orally bioavailable beta3-adrenergic receptor agonists. Curr Med Chem 2006; 13: 25-37.

405. Hicks A, McCafferty GP, Riedel E, Aiyar N, Pullen M, Evans C, Luce TD, Coatney RW, Rivera GC, Westfall TD, Hieble JP. GW427353 (solabegron), a novel, selective beta3-adrenergic receptor agonist, evokes bladder relaxation and increases micturition reflex threshold in the dog. J Pharmacol Exp Ther 2007; 323: 202-209.

406. Leon LA, Hoffman BE, Gardner SD, Laping NJ, Evans C, Lashinger ES, Su X. Effects of the beta 3-adrenergic receptor agonist disodium 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzo dioxole-2,2-dicarboxylate (CL-316243) on bladder micturition reflex in spontaneously hypertensive rats. J Pharmacol Exp Ther 2008; 326: 178-185.

407. Masunaga K, Chapple CR, McKay NG, Yoshida M, Sellers DJ. The beta3-adrenoceptor mediates the inhibitory effects of beta-adrenoceptor agonists via the urothelium in pig bladder dome. Neurourol Urodyn 2010; 29: 1320-1325.

408. Tyagi P, Thomas CA, Yoshimura N, Chancellor MB. Investigations into the presence of functional Beta1, Beta2 and Beta3-adrenoceptors in urothelium and detrusor of human bladder. Int Braz J Urol 2009; 35: 76-83.

409. Galve-Roperh I, Sánchez C, Cortés ML, Gómez del Pulgar T, Izquierdo M, Guzmán M. Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. Nat Med 2000; 6: 313-319.

410. Bifulco M, Laezza C, Portella G, Vitale M, Orlando P, De Petrocellis L, Di Marzo V. Control by the endogenous cannabinoid system of ras oncogene-dependent tumor growth. FASEB J 2001;15: 2745-2747.

411. Sanchez, C., de Ceballos, M. L., del Pulgar, T. G., Rueda, D., Corbacho, C., Velasco, G., Galve-Roperh, I., Huffman, J. W., Ramon y Cajal, S., and Guzman, M. (2001) Inhibition of glioma growth in vivo by selective activation of the CB_2 cannabinoid receptor. Cancer Res 2001; 61: 5784-5789.

412. Casanova ML, Blázquez C, Martínez-Palacio J, Villanueva C, Fernández-Aceñero MJ, Huffman JW, Jorcano JL, Guzmán M. Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors. J Clin Invest. 2003; 111: 43-50.

413. Guzman M. Cannabinoids: potential anticancer agents. Nat Rev Cancer 2003; 3: 745-755.

414. Klein TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol 2005; 5: 400-411.

415. Howlett AC, Qualy JM, Khachatrian LL. Involvement of Gi in the inhibition of adenylate cyclase by cannabimimetic drugs. Mol Pharmacol. 1986; 29: 307-313.

416. Devane WA, Dysarz FA 3rd, Johnson MR, Melvin LS, Howlett AC. .Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 1988; 34: 605-613.

417. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA Nature 1990; 346: 561-564.

418. Gérard CM, Mollereau C, Vassart G, Parmentier M. Molecular cloning of a human cannabinoid receptor which is also expressed in testis. Biochem J 1991; 279: 129-134.

419. Galiègue S, Mary S, Marchand J, Dussossoy D, Carrière D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. Eur J Biochem 1995; 232: 54-61.

420. Straiker AJ, Maguire G, Mackie K, Lindsey J. Localization of cannabinoid CB1 receptors in the human anterior eye and retina. Invest Ophthalmol Vis Sci 1999; 40: 2442-2448.

421. Liu J, Gao B, Mirshahi F, Sanyal AJ, Khanolkar AD, Makriyannis A, Kunos G. Functional CB1 cannabinoid receptors in human vascular endothelial cells. Biochem J 2000; 346: 835-840.

422. Pagotto U, Marsicano G, Fezza F, Theodoropoulou M, Grübler Y, Stalla J, Arzberger T, Milone A, Losa M, Di Marzo V, Lutz B, Stalla GK. Normal human pituitary gland and pituitary adenomas express cannabinoid receptor type 1 and synthesize endogenous cannabinoids: first evidence for a direct role of cannabinoids on hormone modulation at the human pituitary level. J Clin Endocrinol Metab 2001; 86: 2687-2696.

423. Pertwee RG. Evidence for the presence of CB1 cannabinoid receptors on peripheral neurones and for the existence of neuronal non-CB1 cannabinoid receptors. Life Sci 1999; 65: 597-605.

424. Munro S, Thomas K, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993; 365, 61-65.

425. Mukerji G, Yiangou Y, Agarwal SK, Anand P. Increased cannabinoid receptor 1-immunoreactive nerve fibers in overactive and painful bladder disorders and their correlation with symptoms. Urology 2010; 75: 514 e1515-1520.

426. Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Mult Scler 2004; 10: 425-433.

427. Capasso R, Aviello G, Borrelli F, Romano B, Ferro M, Castaldo L, Montanaro V, Altieri V, Izzo AA. Inhibitory effect of standardized cannabis sativa extract and its ingredient cannabidiol on rat and human bladder contractility. Urology 2011; 77: 1006.e9-1006.e15.

428. Strittmatter F, Gandaglia G, Benigni F, Bettiga A, Rigatti P, Montorsi F, Gratzke C, Stief C, Colciago G, Hedlund P. Expression of fatty acid amide hydrolase (FAAH) in human, mouse, and rat urinary bladder and effects of FAAH inhibition on bladder function in awake rats. Eur Urol 2012; 61: 98-106.

429. Miyazato M, Sasatomi K, Hiragata S, Sugaya K, Chancellor MB, de Groat WC, Yoshimura N. GABA receptor activation in the lumbosacral spinal cord decreases detrusor overactivity in spinal cord injured rats. J Urol. 2008; 179: 1178-1183.

430. Kim YT, Kwon DD, Kim J, Kim DK, Lee JY, Chancellor MB. Gabapentin for overactive bladder and nocturia after anticholinergic failure. Int Braz J Urol 2004; 30: 275-278.

431. Carbone A, Palleschi G, Conte A, Bova G, Iacovelli E, Bettolo CM, Pastore A, Inghilleri M. Gabapentin treatment of neurogenic overactive bladder. Clin Neuropharmacol. 2006; 29: 206-214.

432. De Blasi A, Conn PJ, Pin J, Nicoletti F. Molecular determinants of metabotropic glutamate receptor signaling. Trends Pharmacol Sci 2001; 22: 114-120.

433. Wollmuth LP, Sobolevsky AI. Structure and gating of the glutamate receptor ion channel. Trends Neurosci 2004; 27: 321-328.

434. Yoshiyama M, Roppolo JR, de Groat WC. Effects of MK-801 on the micturition reflex in the rat - possible sites of action. J Pharmacol Exp Ther 1993; 265: 844-850.

435. Yoshiyama M, Roppolo JR, de Groat WC. Effects of LY215490, a competitive alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist, on the micturition reflex in the rat. J Pharmacol Exp Ther 1997; 280: 894-904.

436. Matsuura S, Downie JW, Allen GV. Micturition evoked by glutamate microinjection in the ventrolateral periaqueductal gray is mediated through Barrington's nucleus in the rat. Neuroscience 2000;101: 1053-1061.

437. Yoshiyama M, Araki I, Zakohji H, Kobayashi H, Du S, Aiba A, Takeda M. Role of metabotropic glutamate receptor subtype 1 in afferent processing of reflex micturition in mice. J Urol 2007;177: 84.

438 Larson JA, Ogagan PD, Chen G, Shen B, Wang J, Roppolo JR, de Groat WC, Tai C. Involvement of metabotropic glutamate receptor 5 in pudendal inhibition of nociceptive bladder activity in cats. J Physiol. 2011; 589: 5833-5843.

439. Hu Y, Dong L, Sun B, Guillon MA, Burbach LR, Nunn PA, Liu X, Vilenski O, Ford AP, Zhong Y, Rong W. The role of metabotropic glutamate receptor mGlu5 in control of micturition and bladder nociception. Neurosci Lett. 2009; 450: 12-17.

440. Narumiya S, Sugimoto Y, Ushikubi F. Prostanoid receptors: structures, properties, and functions. Physiol Rev 1999; 79: 1193-1226.

441. Breyer RM, Bagdassarian CK, Myers SA, Breyer MD. Prostanoid receptors: subtypes and signaling. Ann Rev Pharmacol Toxicol 2001; 41: 661-690.

442. Schneider T, Hein P, Michel, M C. Signal transduction underlying carbachol-induced contraction of rat urinary bladder. I. Phospholipases and Ca^{2+} sources, J Pharmacol Exp Ther 2004; 308: 47-53.

443. Yokoyama O, Yusup A, Oyama N, Aoki Y, Miwa Y, Akino H. Improvement in bladder storage function by tamsulosin depends on suppression of C-fiber urethral afferent activity in rats. J Urol 2007; 177: 771-775.

444. Chuang YC, Yoshimura N, Huang CC, Wu M, Tyagi P, Chancellor MB. Expression of E-series prostaglandin (EP) receptors and urodynamic effects of an EP4 receptor antagonist on cyclophosphamide-induced overactive bladder in rats. BJU Int 2010; 106: 1782-1787.

445. Beppu M, Araki I, Yoshiyama M, Du S, Kobayashi H, Zakoji H, Takeda M. Bladder outlet obstruction induced expression of prostaglandin E2 receptor subtype EP4 in the rat bladder: a possible counteractive mechanism against detrusor overactivity. J Urol 2011; 186: 2463-2469.

446. Yuanjun J, Kobayashi H, Sawada N, Yoshiyama M, Mochizuki, Zakoji H, Araki I, Takeda M. The expression of prostaglandin E2 receptors (EP1, 2, 3, and 4) in the human urinary bladder epithelium of normal and bladder outlet obstruction. J Urol 2008; 179: 452.

447. Green SA, Alon A, Ianus J, McNaughton KS, Tozzi CA, Reiss TF. Efficacy and safety of a neurokinin-1 receptor antagonist in postmenopausal women with overactive bladder with urge urinary incontinence. J Urol 2006;176: 2535-2540

448. Ballet S, Aubel B, Mauborgne A, Poliénor H, Farré A, Cesselin F, Hamon M, Bourgoin AS. The novel analgesic, cizolirtine, inhibits the spinal release of substance P and CGRP in rats. Neuropharmacology 2001; 40: 578-589.

449. Matthew IR, Ogden GR, Frame JW, Wight AJ. Dose response and safety of cizolirtine citrate (E-4018) in patients with pain following extraction of third molars. Curr Med Res Opin. 2000; 16: 107-114.

450. Aubel B, Kayser V, Mauborgne A, Farré A, Hamon M, Bourgoin S. Antihyperalgesic effects of cizolirtine in diabetic rats: behavioral and biochemical studies. Pain 2004;110: 22-32.

451. Aubel B, Kayser V, Farré A, Hamon M, Bourgoin S. Evidence for adenosine- and serotonin-mediated antihyperalgesic effects of cizolirtine in rats suffering from diabetic neuropathy. Neuropharmacology 2007; 52: 487-496.

452. Alvarez I, Andreu F, Buxens J, Colombo M, Dordal A, Fort M, Gutiérrez B, Farré AJ. Pharmacology of cizolirtine: a new analgesic agent. Methods Find Exp Clin Pharmacol 2000; 22: 211-221.

453. Martínez-García R, Abadías M, Arañó P, Perales L, Ruíz JL,

Sust M, Conejero J; ESCLIN 006/00 study group. Cizolirtine citrate, an effective treatment for symptomatic patients with urinary incontinence secondary to overactive bladder: a pilot dose-finding study. Eur Urol 2009; 56:1184-90.

454. Kaan TK, Yip PK, Grist J, Cefalu JS, Nunn PA, Ford AP, Zhong Y, McMahon SB. Endogenous purinergic control of bladder activity via presynaptic $P2X_3$ and $P2X_{2/3}$ receptors in the spinal cord, J Neurosci 2010; 30: 4503-4507.

455. Kim JC, Yoo JS, Park EY, Hong SH, Seo SI, Hwang TK. Muscarinic and purinergic receptor expression in the urothelium of rats with detrusor overactivity induced by bladder outlet obstruction. BJU Int 2008; 101: 371-375.

456. Ito K, Iwami A, Katsura H, Ikeda M. Therapeutic effects of the putative $P2X_3$/$P2X_{2/3}$ antagonist A-317491 on cyclophosphamide-induced cystitis in rats. Naunyn Schmied Arch Pharmacol 2008; 377: 483-490.

457. Sun B, Li Q, Dong L, Rong W. (2010) Ion channel and receptor mechanisms of bladder afferent nerve sensitivity. Auton Neurosci 201 153, 26-32.

458. Moore KH, Ray FR, Barden JA. Loss of purinergic $P2X_3$ and $P2X_2$ receptor innervation in human detrusor from adults with urge incontinence. J Neurosci 2001; 21, RC166.

459. Olsen SM, Stover JD, Nagatomi J. (2011) Examining the role of mechanosensitive ion channels in pressure mechanotransduction in rat bladder urothelial cells. Ann Biomed Eng 2011; 39: 688-697.

460. Kobayashi H, Yoshiyama M, Zakoji H, Takeda M, Araki I. Sex differences in the expression profile of acid-sensing ion channels in the mouse urinary bladder: a possible involvement in irritative bladder symptoms. BJU Int 2009; 104: 1746-1751.

461. Kullmann FA, Shah MA, Birder LA, de Groat WC. Functional TRP and ASIC-like channels in cultured urothelial cells from the rat. Am J Physiol Renal Physiol 2009; 296: F892-901.

462. Corrow K, Girard BM, Vizzard MA. Expression and Response of Acid-Sensing Ion Channels (ASICs) in Urinary Bladder to Cyclophosphamide (CYP)-Induced Cystitis, Am J Physiol Renal Physiol 2010; 298: F1130-1113.

463. Sánchez-Freire V, Blanchard MG, Burkhard FC, Kessler TM, Kellenberger S, Monastyrskaya K. Acid-sensing channels in human bladder: expression, function and alterations during bladder pain syndrome. J Urol 2011; 186: 1509-1516.

464. Drummond HA, Abboud FM, Welsh MJ. Localization of beta and gamma subunits of ENaC in sensory nerve endings in the rat foot pad. Brain Res 2000; 884:1-12.

465. Ferguson DR. Urothelial function, BJU Int 1999; 84: 235-242.

466. Fricke B, Lints R, Stewart G, Drummond H, Dodt G, Driscoll M, von Düring M. Epithelial Na^+ channels and stomatin are expressed in rat trigeminal mechanosensory neurons. Cell Tissue Res. 2000; 299: 327-334.

467. Gillespie PG, Walker RG. Molecular basis of mechanosensory transduction. Nature 2001; 413: 194-202.

468. Kopp UC, Matsushita K, Sigmund RD, Smith LA, Watanabe S, Stokes JB. Amiloride-sensitive Na^+ channels in pelvic uroepithelium involved in renal sensory receptor activation. Am J Physiol 1998; 275: R1780-1792.

469. Burton TJ, Elneil S, Nelson CP, Ferguson DR. Activation of epithelial Na^+ channel activity in the rabbit urinary bladder by cAMP. Eur J Pharmacol 2000; 404: 273-280.

470. Smith PR, Mackler SA, Weiser PC, Brooker DR, Ahn YJ, Harte BJ, McNulty KA, Kleyman TR. Expression and localization of epithelial sodium channel in mammalian urinary bladder. Am J Physiol Renal Physiol 1998; 274: F91-96.

471. Araki I, Du S, Kamiyama M, Mikami Y, Matsushita K, Komuro M, Furuya Y, Takeda M. Overexpression of epithelial sodium channels in epithelium of human urinary bladder with outlet obstruction. Urology 2004; 64: 1255-1260.

472. Du S, Araki I, Mikami Y, Zakoji H, Beppu M, Yoshiyama M, Takeda M. Amiloride-sensitive ion channels in urinary bladder epithelium involved in mechanosensory transduction by modulating stretch-evoked adenosine triphosphate release. Urology. 2007; 69: 590-595.

473. Heppner TJ, Bonev AD, Nelson MT. Ca^{2+}-activated K^+ channels regulate action potential repolarization in urinary bladder smooth muscle, Am J Physiol Cell Physiol 1997; 273: C110-117.

474. Christ GJ, Day NS, Santizo C, Zhao W, Sclafani T, Karicheti V, Valcic M, Melman A. Bladder instillation of "naked" hSlo/pcDNA3 ameliorates detrusor hyperactivity in obstructed rats in vivo. Urology. 2001; 57(6 Suppl 1): 111.

475. Herrera GM, Nelson MT. Differential regulation of SK and BK channels by Ca^{2+} signals from Ca^{2+} channels and ryanodine receptors in guinea-pig urinary bladder myocytes. J Physiol 2002; 541: 483-492.

476. Herrera GM, Pozo MJ, Zvara P, Petkov GV, Bond CT, Adelman JP, Nelson MT. Urinary bladder instability induced by selective suppression of the murine small conductance calcium-activated potassium (SK3) channel. J Physiol 2003; 551: 893-903.

477. Tanaka Y, Okamoto T, Imai T, Yamamoto Y, Horinouchi T, Tanaka H, Koike K, Shigenobu K. BK_{Ca} channel activity enhances with muscle stretch in guinea-pig urinary bladder smooth muscle. Res Commun Mol Pathol Pharmacol 2003; 113-114; 247-252.

478. Oger S, Behr-Roussel D, Gorny D, Bernabé J, Comperat E, Chartier-Kastler E, Denys P, Giuliano F. Effects of potassium channel modulators on myogenic spontaneous phasic contractile activity in human detrusor from neurogenic patients. BJU Int 2011; 108: 604-611.

479. Hristov KL, Chen M, Kellett WF, Rovner ES, Petkov GV. Large-conductance voltage- and Ca^{2+}-activated K^+ channels regulate human detrusor smooth muscle function. Am J Physiol Cell Physiol 2011; 301: C903-912.

480. Christ GJ, Day NS, Day M, Santizo C, Zhao W, Sclafani T, Zinman J, Hsieh K, Venkateswarlu K, Valcic M, Melman A. Bladder injection of "naked" hSlo/pcDNA3 ameliorates detrusor hyperactivity in obstructed rats in vivo. Am J Physiol Regul Integr Comp Physiol 2001; 281: R1699-1709.

481. Meredith AL, Thorneloe KS, Werner ME, Nelson MT, Aldrich RW. Overactive bladder and incontinence in the absence of the BK large conductance Ca^{2+}-activated K^+ channel. J Biol Chem 2004; 279: 36746-36752.

482. Darblade B, Behr-Roussel D, Oger S, Hieble JP, Lebret T, Gorny D, Benoit G, Alexandre L, Giuliano F. Effects of potassium channel modulators on human detrusor smooth muscle myogenic phasic contractile activity: potential therapeutic targets for overactive bladder. Urology 2006; 68: 442-448.

483. Petkov GV. Role of potassium ion channels in detrusor smooth muscle function and dysfunction, Nat Rev Urol 2012; 9: 30-40.

484. Werner ME, Knorn AM, Meredith AL, Aldrich RW, Nelson MT. Frequency encoding of cholinergic- and purinergic-mediated signaling to mouse urinary bladder smooth muscle: modulation by BK channels. Am J Physiol Regul Integr Comp Physiol 2007; 292: R616-624.

485. Shieh CC, Turner SC, Zhang XF, Milicic I, Parihar A, Jinkerson T, Wilkins J, Buckner SA, Gopalakrishnan M. A-272651, a nonpeptidic blocker of large-conductance Ca^{2+}-activated K^+ channels, modulates bladder smooth muscle contractility and neuronal action potentials. Br J Pharmacol 2007;151: 798-806.

486. Andersson KE. Treatment of the overactive bladder: possible central nervous system drug targets, Urology 2002; 59: 18-24.

487. Melman A, Bar-Chama N, McCullough A, Davies K, Christ G. Plasmid-based gene transfer for treatment of erectile dysfunction and overactive bladder: results of a phase I trial. Isr Med Assoc J 2007; 9: 143-146.

488. Kiselyov K, Soyombo A, Muallem S. TRPpathies. J Physiol 2007; 578: 641-653.

489. Nilius B. TRP channels in disease. Biochim Biophys Acta 2007; 1772: 805-812.

490. de Groat WC. The urothelium in overactive bladder: passive bystander or active participant? Urology 2004; 64: 7-11.

491. Goodman M.B, Schwarz EM. Transducing touch in Caenorhabditis elegans. Ann Rev Physiol 2003; 65: 429-452.

492. Birder LA. More than just a barrier: urothelium as a drug target for urinary bladder pain. Am J Physiol Renal Physiol 2005; 289: F489-495.

493. Everaerts W, Gevaert T, Nilius B, De Ridder D. On the origin of bladder sensing: Tr(i)ps in urology. Neurourol Urodyn 2008; 27: 264-273.

494. Corey DP, García-Añoveros J, Holt JR, Kwan KY, Lin SY, Vollrath MA, Amalfitano A, Cheung EL, Derfler BH, Duggan A, Géléoc GS, Gray PA, Hoffman MP, Rehm HL, Tamasauskas D, Zhang DS. $TRPA_1$ is a candidate for the mechanosensitive transduction channel of vertebrate hair cells. Nature 2004; 432: 723-730.

495. Story GM, Peier AM, Reeve AJ, Eid SR, Mosbacher J, Hricik TR, Earley TJ, Hergarden AC, Andersson DA, Hwang SW, McIntyre P, Jegla T, Bevan S, Patapoutian A. $ANKTM_1$, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell 2003; 112: 819-829.

496. Du S, Araki I, Kobayashi H, Zakoji H, Sawada N, Takeda M. Differential expression profile of cold (TRPA1) and cool (TRPM8) receptors in human urogenital organs. Urology 2008; 72: 450-455.

497. Du S, Araki I, Yoshiyama M, Nomura T, Takeda M. Transient receptor potential channel A1 involved in sensory transduction of rat urinary bladder through C-fiber pathway. Urology 2007; 70: 826-831.

498. Andrade EL, Ferreira J, André E, Calixto JB. Contractile mechanisms coupled to $TRPA_1$ receptor activation in rat urinary bladder. Biochem Pharmacol 2006; 72: 104-114.

499. Tsukimi Y, Mizuyachi K, Yamasaki T, Niki T, Hayashi F. Cold response of the bladder in guinea pig: involvement of transient receptor potential channel, $TRPM_8$. Urology 2005; 65: 406-410.

500. Mukerji G, Yiangou Y, Corcoran SL, Selmer IS, Smith GD, Benham CD, Bountra C, Agarwal SK, Anand P. Cool and menthol receptor $TRPM_8$ in human urinary bladder disorders and clinical correlations. BMC Urol 2006; 6: 6.

501. Hayashi T, Kondo T, Ishimatsu M, Yamada S, Nakamura K, Matsuoka K, Akasu T. Expression of the $TRPM_8$-immunoreactivity in dorsal root ganglion neurons innervating the rat urinary bladder. Neurosci Res 2009; 65: 245-251.

502. Benham CD, Davis JB, Randall AD. Vanilloid and TRP channels: a family of lipid-gated cation channels, Neuropharmacology 2002; 42: 873-888.

503. Gunthorpe MJ, Benham CD, Randall A, Davis JB. The diversity in the vanilloid (TRPV) receptor family of ion channels, Trends Pharmacol Sci 2002; 23: 183-191.

504. Nilius B, Watanabe H, Vriens J. The $TRPV_4$ channel: structure-function relationship and promiscuous gating behaviour. Pflugers Arch 2003; 446: 298-303.

505. Nilius B, Vriens J, Prenen J, Droogmans G, Voets T. $TRPV_4$ calcium entry channel: a paradigm for gating diversity. Am J Physiol Cell Physiol 2004; 286: C195-205.

506. Chung MK, Lee H, Mizuno A, Suzuki M, Caterina MJ. 2-aminoethoxydiphenyl borate activates and sensitizes the heat-gated ion channel $TRPV_3$. J Neurosci 2004; 24: 5177-5182.

507. 130. Hu HZ, Gu Q, Wang C, Colton CK, Tang J, Kinoshita-Kawada M, Lee LY, Wood JD, Zhu MX. 2-aminoethoxydiphenyl borate is a common activator of TRPV1, TRPV2, and $TRPV_3$. J Biol Chem 2004; 279: 35741-35748.

508. Avelino A, Cruz F. TRPV1 (vanilloid receptor) in the urinary tract: expression, function and clinical applications. Naunyn Schmied Arch Pharmacol 2006; 373: 287-299.

509. Nilius B, Owsianik G, Voets T, Peters JA. Transient receptor potential cation channels in disease.Physiol Rev 2007; 87: 165-217.

510. Sharif Naeini R, Witty MF, Seguela P, Bourque CW. An N-terminal variant of Trpv1 channel is required for osmosensory transduction. Nat Neurosci 2006; 9: 93-98.

511. Ciura S, Bourque CW. Transient receptor potential vanilloid 1 is required for intrinsic osmoreception in organum vasculosum lamina terminalis neurons and for normal thirst responses to systemic hyperosmolality. J Neurosci 2006; 26: 9069-9075.

512. Daly D, Rong W, Chess-Williams R, Chapple C, Grundy D. Bladder afferent sensitivity in wild-type and $TRPV_1$ knockout mice. J Physiol 2007; 583: 663-674.

513. Brady CM, Apostolidis AN, Harper M, Yiangou Y, Beckett A, Jacques TS, Freeman A, Scaravilli F, Fowler CJ, Anand P. Parallel changes in bladder suburothelial vanilloid receptor $TRPV_1$ and pan-neuronal marker PGP9.5 immunoreactivity in patients with neurogenic detrusor overactivity after intravesical resiniferatoxin treatment. BJU Int 2004; 93: 770-776.

514. Silva C, Silva J, Castro H, Reis F, Dinis P, Avelino A, Cruz F. Bladder sensory desensitization decreases urinary urgency. BMC Urol 2007; 7: 9.

515. Li M, Sun Y, Simard JM, Chai TC. Increased transient receptor potential vanilloid type 1 ($TRPV_1$) signaling in idiopathic overactive bladder urothelial cells. Neurourol Urodyn 2011; 30: 606-611.

516. Charrua A, Cruz CD, Narayanan S, Gharat L, Gullapalli S, Cruz F, Avelino A. GRC-6211, a new oral specific $TRPV_1$ antagonist, decreases bladder overactivity and noxious bladder input in cystitis animal models. J Urol 2009; 181: 379-386.

517. Round P, Priestley A, Robinson J. An investigation of the safety and pharmacokinetics of the novel $TRPV_1$ antagonist XEN-D0501 in healthy subjects. Br J Clin Pharmacol 2011; 72: 921-931.

518. Dmochowski R, Chapple C, Nitti VW, Chancellor M, Everaert K, Thompson C, Daniell G, Zhou J, Haag-Molkenteller C. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol 2010; 184: 2416-2422.

519. Ha US, Park EY, Kim JC. (2011) Effect of botulinum toxin on expression of nerve growth factor and transient receptor potential vanilloid 1 in urothelium and detrusor muscle of rats with bladder outlet obstruction-induced detrusor overactivity. Urology 2011; 78: 721.e1-721.e6.

520. Voets T, Talavera K, Owsianik G, Nilius B. Sensing with TRP channels. Nat Chem Biol 2005; 1: 85-92.

521. Suzuki M, Mizuno A, Kodaira K, Imai M. Impaired pressure sensation in mice lacking $TRPV_4$. J Biol Chem 2003; 278: 22664-22668.

522. Liedtke W, Friedman JM. Abnormal osmotic regulation in trpv4-/- mice. Proc Natl Acad Sci U S A 2003; 100: 13698-13703.

523. Birder L, Kullmann FA, Lee H, Barrick S, de Groat W, Kanai A, Caterina M. Activation of urothelial transient receptor potential vanilloid 4 by 4,alpha-phorbol 12,13-dideca-noate contributes to altered bladder reflexes in the rat. J Pharmacol Exp Ther 2007; 323: 227-235.

524. Gevaert T, Vriens J, Segal A, Everaerts W, Roskams T, Talavera K, Owsianik G, Liedtke W, Daelemans D, Dewachter I, Van Leuven F, Voets T, De Ridder D, Nilius B. Deletion of the transient receptor potential cation channel $TRPV_4$ impairs murine bladder voiding. J Clin Invest 2007; 117: 3453-3462.

525. Mochizuki T, Sokabe T, Araki I, Fujishita K, Shibasaki K, Uchida K, Naruse K, Koizumi S, Takeda M, Tominaga M. The $TRPV_4$ cation channel mediates stretch-evoked Ca^{2+} influx and ATP release in primary urothelial cell cultures. J Biol Chem 2009; 284: 21257-21264.

526. Angelico P, Testa R. $TRPV_4$ as a target for bladder overactivity. F1000 Biol Rep 2010; 2.

527. Everaerts W, Vriens J, Owsianik G, Appendino G, Voets T, De Ridder D, Nilius B. Functional characterization of

transient receptor potential channels in mouse urothelial cells. Am J Physiol Renal Physiol 2010; 298: F692-701.

528. Everaerts W, Zhen X, Ghosh D, Vriens J, Gevaert T, Gilbert JP, Hayward NJ, McNamara CR, Xue F, Moran MM, Strassmaier T, Uykal E, Owsianik G, Vennekens R, De Ridder D, Nilius B, Fanger CM, Voets T. Inhibition of the cation channel $TRPV_4$ improves bladder function in mice and rats with cyclophosphamide-induced cystitis. Proc Natl Acad Sci U S A 2010; 107: 19084-19089.

529. Vincent F, Duncton MA. $TRPV_4$ agonists and antagonists. Curr Top Med Chem 2011; 11: 2216-2226.

530. Macpherson LJ, Dubin AE, Evans MJ, Marr F, Schultz PG, Cravatt BF, Patapoutian A. Noxious compounds activate TRPA1 ion channels through covalent modification of cysteines. Nature 2007; 445: 541-545.

531. Hinman A, Chuang HH, Bautista DM, Julius D. TRP channel activation by reversible covalent modification. Proc Natl Acad Sci U S A 2006; 103: 19564-19568.

532. Nilius B, Voets T, Peters J. TRP channels in disease. Sci STKE 2005; 2005: re8.

533. Nagata K, Duggan A, Kumar G, García-Añoveros J. Nociceptor and hair cell transducer properties of $TRPA_1$, a channel for pain and hearing. J Neurosci 2005; 25: 4052-4061.

534. Andrade EL, Forner S, Bento AF, Leite DF, Dias MA, Leal PC, Koepp J, Calixto JB. $TRPA_1$ receptor modulation attenuates bladder overactivity induced by spinal cord injury. Am J Physiol Renal Physiol 2011; 300: F1223-1234.

535. Streng T, Axelsson HE, Hedlund P, Andersson DA, Jordt SE, Bevan S, Andersson KE, Högestätt ED, Zygmunt PM. Distribution and function of the hydrogen sulfide-sensitive $TRPA_1$ ion channel in rat urinary bladder. Eur Urol 2008; 53: 391-399.

536. Lashinger ES, Steiginga MS, Hieble JP, Leon LA, Gardner SD, Nagilla R, Davenport EA, Hoffman BE, Laping NJ, Su X. AMTB, a $TRPM_8$ channel blocker: evidence in rats for activity in overactive bladder and painful bladder syndrome. Am J Physiol Renal Physiol 2008; 295: F803-810.

537. Nomoto Y, Yoshida A, Ikeda S, Kamikawa Y, Harada K, Ohwatashi A, Kawahira K. Effect of menthol on detrusor smooth-muscle contraction and the micturition reflex in rats. Urology 2008; 72: 701-705.

538. Hayashi T, Kondo T, Ishimatsu M, Takeya M, Igata S, Nakamura K, Matsuoka K. Function and expression pattern of $TRPM_8$ in bladder afferent neurons associated with bladder outlet obstruction in rats. Auton Neurosci. 2011; 164: 27-33.

539. Shibata Y, Ugawa S, Imura M, Kubota Y, Ueda T, Kojima Y, Ishida Y, Sasaki S, Hayashi Y, Kohri K, Shimada S. $TRPM_8$-expressing dorsal root ganglion neurons project dichotomizing axons to both skin and bladder in rats. Neuroreport 2011; 22: 61-67.

540. Lesko L J, Atkinson AJ Jr. Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. Ann Rev Pharmacol Toxicol 2001; 41: 347-366.

541. Rolan P. The contribution of clinical pharmacology surrogates and models to drug development - a critical appraisal. Br J Clin Pharmacol 1997; 44: 219-225.

542. Hartwell L, Mankoff D, Paulovich A, Ramsey S, Swisher E. Cancer biomarkers: a systems approach. Nat Biotechnol 2006; 24: 905-908.

543. Madu CO, Lu Y. Novel diagnostic biomarkers for prostate cancer. J Cancer 2010; 1: 150-177.

544. Cartwright R, Afshan I, Derpapas A, Vijaya G, Khullar V. Novel biomarkers for overactive bladder. Nat Rev Urol 2011; 8: 139-145.

545. Romanzi LJ, Groutz A, Heritz DM, Blaivas JG. Involuntary detrusor contractions: correlation of urodynamic data to clinical categories. Neurourol Urodyn 2001; 20: 249-257.

546. Haylen BT, Chetty N, Logan V, Schulz S, Verity L, Law M, Zhou J. Is sensory urgency part of the same spectrum of bladder dysfunction as detrusor overactivity? Int Urogynecol J Pelvic Floor Dysfunct 2007; 18: 123-128.

547. Malone-Lee J, Henshaw DJ, Cummings K. Urodynamic verification of an overactive bladder is not a prerequisite for antimuscarinic treatment response. BJU Int 2003; 92: 415-417.

548. Chung SD, Liao CH, Chen YC, Kuo HC. Urgency severity scale could predict urodynamic detrusor overactivity in patients with overactive bladder syndrome. Neurourol Urodyn 2011; 30: 1300-1304.

549. Hyman MJ, Groutz A, Blaivas JG. Detrusor instability in men: correlation of lower urinary tract symptoms with urodynamic findings. J Urol 2001; 166: 550-552.

550. Mitterberger M, Pallwein L, Gradl J, Frauscher F, Neuwirt H, Leunhartsberger N, Strasser H, Bartsch G, Pinggera GM. Persistent detrusor overactivity after transurethral resection of the prostate is associated with reduced perfusion of the urinary bladder. BJU Int 2007; 99: 831-835.

551. Tyagi P, Barclay D, Zamora R, Yoshimura N, Peters K, Vodovotz Y, Chancellor MB. Urine cytokines suggest an inflammatory response in the overactive bladder: a pilot study. Int Urol Nephrol 2010; 42: 629-635.

552. Ghoniem G, Faruqui N, Elmissiry M, Mahdy A, Abdelwahab H, Oommen M, Abdel-Mageed AB. Differential profile analysis of urinary cytokines in patients with overactive bladder. Int Urogynecol J 2011; 22: 953-961.

553. Smaldone MC, Vodovotz Y, Tyagi V, Barclay D, Philips BJ, Yoshimura N, Chancellor MB, Tyagi P. Multiplex analysis of urinary cytokine levels in rat model of cyclophosphamide-induced cystitis. Urology; 73: 421-426.

554. Yokoyama O, Miwa Y, Oyama N, Aoki Y, Ito H, Akino H. Antimuscarinic drug inhibits detrusor overactivity induced by topical application of prostaglandin E_2 to the urethra with a decrease in urethral pressure. J Urol 2007; 178: 2208-2212.

555. Takagi-Matsumoto H, Ng B, Tsukimi Y, Tajimi M. Effects of NSAIDs on bladder function in normal and cystitis rats: a comparison study of aspirin, indomethacin, and ketoprofen. J Pharmacol Sci 2004; 95: 458-465.

556. Yamauchi H, Akino H, Ito H, Aoki Y, Nomura T, Yokoyama O. Urinary prostaglandin E was increased in patients with suprapontine brain diseases, and associated with overactive bladder syndrome. Urology 2010; 76: 1267 e1213-1269.

557. Aoki K, Hirayama A, Tanaka N, Yoneda T, Yoshida K, Fujimoto K, Hirao Y. A higher level of prostaglandin E_2 in the urinary bladder in young boys and boys with lower urinary tract obstruction. Biomed Res 2009; 30: 343-347.

558. Hall A, Billinton A, Giblin GM. EP_1 antagonists for the treatment of inflammatory pain. Curr Opin Drug Discov Devel 2007; 10: 597-612.

559. Andersson KE. Prostanoid receptor subtypes: new targets for OAB drugs? J Urol 2009; 182: 2099-2100.

560. Sugaya K, Nishijima S, Kadekawa K, Miyazato M, Mukouyama H. Relationship between lower urinary tract symptoms and urinary ATP in patients with benign prostatic hyperplasia or overactive bladder. Biomed Res 2009; 30: 287-294.

561. Steers WD, Kolbeck S, Creedon D, Tuttle JB. Nerve growth factor in the urinary bladder of the adult regulates neuronal form and function. J Clin Invest 1991; 88: 1709-1715.

562. Kim JC, Park EY, Hong SH, Seo SI, Park YH, Hwang TK. Changes of urinary nerve growth factor and prostaglandins in male patients with overactive bladder symptom. Int J Urol 2005; 12: 875-880.

563. Liu HT, Kuo HC. Urinary nerve growth factor levels are increased in patients with bladder outlet obstruction with overactive bladder symptoms and reduced after successful medical treatment. Urology 2008; 72: 104-108.

564. Liu HT, Chancellor MB, Kuo HC. Urinary nerve growth factor levels are elevated in patients with detrusor overactivity

and decreased in responders to detrusor botulinum toxin-A injection. Eur Urol 2009; 56: 700-706.

565. Liu HT, Chancellor MB, Kuo HC. Urinary nerve growth factor level could be a biomarker in the differential diagnosis of mixed urinary incontinence in women. BJU Int 2008; 102: 1440-1444.

566. Liu HT, Kuo HC. Urinary nerve growth factor levels are elevated in patients with overactive bladder and do not significantly increase with bladder distension. Neurourol Urodyn 2009; 28: 78-81.

567. Liu HT, Chancellor MB, Kuo HC. Decrease of urinary nerve growth factor levels after antimuscarinic therapy in patients with overactive bladder. BJU Int 2009; 103: 1668-1672.

568. Liu HT, Tyagi P, Chancellor MB, Kuo HC. Urinary nerve growth factor but not prostaglandin E2 increases in patients with interstitial cystitis/bladder pain syndrome and detrusor overactivity. BJU Int 2010; 106: 1681-1685.

569. Kuo HC, Liu HT, Chancellor MB. Urinary nerve growth factor is a better biomarker than detrusor wall thickness for the assessment of overactive bladder with incontinence. Neurourol Urodyn 2010; 29: 482-487.

570. Jacobs BL, Smaldone MC, Tyagi V, Philips BJ, Jackman SV, Leng WW, Tyagi P. Increased nerve growth factor in neurogenic overactive bladder and interstitial cystitis patients. Can J Urol 2010; 17: 4989-4994.

571. Liu HT, Kuo, HC. Urinary nerve growth factor level could be a potential biomarker for diagnosis of overactive bladder. J Urol 2008; 179: 2270-2274.

572. Chung SD, Liu HT, Lin H, Kuo HC. Elevation of serum c-reactive protein in patients with OAB and IC/BPS implies chronic inflammation in the urinary bladder. Neurourol Urodyn 2011; 30: 417-420.

573. Khullar V, Cardozo LD, Salvatore S, Hill S. Ultrasound: a noninvasive screening test for detrusor instability, Br J Obstet Gynaecol 1996; 103: 904-908.

574. Blatt AH, Titus J, Chan L. Ultrasound measurement of bladder wall thickness in the assessment of voiding dysfunction. J Urol 2008; 179: 2275-2278.

575. Oelke M, Hofner K, Wiese B, Grunewald V, Jonas U. Increase in detrusor wall thickness indicates bladder outlet obstruction (BOO) in men. World J Urol 2002; 19: 443-452.

576. Sreedhar B, Yeung CK, Leung VY, Chu CW. Ultrasound bladder measurements in children with severe primary nocturnal enuresis: pretreatment and posttreatment evaluation and its correlation with treatment outcome. J Urol 2008: 179, 1568-1572.

577. Oelke M, Hofner K, Jonas U, de la Rosette JJ, Ubbink DT, Wijkstra H. Diagnostic accuracy of noninvasive tests to evaluate bladder outlet obstruction in men: detrusor wall thickness, uroflowmetry, postvoid residual urine, and prostate volume. Eur Urol 2007: 52: 827-834.

578. Kessler TM, Gerber R, Burkhard FC, Studer UE, Danuser H. Ultrasound assessment of detrusor thickness in mencan it predict bladder outlet obstruction and replace pressure flow study? J Urol 2006; 175: 2170-2173.

579. Manieri C, Carter SS, Romano G, Trucchi A, Valenti M, Tubaro A. The diagnosis of bladder outlet obstruction in men by ultrasound measurement of bladder wall thickness. J Urol 1998; 159: 761-765.

580. Lekskulchai O, Dietz HP. Detrusor wall thickness as a test for detrusor overactivity in women. Ultrasound Obstet Gynecol 2008; 32: 535-539.

581. Kuo HC. Measurement of detrusor wall thickness in women with overactive bladder by transvaginal and transabdominal sonography. Int Urogynecol J Pelvic Floor Dysfunct 2009; 20: 1293-1299.

582. Panayi DC, Khullar V, Digesu GA, Hendricken C, Fernando R, Tekkis P. Is ultrasound estimation of bladder weight a useful tool in the assessment of patients with lower urinary tract symptoms? Int Urogynecol J Pelvic Floor Dysfunct 2009; 20: 1445-1449.

583. Chung SD, Chiu B, Kuo HC, Chuang YC, Wang CC, Guan,Z, Chancellor MB. Transabdominal ultrasonography of detrusor wall thickness in women with overactive bladder. BJU Int 2010; 105: 668-672.

584. Serati M, Salvatore S, Cattoni E, Soligo M, Cromi A, Ghezzi F. Ultrasound measurement of bladder wall thickness in different forms of detrusor overactivity. Int Urogynecol J 2010; 21: 1405-1411.

585. Morris V, Steventon N, Hazbun S, Wagg A. A cross-sectional study of ultrasound estimated bladder weight in a sample of men and women without lower urinary tract symptoms. Neurourol Urodyn 2009; 28: 995-997.

586. Muller L, Bergstrom T, Hellstrom M, Svensson E, Jacobsson B. Standardized ultrasound method for assessing detrusor muscle thickness in children. J Urol 2000; 164: 134-138.

587. Kuhn A, Genoud S, Robinson D, Herrmann G, Gunthert A, Brandner S, Raio L. Sonographic transvaginal bladder wall thickness: does the measurement discriminate between urodynamic diagnoses? Neurourol Urodyn 2011; 30: 325-328.

588. Kuhn A, Bank S, Robinson D, Klimek M, Kuhn P, Raio L. How should bladder wall thickness be measured? A comparison of vaginal, perineal and abdominal ultrasound. Neurourol Urodyn 2010; 29: 1393-1396.

589. Farag FF, Heesakkers JP. Non-invasive techniques in the diagnosis of bladder storage disorders. Neurourol Urodyn 2011;30: 1422-1428.

590. Kalantar J, Howell S, Talley J. Prevalence of faecal incontinence and associated risk factors. An underdiagnosed problem in the Australian community? Med J Australia 2002; 176: 54-57.

591. Rao SS. Pathophysiology of adult fecal incontinence. Gastroenterology. 2004; 126 (Suppl 1): S14-22.

592. Fynne L, Worsøe J, Laurberg S, Krogh K. Faecal incontinence in patients with systemic sclerosis: is an impaired internal anal sphincter the only cause? Scand J Rheumatol 2011; 40: 462-466.

593. De Ocampo S, Remes-Troche JM, Miller MJ, Rao SS.Rectoanal sensorimotor response in humans during rectal distension. Dis Colon Rectum 2007; 50: 1639-1646.

594. Stebbing JF, Brading AF, Mortensen NJ. Nitric oxide and the rectoanal inhibitory reflex: retrograde neuronal tracing reveals a descending nitrergic rectoanal pathway in a guinea-pig model. Br J Surg 1996; 83: 493-498.

595. de Lorijn F, de Jonge WJ, Wedel T, Vanderwinden JM, Benninga MA, Boeckxstaens GE. Interstitial cells of Cajal are involved in the afferent limb of the rectoanal inhibitory reflex. Gut 2005; 54: 1107-1113.

596. Cheeney G, Remes-Troche JM, Attaluri A, Rao SS. Investigation of anal motor characteristics of the sensorimotor response (SMR) using 3-D anorectal pressure topography. Am J Physiol Gastrointest Liver Physiol 2011; 300: G236-240.

597. Frenckner B, Euler CV. Influence of pudendal block on the function of the anal sphincters. Gut 1975; 16: 482-489.

598. Lestar B, Pennickx F, Kerremans R. The composition of anal basal pressure. An in vivo and in vitro study in man. Int J Colorectal Dis 1989; 4: 118-122.

599. Perry S, Shaw C, McGrother C, Matthews R, Assassa R, Dallosso H Williams K, Brittain K, Azam U, Jagger C, Mayne C, Castleden C. Prevalence of faecal incontinence in adults aged 40 years or more living in the community. Gut 2002; 50: 480-484.

600. Kaur G, Gardiner A, Duthie GS. Rectoanal reflex parameters in incontinence and constipation. Dis Colon Rectum 2002; 45: 928-933.

601. Cobine CA, Hennig GW, Bayguinov YR, Hatton WJ, Ward SM, Keef KD. Interstitial cells of Cajal in the cynomolgus monkey rectoanal region and their relationship to sympathetic and nitrergic nerves. Am J Physiol Gastrointest Liver Physiol 2010; 298: G643-656.

602. Radomirov R, Ivancheva C, Brading AF, Itzev D, Rakovska A, Negrev N. Ascending and descending reflex motor activ-

ity of recto-anal region-cholinergic and nitrergic implications in a rat model. Brain Res Bull 2009; 79: 147-155.

603. Frenckner B, Ihre T. Influence of autonomic nerves on the internal anal sphincter in man. Gut 1976; 17: 306-312.

604. Parks A, Fishlock D, Cameron J, May H. Preliminary investigation of the pharmacology of the human internal anal sphincter. Gut 1969; 10: 674-677.

605. Burleigh DE, D'Mello A, Parks AG. Responses of isolated human internal anal sphincter to drugs and electrical field stimulation. Gastroenterology 1979; 77: 484-490.

606. O'Kelly T, Brading A, Mortensen N. Nerve mediated relaxation of the human internal anal sphincter: the role of nitric oxide. Gut 1993; 34: 689-693.

607. Rayment SJ, Eames T, Simpson JA, Dashwood MR, Henry Y, Gruss H, Acheson AG, Scholefield JH, Wilson VG. Investigation of the distribution and function of alpha-adrenoceptors in the sheep isolated internal anal sphincter. Br J Pharmacol. 2010; 160: 1727-1740.

608. Banwait K, Rattan S. Role of nitric oxide in 3-adrenoceptor activation on basal tone of internal anal sphincter. Am J Physiol Gastrointest Liver Physiol 2003; 285: G547-555

609. Ballester C, Sarriá B, García-Granero E, Mata M, Milara J, Morcillo EJ, Lledó S, Cortijo J. Relaxation by beta3-adrenoceptor agonists of the isolated human internal anal sphincter. Life Sci 2010; 86: 358-364

610. Cellek S, Thangiah R, Bassil AK, Campbell CA, Gray KM, Stretton JL, Lalude O, Vivekanandan S, Wheeldon A, Winchester WJ, Sanger GJ, Schemann M, Lee K. Demonstration of functional neuronal beta3-adrenoceptors within the enteric nervous system. Gastroenterology 2007; 133: 175-183.

611. Schemann M, Hafsi N, Michel K, Kober OI, Wollmann J, Li Q, Zeller F, Langer R, Lee K, Cellek S. The β3-adrenoceptor agonist GW427353 (Solabegron) decreases excitability of human enteric neurons via release of somatostatin. Gastroenterology 2010; 138: 266-2674.

612. Rattan S, Al Haj R, De Godoy MA. Mechanism of internal anal sphincter relaxation by CORM-1, authentic CO, and NANC nerve stimulation. Am J Physiol Gastrointest Liver Physiol 2004; 287:G605-611

613. Rattan S, Regan RF, Patel CA, De Godoy MA. Nitric oxide not carbon monoxide mediates nonadrenergic noncholinergic relaxation in the murine internal anal sphincter. Gastroenterology 2005; 129: 1954-1966.

614. Terauchi A Kobayashi D, Mashimo H. Distinct roles of nitric oxide synthases and interstitial cells of Cajal in rectoanal relaxation. Am J Physiol Gastrointest Liver Physiol 2005; 289: G291-299.

615. Rogers J. Testing for and the role of anal and rectal sensation. Baillieres Clin Gastroenterol 1992; 6: 179-191.

616. Feng B, Brumovsky PR, Gebhart GF. Differential roles of stretch-sensitive pelvic nerve afferents innervating mouse distal colon and rectum. Am J Physiol Gastrointest Liver Physiol 2010; 298: G402-409.

617. Lynn PA, Chen BN, Zagorodnyuk VP, Costa M, Brookes SJ. TNBS-induced inflammation modulates the function of one class of low-threshold rectal mechanoreceptors in the guinea pig. Am J Physiol Gastrointest Liver Physiol 2008; 295: G862-871.

618. Rattan S. The internal anal sphincter: regulation of smooth muscle tone and relaxation. Neurogastroenterol Motil 2005; 17 Suppl 1: 50-59.

619. Mills K, Chess-Williams R. Pharmacology of the internal anal sphincter and its relevance to faecal incontinence. Autocoid Autonom Pharmacol 2009; 29: 85-95.

620. Carapeti EA, Kamm MA, Nicholls RJ, Phillips RK. Randomized, controlled trial of topical phenylephrine for fecal incontinence in patients after ileoanal pouch construction. Dis Colon Rectum 2000; 43: 1059-1063.

621. Carapeti EA, Kamm MA, Phillips RK. Randomized controlled trial of topical phenylephrine in the treatment of faecal incontinence. Br J Surg 2000; 87: 38-42.

622. Cheetham MJ, Kamm MA, Phillips RK. Topical phenylephrine increases anal canal resting pressure in patients with faecal incontinence. Gut 2001; 48: 356-359.

623. Mills K, Hausman N, Chess-Williams R. Characterisation of the α1-adrenoceptor subtype mediating contraction of the pig internal anal sphincter. Br J Pharmacol 2008; 155: 110-117.

624. Rattan S, Phillips BR, Maxwell PJ. RhoA/Rho-kinase: pathophysiologic and therapeutic implications in gastrointestinal smooth muscle tone and relaxation. Gastroenterology 2010; 138: 13-8.e1-3.

625. de Godoy MA, Rattan S. Role of rho kinase in the functional and dysfunctional tonic smooth muscles. Trends Pharmacol Sci 2011; 32: 384-393.

626. Patel CA, Rattan S. Spontaneously tonic smooth muscle has characteristically higher levels of RhoA/ROK compared with the phasic smooth muscle. Am J Physiol Gastrointest Liver Physiol 2006; 291: G830-837.

627. Patel CA, Rattan S. Cellular regulation of basal tone in internal anal sphincter smooth muscle by RhoA/ROCK. Am J Physiol Gastrointest Liver Physiol 2007; 292: G1747-1756.

628. Singh J, Maxwell PJ 4th, Rattan S. Immunocytochemical evidence for PDBu-induced activation of RhoA/ROCK in human internal anal sphincter smooth muscle cells. Am J Physiol Gastrointest Liver Physiol. 2011 Aug;301(2):G317-25. Epub 2011 May 12.

629. Hagger R, Gharaie S, Finlayson C, Kumar D. Distribution of the interstitial cells of Cajal in the human anorectum. J Auton Nerv Syst 1998; 73: 75-79.

630. Kito Y. The functional role of intramuscular interstitial cells of Cajal in the stomach. J Smooth Muscle Res 2011; 47: 47-53.

631. Ward SM, Beckett EA, Wang X, Baker F, Khoyi M, Sanders KM. Interstitial cells of Cajal mediate cholinergic neurotransmission from enteric motor neurons. J Neurosci 2000; 20: 1393-1403.

632. Sanders KM, Koh SD, Ward SM. Interstitial cells of cajal as pacemakers in the gastrointestinal tract. Ann Rev Physiol 2006; 68: 307–343.

633. Huizinga JD, Zarate N, Farrugia G. Physiology, injury, and recovery of interstitial cells of Cajal: basic and clinical science. Gastroenterology 2009; 137: 1548–1556.

634. McHale NG, Hollywood MA, Sergeant GP, Shafei M, Thornbury KT, Ward SM. Organization and function of ICC in the urinary tract. J Physiol 2006; 576: 689–694.

635. Duffy AM, Cobine CA, Keef KD. Changes in neuromuscular transmission in the W/W(v) mouse internal anal sphincter. Neurogastroenterol Motil 2012; 24: e41-55.

636. Ward SM, Sanders KM, Hirst GD. Role of interstitial cells of Cajal in neural control of gastrointestinal smooth muscles. Neurogastroenterol Motil 2004; 16 Suppl 1: 112-117.

637. Mongardini M, Lisi A, Giofrè M, Ledda M, Grimaldi S, Scarnò M, Trucchia A, Kyriacou AK, Badiali D, Custureri F. Human muscle-derived stem cells. Effectiveness in animal models of faecal incontinence. Research scheduling. G Chir 2011; 32: 357-360.

638. Somara S, Gilmont RR, Dennis RG, Bitar KN. Bioengineered internal anal sphincter derived from isolated human internal anal sphincter smooth muscle cells. Gastroenterology 2009; 137: 53-61.

Committee 3

Neural Control

Chair

L. Birder (USA)

Members

T. Chai (USA)

D. Griffiths (CAN)

D. Grundy (UK)

K. Thor (USA)

R. Valentino (USA)

Consultant

P. Sadananda (UK)

CONTENTS

OVERVIEW

I. UROTHELIUM

1. ANATOMY AND BARRIER FUNCTION
2. UROTHELIAL CELLS AND REPAIR
3. UROTHELIAL HETEROGENEITY
4. ROLE OF UROTHELIAL CELLS IN VISCERAL SENSATION
5. CLINICAL SIGNIFICANCE OF THE SENSORY WEB

II. AFFERENT NEURONS

1. OVERVIEW: PROPERTIES OF AFFERENT NEURONS
2. PATHWAYS TO THE SPINAL CORD
3. FUNCTIONAL PROPERTIES OF BLADDER AFFERENTS
4. MODULATING AFFERENT SENSITIVITY
5. CROSS-TALK BETWEEN THE BLADDER AND THE BOWEL

III. NEURAL CONTROL OF FEMALE PELVIC FLOOR MUSCLE AND RHAB-DOSPHNICTERS

1. STRUCTURAL ELEMENTS OF THE PELVIC FLOOR
2. PERIPHERAL INNERVATION OF THE FEMALE LEVATOR ANI (LA) MUSCLES
3. REFLEX ACTIVATION OF PELVIC FLOOR MUSCLES
4. PERIPHERAL INNERVATION OF URETHRAL AND ANAL RHABDOSPHINCTERS
5. REFLEX ACTIVATION OF URETHRAL AND ANAL RHABDOSPHINCTERS
6. INHIBITION OF URETHRAL RHABDOSPHINCTER (URS) REFLEXES DURING VOIDING
7. SUPRASPINAL ACTIVATION OF RHABDOSPHINCTERS AND PELVIC FLOOR MUSCLES
8. NEUROCHEMICAL ANATOMY OF RHABDOSPHINCTER MOTOR NEURONS
9. LA AND RHABDOSPHINCTER NEUROPATHY

IV. EFFERENT PATHWAYS TO THE BLADDER

1. PREGANGLIONIC NEURONS
2. GANGLIA
3. TERMINAL NERVE FIBERS
4. TRANSMITTERS
5. PELVIC ORGAN INTERACTIONS ATTHEEFFERENT NEURAL LEVEL
6. EFFERENT INHIBITION
7. PERIPHERAL EXCITATORY MECHANISMS

V. PONTINE-MIDBRAIN CONTROL OF BLADDER FUNCTION

1. AFFERENT PATHWAYS LINKING THE BLADDER AND URETHRA TO THE PONS AND MIDBRAIN
2. DEFINING THE CENTRAL CIRCUITRY REGULATING BLADDER FUNCTION BY TRANSNEURONAL TRACING
3. BARRINGTON'S NUCLEUS: THE PONTINE MICTURITION CENTER (PMC)
4. BARRINGTON'S NUCLEUS, THE LOCUS COERULEUS AND CENTRAL RESPONSES TO BLADDER INFORMATION
5. SUPRASPINAL INPUTS TO BARRINGTON'S NUCLEUS
6. DEFENSIVE STRATEGIES AND MICTURITION
7. COORDINATION OF BLADDER WITH OTHER PELVIC VISCERA BY BARRINGTON'S NUCLEUS
8. THE PONTINE CONTINENCE CENTER (PCC)
9. NEUROTRANSMITTERS & MODULATORS WITHIN BRAINSTEM NETWORKS CONTROLLING BLADDER

VI. FOREBRAIN CONTROL OF BLADDER FUNCTION

1. BACKGROUND
2. ROLE AND IMPORTANCE OF CEREBRAL CONTROL OF VOIDING
3. CORTICAL AND SUBCORTICAL CENTRES INVOLVED IN BLADDER CONTROL. EVIDENCE FROM OBSERVATIONS OF LESIONS AND FROM FUNCTIONAL BRAIN IMAGING IN HUMANS
4. VOIDING
5. WORKING MODEL OF BRAIN/BLADDER CONTROL
6. CONCLUSION: CORTICAL CONTROL OF BLADDER FUNCTION

VII. ABNORMAL LOWER URINARY TRACT FUNCTION

1. ABNORMALITIES INVOLVING AFFERENT SIGNALING
2. INVOLVING ABNORMAL URINE STORAGE
3. INVOLVING ABNORMAL VOIDING
4. CO-MORBID DISORDERS

Neural Control

L. Birder,

T. Chai, D. Griffiths, D. Grundy, K. Thor, R. Valentino

Consultant
P. Sadananda

OVERVIEW

This chapter deals with individual components regulating the neural control of the urinary bladder. This chapter has been completely remodeled and updated with the focus on factors and processes involved in the two models of operation of the bladder: storage and elimination. There has been significant new information since the last consultation in a number of fields:

- The urothelium and impact of various stresses on barrier as well as cell-signaling ('sensory web') as well as possible therapeutic targets
- The location and properties of bladder afferents including factors involved in regulating afferent sensitization including cross-talk between bladder and the bowel
- The neural control of the pelvic floor muscle and pharmacology of urethral and anal sphincters highlighting integral role in coordinating somatic and visceral function
- Efferent pathways to the urinary bladder
- Abnormal lower urinary tract function including abnormalities in afferent signaling, urine storage, voiding as well as co-morbid disorders associated with bladder pain syndrome and incontinence

Also incorporated are sections dealing with the current understanding of brainstem neuronal networks, which regulate lower urinary tract function[1-4]. The importance is reflected in the current advances in functional brain imaging which have had a major impact on understanding CNS control of the human bladder. This section has been completely revised to include recent advances in understanding of the central pathways regulating the control of detrusor and sphincter, discussion of homeostatic function and evidence that structural damage to critical connecting neural pathways may contribute to urgency incontinence.

Levels of Evidence

This book attempts to use Levels of Evidence throughout. The Oxford Centre for Evidence Based Medicine has laid down guidelines that apply to Levels of Therapeutic Interventions and Grades of Recommendations to Patients; the existence of dispute regarding each major conclusion should be documented. However this advice does not really apply to the basic sciences, where randomized controlled trials are not a common format of investigation, and acute studies with internal controls are more common.

Within this chapter we intend to be selective and report scientific evidence that has appropriate controls and achieves statistical significance. Other categories of evidence, e.g. uncontrolled studies, anecdotal information, hypothesis or speculation will be referred to as such.

Of some importance in this field are species differences, and efforts have been made to make it very clear when each new topic is introduced in which species the observation was made with special emphasis as to the extent comparable data exists for humans.

In this report, we intend to indicate whether the conclusions are based on (A) peer-reviewed papers in reputable journals (B) evidence in book chapters or reviews, and (C) Abstracts: abstracts will only be mentioned if they refer to a systematic study with good statistical methodology.

I. UROTHELIUM

The urothelium can be thought of as a first responder to various types of stress that can include physiological, psychological and disease-related factors. Alterations of bladder urothelium at the molecular and structural levels have been reported in both patients and animals modeled for various bladder disorders. It is likely that many therapies currently used in the treatment of bladder disease may target urothelial receptors and/or their release mechanisms.

1. ANATOMY AND BARRIER FUNCTION

The urothelium is the epithelial lining of the lower urinary tract between the renal pelvis and the urinary bladder. Urothelium is composed of at least three layers (the exact number of layers is species dependent): a basal cell layer attached to a basement membrane, an intermediate layer, and a superficial or apical layer composed of large hexagonal cells (diameters of 25-250 μm) known as 'umbrella cells'.[5-8] These umbrella cells exhibit a distinctive plasma membrane that contains both 'hinge' and 'plaque' regions **(Figure 1**). The umbrella cells (which are also termed facet or superficial cells) are interconnected by tight junctions (which are composed of multiple proteins such as the claudins) and are covered on their apical surface (nearly 70-80%) by crystalline proteins called uroplakins that assemble into hexagonal plaques.[9-11] Uroplakins and other urothelial cellular differentiation markers, such as cytokeratin 20, are not expressed in the stratified epithelium of the urethra. There have been suggestions in early studies in some species, that the umbrella cells and perhaps also the intermediate cells may have projections to the basement membrane.[6, 7]The ability of the bladder to maintain the barrier function, despite large alterations in urine volume and increases in pressure during bladder filling and emptying, is dependent on several features of the umbrella cell layer. These features include tight-junction complexes that reduce the movement of ions and solutes between cells and specialized lipid molecules and uroplakin proteins in the apical membrane, which reduce the permeability of the cells to small molecules (water, urea, protons).[7, 12] The lipid composition of the apical membrane is unusual in composition and is rich in cholesterol, phosphatidylcholine, phosphatidylethanolamine and cerebroside.[13] Recent studies suggest that liposomes, consisting of an aqueous core enclosed in one or more phospholipid bilayers, may help to restore urothelial-barrier function. Liposomes have typically been used to transport drug molecules in a variety of cells. Urothelial cells appear to take up liposomes via an endocytotic process, providing evidence for a possible mechanism by which liposomes act as a drug delivery system.[14] In addition, empty liposomes have shown promise to repair and enhance the barrier function of a dysfunctional urothelium.[15-19] (**Figure 2**)

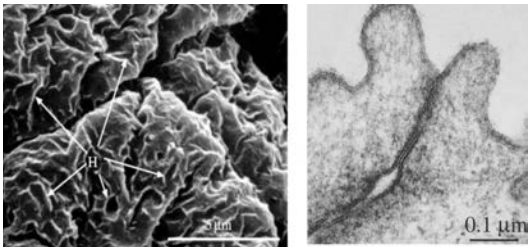


Figure 1 . Ultrastructural features of umbrella cell apical membrane. Left: Scanning electron micrograph (high magnification) of apical surface of rabbit umbrella cell layer (hinges «H» marked with arrows). Right, high power view of tight junctions. (from Apodaca, 2004; Truschel et al., 1999).

The apical surface of the urothelium is also covered with a sulfated polysaccharide glycosaminoglycan (GAG) or mucin layer that is thought to act as a nonspecific anti-adherence factor and as a defense mechanism against infection.[20-22] In addition, during bladder filling the umbrella cells become flat and squamous and this shape change is accompanied by vesicular traffic (i.e. exocytosis/endocytosis), adding membrane to the apical surface thereby increasing overall urinary bladder surface area.[11, 23, 24] This process of ongoing replacement of apical membrane by newly fused discoid vesicles also serves to maintain the urothelial barrier. [25]There is evidence that this stretch-induced exocytosis is dependent on activation of epidermal growth factor receptor (EGFR).[26, 27] These processes allow the bladder to accommodate increasing volumes of urine during filling without compromising the barrier function. There is some evidence that superficial urothelial cells exhibit a lower level of endocytotic activity, which may be a protective mechanism against internalization of toxic substances excreted in the urine.[28] Exocytosis/endocytosis (vesicular recycling) may also play an important role in modulating the release of a number of neurotransmitters/mediators as well as regulation of the function of many receptors and ion channels in urothelial cells. [29, 30]

2. UROTHELIAL CELLS AND REPAIR

Epithelial integrity is maintained through a complex process of migration and proliferation (to restore cell numbers) and differentiation (to restore function).[31] Basal cells, which are thought to be precursors for other cell types, normally exhibit a low (3-6 month) turnover rate, in fact the slowest turnover of

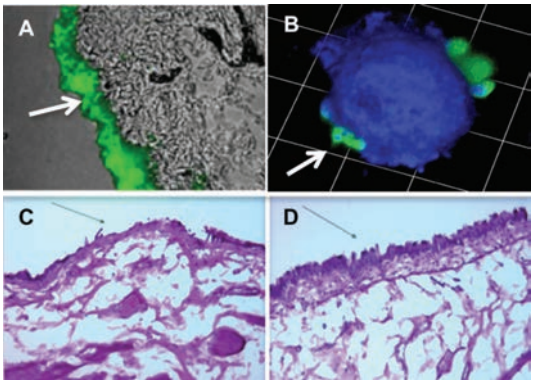


Figure 2. (A,B) Fluorescent images following application of liposomes. A, liposomes instilled in a rat bladder forming a coating (green) on urothelial surface and in B, liposomes (in green) attached to primary cultured urothelial cell membrane. In C, rats treated intravesically with protamine sulfate (PS) exhibit damaged urothelium; D, rats treated with PS followed by liposomes had intact urothelium demonstrating protective effect of liposomes (from Kaufman et al., 2009 and Nirmal et al.,2012)

any mammalian epithelial cells.[13, 32] It has been suggested that neither urine-derived factors nor cyclic mechanical changes contribute to urothelial proliferation and differentiation. However differentiation of urothelial cells in culture can be stimulated by prostaglandin (which is abundant in the urine) [9, 33] and accelerated proliferation can occur in various bladder pathologies. For example, using agents (protamine sulfate; cyclophosphamide) that damage the umbrella cell layer, it has been shown that the urothelium rapidly undergoes both functional and structural changes in order to restore the barrier in response to injury.[28, 34, 35] Following disruption of the barrier, in the early stages of regeneration the superficial cells may appear smaller in size and often covered with microvilli.[34] In some pathologies, a deficiency or defect in maturation or terminal differentiation of superficial umbrella cells have been reported, though the factors which may be involved are not yet known.[36]

The processes underlying urothelial repair is complex, involving several structural elements, signaling pathways, trophic factors and the cellular environment. Furthermore, the interaction between these biochemical signals and mechanical forces in the bladder during the course of urothelial repair is not well understood. For example, the initiation of urothelial proliferation or differentiation of intermediate cells is thought to involve up-regulation of growth factors such as fibroblast growth factor and nerve growth factor (NGF).[37, 38] In addition, members of the PPARγ and EGFR signaling pathways may contribute to urothelial 're-epithelialization' in wound repair.[33] There is also evidence that Hedgehog/Wnt signaling acting across the basal urothelial cell-stromal cell boundary, contributes to increases in urothelial proliferation in response to injury.[39] Though the urothelium maintains a tight barrier to ion and solute flux, a number of local factors or stressors such as tissue pH, mechanical or chemical trauma, hormonal changes or bacterial infection can modulate the barrier function of the urothelium.[7, 29, 40] Stress-mediated activation of the hypothalamic-pituitary-adrenal axis can result in increased production of corticotrophin releasing factor, which can regulate neuroendocrine and autonomic responses to stress. The net effect can include disruption of the epithelial barrier and increased prevalence of infection. In addition, altered levels of circulating estrogens have been associated with changes to the urothelial structure including epithelial shedding or mucosal atrophy.[41, 42] Other conditions such as bladder pain syndrome/interstitial cystitis (BPS/IC), senescence or spinal cord injury are also associated with changes in the urothelial barrier.[43, 44] Studies utilizing aged animals have demonstrated significant alterations to the bladder mucosa including areas of mucosal denudation.[45, 46] In addition, there is evidence in many types of epithelium (including uro-epithelium) that adhesion molecules such as members of the cadherin family play important roles in establishing and maintaining epithelial-cell contacts.[47] Altered urothelial-cadherin expression has been reported in BPS/IC patient bladder urothelium. Disruption of urothelial barrier integrity has also been linked to the expression of substances such as antiproliferative factor (APF), which also slows urothelial cell growth.[48-50] APF, a frizzled 8 protein detected in the urine of patients with BPS/IC, is secreted by bladder epithelial cells obtained from these patients. Treatment of urothelial cells from normal patients with purified APF decreases the expression of adhesion and tight junction proteins.

Both physiological and psychological stress can result in a failure of urothelial and suburothelial 'defensive' systems and thereby promote changes in both urothelial barrier and signaling function. For example, alterations in proteins including proteoglycans and bacterial defense molecules may lead to distinctive changes in urothelial structure and play a role in bacteria adherence.[51] In this regard, urinary tract infections produced by uropathogenic Escherichia coli (UPEC) are initiated by bacterial adherence to uroplakin proteins on the apical surface of umbrella cells.[40, 52] (**Figure 3A**) The UPEC express filamentous adhesive organelles

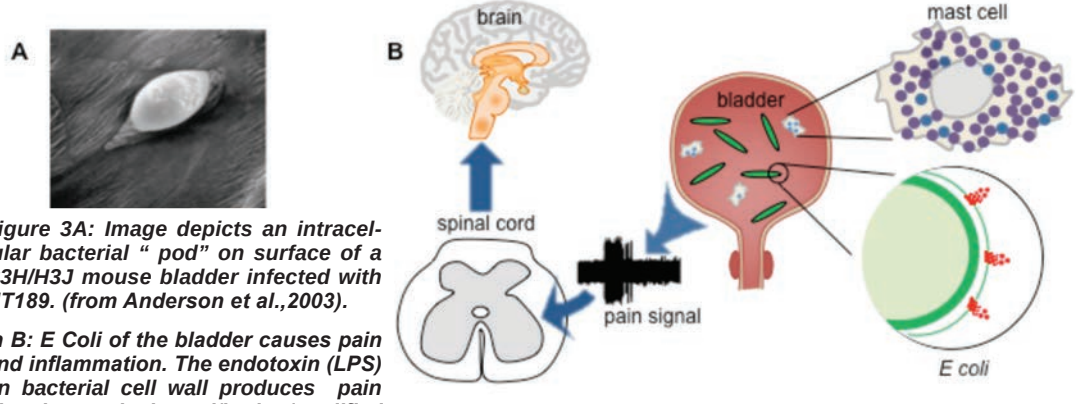


Figure 3A: Image depicts an intracellular bacterial " pod" on surface of a C3H/H3J mouse bladder infected with UT189. (from Anderson et al.,2003).

In B: E Coli of the bladder causes pain and inflammation. The endotoxin (LPS) on bacterial cell wall produces pain signals to spinal cord/brain. (modified from ICA update 2011).

(type 1 pili) that mediate bacterial attachment, invasion and apoptosis of the urothelial cells. It has been suggested that urothelial differentiation (and increased uroplakin III expression) plays a pivotal role in sensitizing urothelial cells to UPEC-induced infection and possible cell death.[53] Even acute contact (within hours) of the mucosal surface by bacteria may result in altered urothelial barrier function.[54] UPEC can also internalize within umbrella cells forming intracellular colonies (biofilm-like pods) of UPEC that has been implicated in the mechanism of chronic urinary tract infections. UPEC are able to commandeer the endocytic/exocytic machinery of urothelial cells, residing inside fusiform vesicles. [55] This permits the bacteria to escape elimination during voiding and re-emerge into the urine during distension. When expelled into the urine during the storage phase, the urine may provide a nutrient-rich environment optimizing bacterial survival. Evidence supports a role for endotoxin (lipopolysaccharide, LPS) on the bacterial cell wall in mediating the pain associated with UPEC infection.[56] (**Figure 3B**).

Disruption of urothelial function can also be induced by more remote pathological conditions that influence neural or hormonal mechanisms. For example, spinal cord transection in rats leads to a rapid alteration in the urothelial barrier including ultrastructural changes and increased permeability.[44] The changes are blocked by pretreatment with a ganglionic blocking agent, suggesting an involvement of efferent autonomic pathways in the acute effects of spinal cord injury on bladder urothelium. Other types of urothelial-neural interactions are also likely, based on the recent reports that various stimuli induce urothelial cells to release chemical mediators that can in turn modulate the activity of afferent nerves.[7, 29] This has raised the possibility that the urothelium may have a role in sensory mechanisms in the urinary tract.

In summary, modification of the urothelium and/or loss of epithelial integrity in a number of pathological conditions can result in passage of toxic/irritating urinary constituents through the urothelium or release of neuroactive substances from the urothelium. This may lead to changes in the properties of sensory nerves and in turn sensory symptoms such as urinary frequency and urgency. Thus chemical communication between the nervous system and the urothelial cells may play an important role in the generation of urinary bladder dysfunction.

3. UROTHELIAL HETEROGENEITY

Studies (comparing a number of species) have shown that the major part of the urinary tract is lined with a fully differentiated urothelium.[9] Findings in cultured cells reveal a distinct difference in morphology of ureteral and bladder urothelial cells, supporting a difference in cell lineage. Present evidence suggests at least 3 urothelial lineages: 1) those of the ureter/renal pelvis, 2) detrusor/trigone and 3) bladder neck/proximal urethra.[57] There seems to be no apparent difference between the urothelium of the trigone compared to the detrusor, in contrast to cells from the proximal urethra.[9, 58] In this region, there is a transition from urothelium to a stratified or columnar epithelium accompanied by a lack of urothelial-specific differentiation markers. In addition, peptide/amine-producing endocrine cells termed 'paraneurons' are distributed within the urethral epithelia. These cells, which are often exposed to the lumen and may share similarities to GI enterochromaffin cells, are covered with microvilli (**Figure 4**), and may also serve a sensor role for chemical as well as mechanical signals. [59] The functional significance of these findings has yet to be determined.

4. ROLES FOR UROTHELIAL CELLS IN VISCERAL SENSATION

While urothelial cells are often viewed as bystanders in the process of visceral sensation, recent evidence has supported the view that these cells function as primary transducers of some physical and chemical stimuli and are able to communicate with underlying cells including bladder nerves, smooth muscle and inflammatory cells. **(Figure 5**)

The urothelium is able to respond to a wide variety of mechanical stresses during bladder filling and emptying by activating a number of possible transducer proteins. Possibilities of mechanical signals include bladder pressure, tension in the urothelium

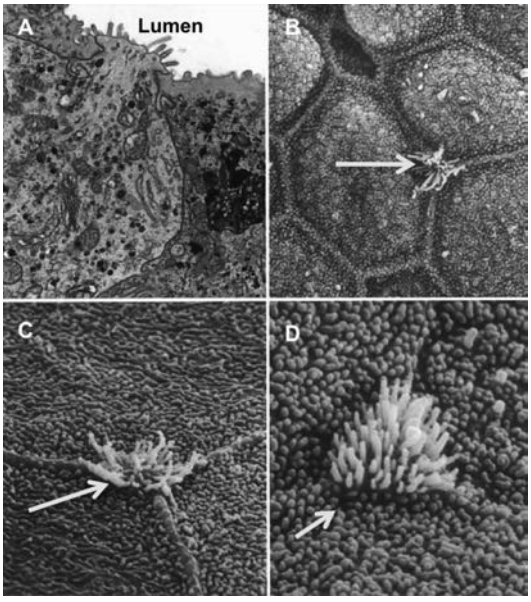


Figure 4. Images despicts " open type" paraneurons in the dog urethra. A, paraneuron reaching the lumen; B-D, Scanning EM identifies (arrows) microvillous cells among the epithelial cells. A: x14.000; b: x4600, c: x12,000, d: x16,000. (from Hashimoto et al., 1999).

or bladder wall, torsion, geometrical tension, movement of visceral organs and even urine tonicity. Alterations in the composition of urine are a type of stress whose contents can vary in both their rate of delivery as well as the particular constituents.

Additional lines of evidence suggest that urothelial cells participate in the detection of both physical and chemical stimuli. Bladder nerves (afferent and efferent) are localized in close proximity, and some within, the urothelium.[60-63] In addition, urothelial cells express numerous receptors/ion channels similar to that found in both nociceptors and mechanoreceptors. And finally, these cells secrete a number of transmitters or mediators capable of modulating, activating or inhibiting sensory neurons.

a) Urothelial-Neuronal Signaling

Recent studies have shown that both afferent and autonomic efferent nerves are located in close proximity to the urothelium. Peptidergic, P2X- and TRPV1- immunoreactive nerve fibers presumed to arise from afferent neurons in the lumbosacral dorsal root ganglia are distributed throughout the urinary bladder musculature as well as in a plexus beneath and extending into the urothelium.[29, 62] In humans with neurogenic detrusor overactivity intravesical administration of resiniferatoxin, a C-fiber afferent neurotoxin, reduces the density of TRPV1 and P2X3 immunoreactive suburothelial nerves, indicating that these are sensory nerves.[64, 65] In addition, immunohistochemical studies have also revealed both adrenergic (tyrosine hydroxylase) positive as well as cholinergic (choline acetyltransferase, ChAT) positive nerves in close proximity to the urothelium.[61]

A network of cells with morphologic characteristics similar to those of myofibroblasts or interstitial cells is also detected in the suburothelial space of the bladder in both humans and animals.[66-70] These cells, which are extensively linked by gap junctions and have close contacts with nerves, can respond to neurotransmitters, such as ATP released from nerves or urothelial cells, suggesting that they could act as intermediaries in urothelial-nerve interactions.[66, 69, 71] Thus the anatomic substrates for bidirectional urothelial-neural communication exist within the urinary bladder.

b) Involvement of the Urothelium in "Sensing" Chemical and Mechanical Stimuli

The involvement of urothelial function in sensory signaling is suggested by the finding that urothelial cells express various receptors that are linked to mechano- or nociceptive sensations. Examples of neuronal "sensor molecules" (receptors / ion channels) that have been identified in urothelium include receptors for purines (P2X [1-7] and P2Y [1,2,4]) adenosine (A1, A2a, A2b and A3), norepinephrine (α and β), acetylcholine (muscarinic and nicotinic), protease-activated receptors (PARs), amiloride- and mechanosensitive epithelial sodium channels (ENaC), bradykinin (B1 and B2), neurotrophins (p75, trkA, EGF family Erb1-3), corticotrophin releasing factor (CRF1 and CRF2), estrogens (ERα and ERβ), endothelins and various TRP channels (TRPV1, TRPV2, TRPV4, TRPM8 and TRPA1). [72-82]The expression of these various receptors enable the urothelium to respond to a number of "sensory inputs" from a variety of sources. These inputs include increased stretch

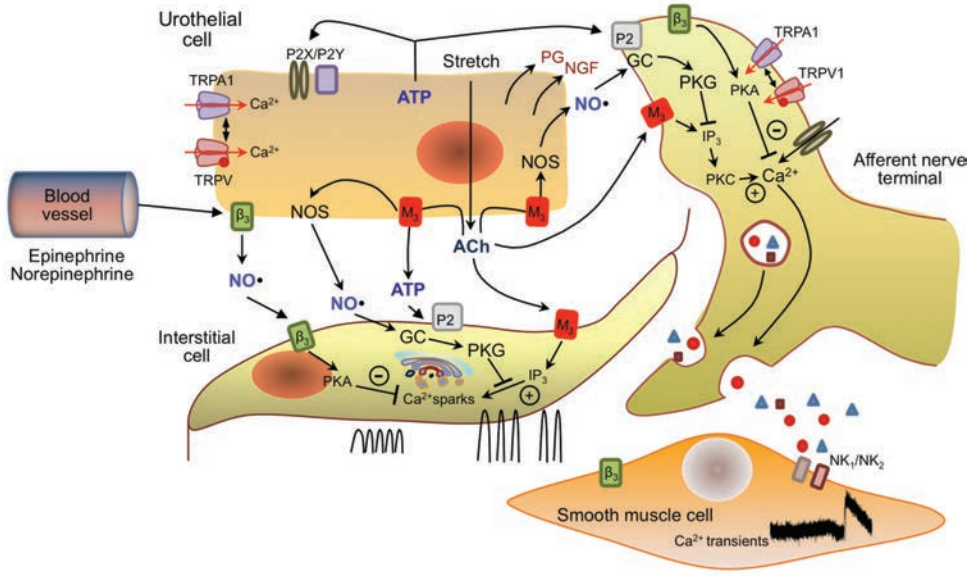


Figure 5. Hypothetical model depicting possible interactions between bladder nerves, urothelial cells, smooth muscle, interstitial cells and blood vessels. Urothelial cells can also be targets for transmitters released from nervesor other cell types. Urothelial cells can be activated by either autocrine (i.e. auto regulation) or paracrine (release from nearby nerves or other cells) mechanisms.

during bladder filling, soluble factors (many found in the urine) such as epidermal growth factor (EGF), or chemical mediators/peptides/transmitters such as substance P, calcitonin gene-related peptide (CGRP), corticotrophin releasing factor (CRF), acetylcholine, adenosine or norepinephrine released from nerves, inflammatory cells and even blood vessels.[29, 30, 83, 84]

Various stimuli can lead to secretion of numerous chemical substances such as neurotrophins, peptides, ATP, acetylcholine, prostaglandins, prostacyclin, nitric oxide (NO) and cytokines that are capable of modulating the activity of underlying smooth muscle [71, 85] as well as nearby sensory neurons. For example, urothelial-specific overexpression of NGF results in increased bladder nerve 'sprouting' and increased voiding frequency.[86, 87] It has been shown that urothelial-derived NO can be released in response to mechanical as well as chemical stimulation and may either facilitate or inhibit the activity of bladder afferent nerves conveying bladder sensation.[82, 88] In this regard, activation of urothelial-receptors and release of inhibitory mediators may explain in part, the mechanism of action for therapies (e.g. β3-adrenergic receptor agonists) in treatment of bladder disorders such as OAB.[89-91]

The mechanism underlying release of chemical mediators from the urothelium, including whether all sensory "inputs" stimulate membrane turnover (i.e. vesicular exocytosis) is not well understood. What little is known about the roles and dynamics of membrane-bound cytoplasmic vesicles in urothelial cell physiology is derived from measurements of membrane capacitance and microscopy of fixed tissues and cells. For example, there is evidence that once released, ATP can act as an important autocrine mediator, which can induce membrane turnover as well as enhance both stretch induced exocytosis and endocytosis.[92] Alterations in membrane turnover can not only increase apical surface area (as described above) but also regulate the number and function of receptors and channels at the cell surface.

There is evidence that epithelial cells in different organ systems may express similar receptor subtypes.[93-95] Accordingly, epithelial cells could use multiple signaling pathways, whose intracellular mechanisms differ according to location and environmental stimuli. This would permit a greater flexibility for the cell to regulate function and respond to complex changes in their surrounding microenvironment. Whether urothelial-sensor molecules all feed into a diverse array of signaling pathways or share similarities with systems such as olfaction, whereby hundreds of receptors share identical transduction cascades[96], is yet to be uncovered.

1. Purinergic Receptors

Since the first report of distension-evoked ATP release from the urothelium there is now abundant evidence supporting a role for urothelially-derived release of ATP in autocrine and paracrine signaling within the lower urinary tract. ATP is abundant in the cell cytoplasm and can be released extracellularly by several mechanisms including vesicular exocytosis, transporters such as a member of the ATP-binding cassette (ABC) transporter superfamily, or anion-selective channels such as the maxi-anion channel.[75] ATP is released from both the apical and basolateral urothelial surfaces in response to bladder stretch and can act on P2X2 and P2X3 urothelial receptors to stimulate stretch-induced exocytosis.[92] (**Figure 6**) The expression of both P2X and P2Y receptors in nerve fibers and myofibroblasts in close proximity to the bladder lumen and the sensitivity of these cells to ATP suggests that basolateral ATP release from the urothelium may also influence function of myofibroblasts and bladder nerves.[97] The amiloride-sensitive apical sodium channel, ENaC, may be involved in mechanotransduction by controlling basolateral release of ATP.[98] In addition, intercellular communication mediated by gap junctions in myofibroblasts could provide a mechanism for long-distance spread of signals from the urothelium to the detrusor muscle.[71] Interestingly, this type of nucleotide-mediated wave of cell-cell communication may also play a role in the response to injury.[99] While evidence supports a role for ATP and purinergic receptors in modulating symptoms in several urologic diseases, the mechanisms underlying activation of the micturition pathway at lower bladder volumes (during urgency) and mediators (amount; type) involved are not understood. In addition, the directionality of transmitter release, the mixture of receptor subtypes in the apical and basolateral domains and interactions between multiple-transmitters is likely to affect the nature of the output in both health and disease.

2. TRP Channels

The ability of capsaicin to evoke NO release from rat urothelium, reported in 1998, provided the first, albeit indirect, demonstration that TRPV1 channels

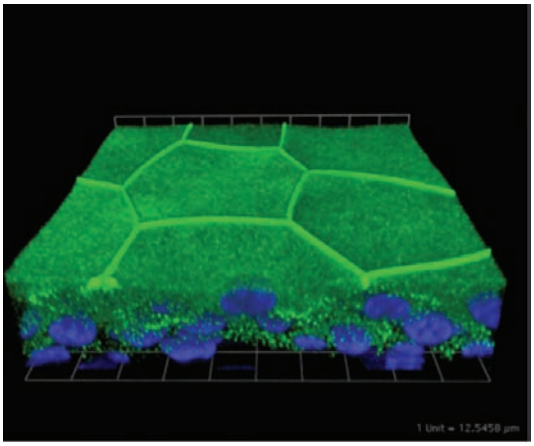


Figure 6. Image is a 3-dimensional reconstruction (taken with a confocal microscope) depicting localization of P2X3 (green; nuclei blue) in the urothelium (from wang et al.2005).

are expressed in urothelial cells and that urothelial cells and afferent nerves, which also express these channels, share a number of common properties. [100] This ion-channel protein is activated by capsaicin, as well as to moderate heat, protons, nitro-fatty acids and lipid metabolites such as anandamide (an endogenous ligand of both cannabinoid and vanilloids receptors).[101, 102] Activation of urothelial cells with capsaicin or resiniferatoxin can increase intracellular calcium, evoke transmitter (nitric oxide, NO or ATP) release and elicit transient currents.[82, 103] Similar to that in sensory neurons, urothelial-response to vanilloids are enhanced by low pH, blocked by TRPV1 antagonists and eliminated in TRPV1 null mice.[62] In afferent neurons, TRPV1 is thought to integrate/amplify the response to various stimuli and to play an essential role in the development of inflammation-induced hyperalgesia. It seems likely that urothelial-TRPV1 might participate in a similar manner, in the detection of irritant stimuli following bladder inflammation or infection.

Though TRPV1-null mice are anatomically normal, they exhibit a number of alterations in bladder function, including a reduction in stretch-evoked and hypotonic-evoked ATP release and stretch-evoked increase in membrane capacitance.[62] In addition, TRPV1 knockout mice have a higher frequency of low-amplitude, non-voiding bladder contractions suggesting the possibility of a small but ongoing role for TRPV1 in normal urine storage function. Altered responses to distension were also detected in TRPV1 null mice, demonstrating a role of TRPV1 in excitability of lower threshold bladder afferents.[104] These relatively benign changes may result from TRPV1 expression not only in afferent nerves that form close contacts with bladder epithelial (urothelial) cells but also in urothelial cells themselves. These findings demonstrate that the functional significance of TRPV1 in the bladder extends beyond pain sensation to include participation in normal voiding function, and is essential for mechanically evoked purinergic signaling by the urothelium.

3. Additional TRP channels

Much less is known about the involvement of other TRPs in bladder function or disease. TRPV4 which is a nonselective cation channel activated by a number of stimuli including heat, shear stress, changes in osmolarity and lipid ligands is expressed mainly within the epithelium of the urinary bladder.[105] While a definitive role for TRPV4 in bladder function has not been established, there is evidence that null mice exhibit impaired voiding responses and, intravesical instillation of a TRPV4 agonist in the rat triggers a novel voiding reflex which could regulate the late phase of micturition.[63, 106] Additional studies suggest activation of urothelial-TRPV4 facilitates bladder reflexes via activation of mechanosensitive, capsaicin- (insensitive) C fibers.[107] In addition, in the awake ewe, TRPV4 may also be involved in a urethra to bladder reflex, proposed to facilitate bladder emptying.[108] Another member of the TRP family, TRPA1 (characterized as a thermoreceptor activated by noxious cold), is expressed in C-fiber afferents as well as urothelium and agonists to this channel induce bladder hyperreflexia.[109] Of interest is the finding that hydrogen sulfide, which may be formed during infection/inflammation, is an activator of TRPA1. [110]

4. Acetylcholine and the Urothelium

There is evidence that the urothelium expresses the full complement of muscarinic receptors as well as enzymes necessary for the synthesis and release of acetylcholine.[83, 111] Further, the urothelium is able to release acetylcholine following both chemical and mechanical stimulation. [83] The mechanism underlying acetylcholine release from urothelium may be through organic cationic transporters (OCTs) rather than vesicular exocytosis, differing from that of bladder nerves.[112] Once released, urothelial-derived acetylcholine is likely to exert effects via a number of sites including smooth muscle, nerves as well as urothelial associated-muscarinic or nicotinic receptors, the latter that could contribute to feedback mechanisms modifying urothelial function.[79, 113] In addition, stimulation of urothelial-cholinergic receptors elicits release of mediators such as nitric oxide, prostaglandin as well as ATP, which could alter bladder sensation by stimulating nearby sensory afferent nerves.[79, 114-116]

Thus, targeting muscarinic receptors and/or urothelial synthesis or release mechanisms may play an important role in the treatment for a number of bladder disorders. By inhibiting SNARE-dependent exocytotic processes, botulinum toxin A (BoNT/A) can prevent the release of transmitters from bladder nerves as well as translocation of various receptors and channels to the plasma membrane.[117] Urothelial-derived acetylcholine may not be sensitive to BoNT/A, however studies have shown that other transmitters (such as ATP) released by the urothelium can be blocked by this treatment in addition to normalizing the expression of urothelial-receptors (TRPV1; muscarinic) and trophic factors.[118, 119] [120, 121] Preliminary studies using immunoblotting indicate expression of the SNARE proteins SNAP23; SNAP25 (Birder unpublished observations) as well as the high affinity binding site SV2 in both rodent (Birder unpublished observations) and human mucosa[122]. These and other studies suggest that the urothelium may be a target for this treatment and that urothelial-released mediators may contribute to sensory urgency.

5. CLINICAL SIGNIFICANCE OF THE SENSORY WEB

Defects in urothelial sensor molecules and urothelial-cell signaling are likely to contribute to the pathophysiology of bladder diseases. For example, a number of bladder conditions (BPS/IC, spinal cord injury (SCI), chemically-induced cystitis) are associated with

augmented release of urothelial-derived ATP, which is likely to result in altered sensations or changes in bladder reflexes induced by excitation of purinergic receptors on nearby sensory fibers.[76, 123] ATP can also act in an autocrine manner that would act to facilitate its own release from urothelial cells. Augmented expression/release of urothelial-derived chemical mediators is likely to reduce the threshold for activation of nearby bladder afferents. Thus, the urothelium has the potential for amplifying signals, both within the urothelium and the bladder wall and contributing to a gain of function in sensory processing. Stressors that can impact on this 'gain of function' include alterations in levels of trophic factors as well as stress and steroid hormones. For example, altered levels of circulating estrogens may play a role in urinary bladder dysfunction, including urgency and frequency.[124] The resulting structural and functional abnormalities may lead to enhanced signaling between the urothelium and underlying cells.

Changes in epithelial signaling/barrier function would not be unique to the urinary bladder. For example, airway epithelia in asthmatic patients as well as keratinocytes in certain types of skin diseases also exhibit a number of similar abnormalities and compromised repair processes.[125, 126] This is particularly relevant given the high incidence of associated diseases that can include both visceral and somatic conditions, many of which exhibit a shared loss of epithelial barrier function. Taken together, epithelial cells can respond to a number of challenges (including environmental pollutants and mediators released from nerves or nearby inflammatory cells) resulting in altered expression and/or sensitivity of various receptor/channels as well as changes in release of mediators, all of which could impact function.

II. AFFERENT NEURONES

1. OVERVIEW: PROPERTIES OF AFFERENT NEURONES

The bladder and lower urinary tract serves to store and evacuate urine and is controlled by a complex hierarchy of neural mechanisms organized by local, spinal and brain circuits. Most of the time is spent in storage mode during which the bladder accommodates urine and maintains continence via reflexes that prevent contraction of bladder smooth muscle and contract the urethral sphincter. This switches during micturition when the bladder contracts and the sphincter opens to facilitate voiding. This switch relies on sensory signals, which provide the input to the reflex circuits that control bladder filling and emptying and are also the source of both non-painful sensations of fullness and pain. Dysfunction leads to a number of distressing disorders such as overactive bladder syndrome (OAB) and Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) with symptoms including urgency, pain and urinary incontinence. Currently available therapeutic approaches are aimed primarily at reducing bladder contraction in order to relieve intravesical pressure and maintain continence. Interest in bladder afferent signalling has been fuelled by the recent realization that symptoms are a feature of dysregulated storage rather than exaggerated contractile responses and therefore targeting afferent mechanisms may be a rational approach to treatment.

Our understanding of bladder afferent signalling has been advanced by studies that are designed to reveal firstly, the morphological features of the afferent terminations in both the periphery and spinal cord; secondly, identify the receptors and ion channels present on these terminations that determine afferent excitability and, thirdly, by recording electrophysiologically the action potentials in afferent fibres it has been possible to characterize the stimulus-response functions of the various populations of afferents conveying sensory information towards the CNS. Such afferent recordings have been performed in vivo in anaesthetized animals and in vitro using isolated tissue preparations. In vivo studies have the advantage that reflex function remains intact although they may be influenced by the use of anaesthetics. Also, by maintaining vascular perfusion, tissue oxygenation will be better maintained, and blood borne factors, including leukocytes, important for neuro-immune functions, can be recruited to the bladder milieu. Similarly, any biochemical factors released into the tissue will be rapidly eliminated into the blood stream. However, an intact vascular supply may also offer a number of disadvantages. Reflex changes in blood flow may lead to secondary alterations in afferent firing, while in the absence of blood flow there is the potential for surgical and pharmacological interventions to probe stimulus-response function. For example, flat-sheet preparations with the urothelium uppermost in a tissue bath allow the pinpoint mapping of receptive fields and the localized application of stimuli directly to the surface of the urothelium. In contrast, surgical removal of the urothelium and sub-urothelial tissue has been used to determine the source of afferent signals from different layers of the bladder wall and the role of urothelial factors in afferent activation. The perfusion medium can incorporate drugs to target specific ion channels and receptors that would be lethal to the whole animal or can be manipulated (calcium-free conditions) to attenuate processes that require calcium entry for downstream signalling. The combination of these different approaches has been essential in understanding the nature of sensory signalling from the lower urinary tract.

2. PATHWAYS TO THE SPINAL CORD

Afferent fibres reach the lower urinary tract via pelvic, hypogastric (lumber splanchnic) and pudendal nerves. These nerves are mixed nerves that also contain the efferent parasympathetic, sympathetic and motor fibres supplying the bladder, urethra and sphincters. Axonally transported dyes applied to these nerves are taken up and transported to the

cell bodies in the lumbosacral dorsal root ganglia and the terminations in the spinal cord. Mapping the distribution of these dorsal root ganglia (DRG) allows the pattern of innervation to be determined in detail and when used in combination with immunocytochemistry provide information on the neuronal phenotype. Moreover, these neurones can be isolated and maintained in cell culture and the labelling using to identify specific functional properties of bladder projecting sensory neurones.

Only a small proportion of DRG neurones supply the viscera with majority supplying somatic targets in the skin and skeletal muscles. Those supplying the bladder are pseudounipolar with a central projection into the dorsal horn of the spinal cord and a peripheral axon that terminates at different levels in the bladder wall. DRGs supplying pelvic and pudendal afferents originate in the thoracic, lumbar and sacral regions while hypogastric afferents arise mainly from the rostral lumbar dorsal root ganglia. The central projections of these DRG neurons carry the sensory information from the lower urinary tract to second order neurons in the spinal cord. These second order neurons provide the basis for spinal reflexes and ascending pathways to higher brain regions involved in micturition and in mediating sensation (described elsewhere in this volume).

The cell size of bladder DRGs is consistent with there being 2 populations of afferent with one connecting to small unmyelinated C-fibre afferents and the other to finely myelinated A-delta fibres. These cell bodies can be further classified according to the presence or absence of certain biochemical markers, namely peptidergic and non-peptidergic. Many unmyelinated afferents are peptidergic, containing calcitonin-gene related peptide (CGRP) and many of these also contain substance P as well as various other peptides. However, some small myelinated fibres also express CGRP. Non-peptidergic neurones can be identified by labelling for isolectin IB4, which recognizes terminal sugar residues on the cell membrane. Both small and medium sized DRGs are labelled with IB4. This non-peptidergic subgroup also expresses P2X3 receptors, which is predominantly found in small unmyelinated fibres. TRPV1 and other sensory markers described below are expressed on both peptidergic and non-peptidergic populations.

Staining for these sensory markers have also been used to identify the terminations of sensory afferents in the bladder wall. CGRP-containing afferent fibres are abundant in the bladder wall and distributed within 4 different layers distinct layers: within the urothelium, around the base of the urothelium within the lamina propria, in the muscle and associated with blood vessels in the serosa. These fibres have conspicuous varicosity, which are release sites for stored transmitter indicating a role for these afferents in so called “axon reflexes”. Upon activation the afferents convey information towards the CNS but also release mediators onto cells in their vicinity to mediate localized responses. Targets for these mediators include vascular smooth muscle, detrusor muscle, urothelium, fibroblast-like cells, mast cells and other neurons. In the human bladder, CGRP containing fibres occur only infrequently in nerves in the muscle but are moderately frequent in the suburothelial layer. Some of these fibres synapse on intramural ganglia within the bladder forming the basis for local neural reflexes.[127-130] Ultrastructural studies of human bladder have found only unmyelinated nerves in the urothelium and immediate suburothelial layer, small myelinated nerves being closely associated with the smooth muscle layers.[131] The plexus of afferent nerves in the lamina propria is thickest in the neck of the bladder and in the initial portion of the urethra, and becomes progressively less dense in the adjacent regions such that cranial region of the bladder have no afferent axons. In contrast, the afferent innervation of the musculature is more uniform throughout the bladder.

3. FUNCTIONAL PROPERTIES OF BLADDER AFFERENTS

Recording from bladder afferents has confirmed the diversity of afferent populations described above based on morphology.[132] Conduction velocity measurements confirm the predominance of fibres conducting action potentials in the A-delta and C-fibre range. The majority of these are mechanosensitive, responding to bladder filling with a range of thresholds from volumes that would be encountered under normal bladder filling to extreme levels of distension that would be considered noxious and give rise to pain. Those with lower thresholds have small myelinated axons while unmyelinated fibres have generally higher thresholds for activation. Other afferents do not respond to bladder filling. Some can be activated by intraluminal chemicals such as hypertonic saline, capsaicin or ATP, suggesting they may function as chemoreceptors. Others may be so called “silent afferents” that have been described elsewhere including the gastrointestinal tract. These afferents can be sensitized during inflammation suggesting a role in signaling pain.

A series of studies have used open-sheet preparations of guinea-pig bladder to examine the diversity of bladder afferents and to attempt to correlate structure with function. Low threshold afferents have terminals in the muscle where they have been described as having “antenna-like endings” and are referred to as stretch sensitive muscular mechanoreceptors. [133-135] Since these afferents also respond to contraction of the detrusor muscle there are also called tension receptors since they respond to tension generated by both elongation during stretch and shortening during contraction. High threshold afferents are also likely to terminate in the deeper muscle layers or in the serosa. These mechanosensitive endings have receptive fields (located by mechanical probing) associated with blood vessels. These likely respond to high levels of stretch that distort the bladder wall but may also become sensitized in response to inflammation.

Another class of mechanoreceptor can be activated by stretch and by light stroking of the urothelium. These endings are referred to as muscular-mucosal by analogy to similar endings in the bowel wall but muscular-urothelial mechanoreceptor may be a more correct term. Their sensitivity could arise because the afferent terminal branches to supply the muscle and urothelium or a single ending in the lamina propria might detect changes in muscle tension and stimulation of the urothelium.[136] Zagorodynuk et al suggest that non-peptidergic “grape like” endings in the lamina propria may be the substrate for these endings. Other urothelial endings respond to stroking but not stretch and some of these are stimulated by luminal chemicals such as capsaicin, acid and are temperature-sensitive. Peptidergic afferents identified by dye filling from the pelvic nerve may be the basis for these epithelial responses.

Mechanosensitivity can arise either directly as a consequence of mechanosensitive ion channels on the sensory nerve ending or secondary to chemicals released in response to stimulation, which in turn activate the ending secondary to stimulation of ligand-gated ion channels. As outlined below there is considerable debate as to the role of the urothelium in sensory signaling. One attempt to resolve this has been to dissect off the urothelium and lamina propria and determine the impact on mechanosensitivity. In the case of muscular and serosal mechanoreceptors removal of the urothelium has little impact on distension response, suggesting these endings may be directly responsive, although the nature of the mechanosensitive ion channels has yet to be elucidated. In contrast the response of muscular-urothelial endings to distension is markedly attenuated following removal of the surface layers of urothelium.[135] The same is true for the mucosal endings. This could imply that the urothelium is involved in transducing stimuli. However, an alternative view might be that dissection causes damage to the underlying nerves that are no longer able to respond to any stimulus. An alternative approach to determining the role of the urothelium may rely on pharmacological manipulations that interfere with urothelial signaling. In this respect the response of low threshold mechanoreceptors was unchanged in calcium-free buffer, which would be expected to prevent urothelial mediator release through exocytosis.

More recent studies in the mouse identified similar populations of afferents and used a systematic classification system to establish the relative proportion of these different types of afferents in the pelvic and lumbar splanchnic nerve supply. The basis for classification and the relative distribution of the terminals and projecting pathway is shown in **Figure 7**. Another important observation in this study was the finding that both low threshold and high threshold mechosensitivity became heightened following exposure to inflammatory mediators which has implications for our understanding of how sensory signaling is altered in disease and a basis for altered micturition and sensations such as pain.[137] There are also recent studies that identified and characterized sacral afferents responding to ‘flow’ through the urethra.[138] These are important observations whereby properties of these flow-responsive afferents seem

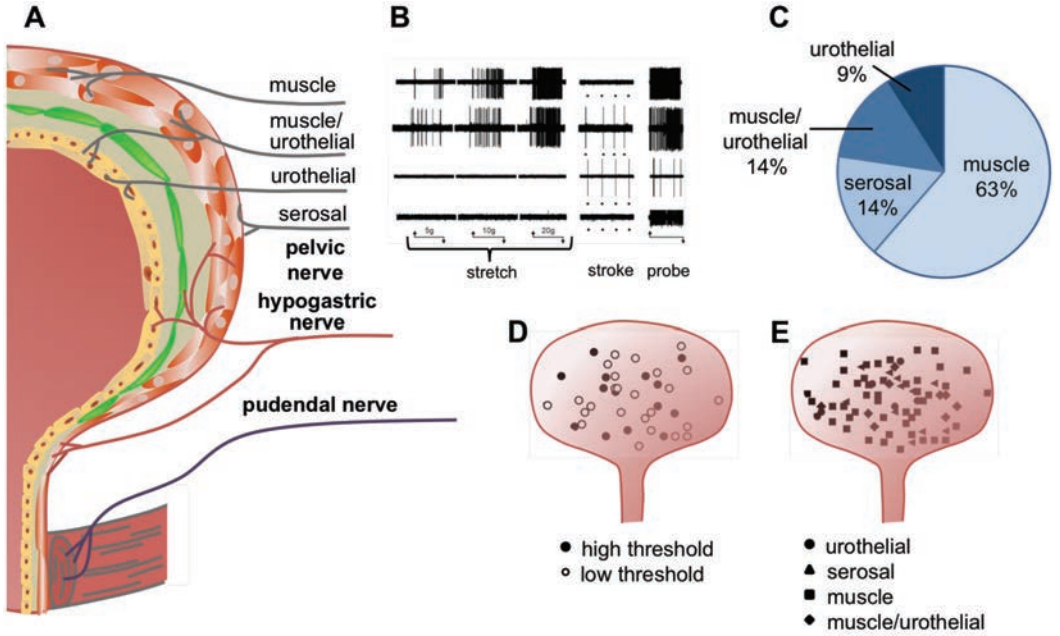


Figure 7. LUT afferent nerve classes and distribution. A, fiber classes in bladder wall and urethra. B, in pelvic nerve 4 types of mechanosensitive fibers were identified by stretch, stroke and probe. C, proportion of afferent fiber types recorded in pelvic nerve. D, low and high threshold receptive fields of pelvic nerve muscle fibers based on response to stretch. E, receptive fields of 4 pelvic nerve fiber classes (Kanai and Andersson, 2010).

to parallel that of cutaneous afferents. This could be important in terms of restoration of bladder emptying following spinal cord injury.

4. MODULATING AFFERENT SENSITIVITY

The discussion above has emphasized how stimulus-response function can be used to define the features of the various sub-populations of afferents that supply the lower urinary tract. The relationship between stimulus and response is not fixed but can be changed according to the mechanical and chemical environment of the sensory ending. Contractions can distort the afferent ending while connective tissue elements will transmit or dissipate stimulus energy within the tissue determining for example whether a response is rapidly or slowly adapting to maintained stretch. Similarly, chemicals released from a variety of cells within the bladder wall and particular the urothelium and lamina propria will influence afferent firing.

Many mediators are released during inflammation, injury and ischemia, from platelets, leukocytes, lymphocytes, macrophages, mast cells, glia, fibroblasts, blood vessels, muscle and neurons. Each cell type may release several of these modulating agents. Some mediators act directly on sensory nerve terminals, while others act indirectly, causing release of yet other agents from nearby cells. This "inflammatory soup" acts on sensory nerve terminals to modify signalling (this is often referred to as "plasticity"). The increased sensitivity to both mechanical and chemical stimuli may contribute to chronic pain states – a feature of clinical relevance. Moreover, since these afferents also trigger reflexes that coordinate bladder function, sensitization can also cause detrusor overactivity or dysreflexia. Various experimental models have been employed to examine changes in the bladder innervation in disease. These include spinal cord injury, bladder outlet obstruction, and various models of hyperactivity based upon chemical injury and autoimmune reactions to name just a few. While these models have generated a wealth of information there is some concern about their translational value and as a consequence their predictive value when testing novel therapeutics.[139]

Local mediators may include neurotrophins, amines, purines, prostanoids, proteases, and cytokines. They produce their effects on visceral afferent nerves by three distinct processes. First, they can act directly, by opening ion channels on the nerve terminals. Secondly, they can sensitize endings, without causing direct stimulation, but causing hyperexcitability to other chemical and mechanical stimuli. This can occur when G-protein coupled receptors (GPCRs) are activated by mediators, which act via second messenger systems, to phosphorylate membrane receptors and ion channels that control excitability. Thirdly, as is the case for neurotrophins, they can change the phenotype of the afferent nerve over long periods. For example, they may alter expression of channels, receptors or mediators in the sensory neuron.[140] They may also modulate ligand-binding characteristics or coupling efficiency of receptors. The result of sensitization is a leftward shift in the stimulus-response function. This means that for any given level of stimulation a greater afferent barrage is generated. Peripheral sensitization normally develops rapidly and is relatively short-lived. However, in the presence of maintained injury or inflammation, the sensitization can be prolonged by changes in gene expression. Genes influenced in this way include those that determine the amount and pattern of neurotransmitters release by central nerve terminals in the brain and spinal cord. This alters the way that sensory signals are processed within the CNS and contributes to "central sensitization". [141]

Role of the urothelium in sensory signal transduction

The urothelium can no longer be considered a passive barrier protecting against diffusion of urine constituents. Recent evidence suggests instead that the urothelium possesses sensory functions and may transduce mechanical and chemical stimuli to underlying structures including smooth muscle, fibroblast-like cells, immune cells and bladder nerves including the terminals of afferents which are located in close proximity, or even within, the urothelium. The recent evidence supporting involvement of a number of these urothelially-derived factors in sensory signalling and the therapeutic potential of targeting these signalling pathways is considered below.

a) Nitric oxide

Enzymes responsible for the generation of nitric oxide (NO) are expressed in both the urothelium and in the adjacent nerve fibres. Knockout mice in which neuronal NOS has been deleted do not have an obvious bladder phenotype. The same is true when inducible NOS is knocked out. However, NO may be involved in bladder dysfunction since expression of NOS is elevated in neurogenic bladder and release of NO may be reduced in experimental interstitial cystitis. Munoz et al [142]recently found that while electrical stimulation-evoked release of some urothelial mediators (ATP) was attenuated by disruption of the urothelium, release of NO was maintained which may suggest that under these conditions NO is derived from suburothelial structures. Interestingly, NO release triggered by cholinoreceptor stimulation was lost after urothelial disruption, consistent with NO derived from multiple sources including the urothelium.

A recent study by Aizawa et al (2010) examined the effect of NO on sensory signalling by directly recording afferent activity arising from the bladder in vivo. [107] Release of NO can be inhibited using non-metabolyzable analogues that compete with L-arginine as substrate for NOS. On such inhibitor, L-NAME, increased the afferent response to bladder filling by about 50%, which was reversed by activation of NO pathways with L-arginine. This data suggests that NO is able to inhibit afferent activity, an observation consistent with earlier cystometric analysis of

the effect of activating the NO pathway.[143, 144] In addition to studying NO mechanisms in the normal bladder, Aizawa and colleagues also showed that application of L-arginine significantly inhibited hypersensitivity induced by the cyclophosphamide metabolite acrolein that is used experimentally as a model for BPS/IC. The actions of NO are mediated through elevation of the intracellular second messenger cGMP. In contrast, phosphodiesterase (PDE) type 5 terminates the action of NO, and PDE inhibitors can be used therapeutically to prolong the action of NO. Behr-Roussel et al found that inhibition of PDE5 attenuated bladder afferent activity in a rat model of spinal cord injury,[145] an indication that this might represent a target for treatment of hypersensitivity disorders of the bladder such as BPS and OAB.

b) Purinergic Signalling

ATP acting via purinergic receptors modulates bladder function mediated by both afferent and efferent pathways involved in urine storage and emptying. It is well established that the urothelium releases ATP in response to stretch and that this acts in a paracrine fashion to influence the function of myofibroblasts and bladder afferent nerves. P2X2 and P2X3 receptors are expressed on unmyelinated afferent fibres innervating the bladder, and thus the hypothesis has been put forward that mechanosensitivity, at least in those afferents in proximity to the urothelium, involved ATP release by stretch and activation of P2X2 and P2X2/3 receptors on the afferents.[146, 147] The sensitivity of bladder afferents to ATP and mechanical stimuli has been directly examined. In the rat, 90% of bladder afferent neurons responded to the P2X agonist αβ-methylene ATP and were inhibited by the P2X antagonist 2', 3'-O-trinitrophenyl-ATP (TNP-ATP) which suggests that pelvic nerve afferents from the rat bladder express predominantly P2X(2/3) heteromeric receptors. In the mouse the majority of both low and high threshold receptors were sensitized by αβ-methylene ATP, i.e. the mechanical threshold was reduced and peak activity was increased during distensions.[148] In addition some 'silent' afferents became mechanosensitive after treatment with ATP. The absence of sensitization in P2X3 knockout mice indicated that the responses were mediated by the P2X3 receptor. These knockout mice exhibit a marked urinary bladder hyporeflexia, characterized by decreased voiding frequency and increased bladder capacity, but normal bladder pressures.[149, 150] In addition, they have reduced pain-related behaviour in response to injection of ATP. Recently, Sadananda et al [151] investigated whether other stimuli, besides bladder distension, could stimulate urothelial ATP release. They compared ATP release levels in rat bladder when subjected to stretch, capsaicin and acid. Interestingly, the amiloride-sensitive apical sodium channel, ENaC, may be involved in mechanotransduction by controlling basolateral release of ATP.[98] Adenosine is also produced and released by the urothelium, and may play important roles in modulating sensory afferent function and smooth muscle contraction.[152]

In the normal bladder, it is believed that a balance between the excitatory effects of ATP and inhibitory effects of NO release may determine micturition thresholds and frequency and that this balance may be disturbed in bladder disorders. Elevated ATP levels have been demonstrated in patients with detrusor overactivity and BPS [153], Munoz et al, using a rat model of detrusor overactivity (diabetic bladder), found increased levels of ATP but normal levels of NO.[142] Conversely in an underactive bladder model, induced by chronic sugar intake, NO levels were increased while ATP remained normal. This suggests that the balance between ATP and NO is altered in bladder dysfunction.

c) Cholinergic Mechanisms

The discovery that ACh can be released from the human bladder urothelium has led to the concept that cholinergic mechanisms could contribute to sensory signalling.[154] This concept has been reinforced by clinical findings showing that anticholinergic drugs, the current mainstay for the treatment of bladder overactivity, appear to exhibit efficacy during the bladder storage phase when parasympathetic cholinergic activity is minimal.

A number of studies have examined the effect of cholinoreceptors on bladder afferent firing. However, the data are conflicting and a consensus has yet to emerge. In vivo studies using clinical anticholinergic agents such as oxybutynin and darifenicin suggest that inhibiting muscarinic receptors, attenuates the afferent response to bladder filling.[155, 156] However, due to the nature of in vivo studies it is unclear if these effects are direct, at the level of the sensory terminal, or secondary to altered muscle tone following either peripheral or central effects on parasympathetic transmission. Similarly, Matsumoto et al found that stimulating muscarinic receptors induced bladder hyperactivity, and that this was blocked by inhibiting the M2 receptor, suggesting that M2 receptors play a role in cholinergic modulation of bladder afferent excitability. However, it is important to note that in this study, excitability was inferred from cystometry and afferent activity was not measured directly.[157] In contrast, Masuda et al (2009) found that pharmacological activation of muscarinic receptors attenuated micturition reflexes in the rat suggesting that muscarinic receptor activation leads to attenuated afferent signalling.[158] Such inhibition has been observed in afferent recording studies using isolated bladder preparations in which any secondary effects on muscle tone could be controlled [104]. In these studies blocking cholinesterase activity to augment endogenous cholinergic activity lead to attenuated afferent signalling that could be reversed by antimuscarinics. Surprisingly, antimuscarinics alone had no effect on bladder afferent re-

sponses to distension suggesting that acetylcholine release during stretch was not part of the sensory transduction pathway but cholinergic influences become manifested only under circumstances in which acetylcholine release is increased.

How ACh and muscarinic receptor pathways could modulate transmission is unclear. It is possible that there is a direct action and in this respect DRG neurones retrogradely labelled from the bladder have been shown to express M2, M3 and M4 receptors. [159] However, stimulation of muscarinic receptors on the urothelium causes the release of other excitatory and inhibitory mediators including ATP and NO.[83, 160] It is possible therefore that muscarinic receptors modulation of afferent activity is indirect via the release of a secondary mediator. Such a view is supported by the observation that bladder hypersensitivity, triggered by cholinergic stimulation was abolished by inhibition of P2X receptors, suggesting that muscarinic receptors and purinergic receptors may work in tandem to modulate afferent transmission. [161] These studies highlight the complex nature of cholinergic signalling in the bladder, and indicate that more research is necessary to fully understand whether muscarinic receptors on the afferent limb could become a therapeutic target for OAB.

d) Botulinum Toxin

Botulinum toxin A (BoNT/A) inhibits the vesicular release of acetylcholine following uptake into presynaptic nerve terminals (see **Figure 8**) and proteolytic cleavage of the SNARE protein SNAP-25 which prevents docking and fusion of synaptic vesicles at the neuro-muscular junction. BoNT/A was first clinically used in the bladder to treat neurogenic bladder overactivity caused by spinal cord injury[162]. Since then, intravesical injections of BoNT/A has proved a highly effective treatment for patients with detrusor overactivity, with numerous studies reporting improvements in the sensory symptoms of urgency and urinary frequency.[163] Since acetylcholine can be released from the urothelium it is possible that BoNT/A is acting at this level to modulate sensory signalling. In addition, there is recent evidence that SNAP-25, the intracellular target for proteolysis by BoNT/A, is expressed in the urothelium (Birder unpublished). This is consistent with experimental data showing that BoNT/A inhibits the release of ATP and augments NO release from the urothelium in animal models of spinal cord injury.[164] Others have shown that application of BoNT/A directly attenuated afferent firing in ex vivo mouse models [165-167]. Other potential targets for BoNT/A include the suburothelial sensory nerve endings, and in this respect a decrease in suburothelium immunoreactivity for P2X3 and TRPV1 has been reported in human bladders following treatment with BoNT/A[168]. BoNT/A has been shown to inhibit the release of CGRP and substance P from afferent nerve terminals.[169]

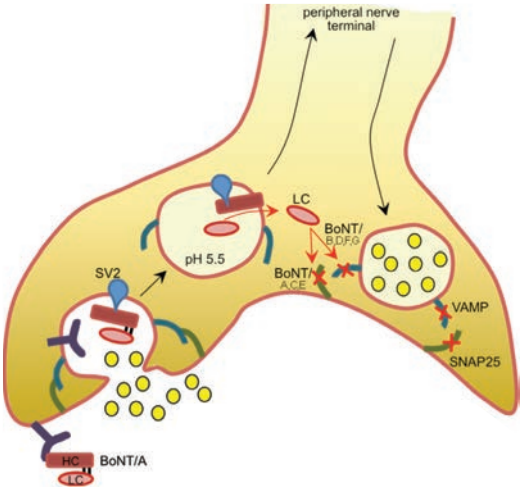


Figure 8. Hypotheses for the pathways mediating the effects of botulinum toxin in afferents.

e) Transient Receptor Potential (TRP) Cation Channels

A number of different members of the transient receptor potential (TRP) channel family are expressed in the bladder mostly in association with sensory nerve fibres involved in mechanotransduction and nociception. TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1, have all been shown to be expressed in the bladder. TRPV1 has been shown to play an integral role in modulating the excitability of bladder afferents and the generation of hypersensitivity, induced by bladder inflammation.[62, 65] It is through desensitization of this receptor that agents like resiniferatoxin act to treat symptoms in OAB.[170] TRPV1 is predominantly expressed on sensory nerves and has been identified within nerve plexuses running in both the muscle layer and suburothelium. In addition some investigators have also demonstrated that TRPV1 is expressed within the urothelium, however the specificity of commercially available TRPV1 receptor antibodies has been questioned.[106]

Interest in TRPV4 has been fuelled by the observation of impaired voiding behaviour in knockout mice. [106] This channel shows mechanosensitivity and is proposed to play a role in the micturition reflex by activating C-fibre afferents.[171] However, the site of action of TRPV4 agonists may in fact be the urothelium which expresses the TRPV4 channel,[63] particularly in association with adherence junctions where they may be preferentially activated by stretch and lead to the release of ATP.[172] Inhibition of TRPV4 has recently been shown to improve symptoms in a model of experimental cystitis.[173]

TRPA1 is also expressed in the bladder and is particularly associated with C-fibre endings in the suburothelium that co-localize CGRP. Agonists acting at the receptor cause bladder hyper-reflexia and is suggested to play a role in mechanotransduction and in signalling pain. TRPA1 has also been demonstrated in the urothelium at both transcriptional and protein

levels. Expression is increased in a spinal cord injury model and both pharmacological blockade and RNA knockdown of TRPA1 were effective in normalizing bladder reflex function. [174]

TRPM8 was first described as a cold receptor and interest in its role in the bladder stems from the observation that instillation of cold saline into the bladder elicits a contractile response (at pressures or volumes below the threshold for normal voiding). This response to a cooling stimulus (which has been referred to as the bladder cooling reflex) was originally thought to indicate a supraspinal neurological lesion and the test (termed the 'ice water test')[175] has been used in the diagnosis of bladder disorders such as detrusor overactivity. Expression of TRPM8 has been identified on bladder afferent fibers and on the cell bodies in the DRG where it co-localizes with nociceptive markers such as CGRP and IB4. [176]Previously Lashinger et al (2008) showed that application of a TRPM8 channel blocker, decreased voiding frequency and abdominal motor responses in the rat[177] suggesting that in addition to cold sensing TRPM8 may also be involved in the afferent control of micturition and nociception.

f) Cannabinoids

The multi-centre CAMS study (Cannabinoids in Multiple Sclerosis) reported that the use of cannabis based extracts significantly improved symptoms of urge incontinence and detrusor overactivity in patients with multiple sclerosis. This observation has provoked interest in the study of expression and function of cannabinoid receptors in the bladder. Endogenous cannabinoids can potentially interact with TRPV1 but in addition can act on G-protein coupled cannabinoid receptors 1 and 2 (CB1, CB2). In the human bladder, both receptors could be identified in the urothelium and detrusor where CB1 receptors were more abundant than CB2.[178] In patients with bladder pain syndrome and idiopathic detrusor overactivity (IDO), a significant increase in nerve fibres expressing CB1 in the urothelium was observed, strongly suggesting a role for CB1 in overactive bladder.[179] In contrast, Gratzke and colleagues[180] found CB2 receptors predominated in the urothelium, suburothelium and on sensory nerve fibres and found that CB2 agonists inhibited nerve induced contractions of the bladder providing evidence that CB2 receptors are important in micturition.

Expression of CB1 receptors were also identified in the urothelium and on nerve fibres in the detrusor of mouse bladder.[181] These receptors co-localized with P2X3 receptors, suggesting an interaction between cannabinoid and purinergic systems. In addition, a synthetic cannabinoid active at both CB1 and CB2 receptor was shown to inhibit the evoked release of CGRP from afferent nerve terminals. [182] Functional experiments also found a reduction in distension evoked afferent firing in response to application of a CB1 agonist. In particular, high threshold afferents typically associated with noxious stimuli were directly affected. Taken together these studies suggest that CB receptors in the bladder may have a modulatory role in sensory afferent signalling and a greater understanding of which could lead to new therapeutic strategies for treatment of bladder disorders. Understanding the differential roles of CB1 and CB2 receptors may add a new dimension to our ability to target these pathways.

g) Adrenoreceptors

Alpha-1-adrenoreceptor (α1-AR) antagonists are the current first line for treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). By inhibiting prostatic smooth muscle contraction, these agents relieve bladder outlet obstruction (BOO). In addition, recent data report an improvement in other symptoms, such as frequency, nocturia and urgency, suggesting that they may also act via the afferent system to influence storage function. Adrenoreceptors have been detected throughout the urothelium and on the sensory neurones innervating the bladder.[183, 184] Bladder afferent responses to distension in vivo are inhibited following intravesical application of the clinical α1-AR antagonist Tamulosin. Moreover, chronic systemic treatment with two different α1-AR antagonists inhibited reflex voiding in a rat model of BOO.[185] A recent experimental study by Nagabukuro et al investigated changes in afferent firing following treatment with a number of commonly used clinical drugs. The study found that Tamulosin treatment significantly attenuated activation of the early gene c-fos in the spinal cord, used as a marker for sensory neuronal activation. [186]

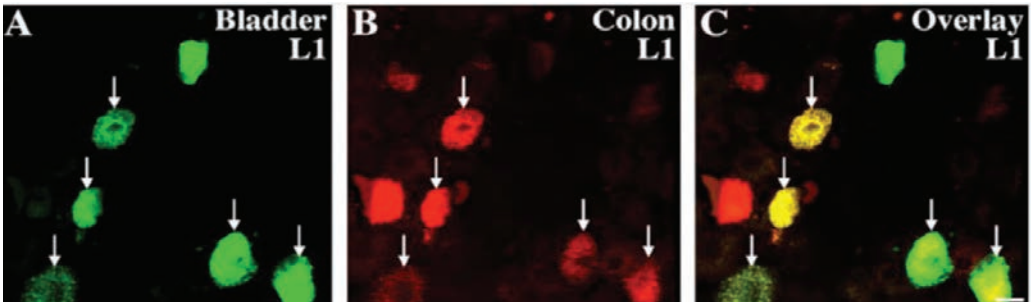


Figure 9: Dichotomizing afferents. Panels depict retrogradely labeled cell bodies in rat DRG following urinary bladder and colon injections of Alexa Fluor 388 and 647-conjugated cholera toxin B (CTB). A, CTB-positive bladder afferents, B, CTB-positive distal colon afferents and C-dual labeled cells. (from Christianson et al., 2007).

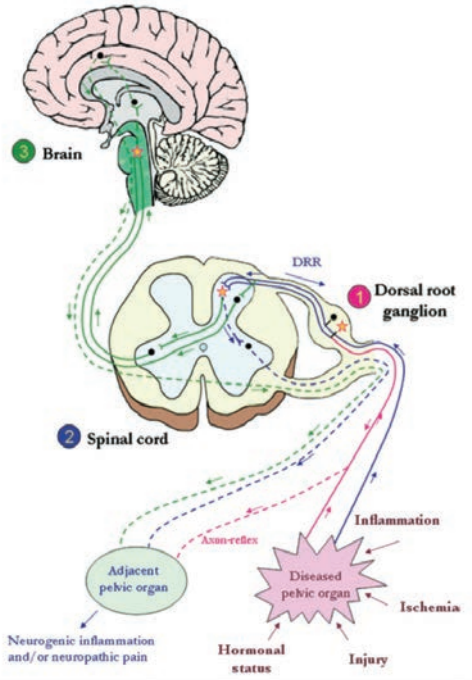


Figure 10: Schematic representation of convergent afferent pathways: (1) Convergence of sensory neural pathways within a DRG, (2) Convergence of afferent information in the spinal cord. (3) convergence of afferent inputs from two diffrent pelvic organs in the brain. Anterograde AP propagation from the brain, spinal cord and DRG to the periphery is shown by dotted lines. (from Malykhina 2007).

In contrast to the α-adrenoreceptors, the beta adrenoreceptors (βARs) mediate relaxation of the bladder smooth muscle in response to sympathetically released noradrenaline. The β3-AR subtype is the predominant isoform responsible for relaxation of the human detrusor and β3-AR agonists are currently in clinical trials for the treatment of OAB. A recent study by Kullmann et al demonstrated the presence of the β3-AR in the urothelium and observed inhibition of voiding contractions in response to the β3-AR agonists TAK-677 and BRL37344. This effect was independent of any changes in smooth muscle tone suggesting that β3-AR could also participate in bladder afferent function.[187]

5. CROSS TALK BETWEEN THE BLADDER AND BOWEL

Patients with IBS often report bladder symptoms including nocturia, frequent and urgent micturition, and incomplete emptying.[188] The counterpart is also true with patients with BPS complaining of bowel symptoms.[189] These observations are consistent with the concept of cross-organ sensitization which extends to different abdominal and pelvic structures and contributes to a more generalized chronic pelvic pain syndrome reviewed recently by Brumovski et al.[190] In experimental models inflammation of the colon has been shown to lead to increased frequency of bladder contractions and altered micturition reflexes.[191] In contrast, experimental bladder inflammation has been reported to sensitize the bowel to distension. [192] Such cross-organ sensitization has also been demonstrated between the uterus, pelvic urethra and vagina. In men there is the potential for cross-organ sensitization between the prostate and other pelvic organs.

The mechanisms underlying cross-organ sensitization have not been fully elucidated but there are potentially several levels at which the sensory innervation to the different pelvic structures can interact. In terms of periphery mechanisms there is evidence that afferent fibres branch extensively to innervate multiple target structures. Different retrograde tracer injected into the bladder and bowel results in a number of DRG neurones carrying both labels although the numbers are low (**Figure 9**)[193]. Similarly, dichotomizing afferents have been shown to innervate the colon and uterus with DRGs expressing TRPV1 and P2X3 receptors implying a role in nociception. Sensitization of the endings in one organ by local inflammation would likely impact on overall sensitivity following upregulation in excitability in all terminal receptive fields. Central sensitization may also contribute to cross-organ sensitization (**Figure 10**). Excitability of spinal neurons receiving afferent input from the bladder has been shown to respond to afferent input from other pelvic structures such as the colon.[194, 195] Second order neurones in the spinal cord therefore receive convergent input from various visceral structures as well as somatic inputs. The later explains the phenomenon of referred pain where sensations from the viscera are experienced in the associated somatic sensory field, the classic example being angina. Such viscero-somatic convergence has been extensively investigated and only recently has viscero-visceral referral received attention. Nevertheless convergent inputs would explain the poor localization of pelvic pain and the difficulty in diagnosis and treatment.

III. NEURAL CONTROL OF FEMALE PELVIC FLOOR MUSCLES AND RHABDOSPHINCTERS

The urethral rhabdosphincter and pelvic floor muscles are important in maintenance of urinary continence and in preventing descent of pelvic organs (i.e. pelvic organ prolapse, POP). It is estimated that 11 % of US women will undergo a surgical procedure for POP or urinary incontinence during their lifetime.[196] Because of the importance of understanding pelvic floor function, recent clinical and preclinical studies have focused on this topic. Reviews of functional anatomy[197] and neural control[198] of the pelvic floor muscles and the urethral and anal rhabdosphincter have been published.

1. STRUCTURAL ELEMENTS OF THE PELVIC FLOOR (FIG. 11)

The pelvic floor [197] in women is a bowl-shaped structure comprised of bone, muscle, and connective

tissue. The rim of the bowl is formed by the bones of the pelvic girdle (sacrum, ilium, ischium, and pubis). The "bottom" of the bowl is lined with striated muscle: the iliococcygeus and pubococcygeus (which together comprise the levator ani - LA - muscle), the coccygeus, and puborectalis [197, 199, 200] muscles. The muscles are attached to the bone and to each other with various connective tissue supports. These three components, bone, muscle, and connective tissue provide support of the pelvic viscera (i.e. rectum, vagina, and bladder) but also allow for excretory and sexual function.

The viscera, as well as striated muscles that serve as true sphincters - urethral and anal rhabdosphincters, attach to pelvic floor muscles and each other by connective tissue but do not attach directly to bone. The urethrovaginal sphincter, the compressor urethrae muscle, the ischiocavernosus, and bulbospongiosus muscles are additional striated perineal muscles that are intimately associated with the viscera.[197, 199, 200] During embryogenesis, the rhabdosphincter and perineal muscles develop from the cloaca with a two-week delay in striated muscular differentiation compared to the LA and other skeletal muscles.[201, 202] Furthermore, rhabdosphincters are completely separated from the LA muscles by connective tissue.[199] Thus, the striated muscles associated with the viscera (i.e. rhabdosphincters) are quite distinct from the striated skeletal muscle of the pelvic floor (e.g. LA). The urethral rhabdosphincter has been referred to by many names, including the external urethral sphincter, the striated urethral sphincter, the striated urethralis muscle and other names. The term "external urethral sphincter" is downplayed because the urethral rhabdosphincter is not really external to the lower urinary tract; it surrounds the middle of the urethra. Therefore the term urethral rhabdosphincter is recommended.

2. PERIPHERAL INNERVATION OF THE FEMALE LEVATOR ANI (LA) MUSCLES

The LA muscle of the pelvic floor is innervated by the LA nerve in human, (**Fig. 11A**)[203, 204] squirrel monkey [205-207], dog[208], cat (Karicheti and Thor, unpublished observations) and rat.[209, 210] The LA nerve primarily arises from sacral spinal roots (e.g. S3-S5 in humans) and travels along the intrapelvic face of the LA muscle with a high degree of variability in branching patterns.[203] In humans, there is some controversy whether or not the pudendal nerve also innervates the LA muscle. [211-213] In human female fetus samples, a contribution to LA innervation by the pudendal nerve was only seen in about half the samples. A recent detailed study of women 45-55 years of age, using an elaborate Sihler's stain to trace branches down to single fibers, did not describe any contribution of the LA muscle from the pudendal nerve. [204] In animal studies, a number of findings refute

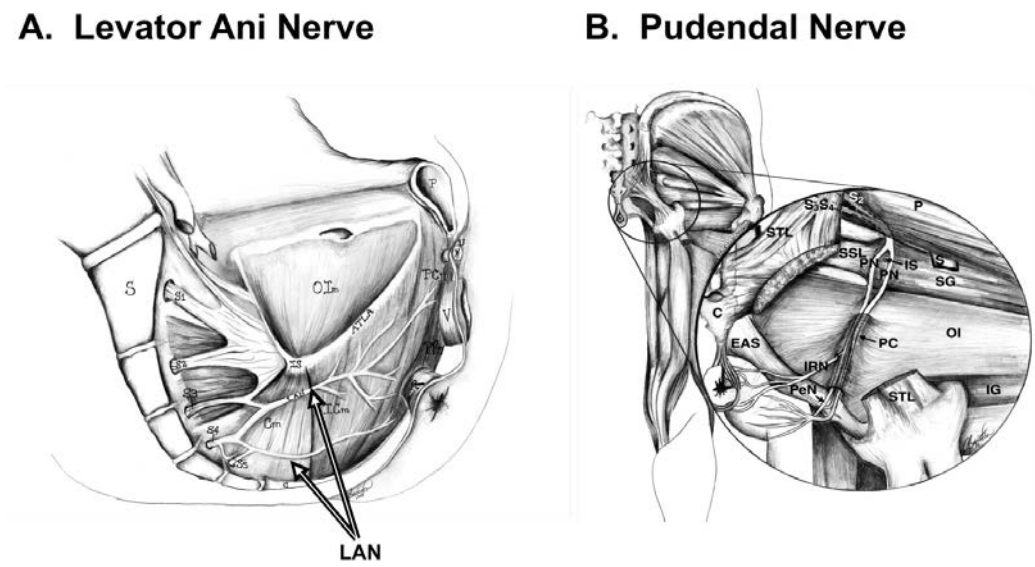


Figure 11. A) Sagittal drawing of medial surface of a woman's pelvic floor showing the course of the LA nerve (LAN) from the sacral roots (S3-S5) across the internal surface of coccyeus (Cm), iliococcygeus (ICm) puborectalis (PRm) and Pubococcygeus (PCm) muscles. S=sacrum; C=coccyx; IS=ischial spine; Olm=obturator internus muscle; ATLA=arcus tendineus LA; U=urethra; V=vagina; R=rectum. B) Drawing of a posterior view of the hip muscles showing the course of the pudendal nerve (PN) from the S2-S4 roots across the lateral surface of the superior gemellus (SG) and obturator internus (Olm) muscles, through the pudendal canal (PC), and its branching into the inferior rectal nerve (IRN) and perineal nerve (PeN). P=periformis muscle; STL=sacroturberous ligament; C=coccyx; IS=ischial spine; SSL=sacrospinous ligament; S=sciatic nerve; EAS=external anal sphincter; IG=inferior gemellus muscle. Adapted from Barber et al., 2002.

an innervation of the LA muscles by the pudendal nerve:

1. a marked decrease in LA muscle mass and myocyte diameter, as well as vacuolization of the muscle following transection of the LA nerve (**Fig. 12**) but not after pudendal neurectomy. [205, 210]
2. transection of the LA nerve abolished LA muscle EMG activity in rats,[209] while transection of the pudendal nerve had no effect on LA EMG activity but abolished rhabdosphincter activity.
3. an absence of contractions of LA muscles upon electrical stimulation of pudendal nerve efferent fibers (Thor and Karicheti, unpublished observations in cats and rats).
4. only a single motor endplate zone is found in the LA muscle, located at the point of LA nerve insertion into the muscle.[205, 210]
5. large α motor neuron axons (i.e. 10 μm diameter), which are a hallmark of skeletal muscle innervation, are not found in the pudendal nerve. [214] [210]
6. distinct populations of motor neurons, extremely unique in phenotype, are labeled following application of tracers to the pudendal nerve versus the LA nerve[208, 215-220].

Thus, divergent techniques support the conclusion that only the LA nerve innervates the LA muscles with no significant contribution from the pudendal nerve in non-human species. These direct observations, coupled with the distinct embryological origins of LA muscles versus rhabdosphincter and perineal muscles [201, 202], as well as a respective "compartmentalization" of the rhabdosphincter and perineal muscles by connective tissue[199], are in line with distinct "special somatic" motor innervation of the rhabdosphincter by the pudendal nerve versus typical skeletal motor innervation of the LA muscle by the LA nerve. The work in human female fetal samples[212, 213] suggests that an innervation of the LA muscle by the pudendal nerve should be considered, especially during the perinatal period. Whether these pudendal branches to the LA muscle recede during maturation or aging should also be considered in light of the difficulty identifying them in older women[204].

The complexity of the perineal region, which consists of various small muscles [puborectalis, compressor urethrae, urethrovaginal sphincter, urethral and anal rhabdosphincter, ischiocavernosus, and bulbocavernosus), blood vessels, connective tissues, and nerves, makes dissection, identification, and nomenclature of specific nerve branches and muscles difficult in cadavers. Indeed, even the nomenclature of the muscles themselves is uncertain[199, 200]. A recent study has suggested more attention to detail and more rigorous adherence to "origin – insertion" nomenclature standards are being adopted[204].

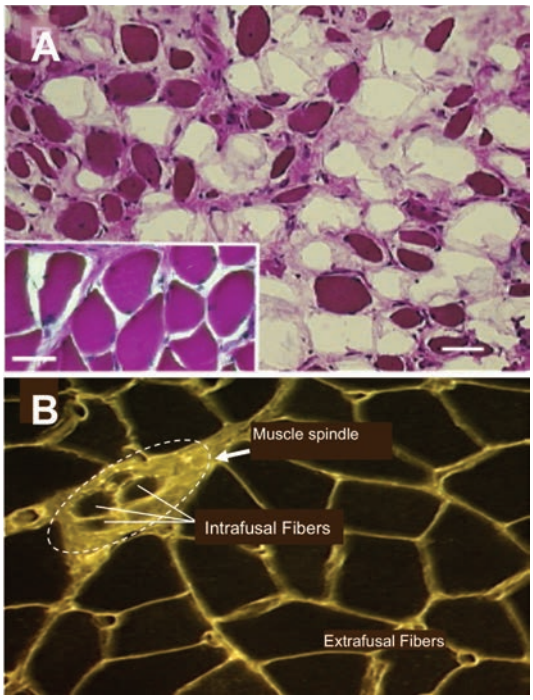


Figure 12: A, H&E stained levator ani (LA) muscle taken from squirrel monkey that had a bilateral LA nerve transection 2 yr earlier. Note shrunken, darkly stained muscle fibers and fat cell inflitraton (unstained areas) compared with healthy muscle fibers from control (inset). (Adapted from Pierce et al.) B, LA muscle stained with wheat germ agglutin-rhodamine isothiocyanate showing muscle spindle and associated intrafusal fibers (L.Pierce and K. Thor, unpublished observations).

Detailed anatomical, histological, and physiological studies of the small, intricate muscles of the perineum coupled with studies of their afferent and efferent neurons in humans and larger laboratory species (where they can be readily visualized) is an important area for future research. As a first step, agreements regarding muscle classification should be established in regard to which muscles actually comprise the LA or pelvic floor versus those that are more intimately associated with the viscera. In other words, should "pelvic floor muscles" include only the skeletal striated muscles such as pubococcygeus, iliococcygeus, coccygeus, and puborectalis muscles, while non-skeletal striated muscle such as urethralis, urethrovaginal sphincter, and compressor urethrae be distinguished from the pelvic floor? Are these latter muscles similar to the urethral and anal rhabdosphincter? Presumably, characteristics of their muscular function, their innervation, their pharmacological responses, or physiological integration with visceral function may allow better understanding of their roles in excretion or sexual function.

Clarity regarding pudendal versus LA nerve innervation is also important because attributes ascribed to pudendal nerve involvement may be more correctly

ascribed to LA nerve involvement. For example, the intrapelvic positioning of the LA nerve on the surface of the muscles may expose it to damage as the fetal head passes through the birth canal[203] and may contribute to the correlation between parity and POP[197]. This positioning also allows exposure to electrical current applied with a St. Mark's electrode situated in the rectum with subsequent EMG activation of the LA muscle. The LA nerve positioning, close to the ischial spine, also risks entrapment by sutures used for various POP suspension surgeries or may account for dyspareunia, pelvic pain, and/or recurrent prolapse[221] associated with such surgery. Finally, since the ischial spine is a landmark for transvaginal "pudendal nerve" block[212], the possibility that this procedure also anesthetizes the LA nerve should be considered.

a) LA Motor Neurons

Retrograde tracing studies in cats[222], dogs[208], and squirrel monkeys[216] identify LA motor neurons in a longitudinal column in the sacral ventral horn of the spinal cord, while in rats[223-225] they are in the L6-S1 ventral horn. In contrast to dense packing of sphincter motor neurons in Onuf's nucleus[215, 217-220], the LA motor neurons are distributed more diffusely. Furthermore, LA motor neurons show a bimodal distribution of large neurons (presumably α motor neurons) and small neurons (presumably γ motor neurons) in contrast to the uniform intermediate size of pudendal motor neurons. The two sizes of LA motor neurons are in keeping with the presence of muscle spindles (whose intrafusal muscle fibers are innervated by γ motor neurons) in LA muscle (**Fig. 12A**)[226-228], while muscle spindles are absent from the rhabdosphincter muscles[226, 229-233]; consequently LA may exhibit Iα (muscle spindle) evoked monosynaptic stretch reflexes, whereas the urethral rhabdosphincter does not[218, 234-236].

LA motor neuron processes (dendrites or axon collaterals) project into two important areas in the sacral spinal cord [206]. One area, medial lamina VI, is where primary afferent fibers from muscle spindles and Golgi tendon organs terminate[237, 238], again suggesting an important role for stretch-activated reflex contractions of LA muscles. The second area is to Onuf's nucleus that contains rhabdosphincter motor neurons. These LA motor neuron processes form close appositions with sphincter motor neurons in both monkey[216] and rat[223, 225]. Presumably, these appositions reflect a neuroanatomical substrate for coordination of the rhabdosphincter and the pelvic floor muscles during micturition and defecation. These projections could be dendrites receiving common afferent input with rhabdosphincter motor neurons or axon collaterals transmitting information to rhabdosphincter motor neurons, which might provide insight into functional coordination.

Ovariectomy in rats reduced LA neuron dendritic arbors, while estradiol and progesterone expanded them, indicating hormonal regulation[239]

b) LA Afferent Innervation

Afferent LA fibers innervate muscle spindles (**Fig. 12A**)[205, 226] and Golgi tendon organs[227] which are common in skeletal muscles but absent in the rhabdosphincters[226, 229-233]. Cholera toxin B (CTB) injection into the LA muscle[206] of squirrel monkeys labels approximately 4 times as many afferent neurons versus motor neurons. About 25% of these primary afferent neurons are large, myelinated (i.e. RT-97 neurofilament positive) neurons and are negative for the peptide transmitter calcitonin-gene-related peptide (CGRP), binding sites for isolectin-B4 (IB-4), and the growth factor receptor, TrkA. Of the remaining small, RT97 negative neurons, approximately 50% contain CGRP, IB-4 binding sites, and TrkA. It is tempting to speculate that large, myelinated afferent neurons signal proprioceptive information from muscle spindles [205] and Golgi tendon organs and in turn control reflex activity of the LA muscles, while the small peptidergic, IB-4, TrkA positive neurons transmit nociceptive information. In addition, large sensory neurons may regulate bladder reflex pathways during LA motor activity; while the small peptidergic fibers might play a role in bladder hyperreflexia associated with pelvic floor trauma or nerve entrapment.

CTB labeled afferent terminals were only seen in medial lamina VI of the lumbosacral spinal cord[206], an area for termination of large, myelinated proprioceptive terminals[237, 238]. The absence of CTB labeling in the superficial dorsal horn, which should contain the central terminals of small peptidergic, IB-4, and TrkA positive afferent neurons, is likely due to an inability of small afferent neurons to transganglionically transport CTB rather than a true absence of LA nociceptive terminals in the region. Experiments with a tracer (e.g. horseradish peroxidase, HRP) that is transported to nociceptive spinal terminals should be done to confirm this.

3. REFLEX ACTIVATION OF PELVIC FLOOR MUSCLES

There is little preclinical information regarding reflex control of pelvic floor muscles associated with visceral function (e.g. micturition). A recent study in female rabbits[240] showed that during bladder filling (i.e. the storage phase), the pubococcygeus muscle was active, while during micturition it was quiet. The same study showed the opposite relationship for the ischiocavernosus and bulbospongiosus muscles, which were silent during bladder filling but active during micturition. One study in the male rat[241] indicated that the pubocaudalis muscle is active during bladder contractions and shows high frequency bursting like the urethral rhabdosphincter EMG.

Preliminary studies (**Fig. 13**, Mori and Thor, unpublished) in female rats also indicated that the pelvic floor muscles could be activated during a micturition contraction under certain circumstances. Pubocaudalis EMG activity increased during a micturition contraction in 50% of the rats under control

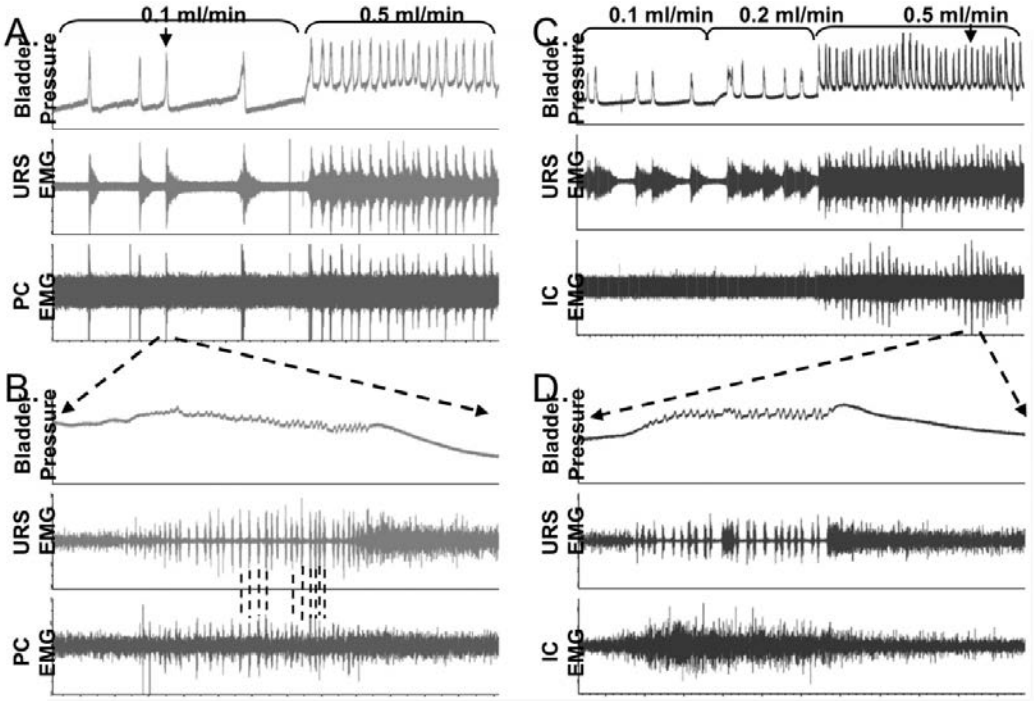


Figure 13. Examples of pubocaudalis (A and B) and iliocaudalis (C and D) EMG activity during continuous filling cystometry in female rats. Top tracing: bladder pressure; middle tracing: urethral rhabdosphincter (URS) EMG activity; and bottom tracing: pubocaudalis (PC, A and B) or iliocaudalis (IC, C and D) EMG activity. In A, the rat of bladder infusion was increased from 0.1 to 0.5 ml/min and in C from 0.1 to 0.2 to 0.5 ml/min as indicated by the brackets. In panel A, note that the URS activity increases preceding the bladder contraction and the activity is maintained for a period of approximately 30 sec after the contraction while the PC EMG is only active during the bladder contraction. Increasing the infusion rate produces continuous activity of the URS while the PC is activated only during the bladder contraction. Panel B shows the contraction marked by the arrow in panel A at a faster time scale. Note the characteristic phasic bursting pattern of the URS EMG during the high frequency oscillations (HFOs) of the bladder pressure. Note that the PC EMG also shows phasic activity during the bladder contraction that is temporally correlated with the URS bursting (indicated by dashed lines). In panel C from a different rat, activity in the iliocaudalis is not detectable during bladder contractions until the bladder infusion rate is increased to 0.5 ml/min, when the IC EMG is consistently activated with each bladder contraction at the same time as the URS EMG. Panel D shows the contraction marked by the arrow in panel A at a faster time scale. Note that in contrast to the bursting pattern of the URS during the bladder HFOs that the IC EMG shows only asynchronous, tonic activity with no evidence of bursting. (S. Mori and K.B. Thor, unpublished).

conditions. The remaining rats showed micturition-associated pubocaudalis EMG activity after administration of various drugs (e.g. α2 adrenoceptor antagonists) known to enhance motor neuron reflexes[242]. The pubocaudalis muscle EMG was always smaller (about 80% smaller) than the urethral rhabdosphincter EMG and was only elicited by a fast bladder-filling rate, suggesting that the pubocaudalis reflexes require a stronger afferent drive from the bladder than rhabdosphincter reflexes (**Fig. 13**). The micturition-related pubocaudalis EMG activity exhibited phasic, high frequency bursting (like the rhabdosphincter EMG) but was much less prominent (dashed lines in **Fig. 13B**). Furthermore, the pubocaudalis muscle exhibited very little activity preceding or following a bladder contraction in contrast to rhabdosphincter EM. Thus although there are some similarities in pubocaudalis and rhabdosphincter EMG activity, there are also distinctions that suggest separate but possibly overlapping control mechanisms.

The iliocaudalis muscle also exhibited an increase in EMG activity during bladder contractions (**Fig. 13C**) in 60% of the rats. However, the iliocaudalis activity never showed phasic bursting during micturition and instead showed only an asynchronous tonic discharge (**Fig. 13D**). Even after facilitatory drug treatments, when the iliocaudalis activity was strongest, no bursting was observed. To evoke iliocaudalis EMG activity, the bladder infusion rate was rapid, and the signal was again smaller than the rhabdosphincter EMG signal. Thus, both the iliocaudalis and pubocaudalis appear to have a weaker activation from bladder pathways than the rhabdosphincter. The pubocaudalis muscle exhibits a weak phasic bursting pattern during micturition

(similar but weaker than that of the urethral rhabdosphincter), while the iliocaudalis shows only asynchronous, tonic firing during micturition.

A recent detailed study of pelvic floor muscle activity in female rats during bladder filling and voiding also found that "pelvic floor muscle" activity was highly variable during bladder filling and voiding, while the rhabdosphincter EMG activity was reliable[209]. This study also reported that LA EMG activity did not increase in response to bladder pressure elevation by manual compression of the bladder with a cotton swab but did increase in response to a pinch of the perineal skin. Transecting the pudendal or LA nerves eliminated only rhabdosphincter or pelvic floor muscle activity, respectively. Thus it appears that segmental activation of LA muscle by bladder pathways is very weak.

4. PERIPHERAL INNERVATION OF URETHRAL AND ANAL RHABDOSPHINCTERS

The urethra and anal canal are surrounded by bands of striated muscle fibers; the urethral and anal rhabdosphincters, respectively as they pass through the pelvic diaphragm. The muscles do not attach to skeletal structures and thus act as true sphincters (i.e. contraction produces virtually no movement except constriction of the lumen). In addition, there are small, thin bands of striated muscle (compressor urethra, urethrovaginal sphincter, bulbocavernosus, and ischiocavernosus) that surround the urethra, vagina, and/or rectum and have connective tissue attachments to the perineal body[197].

The urethral rhabdosphincter, anal rhabdosphincter, bulbocavernosus, and ischiocavernosus muscles are innervated by the pudendal nerve[203, 215, 217-220, 241, 243], which originates from the S2-4 sacral roots and passes along the lateral surface of the internal obturator and coccygeus muscles and through Alcock's canal (**Fig. 11B**). As the nerve passes through the canal, it branches into the inferior rectal nerve (which innervates the anal rhabdosphincter), the perineal nerve (which innervates the urethral rhabdosphincter, the bulbospongiosus muscle, the ischiocavernosus muscle, superficial transverse perineal muscle, and the labial skin), and the dorsal nerve of the clitoris. The branches of the perineal nerve are more superficial than the dorsal nerve of the clitoris and, in most cases, travel on the superior surface of the perineal musculature. The terminal branch of the perineal nerve to the striated urethral sphincter travels on the surface of the bulbocavernosus muscle then penetrates the urethra to innervate the sphincter from the lateral aspects (**Fig. 11B**). The specific innervation of the smaller bands of muscles attached to the perineal body has not been characterized.

Nerve fascicles[244], as well as the motor nerve terminals and end plates[228] of the urethral rhabdosphincter, are preferentially located along the lateral aspects of the urethra in rat. Overlap, or crossing of the midline, between the left and right pudendal nerve terminal fields has been described in monkey anal rhabdosphincter[245]. The rhabdosphincter of both men and women contain neuronal nitric oxide synthase (nNOS), which is contained in a subpopulation (43%) of the muscle fibers, as well as nerve fibers, with concentration at the neuromuscular junction in humans and sheep[246-248]. Additionally, nNOS has been localized to pudendal motor neurons, which innervate the rhabdosphincter in rats, cats, monkeys, and humans[249, 250]. nNOS is responsible for producing the transmitter nitric oxide (NO). While NO is known to increase cGMP levels in many types of smooth muscle; its role in control of striated muscle and in neuromuscular transmission is not well established[251]. An NO donor has been shown to reduce urethral pressures at the level of the rhabdosphincter[252], but it is difficult to determine if the effect is on smooth or striated muscle.

The possibility that the urethral rhabdosphincter receives a "triple innervation" from somatic, parasympathetic, and sympathetic nerves[253] was raised in early histological studies. However, this has been disputed by subsequent studies[254] that showed no physiological effects of autonomic nerve stimulation on striated sphincter function and showed that the autonomic fibers are only "passing through" the outer layer of striated muscle to reach the inner layers of smooth muscle.

a) Urethral and Anal Rhabdosphincter Motor Neurons

Pudendal motor neurons that innervate the urethral and anal rhabdosphincters (and bulbocavernosus and ischiocavernosus) muscles are situated along the lateral border of the sacral ventral horn in Onuf's nucleus in human[255] monkey[217, 256], dog, cat[219, 220, 257], hamster[258] and guinea pig[259]. Studies in cat[218], monkey[217], and human [255] show that urethral rhabdosphincter motor neurons occupy a ventrolateral position and anal rhabdosphincter motor neurons occupy a dorsomedial position within the confines of Onuf's nucleus (**Fig. 14A**). However in other species, urethral and anal rhabdosphincter motor neurons are located in separate nuclei (**Fig. 14E**). In rat[215], anal sphincter (and bulbospongiosus) motor neurons are located medially in the ventral horn, just ventrolateral to the central canal; while the urethral sphincter (and ischiocavernosus) motor neurons are located in the same region as others species, i.e. along the lateral edge of the ventral horn. In the domestic pig[260] and Mongolian gerbil[261], anal sphincter (and bulbospongiosus) motor neurons are located just dorsolateral to the central canal.

Sphincter motor neurons are different from motor neurons that innervate skeletal muscles. They are densely packed within the confines of Onuf's nucleus and exhibit tightly bundled dendrites that run rostrocaudally within the confines of the nucleus.

Transverse dendrites are particularly unique in bundling and projecting laterally into the lateral funiculus, dorsally towards the sacral parasympathetic nucleus, and dorsomedially towards the central canal (**Fig. 14**)[218, 257, 262]. This is similar to bladder preganglionic neurons[263], suggesting that rhabdosphincter motor neurons and preganglionic neurons receive inputs from similar spinal regions. The dense packing and dendritic bundling of sphincter motor neurons may be related to their special sphincteric function and facilitate simultaneous activation of sphincter motor units. Recurrent axon collaterals (**Fig. 14D**)[257] in the absence of recurrent inhibition[234, 264] suggests a recurrent facilitation that may also reinforce simultaneous activation. Finally, the arrangement of peripheral motor nerve terminals bilaterally at dorsolateral and ventrolateral positions in the urethra may also provide symmetrical force generation[228].

Rhabdosphincter motor neurons are also physiologically different from skeletal muscle motor neurons in that they do not exhibit significant monosynaptic inputs[234], Renshaw cell inhibition[234], nor crossed disynaptic inhibition[264]. Patch clamp recordings from urethral rhabdosphincter motor neurons in spinal slices[265] demonstrate higher resting membrane potentials, higher membrane resistance, and a lower rheobase compared to other motor neurons in the slice (**Fig. 15A-C**). These in vitro results are similar to in vivo results that also showed unique passive membrane properties (e.g. high input resistance, low rheobase, short after-hyperpolarization,

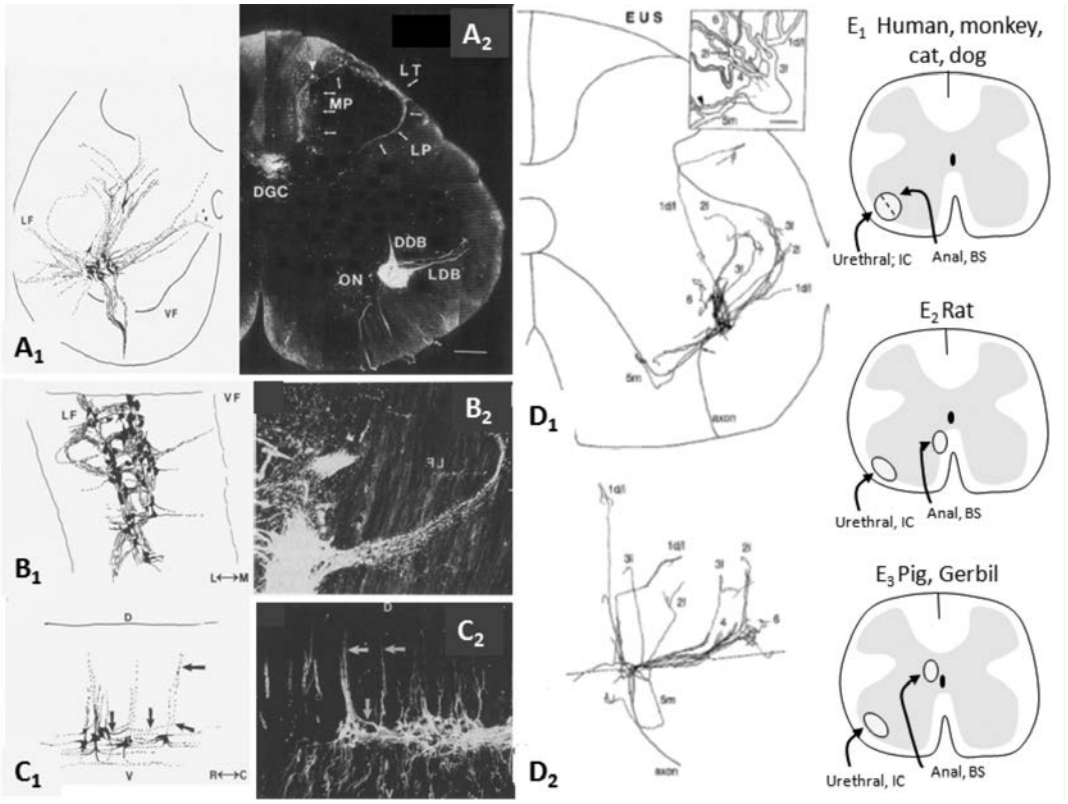


Figure 14. A-C. Composite drawings (A1-C1) and photomicrographs (A2-C2) of pudendal motor neurons in cat labeled by application of horseradish peroxidase (HRP) to the pudendal nerve as seen in transverse (A), horizontal (B), and sagittal (C) sections. The photographs provide raw data from 1 of the single sections used to make the corresponding composite drawing. Note that the dendrites of pudendal motor neurons project into the lateral funiculus (LF). D=dorsal, V=ventral, M=medial, L=lateral, R=rostral, C=caudal. DDB=dorsal dendritic bundle, LDB=lateral dendritic bundle. Primary afferent terminal labeling can also be seen in Lissauer's tract (LT), the lateral pathway (LP), medial pathway (MP), and dorsal gray commissure (DGC) in panel A1. (Primary afferents were not drawn in panel A1, only motor neurons). Adapted from Thor et al., 1989. D. Composite drawing of a single pudendal motor neuron labeled by intracellular injection of HRP showing the transverse (D1) and sagittal (D2) distribution of dendrites (Designations, such as 1d/l, 2l, 3l, 6 etc., indicate individual dendrites that are seen in both panels D1 and D2). The arrow head in the insert of D1 indicates the cell's axon. The dashed line in D2 represents the border between the ventral horn and ventral funiculus. Inset in D1 is a 3D rendition of the neuron. Adapted from Sasaki et al 1994. E. Diagrams comparing locations of urethral rhabdosphincter and ischiocavernosus (IC) versus anal rhabdosphincter and bulbospongiousus (BS) motor neurons in various species.

membrane bistability, and non-linear responses to depolarizing current injection, which was recently reviewed[266]). This combination of biophysical properties is uniquely conducive to simultaneous, prolonged, tonic activity, in keeping with the anatomical and functional properties described above.

b) Afferent Innervation of the Urethral and Anal Rhabdosphincters

Various studies have characterized primary afferent neurons sending axons into the pudendal nerve[215, 218, 267]. However this nerve carries the innervation to many visceral structures (e.g. urethra, genitalia, rectum, vagina) in addition to skin and rhabdosphincters, thus it is difficult to specifically characterize the sensory innervation of the sphincters per se. Nevertheless, the paucity of large sensory neurons in sacral dorsal root ganglia following application of tracers to the pudendal nerve suggests that the sensory innervation of the rhabdosphincters does not contain large myelinated fibers (i.e. Type Ia and Ib) that innervate these sensory organs[226, 229-233] that typically innervate muscle spindles, Golgi tendon organs, or Pacinian corpuscles. Indeed, multiple investigators using various techniques have not found muscle spindles or Golgi tendon organs in the rhabdosphincters. This is consistent with the finding that the pudendal nerves lack small g motor neuron axons (which innervate muscle spindles) [231] and the absence of rhabdosphincter connections to bone by tendons. On the other hand, Pacinian corpuscle-like structures have been found in the urethra of cat[233] and may play a role in sensing urine flow during micturition to inhibit sphincter activity and/or reinforce detrusor contractions.

The spinal terminals of pudendal primary afferent fibers are distributed throughout laminae I, V, VII, and the dorsal gray commissure (**Fig. 14A2**), while labeling in laminae III and IV is well-defined and restricted to the medial third of the dorsal horn[218]. This restricted pattern in laminae III and IV is consistent with the somatotopic organization expected for cutaneous mechanoreceptors originating in the perineal skin[268]. Local injection of tracers targeted to the urethral and anal rhabdosphincters [218, 269] only produced labeling of the spinal terminals of primary afferent neurons in lateral and medial lamina I, the intermediate gray matter, and the dorsal commissure gray matter, not in laminae III or IV. Since the HRP likely spread into the urethra and rectum, it is possible that this labeling occurred in visceral as well as rhabdosphincter afferent pathways. However, since no labeling was seen in large diameter primary afferent neurons nor in terminals in medial laminae III and IV (cutaneous fields) nor medial lamina VI, an area where large diameter myelinated fibers of muscle spindle and Golgi tendon organs nerves terminate [237, 238] it is reasonable to conclude that the rhabdosphincters are not significantly innervated by large myelinated nerve fibers typically associated with other striated muscle.

5. REFLEX ACTIVATION OF URETHRAL AND ANAL RHABDOSPHINCTERS

Rhabdosphincter motor neurons can be activated via segmental[214, 234-236] and descending pathways (**Fig**. **16**)[234, 270, 271]. The segmental inputs can be activated by stretch receptors and nociceptors in the bladder or urethra or genitalia[272-274]. Electrophysiological studies in cats[214, 218, 235, 236, 275, 276] show that stimulation of either pelvic nerve or pudendal nerve afferent fibers can activate polysynaptic spinal segmental reflexes that can be recorded at central delays of 1.5 msec with intracellular electrodes in sphincter motor neurons[277, 278] and at a latency of about 10 msec from electrodes placed on pudendal nerve efferent fibers or inserted directly into the urethral or anal rhabdosphincter muscles[275, 279-281]. The segmental reflex is considered polysynaptic based on the latency[234, 277, 278] and retrograde transynaptic labeling of interneurons in laminae I and V of the dorsal horn and in the dorsal gray commissure by pseudorabies virus (PRV) injected into the urethral rhabdosphincter[269]. The dorsal horn interneurons are likely those that participate in the segmental reflex activation of sphincter motor neurons while the dorsal gray commissure interneurons are likely inhibitory (see below). Studies in rats also show that electrical stimulation of afferent axons in the pelvic nerve elicits reflexes in pudendal nerve efferent fibers or the urethral rhabdosphincter[282, 283] similar to the cat. Also similar to the cat, PRV injected into the urethral rhabdosphincter[284] labels interneurons in laminae I and V of the dorsal horn and in the dorsal gray commissure.

Previously, the afferent inputs from the urinary bladder have been emphasized as being of primary importance for activation of the segmental reflex by pelvic nerve stimulation because bladder distension will activate the urethral rhabdosphincter[285]. This reflex activation is often referred to as the “guarding reflex” or “continence reflex”. However, recent studies are placing greater emphasis on urethral afferent fibers[273, 286, 287]. It is tempting to speculate that the guarding reflex is actually activated more vigorously by urethral afferent fibers if urine inadvertently begins to pass through the bladder neck and into the proximal urethra, with a requirement for a rapid closure of the more distal urethral sphincter (i.e. guarding against urine loss) compared to simple bladder distension or increases in intravesical pressure.

The greater importance of urethral afferent fibers is also suggested by experiments where bladder afferent fibers are electrically stimulated. For example, in studies by McMahon et al[235], electrical stimulation of pelvic nerve fibers close to the bladder was not able to evoke pudendal nerve firing in a large proportion of cats but placement of electrodes more centrally on the pelvic nerve was able to evoke firing. Karicheti and Thor (unpublished observations) also found that stimulating nerve bundles close to the

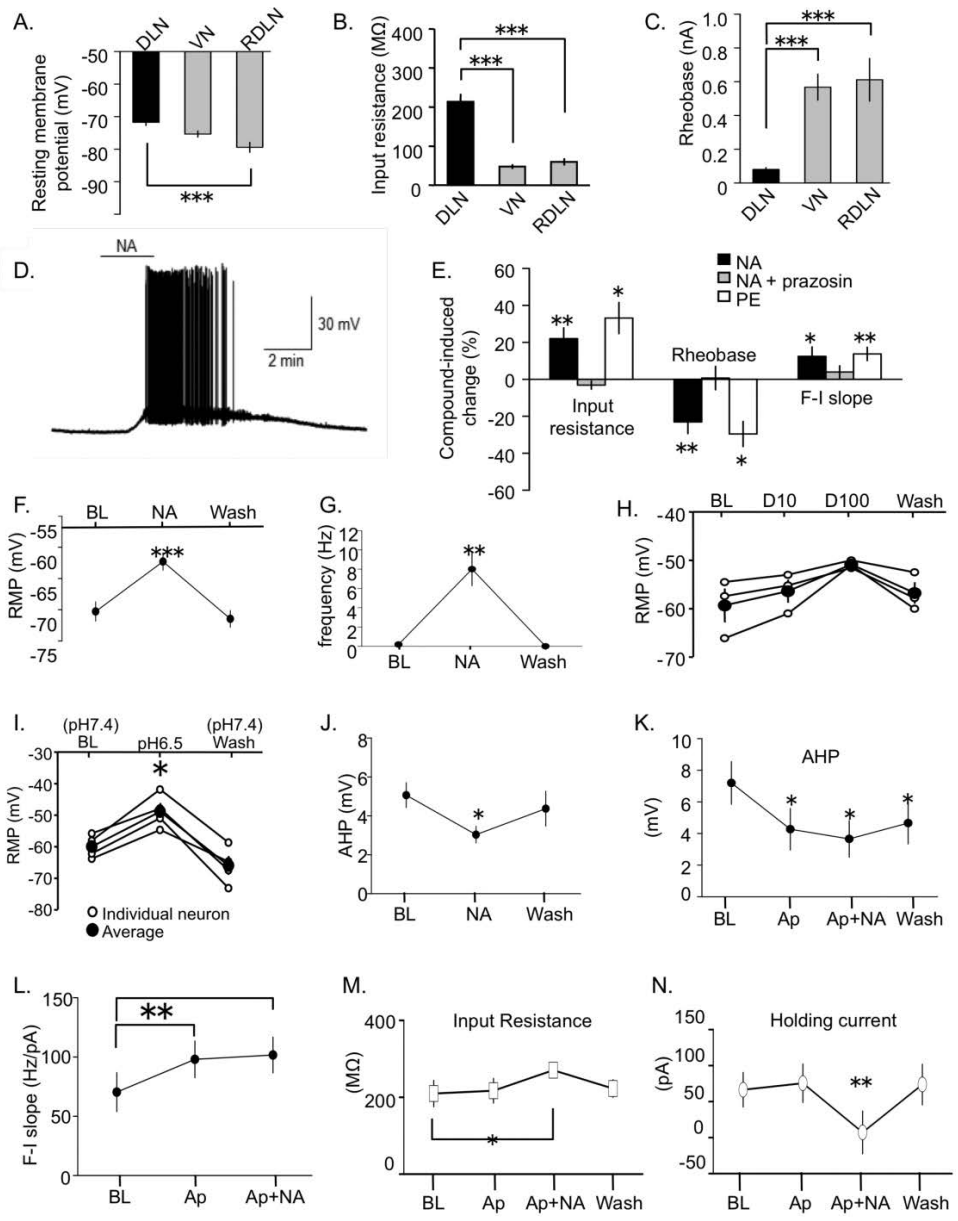


Figure 15. Membrane properties, responses to noradrenaline, and involvement of TASK and SKCa channels in retrogradely-labeled rhabdosphincter motor neurons recorded using patch clamp electrophysiology in L5/6 spinal cord slices from 6-14 day old female rats. Comparison of resting membrane potential (RMP, A), input resistance (B), and rheobase (C) in urethral rhabdosphincter motor neurons (dorsolateral nucleus, DLN), axial motor neurons (Ventral nucleus, VN), and hindlimb motor neurons (retrodorsolateral nucleus, RDLN). D) Noradrenaline (NA, 20 μM) depolarizes rhabdosphincter motor neurons and induces robust firing. E) NA and phenylephrine (PE), and alpha1 adrenoceptor agonist, increase input resistance, rheobase, and firing rate-current injection (F-I slope) relationship in a prazosin-sensitive (alpha1 adrenoceptor antagonist) manner in rhabdosphincter motor neurons. Significant and reversible, mean increases in RMP (F) and firing frequency (G) in rhabdosphincter motor neurons produced by NA (20 μM). Doxapram (H), a TASK channel blocker, at 10 μM (D10) and 100 μM (D100), mimics NA's ability to depolarize rhabdosphincter motor neurons. Decreasing extracellular pH to 6.5 (I), which closes TASK channels, mimics NA's ability to depolarize these neurons. NA significantly reduces the afterhyperpolarization (AHP) in rhabdosphincter motor neurons (J) in a prazosin-resistant manner. Apamin (A), an SKCa channel blocker, reduces AHP (K), increases the F-I slope (L) and occludes NA's ability to reduce the AP and increase the F-I slope. Apamin does not influence the input resistance (M) or holding current (N), nor occludes NA's ability to do so. From Yashiro et al., 2010.

bladder is often ineffective in producing a spinal reflex to the urethral rhabdosphincter, but in the same animals it evokes reflex activity on the hypogastric nerve (indicating that the electrical stimulation is activating bladder afferent fibers). Furthermore, it was possible to consistently evoke a reflex when the stimulus was applied more centrally on the pelvic nerve, which would include fibers from the urethra. Since the more central electrode placement would also activate colonic and genital afferent fibers, additional experiments are needed to specifically compare urethral versus bladder versus colonic afferent fibers in evoking the "guarding reflex".

Electrical stimulation of pudendal afferent fibers also evokes a spinal reflex to activate the rhabdosphincter in cat[235, 279, 288] and rat[282, 283]. Since some urethral afferent fibers (as well as rectal, genital, and cutaneous afferent fibers) travel in the pudendal nerve, it is possible that the spinal urethral rhabdosphincter activation by pudendal afferent stimulation is also a manifestation of the "guarding reflex".

Sphincter reflexes in the cat also exhibit prolonged changes in excitability following short trains (5-10 second) of electrical stimulation of afferent axons in the pudendal nerves[288]. Recordings from sphincter motor neurons in the sacral spinal cord and from rhabdosphincter peripheral motor axons revealed that stimulation of pudendal afferent axons elicited not only short latency transient responses but also sustained activity persisting for 3-30 seconds after the end of the stimulus train [288]. The persistent activity was associated with a small membrane depolarization and was terminated by small hyperpolarizing currents. Similar persistent activity has been observed in hindlimb motor neurons with slow axonal conduction velocities similar to those of sphincter motor neurons[289].

6. INHIBITION OF URETHRAL RHABDOSPHINCTER (URS) REFLEXES DURING VOIDING

Voiding is induced voluntarily or reflexively by neural circuitry in the brain.[3] For voiding to occur, there must be contraction of the bladder and simultaneous relaxation of the urethral rhabdosphincter. These responses are mediated by descending projections from neurons in the pontine micturition center (PMC) that excite the sacral autonomic outflow to the bladder and inhibit the motor outflow to the sphincter (**Fig. 16**). This coordination is lost following spinal cord injury.[3] Electrical or chemical stimulation in the PMC in cats excites the bladder and inhibits sphincter EMG activity[269, 270, 290-292] and hyperpolarizes sphincter motor neurons[288]. The descending inhibitory pathway from the PMC to sphincter motor neurons is thought to involve spinal GABAergic inhibitory neurons in the dorsal commissure of the sacral spinal cord (**Fig. 16**) [293, 294]. A role for glycinergic and enkephalinergic interneurons in the dorsal commissure has also been proposed[269, 294-298] in mediating inhibition of the sphincter during voiding (**Fig. 16**).

In addition to supraspinal inhibitory mechanisms, a "spinal, urine storage reflex, inhibitory center" (SUSRIC) was found that inhibited both the somatic and the sympathetic urine storage reflexes controlling the urethral rhabdosphincter and smooth muscle, respectively, in the cat[280, 299]. Activation of this inhibitory center by electrical stimulation of the pelvic nerve afferent fibers occurs simultaneously with the activation of the URS reflex itself. The latency of the inhibition was < 50 msec and had a duration of 500-1,000 msec. Activation of this inhibitory center explains the diminished capacity of the URS evoked reflex to follow frequencies of pelvic afferent stimulation greater than 5 Hz[280, 299]. Physiological stimulation of the pelvic nerve afferent fibers, which occurs with distension of the bladder, has also been reported to inhibit rhabdosphincter EMG activity in both spinal intact [276] and spinalized cats [236] in the absence of a bladder contraction and its associated inhibitory mechanisms. Possibly the inhibition of rhabdosphincter activity by distension of the bladder represents a physiological corollary for the inhibition of rhabdosphincter activity by high frequency electrical stimulation of pelvic nerve afferent fibers. Although the inhibitory effects are localized to the spinal cord caudal to the T12 level, they are regulated by supraspinal systems that respond to 5-HT1A receptor activation and enhance sphincter activity through disinhibition[300-302]. A possible clinical correlation of SUSRIC activation may be the elegant demonstration in men that conditioning stimuli applied to the dorsal nerve of the penis (i.e. pudendal nerve afferent fibers) inhibited urethral rhabdosphincter contractions reflexively evoked by magnetic stimulation of the spinal cord applied at intervals of 20 - 100 msec after the conditioning stimuli[303].

The situation is different is rats, where the urethral rhabdosphincter activity shifts from a tonic, asynchronous firing pattern during urine storage to a phasic bursting pattern during voiding, resulting in well-documented "high frequency oscillations" (HFOs) of pressure recorded from the urethra or bladder[269]. These HFOs contribute to efficient voiding in the rat, and their suppression due to drug treatment[300], pudendal nerve damage[269, 304, 305], spinal cord transection[269, 282, 306], or STZ-induced diabetes[307-312] (Kullmann and Thor, unpublished observation) results in a significant drop in voiding efficiency and an increase in postvoid residual urine volumes.

7. SUPRASPINAL ACTIVATION OF RHABDOSPHINCTERS AND PELVIC FLOOR MUSCLES

Supraspinal activation of urethral and anal rhabdosphincter motor neurons can be mediated in response to voluntary (i.e. corticospinal[256]), as well as involuntary reflexic inputs (e.g. during coughing, sneezing, vomiting) presumably from nucleus retroambiguus in

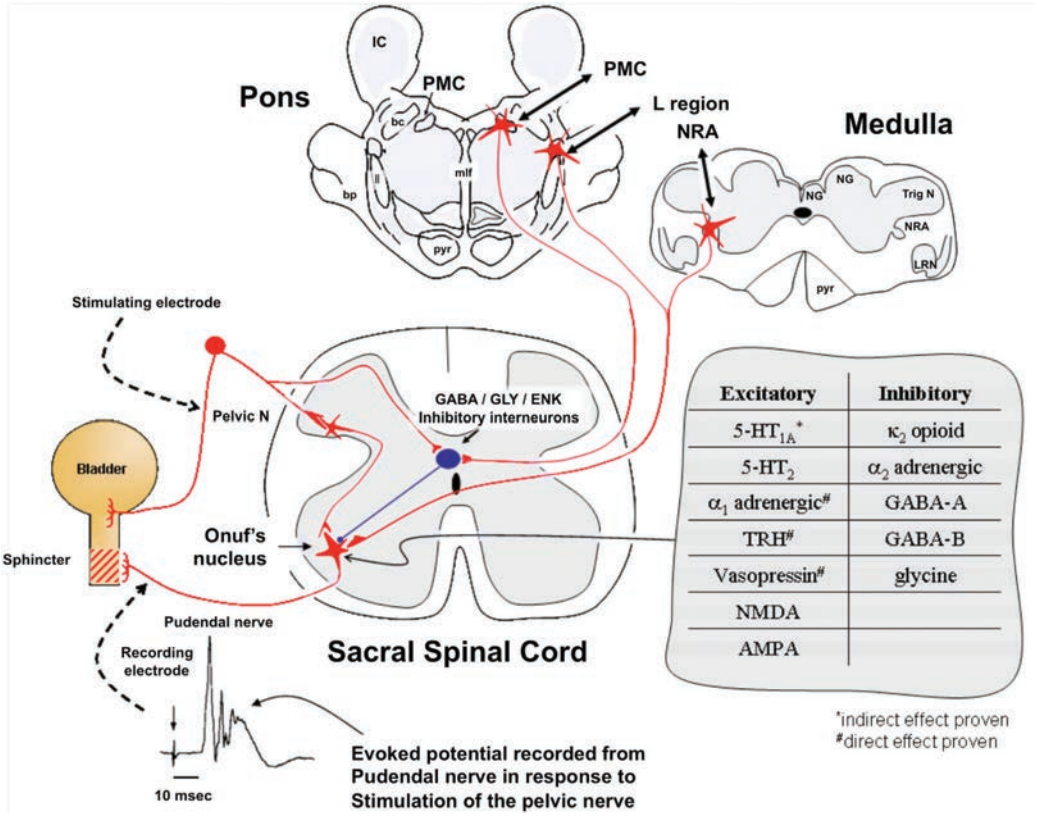


Figure 16. Drawing of proposed model for spinal and Supraspinal excitation and inhibition of rhabdosphincter pudendal motor neurons with an example of the evoked potential recorded by an electrode on the pudendal nerve in response to electrical stimulation of the pelvic nerve at 0.5 Hz and a table showing the predominant effects of various receptor subtypes on evoked potentials recorded from the pudendal nerve or urethral rhabdosphincter. Red stellate shapes and lines represent excitatory neurons and their axonal pathways, respectively; while the black oval shape and line represent an inhibitory interneuron and its axonal pathway. Simulation of the pelvic nerve activates a polysynaptic spinal reflex arc that produces an evoked potential recorded from axons of sphincter motor neurons in Onuf's nucleus at a latency of about 10 msec. In addition, this stimulation also activates inhibitory interneurons that, after 50 msec delay, produce inhibition of sphincter motor neurons for about 1,000 msec (see text for details). Presumably this arrangement allows low frequency pelvic afferent activity (1 Hz) to increase sphincter activity during urine storage and to inhibit sphincter activity when the pelvic afferent activity markedly increases (> 5 Hz) as might occur with very large bladder volumes or during a micturition contraction. The model includes GABAergic, glycinergic, or enkephalinergic inhibitory neurons located in the dorsal gray commissure.

In addition to spinal excitatory sphincter reflexes, Supraspinal pathways originating in the medullary nucleus retroambiguus (NRA) and the pontine "L region" can activate sphincter motor neurons during Valsalva maneuvers and during urine storage, respectively. When micturition occurs, neurons in the pontine micturition center (PMC) provide descending activation of the GABAergic, glycinergic, or enkephalinergic neurons in the dorsal gray commissure to inhibit sphincter motor neurons and allow voiding to begin. In addition to these predominant pathways, various other areas of the brain (e.g. medullary raphe serotonergic pathways, pontine locus coeruleus noradrenergic pathways, etc) provide "modulation" of the reflexes. Those excitatory and inhibitory modulatory pathways that have been explored pharmacologically are also listed in the table. For simplicity, the inhibition associated with PMC activation and the inhibition associated with pelvic nerve stimulation are shown passing through the same inhibitory interneuron. However, no evidence yet exists that this is the case.

Abbreviations: IC=inferior colliculus; NG=nucleus gracilis; NC=nucleus cuneatus; TrigN=spinal nucleus of the trigeminal nerve; LRN=lateral reticular nucleus; pyr=pyramidal tract; mlf=medial longitudinal fasciculus; ll=lateral lemniscus; bc=brachium conjunctivum; bp=brachium pontis; GABA=gamma amino butyric acid; GLY=glycine; ENK=enkephalin; TRH=thyrotropin releasing hormone; NMDA=N=methyl D=aspartate; AMPA=a-amino=3=hydroxy=5-methyl=4=isoxazoleproprionic acid; 5-HT=5-dihydroxytryptamine (from Thor 2010).

the caudal medulla (**Fig. 16**)[271, 285, 313-316]. Nucleus retroambiguus also innervates the pelvic floor muscles[222, 317], as well as abdominal muscles, consistent with a role in raising intra-abdominal pressure during Valsalva maneuvers. Generally, the pelvic floor and rhabdosphincter muscles are activated as a functional unit when voluntarily contracted. However, differential activation of the rhabdosphincter and the pelvic floor muscles has been demonstrated[244], indicating distinct CNS control systems and innervation.

Rhabdosphincter motor neurons are unique among somatic motor neurons in receiving input from the paraventricular hypothalamus[270], although the function of this input has not been determined. In addition, their input from brainstem serotonergic and noradrenergic neurons is among the densest in the spinal cord [318-321].

8. NEUROCHEMICAL ANATOMY OF RHABDOSPHINCTER MOTOR NEURONS

In addition to their unique morphology, neurophysiology, and supraspinal inputs, rhabdosphincter motor neurons in Onuf's nucleus also exhibit a plethora of unique and highly diverse neurotransmitters, receptors, ion channels, and growth factors (**Figs. 16, 17** and **Table 1**) and indicate a role in continence and/or sexual function.

a) Pharmacology of Urethral and Anal Rhabdosphincters (Fig. 16)

The excitatory amino acid neurotransmitter, glutamate, mediates initiation of action potentials in rhabdosphincter motor neurons (and subsequent rapid contraction of the muscle) by binding to NMDA and AMPA receptors [242, 282, 322-329]. Thus it is useful to think of these transmitters as part of the "hardwired" reflex circuitry that is involved in all or none activation of consistent and reliable storage reflexes, as compared to monoamines and peptide transmitters (see below).

The inhibitory amino acids glycine, acting through strychnine-sensitive ionotropic receptors[297, 298], and GABA, acting through both GABA-A (ionotropic) and GABA-B (metabotropic) receptors[260, 295, 330, 331] are thought to be major inhibitory transmitters regulating rhabdosphincter activity. Clinical studies indicate that systemic[332] or intrathecal[331, 333] administration of the GABA-B agonist, baclofen, may reduce bladder-sphincter dyssynergia in some patients with neurogenic bladder.

In addition to amino acid transmitters, the monoamine transmitters (norepinephrine and serotonin) are also important in modulating rhabdosphincter motor neuron activity [334]. It was the preferential distribution of norepinephrine and serotonin terminals in Onuf's nucleus[318-321] that led to extensive animal studies of noradrenergic and serotonergic control of rhabdosphincter function and eventual clinical studies of duloxetine, a norepinephrine and serotonin reuptake inhibitor, as a treatment for stress urinary incontinence [274, 315, 316, 335-338]. Elegant studies in humans using magnetic stimulation of brain and sacral nerve roots[339] have indicated that duloxetine increases the excitability of rhabdosphincter motor neurons to both supraspinal and segmental inputs to increase urethral pressures. Importantly, duloxetine's ability to increase urethral rhabdosphincter activity did not interfere with the inhibition of sphincter activity during voiding (i.e. bladder-sphincter synergy was well-maintained)[274]. Similar clinical results occurred after administration of S,S-reboxetine, a selective norepinephrine reuptake inhibitor[340, 341]. This approach of increasing synaptic levels of serotonin and/or norepinephrine is logical, since it has been shown that noradrenergic and serotonergic terminals associated with rhabdosphincter motor neurons show an age-dependent decrease in density in rats[342] that might explain the increased incidence of stress incontinence with aging.

Multiple adrenergic receptor subtypes play a role in control of rhabdosphincter motor neurons, and the results with norepinephrine reuptake inhibitors indicate that these receptors can be activated by endogenous norepinephrine[275]. Strong evidence exists that a1 adrenoceptors excite rhabdosphincter motor neurons[275, 343]. Patch clamp studies[265] have shown that norepinephrine produces a direct depolarizing effect, accompanied by an increase in input resistance and decreased rheobase (**Fig. 15D-G**). These excitatory effects are largely mimicked by the α1 adrenoceptor agonist, phenylephrine, blocked by the α1 adrenoceptor antagonist, prazosin, but were resistant to apamin (**Fig**. **15M-N**), a small conductance Ca+2 activated K+ (SKCa) channel blocker. The depolarization, increase in input resistance, and decrease in rheobase produced by norepinephrine was mimicked by a doxapram, a TASK (TWIK-related acid-sensitive K1) channel blocker, or reducing extracellular pH to 6.5 (**Fig. 5H-I**, manuscript in preparation, Yashiro, Thor, Burgard, et al., 2012). Doxapram and pH 6.5 effects also occluded the responses to norepinephrine (manuscript in preparation, Yashiro, Thor, Burgard, et al., 2012). These findings indicate that norepinephrine is working through a second messenger system to close TASK K+ channels and increase rhabdosphincter motor neuron excitability (manuscript in preparation, Yashiro, Thor, Burgard, et al., 2012). In addition to the depolarization, increase in membrane resistance, and decrease in rheobase, norepinephrine also increased excitability of rhabdosphincter motor neurons by reducing the afterhyperpolarization (**Fig. 15J**) and increasing the firing frequency of the neurons (**Fig. 15D**)[265]. Both of these effects are blocked by apamin (**Fig. 15K-L**), indicating closure of SKCa channels is responsible for the reduction in afterhyperpolarization. Surprisingly, afterhyperpolarization reduction by norepinephrine was resistant to prazosin, indicating that this effect is not mediated by α1 adrenoceptors.

Excitatory effects of α1 adrenoceptor stimulation on rhabdosphincter neurons are supported by clinical studies[343] where decreases in rhabdosphincter

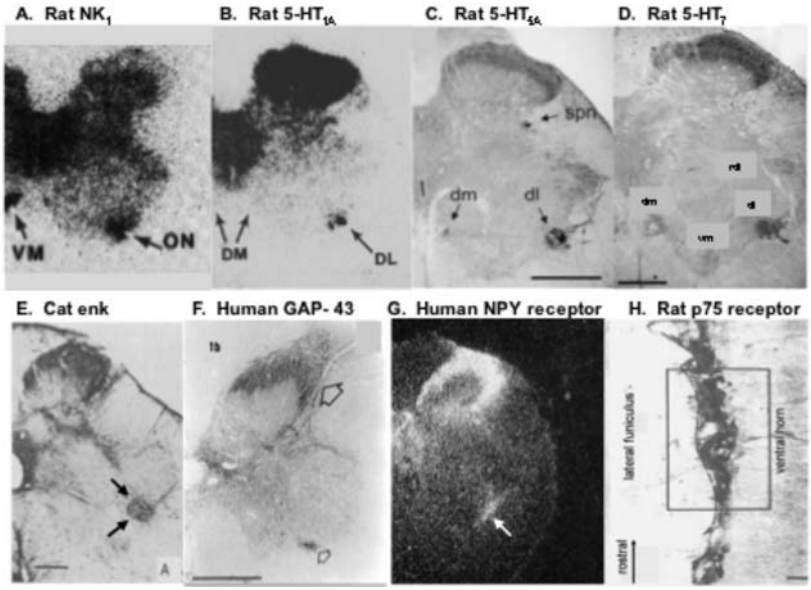


Figure 17. Examples of the unique and remarkable association of various neurotransmitters and receptors with pudendal motor neurons in various species. A-D. NK-1 receptors binding (A) from Charlton et al., 1985, 5-HT1A receptor binding (B) from Thor et al., 1993, 5-HT5A receptor immunoreactivity (C) from Doly et al., 2004, 5-HT7 receptor immunoreactivity (D) from Doly et al. 2005 in rat L6 transverse spinal sections. E. Cat Leu-enkephalin immunoreactivity in S1 transverse section from Glazer et al 1980. F. GAP-43 immunoreactivity in transverse section of human S1 spinal cord. Large and small open arrows indicate GAP-43 staining in the dorsal horn and Onuf's nucleus, respectively. Adapted from Brook et al., 1998. G. [125]I-NPY autoradiograph of transverse section of human S3 spinal cord. Adapted from Mantyh et al., 1994. H. p75 immunoreactivity in a longitudinal section from rat L6 spinal cord through the dorsolateral nucleus of the pudendal nerve. Adapted from Koliatos et al., 1994. DH=dorsal horn, CC=central canal, DM=dorsomedial nucleus of the pudendal nerve, DL=dorsolateral of the pudendal nerve, SPN=sacral parasympathetic nucleus, vm=ventromedial nucleus, RDL=retrodorsolateral nucleus, df=dorsal funiculus, ON=Onuf's nucleus.

activity were seen after administration of prazosin to human subjects. On the other hand, strong evidence exists that α2 adrenoceptor stimulation has the opposite effect, i.e. inhibition, of rhabdosphincter activity[275, 344, 345]. Importantly, reflex activity in the sympathetic pathway to the urethral and anal smooth muscle (i.e. the hypogastric nerve) shows similar adrenergic pharmacology - an enhancement of activity by α1 adrenoceptors[275, 346] and inhibition of activity by α2 adrenoceptors[275, 347]. Our lab (Yashiro, Thor, and Burgard) has been unable to demonstrate direct inhibitory effects of α2 adrenoceptor agonists in extensive patch clamp studies of rhabdosphincter neurons in neonatal rat spinal cord slices, indicating that the inhibitory effects seen in vivo are mediated via presynaptic or interneuronal actions.

Multiple subtypes of serotonin (5-hydroxytrptamine, 5-HT) receptors are also involved in modulating rhabdosphincter motor neuron excitability. Strong evidence exists that 5-HT2 receptors can excite sphincter motor neurons[279]. Indeed duloxetine's facilitatory effects on rhabdosphincter activity in anesthetized cats are mediated in part through activation of 5-HT2 receptors[274]. Both 5-HT2A and 5-HT2C receptor agonists increase rhabdosphincter EMG activity in dogs, guinea pigs, and rats[348, 349]. Recent in vitro rat spinal cord slice patch clamp studies show that part of this effect may be directly on rhabdosphincter motor neurons, as opposed to interneurons[350], since 5-HT induces a direct depolarization of rhabdosphincter motor neurons. The effect of 5-HT to enhance the bistable behavior, plateau potentials and persistent firing of motor neurons[351] very likely contributes to its facilitatory effect on sphincter reflexes and sphincter motor neuron firing[288]. Interestingly, substance P, a peptide transmitter that is co-localized with 5-HT in raphespinal nerve terminals, also produces direct depolarization of rhabdosphincter motor neurons in rat spinal cord slices[352], and thyrotropin releasing hormone (TRH), another peptide transmitter co-localized with 5-HT in nerve terminals, induces excitation of rat sphincter activity[353, 354] in vivo.

Immunohistochemical and molecular studies in humans and dogs[348] have shown that 5-HT2A, 5-HT2B, and 5-HT2C receptor subtypes are associated with Onuf's nucleus motor neurons. In addition, 5-HT2C receptor mRNA has been localized to anal sphincter motor neurons in the rat[355]. On the other hand, another immunohistochemistry study with retrograde labeling of urethral rhabdosphincter motor neurons and ischiocavernosus motor neurons in male rats indicates that the 5-HT5A receptor is associated with the rhab-

dosphincter motor neurons, while the 5-HT2A receptor is preferentially associated with the ischiocavernosus motor neurons[137] and thus may be preferentially involved in sexual function.

As described above, supraspinal 5-HT1A receptor stimulation also enhances rhabdosphincter activity in cats[280, 299-302]. Importantly, the excitatory effects of 5-HT1A receptor agonists on the rhabdosphincter can still be "over ridden" by inhibitory mechanisms during voiding, i.e. bladder-sphincter synergy remains despite 8-OH-DPAT induced enhancement of rhabdosphincter activity[280, 299, 301, 302, 356]. The enhancement of sphincter activity by 8-OH-DPAT in cats is not seen following acute[280, 299] or chronic[300, 301] spinal cord transection, indicating the 5-HT1A receptors mediating these effects are located supraspinally. 5-HT1A receptor activation may inhibit supraspinal neurons that facilitate SUSRIC-mediated inhibition of sphincter reflexes and thereby facilitate URS activity through disinhibition.

In spinal cord injured rats that have lost micturition-associated HFO bursting of the urethral rhabdosphincter, 5-HT1A receptors have been shown to restore the bursting. Chang et al[306] further showed that the center responsible for bursting activity in spinal rats was located between the T11 and L4 spinal segments. In the studies of Gu et al[301], 5-HT1A receptor stimulation had no effect on sphincter activity in control rats or on the asynchronous rhabdosphincter activity that precedes, and follows, micturition-associated bursting, in the spinal rats. 8-OH-DPAT only restored the bursting pattern during micturition in spinal rats.

In addition to amino acid and monoamine control of the rhabdosphincter motor neurons, peptides have also been shown to influence their activity. Onuf's nucleus is densely innervated by the opioid peptides encephalin (**Fig. 17E**) and dynorphin[296, 357-359]. In cats, the k opioid receptor agonist, ethylketocyclazocine, selectively inhibits spinal rhabdosphincter reflexes[281]. However, attempts to block sphincter inhibition during voiding with high doses of the opioid receptor antagonist, naloxone, were unsuccessful, indicating the enkephalins are not mediating physiological inhibition. In spinal intact rats, it was found that a k2 opioid receptor agonist inhibits the rhabdosphincter bursting pattern associated with micturition, leading to decreased voiding efficiency[300]. In these studies, k opioid receptor stimulation had no influence on the asynchronous rhabdosphincter activity that precedes and follows micturition-associated bursting, only on the bursting itself. Onuf's nucleus is abundantly invested with other peptidergic terminals. Excitatory effects of peptides; vasopressin, thyrotropin-releasing hormone (TRH) and substance P (SP), on rhabdosphincter motor neurons have been demonstrated[352-354].

9. LA AND RHABDOSPHINCTER NEUROPATHY

Childbirth is a risk factor for development of pelvic organ prolapse (POP)[360]. Furthermore, various studies have indicated damage to the innervation of the pelvic floor muscles, which might be expected to initiate pelvic descent and prolapse[361-366]. Early studies using pudendal nerve terminal latency as a measure of nerve damage[367] were met with skepticism for many reasons, however with more sophisticated analyses using EMG interference patterns a more recent series of elegant studies[365, 366, 368, 369] have provided evidence that LA nerve damage accompanies parturition in about 25% of women with approximately 1/3 of those continuing to show evidence of nerve damage at 6 months after parturition[365, 369]. Importantly, women undergoing elective Caesarian section (i.e. without preceding labor) showed no signs of LA nerve damage[366]. Furthermore, changes in function of the urethral rhabdosphincter were also associated with pregnancy (i.e. before labor), and these remained evident at 6 months postpartum[365, 366]. In rabbits[370], it has also been shown that multiparous females have thinner, longer, and weaker pubococcygeus muscles than nulliparous females, which may indicate nerve damage also occurs in this species. A recent study comparing continent and incontinent women[371] also demonstrated that incontinent women showed evidence of poor neuromuscular function of the rhabdosphincter, and the authors indicated that there was a correlation with age.

Because the pelvic floor supports the viscera, damage to the LA innervation and subsequent muscle flaccidity was thought to promote POP. To test this expectation experimentally, the LA muscles were bilaterally denervated in 7 squirrel monkeys[207], which is a species that shows age- and parity- correlated POP similar to humans[372]. Surprisingly, these monkeys showed no POP following this procedure for 2-3 years after surgery, despite showing statistically significant decreases in LA muscle mass and myocyte diameter (**Fig. 12A**), as well as vacuolization of the muscle. Thus, these experiments suggest that, in the absence of childbirth, the pelvic floor muscle innervation plays a minor role in providing visceral support and suggests that the connective tissue plays the major role. In women, the appearance of levator ani muscle abnormalities in magnetic resonance images after vaginal delivery concluded that frank damage of the LA muscle (and presumably the associated connective tissue) is correlated with sphincter damage, prolapse and incontinence [373, 374]. Thus, future research might focus on the changes in pelvic ligaments or extracellular matrix that occur with pregnancy, childbirth, and aging. Possibly after childbirth and stretching of the pelvic connective

tissue, the muscle plays a compensatory role. In support of this possibility, it was shown that LA muscle mass and myocyte diameter in monkeys with naturally occurring POP was equal to or greater than age-, parity-, and weight-matched monkeys without POP[207, 375], suggesting that LA muscle stretching might induce reflexes and subsequent muscle activity and hypertrophy.

Relative contribution of LA and pudendal nerves to continence mechanisms during sneezing in rats and cats.

Analysis of the urethral closure mechanisms during sneeze-induced stress conditions in anesthetized female rats and cats has revealed that pressure increases in the middle portion of the urethra are mediated by reflex contractions of the rhabdosphincter as well as the pelvic floor muscles[285, 376]. Transection of the pudendal nerves reduced sneeze-induced urethral reflex responses by 67% and transecting the nerves to the iliococcygeus and pubococcygeus muscles reduced urethral reflex responses by an additional 25%. Transecting the hypogastric nerves and visceral branches of the pelvic nerves did not affect the urethral reflexes indicating that sneeze-evoked urethral reflexes in normal rats were not mediated by these autonomic pathways. However, hypogastric nerve transection in conscious, chronic spinal cord injured, female rats reduced urethral baseline pressure, reduced post-void residual urine volumes, reduced maximal voiding pressure, and increased voiding efficiency. This indicates that sympathetic pathways to the bladder neck and proximal urethra contribute to urethral pressure and functional outlet obstruction and voiding dysfunction after spinal cord injury in unanesthetized animals, but not during sneezing[377].

Summary

Neural control of the pelvic floor (LA and coccygeus) is provided by the LA nerve, while the urethral and anal rhabdosphincters are controlled by the pudendal nerve. LA motor neurons are similar in morphology to other skeletal motor neurons, showing large α and small γ neuronal populations diffusely distributed in the sacral ventral horn. One distinguishing feature, however, is projections from LA motor neurons into Onuf's nucleus, the location of rhabdosphincter motor neurons. Presumably these projections coordinate pelvic floor and rhabdosphincter function. This proposed coordination of visceral and rhabdosphincter activity with pelvic floor muscle activity is one important area for future research. Rhabdosphincter muscles and their innervation are remarkably different from skeletal muscles. The rhabdosphincter striated muscles do not have Golgi tendon organs and muscle spindles, which are common in skeletal muscles. In addition, the rhabdosphincters are intimately associated with the urethra and anal canal and participate extensively in voiding and sexual function. Thus it should not be surprising that rhabdosphincter motor neurons are quite distinctive from skeletal muscle motor neurons. In contrast to the diffuse distribution of LA motor neurons in the sacral ventral horn, the rhabdosphincter motor neurons are densely packed within Onuf's nucleus (and homologous nuclei in other species). Finally, rhabdosphincter neurons exhibit a number of unique membrane properties that may contribute to simultaneous activation and which are distinctive from skeletal muscle motor neurons. Important species differences exist in the spinal localization of anal sphincter neurons. Other distinguishing characteristics of rhabdosphincter motor neurons are their unique morphology, their association with abundant neurotransmitters and receptors, a diverse physiology, and a rich pharmacology. These differences presumably reflect their integral role in coordinating somatic and visceral function during micturition, defecation, and copulation. Denervation of both the pelvic floor and the rhabdosphincters has been associated with childbirth and aging.

Marker		References
Transmitters	Enkephalin	(296, 357, 358, 378)
	CGRP	(378, 379)
	Somatostatin	(378, 380)
	Norepinephrine	(318, 321)
	Serotonin	(318, 319, 321, 358)
	Dopamine	(381)
	Substance P	(358)
	nNOS	(247, 248, 250)
	CRF	(382)
	CPON	(378)
Receptors	5-HT_{1A}	(383)
	5-HT_{2A}	(384)
	5-HT_{2C}	(348, 355)
	5-HT_{5A}	(384, 385)
	5-HT_{7}	(386)
	D_2	(387)
	NPY_2	(388)
	NK_1	(389)
	TRP-V2	(390)
Ion channel	$CaV_{1.3}$	(391)
Growth-related	P_{75} (growth factor receptor)	(392)
	CNTF receptor a	(393)
	GAP-43	(394, 395)
	TrkC	(396)

Table 1. Neuronal markers preferentially associated with rhabdosphincter motor neurons in Onuf's nucleus. nNOS = neuronal nitric oxide synthase; CRF = corticotrophin releasing factor; CPON = C-flanking peptide of neuropeptide Y; 5-HT = 5-hydroxytryptamine; D = dopamine; NPY = neuropeptide Y; NK = neurokinin; TRP = transient receptor potential; CaV = voltage sensitive Ca+2; CNTF = ciliary neurotrophic factor; GAP = growth associated peptide; trk = receptor tyrosine kinase

IV. EFFERENT PATHWAYS TO THE BLADDER

Three main neural pathways regulate lower urinary tract efferent activity: 1) sacral parasympathetic (pelvic) nerves provide excitatory input to the bladder; 2) thoracolumbar sympathetic nerves provide inhibitory input to the bladder and excitatory input to the bladder neck and urethra; and 3) sacral somatic (pudendal) nerves innervate the striated muscles of the sphincters and pelvic floor.[397] This section will describe the spinal and then peripheral pathways controlling efferent drive to the bladder. Efferent innervation to the rhabdosphincter is discussed in Section III.

Parasympathetic and sympathetic pre-ganglionic neurons release acetylcholine, which acts on nicotinic receptors to activate post-ganglionic fibres. In some species they also release opioid peptide transmitters and express nitric oxide synthase[398]; there is also evidence of involvement of pituitary adenylate cyclase activating peptide (PACAP), a peptide present in visceral afferent neurones, and of prostaglandins within the spinal cord.[399]

Parasympathetic post-ganglionic fibres terminate predominately at the detrusor muscle and release acetylcholine, resulting in detrusor contraction during voiding. Studies in animals have shown that sympathetic post-ganglionic fibres predominately terminate at the mucosal and urothelial level, releasing noradrenaline (NA), contributing to bladder relaxation during storage (via stimulation of beta-adrenergic receptors expressed in detrusor).

1. PREGANGLIONIC NEURONS

Parasympathetic preganglionic neurons are located in the lateral part of the sacral intermediolateral gray matter in a region termed the sacral parasympathetic nucleus. The neurons are small, fusiform-shaped cells which send dendrites into lateral lamina I of the dorsal horn, the lateral funiculus and medially into the dorsal grey commissure (DGC). The bladder preganglionic motor neurons are located in the S1-S3 segments in the cat,[400] guinea-pig[401], dog[401] and monkey[402]. In cat and guinea pig, these motor neurons are bilaterally located ventrolaterally in the intermediolateral column. The rat is different, as preganglionic motor neurons are located at L6-S1;[403, 404] unilateral ventral root rhizotomy at the L5 level in the rat decreases peak cystometric pressures. [405] The parasympathetic preganglionic neurones project through the ventral spinal roots to the major pelvic ganglion.[406-408]

At spinal levels L1–L2, both the intermediolateral horn and the DGC contain sympathetic preganglionic neurones whose axons also project to the major pelvic ganglion. Electrical stimulation of the lumbar sympathetic chain evokes firing in the pelvic nerve and in postganglionic nerves on the surface of the bladder and colon, at latencies of 60-150 ms.[409] With ageing, there is selective attrition of preganglionic sympathetic neurones in L1–L2, which project to the pelvic ganglion, with reductions in the extent of the dendritic arbors of remaining cells. [406, 407, 410]

In spinal cord injured patients, where disruption to pathways at pre-ganglionic levels is observed, several groups have used neural stimulation techniques to restore normal bladder function. Stimulating parasympathetic pre-ganglionic roots at S3 with implanted electrodes elicits two principal responses[411]: at low levels of stimulation, the external urethral sphincter, external anal sphincter and pelvic floor muscles are contracted. At high levels of stimulation, parasympathetic activation contracts the detrusor muscle, leading to efficient emptying of the bladder when the sphincter muscle relaxes.[412]

The recent increase in the use of sacral neuromodulation for the treatment of detrusor overactivity has resulted in numerous potential theories of its actions, including stimulation of efferents, direct effect on the muscle, stimulation of the afferents, induction of spinal plasticity, and modifications of cortical activation.[413]

The DGC also contains a group of interneurones, which have recently received more attention as main players in the guarding reflex (these are further discussed below in Bladder and Outlet.[414]

2. GANGLIA

The peripheral ganglia are the link in the relay of autonomic innervation to the lower urinary tract and reproductive organs, along with a substantial part of the extrinsic motor innervation of the lower bowel. There are species differences in organization and neurochemistry of pelvic ganglion cells and their spinal inputs. Large mammals have a plexus of pelvic and intramural ganglia, containing both sympathetic and parasympathetic neurons. The guinea pig is intermediate in complexity, with separate posterior and anterior plexuses innervating different pelvic organs. In the rat and mouse, the pelvic plexus consists of the major pelvic ganglia (MPG) and a number of small accessory ganglia.

Within the pelvic plexus there is topographical representation of the pelvic organs. In the female dog, neurons supplying different pelvic organs are located in separate ganglia, which possess a distinctive composition of neurone types and different preganglionic supply.[415] Neurons retrogradely labelled from the urinary bladder mainly occur in ganglia located at the vesico-ureteric junction. They comprise catecholaminergic calbindin neurons and noncatecholaminergic neurons containing calbindin or NOS, with relatively sparse pericellular varicose nerve fibres. In male mice[416], the major pelvic ganglia are close to the dorsal surface of the prostate gland. Their main inputs are the pelvic nerves, and the hypogastric nerve from the inferior mesenteric ganglion. The

major outputs are the penile (cavernous) nerve and the supply to the urogenital organs.

Functionally, the preganglionic sympathetic and parasympathetic neurons synapse on post-ganglionic fibres within the specific ganglia, releasing acetylcholine, which acts on nicotinic receptors. Patients with megacystis-microcolon-intestinal-hypoperistalsis syndrome (MMHIS)[417] have reduced or no alpha-3 nicotinic receptor subunit.[418] Selective gene knockout mice lacking the alpha-3 nicotinic receptor subunit alone or the beta-2 and beta-4 subunits in combination[419], develop severe bladder distension soon after birth, and later overflow incontinence. The detrusor muscle in these animals contracts in response to field stimulation or muscarinic agonists, but not nicotinic agonists[420], indicating the potential importance of alpha-3, beta-2, and beta-4 nicotinic receptor components in functional control of voiding, but not their location.

About half of the cholinergic ganglion cells contain VIP, distributed throughout most of the ganglion, with a cluster near the origin of the penile nerve.[416] Neurones with NPY are numerous and apparently randomly distributed throughout the ganglion, with marked variation between mouse strains. All noradrenergic neurons contain NPY, but many NPY neurons are not noradrenergic. Many of the cholinergic NPY neurons also contain VIP. Neurons immunostained for choline acetyl transferase (ChAT) have a complementary distribution to noradrenenergic neurons. ChAT is seen in varicose axon terminals closely associated with ganglion neurons. Neither NPY nor VIP is present in preganglionic terminals, except for a small number of individual neurones. The latter may arise from viscerofugal neurons in the myenteric plexus of the lower bowel.[421] Tyrosine hydroxylase (TH) is expressed by one-third of neurons, almost all co-expressing dopamine beta hydroxylase (DBH). Numerous TH axons are present in the hypogastric nerve, but very few in the pelvic nerve, supporting a primarily sympathetic origin. Non-neuronal cells containing TH are also present, resembling small, intensely fluorescent cells observed in many other autonomic ganglia.

The bladder wall itself contains intramural ganglia, and small clusters of autonomic ganglion cells are present in the adventitial connective tissue and among the detrusor muscle bundles. There is species variation in the extent of intramural innervation of the bladder; ganglia are present in many species such as the guinea pig, while the rat bladder contains the postsynaptic innervation alone.[422] The ganglia are found throughout the bladder wall and vary considerably in size.[130, 423] They show immunoreactivity to vasoactive intestinal polypeptide (VIP), nitric oxide synthase (NOS), neuropeptide Y (NPY) and galanin (Gal) in varying amounts. However, they do not contain enkephalin (ENK), substance P (SP), calcitonin gene related peptide (CGRP) or somatostatin (Som)[129], suggesting that cell bodies of sensory neurones are not located in the intramural ganglia. Postganglionic sympathetic nerves, identified with antibodies to TH and NPY, also synapse on these neurones. Nicotinic receptors have been identified on intramural nerve cell bodies within the bladder. [420]

3. TERMINAL NERVE FIBERS

Smooth muscle cells in the bladder are grouped into fascicles, several of which make up a muscle bundle. They receive a dense innervation, which runs in line with the axis of the fascicle and is derived from coarse nerve trunks in the connective tissue around the fascicles and bundles. This innervation mediates the widespread co-ordinated detrusor contraction accompanying voiding. The anatomical relationship between the preterminal innervation and the muscle fascicles has been described in a serial sectioning study in the human bladder.[424] The nerve supply is distributed by a series of dichotomous branchings, illustrated schematically in **Figure 18**. Adjacent to the muscle bundles, 1 or 2 primary nerve trunks run parallel to the long axis of the bundle. These give rise to circumferential peribundle branches. Both the longitudinal and circumferential trunks give off transverse interfascicular branches, entering the bundle perpendicular to its long axis, approximately at the midpoint of the bundle. Within the bundle they give axial interfascicular branches running along the long axis within and closely adjacent to individual fascicles, ending in the preterminal and terminal varicose intrafascicular axial innervation.

The majority of nerves running in the detrusor stains positively for acetylcholinesterase and for vesicular acetylcholine transferase (VAChT)[423, 425, 426] and are thought to be parasympathetic. Electrical field stimulation studies have been used to elucidate the neurotransmitter content from muscle strips (with or without mucosa). Acetylcholine and ATP appear to provide the bulk of the excitatory input, since electrical field stimulation responses are blocked by muscarinic receptor antagonists combined with purinergic antagonists. Both transmitters are released in the innervated muscle layer and persist after removal of urothelium. By using high-frequency field stimulation, it is possible to delineate the cholinergic and purinergic component.[427] Apart from acetylcholine and ATP, there are additional substances present in parasympathetic efferents (VIP, NOS, Gal), which allow immunohistochemical subclassification of nerve fibres, and raise the question as to whether additional transmitters (other than ACH/ATP) have a role in normal micturition function or disease pathophysiology.

Cholinergic nerves are also present in the suburothelium; most of them in addition contain NPY and TH and some contain NOS. In the muscle of the trigone, the most common axons contain both VIP and NPY, with noradrenergic axons forming only a sparse supply. Indeed, noradrenergic neurons are rare in the detrusor and absent in the mucosa.[416]

4. TRANSMITTERS

a) Glutamate

Glutamate is present in the terminals of primary afferent neurons in the spinal cord along with interneurons and fibres originating in the medulla oblongata. In general, glutamatergic neurons tend to be excitatory, contrasting with generally inhibitory effects of glycinergic neurons; however, excitatory/ inhibitory effects of transmitters can be reversed by the nature of the post-synaptic neuron. Thus, glutamatergic neurons can indirectly have an inhibitory effect if an inhibitory neuron is interposed before the ultimate target.[428] Glutamate acts on spinal neurons through a variety of receptor subtypes. These include NMDA receptors, which are important in controlling polysynaptic reflex pathways at the lumbosacral levels. The NMDAR1 glutamatergic receptor subunit is present in the spinal cord of male rats, and is expressed in the SPN. Glutamate is present in the dorsal root ganglion cells supplying the bladder[429], and the NMDAR1 sub-unit is also present in L6 dorsal root ganglion cells of the rat.[430] In female rats intrathecal injection of an NMDA receptor antagonist decreases bladder contraction pressure.[431] With ageing, there is a decrease in the density of glutamatergic synaptic inputs, which may influence urinary tract function.[408]

b) Glycine/ gamma amine butyric acid

Glycinergic and GABAergic interneurones have a major role in neural control processes mediating bladder function. [432]Glycinergic/ GABAergic projections to the lumbosacral cord inhibit the micturition reflex and also inhibit glutamatergic neurons. [433] Clinically, detrusor overactivity can be inhibited by GABA receptor activation.[330] Rectal distention prolongs the interval, decreases the amplitude and shortens the duration of bladder contractions in rats; this effect is not seen after simultaneous intrathecal injection of low dose strychnine (a selective glycine-receptor antagonist) and bicuculline (GABA-A receptor antagonist), suggesting that the inhibitory rectovesical reflex involves glycinergic and GABAergic mechanisms in the lumbosacral spinal cord, which may be synergistic.[434]

Indeed, in the spinal cord, several transmitters synergistically mediate the effects of modulatory pathways that influence the onward progression of efferent activity. In a rat model of neurogenic bladder dysfunction (autoimmune encephalomyelitis), an exaggerated descending excitatory control arises at the spinal segmental level, which gives rise to detrusor overactivity. Some animals with autoimmune encephalomyelitis develop detrusor areflexia rather than overactivity;[413] in these animals, the excitatory control is probably dominated by segmental inhibition, mediated primarily by glycine receptor activation. Spinal shock in rats induces an alteration of glycine/glutamate concentration ratio. [433] A change in the ratio of excitation and inhibition was also observed in humans suffering from spasticity and pain [435]. This balance of inputs, and the potential plasticity of neuronal circuits, is crucial in understanding pathophysiological processes.

c) Serotonin

Spinal reflex circuits involved in voiding function have a dense serotonergic innervation.[436] Immunocytochemical studies in rats, cats and primates show that lumbo-sacral sympathetic and parasympathetic autonomic nuclei receive serotonergic inputs from the raphe nuclei.[320, 321, 437, 438] Activation of the central serotonergic system can suppress voiding by inhibiting the parasympathetic excitatory input to the urinary bladder, and 5-HT elicits a prolonged activation of thoracic sympathetic preganglionic neurons. Stimulation of the raphe nuclei in the cat inhibits reflex bladder activity.[439-441] 5-HT1A and 5-HT2 receptors are present in the SPN. However, in different species serotonin (5-hydroxy tryptamine, 5-HT) may have varying functions in the central nervous control of bladder activity. For example, activation of 5-HT1A receptors facilitates reflex bladder activity in rats,[436, 442] and has been used to reverse the effects of diabetes mellitus [443].

Inhibitory effects on bladder activity are most likely mediated primarily by 5-HT1A receptors. The transmitter released by inhibitory interneurons has not been identified. Activation of 5-HT1A and 5-HT3 receptors also inhibits afferent input passing from the bladder to the brain. Blockade of 5-HT1A receptors in raphe neurons would increase raphe neuron firing and enhance serotonergic control of spinal reflex mechanisms. This effect would promote urine storage by enhancing sphincter activity and depressing bladder activity.[302, 444] Indeed, 5-HT1A receptor activation is associated with increased rhabdosphincter activity in spinal intact but not spinalised animals [280].

d) Adrenergic

Descending catecholaminergic neurones are primarily located in the upper medulla or pons[342] (**Figure 18**). In clinical use, non-selective α1-adrenergic antagonists influence urine flow and storage phase lower urinary tract symptoms; the two effects probably occur by different mechanisms, and central or peripheral locations may be responsible.[445] Reflex bladder activity is modulated by at least two spinal α1-adrenergic mechanisms. Firstly, there is inhibitory control of reflex bladder contractions, probably by modulation of afferent processing. Secondly, there is excitatory modulation of the amplitude of bladder contractions due to regulation of the descending glutamatergic limb of the spinobulbospinal bladder reflex pathway.[446, 447] α1A adrenoceptors comprise 70% and α1B-adrenoceptor 30% of the α-adrenergic receptors in the rat lumbar spinal cord,[448] while α1D adrenoceptors do not appear to have a significant role.

Blood pressure, vascular resistance and tissue blood flow are also regulated by α-adrenergic receptors.

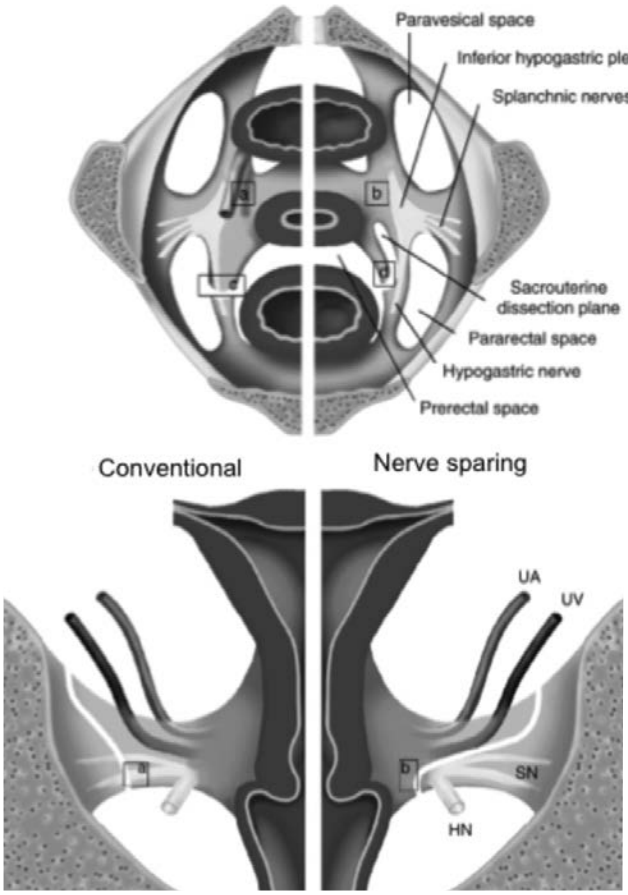


Figure 18: Diagram of the pelvic autonomic nerves in radical hysterectomy. Top panel Transverse section through the pelvis showing the bladder, cervix and rectum. Left side represents the conventional technique, right side represents the nerve sparing technique. Scale bar 250 µm. a, Vesicouterine ligament, conventional, b, vesicouterine ligament, nerve sparing; c, Sacrouterine ligament, conventional; d, Sacrouterine ligament, nerve sparing. Lower panel: Frontal sections through the uterus and cardinal ligament. UA, uterine artery, UV, uterine vein, SN, splanchnic nerves, HN, hypogastric nerve. Left side represents the conventional technique, right side represents the nerve sparing technique. Scale bar 250 µm. A, Posterior cardinal ligament, conventional; B, posterior cardinal ligament, nerve sparing. From (Maas, 2005).

Aging is thought to impact pelvic blood flow and thus, bladder function. Pharmacological blockade of the vascular α1B-adrenoceptor may increase pelvic blood flow and contribute to an improvement in bladder dysfunctions associated with aging and/or hypertension.[449] β3-adrenoceptors, although well documented peripherally, are also present in the rat sacral spinal cord. They are upregulated in rat models of partial urethral obstruction.

e) Substance P

Substance P- containing terminals are closely apposed to both sympathetic and parasympathetic preganglionic neurons projecting to the major pelvic ganglion.[450] Substance P- containing afferents in the pelvic nerve terminate in the outer laminae of the dorsal horn and in the region of the SPN and DGC.[451] Substance P is also located in intraspinal neurons located in the dorsal horn[452] or DGC[453]. In young adult rats, substance P in the ventral horn is almost exclusively co-localized with serotonin and derived from descending axons of medullary neurons[454, 455] and is also often co-localized with serotonin in axon terminals in the lumbosacral spinal cord.[456] Functionally, substance P affects micturition reflex activity;[457] intrathecal administration of Substance P at spinal levels L5–S1 induces bladder contraction. [458] Substance P also increases the firing rate of sympathetic preganglionic neurons.[459] Studies in the rat show that substance P levels decline with ageing in both the dorsal and ventral regions of the lumbosacral cord.[460, 461] Substance P-immunoreactive innervation of the dorsolateral nucleus (supplying the EUS) is not obviously altered with ageing. [462]

f) Purinergic

ATP is released together with noradrenaline and neuropeptide Y from sympathetic nerves. It is also released as a cotransmitter with acetylcholine from parasympathetic nerves supplying the bladder. Cotransmission likely offers subtle, local variations in neurotransmission and neuromodulation mechanisms.[463]

5. PELVIC ORGAN INTERACTIONS AT THE EFFERENT NEURAL LEVEL

a) Bladder and Outlet

Neural coordination of physiological and behavioral functions depends on convergence within the nervous system of information from relevant areas. There is extensive convergence of pelvic organ input[464, 465] at the levels of the spinal cord, dorsal column nuclei, solitary nucleus, medullary reticular formation, and thalamus.[466] The fundamental role

of spinal and supraspinal mechanisms in maintaining normal lower urinary tract synergy, between the bladder and sphincter, is well recognized.

In this context, the role of spinal interneurons must be considered. Involuntary bladder emptying during urine storage is considered to involve somatic nerve activity originating from cells in the lateral ventral horn, in a region called Onuf's nucleus. Normally, cholinergic sphincter moto-neurons project to the urethral striated muscle/rhabdosphincter via the pudendal nerve, resulting in its contraction.[3] This contraction can be activated by bladder afferent activity conveyed through pelvic nerves, and is considered to be organized by interneuronal circuitry in the spinal cord. It is thought to come into play in response to sudden increases in bladder pressure – for example, during a cough, sneeze, laugh. With aging, there is a loss of innervation at the terminal muscle level, which is displayed as a loss of striated muscle fibres in the sphincter and thus, a loss of urethral closing pressure. [467]

Synergic lower urinary tract function may also be a feature of the peripheral innervation, independent of CNS co-ordination. In the female minipig, pre-ganglionic pelvic nerve stimulation evokes a pressure increase in the bladder and a pressure decrease in the urethra.[468] It remains to be determined whether this observation suggests pre-determined, separate inputs to the bladder (excitatory to the bladder, inhibitory to the outlet), or whether the divergence occurs at postganglionic motorneuron level, which send branches supplying both bladder and urethra. In the latter arrangement, release of different neuromuscular transmitters from branches of the same motorneurone, or interposition of an additional intermediary cell would be required. The former is circumstantially supported by the observed co-localization of acetylcholine- and nitric oxide-related enzymes.[469]

b) Bladder and Bowel

Clinicians are familiar with the detrimental effect of bowel disorders on lower urinary tract activity. Physiologically, the efferent limb of the micturition reflex is inhibited by afferent input from the rectum;[470] thus, rectal distention inhibits bladder activity via glycinergic and GABAergic mechanisms in rats. Dual labeling studies show that many neurones in Barrington's nucleus supply both colon and bladder, with smaller populations supplying the two organs separately (**Figure 19**) – with dorsal neurons being bladder-related and ventral neurons being colon-related.[471] At the level of the major pelvic ganglion, double-labeled cells are relatively infrequent, but processes of colonic-retrograde-labeled cells often surround cell bodies of equivalent cells for the bladder. Dual-labeled cells in the spinal cord are rare.

c) Bladder and Prostate/Uterus

Voiding dysfunction is commonly associated with symptoms of chronic prostatitis/chronic pelvic pain syndrome, suggesting a prostate-bladder neural reflex. Electrical stimulation of the prostate following transection of the prostate nerves or lidocaine injections into the prostate, evokes changes in bladder cystometry parameters.[472] Anatomically, voiding cannot be initiated unless the prostate first rotates around the symphysis.[473] This preceding action of the prostate is suggestive of a higher centre efferent coordination.

Neurons labeled from the prostate are found mainly in L1-L2 whereas neurons labeled from the bladder are found mainly in L6-S1. Double-labeled neurons are located in L1-L2 mainly in the dorsal gray commissure. However, the number of bladder neurons are much greater than that of prostate, and both neurons increase significantly at longer incubation times. [474] At the brainstem level, double-labeled neurons are more common (**Figure 20**).

Inflammation of the uterine horn or colon gives rise to inflammation in the bladder, an effect that can be eliminated by sectioning the hypogastric nerve.[475] Similarly, inflammation of the bladder causes heightened sensitivity of uterine cannabinoid receptors, likely inhibiting its adrenergic input.[476] Bladder overactivity induced by inflammation is influenced by estradiol, probably mediated through effects on the sympathetic nervous control of the bladder.[477] There are several potential mechanisms by which neural input could contribute to emergence of inflammation in neighboring organs (**Figure 21**);

1. A dorsal root reflex; hypogastric afferents from the inflamed organ could, via a spinal interneuron, sensitize and antidromically activate other hypogastric afferents from a non-inflamed organ.[478]

2. Axon reflexes occurring in hypogastric sensory nerves that branch to supply more than one pelvic organ. Though such branching has not yet been specifically identified, a small proportion of single afferent fibres may branch to supply the colon and bladder.[478]

3. Input from the inflamed organ (via the hypogastric nerve) activates neurons in the dorsal horn that activate postganglionic neurons in the pelvic ganglion via thoracolumbar preganglionic neurons.

4. A spinal mechanism could be mediated by intraspinal connections to lumbosacral preganglionic neurons (as seen for gynaecological organs). [479]

5. A suprasacral mechanism could be mediated through the brain stem.[471, 480, 481]

6. EFFERENT INHIBITION

The sympathetic pathway contributes to inhibition of parasympathetic efferent input to the detrusor smooth muscle. In isolated whole bladders, there is a high level of spontaneous contractile activity,[482-487] suggesting active neural inhibition of

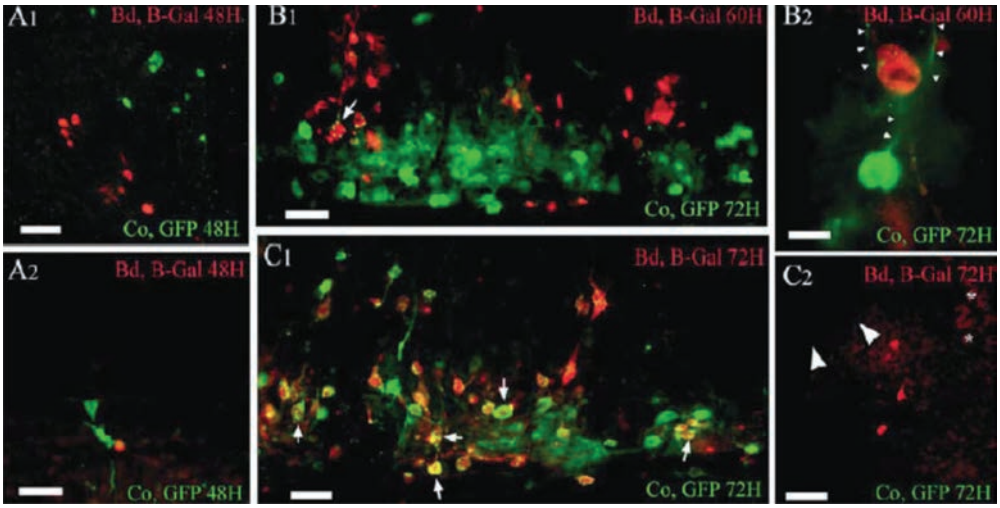


Figure 19: A, Fluorescent micrographs of sections at the level of (A1) the major pelvic ganglion, (A2, B1, B2 and C1) the lumbosacral spinal cord and (C2) Barrington's nucleus of rats injected with PRV-Beta-GAL in the bladder and PRV-GFP in the colon and having different survival times. The viscera, tracer and survival time are indicated in each photomicrograph. BD, bladder. CO, colon. A1. Separate labeling from both viruses is apparent in the MPG at 48 hours. A2. In the same case, only occasional cells are labeled in the spinal cord. B1. Substantial labeling from both organs is visible in the preganglionic parasympathetic column of the spinal cord and most cells are singly labeled from either the colon or the bladder. The arrow points to a rare double-labelled neuron. B2. Bladder- and colon-related neurons in close proximity. Processes from the colon-related neuron (arrow heads) are apposed to the bladder-related neuron. C1. Increasing survival time results in greater number of double-labelled cells (arrows). In most double labeled cells PRV-Beta-GAL label from the bladder is surrounded by PRV-GFP label from the colon. C2. Section from Barrington's nucleus from the same case as C1 indicating that only a few cells are transsynaptically labeled from the bladder and none from the colon at the survival time. Arrow heads point to the surface of the fourth ventricle and stars indicate the location of trigeminal mesencephalic neurons. Calibration bars: 50 µm A1 and A2, 30 µm B2 and C1, 50 µm B2, 50 µm C2. From Rouzade-Dominquez et al., 2003.

the bladder during urine storage. In a novel perfused decerebrate preparation of the whole rat, ganglion blockade using hexamethonium also leads to an increase in spontaneous activity.[488] Rat brainstem/ spinal cord/ bladder preparations or neonatal spinal cord/ bladder preparations show tonic inhibition, arising at L6-S1 and involving a peripheral ganglionic synapse.[489, 490] Clearly, efferent inhibition of the bladder facilitates urine storage.

In the neonatal rat, considerable activity arises in the bladder wall when inputs from the lumbosacral spinal cord are disrupted.[485] Selective spinal cord and root lesions indicate that intrinsic bladder activity of the neonatal rat is tonically inhibited by parasympathetic efferent outflow. This path is additional to the predominant cholinergic preganglionic efferents mediating the main voiding reflexes. The functional difference in the two sets of cholinergic ventral root efferents may result from differing synaptic targets, since both are blocked by the nicotinic antagonist hexamethonium. Thus, inhibitory efferents must synapse with noncholinergic inhibitory neurons in the major pelvic ganglia, in contrast to excitatory efferents synapsing with the cholinergic detrusor innervation.

In addition to efferent input, local reflexes may contribute to the inhibition of detrusor activity, probably driven by interstitial cells[491], so that peripheral autonomous activity increases as a result of bladder distension.[486] This has been proposed to signify the presence of a regional regulatory influence[492] and a peripheral "pacemaker" [493]and various mechanisms for the propagation of activity within the bladder wall.

7. PERIPHERAL EXCITATORY MECHANISMS

Agonist exposure appears to elicit contraction by two different mechanisms, comprising a component derived from direct stimulation of the muscle cell ('classical' efferent), and a separate component that is more phasic, responsible for the obvious pressure fluctuations. The latter 'intrinsic' mechanism may involve an intermediary cell type.[494] Optical imaging and calcium-/ voltage-sensitive dyes in whole rat bladder preparations have detected electrical activity moving in a coordinated manner from localized regions over the entire bladder.[99, 495] The isolated whole bladder shows regionalized responses when exposed to cholinergic/ muscarinic agonists.[485, 494, 496, 497] Dynamic migrating localities of contraction and elongation, give rise to a complex mix of micro motion phenomena, including micro contractions, micro stretches and propagating waves.

Several species show differences in contractile activity according to the region of the bladder from which a muscle strip is taken. Different effects are seen according to stage of development- spontaneous activity is high in bladder strips from neonatal rats, but small or almost non-existent in adults and reemerges in older bladders.[498] The likely functional significance of peripheral excitatory mechanisms is exemplified by the rodent neonate voiding reflex, which is induced by parental stimulation of the perineum, prior to establishment of mature control by the higher micturition centres.[499] The physiological role of such activity in the older adult is not known, but could include; 1. Optimization of the bladder wall configuration for volume contained, to ensure efficient voiding regardless of volume,[500] 2. Stimulation of 'in series' receptors for signaling bladder volume,[501] 3. A mechanistic component of accommodation during filling, a counterintuitive suggestion supported by the observation that accommodation in the colon involves synchronous contraction and relaxation,[502] 4. Maintaining the voiding contraction until complete evacuation is achieved.[503]

V. PONTINE-MIDBRAIN CONTROL OF BLADDER FUNCTION

The integral role of the brainstem in bladder function was initially realized by the demonstration in cats that micturition was abolished by lesions at the level of the inferior colliculus whereas lesions anterior to the colliculus facilitated micturition, presumably by removing inhibitory influences.[1, 504] Anatomical and physiological studies in both rat and cat have delineated midbrain-pontine-spinal cord circuits in reflexes controlling filling, storing and emptying of the bladder. The roles of pontine nuclei revealed by animal models translates well to humans as indicated by brain imaging during micturition[505-507] and clinical cases showing that specific pontine lesions can result in either bladder continence or incontinence problems.[506, 508, 509] This section will review the anatomical and physiological evidence for the pontine-midbrain circuitry that regulates the parasympathetic and sympathetic motor innervation of the detrusor and smooth muscle of the urethral

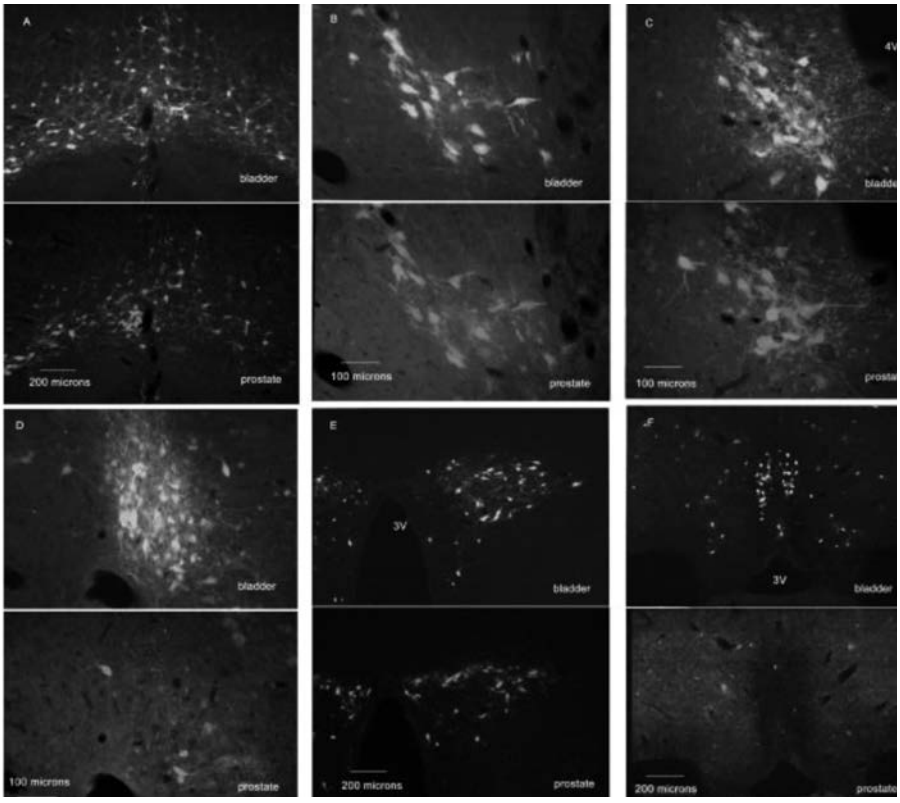


Figure 20. Neurons in selected brain nuclei, arranged in caudal to rostral order labeled by virus from the bladder or from the prostate. A: Raphe and gigantocellular reticular nuclei. Double-labeled neurons are common. B: The A5 adrenergic nucleus. Note that there are numerous double-labeled neurons. C: The locus coeruleus. Several neurons are double-labeled. D: Barrington›s nucleus (the pontine micturition center). Bladder virus labels the overwhelming number of neurons. Only a few neurons contain prostate virus. E: The paraventricular nucleus. Approximately equal numbers of bladder and prostate neurons. Some are double-labeled. F: The medial preoptic nucleus. Only bladder neurons are found. From Nadelhaft et al., 2002.

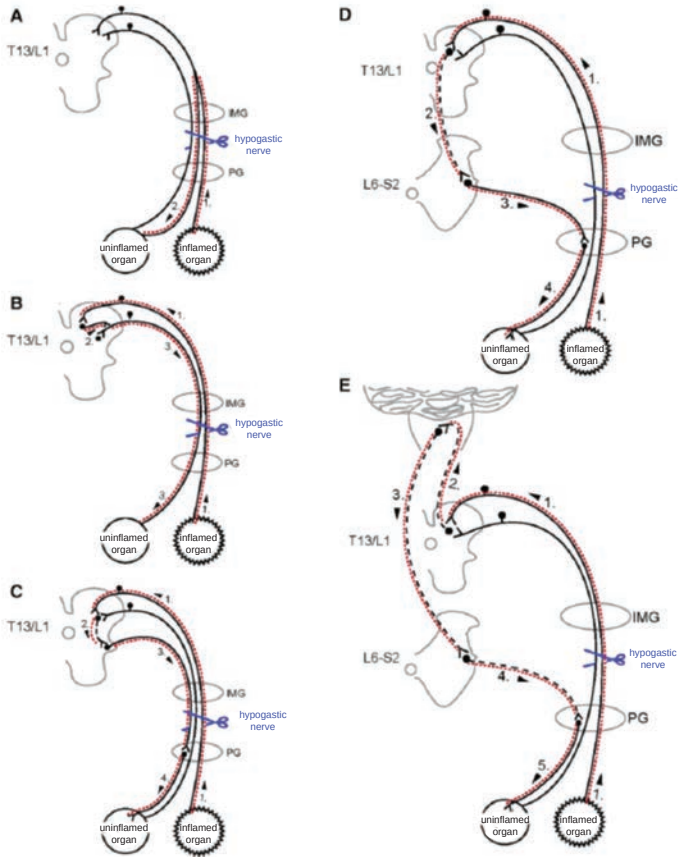


Figure 21. Five compatible mechanisms by which hypogastric nerve fibres can contribute to the process of inflammatory induction between organs. A.Branching sensory afferents. B. Dorsal root reflex. C. Multisynaptic route involving sensory afferents from the inflamed organ to the T-13/L1 segment of the cord followed by output from preganglionic fibres in the T13/L1 segment to postganglionic in the pelvic ganglion that innervate the uninflamed organ. D. Multisynaptic route involving sensory afferents from the inflamed organ to the T13/L1 segment of the cord followed by output from preganglionic fibres in the L6-S2 segments to postganglionic fibres in the pelvic ganglion that innervate the uninflamed organ. E. Multisynaptic route involving sensory afferents from the inflamed organ to the T-13/L1 segment of the cord followed by output from preganglionic fibres in the L6-S2 segments to postganglionic fibres in the pelvic ganglion that innervate the uninflamed organ. In this case the multisynaptic route includes ascending connections from spinal cord to brain and descending connections from brain to L6-S2. From Winnard et al., 2006.

sphincter. Additionally, recent evidence that this circuitry is positioned to coordinate the visceral response of micturition with a central limb that is important for initiating micturition-associated behaviors will be discussed.

1. AFFERENT PATHWAYS LINKING THE BLADDER AND URETHRA TO THE PONS AND MIDBRAIN

Sensations of bladder fullness are conveyed to the spinal cord by the pelvic and hypogastric nerves, while input from the bladder neck and urethra is carried in the pudendal and hypogastric nerves. Afferents arising from the bladder and urethra are mechanoreceptive (Aδ fibres) and nociceptive (C fibres). The most important afferents for initiating micturition are those passing in the pelvic nerves, whose fibers terminate in discrete regions of the lateral aspect of the dorsal horn of the lumbar and sacral spinal cord (see [3, 510, 511] for reviews). Many of these dorsal horn neurons make spinal connections that mediate segmentally organized reflex responses. However, a proportion of the spinal interneurons send ascending projections to specific nuclei in the pons and midbrain that can regulate bladder activity through a descending loop (**Figure 22)**. The interpretations of the circuitry through which the bladder initially communicates with the brain vary somewhat depending on the species in which the anatomy was characterized. Initial characterizations using the cat as a model point to the periaqueductal gray (PAG) region of the midbrain as the initial site of termination of spinal afferents. [512] In this species anterogradely labeled fibers from the lumbosacral spinal cord form a dense terminal field particularly in the lateral PAG. As the PAG is a prominent afferent to Barrington's nucleus (the pontine micturition center), which in turn projects to the preganglionic parasympathetic neurons that innervate the detrusor, the anatomical findings in the cat suggested a loop comprised of spinal neurons carrying bladder information to the PAG and the PAG in turn relaying this information to back to the bladder through descending projections from Barrington's nucleus to the preganglionic parasympathetic neurons that innervate the detrusor. Later studies in the rat using retrograde tracing from Barrington's nucleus and anterograde tracing from the spinal cord provided evidence for direct projections from spinal neurons to Barrington's nucleus, taking the PAG out of the primary loop in this species.[513] This would be consistent with the finding that lesions anterior to the inferior colliculus (i.e., between the Barrington's nucleus and the PAG) do not abolish the micturition reflex. Given the role of the PAG in nociception and defensive behavior it is likely that in rats the PAG exerts an influence on micturition through Barrington's nucleus under specific conditions but that it is not necessary for micturition to occur with

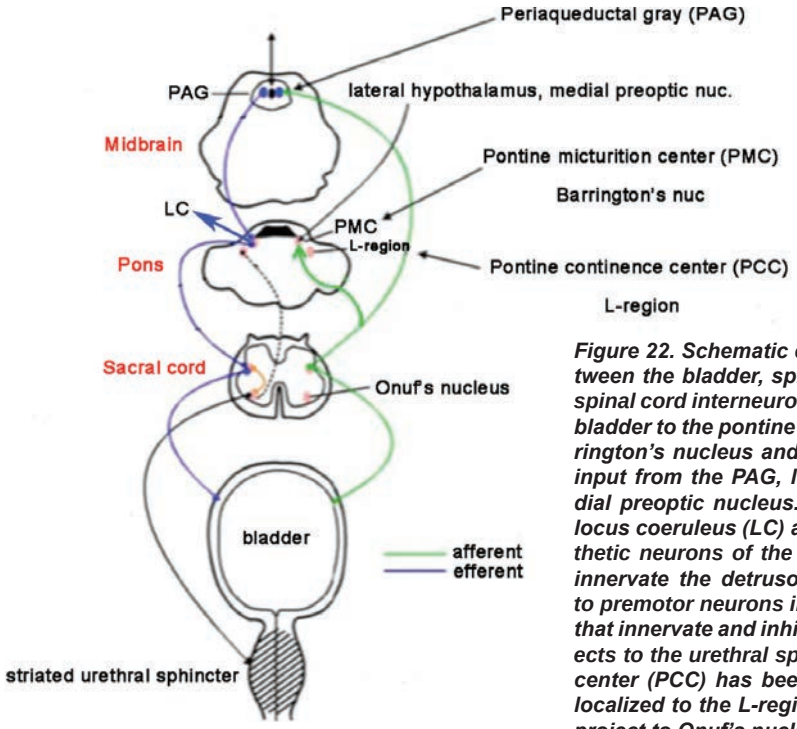


Figure 22. Schematic depicting information flow between the bladder, spinal cord and brain. In the rat spinal cord interneurons relay information about the bladder to the pontine micturition center (PMC), Barrington's nucleus and the PAG. The PMC also gets input from the PAG, lateral hypothalamus and medial preoptic nucleus. PMC neurons project to the locus coeruleus (LC) and preganglionic parasympathetic neurons of the lumbosacral spinal cord that innervate the detrusor. There are also projections to premotor neurons in the dorsal gray commissure that innervate and inhibit Onuf's nucleus which projects to the urethral sphincter. A pontine continence center (PCC) has been proposed in the cat and is localized to the L-region of the pons. Neurons here project to Onuf's nucleus.

bladder filling. The PAG may also play an important role in relaying bladder information to limbic and cortical brain regions as well as in integrating descending information from these regions, which provide contextual information concerning the appropriateness for micturition. [511]. Although these putative circuits are based on animal models, a pivotal role for both the PAG and PMC has been confirmed in man using positron emission tomography and functional magnetic imaging with and without a full bladder (see **Figure 23**).[2, 514, 515] [516]

2. DEFINING THE CENTRAL CIRCUITRY REGULATING BLADDER FUNCTION BY TRANSNEURONAL TRACING

Transneuronal retrograde tracing from end organs with pseudorabies virus (PRV) has been an invaluable tool in delineating the central circuitry that regulates visceral function.[517] The population of rat brain neurons labeled from PRV injections in either the bladder wall or urethra of the rat exhibit an overlap and similar time course of labeling, supporting a close coordination of detrusor and urethral muscle function by brain circuits as previously suggested. [284, 518-520] The first neurons to be labeled in brain from bladder or urethra and therefore the most direct links to the spinal efferents are the ventral medullary raphe, parapyramidal reticular formation, A5 and Barrington's nucleus. The PAG, hypothalamus and medial preoptic nucleus, which are prominent afferents to Barrington's nucleus, are labeled at a slightly later time when the LC, cortex and red nucleus are also labeled. Interestingly, PRV labeling from other pelvic viscera including the distal colon yield a similar pattern and time course suggesting a certain degree of central coordination of these functions.[471, 521]

The PRV studies provide information regarding some hierarchy of neurons that is anatomically linked to the bladder and/or urethra. However, the PRV technique does not imply precise information about connectivity or functionality. This must be delineated by additional tract tracing between putatively connected brain nuclei and physiological studies. Of the brain regions that are initially labeled with PRV from the bladder or urethra, most anatomical, electrophysiological and imaging studies to date implicate Barrington's nucleus as pivotal in regulating bladder function in both animals and man.

3. BARRINGTON'S NUCLEUS: THE PONTINE MICTURITION CENTER (PMC)

In 1925 Barrington was the first to describe a pontine control centre for micturition in the cat through lesion studies. [1, 504]This region was better localized to a nucleus in the dorsal pons (now termed Barrington's nucleus) using more discrete lesions that abolished micturition and caused urinary retention in cats and rats.[522, 523] Lesions in humans as a result of stroke or multiple sclerosis in an analogous region similarly result in urinary retention in man. [524]

In both cat and rat, Barrington's nucleus is in the dorsal pons lying ventromedial to the rostral pole of the locus coeruleus (LC) in the rat and within the

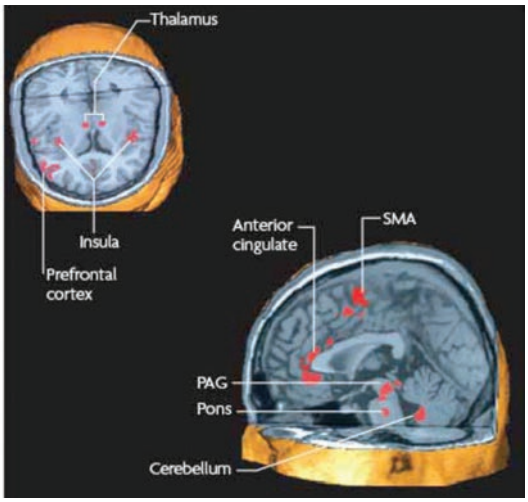


Figure 23. Brain areas involved in the regulation of urine storage. Ameta-analysis of positron-emission tomography and functional MRI studies that investigated which brain areas are involved in the regulation of micturition reveals that the thalamus, the insula, the prefrontal cortex, the anterior cingulate, the periaqueductal grey (PAG), the pons, the medulla and the supplementary motor area (SMA) are activated during the urinary storage. From DasGupta et al.,2007.

LC in the cat. Notably the LC in rats and cats differ substantially in that the LC is homogeneous in the rat with all neurons containing norepinephrine, whereas it is more heterogeneous in the cat, with norepinephrine neurons being interdigitated with non-norepinephrine neurons.[525] In humans, comparable regions in the pons can be imaged and found activated when the bladder is full (see **Figure 23**) [2]. Barrington's nucleus is retrogradely labeled from the lumbosacral spinal cord and in the rat is distinct from cholinergic neurons of the lateral dorsotegmental nucleus and norepinephrine neurons of the LC (**Figure 24A**).[526, 527] Anterogradely-labeled axon terminals from Barrington's nucleus target the lumbosacral preganglionic column. Ultrastructural studies in cat demonstrate direct projections from Barrington's nucleus that form asymmetric (excitatory-type) synapses with parasympathetic preganglionic motoneurones innervating the bladder.[293] Barrington's nucleus neurons are antidromically activated from the dorsolateral funiculus of the first sacral segment, providing physiological confirmation of its spinal projections.[528-530]

Physiological studies have confirmed the role of Barrington's nucleus in micturition. Both electrical and chemical activation of Barrington's nucleus neurons in rats and cats initiates bladder contractions and relaxes the urethral sphincter.[292, 531-533] Precise mapping of sites at which chemical stimulation elicits bladder contractions demonstrates a well-defined area localized to Barrington's nucleus.[533] Single unit recordings in rat pons revealed 3 types of responses to bladder contraction, an excitation that occurred only prior to contraction (E1), an excitation that occurred prior to and was maintained during contraction (E2) and an inhibition during contraction.[534] Neurons that were activated just prior to contraction and that maintained activation during contraction were found in Barrington's nucleus while the other two types of neurons were scattered throughout the pontine tegmentum. Similar results were reported in cats during cystometry.[530] More recently, bladder distention was found to excite nearly 80% of juxtacellularly labeled Barrington's nucleus neurons.[481]

Neuronal recordings in cats that were localized to the rostral medial medulla (reticularis gigantocellularis and magnocellularis) revealed many neurons that were activated antidromically from the spinal cord (L1) and discharged in or out of phase with bladder contractions.[530] Some of these neurons responded at short latency following stimulation of Barrington's nucleus, supporting direct orthodromic activation. This suggested the existence of two descending pathways from Barrington's nucleus for initiating micturition: one direct to the parasympathetic preganglionic neurones and the other via the medial reticular formation.

Micturition also requires an inhibition of the urethral sphincter to be coordinated with detrusor contraction. This is controlled by somatic motoneurons of Onuf's nucleus. Barrington's nucleus neurons do not project to Onuf's nucleus. Rather, in the cat a diffuse region ventrolateral to Barrington's nucleus, termed the L-region, is though to provide pontine control of sphincter function through its projections to Onuf's nucleus.[535] For coordination between the detrusor and sphincter, there should be some form of reciprocal communication between these regions. However, a lack of connections between Barrington's nucleus and the L-region are argue against sphincter regulation by Barrington's nucleus through this route.[536] Rather it has been proposed that Barrington's nucleus indirectly inhibits Onuf's nucleus neurons though excitatory projections to GABA premotor interneurons in the dorsal gray commissure.[536] Additionally, Barrington's nucleus projections onto inhibitory interneurones located in the intermediolateral cell column at the sacral segmental level have been described that may provide an inhibitory influence over Onuf's nucleus and both glycine and GABA are thought to play a role here.[294, 298]

Together, the anatomical and physiological findings described above point to Barrington's nucleus as being the command center for initiating and orchestrating the act of bladder emptying. More recent evidence discussed below suggests a more complex role for Barrington's nucleus neurons in coordinating a central response to bladder filling with the visceral response of bladder emptying through Barrington's nucleus projections to the norepinephrine nucleus, locus coeruleus (LC).

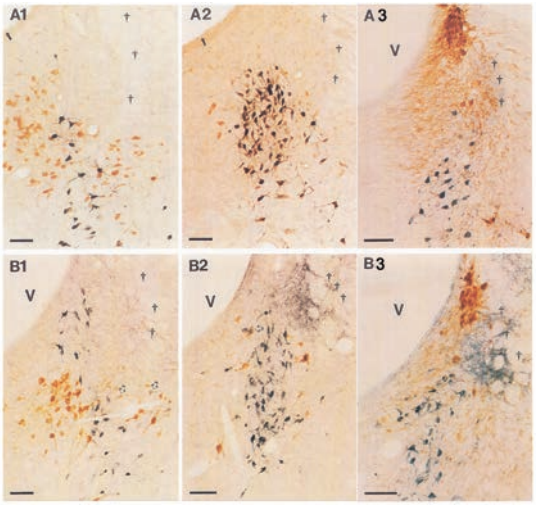


Figure 24. Barrington's nucleus at different rostrocaudal levels in the rat identified by retrograde labeling from the lumbosacral spinal cord (A) or its CRF-immunoreactive neurons (B). A1-A3) Coronal sections through the rat pons proceeding from rostral to caudal. The blue-black labeled neurons are retrogradely labeled from the lumbosacral spinal cord. In A1 and A2, the brown labeling is choline acetyltransferase immunoreactivity, indicating cholinergic neurons of the lateral dorsal tegmental nucleus. In A3 the most caudal section is at the level of the rostral pole of the LC with brown labeling indicating immunoreactivity for tyrosine hydroxylase, the enzyme that synthesizes norephinephrine. In B1-B3 the blue-black labeled neurons show CRF-immunoreactivity with the brown labeling as described for panel A above. In B2 and B3 a dense CRF terminal field is present just dorsolateral to Barrington's nucleus. Note the similar distribution of retrogradely labeled and CRF immunoreactive neurons at each level. The retrogradely labeled neurons are a distinct population from the choline acetyltransferase immunoreactive neurons and LC neurons. Open arrows in B show dual labeled CRF and choline acetyltransferase immunoreactive neurons. V= fourth ventricle, daggers indicate the mesencephalic trigeminal nucleus. Bar=80 µm. Modified from Valentino et al., 1995.

4. BARRINGTON'S NUCLEUS, THE LOCUS COERULEUS AND CENTRAL RESPONSES TO BLADDER INFORMATION.

Micturition requires a central component so that bladder emptying is coordinated with a set of behaviors. If animals are asleep they must be aroused. If engaged in some ongoing behavior that is not compatible with urination, this must be interrupted and behavior should be redirected to be compatible with the visceral response. Recent evidence suggests that neurons of Barrington's nucleus neurons serve the role of coordinating visceral and behavioral limbs of micturition through collateral projections to the preganglionic parasympathetic spinal neurons and the major norepinephrine nucleus, locus coeruleus (LC).[537]

a) Normal Function

The LC, a cluster of neurons lying along the wall of the fourth ventricle just dorsolateral to Barrington's nucleus, is the major source of norepinephrine in the brain.[538, 539] A characteristic anatomical feature of LC neurons is their massive projection system that innervates the entire neuraxis, serving as the sole source of norepinephrine in cortex and hippocampus.[538, 540] The LC-norepinephrine system initiates arousal in response to diverse stimuli. A representative example of this is the increase in LC neuronal activity elicited by elevations in bladder intravesicular or colonic intraluminal pressure.[541-543] LC activation elicited by these visceral stimuli is temporally correlated with cortical electroencephalographic (EEG) indices of arousal (e.g., desynchronization and a shift from high amplitude, low frequency activity to high frequency activity).[540, 542] In rats Barrington's nucleus is involved in this response as lesions prevent LC activation by pelvic visceral stimuli.[544] Notably, simultaneous recordings of cortical EEG and bladder pressure during cystometry in unanesthetized rats indicate an offset between EEG correlates of arousal and micturition threshold such that cortical arousal precedes bladder emptying (**Figure 25**)[545]. This is consistent with the idea that the behavioral program for voiding should be initiated before bladder emptying.

Recordings of LC neurons in non-human primates performing operant tasks suggest a role for the LC-norepinephrine system in facilitating decisions related to task-directed behavior, i. e., whether to maintain behavior in an ongoing task or to disengage and seek alternative strategies in a dynamic environment.[546] Tonic LC activation favors disengagement from ongoing behavior and tasks involving focused attention and promotes scanning of the environment for alternate strategies.[546-548] As bladder pressure rises towards micturition threshold the tonic excitation of LC neurons is speculated to increase arousal and facilitate disengagement from ongoing behavior and a shift towards the initiation of elimination-related behaviors. Thus, Barrington's nucleus neurons are central to coordinating the descending limb of the micturition reflex with a central limb that facilitates a switch from on-going non-voiding related behavior to voiding behaviors (**Figure 26A**) [549]. Importantly, the LC projects to cortical regions that are proposed to exert conscious control over micturition.

b) Pathological Consequences

Barrington's nucleus projections to the LC can also relay signals from pathologic events in bladder to the forebrain, thereby providing a mechanism by which bladder disorders can have neurobehavioral consequences (**Figure 26B**). This was demonstrated in a rat model of partial bladder outlet obstruction

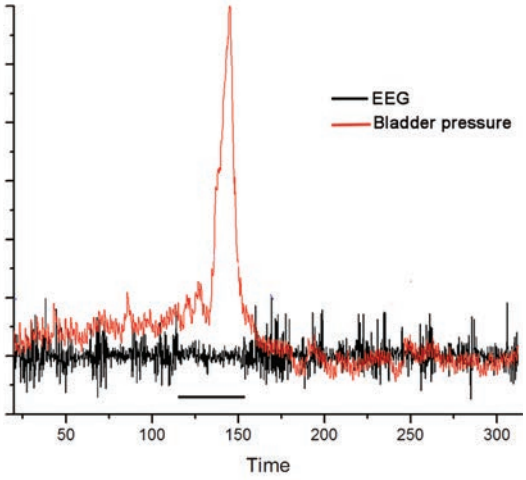


Figure 25. Cortical EEG activation precedes the micturition threshold. Simultaneous recording of cortical EEG (black trace) and bladder pressure (red trace) in a rat. Note the desynchronization (decreased amplitude and increased frequency) of the cortical EEG as bladder pressure begins to rise and continuing until after the micturition threshold is reached. Following micturition, cortical EEG resumes to a state of decreased activity as indicated by high amplitude waves. From Kiddoo et al., 2006.

(PBOO).[550] Baseline LC neuronal activity was tonically elevated in PBOO rats compared to rats with sham surgery and was not further increased by elevations in bladder pressure. This was reflected at the level of the cortical EEG as a persistent desynchronization and a shift from high amplitude, low frequency activity to low amplitude, high frequency activity, effects indicative of hyperarousal (**Figure 27**).[550] Additionally, a prominent theta frequency oscillation was apparent in PBOO rats, especially those with a urodynamic profile characterized by numerous non-voiding contractions.[550] Theta oscillations are hypothesized to coordinate activity in different brain regions in preparation for motor responses to sensory input.[551] Tonic LC activation is necessary for PBOO effects on cortical EEG activity because selective chemical lesion of forebrain LC projections prevents these effects without altering urodynamics.[550] The persistence of an activated cortical EEG and theta rhythm in PBOO rats suggests a state of hyperarousal and a decreased ability to grade or discriminate between different magnitudes of bladder pressure changes. This could explain the finding that some individuals can have chronic retention and enlarged bladder, yet no sensation or urge to urinate. Importantly, an effect on sensorimotor processing could also affect cortical processing of non-bladder related stimuli and adversely impact on functions requiring focused attention.

The PBOO model exemplifies how pathology that originates in the bladder can have pronounced adverse central consequences through the Barrington's

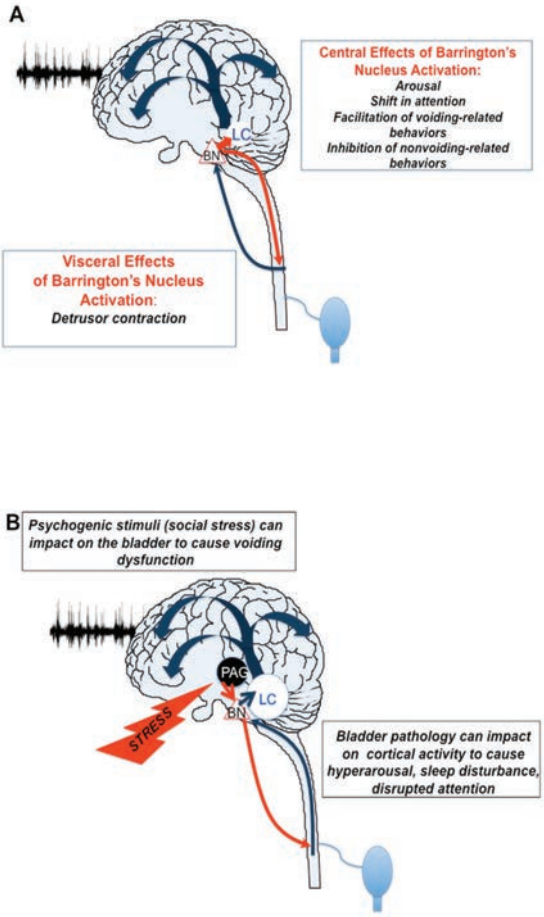


Figure 26. Schematic indicating how Barrington's nucleus projections to the LC and spinal cord coordinate visceral and central limbs of micturition and also can relay pathology between the brain and bladder. A) Barrington's nucleus neurons in the rat get afferent information from the bladder (blue arrow). Increasing intravesicular pressure activates these neurons. Through projections to the preganglionic parasympathetic neurons in the lumbosacral spinal cord, Barrington's nucleus initiates bladder contraction. The same neurons are positioned to activate the LC-norepinephrine system which projects to the cortex and can initiate arousal and facilitate a shift toward voiding behaviors. B) The same circuit provides a means by which bladder pathology can have neurobehavioral consequences. Particularly by activating LC neurons, this can produce hyperarousal, anxiety and sleep disturbances. Psychological stressors can impact on this circuit, perhaps through the PAG to affect bladder function. Barrington's nucleus (BN), locus coeruleus (LC), periaqueductal gray (PAG). From Valentino et al., 2011.

nucleus projections to the LC. It is not clear whether this occurs in humans. However, evidence for anxiety and sleep disorders in men with benign prostatic hypertrophy and in males and females exhibiting other bladder disorders is consistent with this process. [552, 553] Evidence for a causal role of the LC-norepinephrine system suggests that pharmacological manipulation of the activity of this system may be a useful therapeutic approach for central sequelae of overactive bladder.

Interestingly, a consequence of PBOO on the Barrington's nucleus circuit is the loss of responses of Barrington's nucleus to acute increases in bladder pressure to micturition threshold. [550]This may be relevant to the visceral pathology because it represents a loss of central regulation of bladder function. Like spinal cord injury, the loss of central control could lead to local spinal regulation of the micturition reflex that is thought to underlie the detrusor overactivity often seen in patients with overactive bladder. [554] Thus, consequences of PBOO on Barrington's nucleus neuronal activity may feed-forward to further contribute to the bladder dysfunction in addition to having central consequences.

5. SUPRASPINAL INPUTS TO BARRINGTON'S NUCLEUS

Afferents to Barrington's nucleus would be positioned to initiate or regulate bladder activity and could be targets for modulating urinary function. The most prominent afferents in the rat are the PAG, lateral hypothalamus and medial preoptic area. [555] Particularly, the lateral and ventrolateral PAG densely innervate Barrington's nucleus. As described above, the PAG receives bladder afferent information from spinal interneurons and this may be an indirect route through which the bladder communicates with Barrington's nucleus that is in addition to a more direct route. The PAG afferents can trigger micturition as evidenced by the finding that chemical stimulation of ventrolateral PAG can cause voiding.[556] PAG stimulation can also elicit sphincter activation without bladder contraction suggesting an involvement in both voiding and storage functions.[556]

The lateral hypothalamus, particularly, the perifornical region is a major source of afferents to Barrington's nucleus.[555] Like the PAG, the lateral hypothalamus is involved in defensive responses and modulation of Barrington's nucleus by these two afferents likely plays a role in urination as a component of the defense response.[557, 558] A third major afferent arises from the medial preoptic area and these have been demonstrated to directly contact spinal-projecting Barrington's nucleus neurons.[559] Many of these neurons express estrogen receptor alpha, suggesting that this is an estrogen sensitive pathway.[560] The medial preoptic region has been suggested to provide an inhibitory influence during sleep and/or sexual activity to suppress micturition.[511, 526, 561] Neurons in

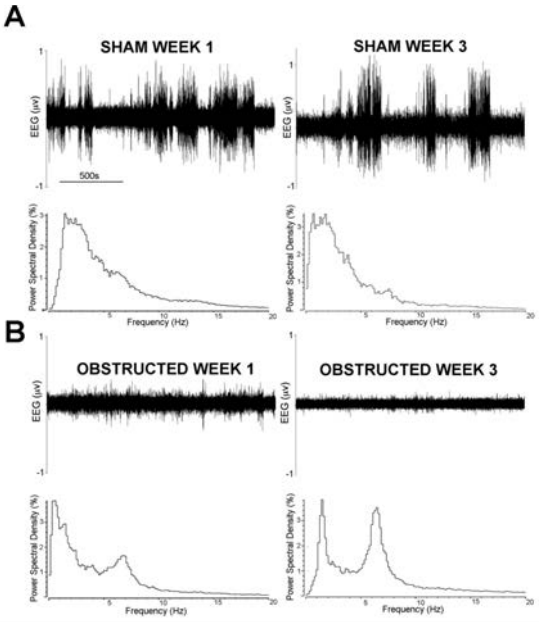


Figure 27. Partial bladder outlet obstruction (PBOO) produces enduring alterations in cortical electroencephalographic (EEG) activity in rat. In both A and B, the top panel shows a raw EEG trace and the bottom panel shows the power spectrum analysis of the same trace. A) EEG recordings and power spectra from an unanesthetized rat exposed to sham surgery recorded at 1 and 3 weeks after the surgery. Note the high amplitude waves in the raw trace and the predominance of power in the 0.4 Hz range in the power spectrum. B) EEG recordings and power spectra from an unanesthetized rat exposed to PBOO surgery recorded at 1 and 3 weeks after the surgery. Note the lack of large amplitude waves in raw traces compared to the sham rat. The power spectra show a theta oscillation (6-8 Hz) that becomes especially prominent at 3 weeks and a shift to the right toward higher frequencies compared to the sham rat. Modified from Rickenbacher et al., 2008.

other brain regions are retrogradely labeled from Barrington's nucleus although these are not as prominent as the PAG, lateral hypothalamus and medial preoptic area. Most notably, some neurons in motor cortex, insular cortex and infralimbic cortex are retrogradely labeled from Barrington's nucleus and may serve to provide cortical control over bladder function.[555] The primary afferents to Barrington's nucleus in the cat are similar to those reported in rat.[562] In addition inputs are described from the ventromedial pontomedullary tegmental field and this has been hypothesized to play a role in establishing a neuronal set-point or threshold beyond which micturition occurs.[563]

6. DEFENSIVE STRATEGIES AND MICTURITION.

It is fitting that two of the most prominent afferents to Barrington's nucleus (the periaqueductal gray and lateral hypothalamus) are critical components of the circuitry that underlies acute defensive behaviors because urination is a component of the acute defensive response. Stimulation of the PAG can trigger micturition together with defensive behaviours.[564, 565] Certain laboratory stressors, such as water avoidance, can produce an enduring increase in micturition frequency.[566] On the other hand, inhibition of micturition can also be evoked by stimulation of rostral dorsal and caudal ventral PAG regions.[567] This may be related to the finding that social stress in rodents, such as being a subordinate in a social hierarchy can induce prolonged urinary retention with prominent changes in urological function and structural changes in the bladder. [568],[569-572] In the resident-intruder rodent model of social stress, subordinate rats develop a urodynamic profile that resembles that produced by PBOO, with increased intermicturition interval, bladder capacity and micturition volume and numerous non-micturition contractions (**Figure 28**).[571] Interestingly, the urodynamic profile associated with social stress can be distinguished from that produced by PBOO by its lack of elevated micturition pressure, implying that it results from a loss of central drive to the detrusor as opposed to increased sphincter tone. This suggests that control of the two muscles is not necessarily interdependent. Like PBOO, social stress increases bladder mass and in mice some of the same transcription factors that are thought to be involved in PBOO-related bladder remodeling are upregulated by social stress, including NFAT and MEF2.[572] Urinary retention may be a visceral component of a defensive response to subordination that is mediated in part by certain aspects of the periaqueductal gray.

Social stress-induced urinary retention may involve the stress-related neuropeptide, corticotropin-releasing factor, CRF, which is highly expressed in Barrington's nucleus neurons and has an inhibitory influence within Barrington's nucleus projections to the preganglionic parasympathetic neurons that drive the bladder (**Figure 30B**)(see below). CRF mRNA and protein are overexpressed in Barrington's nucleus neurons in rats exposed to repeated social stress but not to repeated restraint stress, which does not alter urodynamic function.[571]

The social stress-induced voiding dysfunction in the rodent may model dysfunctional voiding characterized by urinary retention in humans. In children dysfunctional voiding associated with detrusor hypoactivity has been hypothesized to arise from adverse events that are temporally proximal to toilet training[573, 574]. Consistent with this, children with voiding postponement have a less balanced family environment and more psychiatric co-morbidity compared to children with other types of voiding dysfunction.[575] In adults urinary retention has been associated with a history of sexual abuse, depression and social anxiety.[576, 577] As in the rat model, the persistence of retention can have severe structural consequences and proceed to chronic renal insufficiency.[578] Even in the absence of such severe consequences, the importance of the impact of social stress on urological health is underscored by a recent study of over 1000 women demonstrating statistically significant associations between urinary incontinence and psychosocial problems with feelings of vulnerability.[579]

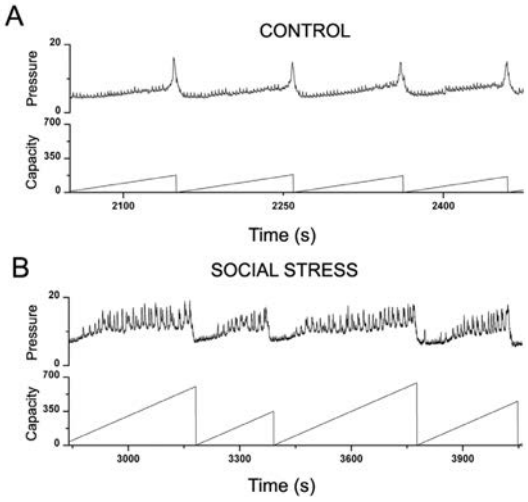


Figure 28. Social stress alters bladder urodynamics. Cystometric recordings of bladder pressure and bladder capacity of A) a control rat and B) a rat that was exposed to resident-intruder stress for a period of 7 days. The bladder of the stressed rat shows numerous nonvoiding contractions, prolonged intermicturition intervals and greater bladder capacity, compared to the unstressed control rat. From Wood et al., 2009.

7. COORDINATION OF BLADDER WITH OTHER PELVIC VISCERA BY BARRINGTON'S NUCLEUS

Transneuronal tracing studies with pseudorabies virus injection into different pelvic viscera suggests that Barrington's nucleus neurons are also positioned to regulate activity of multiple pelvic viscera, including bladder, distal colon and sex organs, and perhaps coordinate activity between viscera. Dual PRV labeling from colon and bladder results in a large population of Barrington's nucleus neurons that are double labeled from both viscera, suggesting that their axons diverge to innervate both bladder and colonic parasympathetic efferents[481]. PRV labeling from the penis, prostate and perineal muscles also suggests an overlap of central neurons and time course of labeling with bladder.[521] Chemical stimulation of Barrington's nucleus neurons increases distal colonic intraluminal pressure and this is abolished by muscarinic antagonists.[580] Notably, most Barrington's

nucleus neurons are activated by increases in bladder pressure and many of these are also activated by increases in colonic intraluminal pressure indicating that these neurons receive convergent information from both viscera.[471) Although these findings suggest a role for Barrington's nucleus in coordinating bladder and colonic activity, currently there is no evidence that Barrington's nucleus impacts on ongoing distal colon activity. Furthermore, the activity of the distal colon is highly dependent on other factors such as pressure gradients and the enteric nervous system. Nonetheless, the link between Barrington's nucleus neurons and other pelvic viscera implies that pathology arising from pelvic viscera other than the bladder could have similar central consequences as those reported for bladder. For example, this circuit may underlie the well-documented co-morbidity of psychiatric and colonic symptoms that characterize irritable bowel disorder.[581, 582]

8. THE PONTINE CONTINENCE CENTRE (PCC)

The bladder's function of urine storage requires detrusor relaxation accompanied by urethral sphincter contraction. Studies in the cat identified a pontine continence center also termed the L-region that is distinct from and lying ventrolateral to the micturition center[535]. Neurons in this region project selectively to Onuf's nucleus in the sacral cord, which contains the urethral sphincter motoneurones, and do not project to spinal regions influencing detrusor. The majority of neurons in this continence center, fire during the relaxation phase of bladder contractions and the onset of their firing can be prior to the initiation of bladder relaxation.[583] Indeed, this would make sense if their prime function were to close the urethral sphincter. Another potential role for these neurons is in off-switching micturition. Supporting this, stimulation of this region stops micturition, excites the pelvic floor musculature and contracts the urethral sphincter.[531] Conversely, bilateral lesions of the PCC cause incontinence, excessive detrusor activity, an inability to store urine and relaxation of the urethral sphincter.[531] However, there is no anatomical evidence for connections between Barrington's nucleus and the L-region and it has been suggested that Barrington's nucleus and the "continence center" function independently.[536] Notably, the L-region has been characterized primarily in cat and there is little evidence to date for a similar region in rat or human.

9. NEUROTRANSMITTERS & MODULATORS WITHIN BRAINSTEM NETWORKS CONTROLLING BLADDER

Knowledge of the neurochemical signals within the central circuits controlling micturition is important for understanding how these circuits function and how they can be manipulated for the treatment of bladder dysfunctions. These are reviewed in detail in [3, 510] Much of the current knowledge is based on studies using cat and less is known of rat or primate.

Glutamate is thought to be the primary neurotransmitter within Barrington's nucleus neurons that innervate the preganglionic parasympathetic neurons responsible for detrusor contraction. Both NMDA and non-NMDA receptors have been implicated in this response.[322, 584-586]

Barrington's nucleus neurons express CRF mRNA and protein and a dense CRF terminal field is present in the region of preganglionic parasympathetic neurons of the rat lumbosacral spinal cord.[587, 588] Recent findings suggest that CRF has an inhibitory influence in this same pathway.[533] Thus, discrete chemical activation of Barrington's nucleus neurons elicits bladder contraction that is enhanced by blocking the CRF influence in the lumbosacral spinal cord with a CRF antagonist. Interestingly, CRF excites LC neurons and this is temporally correlated with cortical EEG correlates of arousal.[589] It is tempting to speculate that CRF release in the divergent spinal and LC projections of Barrington's nucleus neurons serves to increase arousal while inhibiting bladder contraction. In this way it may be important in creating the offset between central and visceral components of micturition so that the appropriate behaviors can be initiated prior to bladder emptying. CRF is upregulated in Barrington's nucleus neurons by the same social stress that causes urinary retention (see above), suggesting that this may be causal to the social stress-induced urinary retention that results in bladder dysfunction.[571]

Serotonin appears to affect nervous control of bladder function at multiple levels including sensory processing of bladder wall afferents within the dorsal horn of the spinal cord and at the level of the spinal motoneurones. In all cases this appeared to be an inhibitory influence on detrusor muscle activity but excitatory on urethral sphincter.[350] It was proposed that 5-HT1A receptors were located on the terminals of sensory afferent fibers to depress neurotransmitter release. Similarly, a predominance of an inhibitory effect evoked from the midline raphe system extending from the pons to medulla on micturition in cats has been described.[590] However, the site of this inhibitory action (i.e. supra-brainstem, pons or spinal cord) is unknown. A study of raphe neuronal recordings demonstrated that their firing was related to bladder pressure with 66% related to storage.[590] These data support a role of the raphe system in suppressing micturition and facilitating external urethral sphincter activity in cats, which is consistent with earlier studies identifying a central inhibitory role for 5-HT1A receptors.[302] In stark contrast, this does not seem to be the case in the rat where 5-HT1A system facilitates micturition as indicated by the effects of 5-HT1A antagonists, underscoring the importance of species differences in interpreting effects.[591, 592]

Future challenges

Although advances have been made in our understanding of central control of bladder function during

the last few years, many challenges remain. If we are to study the human condition in the laboratory, it is important to find species that best models human physiology and pathology. Much of our knowledge has been based on physiological and anatomical studies in the cat although more recent studies have focused on rat. Some of the species differences that would lead to different interpretations have been discussed above. The last decade has seen a major shift towards the use of genetically altered mice in neuroscience as these provide invaluable tools for creating unique animal models of disease and elucidating the roles of specific genes and proteins in specific functions. Although there is many examples of studies using genetically altered mice to understand bladder tissue, the use of mouse models for understanding neural regulation of the bladder is rare. In vivo mouse studies present challenges of size. Nonetheless, these can be overcome as new technology for recording and stimulating brain regions advances.

Although our knowledge in how the brain regulates the detrusor has advanced, less is known of the central regulation of the urethral sphincter. Particularly, the coordination between detrusor and sphincter activity at the level of the spinal cord or its regulation by supraspinal circuits is not well understood. This is critical for understanding the pathophysiology and treatment of urinary incontinence.

Very little has been done in the realm of sex differences in regulation of bladder function. Clearly, there are sex differences in certain types of bladder disorders. Notably, Barrington's nucleus is regulated by afferents from a sexually dimorphic nucleus, the medial preoptic nucleus that are also sensitive to estrogen. Basic research studies are often performed in either male or female animals with little consideration as to the role of sex and there are no studies of systematic comparisons between male and female subjects. By contrast, brain imaging in humans have been addressing this issue.[505, 593-595] Nonetheless, the human studies are limited by the degree of anatomical resolution and do not allow for precise manipulation of specific circuit components that can be done in animals.

Whereas neuroscience research has come a long way in understanding how the brain processes visual, olfactory and auditory signals, the analogous processing of visceral information by the brain is has received comparatively little attention. This may stem in part because of a tendency for specialize rather than integration. Electrophysiological recording technology, optogenetic methods of neuronal stimulation, computational analysis and network modeling has greatly advanced in the last decade. This technology is currently available for understanding how the brain processes information from the bladder in normal and diseased states, how neural circuits in turn respond to control bladder function and how this is organized with respect to processing other information and regulation of other behaviors. The next few years should make use of this state-of-the-art technology to advance into this frontier.

VI. FOREBRAIN CONTROL OF BLADDER FUNCTION

1. BACKGROUND

This chapter is based on the material presented at the previous International Consultation on Incontinence, which was largely written by Professor Clare Fowler, and I am grateful to her for this and for allowing me to use material from other recent reviews. The aim of the chapter is to update the clinical and experimental evidence for the role of the forebrain in bladder control, and to summarize in a simple working model our understanding of the brain regions mediating specific aspects of human bladder behaviour.

The importance of the frontal cortex and pons in the control of voiding was clearly recognized prior to functional brain imaging, which, however, has tended to obscure the older clinical evidence summarized in **Table 2**. Most functional imaging studies have been carried out using either positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). A few used single-photon emission computed tomography (SPECT) or near-infrared spectroscopy (NIRS). All these methods provide indirect measures of regional blood flow, assumed to be related to local neuronal activity, but PET is good for measuring long-lasting states of a system, while fMRI is better for following relatively fast events. SPECT has rather poor temporal and spatial resolution. Functional NIRS is a relative newcomer that measures absorption of near-infrared light so as to quantify cortical activity from the changing concentrations of deoxy- and oxy-haemoglobin just beneath the skull. Despite limited penetration depth (≈ 10 mm) and modest spatial resolution, it has great advantages: it requires no scanner, is relatively inexpensive, can be used in an ordinary urodynamics laboratory, and has good temporal resolution that can present results in real time, simultaneously with urodynamic pressure and flow signals. Preliminary results suggest that similar regions to those seen with fMRI are activated with bladder filling or detrusor overactivity.

2. ROLE AND IMPORTANCE OF CEREBRAL CONTROL OF VOIDING

In order to understand the cerebral control of voiding it is helpful first to examine what would happen if there were no such control. Provided brainstem and midbrain are intact, micturition is organized in 2 phases, storage and voiding, governed by reflexes involving the brainstem and spinal cord. During storage (99.8% of the time in health) the urethral sphincter mechanism contracts tonically, preventing urine leakage, while the detrusor remains relaxed, so as to avoid developing a pressure that would expel urine. Urethral contraction is maintained by sacral reflexes

Table 2. Clinical evidence for the involvement of specific brain regions in bladder control.

Key brain regions	Pathology	Number of cases	Effect on bladder behaviour
Frontal			
	Various causes of frontal lobe pathology (4)	36	Altered bladder sensation and incontinence in absence of intellectual deterioration or retention 3 cases had retention
	Frontal lobe tumours (600)	7	Frequency, urgency incontinence
	Frontal abscess (603)	1	Retention
	Frontal abscess/haematoma(602)	2	Retention
	Anterior cerebral vascular lesions (601)		Various bladder disorders and hemiparaesis
ACG			
	Bilateral infarction of anterior cingulate gyri (614)	1	Complex behavioural changes and incontinence
	Glioma of ACG and supplementary motor cortex (615)	1	Urgency incontinence with loss of sensation
Insula			
	Glioma of insula and inferior frontal gyrus (615)	1	Incontinence without loss of bladder sensation
Hypothalamus			
	Pituitary tumours extending into the hypothalamus (603)	3	Urgency incontinence, weight loss, psychiatric symptoms
	Cystic lesion of hypothalamus (632)	1	
	Ruptured anterior cerebral aneurysm (634)	5	
PAG			
	Presumed inflammatory lesion (91)	1	Urinary retention
Pons	Posterior fossa tumours		Voiding difficulty
	Brain stem tumors(638)		
	Brainstem vascular lesions (601)		
	Brainstem gliomas in children (639)	24	Voiding difficulty
	Developmental malformation (635)	1	Urinary retention and disordered eye movements
	Low grade glioma (636)	1	Paraparesis, urinary retention and disordered eye movements
	R pontine lesion, unknown (524)	1	Urinary retention and disordered eye movements
	Herpes encephalitis (637)	1	Urinary retention and disordered eye movements

known collectively as the 'guarding reflex'; detrusor relaxation is ensured by absence of excitatory parasympathetic input as well as active sympathetic inhibition provided by spinal reflexes.[3]

During human voiding the urethral sphincter relaxes, facilitating urine flow, and the detrusor contracts so as to expel urine. This coordinated relaxation and contraction of urethra and bladder respectively is driven by a long-loop spinobulbospinal reflex[3], shown schematically in **Figure 22** of the companion chapter on pontine-midbrain control. As the bladder fills, increasingly strong bladder afferents travel via synapses in the sacral cord to the brainstem and midbrain, where they synapse in the central periaqueductal gray (PAG) and possibly Barrington's nucleus or pontine micturition center (PMC) (green lines in **Figure 22**). There are differing views about how the brainstem circuitry is organized. One is that, if the afferent signals exceed a trigger level in the PAG, efferent fibres in the PAG are excited and they in turn excite the pontine micturition center (PMC).[596, 597] Another is that there is continuous communication between PAG and PMC and the trigger level is set in the PMC (DeGroat 2012, in press), which may also receive direct afferent input. In cats, the voiding reflex is intact after brain transection between PAG and PMC[598], consistent with the second view. Regardless, if the trigger level is exceeded, efferent signals from the PMC descend to the sacral cord (blue lines in **Figure 22**), where they excite an indirect inhibitory pathway via the nucleus of Onuf that leads to sphincter relaxation[599] and an excitatory pathway to the bladder that leads to detrusor contraction; thus voiding occurs. Therefore the

spinobulbospinal voiding-reflex pathway functions as a switch, either “off” (storage) or “on” (voiding).

In the absence of higher control, this switching behaviour would lead to involuntary bladder emptying (i.e. incontinence) whenever the bladder volume reached a critical level sufficient to trigger the brainstem switch. However underlying this apparently simple mode of behaviour are complex networks of cerebral neurons. During storage of urine the ascending afferent signals received by the PAG are relayed to higher regions of the brain, generating unconscious changes as well as conscious bladder sensations which are factored into the assessment of whether voiding is appropriate. Crucially, motor output from these higher centres is able to suppress or promote voiding by manipulating the brainstem switch.

This arrangement forms the substrate for the bladder behaviour characteristic of our species. Embarrassment caused by inappropriate voiding and feelings of shame about incontinence are deeply embedded in human behaviour. Voiding at a socially acceptable time and place is achieved by maintaining strict voluntary control of the voiding reflex. Knowledge of the extent to which one’s bladder content is ‘safe’ is central in this process. Thus, voluntary control of the bladder and urethra has 2 important aspects: registration of bladder filling sensations and manipulation of the voiding reflex switch. The PAG seems to have a pivotal role in both. On the one hand it receives bladder afferents[599] and transmits them to higher brain centres and into the realm of conscious sensation. On the other hand it receives projections from many higher centres and provides critical input to the PMC. [511] This input, together with some direct input from the hypothalamus (**Figure 22**), normally suppresses excitation of the PMC during bladder filling, so preventing voiding or incontinence. Thus the net effect of higher control is tonic suppression of the voiding reflex. If voiding is necessary (bladder volume is adequate), and is judged (perhaps unconsciously) to be safe, and is consciously assessed to be socially acceptable, suppression can be voluntarily interrupted to allow the brainstem switch to be turned on.

3. CORTICAL AND SUBCORTICAL CENTRES INVOLVED IN BLADDER CONTROL. EVIDENCE FROM OBSERVATIONS OF LESIONS AND FROM FUNCTIONAL BRAIN IMAGING IN HUMANS

a) Frontal Lobes

Although Andrew and Nathan [4] were not the first to describe disturbances of micturition resulting from a variety of causes of frontal lobe pathology, their celebrated paper reporting the syndrome of frequency, urgency (and in some patients faecal) incontinence, is regarded as seminal in the field. Their description of these patients cannot be improved upon:

“[They] were not demented, indifferent or lacking in social awareness; they were much upset and embarrassed … The acts of micturition and defaecation occur in a normal manner; what is disturbed … is the higher control of these acts. The lesion causes frequency and extreme urgency of micturition when the patient is awake, incontinence when asleep. The sensation of gradual awareness of increasing fullness of the bladder and the sensation that micturition is imminent, are impaired. When the syndrome is less pronounced, the sensation underlying the desire to micturate is absent, whereas the sensation that micturition is imminent still occurs. Then the patient is waylaid by a sudden awareness that he is about to pass urine; when neither sensation is experienced, the patient is amazed to find that he has passed urine. The threshold of the micturition reflex is much lowered. In the most complete form of the syndrome, the patient cannot inhibit the detrusor contraction of the micturition reflex; he is thus forced to empty his bladder as soon as the reflex occurs. When the syndrome is less pronounced, the patient can make a conscious effort to stop the act of micturition, and he may or he may not succeed …”

The cases of leucotomy in Andrew and Nathan’s series were regarded as most useful for localizing the lesion causing the syndrome. The significant plane of the lesion lay Immediately anterior to the tips of the ventricles and the genu of the corpus callosum. Such lesions involved grey matter, in particular the superomedial part of the frontal lobe (**Figure 29D**); but they caused a permanent disorder of the control of micturition and of defaecation only when they involved some of the white matter lateral to the anterior horns of the lateral ventricle (**Figure 29 A-C**).

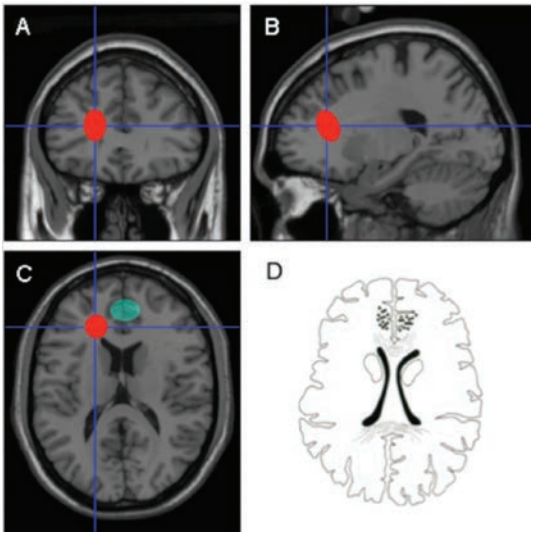


Figure 29 A, B and C. Location of white-matter lesions causing persisting incontinence (red ellipses), based on Andrew and Nathan’s Figures 10A,B and C (1). D: Nathan’s sketch of the grey-matter lesions causing transient incontinence (stippled black dots) (private commnunication).

Subsequently the same features were observed in 7 patients out of a series of 50 consecutive frontal tumours[600]. In an analysis of patients with acute hemispheric strokes the occurrence of disturbance of micturition was found to be more common in frontal than occipital lobe lesions and there was an association with hemiparesis.[601]

In 3 cases, Andrew and Nathan observed that lesions in similar areas to those discussed above led to urinary retention rather than incontinence (**Table 2**). Three further cases of frontal lesions with urinary retention have been reported. Successful treatment brought recovery of bladder function. [602, 603]

White-matter damage that causes permanent incontinence (**Figure 29 A-C**) appears to do so by disrupting a pathway (from medial frontal cortex to brainstem, either direct or via the thalamus) carrying the signal that maintains continence by tonically inhibiting the voiding reflex during storage (see discussion below and **Figure 32**). In confirmation, recent studies have identified white-matter disease (white-matter hyperintensities [WMH] or leukoaraiosis) as the pathology underlying a triad of symptoms commonly seen in the elderly – incontinence, impairment of gait and cognitive disability.[604-606] The Kuchel group used structural MRI (FLAIR) to demonstrate that the burden of white-matter disease in right inferior frontal regions and selected white-matter tracts predicted incontinence, incontinence severity, and degree of bother. The Pittsburgh group[606] used fMRI to show that, in elderly incontinent women, regional brain activations and deactivations became more prominent with increased global WMH burden, suggesting that activity aimed at suppressing urgency was augmented. Damage affecting the anterior thalamic radiation seemed to be particularly associated with urinary incontinence and indeed this tract includes the pathway from medial prefrontal cortex to brainstem that appears to be critical for continence (see **Figure 32**). It would appear from this account that bilateral lesions would be required to cause incontinence, yet in practice a lesion on one side seems to be sufficient. Andrew and Nathan's suggestion – that this is because a unilateral lesion is likely to involve the fibres connecting one side with the other– is difficult to follow.

Imaging studies (see **Table 2**), using PET[514, 593, 607-609] or fMRI[60, 515, 610, 611], are in agreement that, during bladder filling, storage and withholding of urine, there is activity in the right inferior frontal or dorsolateral prefrontal cortex, perhaps extending into the lateral part of the superior frontal cortex (**Figure 30A,B**). There is some right-sided predominance. In contrast there is little evidence for activation of the medial parts of the frontal cortex during storage (**Figure 30C**). One PET study showed medial frontal activity during sacral nerve stimulation[611], but this is difficult to interpret; another study that showed medial frontal activity during filling[612] employed SPECT imaging, which has poor spatial resolution. An fMRI study showed abnormally weak activation in medial prefrontal cortex in subjects with urge incontinence[515], and further analysis suggested that bladder filling tends to provoke deactivation in this region.[594] Regardless, there is little overlap with the superomedial frontal region described by Andrew and Nathan [4], except possibly in part of the anterior cingulate gyrus (see **Figure 30D**). These observations are consistent with the concept that functional imaging reveals grey-matter activation or deactivation, while lesions may damage critical links in white-matter connecting pathways also.

There have been many studies showing connections between the medial and orbital prefrontal cortex and PAG; see [511, 613] for summary. Presumably this pathway is the one discussed above that is responsible for tonic suppression of the voiding reflex and maintenance of continence, and is susceptible to disruption by white-matter lesions. Prefrontal involvement in voiding is considered in section 3.

b) Anterior Cingulate Gyrus (ACG), Supplementary Motor Cortex (SMA) and Insula

The anterior cingulate is an extensive area with parts serving varied functions. The cases of aneurysm in Andrew and Nathan's series of frontal lobe pathologies were thought to have involved the anterior end of the cingulate gyrus.[4] Incontinence was observed as part of a complex behavioural disorder following bilateral infarction of the anterior cingulate gyri.[614] A recent report of a patient in whom a glioma in the right posterior ACG and supplementary motor area was resected described how she experienced urgency incontinence and loss of bladder sensation following surgery.[615]

Many functional imaging studies have observed responses (mostly activations) in ACG to bladder filling, storage or withholding[514, 515, 593, 607, 609, 612, 616]. The reported locations form a trail extending from dorsal to ventral ACG, suggesting that different parts of the ACG respond to the very varied experimental paradigms that were used (**Figure 30D**). Response to bladder filling in the dorsal ACG and adjacent supplementary motor area (SMA) is abnormally pronounced in patients with urge incontinence[515, 594] when, with full bladder but without any actual bladder contraction, they experience the abnormal sensation of urgency (a compelling desire to void that is difficult to inhibit [617], also associated with fear of leakage, i.e. embarrassment).[618] Thus urgency is a powerful homeostatic and social emotion that provides strong motivation to void together with motor output aimed at suppressing incontinence until a

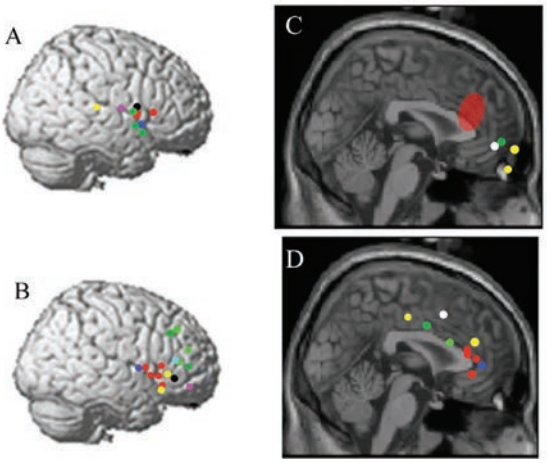


Figure 30: A, Reported locations of peak of activation during bladder filling, storage and withholding of urine projected onto right lateral surface of brain. This shows insula and adjacent lateral frontal area activation. The insula is about 2-mm deeper than the brain surface shown. In B, As in A but showing regions of activation projected onto lateral surface of the brain, mostly activation of lateral prefrontal cortex. Note the overlap with A. In C, Medial prefrontal area activated during withholding of urine with the ellipse as the projection of the white matter area shown in Fig 29 in the midline plane. In D, Cingulate gyrus areas activated on withholding of urine or full bladder. From Griffiths and Tadic, 2008.

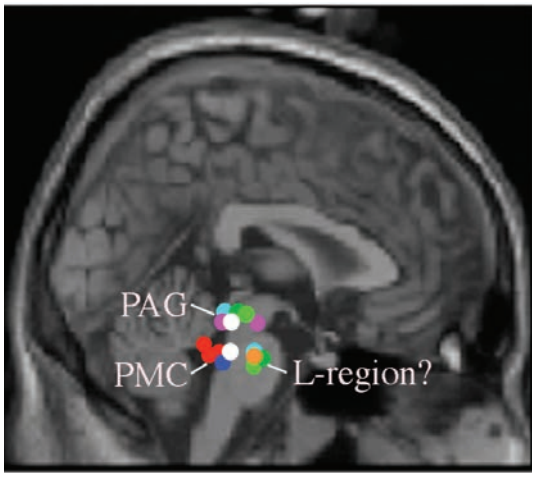


Figure 30E. Brainstem areas activated during storage or voiding. From Griffiths and Tadic, 2008.

socially acceptable location can be reached. fMRI observations in rats confirm activation in the cingulate cortex during bladder filling[619] although whether this region is homologous with the human dACC, and whether rats ever experience urgency, is not known.

The dACC or midcingulate is the cortical region associated with motivation and can be considered as the limbic motor cortex.[620] It is an essential integrator of afferent bodily function that drives sympathetic output[621], playing a similar role for several organ systems. For example it contributes to heart rate regulation via the sympathetic nervous system.[621, 622] By analogy, the dACC may be involved in sympathetic regulation of bladder and urethra, acting on alpha- and beta-adrenoreceptors that can respectively tighten the urethral smooth muscle and relax the bladder, thus helping to control incontinence.

dACC and adjacent sensorimotor areas, especially the supplementary motor area (SMA) (see **Table 3**), seem to form a functional complex that is often co-activated. The SMA is also activated during purely voluntary contraction of the pelvic floor muscles and striated urethral sphincter.[607, 623-626] Thus SMA activation during urgency may reflect tightening of the striated urethral sphincter, via somatic pathways that might include the brainstem nucleus called the pontine continence center or L-region[531] (see **Figure 32** and **Figure 22**).

Co-activation of the insula and ACC is frequently seen in functional brain imaging studies[627] and has been seen in almost all functional imaging bladder experiments. The insula, an island of cortex deep beneath the operculum of the temporal and fronto-parietal lobes, is regarded as the seat of “interoception”, the sense of the physiological condition of the entire body,[628] including visceral sensation.[629, 630] A key feature of such sensations is an association with an affective, motivational aspect: hence their value in homeostasis. Consistent with this role, the Pittsburgh group has shown a correlation between the degree of bladder filling and insula activation in healthy controls with an exaggerated increase in activation at high volumes in women with poor bladder control.[515] The homolog of the insula in the rat responds to bladder filling, although it is also activated during voiding[619].

Given these observations it is remarkable that there has not been more reported cases of bladder dysfunction from insular lesions. One patient in whom a glioma affecting the inferior frontal gyrus and the insula was excised experienced incontinence without loss of bladder sensation.[615]

Imaging studies during storage or withholding of urine show that regions reported as insula form a cluster near the expected location (**Figure 30A**).

Table 3. Selected regional activations and deactivations during the storage phase (bladder filling, withholding of urine, or full bladder with urgency but without bladder contraction). BA = Brodmann Area; [x y z] = Montreal Neurological Institute (MNI) coordinates.

Region	(BA) [MNI]	activation (+) or deactivation (-)	subjects & situation	Reference
R frontal operculum, anterior insula	[38 10 12]	+	normal women	(599)
L anterior Insula	[-26 -3 15]	+	normal males, using PET	(609)
L insula	[-40 14 2]	+	Normal males – PET	(608)
R posterior insula	[50 -4 2]	+	normal women	(594)
R insula	[44 6 4]	+	normal women	(649)
R insula	[38 -4 16]	+	women with OAB and urgency	(649)
R anterior insula/ lateral frontal cortex	[32 32 -8]	+	normal women	(594)
R & L insula	[34 8 16] & [-46 0 4]	+	normal women	(640)
R & L insula	[34 2 10] & [-34 14 10]	+	women with OAB	(594)
R & L insula	(BA 13) [±38 12 2]	+	women with urgency	(650)
R inf frontal	[50 8 14]	+	women with urgency	(649)
R & L inf frontal	[58 6 14] & [-30 28 -6]	+	normal women with full bladder	(649)
R Inf frontal	[56 40 16]	+	normal males with increasing volume	(514)
L & R middle frontal	[-36 38 44] & [46 48 26]	+	normal males with increasing volume	(514)
dACC	[-6 14 34]	+	bladder filling in women with OAB	(594)
dACC	[0 6 30]	+	normal women	(640)
dACC	(BA 32) [-8 8 42]	+	women with urgency	(650)
Cingulate (dACC)	[-2 18 22]	+	normal males with increasing volume – PET	(514)
L & R cingulate	[-2 -4 36] & [10 6 36]	-	men - deactivation with increasing 'urge' - PET	(514)
ACC	(BA 32) [8 43 7]	+	normal males during storage	(609)
ACC	(BA 24,32) [8 36 -4]	-	deactivated in normal men – PET	(607)

L & R parietal	[-56 -48 52] & [58 -28 56]	+	normal males with increasing volume	(514)
R inf parietal lobule	[36 -44 44]	+	women with urgency	(649)
R & L inf parietal lobule	[62 -22 26] & [-60 -26 28]	+	normal women	(640)
L & R premotor cortex	[-62 6 12] & [50 2 28]	-	normal males, deactivation with 'urge' – PET	(514)
Medial thalamus	[4 -6 8]	+	normal women with bladder filling	(640)
Medial thalamus	[2 -2 8]	+	bladder filling in women with OAB	(594)
R & medial thalamus	[22 -17 17] & [-2 -13 17]	+	normal males during storage	(609)
Hypothalamus	[4 -12 -6]	-	normal males deactivation with 'urge' – PET	(514)
Hypothalamus	[4 -14 -8]	+	[activation in normal response to bladder filling]	(594)
R putamen	[22 4 2]	+	[activation during storage]	(609)
R & L putamen	[22 -6 10] & [-28 –6 10]		Connectivity with R Ins and dACC during storage	(640)
L & R caudate	[-18 -18 30] & [14-22 24]	-	deactivation in OAB women	(606)
Claustrum	[30 14 8]	+	Urgency in UI women	(649)
Precuneus	[-16 -44 42]	+	bladder filling in women with OAB	(594)
Cuneus	[10 -90 8]	+	bladder filling in women with OAB	(594)
Medial prefrontal	[6, 62, 24]	-	deactivation with filling	(640)
Genual ACC	[4, 38, -2]	-	deactivation with filling	(640)
Medial frontal	(BA 10) [-4 60 -8	-	OAB women, deactivation with urgency	(650)
Medial superior frontal	(BA 9) [-8 52 22]	-	deactivation in OAB women	(606)
Subgenual ACC	(BA 32) [-6 38 -4]	-	deactivation with urgency in OAB women	(650)
L & R parahippocampal gyrus	(BA 19) [-26 -44 -2] & [28 -48 -8]	-	deactivation in OAB women	(606)
Fusiform gyrus	(BA 19) [34 -72 -12]	+	OAB women with urgency	(650)
Medial temporal gyrus	(BA 21) [50 -1 0]	-	deactivated in normal men – PET	(607)

[505, 515, 593, 608, 612, 631] There is slight right-sided predominance, not visible in **Figure 30** where right and left sides are projected on the same brain surface. In healthy subjects, insular activation becomes stronger with increasing filling of the bladder, consistent with its postulated role in bladder sensation.[594] In normal elderly, this insular response to bladder filling decreases with age, consistent with age-associated loss of sensation. However, insula activity cannot by itself be responsible for conscious desire to void or urgency, because these sensations are lost following extensive frontal lesions,[632] suggesting that integrity of connecting pathways between insula and frontal cortex is essential for conscious sensation. Cingulate and insula involvement in voiding is considered in section 3.

c) Periaqueductal Grey (PAG)

A single case history describes a young man presenting with urinary retention in whom the only abnormality found was a small, presumed inflammatory lesion in the PAG.[633] Presumably in other cases the clinical picture was dominated by other symptoms and deficits that were more striking to a neurologist.

The brainstem/midbrain activations reported during the storage and voiding phases seem to cluster in 3 distinct regions (**Figure 30E**), one of them being the PAG. PAG response to bladder filling is reported in 3 studies.[514, 515, 609] This response may reflect increased afferent signals arriving at the PAG (**Figure 22**) or increased inhibitory activity from the medial PFC, needed to prevent triggering of the voiding reflex (see **Figure 32**). The PAG responded to imagined voiding in one fMRI study[624], but not to real voiding.

d) Hypothalamus

Lesions at this site as a cause of bladder symptoms are rare but 3 cases of pituitary tumours, extending upwards into the hypothalamus have been described with urgency incontinence or retention, weight loss, psychiatric disturbance and bitemporal field restriction.[603] Other instances include gliomas involving the hypothalamus or vascular disturbances of the anterior hypothalamus. Andrew and Nathan also reported five patients with bladder symptoms appearing after a ruptured cerebral aneurysm and speculated that the site of lesion responsible was the anterior hypothalamus.[634]

Animal observations suggest that the anterior and caudal hypothalamus have monosynaptic projections to the PAG and PMC.[511] Correspondingly, two human brain imaging reports suggest response to bladder filling in a region near the caudal hypothalamus,[514, 594] and one near the preoptic area.[515] It has been suggested that these connections allow the hypothalamus to inhibit voiding unless the situation is judged to be safe.

e) Pons

The demonstration by Barrington[504] in the cat that a centre existed at the level of the pons necessary for activation of micturition, provided the background for recognizing a comparable centre in humans and the early report of the association of difficulty with micturition with posterior fossa tumours. Later histories of individual cases of discrete pontine lesions[524, 635-637] and reports of difficulties with micturition or retention as a feature of brainstem gliomas in children[638, 639] or vascular lesions [509], confirmed the likely existence of a comparable centre in humans. Studies using MRI to visualize the precise location of the responsible lesions, sited this in the dorsolateral pons, including the pontine reticular nucleus and the reticular formation, adjacent to the medial parabrachial nucleus and locus coeruleus[509]. Lesions in this location are frequently associated with disturbances of consciousness and respiration and bladder symptoms may therefore be overlooked. The commonest clinical association of urinary retention arising from a pontine lesion is an internuclear opthalmoplegia or disorder of eye movements.

Functional imaging experiments have shown a cluster of activations near the postulated location of this pontine micturition centre (PMC), **Figure 29E**. There are 3 reports of PMC activation during voiding[505, 593, 608], consistent with the “switch” concept. One report of response to bladder filling seems to support the view (see section 2) that the PMC receives continuous input from PAG and/or afferents from the bladder. However, excitation during bladder filling[594] might be either excitatory or inhibitory, a distinction that cannot be made by functional imaging. The PMC homolog is activated during voiding in the rat.[619]

A few studies suggest activation of the postulated pontine L-region or continence centre, somewhat ventral, lateral and/or caudal to the PMC (**Figure 22**): during storage[514], during failed attempt to void[593], during imagined voiding[505], and during imaginary inhibition of voiding[624]. However, not all these studies recognized the L-region as such.

f) Other Regions

The regions discussed in sections 3.1 to 3.5 are observed in lesion, imaging and (in some cases) animal studies of bladder function. The triad insula/ACG/prefrontal cortex is well known from studies of other organ systems[621]. Other regions relevant to bladder control however have been revealed only by functional imaging (see **Table 3**). They include parts of parietal and frontoparietal

cortices, posterior cortex (precuneus, posterior cingulate cortex), parts of the limbic system (hippocampal complex, amygdala), and various parts of the cerebellum.

Functional imaging has occasionally shown activity in the basal ganglia, particularly the striatum (e.g. caudate- see **Table 3**) and putamen [640]. Correspondingly, dopamine pathways are thought to have a profound inhibitory effect on the PMC in health which is lost in Parkinson's Disease (PD) [641]. The subthalamic nucleus (STN), also part of the basal ganglia, is the site of deep brain stimulation (STN-DBS) used to treat PD. Patients whose motor symptoms are effectively treated experience an increased bladder volume at first sensation and at capacity with the stimulator on.[642-644] A detailed PET imaging study showed a significant interaction between bladder state and STN-DBS in ACC and lateral frontal cortex. [644]

4. VOIDING

Forebrain changes have been much less studied during voiding than during storage, mainly because of technical limitations of fMRI. The insula was activated in only one[608] of four imaging studies of real [593, 607] or imagined [624] voiding, suggesting that it is not strongly involved in this phase of micturition. All 4 studies revealed ACG involvement, particularly of the perigenual part of the ACC adjacent to the ventromedial prefrontal complex.

Further reports are as follows.

PET studies of voiding. One fMRI study of voiding in the anesthetized rat[619] showed several regional activations, but human homologs are difficult to establish. Blok and Holstege used PET to show that a pontine region probably homologous with the PMC was activated during voluntary voiding in humans, suggesting that the voiding reflex had indeed been triggered.[505, 593] They showed also that the right inferior frontal gyrus (or lateral prefrontal cortex) was activated during voiding. The perigenual cingulate, close to the ventromedial prefrontal cortex which, during storage, is typically deactivated (see **Table 3**), was activated during voiding. This change may indicate that the tonic inhibition of the voiding reflex, which the medial frontal cortex exerts to maintain continence (**Figure 32**), has been switched off, allowing voiding to take place. During voiding the PAG was activated, as were a number of other regions, including the hypothalamus and right inferior frontal gyrus.

Some subjects who were unable to void in the scanner failed to show activation either in the perigenual region or in the PMC. They did however show activation of a different region in the pons, believed to be the L-region[531] or pontine storage center (see **Figure 32** and **Figure 22**). This suggests involuntary tightening of the urethral sphincter.

Nour et al [608] using PET, demonstrated many regional activations during voiding, including the PAG and a pontine region close to the PMC. However, the perigenual region was not activated, while the supplementary motor area, dACC, and left insula were unexpectedly active.

Imagined voiding. In a group of 11 healthy women, relaxation of the pelvic floor, as if intending to void but without actually voiding, evoked activations in many of the same regions as contraction of the pelvic floor muscles.[624] Thus this does not seem to be a good model of real voiding. In fact, a pontine region apparently homologous with the pontine continence center or L-region (but not recognized as such by the authors), was activated, just as in Blok's subjects who tried but were unable to void in the scanner. [505]

Involuntary voiding. A preliminary fMRI study of involuntary voiding (detrusor overactivity, DO)[645] showed marked deactivation of the frontal cortex during DO, a finding that awaits confirmation.

5. WORKING MODEL OF BRAIN / BLADDER CONTROL

We have seen that many forebrain regions respond with altered neuronal activity to bladder filling or voiding, and thus presumably form part of the brain-bladder control network **(Table 2**). Some are part of a general 'homeostatic afferent brain network' that processes sensation and generates appropriate output for many different organ systems.[594, 629, 630] This is not surprising because the ultimate purpose of bladder control is to maintain homeostasis by ensuring that the bladder is emptied regularly, yet only when safe and appropriate. Sensations such as desire to void and urgency are homeostatic emotions[621, 622, 630] that both motivate behaviour and provide corresponding motor output. [596]

The brain regions involved in bladder control are believed to be organized in neural circuits that perform different tasks related to homeostasis, answering questions regarding the adequacy of bladder filling, and the safety and social appropriateness of voiding, as well as the reflex or mechanical aspects dealt with by the brainstem switch. We should therefore expect forebrain control of the switch to involve both limbic circuits (concerned with basic emotion and safety) and cortical circuits (concerned with social propriety [646] and conscious decision-making). In the working model shown in **Figure 32**, the PAG and PMC form the brainstem switch. The PMC is the final efferent brain nucleus involved in bladder control. The PAG receives numerous projections from forebrain regions,[647, 648] including the medial and orbital

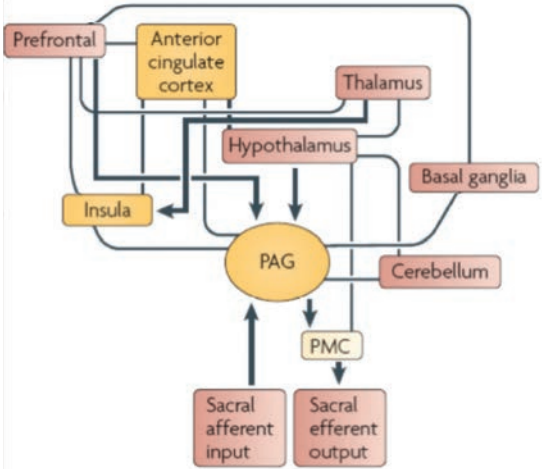


Figure 31. An early conceptual framework that suggests a scheme for the connections between various forebrain and brainstem structures that are involved in the control of the bladder and the sphincter in humans. Arrows show probable directions of connectivity but do not preclude connections in the opposite direction. Reproduced, with permission Fowler et al., 2008 and based on the work of Kavia et al.2005.

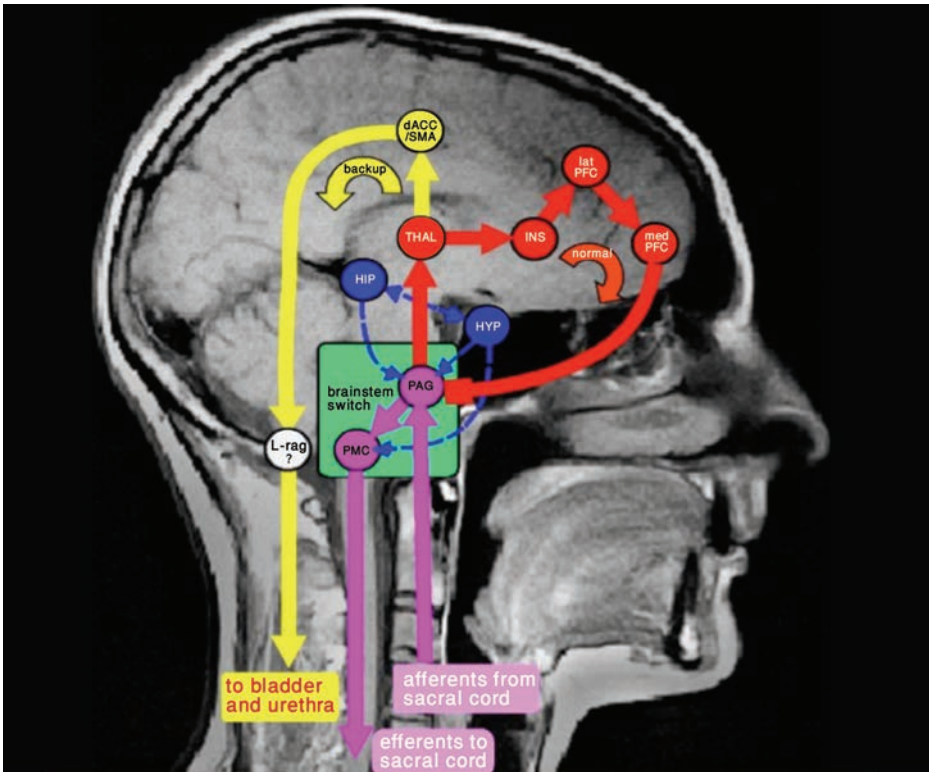


Figure 32. Working model of forebrain control of micturition, showing the brainstem switch and neural circuits that mediate 2 possible continence mechanisms. The normal mechanism (red) operates when there is a normal sensation of bladder filling. It depends on tonic inhibition of the brainstem switch via a long return pathway from the medial prefrontral cortex to the brainstem switch (probably via the anterior thalamic radiation, but shown for simplicity as a direct connection to the PAG). The inhibition is switched off for voiding. A backup mechanism (yellow) corresponds to the abnormal sensation or urgency. It may operate via brainstem nuclei such as the L-region (pontine storage center) or by modulating the sympathetic input to bladder and urethra. The dashed blue arrows show a possible circuit concerned with monitoring safety and/or maintaining continence without conscious sensation. PMC = pontine micturition center; PAG = periaqueductal grey; L-reg = L-region; THAL = thalamus; INS = insula; lat PFC = lateral prefrontal cortex; med PFC = medial prefrontal cortex; dACC = dorsal anterior cingulate cortex; SMA = supplementary motor area; HYP = hypothalamus; HIP = (para)hippocampal complex (may include amygdala, inferior parts of temporal lobe and parts of posterior cortex).

prefrontal cortex.[613] Possible pathways that connect these regions to form the neural circuits that govern bladder and urethral behaviour are shown schematically in **Figure 31** and sketched provisionally in the working model (**Figure 32**), which incorporates as far as possible the lesion and functional imaging observations described above.

a) The Normal Continence Mechanism

During urine storage, as the bladder fills it generates afferent signals (purple ascending pathway in **Figure 32**) that are transmitted to the brainstem switch but do not trigger it. They are relayed from the PAG via the thalamus to the insula (red circuit) and, if activation is strong enough, generate a desire to void. Propagation of this insular activity to the lateral and medial prefrontal cortex enables both a conscious decision about voiding and an assessment of social propriety and possible embarrassment. If no voiding is planned, a return pathway from the medial frontal cortex to the brainstem tonically suppresses the voiding reflex. The pathway may run directly or via the thalamus in the anterior thalamic radiation (not shown in **Figure 32**). The resulting red circuit is postulated to be the normal continence mechanism. When there is a normal sensation of bladder filling it exerts negative feedback on the brainstem switch, preventing incontinence. Interruption of the negative feedback, for example by white-matter damage in the mPFC-PAG pathway, leads to incontinence. During normal daily life however there is usually no conscious awareness of the bladder at all. The mechanism that monitors bladder behaviour in this situation requires further research. One possibility is a circuit involving the parahippocampal complex and hypothalamus (**Figure 32** and section 5.3).

b) A Back-up Continence Mechanism

Activation of dACC and SMA, associated with urgency, suggests the possibility of another neural circuit – in yellow in **Figure 32** – in which an ascending signal from the PAG travels via the thalamus to the dACC and SMA, generates urgency and sends a descending efferent signal that suppresses bladder contraction and tightens the urethral sphincter, using sympathetic (via dACC) and somatic (via SMA) pathways that may involve the pontine L-region. Because urgency is evoked in extreme circumstances this probably should be regarded as a back-up continence mechanism.

What ascending signal activates the dACC and the SMA and generates urgency? The conventional view is that the bladder or the urethra generates abnormal – or merely greater – afferents if leakage threatens, but an alternative is that the PAG should use its knowledge of the brainstem switch to generate a signal indicating how close the switch is to being triggered. This signal, relayed via the thalamus to the dACC, would presumably evoke urgency if triggering were imminent.

c) Limbic or Paralimbic Circuits

Both of the continence mechanisms just described use cortical circuits that involve conscious bladder sensation. However bladder filling, especially in women with OAB experiencing urgency, sometimes provokes subcortical or limbic changes, particularly parahippocampal deactivations (**Table 2** and **Figure 32**). These subcortical changes may have a number of functions:

1) They presumably evoke no conscious sensation, and therefore may reflect an automatic evaluation of bladder events that occurs at small bladder volumes, maintaining continence without conscious awareness.

2) They may reflect evaluation of the safety of voiding. The resulting “safe/unsafe” signal would be relayed to the brainstem switch (PAG and/or PMC), perhaps via the hypothalamus (**Figures 31, 32** and **22**).

3) They may represent the substrate concerned with basic emotions such as fear, on which the ventromedial prefrontal cortex builds the secondary, social emotion called urgency.

d) Voiding

Referring to **Figure 32**, if voiding is voluntarily decided upon in the prefrontal cortex a series of stereotypical actions follows (finding a toilet, adjusting clothing, adopting the correct posture) and ultimately the red return pathway from mPFC to brainstem PAG is silenced, removing inhibition of the voiding reflex and allowing activation of the PMC – provided that other PAG inputs, notably from the hypothalamus (reflecting safety), permit it.

6. CONCLUSION: CORTICAL CONTROL OF BLADDER FUNCTION

The fact that voiding and continence are under forebrain control is now well established by multiple lines of evidence. Some of the brain regions involved are known with reasonable certainty, although further investigations, particularly of normal behaviour, voiding, and different age groups of both genders, will be helpful. The specific functions of these regions and the pathways connecting them are less well known but they can be speculatively organized in a working model comprising a few neural circuits that perform various tasks related to homeostasis and maintenance of continence. There is evidence that structural damage to certain critical connecting pathways causes or contributes to urgency incontinence. The working model is highly simplified, but will help understanding of functional disorders such as overactive bladder and guide new research aimed at ameliorating the scourge of urgency incontinence.

VII. ABNORMAL LOWER URINARY TRACT FUNCTION

Lower urinary tract (bladder and urethra) function, while dependent on autonomic neural control, does not mean that control of urinary continence and micturition is involuntary. On the contrary, unlike other autonomically innervated organs (i.e. heart), control of lower urinary tract function is highly volitional and dependent on neural connections to the brain. This control in humans is established during the unique period of toilet training occurring between ages of 2 and 3. The exact mechanisms and pathways that are involved in this important and ubiquitous event are unknown. It is likely that cortical inhibition of the micturition center are emphasized and strengthened during this time.

Later on in life, continence and/or micturition disturbances (interpreted by the patients as lower urinary tract symptoms) are likely associated with alterations/dyregulation of these neural pathways. However, the current diagnostic tools to detect these alterations are not available. Neurogenic alterations can be differentiated into pathologies that affect afferent versus efferent pathways. Afferent dysfunction would involve abnormalities in sensation (both increased and decreased) including emergence of pain instead of usual bladder filling sensations. Efferent abnormalities can be increased, reduced or uncoordinated. The following is not a comprehensive description of the entire scope of this complex arena, but focuses on key issues relevant in the clinical context.

Basic investigations into abnormalities in lower urinary tract function require a multi-modal approach using both animal models and human subjects. While all animal models have issues related to relevance to human condition, animal models will continue to play a critical role in testing mechanistic hypotheses related to lower urinary tract physiology and pathophysiology. Using human subjects for translational studies, such as exploring for biomarkers related to lower urinary tract dysfunction, will provide additional mechanistic hypotheses that can be taken to the laboratory for testing.

1. ABNORMALITIES INVOLVING AFFERENT SIGNALING

a) Bladder Pain Syndrome / Interstitial Cystitis (BPS/IC)

Although no consensus has been reached on the fundamental causes of BPS/IC, existing data suggest three pathophysiological mechanisms: mast cell activation, neurogenic inflammation and epithelial dysfunction.[651]

Mast Cell Activation – Mast cells may be activated by a number of mechanisms within the bladder wall. Increased permeability with influx of potassium ions may lead to sensory nerve upregulation/activation resulting in mast cell activation. Vasoactive, nociceptive and pro-inflammatory molecules released from mast cells can produce neuronal sensitization and secretion of neurotransmitters that further stimulate mast cells. Mast cell could interact with nerves and provoke a vicious cycle in BPS/IC, contributing to the painful symptoms of the disease.[652]

Neurogenic Inflammation – The close physical relationship between the C fibres and mast cells is of particular importance, as substance P (SP) released from the nerve fibres degranulates mast cells. During degranulation, the mast cells release a multitude of proinflammatory agents including nerve growth factor (NGF), tumour necrosis factor-α (TNFα), histamine, heparin, proteases, interleukins, serotonin and others. This induces an inflammatory response in the form of vasodilatation (redness) and plasma protein extravasation (oedema). Additionally, newly released nerve growth factor (NGF) stimulates a further increase in the number of afferent fibres, thus increasing the potential for further releases of SP and the transmission of nociceptive impulses. Inflammatory models of cystitis result in increased levels of TNF-alpha, SP and NGF production in the bladder, paralleling the hypothesized neuro-inflammatory etiology of IC. [653] During mammalian development, NGF is required for the survival and growth of several populations of neurons. There is evidence to suggest that it also plays a role in the ongoing regulation of neural function, as well as inflammation and pain.[654] In the urinary tract, NGF could be produced by the bladder, smooth muscle and urothelium. In one study, patients with BPS/IC were found to have elevated levels of neurotrophic factors in their urine, including neurotrophin-3, nerve growth factor and glial cell line-derived neurotrophic factor.[655] In another study, urine from BPS/IC patients have increased NGF[656], but interestingly did not have increased prostaglandin E2 (PGE2). Another study showed increased NGF mRNA and protein in bladder biopsies from patients with BPS/IC compared with controls[119]. However, the source of the NGF has not been always traceable, although a likely source of the NGF is the bladder urothelium.

A transgenic mouse with overexpression of NGF restricted to the urothelium [86] was shown to exhibit similar phenotype to BPS/IC patients – that is urinary frequency and pelvic pain. This animal model suggests that alterations in the bladder urothelium can drive overall changes in bladder function and increase pelvic pain sensation. Therefore, this animal model is consistent with the data derived from human studies. The importance of the bladder urothelium in pathophysiology of BPS/IC has been also been demonstrated by the discovery a novel glycononapeptide, antiproliferative factor (APF)[49] secreted by the BPS/IC bladder urothelial cells. APF inhibits in vitro proliferation of normal bladder urothelial cells grown in culture[657] and affects

the ß-catenin signaling pathway.[658] However, whether APF affects neural signaling within the bladder is unknown.

Intravesical NGF is known to sensitize bladder afferent fibres, and sequestration of NGF can reduce inflammation associated with chemical cystitis in a rat model[659]. Blockade of NGF using either endogenous antibody or antibody against the NGF receptor, or a fusion protein that prevents interaction between NGF and its receptor, prevents neural plasticity and bladder overactivity in experimental models of these conditions.[660] Other substances including neurotrophins, prostaglandins, and tachykinins may also contribute to altered afferent excitability.[661] The potential relevance of these changes has been demonstrated in cats diagnosed with feline interstitial cystitis (FIC) (which demonstrates nearly all the characteristics and symptoms of human BPS/IC), in which capsaicin sensitive neurons are larger, with dorsal root ganglia that exhibit increased excitability and slower desensitization to capsaicin.[662] These findings suggest changes in the properties of the primary afferent neurons, a finding that may be associated with tendency of NGF to stimulate TRPV1 expression.

From the translational perspective, a monoclonal antibody to NGF, tanezumab, has been tested in a proof-of-concept trial in treating symptoms associated with BPS/IC. This study showed that tanezumab had significant benefits at alleviating BPS/IC symptoms [663] compared to placebo suggesting promise for this agent that blocks NGF's actions. Further peer-reviewed publications are needed to determine whether this agent will be useful in a larger clinical population of BPS/IC patients.

b) Pelvic Organ Cross-talk

Another neurogenic phenomenon that might be related to BPS/IC is that of pelvic organ crosstalk. Investigators have theorized that because pelvic organs share the same innervation pathways that when one pelvic organ dysfunctions (i.e. colon) this can lead to bladder dysfunction similar to BPS/IC,[664, 665] a term coined cross-sensitization. This theory is based on the notion that afferent input from one pelvic organ can lead to the dysfunction of another pelvic organ. Researchers are focusing on the mechanism of underlying cross-sensitization and how those mechanisms could be targeted for therapeutic intervention.

Clemens recently coined a term "afferent neurourology" to describe the study of sensory signaling related to the genitourinary tract, which encompasses other organs besides the bladder including the prostate, urethra, vagina, testicles and scrotum.[666] Therefore, disorders in afferent neurology would include other urologic symptoms perceived by the patients outside of the bladder including disorders, for example, such as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), pelvic pain syndrome, vaginal pain syndrome, and urethral pain syndrome. These other conditions, because they are not perceived to be related to the bladder, are not the topic of this review. However, Clemens' review suggests that many of these afferent neurologic symptoms, including BPS/IC, may be due to systemic pathophysiology rather than localized to the organ of suspicion.

2. INVOLVING ABNORMAL URINE STORAGE

a) Overactive Bladder / Detrusor Overactivity

Detrusor overactivity can be due to neuropathic conditions, bladder outlet obstruction or unknown causes. Several observations on structural and functional properties of the bladder have been made in individuals with detrusor overactivity:

- Patchy denervation is present within the bladder wall, while sensory neurones and parasympathetic ganglion cells are enlarged
- Exaggerated spontaneous myogenic activity can be seen in isolated detrusor muscle strips, with increased incidence of fused tetanic contractions
- Muscle strips also show altered responsiveness to nervous and pharmacological stimuli
- Characteristic changes in smooth muscle ultrastructure have been described.

Smooth muscle strips dissected from the bladder in detrusor overactivity often show altered responses to nerve stimulation and to various agonists. For example, in obstructed overactive bladders there is reduced contractile response to intrinsic nerve stimulation, along with supersensitivity to muscarinic agonists and potassium solutions.[667-670] Among neuropathic conditions, spina bifida is associated with supersensitivity to cholinergic agonists and potassium solutions, but there is no change in the sensitivity to intrinsic nerve stimulation.[671] In spinal cord injury, there is no reduction in sensitivity to electrical field stimulation, but the maximum force generated by each milligram of bladder tissue is significantly reduced. In idiopathic detrusor overactivity, bladder strips show supersensitivity to potassium, but not to muscarinic agonists, and there is a reduced contractile response to intrinsic nerve stimulation.[672] Where functional denervation is present, there appears to be an increase in spontaneous contractile activity and presence of fused tetanic contractions, a feature more typical of well-coupled smooth muscles.[673, 674] A common ultra-structural feature of the overactive detrusor is the emergence of protrusion junctions and ultra-close abutments between the smooth muscle cells.[675] Overall, the cells may be better coupled electrically in detrusor overactivity, perhaps allowing spontaneous activity to propagate over a wider area. Bladder biopsies from overactive detrusor show a patchy denervation; some muscle bundles may be completely denervated, whilst neighbouring ones appear normal and in other areas sparser innervation is also seen.[672, 676] A similar pattern is seen in animal models.[668, 677] Overall,

these observations suggest that response to loss of local innervation by the smooth muscle cell may explain the altered behaviour of the bladder in detrusor overactivity.[667, 678]

Recent studies using function MRI or positron emission tomography (PET) of the brain in patients with urge incontinence and comparing to normal control subjects suggest that urge incontinence is associated with measureable changes in brain activities.[594, 650] Bladder control depends on neural networks within the brain regions including the pontine micturition center, periaqueductal gray (PAG), anterior cingulate gyrus (ACG), insula, amygdala and prefrontal cortex. Neural targets, in addition to detrusor smooth muscle, may be target for future urge incontinence treatments.

Preclinical studies in animal models of OAB / detrusor overactivity contribute further to our understanding of the importance of neural control in this condition. The main models relevant to OAB include (i) instillation of irritative agents into the bladder during cystometry, (ii) partial bladder outflow obstruction, (iii) the spontaneously hypertensive rat, (iv) spinal cord injury, and other CNS lesions similar to those responsible for bladder dysfunction in humans [679] Irritative agents are employed in animals to evoke a painful or irritant response, in particular through C-fibres. Both acetic acid and citric acid have been used, although the latter probably represents a better model since it is less irritant and therefore less likely to invoke an acute inflammatory response. Both agents have been shown to increase bladder contractile activity, decrease bladder capacity and reduce bladder compliance, while micturition pressure remains normal or is increased, suggesting that this model may contribute to understanding of increased bladder sensory activity, as may occur during the symptom of urgency. These effects are due to stimulation of nociceptive afferent fibres, confirmed through demonstration of increased c-fos expression in rat spinal cord and in regions of the periaqueductal grey. [680] This effect can be eradicated by desensitization of TRPV1 receptors on the sensory neurones following pretreatment with resiniferatoxin.[681]

Partial bladder outflow obstruction has been achieved through application of urethral ligatures or a constricting ring that results in partial urethral occlusion, mimicking the obstruction seen in men with BPH who often develop secondary OAB.[669] The animals develop cystometric features such as increased bladder capacity and non-voiding bladder contractions, with associated histological features (muscle hypertrophy, patchy denervation and enlarged sensory neurones and parasympathetic ganglia) and detrusor functional features (spontaneous myogenic activity and altered response to stimuli) reminiscent of the human condition.[678] Afferent plasticity in animals with bladder outflow obstruction involves NGF, the content of which is increased in obstructed bladders prior to the enlargement of bladder neurons and the development of urinary frequency.[682] The relevance of NGF in the response to obstruction in animals is suggested by the finding that rats immunized with mouse NGF in order to develop autoantibodies do not develop neural plasticity and urinary frequency in response to obstruction.[683] While neuronal changes are evident in the obstructed model, further observations appear to indicate that the overactive phenotype in obstructed rats derives from a combination of increased propensity to localized muscle contraction, together with a tendency towards wider propagation of this activity in an organ that may have developed greater autonomy from central control as a result of the neuronal changes.[424] In this context, the relevance of peripheral contractile modules appears to emerge as the functional units of detrusor activity.

The spontaneously hypertensive rat (SHR) is a genetic model of hypertension, which is also known to exhibit abnormal bladder function; in particular, SHRs have been shown to have reduced bladder capacity and voided volume, increased urinary frequency and increased occurrence of non-voiding contractions, associated with altered detrusor innervation and physiological response. Again, increased bladder smooth muscle NGF levels appear to be associated with these changes.[684] The bladders of SHRs also show increased levels of calcitonin gene-related peptide immunoreactive fibres (presumably afferent) with increased size of neuronal cross-sectional area profiles for bladder afferents in the L6–S1 dorsal root ganglia as well as the major pelvic ganglia.[685] The potential importance of the afferent innervation in this model can be highlighted by the finding that intrathecal application of antisense oligonucleotide against the tetrodotoxin- resistant sodium channel (Nav1.8) reduces bladder hyperactivity.[684, 686]

Spinal cord injury (SCI) in animals has been shown to result in changes in lower urinary tract function similar to those seen in humans.[687] Recovery of bladder function from the initial areflexia after SCI in animal models is dependent in part on plasticity of bladder afferent pathways and the unmasking of reflexes triggered by the normally silent capsaicin-sensitive C-fibre bladder afferent neurons, resulting in cystometric changes akin to those seen in neurogenic detrusor overactivity. Studies in rats indicate that the increased excitability in the C-fibres is associated with an increase in the expression of sodium channels from a high-threshold TTX resistant type to a low-threshold TTX-sensitive type.[688]

Recent clinical studies has been performed to determine whether neurosurgical somatic-to-autonomic nerve re-routing can reverse detrusor areflexia secondary to autonomic neural injury secondary to spinal dysraphism[689]. The intended goal of this procedure is to trigger somatic afferent signal that will be reflected in a autonomic motor reflex. Whether this procedure will have potential for widespread clinical application to other neuro-

logic conditions causing detrusor areflexia remains to be seen. Furthermore, this surgical nerve re-routing procedure has been highly controversial arising from ethical concerns.[690]

Other animal models of CNS lesions associated with bladder dysfunction have also been developed. For example, a model of Parkinsonism secondary to 6-hydroxydopamine injections into the substantia nigra pars compacta in rats has been developed, confirming the relevance of D1/D5 dopaminergic stimulation in improving bladder capacity. Furthermore, a model of bladder overactivity associated with cerebral infarction due to occlusion of the middle cerebral artery in rats has been shown to lead to significant ischaemia within the putamen and cerebral cortex, confirming the importance of these areas in the control of micturition.[691] In this latter model, a role for glutamatergic and dopaminergic stimulation in the development of bladder dysfunction has been demonstrated.[691, 692] These findings are consistent with the observation that anterior brain lesions in humans are more likely to be associated with incontinence than posterior, occipital lesions.[601]

Additional evidence for the importance of emergent C-fibre contribution to afferent signalling in OAB and detrusor overactivity can be found in experimental clinical studies. For example, patients with various idiopathic and neurogenic bladder dysfunctions have reduced current perception threshold to direct bladder stimulation [693] and urethral stimulation [694] frequencies that selectively stimulate C-fibres, indicating increased excitability in the C-fibre afferents in these patients. Similarly, ice water instillation (which excites C-fibres) into the bladder can trigger involuntary detrusor contraction in patients with neurogenic detrusor overactivity.[695] In addition, the efficacy of capsaicin and resiniferatoxin in the treatment of patients with both idiopathic and neurogenic detrusor overactivity confirms the role of C-fibres and the afferent limb of the micturition reflex in bladder storage conditions.[696] While the hyper-excitable C-fibres appear to be the conduit for the abnormal sensory signals from the overactive bladder, the origin of the sensations probably lies in the bladder wall itself, either in uncoordinated asynchronous localized detrusor contractile activity[697] which may lead to urgency with negligible associated pressure rise within the bladder, or in a more co-ordinated propagation of autonomous contractile activity via emergent gap junctions providing more syncytial characteristics to the overactive detrusor.[675]

b) Stress Urinary Incontinence

Stress urinary incontinence (SUI) is characterized by reduced outflow resistance during urinary storage due to weakness in the urethral sphincter mechanism. It is often associated with weakness of the pelvic floor and urethral musculature, but peripheral nerve dysfunction is also implicated, in particular pudendal nerve damage following childbirth in women.[698] Animal models have contributed to understanding of the importance of the peripheral innervation of the urethra in SUI, with development of disease models association with pudendal nerve crush and vaginal distension initiating neuropraxic nerve injury in rats[304] and mice[699]. The role of pharmacological neuromodulation in the treatment of SUI has shown that urethral function and therefore incontinence can be improved by augmenting somatic neuronal discharge using the serotonergic (5HT) and noradrenergic (NE) reuptake inhibitor duloxetine, which is thought to act in the sacral spinal cord at Onuf's nucleus, the pudendal somatic motor nucleus of the spinal cord which is densely innervated by 5HT and NE terminals,[700]. Duloxetine has shown beneficial effect in a placebo-controlled, randomized clinical trial for treating stress urinary incontinence.[335]. The selective noradrenergic reuptake inhibitor, [S,S]-reboxetine in the treatment of SUI, indicate that the serotonergic activity of duloxetine may be redundant and that effects are dependent solely on noradrenergic reuptake inhibition.[340, 701]

3. INVOLVING ABNORMAL VOIDING

a) Bladder Outflow Obstruction

Bladder outflow obstruction (BOO) is typically associated with prostatic enlargement in men, although it is also seen in women following surgery for stress urinary incontinence and in children secondary to proximal urethral valves. Bladder overactivity is seen in many patients with BOO, and this storage dysfunction together with the associated neuronal changes has been described above. The voiding dysfunction per se seen in patients with BOO is caused by a combination of both passive and dynamic obstruction of the proximal urethra and, in some patients, by detrusor decompensation resulting in a deterioration in the contractile function of the bladder during voiding.

During obstructed voiding, the bladder is subject to high pressures required to expel urine through a region of high resistance. These pressures compromise detrusor blood flow during voiding leading to periods of ischaemia and hypoxia, followed by reperfusion.[702) Recurrent cycles of ischaemia and reperfusion result in progressive neuronal damage in the bladder wall, an effect that has been seen in animal models of obstruction and bladder distension, as well as in an in vitro model in which detrusor muscle is intermittently exposed to hypoxic glycopenic perfusate followed by oxygenated glucose-containing perfusate.[703] This neuronal damage initially has a patchy appearance, when it seems to be related to the development of an overactive phenotype in pigs.[678] With time, however, bladder decompensation with incomplete voiding and chronic retention can develop, and this is associated with a more generalized detrusor denervation and reduced contractile response to neuronal stimulation in organ bath studies.[704]

4. CO-MORBID DISORDERS

The significance of neural control mechanism in lower urinary tract dysfunction is further implied by a number of comorbid conditions that have been associated with BPS/IC and incontinence. Patients with BPS/IC and SUI are more likely to report depressive symptoms. Findings on two validated depression measures indicate that patients with interstitial cystitis report significantly greater depressive symptomatology than healthy controls, although less than 20% notice moderate or severe depressive symptoms. This finding is consistent with the observation that patients with chronic pain experience a higher level of depressive symptoms than healthy controls and other chronically ill populations. Patients report low mood (56%), fatigue (63%), difficulty concentrating (49%), insomnia or excessive daytime sleepiness (49%) and are 3 to 4 times more likely to report suicidal thoughts than the general population.[705] The association of BPS/IC [194]and incontinence [706] with depression has been corroborated in other studies, although a more recent study suggests that, after multivariate adjustment for the influence of other urogenital symptoms, only the symptom of nocturia remains significantly associated with depression.[707]

BPS/IC has also been associated with other chronic pain conditions, especially fibromyalgia. An association has also been shown for child abuse.[194, 708] Based on recent improvements in understanding of pain processing pathways in the central nervous system, and in particular the role of limbic structures, especially the anterior cingulated cortex, hippocampus and amygdala, in chronic and affective pain perception, a condition termed limbic associated pelvic pain has been proposed to explain the concurrence of these various chronic pain conditions. This limbic dysfunction is manifest both as an increased sensitivity to nociceptive afferents from pelvic organs, and as an abnormal efferent innervation of pelvic musculature, which undergoes tonic contraction as a result of limbic efferent stimulation, generating a further sensation of pain. The nociceptive afferents from these pelvic organs then follow the medial pain pathway back to the sensitized, hypervigilant limbic system. Chronic stimulation of the limbic system by pelvic pain afferents again produces an efferent contraction of the pelvic muscles, thus perpetuating the cycle.[708]

Investigators have shown in an animal model that social stress in a virgin young male rat can lead to voiding dysfunction not dissimilar to bladder outlet obstruction (smooth muscle hypertrophy, enlarged bladder).[572] The social stress model (also called the social defeat, resident-intruder paradigm[709] is created by placing the virgin young male rat in the same cage as a retired male breeder. These two animals can see and smell each other, but are physically separated by a screen. The molecular mechanism underlying the bladder dysfunction could be secondary to corticotrophin-releasing factor (CRF).[571] The link between CRF and bladder innervations was first reported by de Groat in 1994.[382] Specifically, this early paper showed that CRF-like immunoreactivity was associated with bladder afferent projections in the sacral spinal cord suggesting that CRF may be a neurotransmitter in the afferent pathway. Valentino's work [571] showed that CRF is upregulated in Barrington's nucleus neurons during stress. These studies highlight the importance of higher neural centers integrating bladder function, thus linking bladder disorders to psychological variables such as emotion, behavior, and motivation. Holstege has penned an editorial that highlights these connections with the provocative title "Micturition and the Soul".[511]

Table 4. Bladder Storage and Emptying Disorders, Associated Clinical Conditions / Types of Cells Affected

Phase of Bladder Dysfunction	Clinical Conditions	Potential cell type dysfunction
Bladder Storage Phase Disorders	Detrusor overactivity Overactive bladder (urgency, urgency urinary incontinence) BPS/IC (bladder pain)	Detrusor smooth muscle cells Bladder urothelial cells Suburothelial cells (myofibroblasts) Afferent neuronal cells Central nervous system neuronal cells Urethral smooth muscle cells
Bladder Emptying Phase Disorders	Urinary Retention Bladder outlet obstruction	Detrusor smooth muscle cells Suburothelial cells (myofibroblasts) Efferent neuronal cells Central nervous system neuronal cells Urethral smooth muscle cells

REFERENCES

1. Barrington, F.J.F. 1921. The relation of the hind-brain to micturition. *Brain* 44:23-53.
2. Kavia, R.B., Dasgupta, R., and Fowler, C.J. 2005. Functional imaging and the central control of the bladder. *J Comp Neurol* 493:27-32.
3. Fowler, C.J., Griffiths, D., and de Groat, W.C. 2008. The neural control of micturition. *Nat Rev Neurosci* 9:453-466.
4. Andrew, J., Nathan, P.W. 1964. Lesions of the anterior frontal lobes and disturbances of micturition and defaecation. *Brain* 87:233-262.
5. Apodaca, G. 2004. The uroepithelium: Not just a passive barrier. *Traffic* 5:117-128.
6. Lewis, S.A. 2000. Everything you wanted to know about the bladder epithelium but were afraid to ask. *Am J Physiol* 278:F867-F874.
7. Khanderwal, P., Abraham,S.N., Apodaca,G. 2009. Cell biology and physiology of the uroepithelium. *Am J Physiol* 297:F1477-1501.
8. Truschel, S.T., Ruiz,W.G., Shulman,T., Pilewski,J., Sun,T.T., Zeidel,M.L. and Apodaca,G. 1999. Primary uroepithelial cultures. A model system to analyze umbrella cell barrier function. *J Biol Chem* 274:15020-15029.
9. Sun, T.T. 2006. Altered phenotype of cultured urothelial and other stratified epithelial cells: implications for wound healing. *Am J Physiol* 291:F9-21.
10. Liang, F.X., Riedel,I., Deng,F.M., Zhou,G., Wu,C., Wu,W.R., Kong,W.P., Moll,R., Sun,T.T. 2001. Organization of uroplakin subunits: transmembrane topology, pair formation and plaque composition. *J Biochem* 355:13-18.
11. Hicks, M. 1975. The mammalian urinary bladder: an accomodating organ. *Biol Rev* 50:215-246.
12. Acharya, P., Beckel, J.M., Ruiz, W.G., Wang, E., Rojas, R., Birder, L.A., and Apodaca, G. 2004. Distribution of the tight junction proteins Z0-1, occludin, and claudin-4, -8, and -12 in bladder epithelium. *Am J Physiol* 287:F305-F318.
13. Hicks, M., Ketterer,B., Warren,R. 1974. The ultrastructure and chemistry of the luminal plasma membrane of the mammalian urinary bladder: a structure with low permeability to water and ions. *Phil Trans R Soc Lond* 268:23-38.
14. Nirmal, J., Tyagi,P., Dang,L., Hanna-Mitchell,A., Wolf-Johnston,A., Kaufman,J., Birder,L., Chancellor,M. 2012. Endocytosis uptake of liposomes in urothelium cells detected by transmission electron microscopy. *American Urological Association* 1202359.
15. Tyagi, P., Chancellor,M., Yoshimura,N., Huang,L. 2007. Activity of different phospholipids in attenuating hyperactivity in bladder irritation. *BJU Int* 101:627-632.
16. Tyagi, P., Chuang,Y-C., Yoshimura,N., Kaufman,J., Chancellor,M.B. 2009. Bladder instillation of liposomes for bladder coating and drug delivery platform. *LUTS* 1:S90-93.
17. Chuang, Y.-C., Tyagi,P., Huang,C-C., Yoshimura,N., Wu,M., Kaufman,J., Chancellor,M.B. 2009. Urodynamic and immunohistochemical evaluation of intravesical botulinum toxin A delivery using liposomes. *J Urol* 182:786-792.
18. Kaufman, J., Tyagi,P., Chancellor,M.B. 2009. Intravesical liposomal (LP09) instillation protects bladder urothelium from chemical irritation. *American Urological Association* 1506.
19. Peters, K.M., Hasenau,D.L., Anthony,M., Kaufman,J., Killinger,K.A., Chancellor,M.B. 2012. Novel therapy with intravesical liposomes for ulcerative interstitial cystitis/painful bladder syndrome. *LUTS* in press.
20. Parsons, C.L., Greenspan,C., Moore,SW., Mulholland,S.G. 1977. Role of surface mucin in primary antibacterial defense of bladder. *Urology* 9:48-52.
21. Parson, C.L., Boychuk,D., Jones,S., Hurst,R., Callahan,H. 1990. Bladder surface glycosaminoglycans: an epithelial permeability barrier. *J Urol* 143:139-142.
22. Parsons, C.L., Lilly, J.D., and Stein, P. 1991. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J. Urol* 145:732-735.
23. Truschel, S.T., Wang, E., Ruiz, W.G., Leung, S.M., Rojas, R., Lavelle, J., Zeidel, M., Stoffer, D., and Apodaca, G. 2002. Stretch-regulated exocytosis/endocytosis in bladder umbrella cells. *Molec Biol Cell* 13:830-843.
24. Wang, E., Truschel, S.T., and Apodaca, G. 2003. Analysis of hydrostatic pressure-induced changes in umbrella cell surface area. *Methods* 30:207-217.
25. Born, M., Pahner,I., Ahnert-hilger,G., Jons,T. 2003. The maintenance of the permeability barrier of bladder facet cells requires a continuous fusion of discoid vesicles with the apical plasma membrane. *Eur J Cell Biol* 82:343-350.
26. Cheng, J., Huang,H., Zhang,Z.T. 2002. Overexpression of epidermal growth factor receptor in urothelium elicits urothelial hyperplasia and promotes bladder tumore growth. *Cancer Res* 62:4157-4163.
27. Balestreire, E.M., Apodaca,G. 2007. Apical EGF receptor signaling: regulation of stretch-dependent exocytosis in bladder umbrella cells. *Mol Biol Cell* 13:830-843.
28. Kreft, M.E., Romih,R., Kreft,M., Jezernik,K. 2009. Endocytotic activity of bladder superficial urothelial cells is inversely related to their differentiation stage. *Differentiation* 77:48-59.
29. Birder, L.A., and DeGroat, W.C. 2007. Mechanisms of disease: involvement of the urothelium in bladder dysfunction. *Nat Clin Prac* 4:46-54.
30. Apodaca, G., Balestreire,E., Birder,L.A. 2007. The uroepithelial-associated sensory web. *Kidney Int* 72:1057-1064.
31. Romih, R., Korosec,P., de Mello,W., Jezernik,K. 2005. Differentiation of epithelial cells in the urinary tract. *Cell Tissue Res* 320:259-268.
32. Martin, B.F. 1972. Cell replacement and differentiation in transional epithelium: a histological and autographical study of the guinea-pig bladder and urethra. *J Anat* 112:433-455.
33. Varley, C.L., Stahlschmidt,J., Lee,W.C., Holder,J., Diggle,C., Selby,P.J., Trejdosiewicz,L.K., Southgate,J. 2004. Role of PPAR gamma and EGFR signaling in the urothelial terminal differentiation process. *J Cell Sci* 117:2029-2036.
34. Kreft, M.E., Jezernik,K., Kreft,M., Romih,R. 2009. Apical plasma membrane traffic in superficial cells of bladder urothelium. *Ann NY Acad Sci* 1152:18-29.
35. Lavelle, J., Meyers,S., Ramage,R., Bastacky,S., Doty,D., Apodaca,G., Zeidel,M.L. 2002. Bladder permeability barrier: recovery from selective injury of surface epithelial cells. *Am J Physiol* 283:F242-253.
36. Hurst, R.E., Moldwin, R.M., and Mulholland, S.G. 2007. Bladder defense molecules, urothelial differentation, urinary biomarkers, and interstitial cystitis. *Urology* 69:17-23.
37. de Boer, W.I., Vermeij,M., Diez de Medina,S.G., Bindels,E., Radvanyi,F., van der Kwast,T., Chopin,D. 1996. Functions of fibroblast and transforming growth factors in primary organoid-like cultures of normal human urothelium. *Lab Invest* 75:147-156.
38. Bassuk, J.A., Cockrane,K., Mitchell,M.E. 2003. Induction of urothelial cell proliferation by fibroblast growth factor-7 in RAG1-deficient mice. *Adv Exp Med Biol* 539:623-633.
39. Shin, K., Lee,J., Guo,N., Kim,J., Lim,A., Qu,L., Mysorekar,I.U., Beachy,P.A. 2011. Hedgehog/Wnt feedback supports regenerative proliferation of epithelial stem cells in bladder. *Nature* 472:110-116.
40. Anderson, G., Palermo,J., Schilling,J., Roth,R., Heuser,J., Hultgren,S. 2003. Intracellular bacterial biofilm-like pods in urinary tract infections. *Science* 301:105-107.
41. Erikson, B.C., Hunskar,S. 1991. Urogenital estrogen deficiency syndrome; investigation and treatment with special reference to hormone stimulation. *Tidsskr Nor Laegeforen* 111:2249-2251.
42. Robinson, D., Cardozo,L. 2011. Estrogens and the lower urinary tract. *Neurourol Urodyn* 30:754-757.
43. Lavelle, J.P., Meyers, S.A., Ruiz, W.G., Buffington, C.A.T.,

Zeidel, M., and Apodaca, G. 2000. Urothelial pathophysiological changes in feline interstitial cystitis: A human model. *Am J Physiol* 278:F540-F553.

44. Apodaca, G., Kiss, S., Ruiz, W.G., Meyers, S., Zeidel, M., and Birder, L.A. 2003. Disruption of bladder epithelium barrier function after spinal cord injury. *Am J Physiol* 284:F966-F976.

45. Al-Motabagani, M.A. 2005. Age-related changes in the urinary bladder of the female albino rats. *Int J Morphol* 23:309-316.

46. Canon, E., Timmermans,L.G., Reznik,M., Timmermans,L.M. 1990. Ultrastructural modifications of the bladder wall in senescence. *Acta Urol Belg* 58:29-40.

47. Nawijn, M.C., Hackett,T.L., Postma,D.S., van Oosterhout,A.J.M., Heijink,I.H. 2011. E-cadherin: gatekeeper of airway mucosa and allergic sensitization. *Trends Immuno* 32:248-244.

48. Keay, S.K., Zhang, C.O., Shoenfelt, J., Erickson, D.R., Whitmore, K., Warren, J.W., Marvel, R., and Chai, T.C. 2001. Sensitivity and specificity of antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor as urine markers for interstitial cystitis. *Urology* 57:9-14.

49. Keay, S.K., Szekely, Z., Conrads, T.P., Veenstra, T.D., Barchi, J.J.J., Zhang, C.O., Koch, K.R., and Michejda, C.J. 2004. An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. *Proc Natl Acad Sci USA* 101:11803-11808.

50. Conrads, T.P., Tocci,G.M., Hood,B.L., Zhang,C.O., Guo,L., Koch,K.R., Michejda,C.J., Veenstra,T.D., Keay,S.K. 2006. CKAP4/p63 is a receptor for the frizzled-8 protein-related antiproliferative factor from interstitial cystitis patients. *J Biol Chem* 281:37836-37843.

51. Rostand, K.S., Esko,J.D. 1997. Microbial adherence to and invasion through proteoglycans. *Infect Immun* 65:1-8.

52. Schilling, J., and Hultgren, S. 2002. Recent advances into the pathogenesis of recurrent urinary tract infections: the bladder as a reservoir for uropathogenic Escherichia coli. *Int J Antimicrob Agents* 19:457-560.

53. Thumbikat, P., Berry,R.E., Zhou,G., Billips,B.K., Yaggie,R.E., Zaichuk,T., Sun,T.T., Schaeffer,A.J., Klumpp,D.J. 2009. Bacteria-induced uroplakin signaling mediates bladder response to infection. *PLOS Pathogens* 5:1-17.

54. Wood, M.W., Breitschwerdt,E.B., Nordone,S.K., Linder,K.E., Gookin,J.L. 2011. uropathogenic E. coli promote a paracellular urothelial barrier defect characterized by altered tight junction integrity, epithelial cell sloughing and cytokine release. *J Comp Path* 5:1-9.

55. Bishop, B.L., Duncan,M.J., Song,J., Li,G., Zaas,D., Abraham,S.N. 2007. Cyclic AMP-regulated exocytosis of Escherichia coli from infected bladder epithelial cells. *Nat Med* 13:625-630.

56. Taylor, A., Schaeffer,A., Klumpp,D., Rudick,C. 2011. Rapid attenuation of acute urinary tract infection pain and colonization using an asymptomatic bacteriuria strain. *J Urol* 185:e545-546.

57. Liang, F.X., Bosland,M.C., Huang,H., Romih,R., Baptiste,S., Deng,F.M., Wu,X.R., Shapiro,E., Sun,T.T. 2005. Cellular basis of urothelial squamous metaplasia: roles of lineage heterogeneity and cell replacement. *J Cell Biol* 171:835-844.

58. Thomas, J.C., DeMarco,R.T., Pope,J.C. 2005. Molecular biology of ureteral bud and trigonal development. *Curr Urol Rep* 6:146-151.

59. Hashimoto, Y., Ushiki,T., Uchida,T., Yamada,J, Iwanaga,T. 1999. Scanning electron microscopic observation of apical sites of open-type paraneurons in the stomach, intestine and urethra. *Arch Histol Cytol* 62:181-189.

60. Kunze, A., Neuhaus,J., Stolzenburg,J.U. 2006. Quantitative immunohistochemical study of the innervation of the guinea-pig lower urinary tract. *BJU Int* 98:424-429.

61. Jen, P.Y., Dixon,J.S., Gosling,J.A. 1995. Immunohistochemical localization of neuromarkers and neuropeptides in human fetal and neonatal urinary bladder. *Br J Urol* 75:230-235.

62. Birder, L.A., Nakamura, Y., Kiss, S., Nealen, M.L., Barrick, S.R., Kanai, A.J., Wang, E., Ruiz, W.G., DeGroat, W.C., Apodaca, G., et al. 2002. Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. *Nat Neurosci* 5:856-860.

63. Birder, L.A., Kullmann,F.A., Lee,H., Barrick,S., de Groat,W.C., Kanai,A., Caterina,M. 2007. Activation of urothelial transient receptor potential vanilloid 4 by 4alpha phorbol 12,13-didecanoate contributes to altered bladder reflexes in the rat. *J Pharm Exp Ther* 323:227-235.

64. Brady, C.M., Apostolidis,A., Yiangou,Y., Baecker,P.A., Ford,A.P., Freeman,A., Jacques,T.S. Fowler,C.J., Anand,P. 2004. P2X3-immunoreactive nerve fibres in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin. *Eur Urol* 46:247-253.

65. Apostolidis, A., Brady,C.M., Yoangou,Y., Davis,J., Fowler,C.J., Anand,P. 2005. Capsaicin receptor TRPV1 in urothelium of neurogenic human bladders and effect of intravesical resiniferatoxin. *Urology* 65:400-405.

66. Brading, A.F., McCloskey,K.D. 2005. Mechanisms of disease: specialized interstitial cells of the urothelium: an assessment of current knowledge. *Nat Clin Prac Urol* 2:546-554.

67. Sui, G.P., Wu,C., Fry,C.H. 2004. Electrical characteristics of suburothelial cells isolated from the human bladder. *J Urol* 171:938-943.

68. Ost, D., Roskams,T., Van der Aa,F., de Ridder,D. 2002. Topography of the vanilloid receptor in the human bladder: more than just the nerve fibers. *J Urol* 168:293-297.

69. McCloskey, K.D. 2011. Interstitial cells of Cajal in the urinary tract. *Handb Exp Pharmacol* 202:233-254.

70. Griffiths, D.J., Apostolidis,A. 2010. Neurological control of the bladder in health and disease. In *Pelvic organ dysfunction in neurological disease: clinical management and rehabilitation*. J.N.p.a.A.E. Clare J. Fowler, editor. Cambridge: Cambridge University Press. 1-10.

71. Ikeda, Y., Fry, C., Hayashi, F., Stolz, D., Griffiths, D., and Kanai, A.J. 2007. Role of gap junctions in spontaneous activity of the rat bladder. *Am J Physiol Renal Physiol* 293:F1018-F1025.

72. Carattino, M.D., Sheng,S., Kleyman,T.R. 2005. Mutations in the pore region modify epithelial sodium channel gating by shear stress. *J Biol Chem* 280:4393-4401.

73. Ossovskaya, V.S., Bunnett,N.W. 2004. Protease-activated receptors: contribution to physiology and disease. *Physiol Rev* 84:579-621.

74. Ferguson, D.R., Kennedy, I., and Burton, T.J. 1997. ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes--a possible sensory mechanism? *J Physiol* 505 (Pt 2):503-511.

75. Burnstock, G. 2001. Purine-mediated signalling in pain and visceral perception. *Trends in Pharmcol Sci* 22:182-188.

76. Birder, L.A., Barrick, S.R., Roppolo, J.R., Kanai, A.J., DeGroat, W.C., Kiss, S., and Buffington, C.A.T. 2003. Feline interstitial cystitis results in mechanical hypersensitivity and altered ATP release from bladder urothelium. *Am J Physiol* 285:F423-F429.

77. Chess-Williams, R. 2002. Muscarinic receptors of the urinary bladder: detrusor, urothelial and prejunctional. *Auton Autocoid Pharmacol* 22:133-145.

78. Beckel, J.M., Kanai, A.J., Lee, S.J., DeGroat, W.C., and Birder, L.A. 2006. Expression of functional nicotinic acetylcholine receptors in rat urinary bladder epithelial cells. *Am J Physiol* 290:F103-F110.

79. Beckel, J.M., Birder,L.A. 2012. Differential expression and function of nicotinic acetylcholine receptors in the urinary bladder epithelium of the rat. *J Physiol* PMID:22250215.

80. Chopra, B., Barrick,S.R., Meyers,S., Beckel,J.M., Zeidel,M.L., Ford,A.P., de Groat, W.C., Birder,L.A. 2005. Expression and function of bradykinin B1 and B2 receptors

in normal and inflamed rat urinary bladder urothelium. *J Physiol* 562:859-871.

81. Chopra, B., Gever, J., Barrick, S.R., Hanna-Mitchell, A.T., Beckel, J.M., Ford, A.P., and Birder, L.A. 2008. Expression and function of rat urothelial P2Y receptors. *Am J Physiol* 294:F821-F829.

82. Birder, L.A., Nealen,M.L., Kiss,S., de Groat,W.C., Caterina,M.J., Wang,E., Apodaca,G., Kanai,A.J. 2002. Beta-adrenoceptor agonists stimulate endothelial nitric oxide synthase in rat urinary bladder urothelial cells. *J Neurosci* 22:8063-8070.

83. Hanna-Mitchell, A.T., Beckel, J.M., Barbadora, S., Kanai, A.J., de Groat, W.C., and Birder, L.A. 2007. Non-neuronal acetylcholine and urinary blader urothelium. *Life Sci* 80:2298-2302.

84. LeBerge, J., Malley, S.E., Zvarova, K., and Vizzard, M.A. 2006. Expression of corticotropin-releasing factor and CRF receptors in micturition pathways after cyclophosphamide-induced cystitis. *Am J Physiol* 291:R692-R703.

85. Templeman, L., Chapple, C.R., and Chess-Williams, R. 2002. Urothelium derived inhibitory factor and cross-talk among receptors in the trigone of the bladder of the pig. *J Urol* 167:742-745.

86. Schnegelsberg, B., Sun,T.T., Cain,G., Bhattacharya,A., Nunn,P.A., Ford,A.P., Vizzard,M.A., Cockayne,D.A. 2010. Overexpression of NGF in mouse urothelium leads to neuronal hyperinnervation, pelvic sensitivity, and changes in urinary bladder function. *Am J Physiol* 298:R534-547.

87. Girard, B.M., Malley,S.E., Vizzard,M.A. 2011. Neurotrophin/receptor expression in urinary bladder of mice with overexpression of NGF in urothelium. *Am J Physiol* 300:F345-355.

88. Andersson, K.E., Persson,K. 1995. Nitric oxide synthase and the lower urinary tract: possible implications for physiology and pathophysiology. *Scand J Urol Nephrol* 175:43-53.

89. Igawa, Y., Aizawa,N., Homma,Y. 2010. Beta3-adrenoceptor agonists: possible role in the treatment of overactive bladder. *Korean J Urol* 51:811-818.

90. Tyagi, P., Tyagi,V., Yoshimura,N., Chancellor,M., Yamaguchi,O. 2009. beta3-adrenoceptor agonists for the treatment of overactive bladder. *Drugs of the Future* 34:635-640.

91. Yamaguchi, O., Chapple,C.R. 2007. beta3-adrenoceptors in urinary bladder. *Neurourol Urodyn* 26:752-756.

92. Wang, E.C., Lee, J.M., Ruiz, W.G., Balestreire, E.M., von Bodungen, M., Barrick, S.R., Cockayne, D.A., Birder, L.A., and Apodaca, G. 2005. ATP and purinergic receptor-dependent membrane traffic in bladder umbrella cells. *J Clin Invest* 115:2412-2422.

93. Lumplin, E.A., Caterina,M.J. 2007. Mechanisms of sensory transduction in the skin. *Nat Rev* 445:858-865.

94. Kummer, W., Lips,K.S., Pfell,U. 2008. The epithelial cholinergic system of the airways. *Histochem Cell Biol* 130:219-234.

95. Folkers, G., Nijkamp,F.P. 1998. Airway epithelium: more than just a barrier! *Trends Pharma Sci* 19:334-341.

96. Brunet, L.J., Gold,G.H., Ngai,J. 1996. General anosmia caused by a targeted disruption of the mouse olfactory cyclic nucleotide-gated cation channel. *Neuron* 17:681-683.

97. Sui, G.P., Wu,C., Fry,C.H. 2006. Characterization of the purinergic receptor subtype on guinea-pig suburothelial myofibroblasts. *BJU Int* 97:1327-1331.

98. Du, S., Araki, I., Mikami, Y., Zakoji, H., Beppu, M., Yoshiyama, M., and Takeda, M. 2007. Amiloride-sensitive ion channels in urinary bladder epithelium involved in mechanosensory transduction by modulating stretch-evoked adenosine triphosphate release. *Urology* 69:590-595.

99. Fry, C.H., Sui, G.P., Kanai, A.J., and Wu, C. 2007. The function of suburothelial myofibroblasts in the bladder. *Neurourol Urodyn* 26:914-919.

100. Birder, L.A., Apodaca,G., de Groat,W.C., Kanai,A.J. 1998. Adrenergic and capsaicin-evoked nitric oxide release from urothelium and afferent nerves in urinary bladder. *Am J Physiol* 275:F226-229.

101. Artim, D.E., Bazely,F., Daugherty,S.L., Sculptoreanu,A., Koronowski,K.B., Schopfer,F.J., Woodcock,S.R., Freeman,B.A., de Groat,W.C. 2011. Nitro-oleic acid targets transient receptor potential (TRP) channels in capsaicin sensitive afferent nerves of rat urinary bladder. *Exp Neurol* 232:90-99.

102. Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., and Julius, D. 1997. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 389:816-824.

103. Kullmann, F.A., Shah,M.A., Birder,L.A., de Groat,W.C. 2009. Functional TRP and ASIC-like channels in cultured urothelial cells from the rat. *Am J Physiol* 296:F892-901.

104. Daly, D., Rong,W., Chess-Williams,R., Chapple,C., Grundy,D. 2007. Bladder afferent sensitivity in wild-type and TRPV1 knockout mice. *J Physiol* 583:663-674.

105. Liedtke, W. 2005. TRPV4 plays an evolutionary conserved role in the transduction of osmotic and mechanical stimuli in live animals. *Pflugers Arch* 451:176-180.

106. Gevaert, T., Vriens,J., Segal,A., Evaraerts,W., Roskams,T., Talavera,K., Owsianik,G., Liedtke,W., Daelemans,D., De Wachter,I., Van Leuven,F., Voets,T., De Ridder,D., Nilius,B. 2007. Deletion of the transient receptor potential cation channel TRPV4 impairs murine bladder voiding. *J Clin Invest* 117:3453-3462.

107. Aizawa, N., Igawa, Y., Nishizawa, O., and Wyndaele, J.J. 2011. Effects of nitric oxide on the primary bladder afferent activities of the rat with and without intravesical acrolein treatment. *Eur Urol* 59:264-71.

108. Combrisson, H., Allix,S., Robain,G. 2007. Influence of temperature on urethra to bladder micturition reflex in the awake ewe. *Neurourol Urodyn* 26:290-295.

109. Du, S., Araki,I., Yoshiyama,M., Nomura,T., Takeda,M. 2007. Transient receptor potential channel A1 involved in sensory transduction of rat urinary bladder through C-fiber pathway. *Urology* 70:826-831.

110. Andrade, E.L., Ferreira,J., Andre,E., Calixto,J.B. 2006. Contractile mechanisms coupled to TRPA1 receptor activation in rat urinary bladder. *Biochem Pharm* 72:104-114.

111. Zarghooni, S., Wunsch,J., Bodenbenner,M., Bruggmann,D., Grando,S.A., Schwantes,Y., Wess,J., Kummer,W., Lips,K.S. 2007. Expression of muscarinic and nicotinic acetylcholine receptors in the mouse urothelium. *Life Sci* 80:2308-2313.

112. Kawashima, K., Fujii,T. 2008. Basic and clinical aspects of non-neuronal acetylcholine: overview of non-neuronal cholinergic systems and their biological significance. *J Pharmacol Sci* 106:167-173.

113. Arrighi, N., Bodei,S., Lucente,A., Michel,M.C., Zani,D., Simeone,C., Cunico,S.C., Spano,P., Sigala,S. 2011. Muscarinic receptors stimulate cell proliferation in the human urothelium-derived cell line UROtsa. *Pharmacol Res* 64:420-425.

114. Kullmann, F.A., Artim,D.E., Beckel,J.M., Barrick,S.R., de Groat,W.C., Birder,L.A. 2008. heterogeneity of muscarinic receptor-mediated Ca2+ responses in cultured urothelial cells from rat. *Am J Physiol* 294:F971-981.

115. Kullmann, F.A., Artim,D.E., Birder,L.A., de Groat,W.C. 2008. Activation of muscarinic receptors in rat bladder sensory pathways alters reflex bladder activity. *J Neurosci* 28:1977-1987.

116. Nile, C.J., Gillespie,J.I. 2012. Interactions between cholinergic and prostaglandin signaling elements in the urothelium. *Urology* 79:240.e217-240.e223.

117. Chancellor, M.B., Fowler,C.J., Apostolidis,A., de Groat,W.C., Smith,C.P., Somogyi,G.T., Aoki,R. 2008. Drug insight: biological effects of botulinum toxin A in the lower urinary tract. *Nat Clin Prac Urol* 5:319-328.

118. Datta, S.N., Roosen,A., Pullen,A., Popat,R., Rosenbaum,T.P., Elneil,S., Dasgupta,P., Fowler,C.J., Apostolidis,A. 2010. Immunohistochemical expression of

muscarinic receptors in the urothelium and suburothelium of neurogenic and idiopathic overactive human bladders, and changes with botulinum neurotoxin administration. *J Urol* 184:2578-2585.

119. Liu, H.T., and Kuo, H.C. 2007. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. *Urology* 70:463-468.

120. Barrick, S.R., de Groat,W.C., Chib,M.K., Birder,L.A. 2006. Urothelial cell activation leads to afferent excitability: effects of botulinum toxin A. *FASEB J* 20:A689.

121. Khera, M., G.T., S., Kiss, S., Boone, T.B., and Smith, C.P. 2004. Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. *Neurochem Int* 45:987-993.

122. Giannantoni, A., Amantini,C., Proietti,S., Farfariello,V., Vianello,A., Santoni,G., Porena,M. 2012. Normal human urothelial cell lines express onabotulinumtoxinA SV2 high affinity receptors. *EAU Abstracts*.

123. Sun, Y., Keay,S., DeDeyne,P., Chai,T.C. 2001. Augmented stretch activated adenosine triphosphate release from bladder uroepithelial cells in patients with interstitial cystitis. *J Urol* 166:1951-1956.

124. Hillard, T. 2010. The postmenopausal bladder. *Menopause Int* 16:74-80.

125. Hendrix, S. 2008. Neuroimmune communication in skin: Far from peripheral. *J Invest Derm* 128:260-261.

126. Bosse, Y., Pare,P.D., Seow,C.Y. 2008. Airway wall remodeling in asthma: from the epithelial layer to the adventitia. *Curr Allergy Asthma Rep* 8:357-366.

127. Drake, M.J., Hedlund, P., Mills, I.W., McCoy, R., McMurray, G., Gardner, B.P., Andersson, K.E., and Brading, A.F. 2000. Structural and functional denervation of human detrusor after spinal cord injury. *Lab Invest* 80:1491-1499.

128. Gu, J., Blank, M.A., Huang, W.M., Islam, K.N., McGregor, G.P., Christofides, N., Allen, J.M., Bloom, S.R., and Polak, J.M. 1984. Peptide-containing nerves in human urinary bladder. *Urology* 24:353-357.

129. Smet, P.J., Edyvane, K.A., Jonavicius, J., and Marshall, V.R. 1996. Neuropeptides and neurotransmitter-synthesizing enzymes in intrinsic neurons of the human urinary bladder. *J Neurocytol* 25:112-124.

130. Smet, P.J., Moore, K.H., and Jonavicius, J. 1997. Distribution and colocalization of calcitonin gene-related peptide, tachykinins, and vasoactive intestinal peptide in normal and idiopathic unstable human urinary bladder. *Lab Invest* 77:37-49.

131. Wiseman, O.J., Brady, C.M., Hussain, I.F., Dasgupta, P., Watt, H., Fowler, C.J., and Landon, D.N. 2002. The ultrastructure of bladder lamina propria nerves in healthy subjects and patients with detrusor hyperreflexia. *J Urol* 168:2040-2045.

132. Kanai, A., and Andersson,K.E. 2010. Bladder afferent signaling: recent findings. *J Urol* 183:1288-1295.

133. Zagorodnyuk, V.P., Costa, M., and Brookes, S.J. 2006. Major classes of sensory neurons to the urinary bladder. *Auton Neurosci* 126-127:390-397.

134. Zagorodnyuk, V.P., Brookes, S.J., and Spencer, N.J. Structure-function relationship of sensory endings in the gut and bladder. *Auton Neurosci* 153:3-11.

135. Zagorodnyuk, V.P., Gibbins, I.L., Costa, M., Brookes, S.J., and Gregory, S.J. 2007. Properties of the major classes of mechanoreceptors in the guinea pig bladder. *J Physiol* 585:147-163.

136. Zagorodnyuk, V.P., Brookes, S.J., Spencer, N.J., and Gregory, S. 2009. Mechanotransduction and chemosensitivity of two major classes of bladder afferents with endings in the vicinity to the urothelium. *J Physiol* 587:3523-3538.

137. Xu, L., and Gebhart, G.F. 2008. Characterization of mouse lumbar splanchnic and pelvic nerve urinary bladder mechanosensory afferents. *J Neurophysiol* 99:244-253.

138. Snellings, A.E., Yoo,P.B., and Grill,W.M. 2012. Urethral flow-responsive afferents in the cat sacral dorsal root ganglia. *Neurosci Lett* 516:34-38.

139. Andersson, K.E., Soler, R., and Fullhase, C. Rodent models for urodynamic investigation. *Neurourol Urodyn* 30:636-646.

140. Vergnolle, N. 2008. Postinflammatory visceral sensitivity and pain mechanisms. *Neurogastroenterol & Motil* 20 Suppl 1:73-80.

141. Woolf, C.J. 2011. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 152:S2-15.

142. Munoz, A., Gangitano, D.A., Smith, C.P., Boone, T.B., and Somogyi, G.T. 2010. Removal of urothelium affects bladder contractility and release of ATP but not release of NO in rat urinary bladder. *BMC Urol* 10:10.

143. Ozawa, H., Chancellor, M.B., Jung, S.Y., Yokoyama, T., Fraser, M.O., Yu, Y., de Groat, W.C., and Yoshimura, N. 1999. Effect of intravesical nitric oxide therapy on cyclophosphamide-induced cystitis. *J Urol* 162:2211-2216.

144. Caremel, R., Oger-Roussel, S., Behr-Roussel, D., Grise, P., and Giuliano, F.A. Nitric oxide/cyclic guanosine monophosphate signalling mediates an inhibitory action on sensory pathways of the micturition reflex in the rat. *Eur Urol* 58:616-625.

145. Behr-Roussel, D., Oger, S., Caisey, S., Sandner, P., Bernabe, J., Alexandre, L., and Giuliano, F. 2010. Vardenafil decreases bladder afferent nerve activity in unanesthetized, decerebrate, spinal cord-injured rats. *Eur Urol* 59:272-9.

146. Ferguson, D.R., Kennedy,I., Burton,T.J. 1997. ATP is released from rat urinary bladder epithelial cells by hydrostatic pressure changes-a possible sensory mechanism? *Am J Physiol* 505:503-511.

147. Vlaskovska, M., Kasakov, L., Rong, W., Bodin, P., Bardini, M., Cockayne, D.A., Ford, A.P., and Burnstock, G. 2001. P2X3 knock-out mice reveal a major sensory role for urothelially released ATP. *J Neurosci* 21:5670-5677.

148. Rong, W., Spyer, K.M., and Burnstock, G. 2002. Activation and sensitization of low and high threshold afferent fibres mediated by P2X receptors in the mouse urinary bladder. *J Physiol* 541:591-600.

149. Cockayne, D.A., Hamilton, S.G., Zhu, Q.M., Dunn, P.M., Zhong, Y., Novakovic, S., Malmberg, A.B., Cain, G., Berson, A., Kassotakis, L., et al. 2000. Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X3-deficient mice. *Nature* 407:1011-1015.

150. Cook, S.P., and McCleskey, E.W. 2000. ATP, pain and a full bladder. *Nature* 407:951-952.

151. Sadananda, P., Shang, F., Liu, L., Mansfield, K.J., and Burcher, E. 2009. Release of ATP from rat urinary bladder mucosa: role of acid, vanilloids and stretch. *Br J Pharmacol* 158:1655-1662.

152. Yu, W., Zacharia, L.C., Jackson, E.K., and Apodaca, G. 2006. Adenosine receptor expression and function in bladder uroepithelium. *Am J Physiol* 291:C254-265.

153. Kumar, V., Chapple, C.R., Surprenant, A.M., and Chess-Williams, R. 2007. Enhanced adenosine triphosphate release from the urothelium of patients with painful bladder syndrome: a possible pathophysiological explanation. *J Urol* 178:1533-1536.

154. Yoshida, M., Inadome, A., Maeda, Y., Satoji, Y., Masunaga, K., Sugiyama, Y., and Murakami, S. 2006. Non-neuronal cholinergic system in human bladder urothelium. *Urology* 67:425-430.

155. Iijima, K., De Wachter, S., and Wyndaele, J.J. 2007. Effects of the M3 receptor selective muscarinic antagonist darifenacin on bladder afferent activity of the rat pelvic nerve. *Eur Urol* 52:842-847.

156. De Wachter, S., and Wyndaele, J.J. 2003. Intravesical oxybutynin: a local anesthetic effect on bladder C afferents. *J Urol* 169:1892-1895.

157. Matsumoto, Y., Miyazato, M., Furuta, A., Torimoto, K., Hirao, Y., Chancellor, M.B., and Yoshimura, N. Differential roles of

M2 and M3 muscarinic receptor subtypes in modulation of bladder afferent activity in rats. *Urology* 75:862-867.

158. Masuda, H., Ichiyanagi, N., Yokoyama, M., Sakai, Y., Kihara, K., Chancellor, M.B., de Groat, W.C., and Yoshimura, N. 2009. Muscarinic receptor activation in the lumbosacral spinal cord ameliorates bladder irritation in rat cystitis models. *BJU Int* 104:1531-1537.

159. Nandigama, R., Bonitz, M., Papadakis, T., Schwantes, U., Bschleipfer, T., and Kummer, W. Muscarinic acetylcholine receptor subtypes expressed by mouse bladder afferent neurons. *Neuroscience* 168:842-850.

160. Hawthorn, M.H., Chapple, C.R., Cock, M., and Chess-Williams, R. 2000. Urothelium-derived inhibitory factor(s) influences on detrusor muscle contractility in vitro. *Br J Pharmacol* 129:416-419.

161. Yu, Y., and de Groat, W.C. Effects of stimulation of muscarinic receptors on bladder afferent nerves in the in vitro bladder-pelvic afferent nerve preparation of the rat. *Brain Res* 1361:43-53.

162. Schurch, B., Hauri, D., Rodic, B., Curt, A., Meyer, M., and Alain, B.R. 1996. Botulinum-A Toxin as a treatment of detrusor-sphincter dyssynergia: a prospective study in 24 spinal cord injury patients. *J Urol* 155:1023-1029.

163. Khan, S., Kessler, T.M., Apostolidis, A., Kalsi, V., Panicker, J., Roosen, A., Gonzales, G., Haslam, C., Elneil, S., Fowler, C.J., et al. 2009. What a Patient With Refractory Idiopathic Detrusor Overactivity Should Know About Botulinum Neurotoxin Type A Injection. *J Urol* 181:1773-1778.

164. Khera, M., Somogyi, G.T., Salas, N.A., Kiss, S., Boone, T.B., and Smith, C.P. 2005. In vivo effects of botulinum toxin A on visceral sensory function in chronic spinal cord-injured rats. *Urology* 66:208-212.

165. Collins, V.M., Chapple, C.R., McKay, N.G., Sellers, D.J., and Grundy, D. 2009. Botulinum toxin attenuates sensory afferent nerve firing in an ex vivo mouse bladder model *J Urol* 181:82-83.

166. Kanai, A., Zabbarova, I., Oefelein, M., Radziszewski, P., Ikeda, Y., and Andersson, K.E. 2012. Mechanisms of action of botulinum neurotoxins, beta(3)-adrenergic receptor agonists, and PDE5 inhibitors in modulating detrusor function in overactive bladders. *Neurourol Urodyn* 31:300-8.

167. Ikeda, Y., Zabbarova,I.V., Birder,L.A., de Groat,W.C., McCarthy,C.J., Hanna-Mitchell,A.T., and Kanai,A.J. 2012. Botulinum neurotoxin serotype A suppresses neurotransmitter release from afferent as well as efferent nerves in the urinary bladder. *Eur Urol* PMID:22480459.

168. Apostolidis, A., Popat, R., Yiangou, Y., Cockayne, D., Ford, A.P.D.W., Davis, J.B., Dasgupta, P., Fowler, C.J., and Anand, P. 2005. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. *J Urol* 174:977-983.

169. Lucioni, A., Bales, G.T., Lotan, T.L., McGehee, D.S., Cook, S.P., and Rapp, D.E. 2008. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. *BJU Int* 101:366-370.

170. Kissin, I., and Szallasi, A. Therapeutic targeting of TRPV1 by resiniferatoxin, from preclinical studies to clinical trials. *Curr Top Med Chem* 11:2159-2170.

171. Aizawa, N., Wyndaele,J.J., Homma,Y., Igawa,Y. 2011. Effects of TRPV4 cation channel activation on the primary bladder afferent activities of the rat. *Neurourol Urodyn* PMID: 22038643.

172. Yamada, T., Ugawa, S., Ueda, T., Ishida, Y., Kajita, K., and Shimada, S. 2009. Differential localizations of the transient receptor potential channels TRPV4 and TRPV1 in the mouse urinary bladder. *J Histochem Cytochem* 57:277-287.

173. Everaerts, W., Zhen,X., Ghosh,D., Vriens,J., Gevaert,T., Gilbert,J.P., Hayward,N.J., McNamara,C.R., Xue,F., Moran,M.M., Strassmaier,T., Uykal,E., Owslanik,G., Vennekens,R., de Ridder,D., Nilius,B., Fanger,C.M., Voets,T. 2010. Inhibition of the cation channel TRPV4 improves bladder function in mice and rats with cyclophosphamide-induced cystitis. *Proc Natl Acad Sci* 107:19084-19089.

174. Andrade, E.L., Forner, S., Bento, A.F., Leite, D.F., Dias, M.A., Leal, P.C., Koepp, J., and Calixto, J.B. TRPA1 receptor modulation attenuates bladder overactivity induced by spinal cord injury. *Am J Physiol* 300:F1223-1234.

175. Mukerji, G., Waters,J., Chessell,I.P., Bountra,C., Agarwal,S.K., and Anand,P. 2006. Pain during ice water test distinguishes clinical bladder hypersensitivity from overactivity disorders. *BMC Urol* 6:31.

176. Hayashi, T., Kondo, T., Ishimatsu, M., Yamada, S., Nakamura, K., Matsuoka, K., and Akasu, T. 2009. Expression of the TRPM8-immunoreactivity in dorsal root ganglion neurons innervating the rat urinary bladder. *Neurosci Res* 65:245-251.

177. Lashinger, E.S., Steiginga, M.S., Hieble, J.P., Leon, L.A., Gardner, S.D., Nagilla, R., Davenport, E.A., Hoffman, B.E., Laping, N.J., and Su, X. 2008. AMTB, a TRPM8 channel blocker: evidence in rats for activity in overactive bladder and painful bladder syndrome. *Am J Physiol* 295:F803-810.

178. Tyagi, V., Philips, B.J., Su, R., Smaldone, M.C., Erickson, V.L., Chancellor, M.B., Yoshimura, N., and Tyagi, P. 2009. Differential expression of functional cannabinoid receptors in human bladder detrusor and urothelium. *J Urol* 181:1932-1938.

179. Mukerji, G., Yiangou, Y., Agarwal, S.K., and Anand, P. Increased cannabinoid receptor 1-immunoreactive nerve fibers in overactive and painful bladder disorders and their correlation with symptoms. *Urology* 75:1514. e1515-1514.e1520.

180. Gratzke, C., Streng, T., Park, A., Christ, G., Stief, C.G., Hedlund, P., and Andersson, K.-E. 2009. Distribution and function of cannabinoid receptors 1 and 2 in the rat, monkey and human bladder. *J Urol* 181:1939-1948.

181. Walczak, J.S., Price, T.J., and Cervero, F. 2009. Cannabinoid CB1 receptors are expressed in the mouse urinary bladder and their activation modulates afferent bladder activity. *Neuroscience* 159:1154-1163.

182. Hayn, M.H., Ballesteros, I., de Miguel, F., Coyle, C.H., Tyagi, S., Yoshimura, N., Chancellor, M.B., and Tyagi, P. 2008. Functional and Immunohistochemical Characterization of CB1 and CB2 Receptors in Rat Bladder. *Urology* 72:1174-1178.

183. Trevisani, M., Campi, B., Gatti, R., Andre, E., Materazzi, S., Nicoletti, P., Gazzieri, D., and Geppetti, P. 2007. The influence of alpha1-adrenoreceptors on neuropeptide release from primary sensory neurons of the lower urinary tract. *Eur Urol* 52:901-908.

184. Yanase, H., Wang, X., Momota, Y., Nimura, T., and Kawatani, M. 2008. The involvement of urothelial alpha1A adrenergic receptor in controlling the micturition reflex. *Biomed Res* 29:239-244.

185. Yazaki, J., Aikawa, K., Shishido, K., Yanagida, T., Nomiya, M., Ishibashi, K., Haga, N., and Yamaguchi, O. 2011. Alpha1-adrenoceptor antagonists improve bladder storage function through reduction of afferent activity in rats with bladder outlet obstruction. *Neurourol Urodyn* 30:461-7.

186. Nagabukuro, H., Degenhardt, A., Villa, K.L., Mistry, S.L., Gichuru, L., Jochnowitz, N., and Abbadie, C. Correlation between pharmacologically-induced changes in cystometric parameters and spinal c-Fos expression in rats. *Auton Neurosci* 156:19-26.

187. Kullmann, F.A., Downs, T.R., Artim, D.E., Limberg, B.J., Shah, M., Contract, D., de Groat, W.C., and Rosenbaum, J.S. Urothelial beta-3 adrenergic receptors in the rat bladder. *Neurourol Urodyn* 30:144-150.

188. Whorwell, P.J., McCallum, M., Creed, F.H., and Roberts, C.T. 1986. Non-colonic features of irritable bowel syndrome. *Gut* 27:37-40.

189. Alagiri, M., Chottiner, S., Ratner, V., Slade, D., and Hanno, P.M. 1997. Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. *Urology* 49:52-57.

190. Brumovsky, P.R., and Gebhart, G.F. Visceral organ cross-sensitization - an integrated perspective. *Auton Neurosci* 153:106-115.

191. Pezzone, M.A., Liang, R., and Fraser, M.O. 2005. A model of neural cross-talk and irritation in the pelvis: implications for the overlap of chronic pelvic pain disorders. *Gastroenterology* 128:1953-1964.

192. Bielefeldt, K., Lamb, K., and Gebhart, G.F. 2006. Convergence of sensory pathways in the development of somatic and visceral hypersensitivity. *Am J Physiol* 291:G658-665.

193. Christianson, J.A., Liang,R., Ustinova,E.E., Davis,B.M., Fraser,M.O., and Pezzone,M.A. 2007. Convergence of bladder and colon sensory innervation occurs at the primary afferent level. *Pain* 128:235-243.

194. Clemens, J.Q., Meenan, R.T., O'Keeffe Rosetti, M.C., Kimes, T.A., and Calhoun, E.A. 2008. Case-control study of medical comorbidities in women with interstitial cystitis. *J Urol* 179:2222-2225.

195. Malykhina, A.P. 2007. Neural mechanisms of pelvic organ cross-sensitization. *Neuroscience* 149:660-672.

196. Olsen, A.L., Smith, V.J., Bergstrom, J.O., Colling, J.C., and Clark, A.L. 1997. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstet Gynecol* 89:501-506.

197. Ashton-Miller, J.A., and DeLancey, J.O. 2007. Functional anatomy of the female pelvic floor. *Ann N Y Acad Sci* 1101:266-296.

198. Thor, K.B., and de Groat, W.C. 2010. Neural control of the female urethral and anal rhabdosphincters and pelvic floor muscles. *Am J Physiol* 299:R416-438.

199. Dorschner, W., Biesold, M., Schmidt, F., and Stolzenburg, J.U. 1999. The dispute about the external sphincter and the urogenital diaphragm. *J Urol* 162:1942-1945.

200. Mirilas, P., and Skandalakis, J.E. 2004. Urogenital diaphragm: an erroneous concept casting its shadow over the sphincter urethrae and deep perineal space. *J Am Coll Surg* 198:279-290.

201. Sebe, P., Fritsch, H., Oswald, J., Schwentner, C., Lunacek, A., Bartsch, G., and Radmayr, C. 2005. Fetal development of the female external urinary sphincter complex: an anatomical and histological study. *J Urol* 173:1738-1742.

202. Sebe, P., Schwentner, C., Oswald, J., Radmayr, C., Bartsch, G., and Fritsch, H. 2005. Fetal development of striated and smooth muscle sphincters of the male urethra from a common primordium and modifications due to the development of the prostate: an anatomic and histologic study. *Prostate* 62:388-393.

203. Barber, M.D., Bremer, R.E., Thor, K.B., Dolber, P.C., Kuehl, T.J., and Coates, K.W. 2002. Innervation of the female levator ani muscles. *Am J Obstet Gynecol* 187:64-71.

204. Shobeiri, S.A., Chesson, R.R., and Gasser, R.F. 2008. The internal innervation and morphology of the human female levator ani muscle. *Am J Obstet Gynecol* 199:686 e681-686.

205. Pierce, L.M., Reyes, M., Thor, K.B., Dolber, P.C., Bremer, R.E., Kuehl, T.J., and Coates, K.W. 2003. Innervation of the levator ani muscles in the female squirrel monkey. *Am J Obstet Gynecol* 188:1141-1147.

206. Pierce, L.M., Rankin, M.R., Foster, R.T., Dolber, P.C., Coates, K.W., Kuehl, T.J., and Thor, K.B. 2006. Distribution and immunohistochemical characterization of primary afferent neurons innervating the levator ani muscle of the female squirrel monkey. *Am J Obstet Gynecol* 195:987-996.

207. Pierce, L.M., Coates, K.W., Kramer, L.A., Bradford, J.C., Thor, K.B., and Kuehl, T.J. 2008. Effects of bilateral levator ani nerve injury on pelvic support in the female squirrel monkey. *Am J Obstet Gynecol* 198:585 e581-588.

208. Thuroff, J.W., Bazeed, M.A., Schmidt, R.A., Luu, D.H., and Tanagho, E.A. 1982. Regional topography of spinal cord neurons innervating pelvic floor muscles and bladder neck in the dog: a study by combined horseradish peroxidase histochemistry and autoradiography. *Urol Int* 37:110-120.

209. Jiang, H.H., Salcedo, L.B., Song, B., and Damaser, M.S. 2010. Pelvic floor muscles and the external urethral sphincter have different responses to applied bladder pressure during continence. *Urology* 75:1515 e1511-1517.

210. Bremer, R.E., Barber, M.D., Coates, K.W., Dolber, P.C., and Thor, K.B. 2003. Innervation of the levator ani and coccygeus muscles of the female rat. *Anat Rec A Discov Mol Cell Evol Biol* 275:1031-1041.

211. Grigorescu, B.A., Lazarou, G., Olson, T.R., Downie, S.A., Powers, K., Greston, W.M., and Mikhail, M.S. 2008. Innervation of the levator ani muscles: description of the nerve branches to the pubococcygeus, iliococcygeus, and puborectalis muscles. *Int Urogynecol J Pelvic Floor Dysfunct* 19:107-116.

212. Wallner, C., Maas, C.P., Dabhoiwala, N.F., Lamers, W.H., and DeRuiter, M.C. 2006. Innervation of the pelvic floor muscles: a reappraisal for the levator ani nerve. *Obstet Gynecol* 108:529-534.

213. Wallner, C., van Wissen, J., Maas, C.P., Dabhoiwala, N.F., Deruiter, M.C., and Lamers, W.H. 2007. The contribution of the levator ani nerve and the pudendal nerve to the innervation of the levator ani muscles; a study in human fetuses. *Eur Urol* 54:1143-1144.

214. Bradley, W.E., and Teague, C.T. 1972. Electrophysiology of pelvic and pudendal nerves in the cat. *Exp Neurol* 35:378-393.

215. McKenna, K.E., and Nadelhaft, I. 1986. The organization of the pudendal nerve in the male and female rat. *J Comp Neurol* 248:532-549.

216. Pierce, L.M., Reyes, M., Thor, K.B., Dolber, P.C., Bremer, R.E., Kuehl, T.J., and Coates, K.W. 2005. Immunohistochemical evidence for the interaction between levator ani and pudendal motor neurons in the coordination of pelvic floor and visceral activity in the squirrel monkey. *Am J Obstet Gynecol* 192:1506-1515.

217. Roppolo, J.R., Nadelhaft, I., and de Groat, W.C. 1985. The organization of pudendal motoneurons and primary afferent projections in the spinal cord of the rhesus monkey revealed by horseradish peroxidase. *J Comp Neurol* 234:475-488.

218. Thor, K.B., Morgan, C., Nadelhaft, I., Houston, M., and de Groat, W.C. 1989. Organization of afferent and efferent pathways in the pudendal nerve of the female cat. *J Comp Neurol* 288:263-279.

219. Ueyama, T., Arakawa, H., and Mizuno, N. 1987. Central distribution of efferent and afferent components of the pudendal nerve in rat. *Anat Embryol (Berl)* 177:37-49.

220. Ueyama, T., Mizuno, N., Nomura, S., Konishi, A., Itoh, K., and Arakawa, H. 1984. Central distribution of afferent and efferent components of the pudendal nerve in cat. *J Comp Neurol* 222:38-46.

221. Wieslander, C.K., Roshanravan, S.M., Wai, C.Y., Schaffer, J.I., and Corton, M.M. 2007. Uterosacral ligament suspension sutures: Anatomic relationships in unembalmed female cadavers. *Am J Obstet Gynecol* 197:672 e671-676.

222. Vanderhorst, V.G., and Holstege, G. 1997. Organization of lumbosacral motoneuronal cell groups innervating hindlimb, pelvic floor, and axial muscles in the cat. *J Comp Neurol* 382:46-76.

223. Bremer, R.E., Yang, Z., Jin, H., Thor, K.B., and Dolber, P.C. 2002. Activating transcription factor 3 (ATF3) expression is upregulated by levator ani (LA) nerve transection in the rat. *Society for Neuroscience Abstracts*:70.77.

224. Schroder, H.D. 1980. Organization of the motoneurons innervating the pelvic muscles of the male rat. *J Comp Neurol* 192:567-587.

225. Yang, Z., Bremer, R.B., Jin, H., Dolber, P.C., and Thor, K.B. 2002. Characterization of neurons innervating the pubocaudalis muscle of the rat. *Society for Neuroscience Abstracts*:70.76.

226. Gosling, J.A., Dixon, J.S., Critchley, H.O., and Thompson, S.A. 1981. A comparative study of the human external sphincter and periurethral levator ani muscles. *Br J Urol* 53:35-41.

227. Palmieri, G., Panu, R., Asole, A., Sanna, L., and Farina, V. 1988. Coccygeus and levator ani muscles in the rabbit: morphology and proprioceptive innervation. *Biol Struct Morphog* 1:142-146.

228. Praud, C., Sebe, P., Mondet, F., and Sebille, A. 2003. The striated urethral sphincter in female rats. *Anat Embryol (Berl)* 207:169-175.

229. Borghi, F., Di Molfetta, L., Garavoglia, M., and Levi, A.C. 1991. Questions about the uncertain presence of muscle spindles in the human external anal sphincter. *Panminerva Med* 33:170-172.

230. Martin, W.D., Fletcher, T.F., and Bradley, W.E. 1974. Innervation of feline perineal musculature. *Anat Rec* 180:15-29.

231. Rockswold, G.L., Bradley, W.E., and Chou, S.N. 1980. Innervation of the external urethral and external anal sphincters in higher primates. *J Comp Neurol* 193:521-528.

232. Schroder, H.D., and Reske-Nielsen, E. 1983. Fiber types in the striated urethral and anal sphincters. *Acta Neuropathol* 60:278-282.

233. Todd, J.K. 1964. Afferent Impulses in the Pudendal Nerves of the Cat. *Q J Exp Physiol Cogn Med Sci* 49:258-267.

234. Mackel, R. 1979. Segmental and descending control of the external urethral and anal sphincters in the cat. *J Physiol* 294:105-122.

235. McMahon, S.B., Morrison, J.F., and Spillane, K. 1982. An electrophysiological study of somatic and visceral convergence in the reflex control of the external sphincters. *J Physiol* 328:379-387.

236. Rampal, G., and Mignard, P. 1975. Behaviour of the urethral striated sphincter and of the bladder in the chronic spinal cat. Implications at the Central Nervous System Level. *Pflugers Arch* 353:33-42.

237. Brown, A., and Fyffe, R. 1978. The morphology of group Ia afferent fibre collaterals in the spinal cord of the cat. *J Physiol.* 274:111-127.

238. Brown, A.G., and Fyffe, R.E. 1979. The morphology of group Ib afferent fibre collaterals in the spinal cord of the cat. *J Physiol* 296:215-226.

239. Cuevas, E., Camacho, M., Alvarado, M., Hudson, R., and Pacheco, P. 2006. Participation of estradiol and progesterone in the retrograde labeling of pubococcygeus motoneurons of the female rat. *Neuroscience* 140:1435-1442.

240. Corona-Quintanilla, D.L., Castelan, F., Fajardo, V., Manzo, J., and Martinez-Gomez, M. 2009. Temporal coordination of pelvic and perineal striated muscle activity during micturition in female rabbits. *J Urol* 181:1452-1458.

241. Pacheco, P., Camacho, M.A., Garcia, L.I., Hernandez, M.E., Carrillo, P., and Manzo, J. 1997. Electrophysiological evidence for the nomenclature of the pudendal nerve and sacral plexus in the male rat. *Brain Research* 763:202-208.

242. Furuta, A., Asano, K., Egawa, S., de Groat, W.C., Chancellor, M.B., and Yoshimura, N. 2009. Role of alpha2-adrenoceptors and glutamate mechanisms in the external urethral sphincter continence reflex in rats. *J Urol* 181:1467-1473.

243. Pacheco, P., Martinez-Gomez, M., Whipple, B., Beyer, C., and Komisaruk, B.R. 1989. Somato-motor components of the pelvic and pudendal nerves of the female rat. *Brain Research* 490:85-94.

244. Kenton, K., and Brubaker, L. 2002. Relationship between levator ani contraction and motor unit activation in the urethral sphincter. *Am J Obstet Gynecol* 187:403-406.

245. Wunderlich, M., and Swash, M. 1983. The overlapping innervation of the two sides of the external anal sphincter by the pudendal nerves. *J Neurol Sci* 59:97-109.

246. Gonzalez-Soriano, J., Martin-Palacios, S., Rodriguez-Veiga, E., Triguero, D., Costa, G., and Garcia-Pascual, A. 2003. Nitric oxide synthase in the external urethral sphincter of the sheep: immunohistochemical and functional study. *J Urol* 169:1901-1906.

247. Ho, K.M., Borja, M.C., Persson, K., Brading, A.F., and Andersson, K.E. 2003. Expression of nitric oxide synthase immunoreactivity in the human female intramural striated urethral sphincter. *J Urol* 169:2407-2411.

248. Ho, K.M., McMurray, G., Brading, A.F., Noble, J.G., Ny, L., and Andersson, K.E. 1998. Nitric oxide synthase in the heterogeneous population of intramural striated muscle fibres of the human membranous urethral sphincter. *J Urol* 159:1091-1096.

249. Pullen, A.H., and Humphreys, P. 1999. Protracted elevation of neuronal nitric oxide synthase immunoreactivity in axotomised adult pudendal motor neurons. *J Anat* 194 (Pt 4):547-565.

250. Pullen, A.H., Humphreys, P., and Baxter, R.G. 1997. Comparative analysis of nitric oxide synthase immunoreactivity in the sacral spinal cord of the cat, macaque and human. *J Anat* 191 (Pt 2):161-175.

251. Stamler, J.S., and Meissner, G. 2001. Physiology of nitric oxide in skeletal muscle. *Physiological Reviews* 81:209-237.

252. Reitz, A., Bretscher, S., Knapp, P., Müntener, M., Wefer, B., and Schurch, B. 2004. The effect of nitric oxide on the resting tone and the contractile behaviour of the external urethral sphincter: a functional urodynamic study in healthy humans. *Eur Urol* 45:367-373.

253. Elbadawi, A., and Schenk, E.A. 1974. A new theory of the innervation of bladder musculature. 2. Innervation of the vesicourethral junction and external urethral sphincter. *J Urol* 111:613-615.

254. Creed, K.E., Van Der Werf, B.A., and Kaye, K.W. 1998. Innervation of the striated muscle of the membranous urethra of the male dog. *J Urol* 159:1712-1716.

255. Onufrowicz, B. 1900. On the arrangement and function of the cell groups of the sacral region of the spinal cord in man. *Arch Neurol Psychopathol.* 3:387-411.

256. Nakagawa, S. 1980. Onuf's nucleus of the sacral cord in a South American monkey (Saimiri): its location and bilateral cortical input from area 4. *Brain Res* 191:337-344.

257. Sasaki, M. 1994. Morphological analysis of external urethral and external anal sphincter motoneurones of cat. *J Comp Neurol* 349:269-287.

258. Gerrits, P.O., Sie, J.A., and Holstege, G. 1997. Motoneuronal location of the external urethral and anal sphincters: a single and double labeling study in the male and female golden hamster. *Neurosci Lett* 226:191-194.

259. Kuipers, R., Izhar, Z., Gerrits, P.O., Miner, W., and Holstege, G. 2004. Location of bladder and urethral sphincter motoneurons in the male guinea pig (Cavia porcellus). *Neurosci Lett* 362:57-60.

260. Blok, B.F., Roukema, G., Geerdes, B., and Holstege, G. 1996. Location of external anal sphincter motoneurons in the sacral cord of the female domestic pig. *Neurosci Lett* 216:203-206.

261. Ulibarri, C., Popper, P., and Micevych, P.E. 1995. Motoneurons dorsolateral to the central canal innervate perineal muscles in the Mongolian gerbil. *J Comp Neurol* 356:225-237.

262. Beattie, M.S., Li, Q., Leedy, M.G., and Bresnahan, J.C. 1990. Motoneurons innervating the external anal and urethral sphincters of the female cat have different patterns of dendritic arborization. *Neurosci Lett* 111:69-74.

263. Nadelhaft, I., deGroat, W.C., and Morgan, C. 1980. Location and morphology of parasympathetic preganglionic neurons in the sacral spinal cord of the cat revealed by retrograde axonal transport of horseradish peroxidase. *J Comp Neurol* 193:265-281.

264. Jankowska, E., Padel, Y., and Zarzecki, P. 1978. Crossed disynaptic inhibition of sacral motoneurones. *J Physiol* 285:425-444.

265. Yashiro, K., Thor, K.B., and Burgard, E.C. 2010. Properties of urethral rhabdosphincter motoneurons and their regulation by noradrenaline. *J Physiol* 588:4951-4967.

266. Shefchyk, S.J. 2006. Spinal mechanisms contributing to urethral striated sphincter control during continence and micturition: "how good things might go bad". *Prog Brain Res* 152:85-95.

267. Kawatani, M., Nagel, J., and de Groat, W.C. 1986. Identification of neuropeptides in pelvic and pudendal nerve affer-

ent pathways to the sacral spinal cord of the cat. *J Comp Neurol* 249:117-132.

268. Koerber, H.R., and Brown, P.B. 1982. Somatotopic organization of hindlimb cutaneous nerve projections to cat dorsal horn. *J Neurophysiol* 48:481-489.

269. de Groat, W.C., Fraser, M.O., Yoshiyama, M., Smerin, S., Tai, C., Chancellor, M.B., Yoshimura, N., and Roppolo, J.R. 2001. Neural control of the urethra. *Scand J Urol Nephrol Suppl*:35-43; discussion 106-125.

270. Holstege, G., and Tan, J. 1987. Supraspinal control of motoneurons innervating the striated muscles of the pelvic floor including urethral and anal sphincters in the cat. *Brain* 110 (Pt 5):1323-1344.

271. Miller, A.D., Nonaka, S., Siniaia, M.S., and Jakus, J. 1995. Multifunctional ventral respiratory group: bulbospinal expiratory neurons play a role in pudendal discharge during vomiting. *J Auton Nerv Syst* 54:253-260.

272. Bors, E., and Blinn, K. 1959. Bulbocavernosus reflex. *J Urol* 82:128-130.

273. Chen, Z., Anderson, D.L., Faison, W.L., and Baer, P.G. 2001. Biphasic urethral sphincter responses to acetic acid infusion into the lower urinary tract in anesthetized cats. *J Urol* 166:1539-1548.

274. Thor, K.B., and Katofiasc, M.A. 1995. Effects of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, on central neural control of lower urinary tract function in the chloralose-anesthetized female cat. *J Pharmacol Exp Ther* 274:1014-1024.

275. Danuser, H., Bemis, K., and Thor, K.B. 1995. Pharmacological analysis of the noradrenergic control of central sympathetic and somatic reflexes controlling the lower urinary tract in the anesthetized cat. *J Pharmacol Exp Ther* 274:820-825.

276. Rampal, G., and Mignard, P. 1975. Organization of the nervous control of urethral sphincter. A study in the anaesthetized cat with intact central nervous system. *Pflugers Arch* 353:21-31.

277. Fedirchuk, B., Song, L., Downie, J.W., and Shefchyk, S.J. 1992. Spinal distribution of extracellular field potentials generated by electrical stimulation of pudendal and perineal afferents in the cat. *Exp Brain Res* 89:517-520.

278. Fedirchuk, B., Hochman, S., and Shefchyk, S.J. 1992. An intracellular study of perineal and hindlimb afferent inputs onto sphincter motoneurons in the decerebrate cat. *Exp Brain Res* 89:511-516.

279. Danuser, H., and Thor, K.B. 1996. Spinal 5-HT2 receptor-mediated facilitation of pudendal nerve reflexes in the anaesthetized cat. *Br J Pharmacol* 118:150-154.

280. Karicheti, V., Langdale, C.L., Ukai, M., and Thor, K.B. 2010. Characterization of a spinal, urine storage reflex, inhibitory center and its regulation by 5-HT1A receptors in female cats. *Am J Physiol* 298:R1198-1208.

281. Thor, K.B., Hisamitsu, T., Roppolo, J.R., Tuttle, P., Nagel, J., and deGroat, W.C. 1989. Selective inhibitory effects of ethylketocyclazocine on reflex pathways to the external urethral sphincter of the cat. *J Pharmacol Exp Ther* 248:1018-1025.

282. Chang, H.Y., Cheng, C.L., Chen, J.J., Peng, C.W., and de Groat, W.C. 2006. Reflexes evoked by electrical stimulation of afferent axons in the pudendal nerve under empty and distended bladder conditions in urethane-anesthetized rats. *J Neurosci Methods* 150:80-89.

283. McKenna, K., and Nadelhaft, I. 1989. The pudendo-pudendal reflex in male and female rats. *J Auton Nerv Syst.* 27:67-77.

284. Nadelhaft, I., and Vera, P.L. 1996. Neurons in the rat brain and spinal cord labeled after pseudorabies virus injected into the external urethral sphincter. *J Comp Neurol* 375:502-517.

285. Kamo, I., Torimoto, K., Chancellor, M.B., de Groat, W.C., and Yoshimura, N. 2003. Urethral closure mechanisms under sneeze-induced stress condition in rats: a new animal model for evaluation of stress urinary incontinence. *Am J Physiol* 285:R356-365.

286. Hurtado, E.A., Smith, P.P., Smith, C.P., Boone, T.B., and Somogyi, G.T. 2008. Urethral afferent signaling leads to activation of the external urethral sphincter and abdominal wall muscles. *Neurourol Urodyn* 27:105.

287. Thor, K.B., and Muhlhauser, M.A. 1999. Vesicoanal, urethroanal, and urethrovesical reflexes initiated by lower urinary tract irritation in the rat. *Am J Physiol* 277:R1002-R1012.

288. Paroschy, K.L., and Shefchyk, S.J. 2000. Non-linear membrane properties of sacral sphincter motoneurones in the decerebrate cat. *J Physiol* 523 Pt 3:741-753.

289. Lee, R.H., and Heckman, C.J. 1998. Bistability in spinal motoneurons in vivo: systematic variations in rhythmic firing patterns. *J Neurophysiol* 80:572-582.

290. Kruse, M.N., Mallory, B.S., Noto, H., Roppolo, J.R., and de Groat, W. 1991. Properties of the descending limb of the spinobulbospinal micturition reflex pathway in the cat. *Brain Res* 556:6-12.

291. Mallory, B., Steers, W.D., and deGroat, W.C. 1989. Electrophysiological study of micturition reflexes in rats. *Am J Physiol*:R410-421.

292. Mallory, B.S., Roppolo, J.R., and de Groat, W.C. 1991. Pharmacological modulation of the pontine micturition center. *Brain Res* 546:310-320.

293. Blok, B.F.M., and Holstege, G. 1997. Ultrastructural evidence for a direct pathway from the pontine micturition center to parasympathetic preganglionic motoneurons of the bladder of the cat. *Neurosci Lett* 222:195-198.

294. Blok, B.F., van Maarseveen, J.T., and Holstege, G. 1998. Electrical stimulation of the sacral dorsal gray commissure evokes relaxation of the external urethral sphincter in the cat. *Neurosci Lett* 249:68-70.

295. Blok, B.F., de Weerd, H., and Holstege, G. 1997. The pontine micturition center projects to sacral cord GABA immunoreactive neurons in the cat. *Neurosci Lett* 233:109-112.

296. Konishi, A., Itoh, K., Sugimoto, T., Yasui, Y., Kaneko, T., Takada, M., and Mizuno, N. 1985. Leucine-enkephalin-like immunoreactive afferent fibers to pudendal motoneurons in the cat. *Neurosci Lett* 61:109-113.

297. Shefchyk, S.J., Espey, M.J., Carr, P., Nance, D., Sawchuk, M., and Buss, R. 1998. Evidence for a strychnine-sensitive mechanism and glycine receptors involved in the control of urethral sphincter activity during micturition in the cat. *Exp Brain Res* 119:297-306.

298. Sie, J.A., Blok, B.F., de Weerd, H., and Holstege, G. 2001. Ultrastructural evidence for direct projections from the pontine micturition center to glycine-immunoreactive neurons in the sacral dorsal gray commissure in the cat. *J Comp Neurol* 429:631-637.

299. Thor, K.B., Langdale, C., Ukai, M., and Karicheti, V. 2008. Characterization of a Spinal Urine Storage Reflex Inhibitory Center (SUSRIC) and its regulation by 5-HT1A receptors. *Society for Neuroscience Annual Meeting Abstracts*:582.581.

300. Gu, B., Fraser, M.O., Thor, K.B., and Dolber, P.C. 2004. Induction of bladder sphincter dyssynergia by kappa-2 opioid receptor agonists in the female rat. *J Urol* 171:472-477.

301. Gu, B., Thor, K.B., Reiter, J.P., and Dolber, P.C. 2007. Effect of 5-hydroxytryptamine1 serotonin receptor agonists on noxiously stimulated micturition in cats with chronic spinal cord injury. *J Urol* 177:2381-2385.

302. Thor, K.B., Katofiasc, M.A., Danuser, H., Springer, J., and Schaus, J.M. 2002. The role of 5-HT(1A) receptors in control of lower urinary tract function in cats. *Brain Res* 946:290-297.

303. Wefer, B., Reitz, A., Knapp, P.A., Bannowsky, A., Juenemann, K.P., and Schurch, B. 2005. Conditioning stimulus can influence an external urethral sphincter contraction evoked by a magnetic stimulation. *Neurourol Urodyn* 24:311-317; discussion 318.

304. Damaser, M.S., Broxton-King, C., Ferguson, C., Kim, F.J., and Kerns, J.M. 2003. Functional and neuroanatomical effects of vaginal distention and pudendal nerve crush in the female rat. *J Urol* 170:1027-1031.

305. Damaser, M.S., Samplaski, M.K., Parikh, M., Lin, D.L., Rao, S., and Kerns, J.M. 2007. Time course of neuroanatomical and functional recovery after bilateral pudendal nerve injury in female rats. *Am J Physiol* 293:F1614-1621.

306. Chang, H.Y., Cheng, C.L., Chen, J.J., and de Groat, W.C. 2007. Serotonergic drugs and spinal cord transections indicate that different spinal circuits are involved in external urethral sphincter activity in rats. *Am J Physiol* 292:F1044-1053.

307. Yang, Z., Dolber, P.C., and Fraser, M.O. 2007. Diabetic urethropathy compounds the effects of diabetic cystopathy. *J Urol* 178:2213-2219.

308. Torimoto, K., Fraser, M.O., Hirao, Y., De Groat, W.C., Chancellor, M.B., and Yoshimura, N. 2004. Urethral dysfunction in diabetic rats. *J Urol* 171:1959-1964.

309. Jankowski, R.J., Prantil, R.L., Fraser, M.O., Chancellor, M.B., De Groat, W.C., Huard, J., and Vorp, D.A. 2004. Development of an experimental system for the study of urethral biomechanical function. *Am J Physiol* 286:F225-232.

310. Jung, S.Y., Fraser, M.O., Ozawa, H., Yokoyama, O., Yoshiyama, M., De Groat, W.C., and Chancellor, M.B. 1999. Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. *J Urol* 162:204-212.

311. Kakizaki, H., Fraser, M.O., and De Groat, W.C. 1997. Reflex pathways controlling urethral striated and smooth muscle function in the male rat. *Am J Physiol* 272:R1647-1656.

312. Gasbarro, G., Lin, D.L., Vurbic, D., Quisno, A., Kinley, B., Daneshgari, F., and Damaser, M.S. Voiding function in obese and type 2 diabetic female rats. *Am J Physiol* 298:F72-77.

313. Boers, J., Ford, T.W., Holstege, G., and Kirkwood, P.A. 2005. Functional heterogeneity among neurons in the nucleus retroambiguus with lumbosacral projections in female cats. *J Neurophysiol* 94:2617-2629.

314. Kaiho, Y., Nishiguchi, J., Kwon, D.D., Chancellor, M.B., Arai, Y., Snyder, P.B., and Yoshimura, N. 2008. The effects of a type 4 phosphodiesterase inhibitor and the muscarinic cholinergic antagonist tolterodine tartrate on detrusor overactivity in female rats with bladder outlet obstruction. *BJU Int* 101:615-620.

315. Miyazato, M., Kaiho, Y., Kamo, I., Chancellor, M.B., Sugaya, K., de Groat, W.C., and Yoshimura, N. 2008. Effect of duloxetine, a norepinephrine and serotonin reuptake inhibitor, on sneeze-induced urethral continence reflex in rats. *Am J Physiol* 295:F264-271.

316. Miyazato, M., Kaiho, Y., Kamo, I., Kitta, T., Chancellor, M.B., Sugaya, K., Arai, Y., de Groat, W.C., and Yoshimura, N. 2009. Role of spinal serotonergic pathways in sneeze-induced urethral continence reflex in rats. *Am J Physiol* 297:F1024-1031.

317. Vanderhorst, V.G., and Holstege, G. 1995. Caudal medullary pathways to lumbosacral motoneuronal cell groups in the cat: evidence for direct projections possibly representing the final common pathway for lordosis. *J Comp Neurol* 359:457-475.

318. Kojima, M., Matsuura, T., Kimura, H., Nojyo, Y., and Sano, Y. 1984. Fluorescence histochemical study on the noradrenergic control to the anterior column of the spinal lumbosacral segments of the rat and dog, with special reference to motoneurons innervating the perineal striated muscles (Onuf's nucleus). *Histochemistry* 81:237-241.

319. Kojima, M., Takeuchi, Y., Goto, M., and Sano, Y. 1982. Immunohistochemical study on the distribution of serotonin fibers in the spinal cord of the dog. *Cell Tissue Res* 226:477-491.

320. Kojima, M., Takeuchi, Y., Goto, M., and Sano, Y. 1983. Immunohistochemical study on the localization of serotonin fibers and terminals in the spinal cord of the monkey (Macaca fuscata). *Cell Tissue Res* 229:23-36.

321. Rajaofetra, N., Passagia, J.G., Marlier, L., Poulat, P., Pellas, F., Sandillon, F., Verschuere, B., Gouy, D., Geffard, M., and Privat, A. 1992. Serotoninergic, noradrenergic, and peptidergic innervation of Onuf's nucleus of normal and transected spinal cords of baboons (Papio papio). *J Comp Neurol* 318:1-17.

322. Yoshiyama, M., Roppolo, J.R., and de Groat, W.C. 1995. Effects of GYKI 52466 and CNQX, AMPA/kainate receptor antagonists, on the micturition reflex in the rat. *Brain Res* 691:185-194.

323. Yoshiyama, M., Roppolo, J.R., and de Groat, W.C. 1995. Interactions between NMDA and AMPA/kainate receptors in the control of micturition in the rat. *Eur J Pharmacol* 287:73-78.

324. Yoshiyama, M., Roppolo, J.R., and de Groat, W.C. 1997. Effects of LY215490, a competitive alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist, on the micturition reflex in the rat. *J Pharmacol Exp Ther* 280:894-904.

325. Yoshiyama, M., Roppolo, J.R., Thor, K.B., and de Groat, W.C. 1993. Effects of LY274614, a competitive NMDA receptor antagonist, on the micturition reflex in the urethane-anaesthetized rat. *Br J Pharmacol* 110:77-86.

326. Chang, H.Y., Cheng, C.L., Chen, J.J., and de Groat, W.C. 2006. Roles of glutamatergic and serotonergic mechanisms in reflex control of the external urethral sphincter in urethane-anesthetized female rats. *Am J Physiol* 291:R224-234.

327. Yoshiyama, M., Roppolo, J.R., and de Groat, W.C. 1994. Alteration by urethane of glutamatergic control of micturition. *Eur J Pharmacol* 264:417-425.

328. Yoshiyama, M., Roppolo, J.R., and de Groat, W.C. 1994. Interactions between glutamatergic and monoaminergic systems controlling the micturition reflex in the urethane-anesthetized rat. *Brain Res* 639:300-308.

329. Yoshiyama, M., Roppolo, J.R., Rihmland, J., Blastos, B., and deGroat, W.C. 1991. The effects of MK-801, an NMDA receptor antagonist, on the micturition reflex in the rat. *Neurosci Lett* 126:141-144.

330. Miyazato, M., Sasatomi, K., Hiragata, S., Sugaya, K., Chancellor, M.B., de Groat, W.C., and Yoshimura, N. 2008. GABA receptor activation in the lumbosacral spinal cord decreases detrusor overactivity in spinal cord injured rats. *J Urol* 179:1178-1183.

331. Teague, C.T., and Merrill, D.C. 1978. Effect of baclofen and dantrolene on bladder stimulator-induced detrusor-sphincter dyssynergia in dogs. *Urology* 11:531-535.

332. Leyson, J.F., Martin, B.F., and Sporer, A. 1980. Baclofen in the treatment of detrusor-sphincter dyssynergia in spinal cord injury patients. *J Urol* 124:82-84.

333. Nanninga, J.B., Frost, F., and Penn, R. 1989. Effect of intrathecal baclofen on bladder and sphincter function. *J Urol* 142:101-105.

334. Thor, K.B. 2004. Targeting serotonin and norepinephrine receptors in stress urinary incontinence. *Int J Gynaecol Obstet* 86 Suppl 1:S38-52.

335. Dmochowski, R.R., Miklos, J.R., Norton, P.A., Zinner, N.R., Yalcin, I., and Bump, R.C. 2003. Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. *J Urol* 170:1259-1263.

336. Millard, R.J., Moore, K., Rencken, R., Yalcin, I., and Bump, R.C. 2004. Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial. *BJU Int* 93:311-318.

337. Norton, P.A., Zinner, N.R., Yalcin, I., and Bump, R.C. 2002. Duloxetine versus placebo in the treatment of stress urinary incontinence. *Am J Obstet Gynecol* 187:40-48.

338. van Kerrebroeck, P., Abrams, P., Lange, R., Slack, M., Wyndaele, J.J., Yalcin, I., and Bump, R.C. 2004. Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. *BJOG* 111:249-257.

339. Boy, S., Reitz, A., Wirth, B., Knapp, P.A., Braun, P.M., Haferkamp, A., and Schurch, B. 2006. Facilitatory neuromodulative effect of duloxetine on pudendal motor neurons controlling the urethral pressure: a functional urodynamic study in healthy women. *Eur Urol* 50:119-125.

340. Klarskov, N., Scholfield, D., Soma, K., Darekar, A., Mills, I., and Lose, G. 2008. Evaluation of the sensitivity of urethral pressure reflectometry and urethral pressure profilometry to detect pharmacological augmentation of urethral pressure using [S,S]-reboxetine. *J Urol* 179:521-522.

341. Zinner, N., Scholfield, D., Soma, K., Darekar, A., Grant, L., and Mills, I. 2008. A phase 2, 8 week, multicenter, randomized, double blind, placebo controlled parallel group study evaluating the efficacy, tolerability, and safety of [S,S]-reboxetine (PNU-165442G) for stress urinary incontinence in women. *J Urol* 179:569-570.

342. Ranson, R.N., Dodds, A.L., Smith, M.J., Santer, R.M., and Watson, A.H. 2003. Age-associated changes in the monoaminergic innervation of rat lumbosacral spinal cord. *Brain Res* 972:149-158.

343. Gajewski, J., Downie, J.W., and Awad, S.A. 1984. Experimental evidence for a central nervous system site of action in the effect of alpha-adrenergic blockers on the external urinary sphincter. *J Urol* 132:403-409.

344. Downie, J.W., and Bialik, G.J. 1988. Evidence for a spinal site of action of clonidine on somatic and viscerosomatic reflex activity evoked on the pudendal nerve in cats. *J Pharmacol Exp Ther* 246:352-358.

345. Downie, J.W., Espey, M.J., and Gajewski, J.B. 1991. Alpha 2-adrenoceptors not imidazole receptors mediate depression of a sacral spinal reflex in the cat. *Eur J Pharmacol* 195:301-304.

346. Ramage, A.G., and Wyllie, M.G. 1995. A comparison of the effects of doxazosin and terazosin on the spontaneous sympathetic drive to the bladder and related organs in anaesthetized cats. *Eur J Pharmacol* 294:645-650.

347. Krier, J., Thor, K.B., and de Groat, W.C. 1979. Effects of clonidine on the lumbar sympathetic pathways to the large intestine and urinary bladder of the cat. *Eur J Pharmacol* 59:47-53.

348. Conlon, K., Miner, W., Christy, C., McCleary, S., Brinkman, H., Rees, H., and McMurray, G. 2005. Identification of 5-HT2C-mediated mechanisms involved in urethral sphincter reflexes. *Abstract Society for Neuroscience* Program No. 48.14.

349. Mbaki, Y., and Ramage, A.G. 2008. Investigation of the role of 5-HT(2) receptor subtypes in the control of the bladder and the urethra in the anaesthetized female rat. *Br J Pharmacol* 155:343-56.

350. Burgard, E.C., Fraser, M.O., and Thor, K.B. 2003. Serotonergic modulation of bladder afferent pathways. *Urology* 62:10-15.

351. Hounsgaard, J., Hultborn, H., Jespersen, B., and Kiehn, O. 1988. Bistability of alpha-motoneurones in the decerebrate cat and in the acute spinal cat after intravenous 5-hydroxytryptophan. *J Physiol* 405:345-367.

352. Ogier, R., Tribollet, E., Suarez, P., and Raggenbass, M. 2006. Identified motoneurons involved in sexual and eliminative functions in the rat are powerfully excited by vasopressin and tachykinins. *J Neurosci* 26:10717-10726.

353. Holmes, G.M., Rogers, R.C., Bresnahan, J.C., and Beattie, M.S. 1997. Differential effects of intrathecal thyrotropin-releasing hormone (TRH) on perineal reflexes in male rats. *Physiol Behav* 61:57-63.

354. Kimura, Y., Hamada, K., Taniguchi, N., Ukai, Y., Yoshikuni, Y., and Kimura, K. 1996. CNS-mediated influence of TRH and its analog, NS-3, on the function of the rabbit lower urinary tract. *J Auton Nerv Syst* 60:1-11.

355. Holmes, G.M. 2005. 5-Hydroxytryptamine2C receptors on pudendal motoneurons innervating the external anal sphincter. *Brain Res* 1057:65-71.

356. Dolber, P.C., Gu, B., Zhang, X., Fraser, M.O., Thor, K.B., and Reiter, J.P. 2007. Activation of the external urethral sphincter central pattern generator by a 5-HT(1A) receptor agonist in rats with chronic spinal cord injury. *Am J Physiol* 292:R1699-1706.

357. Glazer, E.J., and Basbaum, A.I. 1980. Leucine enkephalin: localization in and axoplasmic transport by sacral parasympathetic preganglionic neurons. *Science* 208:1479-1481.

358. Tashiro, T., Satoda, T., Matsushima, R., and Mizuno, N. 1989. Convergence of serotonin, enkephalin- and substance P-like immunoreactive afferent fibers on single pudendal motoneurons in Onuf's nucleus of the cat: a light microscope study combining the triple immunocytochemical staining technique with the retrograde HRP- tracing method. *Brain Res* 481:392-398.

359. Thor, K.B., Roppolo, J.R., Kawatani, M., Erdman, S., and deGroat, W.C. 1994. Plasticity in spinal opioid control of lower urinary tract function in paraplegic cats. *Neuroreport* 5:1673-1678.

360. Dietz, H.P., and Wilson, P.D. 2005. Childbirth and pelvic floor trauma. *Best Pract Res Clin Obstet Gynaecol* 19:913-924.

361. Allen, R.E., Hosker, G.L., Smith, A.R., and Warrell, D.W. 1990. Pelvic floor damage and childbirth: a neurophysiological study. *Br J Obstet Gynaecol* 97:770-779.

362. Smith, A.R., Hosker, G.L., and Warrell, D.W. 1989. The role of partial denervation of the pelvic floor in the aetiology of genitourinary prolapse and stress incontinence of urine. A neurophysiological study. *Br J Obstet Gynaecol* 96:24-28.

363. Snooks, S.J., Setchell, M., Swash, M., and Henry, M.M. 1984. Injury to innervation of pelvic floor sphincter musculature in childbirth. *Lancet* 2:546-550.

364. Snooks, S.J., Swash, M., Mathers, S.E., and Henry, M.M. 1990. Effect of vaginal delivery on the pelvic floor: a 5-year follow-up. *Br J Surg* 77:1358-1360.

365. South, M.M., Stinnett, S.S., Sanders, D.B., and Weidner, A.C. 2009. Levator ani denervation and reinnervation 6 months after childbirth. *Am J Obstet Gynecol* 200:519 e511-517.

366. Weidner, A.C., Jamison, M.G., Branham, V., South, M.M., Borawski, K.M., and Romero, A.A. 2006. Neuropathic injury to the levator ani occurs in 1 in 4 primiparous women. *Am J Obstet Gynecol* 195:1851-1856.

367. Snooks, S.J., Swash, M., Henry, M.M., and Setchell, M. 1986. Risk factors in childbirth causing damage to the pelvic floor innervation. *Int J Colorectal Dis* 1:20-24.

368. Weidner, A.C., Barber, M.D., Visco, A.G., Bump, R.C., and Sanders, D.B. 2000. Pelvic muscle electromyography of levator ani and external anal sphincter in nulliparous women and women with pelvic floor dysfunction. *Am J Obstet Gynecol* 183:1390-1399; discussion 1399-1401.

369. Weidner, A.C., South, M.M., Sanders, D.B., and Stinnett, S.S. 2009. Change in urethral sphincter neuromuscular function during pregnancy persists after delivery. *Am J Obstet Gynecol* 201:529 e521-526.

370. Fajardo, V., Pacheco, P., Hudson, R., Jimenez, I., and Martinez-Gomez, M. 2008. Differences in morphology and contractility of the bulbospongiosus and pubococcygeus muscles in nulliparous and multiparous rabbits. *Int Urogynecol J Pelvic Floor Dysfunct* 19:843-849.

371. Kenton, K., Mueller, E., and Brubaker, L. 2011. Continent women have better urethral neuromuscular function than those with stress incontinence. *Int Urogynecol J* 22:1479-1484.

372. Coates, K.W., Galan, H.L., Shull, B.L., and Kuehl, T.J. 1995. The squirrel monkey: an animal model of pelvic relaxation. *Am J Obstet Gynecol* 172:588-593.

373. DeLancey, J.O., Kearney, R., Chou, Q., Speights, S., and Binno, S. 2003. The appearance of levator ani muscle abnormalities in magnetic resonance images after vaginal delivery. *Obstet Gynecol* 101:46-53.

374. Heilbrun, M.E., Nygaard, I.E., Lockhart, M.E., Richter, H.E., Brown, M.B., Kenton, K.S., Rahn, D.D., Thomas, J.V., Weidner, A.C., Nager, C.W., et al. Correlation between levator ani muscle injuries on magnetic resonance imaging and fecal incontinence, pelvic organ prolapse, and urinary incontinence in primiparous women. *Am J Obstet Gynecol* 202:488 e481-486.

375. Kramer, L.A., Gendron, J.M., Pierce, L.M., Runge, V.M., Shull, B.L., and Kuehl, T.J. 2006. Magnetic resonance imaging of the levator ani in the squirrel monkey: a comparison of muscle volume between a cohort with pelvic organ prolapse and matched normals. *Am J Obstet Gynecol* 194:1467-1471.

376. Bernabe, J., Julia-Guilloteau, V., Denys, P., Chartier-Kastler, E., Alexandre, L., Peeters, M., and Giuliano, F. 2008. Peripheral neural lesion-induced stress urinary incontinence in anaesthetized female cats. *BJU Int* 102:1162-7.

377. Yoshiyama, M., and de Groat, W.C. 2002. Effect of bilateral hypogastric nerve transection on voiding dysfunction in rats with spinal cord injury. *Exp Neurol* 175:191-197.

378. Gibson, S.J., Polak, J.M., Katagiri, T., Su, H., Weller, R.O., Brownell, D.B., Holland, S., Hughes, J.T., Kikuyama, S., Ball, J., et al. 1988. A comparison of the distributions of eight peptides in spinal cord from normal controls and cases of motor neurone disease with special reference to Onuf's nucleus. *Brain Res* 474:255-278.

379. Blanco, C.E., Popper, P., and Micevych, P. 1997. alpha-CGRP mRNA levels in motoneurons innervating specific rat muscles. *Brain Res Mol Brain Res* 44:253-261.

380. Schroder, H.D. 1984. Somatostatin in the caudal spinal cord: an immunohistochemical study of the spinal centers involved in the innervation of pelvic organs. *J Comp Neurol* 223:400-414.

381. Holstege, J.C., Van Dijken, H., Buijs, R.M., Goedknegt, H., Gosens, T., and Bongers, C.M. 1996. Distribution of dopamine immunoreactivity in the rat, cat and monkey spinal cord. *J Comp Neurol* 376:631-652.

382. Kawatani, M., Suzuki, T., and DeGroat, W.C. 1996. Corticotropin releasing factor-like immunoreactivity in afferent projections to the sacral spinal cord of the cat. *J Auton Nerv Syst* 61:218-226.

383. Thor, K.B., Nickolaus, S., and Helke, C.J. 1993. Autoradiographic localization of 5-hydroxytryptamine1A, 5- hydroxytryptamine1B and 5-hydroxytryptamine1C/2 binding sites in the rat spinal cord. *Neuroscience* 55:235-252.

384. Xu, C., Giuliano, F., Sun, X.Q., Brisorgueil, M.J., Leclerc, P., Verge, D., and Conrath, M. 2007. Serotonin 5-HT2A and 5-HT5A receptors are expressed by different motoneuron populations in rat Onuf's nucleus. *J Comp Neurol* 502:620-634.

385. Doly, S., Fischer, J., Brisorgueil, M.J., Verge, D., and Conrath, M. 2004. 5-HT5A receptor localization in the rat spinal cord suggests a role in nociception and control of pelvic floor musculature. *J Comp Neurol* 476:316-329.

386. Doly, S., Fischer, J., Brisorgueil, M.J., Verge, D., and Conrath, M. 2005. Pre- and postsynaptic localization of the 5-HT7 receptor in rat dorsal spinal cord: immunocytochemical evidence. *J Comp Neurol* 490:256-269.

387. van Dijken, H., Dijk, J., Voom, P., and Holstege, J.C. 1996. Localization of dopamine D2 receptor in rat spinal cord identified with immunocytochemistry and in situ hybridization. *Eur J Neurosci* 8:621-628.

388. Mantyh, P.W., Allen, C.J., Rogers, S., DeMaster, E., Ghilardi, J.R., Mosconi, T., Kruger, L., Mannon, P.J., Taylor, I.L., and Vigna, S.R. 1994. Some sensory neurons express neuropeptide Y receptors: potential paracrine inhibition of primary afferent nociceptors following peripheral nerve injury. *J Neurosci* 14:3958-3968.

389. Charlton, C.G., and Helke, C.J. 1985. Autoradiographic localization and characterization of spinal cord substance P binding sites: high densities in sensory, autonomic, phrenic, and Onuf's motor nuclei. *J Neurosci* 5:1653-1661.

390. Lewinter, R.D., Skinner, K., Julius, D., and Basbaum, A.I. 2004. Immunoreactive TRPV-2 (VRL-1), a capsaicin receptor homolog, in the spinal cord of the rat. *J Comp Neurol* 470:400-408.

391. Zhang, M., Moller, M., Broman, J., Sukiasyan, N., Wienecke, J., and Hultborn, H. 2008. Expression of calcium channel CaV1.3 in cat spinal cord: light and electron microscopic immunohistochemical study. *J Comp Neurol* 507:1109-1127.

392. Koliatsos, V.E., Price, D.L., and Clatterbuck, R.E. 1994. Motor neurons in Onuf's nucleus and its rat homologues express the p75 nerve growth factor receptor: sexual dimorphism and regulation by axotomy. *J Comp Neurol* 345:510-527.

393. MacLennan, A.J., Devlin, B.K., Neitzel, K.L., McLaurin, D.L., Anderson, K.J., and Lee, N. 1999. Regulation of ciliary neurotrophic factor receptor alpha in sciatic motor neurons following axotomy. *Neuroscience* 91:1401-1413.

394. Brook, G.A., Schmitt, A.B., Nacimiento, W., Weis, J., Schroder, J.M., and Noth, J. 1998. Distribution of B-50(GAP-43) mRNA and protein in the normal adult human spinal cord. *Acta Neuropathol* 95:378-386.

395. Nacimiento, W., Topper, R., Fischer, A., Mobius, E., Oestreicher, A.B., Gispen, W.H., Nacimiento, A.C., Noth, J., and Kreutzberg, G.W. 1993. B-50 (GAP-43) in Onuf's nucleus of the adult cat. *Brain Res* 613:80-87.

396. Arvidsson, U., Risling, M., Frisen, J., Piehl, F., Fried, K., Hokfelt, T., and Cullheim, S. 1994. trkC-like immunoreactivity in the primate descending serotoninergic system. *Eur J Neurosci* 6:230-236.

397. Kluck, P. 1980. The autonomic innervation of the human urinary bladder, bladder neck and urethra: a histochemical study. *Anat Rec* 198:439-447.

398. Vizzard, M.A., Erdman, S.L., Forstermann, U., and de Groat, W.C. 1994. Differential distribution of nitric oxide synthase in neural pathways to the urogenital organs (urethra, penis, urinary bladder) of the rat. *Brain Res* 646:279-291.

399. Ishizuka, O., Alm, P., Larsson, B., Mattiasson, A., and Andersson, K.E. 1995. Facilitatory effect of pituitary adenylate cyclase activating polypeptide on micturition in normal, conscious rats. *Neuroscience* 66:1009-1014.

400. Morgan, C., Nadelhaft, I., and de Groat, W.C. 1979. Location of bladder preganglionic neurons within the sacral parasympathetic nucleus of the cat. *Neurosci Lett* 14:189-194.

401. Petras, J.M., and Cummings, J.F. 1978. Sympathetic and parasympathetic innervation of the urinary bladder and urethra. *Brain Res* 153:363-369.

402. Nadelhaft, I., Roppolo, J., Morgan, C., and de Groat, W.C. 1983. Parasympathetic preganglionic neurons and visceral primary afferents in monkey sacral spinal cord revealed following application of horseradish peroxidase to pelvic nerve. *J Comp Neurol* 216:36-52.

403. Banrezes, B., Andrey, P., Maschino, E., Schirar, A., Peytevin, J., Rampin, O., and Maurin, Y. 2002. Spatial segregation within the sacral parasympathetic nucleus of neurons innervating the bladder or the penis of the rat as revealed by three-dimensional reconstruction. *Neuroscience* 115:97-109.

404. Nadelhaft, I., and Booth, A.M. 1984. The location and morphology of preganglionic neurons and the distribution of visceral afferents from the rat pelvic nerve: a horseradish peroxidase study. *J Comp Neurol* 226:238-245.

405. Liao, J.M., Cheng, C.L., Lee, S.D., Chen, G.D., Chen, K.J., Yang, C.H., Pan, S.F., Chen, M.J., Huang, P.C., and Lin, T.B. 2006. Impaired micturition reflex caused by acute selective dorsal or ventral root(s) rhizotomy in anesthetized rats. *Neurourol Urodyn* 25:283-289.

406. Dering, M.A., Santer, R.M., and Watson, A.H. 1996. Age-related changes in the morphology of preganglionic neurons projecting to the rat hypogastric ganglion. *J Neurocytol* 25:555-563.

407. Dering, M.A., Santer, R.M., and Watson, A.H. 1998. Age-related changes in the morphology of preganglionic neurons projecting to the paracervical ganglion of nulliparous and multiparous rats. *Brain Res* 780:245-252.

408. Santer, R.M., Dering, M.A., Ranson, R.N., Waboso, H.N., and Watson, A.H. 2002. Differential susceptibility to ageing of rat preganglionic neurones projecting to the major pelvic ganglion and of their afferent inputs. *Auton Neurosci* 96:73-81.

409. Kuo, D.C., Hisamitsu, T., and de Groat, W.C. 1984. A sympathetic projection from sacral paravertebral ganglia to the

pelvic nerve and to postganglionic nerves on the surface of the urinary bladder and large intestine of the cat. *J Comp Neurol* 226:76-86.

410. Warburton, A.L., and Santer, R.M. 1994. Sympathetic and sensory innervation of the urinary tract in young adult and aged rats: a semi-quantitative histochemical and immunohistochemical study. *Histochem J* 26:127-133.

411. Brindley, G.S. 1977. An implant to empty the bladder or close the urethra. *J Neurol Neurosurg Psychiatry* 40:358-369.

412. Brindley, G.S. 1994. The first 500 patients with sacral anterior root stimulator implants: general description. *Paraplegia* 32:795-805.

413. Vignes, J.R., Deloire, M., and Petry, K. 2009. Animal models of sacral neuromodulation for detrusor overactivity. *Neurourol Urodyn* 28:8-12.

414. Vizzard, M.A. 2010. Spinal interneurons and micturition reflexes: focus on "Characterization of a spinal, urine storage reflex, inhibitory center and its regulation by 5-HT1A receptors in female cats". *Am J Physiol* 298:R1195-1197.

415. Li, M.Z., and Masuko, S. 2001. Target specific organization and neuron types of the dog pelvic ganglia: a retrograde-tracing and immunohistochemical study. *Arch Histol Cytol* 64:267-280.

416. Wanigasekara, Y., Kepper, M.E., and Keast, J.R. 2003. Immunohistochemical characterization of pelvic autonomic ganglia in male mice. *Cell Tissue Res* 311:175-185.

417. Anneren, G., Meurling, S., and Olsen, L. 1991. Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), an autosomal recessive disorder: clinical reports and review of the literature. *Am J Med Genet* 41:251-254.

418. Richardson, C.E., Morgan, J.M., Jasani, B., Green, J.T., Rhodes, J., Williams, G.T., Lindstrom, J., Wonnacott, S., Thomas, G.A., and Smith, V. 2001. Megacystis-microcolon-intestinal hypoperistalsis syndrome and the absence of the alpha3 nicotinic acetylcholine receptor subunit. *Gastroenterology* 121:350-357.

419. Xu, W., Orr-Urtreger, A., Nigro, F., Gelber, S., Sutcliffe, C.B., Armstrong, D., Patrick, J.W., Role, L.W., Beaudet, A.L., and De Biasi, M. 1999. Multiorgan autonomic dysfunction in mice lacking the beta2 and the beta4 subunits of neuronal nicotinic acetylcholine receptors. *J Neurosci* 19:9298-9305.

420. De Biasi, M., Nigro, F., and Xu, W. 2000. Nicotinic acetylcholine receptors in the autonomic control of bladder function. *Eur J Pharmacol* 393:137-140.

421. Gabella, G. 1990. Intramural neurons in the urinary bladder of the guinea-pig. *Cell Tissue Res* 261:231-237.

422. Gabella, G., Berggren, T., and Uvelius, B. 1992. Hypertrophy and reversal of hypertrophy in rat pelvic ganglion neurons. *J Neurocytol* 21:649-662.

423. Dixon, J.S., Gilpin, S.A., Gilpin, C.J., and Gosling, J.A. 1983. Intramural ganglia of the human urinary bladder. *Br J Urol* 55:195-198.

424. Drake, M.J., Hedlund, P., Harvey, I.J., Pandita, R.K., Andersson, K.E., and Gillespie, J.I. 2003. Partial outlet obstruction enhances modular autonomous activity in the isolated rat bladder. *J Urol* 170:276-279.

425. Maas, C.P., Kenter, G.G., Trimbos, J.B., and Deruiter, M.C. 2005. Anatomical basis for nerve-sparing radical hysterectomy: immunohistochemical study of the pelvic autonomic nerves. *Acta Obstet Gynecol Scand* 84:868-874.

426. Ek, A., Alm, P., Andersson, K.E., and Persson, C.G. 1977. Adrenergic and Cholinergic Nerves of the Human Urethra and Urinary Bladder. A histochemical study. *Acta Physiol Scand* 99:345-352.

427. Lawrence, G.W., Aoki, K.R., and Dolly, J.O. 2010. Excitatory cholinergic and purinergic signaling in bladder are equally susceptible to botulinum neurotoxin a consistent with co-release of transmitters from efferent fibers. *J Pharmacol Exp Ther* 334:1080-1086.

428. de Groat, W.C., and Yoshimura, N. 2001. Pharmacology of the lower urinary tract. *Annu Rev Pharmacol Toxicol* 41:691-721.

429. Keast, J.R., and Stephensen, T.M. 2000. Glutamate and aspartate immunoreactivity in dorsal root ganglion cells supplying visceral and somatic targets and evidence for peripheral axonal transport. *J Comp Neurol* 424:577-587.

430. Gougis, S., Prud'homme, M.J., and Rampin, O. 2002. Presence of the N-methyl-D-aspartic acid R1 glutamatergic receptor subunit in the lumbosacral spinal cord of male rats. *Neurosci Lett* 323:224-228.

431. Nishizawa, O., Igawa, Y., Satoh, T., Yamashiro, S., and Sugaya, K. 1999. Effects of glutamate receptor antagonists on lower urinary tract function in conscious unanesthetized rats. *Adv Exp Med Biol* 462:275-281.

432. Shefchyk, S.J. 2002. Spinal cord neural organization controlling the urinary bladder and striated sphincter. *Prog Brain Res* 137:71-82.

433. Miyazato, M., Sugaya, K., Nishijima, S., Ashitomi, K., Hatano, T., and Ogawa, Y. 2003. Inhibitory effect of intrathecal glycine on the micturition reflex in normal and spinal cord injury rats. *Exp Neurol* 183:232-240.

434. Miyazato, M., Sugaya, K., Nishijima, S., Ashitomi, K., Ohyama, C., and Ogawa, Y. 2004. Rectal distention inhibits bladder activity via glycinergic and GABAergic mechanisms in rats. *J Urol* 171:1353-1356.

435. Mertens, P., Ghaemmaghami, C., Bert, L., Perret-Liaudet, A., Sindou, M., and Renaud, B. 2000. Amino acids in spinal dorsal horn of patients during surgery for neuropathic pain or spasticity. *Neuroreport* 11:1795-1798.

436. de Groat, W.C. 2002. Influence of central serotonergic mechanisms on lower urinary tract function. *Urology* 59:30-36.

437. Skagerberg, G., and Bjorklund, A. 1985. Topographic principles in the spinal projections of serotonergic and non-serotonergic brainstem neurons in the rat. *Neuroscience* 15:445-480.

438. Mizukawa, K. 1980. The segmental detailed topographical distribution of monoaminergic terminals and their pathways in the spinal cord of the cat. *Anat Anz* 147:125-144.

439. Chen, S.Y., Wang, S.D., Cheng, C.L., Kuo, J.S., De Groat, W.C., and Chai, C.Y. 1993. Glutamate activation of neurons in CV-reactive areas of cat brain stem affects urinary bladder motility. *Am J Physiol* 265:F520-529.

440. McMahon, S.B., and Spillane, K. 1982. Brain stem influences on the parasympathetic supply to the urinary bladder of the cat. *Brain Res* 234:237-249.

441. Sugaya, K., Ogawa, Y., Hatano, T., Koyama, Y., Miyazato, T., and Oda, M. 1998. Evidence for involvement of the subcoeruleus nucleus and nucleus raphe magnus in urine storage and penile erection in decerebrate rats. *J Urol* 159:2172-2176.

442. Lecci, A., Giuliani, S., Santicioli, P., and Maggi, C.A. 1992. Involvement of 5-hydroxytryptamine1A receptors in the modulation of micturition reflexes in the anesthetized rat. *J Pharmacol Exp Ther* 262:181-189.

443. Gu, B., Wu, G., Si, J., Xu, Y., and Andersson, K.E. 2011. Improving voiding efficiency in the diabetic rat by a 5-HT1A serotonin receptor agonist. *Neurourol Urodyn* 31:168-73.

444. Thor, K.B., Hisamitsu, T., and de Groat, W.C. 1990. Unmasking of a neonatal somatovesical reflex in adult cats by the serotonin autoreceptor agonist 5-methoxy-N,N-dimethyltryptamine. *Brain Res Dev Brain Res* 54:35-42.

445. Somogyi, G.T., Tanowitz, M., and de Groat, W.C. 1995. Prejunctional facilitatory alpha 1-adrenoceptors in the rat urinary bladder. *Br J Pharmacol* 114:1710-1716.

446. de Groat, W.C., Yoshiyama, M., Ramage, A.G., Yamamoto, T., and Somogyi, G.T. 1999. Modulation of voiding and storage reflexes by activation of alpha1-adrenoceptors. *Eur Urol* 36 Suppl 1:68-73.

447. Yoshiyama, M., Yamamoto, T., and de Groat, W.C. 2000. Role of spinal alpha(1)-adrenergic mechanisms in the control of lower urinary tract in the rat. *Brain Res* 882:36-44.

448. Wada, T., Otsu, T., Hasegawa, Y., Mizuchi, A., and Ono, H. 1996. Characterization of alpha 1-adrenoceptor subtypes in rat spinal cord. *Eur J Pharmacol* 312:263-266.

449. Yono, M., Tanaka, T., Tsuji, S., Irie, S., Sakata, Y., Otani, M., Yoshida, M., and Latifpour, J. 2011. Effects of age and hypertension on alpha1-adrenoceptors in the major source arteries of the rat bladder and penis. *Eur J Pharmacol* 670:260-265.

450. Wu, W., Elde, R., and Wessendorf, M.W. 1993. Organization of the serotonergic innervation of spinal neurons in rats--III. Differential serotonergic innervation of somatic and parasympathetic preganglionic motoneurons as determined by patterns of co-existing peptides. *Neuroscience* 55:223-233.

451. Pascual, J.I., Insausti, R., and Gonzalo, L.M. 1993. Urinary bladder innervation in male rat: termination of primary afferents in the spinal cord as determined by transganglionic transport of WGA-HRP. *J Urol* 150:500-504.

452. Ljungdahl, A., Hokfelt, T., and Nilsson, G. 1978. Distribution of substance P-like immunoreactivity in the central nervous system of the rat--I. Cell bodies and nerve terminals. *Neuroscience* 3:861-943.

453. Sasek, C.A., Seybold, V.S., and Elde, R.P. 1984. The immunohistochemical localization of nine peptides in the sacral parasympathetic nucleus and the dorsal gray commissure in rat spinal cord. *Neuroscience* 12:855-873.

454. Micevych, P.E., Coquelin, A., and Arnold, A.P. 1986. Immunohistochemical distribution of substance P, serotonin, and methionine enkephalin in sexually dimorphic nuclei of the rat lumbar spinal cord. *J Comp Neurol* 248:235-244.

455. Johansson, O., Hokfelt, T., Pernow, B., Jeffcoate, S.L., White, N., Steinbusch, H.W., Verhofstad, A.A., Emson, P.C., and Spindel, E. 1981. Immunohistochemical support for three putative transmitters in one neuron: coexistence of 5-hydroxytryptamine, substance P- and thyrotropin releasing hormone-like immunoreactivity in medullary neurons projecting to the spinal cord. *Neuroscience* 6:1857-1881.

456. Maxwell, L., Maxwell, D.J., Neilson, M., and Kerr, R. 1996. A confocal microscopic survey of serotoninergic axons in the lumbar spinal cord of the rat: co-localization with glutamate decarboxylase and neuropeptides. *Neuroscience* 75:471-480.

457. Lecci, A., and Maggi, C.A. 2001. Tachykinins as modulators of the micturition reflex in the central and peripheral nervous system. *Regul Pept* 101:1-18.

458. Mersdorf, A., Schmidt, R.A., Kaula, N., and Tanagho, E.A. 1992. Intrathecal administration of substance P in the rat: the effect on bladder and urethral sphincteric activity. *Urology* 40:87-96.

459. Gilbey, M.P., McKenna, K.E., and Schramm, L.P. 1983. Effects of substance P on sympathetic preganglionic neurones. *Neurosci Lett* 41:157-159.

460. Goettl, V.M., Tejwani, G.A., Neff, N.H., and Hadjiconstantinou, M. 1999. Decreased neuropeptide content in the spinal cord of aged rats: the effect of GM1 ganglioside. *Neuroreport* 10:513-516.

461. Johnson, H., Ulfhake, B., Dagerlind, A., Bennett, G.W., Fone, K.C., and Hokfelt, T. 1993. The serotoninergic bulbospinal system and brainstem-spinal cord content of serotonin-, TRH-, and substance P-like immunoreactivity in the aged rat with special reference to the spinal cord motor nucleus. *Synapse* 15:63-89.

462. Ranson, R.N., Priestley, D.J., Santer, R.M., and Watson, A.H. 2005. Changes in the substance P-containing innervation of the lumbosacral spinal cord in male Wistar rats as a consequence of ageing. *Brain Res* 1036:139-144.

463. Burnstock, G. 2009. Purinergic signalling: past, present and future. *Braz J Med Biol Res* 42:3-8.

464. Foreman, R.D. 2000. Integration of viscerosomatic sensory input at the spinal level. *Prog Brain Res* 122:209-221.

465. Kaddumi, E.G., and Hubscher, C.H. 2006. Convergence of multiple pelvic organ inputs in the rat rostral medulla. *J Physiol* 572:393-405.

466. Bruggemann, J., Shi, T., and Apkarian, A.V. 1994. Squirrel monkey lateral thalamus. II. Viscerosomatic convergent representation of urinary bladder, colon, and esophagus. *J Neurosci* 14:6796-6814.

467. Strasser, H., Tiefenthaler, M., Steinlechner, M., Eder, I., Bartsch, G., and Konwalinka, G. 2000. Age dependent apoptosis and loss of rhabdosphincter cells. *J Urol* 164:1781-1785.

468. Dalmose, A.L., Rijkhoff, N.J., Andersen, I.S., Stefania, D., Jorgensen, T.M., and Djurhuus, J.C. 2002. Bladder and urethral responses to pelvic nerve stimulation in the pig. *Scand J Urol Nephrol Suppl*:34-45.

469. Persson, K., Pandita, R.K., Spitsbergen, J.M., Steers, W.D., Tuttle, J.B., and Andersson, K.E. 1998. Spinal and peripheral mechanisms contributing to hyperactive voiding in spontaneously hypertensive rats. *Am J Physiol* 275:R1366-1373.

470. Kruse, M.N., Mallory, B.S., Noto, H., Roppolo, J.R., and de Groat, W.C. 1992. Modulation of the spinobulbospinal micturition reflex pathway in cats. *Am J Physiol* 262:R478-484.

471. Rouzade-Dominguez, M.L., Miselis, R., and Valentino, R.J. 2003. Central representation of bladder and colon revealed by dual transsynaptic tracing in the rat: substrates for pelvic visceral coordination. *Eur J Neurosci* 18:3311-3324.

472. Song, B., Jiang, C., Wang, Y., Lu, Y., and Li, L. 2009. Newly found prostate-bladder neural reflex in rats--possible mechanism for voiding dysfunction associated with prostatitis/pelvic pain. *Urology* 74:1365-1369.

473. Hocaoglu, Y., Roosen, A., Herrmann, K., Tritschler, S., Stief, C., and Bauer, R.M. 2011. Real-time magnetic resonance imaging (MRI): anatomical changes during physiological voiding in men. *BJU Int* 109:234-239.

474. Nadelhaft, I., Miranda-Sousa, A.J., and Vera, P.L. 2002. Separate urinary bladder and prostate neurons in the central nervous system of the rat: simultaneous labeling with two immunohistochemically distinguishable pseudorabies viruses. *BMC Neurosci* 3:8.

475. Winnard, K.P., Dmitrieva, N., and Berkley, K.J. 2006. Cross-organ interactions between reproductive, gastrointestinal, and urinary tracts: modulation by estrous stage and involvement of the hypogastric nerve. *Am J Physiol* 291:R1592-1601.

476. Dmitrieva, N., and Berkley, K.J. 2002. Contrasting effects of WIN 55212-2 on motility of the rat bladder and uterus. *J Neurosci* 22:7147-7153.

477. Dmitrieva, N., and Berkley, K.J. 2005. Influence of estradiol on micturition thresholds in the rat: involvement of the hypogastric nerve. *Am J Physiol* 289:R1724-1728.

478. Qin, C., Malykhina, A.P., Akbarali, H.I., and Foreman, R.D. 2005. Cross-organ sensitization of lumbosacral spinal neurons receiving urinary bladder input in rats with inflamed colon. *Gastroenterology* 129:1967-1978.

479. Wall, P.D., Hubscher, C.H., and Berkley, K.J. 1993. Intraspinal modulation of neuronal responses to uterine and cervix stimulation in rat L1 and L6 dorsal horn. *Brain Res* 622:71-78.

480. Hubscher, C.H., Kaddumi, E.G., and Johnson, R.D. 2004. Brain stem convergence of pelvic viscerosomatic inputs via spinal and vagal afferents. *Neuroreport* 15:1299-1302.

481. Rouzade-Dominguez, M.-L., Pernar, L., Beck, S., and Valentino, R.J. 2003. Convergent responses of Barrington's nucleus neurons to pelvic visceral stimuli: a juxtacellular labeling study. *Eur J Neurosci* 18:3325-3334.

482. Gevaert, T., Vandepitte, J., Ost, D., Nilius, B., and De Ridder, D. 2007. Autonomous contractile activity in the isolated rat bladder is modulated by a TRPV1 dependent mechanism. *Neurourol Urodyn* 26:424-432; discussion 451-423.

483. Gevaert, T., Ost, D., and De Ridder, D. 2006. Comparison study of autonomous activity in bladders from normal and paraplegic rats. *Neurourol Urodyn* 25:368-378; discussion 379-380.

484. Sugaya, K., and de Groat, W.C. 2007. Bladder volume-dependent excitatory and inhibitory influence of lumbosacral

dorsal and ventral roots on bladder activity in rats. *Biomed Res* 28:169-175.

485. Sugaya, K., and de Groat, W.C. 2002. Inhibitory control of the urinary bladder in the neonatal rat in vitro spinal cord-bladder preparation. *Brain Res Dev Brain Res* 138:87-95.

486. Lagou, M., Gillespie, J., Kirkwood, T., Harvey, I., and Drake, M.J. 2006. Muscarinic stimulation of the mouse isolated whole bladder: physiological responses in young and ageing mice. *Auton Autacoid Pharmacol* 26:253-260.

487. Finney, S.M., Stewart, L.H., and Gillespie, J.I. 2007. Cholinergic activation of phasic activity in the isolated bladder: possible evidence for M3- and M2-dependent components of a motor/sensory system. *BJU Int* 100:668-678.

488. Sadananda, P., Drake, M.J., Paton, J.F., and Pickering, A.E. 2011. An exploration of the control of micturition using a novel in situ arterially perfused rat preparation. *Front Neurosci* 5:62.

489. Sugaya, K., and De Groat, W.C. 1994. Micturition reflexes in the in vitro neonatal rat brain stem-spinal cord-bladder preparation. *Am J Physiol* 266:R658-667.

490. Sugaya, K., and de Groat, W.C. 1994. Effects of MK-801 and CNQX, glutamate receptor antagonists, on bladder activity in neonatal rats. *Brain Res* 640:1-10.

491. Lagou, M., Gillespie, J.I., Andersson, K.E., Kirkwood, T., and Drake, M.J. 2006. Bladder volume alters cholinergic responses of the isolated whole mouse bladder. *J Urol* 175:771-776.

492. Grol, S., van Koeveringe, G.A., de Vente, J., van Kerrebroeck, P.E., and Gillespie, J.I. 2008. Regional differences in sensory innervation and suburothelial interstitial cells in the bladder neck and urethra. *BJU Int* 102:870-877.

493. de Jongh, R., van Koeveringe, G.A., van Kerrebroeck, P.E., Markerink-van Ittersum, M., de Vente, J., and Gillespie, J.I. 2007. Damage to the bladder neck alters autonomous activity and its sensitivity to cholinergic agonists. *BJU Int* 100:919-929.

494. Gillespie, J.I., Harvey, I.J., and Drake, M.J. 2003. Agonist- and nerve-induced phasic activity in the isolated whole bladder of the guinea pig: evidence for two types of bladder activity. *Exp Physiol* 88:343-357.

495. Kanai, A., Roppolo, J., Ikeda, Y., Zabbarova, I., Tai, C., Birder, L., Griffiths, D., de Groat, W., and Fry, C. 2007. Origin of spontaneous activity in neonatal and adult rat bladders and its enhancement by stretch and muscarinic agonists. *Am J Physiol* 292:F1065-1072.

496. Drake, M.J., Harvey, I.J., and Gillespie, J.I. 2003. Autonomous activity in the isolated guinea pig bladder. *Exp Physiol* 88:19-30.

497. Finney, S.M., Stewart, L.H., and Gillespie, J.I. 2008. Volume-induced responses in the isolated bladder: evidence for excitatory and inhibitory elements. *BJU Int* 102:1154-1161.

498. Szigeti, G.P., Somogyi, G.T., Csernoch, L., and Szell, E.A. 2005. Age-dependence of the spontaneous activity of the rat urinary bladder. *J Muscle Res Cell Motil* 26:23-29.

499. Szell, E.A., Yamamoto, T., de Groat, W.C., and Somogyi, G.T. 2000. Smooth muscle and parasympathetic nerve terminals in the rat urinary bladder have different subtypes of alpha(1) adrenoceptors. *Br J Pharmacol* 130:1685-1691.

500. Drake, M.J., Mills, I.W., and Gillespie, J.I. 2001. Model of peripheral autonomous modules and a myovesical plexus in normal and overactive bladder function. *Lancet* 358:401-403.

501. Coolsaet, B.L., Van Duyl, W.A., Van Os-Bossagh, P., and De Bakker, H.V. 1993. New concepts in relation to urge and detrusor activity. *Neurourol Urodyn* 12:463-471.

502. Smith, T.K., and Robertson, W.J. 1998. Synchronous movements of the longitudinal and circular muscle during peristalsis in the isolated guinea-pig distal colon. *J Physiol* 506 (Pt 2):563-577.

503. Drake, M.J. 2007. The integrative physiology of the bladder. *Ann R Coll Surg Engl* 89:580-585.

504. Barrington, F.J.T. 1925. The effect of lesion of the hind- and mid-brain on micturition in the cat. *Quart J Exp Physiol* 15:81-102.

505. Blok, B.F., Willemsen, A.T., and Holstege, G. 1997. A PET study on brain control of micturition in humans. *Brain* 120 (Pt 1):111-121.

506. Fukuyama, H., Matsuzaki, S., Ouchi, Y., Yamauchi, H., Nagahama, Y., Kimura, J., and Shibasaki, H. 1996. Neural control of micturition in man examined with single photon emission computed tomography using 99mTc-HMPAO. *Neuroreport* 7:3009-3012.

507. Kershen, R.T., Kalisvaart, J., and Appell, R.A. 2003. Functional brain imaging and the bladder: new insights into cerebral control over micturition. *Curr Urol Rep* 4:344-349.

508. Charil, A., Zijdenbos, A.P., Taylor, J., Boelman, C., Worsley, K.J., Evans, A.C., and Dagher, A. 2003. Statistical mapping analysis of lesion location and neurological disability in multiple sclerosis: application to 452 patient data sets. *Neuroimage* 19:532-544.

509. Sakakibara, R., Hattori, T., Yasuda, K., and Yamanishi, T. 1996. Micturitional disturbance and the pontine tegmental lesion: urodynamic and MRI analyses of vascular cases. *J Neurol Sci* 141:105-110.

510. de Groat, W.C. 2006. Integrative control of the lower urinary tract: preclinical perspective. *Br J Pharmacol* 147:S25-S40.

511. Holstege, G. 2005. Micturition and the soul. *J Comp Neurol* 493:15-20.

512. Blok, B.F.M., De Weerd, H., and Holstege, G. 1995. Ultrastructural evidence for a paucity of projections from the lumbosacral cord to the pontine micturition center or M-region in the cat: a new concept for the organization of the micturition reflex with the periaqueductal gray as a central relay. *J Comp Neurol* 359:300-309.

513. Ding, Y.-Q., Zheng, H.-X., Gong, L.-W., Lu, Y., Zhao, H., and Qin, B.-Z. 1997. Direct projections from lumbosacral spinal cord to Barrington's nucleus in the rat: a special reference to micturition reflex. *J Comp Neurol* 389:149-160.

514. Athwal, B.S., Berkley, K.J., Hussain, I., Brennan, A., Craggs, M., Sakakibara, R., Frackowiak, R.S., and Fowler, C.J. 2001. Brain responses to changes in bladder volume and urge to void in healthy men. *Brain* 124:369-377.

515. Griffiths, D., Derbyshire, S., Stenger, A., and Resnick, N. 2005. Brain control of normal and overactive bladder. *J Urol* 174:1862-1867.

516. Dasgupta, R., Kavia,R.B., Fowler,C.J. 2007. Cerebral mechanisms and voiding dysfunction. *BJU Int* 99:731-734.

517. Loewy, A.D. 1998. Viruses as transneuronal tracers for defining neural circuits. *Neurosci Biobehav Rev* 22:679-684.

518. Marson, L. 1997. Identification of central nervous system neurons that innervate the bladder body, bladder base, or external urethral sphincter of female rats: a transneuronal tracing study using pseudorabies virus. *J Comp Neurol* 389:584-602.

519. Vizzard, M.A., Erickson, V.L., Card, J.P., Roppolo, J.R., and de Groat, W.C. 1995. Transneuronal labeling of neurons in the adult rat brainstem and spinal cord after injection of pseudorabies virus into the urethra. *J Comp Neurol* 355:629-640.

520. Nadelhaft, I., Vera, P.L., Card, J.P., and Miselis, R.R. 1992. Central nervous system neurons labelled following the injection of pseudorabies virus into the rat urinary bladder. *Neurosci Lett* 143:271-274.

521. Marson, L., and Carson 3rd, C.C. 1999. Central Nervous System Innervation of the Penis, Prostate, and Perineal Muscles: A Transneuronal Tracing Study. *Mol Urol* 3:43-50.

522. Tang, P.C. 1955. Levels of brain stem and diencephalon controlling micturition reflex. *J Neurophysiol* 18:583-595.

523. Satoh, K., Shimizu, N., Tohyama, M., and Maeda, T. 1978. Localization of the micturition reflex center at dorsolateral pontine tegmentum of the rat. *Neurosci Lett* 8:27-33.

524. Komiyama, A., Kubota, A., and Hidai, H. 1998. Urinary re-

tention associated with a unilateral lesion in the dorsolateral tegmentum of the rostral pons. *J Neurol Neurosurg Psychiatry* 65:953-954.

525. Wiklund, L., Leger, L., and Persson, M. 1981. Monoamine cell distribution in the cat brain stem. A fluorescence histochemical study with quantification of indolaminergic and locus coeruleus cell groups. *J Comp Neurol* 203:613-647.

526. Rizvi, T.A., Ennis, M., Luppi, P., Aston-Jones, G., Jiang, M., and Shipley, M.T. 1994. Preoptic projections to Barrington's nucleus and the pericoerulear region: architecture and terminal organization. *J Comp Neurol* 347:1-24.

527. Valentino, R.J., Pavcovich, L.A., and Hirata, H. 1995. Evidence for corticotropin-releasing hormone projections from Barrington's nucleus to the periaqueductal gray region and dorsal motor nucleus of the vagus in the rat. *J. Comp . Neurol.* 363:402-422.

528. Sasaki, M. 2002. Bladder contractility-related neurons in Barrington's nucleus: axonal projections to the spinal cord in the cat. *J Comp Neurol* 449:355-363.

529. Sasaki, M. 2004. Feed-forward and feedback regulation of bladder contractility by Barrington's nucleus in cats. *J Physiol* 557:287-305.

530. Sugaya, K., Ogawa, Y., Hatano, T., Nishijima, S., Matsuyama, K., and Mori, S. 2003. Ascending and descending brainstem neuronal activity during cystometry in decerebrate cats. *Neurourol Urodyn* 22:343-350.

531. Holstege, G., Griffiths, D., de Wall, H., and Dalm, E. 1986. Anatomical and physiological observations on supraspinal control of bladder and urethral sphincter muscles in the cat. *J Comp Neurol* 250:449-461.

532. Noto, H., Roppolo, J.R., Steers, W.D., and De Groat, W.C. 1989. Excitatory and inhibitory influences on bladder activity elicited by electrical stimulation in the pontine micturition center in the rat. *Brain Res* 492:99-115.

533. Pavcovich, L.A., and Valentino, R.J. 1995. Central regulation of micturition in the rat by corticotropin- releasing hormone from Barrington's nucleus. *Neurosci Lett* 196:185-188.

534. Tanaka, Y., Koyama, Y., Kayama, Y., Kawauchi, A., Ukimura, O., and T., M. 2003. Firing of micturition center neurons in the rat mesopontine tegmentum during bladder contraction. *Brain Res* 965:146-154.

535. Holstege, G., Kuypers, H.G., and Boer, R.C. 1979. Anatomical evidence for direct brain stem projections to the somatic motoneuronal cell groups and autonomic preganglionic cell groups in cat spinal cord. *Brain Res* 171:329-333.

536. Blok, B.F., and Holstege, G. 1999. Two pontine micturition centers in the cat are not interconnected directly: implications for the central organization of micturition. *J Comp Neurol* 403:209-218.

537. Valentino, R.J., Chen, S., Zhu, Y., and Aston-Jones, G. 1996. Evidence for divergent projections to the brain noradrenergic system and the spinal parasympathetic system from Barrington's nucleus. *Brain Res* 732:1-15.

538. Swanson, L.W., and Hartman, B.K. 1975. The central adrenergic system. An immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-beta-hydroxylase as a marker. *J Comp Neurol* 163:467-505.

539. Grzanna, R., and Molliver, M.E. 1980. The locus coeruleus in the rat: an immunohistochemical delineation. *Neuroscience* 5:21-40.

540. Lechner, S., Curtis, A., Brons, R., and Valentino, R. 1997. Locus coeruleus activation by colon distention: role of corticotropin-releasing factor and excitatory amino acids. *Brain Res* 756:114-124.

541. Elam, M., Thoren, T., and Svensson, T.H. 1986. Locus coeruleus neurons and sympathetic nerves: activation by visceral afferents. *Brain Res* 375:117-125.

542. Page, M.E., Akaoka, H., Aston-Jones, G., and Valentino, R.J. 1992. Bladder distention activates locus coeruleus neurons by an excitatory amino acid mechanism. *Neuroscience* 51:555-563.

543. Svensson, T.H. 1987. Peripheral, autonomic regulation of locus coeruleus noradrenergic neurons in brain: Putative implications for psychiatry and psychopharmacology. *Psychopharmacol* 92:1-7.

544. Rouzade-Dominguez, M.-L., Curtis, A.L., and Valentino, R.J. 2001. Role of Barrington's nucleus in the activation of rat locus coeruleus neurons by colonic distension. *Brain Res* 917:206-218.

545. Kiddo, D.A., Valentino,R.J., Zderic,S., Ganesh,A., Leiser,S., Hale,L, and Grigoriadis,D.E. 2006. Impact of state of arousal and stress neuropeptides on urodynamic function in freely moving rats. *Am J Physiol* 290:1697-1706.

546. Aston-Jones, G., and Cohen, J.D. 2005. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Ann Rev Neurosci* 28:403-450.

547. Berridge, C.W., and Waterhouse, B.D. 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Res* 42:33-84.

548. Bouret, S., and Sara, S.J. 2005. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. *Trends Neurosci* 28:574-582.

549. Valentino, R.J., Wein,A., Wood,S.K., and Zderic,S.A. 2011. The bladder-brain connection: putative role of corticotrophin-releasing factor. *Nat Urol* 8:19-28.

550. Rickenbacher, E., Baez, M.A., Hale, L., Leiser, S.C., Zderic, S.A., and Valentino, R.J. 2008. Impact of overactive bladder on the brain: central sequelae of a visceral pathology. *Proc Natl Acad Sci U S A* 105:10589-10594.

551. Bland, B.H., and Oddie, S.D. 2001. Theta band oscillation and synchrony in the hippocampal formation and associated structures: the case for its role in sensorimotor integration. *Behav Br Res* 127:119-136.

552. Kirby, R.S. 2000. The natural history of benign prostatic hyperplasia: what have we learned in the last decade? *Urology* 56:3-6.

553. Tubaro, A. 2004. Defining overactive bladder: epidemiology and burden of disease. *Urology* 64:2-6.

554. Steers, W.D., Ciambotti, J., Erdman, S., and de Groat, W.C. 1990. Morphological plasticity in efferent pathways to the urinary bladder of the rat following urethral obstruction. *J Neurosci* 10:1943-1951.

555. Valentino, R.J., Page, M.E., Luppi, P.H., Zhu, Y., Van Bockstaele, E., and Aston-Jones, G. 1994. Evidence for widespread afferents to Barrington's nucleus, a brainstem region rich in corticotropin-releasing hormone neurons. *Neuroscience* 62:125-143.

556. Taniguchi, N., Miyata, M., Yachiku, S., Kaneko, S., Yamaguchi, S., and Numata, A. 2002. A study of micturition inducing sites in the periaqueductal gray of the mesencephalon. *J Urol* 168:1626-1631.

557. Yardley, C.P., and Hilton, S.M. 1986. The hypothalamic and brainstem areas from which the cardiovascular and behavioural components of the defence reaction are elicited in the rat. *J Auton Nerv Syst* 15:227-244.

558. Fuchs, S.A., Edinger, H.M., and Siegel, A. 1985. The organization of the hypothalamic pathways mediating affective defense behavior in the cat. *Brain Res* 330:77-92.

559. Ding, Y.Q., Wang, D., Xu, J.Q., and Ju, G. 1999. Direct projections from the medial preoptic area to spinally-projecting neurons in Barrington's nucleus: an electron microscope study in the rat. *Neurosci Lett* 271:175-178.

560. Rickey, L.M., Sarkey, S., and DonCarlos, L.L. 2008. Estrogen-sensitive projections from the medial preoptic area to the dorsal pontine tegmentum, including Barrington's nucleus, in the rat. *Neurourol Urodyn* 27:440-445.

561. Rizvi, T.A., Murphy, A.Z., Ennis, M., Aston-Jones, G., and Shipley, M.T. 1998. Fos expression in rat pontine tegmental neurons following activation of the medial preoptic area. *Brain Res* 789:256-262.

562. Kuipers, R., Mouton, L.J., and Holstege, G. 2006. Afferent projections to the pontine micturition center in the cat. *J Comp Neurol* 494:36-53.

563. Holstege, G. 1991. Descending motor pathways and the spinal motor system: limbic and non-limbic components. *Prog Brain Res* 87:307-421.

564. Schenberg, L.C., Povoa, R.M., Costa, A.L., Caldellas, A.V., Tufik, S., and Bittencourt, A.S. 2005. Functional specializations within the tectum defense systems of the rat. *Neurosci Biobehav Rev* 29:1279-1298.

565. Vargas, L.C., Marques, T.A., and Schenberg, L.C. 2000. Micturition and defensive behaviors are controlled by distinct neural networks within the dorsal periaqueductal gray and deep gray layer of the superior colliculus of the rat. *Neurosci Lett* 280:45-48.

566. Smith, A.L., Leung, J., Kun, S., Zhang, R., Karagiannides, I., Raz, S., Lee, U., Glovatscka, V., Pothoulakis, C., Bradesi, S., Mayer, E.A., and Rodriguez, L.V. 2011. The effects of acute and chronic psychological stress on bladder function in a rodent model. *Urology* 78:967 e961-967.

567. Liu, Z., Sakakibara, R., Nakazawa, K., Uchiyama, T., Yamamoto, T., Ito, T., and Hattori, T. 2004. Micturition-related neuronal firing in the periaqueductal gray area in cats. *Neuroscience* 126:1075-1082.

568. Desjardins, C., Maruniak, J.A., and Bronson, F.H. 1973. Social rank in house mice: differentiation revealed by ultraviolet visualization of urinary marking patterns. *Science* 182:939-941.

569. Henry, J.P., Meehan, W.P., and Stephens, P.M. 1982. Role of subordination in nephritis of socially stressed mice. *Contrib Nephrol* 30:38-42.

570. Lumley, L.A., Sipos, M.L., Charles, R.C., Charles, R.F., and Meyerhoff, J.L. 1999. Social stress effects on territorial marking and ultrasonic vocalizations in mice. *Physiol & Behav* 67:769-775.

571. Wood, S.K., Baez, M.A., Bhatnagar, S., and Valentino, R.J. 2009. Social stress-induced bladder dysfunction: potential role of corticotropin-releasing factor. *Am J Physiol* 296:R1671-1678.

572. Chang, A., Butler, S., Sliwoski, J., Valentino, R., Canning, D., and Zderic, S. 2009. Social stress in mice induces voiding dysfunction and bladder wall remodeling. *Am J Physiol* 297:F1101-1108.

573. Bauer, S.B. 2002. Special considerations of the overactive bladder in children. *Urology* 60:43-48; discussion 49.

574. Ellsworth, P.I., Merguerian, P.A., and Copening, M.E. 1995. Sexual abuse: another causative factor in dysfunctional voiding. *J Urol* 153:773-776.

575. Lettgen, B., von Gontard, A., Olbing, H., Heiken-Lowenau, C., Gaebel, E., and Schmitz, I. 2002. Urge incontinence and voiding postponement in children: somatic and psychosocial factors. *Acta Paediatr* 91:978-984; discussion 895-976.

576. Perry, S., McGrother, C.W., and Turner, K. 2006. An investigation of the relationship between anxiety and depression and urge incontinence in women: development of a psychological model. *Br J Health Psychol* 11:463-482.

577. Davila, G.W., Bernier, F., Franco, J., and Kopka, S.L. 2003. Bladder dysfunction in sexual abuse survivors. *J Urol* 170:476-479.

578. Varlam, D.E., and Dippell, J. 1995. Non-neurogenic bladder and chronic renal insufficiency in childhood. *Pediatr Nephrol* 9:1-5.

579. Franzen, K., Johansson, J.E., Andersson, G., Pettersson, N., and Nilsson, K. 2009. Urinary incontinence in women is not exclusively a medical problem: a population-based study on urinary incontinence and general living conditions. *Scand J Urol Nephrol* 43:226-232.

580. Pavcovich, L.A., Yang, M., Miselis, R.R., and Valentino, R.J. 1998. Novel role for the pontine micturition center, Barrington's nucleus: evidence for coordination of colonic and forebrain activity. *Brain Res.* 784:355-361.

581. Lydiard, R.B., Fossey, M.D., Marsh, W., and Ballenger, J.C. 1993. Prevalence of psychiatric disorders in patients with irritable bowel syndrome. *Psychosomatics* 34:229-234.

582. Lydiard, R.B., Greenwald, S., Weissman, M.M., Johnson, J., Drossman, D.A., and Ballenger, J.C. 1994. Panic disorder and gastrointestinal symptoms: findings from the NIMH epidemiologic catchment area project. *Am J Psych* 151:64-70.

583. Sakakibara, R., Nakazawa, K., Shiba, K., Nakajima, Y., Uchiyama, T., Yoshiyama, M., Yamanishi, T., and Hattori, T. 2002. Firing patterns of micturition-related neurons in the pontine storage centre in cats. *Auton Neurosci* 99:24-30.

584. Matsumoto, G., Hisamitsu, T., and de Groat, W.C. 1995. Role of glutamate and NMDA receptors in the descending limb of the spinobulbospinal micturition reflex pathway of the rat. *Neurosci Lett* 183:58-61.

585. Matsumoto, G., Hisamitsu, T., and de Groat, W.C. 1995. Non-NMDA glutamatergic excitatory transmission in the descending limb of the spinobulbospinal micturition reflex pathway of the rat. *Brain Res* 693:246-250.

586. Yoshiyama, M., and de Groat, W.C. 2005. Supraspinal and spinal alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and N-methyl-D-aspartate glutamatergic control of the micturition reflex in the urethane-anesthetized rat. *Neuroscience* 132:1017-1026.

587. Imaki, T., Vale, W., and Sawchenko, P.E. 1992. Regulation of corticotropin-releasing hormone mRNA in neuroendocrine and autonomic neurons by osmotic stimuli and volume loading. *Neuroendocrinology* 56:633-640.

588. Valentino, R.J., Kosboth, M., Colflesh, M., and Miselis, R.R. 2000. Transneuronal labeling from the rat distal colon: anatomic evidence for regulation of distal colon function by a pontine corticotropin-releasing factor system. *J Comp Neurol* 417:399-414.

589. Curtis, A.L., Florin-Lechner, S.M., Pavcovich, L.A., and Valentino, R.J. 1997. Activation of the locus coeruleus noradrenergic system by intracoerulear microinfusion of corticotropin-releasing factor: effects on discharge rate, cortical norepinephrine levels and cortical electroencephalographic activity. *J Pharmacol Exp Ther* 281:163-172.

590. Ito, T., Sakakibara, R., Nakazawa, K., Uchiyama, T., Yamamoto, T., Liu, Z., Shimizu, E., and Hattori, T. 2006. Effects of electrical stimulation of the raphe area on the micturition reflex in cats. *Neuroscience* 142:1273-1280.

591. Kakizaki, H., Yoshiyama, M., Koyanagi, T., and De Groat, W.C. 2001. Effects of WAY100635, a selective 5-HT1A-receptor antagonist on the micturition-reflex pathway in the rat. *Am J Physiol* 280:R1407-1413.

592. Conley, R.K., Williams, T.J., Ford, A.P., and Ramage, A.G. 2001. The role of alpha(1)-adrenoceptors and 5-HT(1A) receptors in the control of the micturition reflex in male anaesthetized rats. *Br J Pharmacol* 133:61-72.

593. Blok, B.F., Sturms, L.M., and Holstege, G. 1998. Brain activation during micturition in women. *Brain* 121 (Pt 11):2033-2042.

594. Griffiths, D., Tadic, S.D., Schaefer, W., and Resnick, N.M. 2007. Cerebral control of the bladder in normal and urge-incontinent women. *Neuroimage* 37:1-7.

595. Seseke, S., Baudewig, J., Kallenberg, K., Ringert, R.H., Seseke, F., and Dechent, P. 2008. Gender differences in voluntary micturition control: an fMRI study. *Neuroimage* 43:183-191.

596. Drake, M.J., Fowler, C.J., Griffiths, D., Mayer, E., Paton, J.F., and Birder, L. 2010. Neural control of the lower urinary and gastrointestinal tracts: supraspinal CNS mechanisms. *Neurourol Urodyn* 29:119-127.

597. Beckel, J.M., and Holstege, G. 2011. Neurophysiology of the lower urinary tract. *Handbook of Exp Pharmacol*:149-169.

598. Takasaki, A., Hui, M., and Sasaki, M. 2010. Is the periaqueductal gray an essential relay center for the micturition reflex pathway in the cat? *Br Res* 1317:108-115.

599. Blok, B.F., and Holstege, G. 1998. The central nervous system control of micturition in cats and humans. *Behav Br Res* 92:119-125.

600. Maurice-Williams, R.S. 1974. Micturition symptoms in frontal tumours. *J Neurol, Neurosurgery, and Psychiatry* 37:431-436.

601. Sakakibara, R., Hattori, T., Yasuda, K., and Yamanishi, T. 1996. Micturitional disturbance after acute hemispheric stroke: analysis of the lesion site by CT and MRI. *J Neurolog Sci* 137:47-56.

602. Lang, E.W., Chesnut, R.M., and Hennerici, M. 1996. Urinary retention and space-occupying lesions of the frontal cortex. *Eur Neurol* 36:43-47.

603. Yamamoto, T., Sakakibara, R., Uchiyama, T., Liu, Z., Ito, T., Yamanishi, T., and Hattori, T. 2005. Lower urinary tract function in patients with pituitary adenoma compressing hypothalamus. *J Neurology, Neurosurgery, and Psychiatry* 76:390-394.

604. Sakakibara, R., Hattori, T., Uchiyama, T., and Yamanishi, T. 1999. Urinary function in elderly people with and without leukoaraiosis: relation to cognitive and gait function. *J Neurology, Neurosurgery, and Psychiatry* 67:658-660.

605. Kuchel, G.A., Moscufo, N., Guttmann, C.R., Zeevi, N., Wakefield, D., Schmidt, J., Dubeau, C.E., and Wolfson, L. 2009. Localization of brain white matter hyperintensities and urinary incontinence in community-dwelling older adults. *J Gerontology. Series A, Biolog Sci Med Sci* 64:902-909.

606. Tadic, S.D., Griffiths, D., Murrin, A., Schaefer, W., Aizenstein, H.J., and Resnick, N.M. 2010. Brain activity during bladder filling is related to white matter structural changes in older women with urinary incontinence. *NeuroImage* 51:1294-1302.

607. Blok, B.F., Sturms, L.M., and Holstege, G. 1997. A PET study on cortical and subcortical control of pelvic floor musculature in women. *J Comp Neurol* 389:535-544.

608. Nour, S., Svarer, C., Kristensen, J.K., Paulson, O.B., and Law, I. 2000. Cerebral activation during micturition in normal men. *Brain* 123 (Pt 4):781-789.

609. Matsuura, S., Kakizaki, H., Mitsui, T., Shiga, T., Tamaki, N., and Koyanagi, T. 2002. Human brain region response to distention or cold stimulation of the bladder: a positron emission tomography study. *J Urol* 168:2035-2039.

610. Di Gangi Herms, A.M., Veit, R., Reisenauer, C., Herms, A., Grodd, W., Enck, P., Stenzl, A., and Birbaumer, N. 2006. Functional imaging of stress urinary incontinence. *NeuroImage* 29:267-275.

611. Blok, B.F., Groen, J., Bosch, J.L., Veltman, D.J., and Lammertsma, A.A. 2006. Different brain effects during chronic and acute sacral neuromodulation in urge incontinent patients with implanted neurostimulators. *BJU Int* 98:1238-1243.

612. Yin, Y., Shuke, N., Okizaki, A., Sato, J., Aburano, T., Li, Y., Kaneko, S., Mizunaga, M., and Yachiku, S. 2006. Cerebral activation during withholding urine with full bladder in healthy men using 99mTc-HMPAO SPECT. *J Nuc Med* 47:1093-1098.

613. An, X., Bandler, R., Ongur, D., and Price, J.L. 1998. Prefrontal cortical projections to longitudinal columns in the midbrain periaqueductal gray in macaque monkeys. *J Comp Neurol* 401:455-479.

614. Laplane, D., Degos, J.D., Baulac, M., and Gray, F. 1981. Bilateral infarction of the anterior cingulate gyri and of the fornices. Report of a case. *J Neurolog Sci* 51:289-300.

615. Duffau, H., and Capelle, L. 2005. Incontinence after brain glioma surgery: new insights into the cortical control of micturition and continence. Case report. *J Neurosurg* 102:148-151.

616. Komesu, Y.M., Ketai, L.H., Mayer, A.R., Teshiba, T.M., and Rogers, R.G. 2011. Functional MRI of the Brain in Women with Overactive Bladder: Brain Activation During Urinary Urgency. *Female Pelvic Med & Recon Surg* 17:50-54.

617. Abrams, P., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten, U., van Kerrebroeck, P., Victor, A., and Wein, A. 2002. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Amer J Obstet Gynecol* 187:116-126.

618. Abrams, P., Blaivas, J.G., Stanton, S.L., and Andersen, J.T. 1988. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. *Scan J Urol Nephrol* 114:5-19.

619. Tai, C., Wang, J., Jin, T., Wang, P., Kim, S.G., Roppolo, J.R., and de Groat, W.C. 2009. Brain switch for reflex micturition control detected by FMRI in rats. *J Neurophysiol* 102:2719-2730.

620. Devinsky, O., Morrell, M.J., and Vogt, B.A. 1995. Contributions of anterior cingulate cortex to behaviour. *Brain* 118 (Pt 1):279-306.

621. Critchley, H.D. 2005. Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol* 493:154-166.

622. Lane, R.D., and Wager, T.D. 2009. The new field of Brain-Body Medicine: what have we learned and where are we headed? *NeuroImage* 47:1135-1140.

623. Zhang, H., Reitz, A., Kollias, S., Summers, P., Curt, A., and Schurch, B. 2005. An fMRI study of the role of suprapontine brain structures in the voluntary voiding control induced by pelvic floor contraction. *NeuroImage* 24:174-180.

624. Seseke, S., Baudewig, J., Kallenberg, K., Ringert, R.H., Seseke, F., and Dechent, P. 2006. Voluntary pelvic floor muscle control--an fMRI study. *NeuroImage* 31:1399-1407.

625. Kuhtz-Buschbeck, J.P., van der Horst, C., Wolff, S., Filippow, N., Nabavi, A., Jansen, O., and Braun, P.M. 2007. Activation of the supplementary motor area (SMA) during voluntary pelvic floor muscle contractions--an fMRI study. *NeuroImage* 35:449-457.

626. Schrum, A., Wolff, S., van der Horst, C., and Kuhtz-Buschbeck, J.P. 2011. Motor cortical representation of the pelvic floor muscles. *J Urol* 186:185-190.

627. Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., and Dolan, R.J. 2004. Neural systems supporting interoceptive awareness. *Nat Neurosci* 7:189-195.

628. Craig, A.D. 2002. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 3:655-666.

629. Craig, A.D. 2003. Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol* 13:500-505.

630. Mayer, E.A., Naliboff, B.D., and Craig, A.D. 2006. Neuroimaging of the brain-gut axis: from basic understanding to treatment of functional GI disorders. *Gastroenterol* 131:1925-1942.

631. Kuhtz-Buschbeck, J.P., van der Horst, C., Pott, C., Wolff, S., Nabavi, A., Jansen, O., and Junemann, K.P. 2005. Cortical representation of the urge to void: a functional magnetic resonance imaging study. *J Urol* 174:1477-1481.

632. Andrew, J., Nathan,P.W. 1965. The cerebral control of micturition. *Proc RSM* 58:553.

633. Yaguchi, H., Soma, H., Miyazaki, Y., Tashiro, J., Yabe, I., Kikuchi, S., Sasaki, H., Kakizaki, H., Moriwaka, F., and Tashiro, K. 2004. A case of acute urinary retention caused by periaqueductal grey lesion. *J Neurology, Neurosurgery, and Psychiatry* 75:1202-1203.

634. Andrew, J., Nathan, P.W., and Spanos, N.C. 1966. Disturbances of micturition and defaecation due to aneurysms of anterior communicating or anterior cerebral arteries. *J Neurosurg* 24:1-10.

635. Betts, C.D., Kapoor, R., and Fowler, C.J. 1992. Pontine pathology and voiding dysfunction. *Br J Urol* 70:100-102.

636. Manente, G., Melchionda, D., and Uncini, A. 1996. Urinary retention in bilateral pontine tumour: evidence for a pontine micturition centre in humans. *J Neurology, Neurosurgery, and Psychiatry* 61:528-529.

637. Sakakibara, R., Hattori, T., Fukutake, T., Mori, M., Yamanishi, T., and Yasuda, K. 1998. Micturitional disturbance in herpetic brainstem encephalitis; contribution of the pontine micturition centre. *J Neurology, Neurosurgery, and Psychiatry* 64:269-272.

638. Ueki, K. 1960. Disturbances of micturition observed in some patients with brain tumour. *Neurologica Medica Chirurgica* 2:25.

639. Renier, W.O., and Gabreels, F.J. 1980. Evaluation of diagnosis and non-surgical therapy in 24 children with a pontine tumour. *Neuropediatrics* 11:262-273.

640. Griffiths, D.J., Tadic, S.D., Schaefer, W., and Resnick, N.M. 2009. Cerebral control of the lower urinary tract: how age-related changes might predispose to urge incontinence. *NeuroImage* 47:981-986.

641. Winge, K., and Fowler, C.J. 2006. Bladder dysfunction in Parkinsonism: mechanisms, prevalence, symptoms, and management. *Movement Disorders* 21:737-745.

642. Finazzi-Agro, E., Peppe, A., D'Amico, A., Petta, F., Mazzone, P., Stanzione, P., Micali, F., and Caltagirone, C. 2003. Effects of subthalamic nucleus stimulation on urodynamic findings in patients with Parkinson's disease. *J Urol* 169:1388-1391.

643. Seif, C., Herzog, J., van der Horst, C., Schrader, B., Volkmann, J., Deuschl, G., Juenemann, K.P., and Braun, P.M. 2004. Effect of subthalamic deep brain stimulation on the function of the urinary bladder. *Ann Neurol* 55:118-120.

644. Herzog, J., Weiss, P.H., Assmus, A., Wefer, B., Seif, C., Braun, P.M., Herzog, H., Volkmann, J., Deuschl, G., and Fink, G.R. 2006. Subthalamic stimulation modulates cortical control of urinary bladder in Parkinson's disease. *Brain* 129:3366-3375.

645. Griffiths, D., and Tadic, S.D. 2008. Bladder control, urgency, and urge incontinence: evidence from functional brain imaging. *Neurourol Urodyn* 27:466-474.

646. Amodio, D.M., and Frith, C.D. 2006. Meeting of minds: the medial frontal cortex and social cognition. *Nature Rev Neurosci* 7:268-277.

647. Mantyh, P.W. 1982. Forebrain projections to the periaqueductal gray in the monkey, with observations in the cat and rat. *J Comp Neurol* 206:146-158.

648. Mouton, L.J. 1999. In Department of Medicine. *State University Groningen, Groningen, The Netherlands*.

649. Tadic, S.D., Griffiths, D., Schaefer, W., and Resnick, N.M. 2008. Abnormal connections in the supraspinal bladder control network in women with urge urinary incontinence. *NeuroImage* 39:1647-1653.

650. Tadic, S.D., Griffiths, D., Schaefer, W., Cheng, C.I., and Resnick, N.M. 2010. Brain activity measured by functional magnetic resonance imaging is related to patient reported urgency urinary incontinence severity. *J Urol* 183:221-228.

651. Nazif, O., Teichman, J.M., and Gebhart, G.F. 2007. Neural upregulation in interstitial cystitis. *Urology* 69:24-33.

652. Wein, A.J., and Hanno, P.M. 2002. Targets for therapy of the painful bladder. *Urology* 59:68-73.

653. Gonzalez, R.R., Fong, T., Belmar, N., Saban, M., Felsen, D., and Te, A. 2005. Modulating bladder neuroinflammation: RDP58, a novel anti-inflammatory peptide, decreases inflammation and nerve growth factor production in experimental cystitis. *J Urol* 173:630-634.

654. Steers, W.D., and Tuttle, J.B. 2006. Mechanisms of disease: The role of nerve growth factor in the pathophysiology of bladder disorders. *Nat Clin Prac Urol* 3:101-110.

655. Okragly, A.J., Niles, A.L., Saban, R., Schmidt, D., Hoffman, R.L., Warner, T.F., Moon, T.D., Uehling, D.T., and Haak-Frendscho, M. 1999. Elevated tryptase, nerve growth factor, neurotrophin-3 and glial cell line-derived neurotrophic factor levels in the urine of interstitial cystitis and bladder cancer patients. *J Urol* 161:438-441; discussion 441-432.

656. Liu, H.T., Tyagi, P., Chancellor, M.B., and Kuo, H.C. 2010. Urinary nerve growth factor but not prostaglandin E2 increases in patients with interstitial cystitis/bladder pain syndrome and detrusor overactivity. *BJU Int* 106:1681-1685.

657. Keay, S., Zhang, C.O., Shoenfelt, J.L., and Chai, T.C. 2003. Decreased in vitro proliferation of bladder epithelial cells from patients with interstitial cystitis. *Urology* 61:1278-1284.

658. Yang, W., Chung, Y.G., Kim, Y., Kim, T.K., Keay, S.K., Zhang, C.O., Ji, M., Hwang, D., Kim, K.P., Steen, H., et al. 2011. Quantitative proteomics identifies a beta-catenin network as an element of the signaling response to Frizzled-8 protein-related antiproliferative factor. *MCP* 10:M110 007492.

659. Hu, V.Y., Zvara, P., Dattilio, A., Redman, T.L., Allen, S.J., Dawbarn, D., Stroemer, R.P., and Vizzard, M.A. 2005. Decrease in bladder overactivity with REN1820 in rats with cyclophosphamide induced cystitis. *J Urol* 173:1016-1021.

660. Tyagi, P., Banerjee, R., Basu, S., Yoshimura, N., Chancellor, M., and Huang, L. 2006. Intravesical antisense therapy for cystitis using TAT-peptide nucleic acid conjugates. *Molec Pharmaceu* 3:398-406.

661. Yoshimura, N., and de Groat, W.C. 1997. Neural control of the lower urinary tract. *Int J Urol* 4:111-125.

662. Sculptoreanu, A., de Groat,W.C., Buffington,C.A., Birder,L.A. 2005. Abnormal excitability in capsaicin-responsive DRG neurons from cats with feline interstitial cystitis. *Exp Neurol* 193:437-443.

663. Evans, R.J., Moldwin, R.M., Cossons, N., Darekar, A., Mills, I.W., and Scholfield, D. 2011. Proof of concept trial of tanezumab for the treatment of symptoms associated with interstitial cystitis. *J Urol* 185:1716-1721.

664. Klumpp, D.J., and Rudick, C.N. 2008. Summation model of pelvic pain in interstitial cystitis. *Nat Clin Prac Urol* 5:494-500.

665. Rudick, C.N., Chen, M.C., Mongiu, A.K., and Klumpp, D.J. 2007. Organ cross talk modulates pelvic pain. *Am J Physiol* 293:R1191-1198.

666. Clemens, J.Q. 2010. Afferent neurourology: an epidemiological perspective. *J Urol* 184:432-439.

667. Brading, A.F., and Turner, W.H. 1994. The unstable bladder: towards a common mechanism. *Br J Urol* 73:3-8.

668. Harrison, S.C., Ferguson, D.R., and Doyle, P.T. 1990. Effect of bladder outflow obstruction on the innervation of the rabbit urinary bladder. *Br J Urol* 66:372-379.

669. Sibley, G.N. 1985. An experimental model of detrusor instability in the obstructed pig. *Br J Urol* 57:292-298.

670. Speakman, M.J., Brading, A.F., Gilpin, C.J., Dixon, J.S., Gilpin, S.A., and Gosling, J.A. 1987. Bladder outflow obstruction--a cause of denervation supersensitivity. *J Urol* 138:1461-1466.

671. German, K., Bedwani, J., Davies, J., Brading, A.F., and Stephenson, T.P. 1995. Physiological and morphometric studies into the pathophysiology of detrusor hyperreflexia in neuropathic patients. *J Urol* 153:1678-1683.

672. Mills, I.W., Greenland, J.E., McMurray, G., McCoy, R., Ho, K.M., Noble, J.G., and Brading, A.F. 2000. Studies of the pathophysiology of idiopathic detrusor instability: the physiological properties of the detrusor smooth muscle and its pattern of innervation. *J Urol* 163:646-651.

673. Kinder, R.B., and Mundy, A.R. 1985. Atropine blockade of nerve-mediated stimulation of the human detrusor. *Br J Urol* 57:418-421.

674. Turner, W.H., and Brading, A.F. 1997. Smooth muscle of the bladder in the normal and the diseased state: pathophysiology, diagnosis and treatment. *Pharmacol & Therapeu* 75:77-110.

675. Elbadawi, A., Yalla, S.V., and Resnick, N.M. 1993. Structural basis of geriatric voiding dysfunction. III. Detrusor overactivity. *J Urol* 150:1668-1680.

676. Charlton, R.G., Morley, A.R., Chambers, P., and Gillespie, J.I. 1999. Focal changes in nerve, muscle and connective tissue in normal and unstable human bladder. *BJU Int* 84:953-960.

677. Williams, J.H., Turner, W.H., Sainsbury, G.M., and Brad-

ing, A.F. 1993. Experimental model of bladder outflow tract obstruction in the guinea-pig. *Br J Urol* 71:543-554.

678. Brading, A.F. 1997. A myogenic basis for the overactive bladder. *Urology* 50:57-67; discussion 68-73.

679. McMurray, G., Casey, J.H., and Naylor, A.M. 2006. Animal models in urological disease and sexual dysfunction. *Br J Pharmacol* 147 Suppl 2:S62-79.

680. Mitsui, T., Kakizaki, H., Matsuura, S., Tanaka, H., Yoshioka, M., and Koyanagi, T. 2003. Chemical bladder irritation provokes c-fos expression in the midbrain periaqueductal gray matter of the rat. *Br Res* 967:81-88.

681. Avelino, A., Cruz, F., and Coimbra, A. 1999. Intravesical resiniferatoxin desensitizes rat bladder sensory fibres without causing intense noxious excitation. A c-fos study. *Eur J Pharmacol* 378:17-22.

682. Steers, W.D., Kolbeck, S., Creedon, D., and Tuttle, J.B. 1991. Nerve growth factor in the urinary bladder of the adult regulates neuronal form and function. *J Clin Inves* 88:1709-1715.

683. Steers, W.D., Meythaler, J.M., Haworth, C., Herrell, D., and Park, T.S. 1992. Effects of acute bolus and chronic continuous intrathecal baclofen on genitourinary dysfunction due to spinal cord pathology. *J Urol* 148:1849-1855.

684. Clemow, D.B., Steers, W.D., McCarty, R., and Tuttle, J.B. 1998. Altered regulation of bladder nerve growth factor and neurally mediated hyperactive voiding. *Am J Physiol* 275:R1279-1286.

685. Clemow, D.B., McCarty, R., Steers, W.D., and Tuttle, J.B. 1997. Efferent and afferent neuronal hypertrophy associated with micturition pathways in spontaneously hypertensive rats. *Neurourol Urodyn* 16:293-303.

686. Lee, K.S., Dean-McKinney,T., Tuttle,J.B., Steers,W.D. 2002. Intrathecal antisense oligonucleotide against the tetrodotoxin-resistant sodium channel (NaV1.8) reduces bladder hyperactivity in the spontaneously hypertensive rat. *J Urol* 167:38.

687. de Groat, W.C., and Yoshimura, N. 2006. Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury. *Prog Brain Res* 152:59-84.

688. Yoshimura, N., and de Groat, W.C. 1997. Plasticity of Na+ channels in afferent neurones innervating rat urinary bladder following spinal cord injury. *J Physiol* 503 (Pt 2):269-276.

689. Peters, K.M., Girdler, B., Turzewski, C., Trock, G., Feber, K., Nantau, W., Bush, B., Gonzalez, J., Kass, E., de Benito, J., et al. 2010. Outcomes of lumbar to sacral nerve rerouting for spina bifida. *J Urol* 184:702-707.

690. Xin, H. 2010. Research ethics. Questions from China snag U.S. trial of nerve-rerouting procedure. *Science* 330:741.

691. Yokoyama, O., Yoshiyama, M., Namiki, M., and de Groat, W.C. 2000. Role of the forebrain in bladder overactivity following cerebral infarction in the rat. *Exp Neurol* 163:469-476.

692. Yokoyama, O., Mizuno, H., Komatsu, K., Akino, H., Tanase, K., and Namiki, M. 2004. Role of glutamate receptors in the development and maintenance of bladder overactivity after cerebral infarction in the rat. *J Urol* 171:1709-1714.

693. Ukimura, O., Ushijima, S., Honjo, H., Iwata, T., Suzuki, K., Hirahara, N., Okihara, K., Mizutani, Y., Kawauchi, A., and Miki, T. 2004. Neuroselective current perception threshold evaluation of bladder mucosal sensory function. *Eur Urol* 45:70-76.

694. Kenton, K., Lowenstein, L., Simmons, J., and Brubaker, L. 2007. Aging and overactive bladder may be associated with loss of urethral sensation in women. *Neurourol Urodyn* 26:981-984.

695. Geirsson, G., Fall, M., and Lindstrom, S. 1993. The ice-water test--a simple and valuable supplement to routine cystometry. *Br J Urol* 71:681-685.

696. Evans, R.J. 2005. Intravesical therapy for overactive bladder. *Curr Urol Rep* 6:429-433.

697. Drake, M.J., Harvey, I.J., Gillespie, J.I., and Van Duyl, W.A. 2005. Localized contractions in the normal human bladder and in urinary urgency. *BJU Int* 95:1002-1005.

698. Torrisi, G., Sampugnaro, E.G., Pappalardo, E.M., D'Urso, E., Vecchio, M., and Mazza, A. 2007. Postpartum urinary stress incontinence: analysis of the associated risk factors and neurophysiological tests. *Minerva Ginecologica* 59:491-498.

699. Lin, Y.H., Liu, G., and Daneshgari, F. 2008. A mouse model of simulated birth trauma induced stress urinary incontinence. *Neurourol Urodyn* 27:353-358.

700. Katofiasc, M.A., Nissen, J., Audia, J.E., and Thor, K.B. 2002. Comparison of the effects of serotonin selective, norepinephrine selective, and dual serotonin and norepinephrine reuptake inhibitors on lower urinary tract function in cats. *Life Sciences* 71:1227-1236.

701. Zinner, N.R., Scholfield,D., Soma,K., Darekar,A., Grant,L., Mills,I. 2008. A phase 2, 8-week, multicenter, randomized, double-blind, placebo controlled, parallel group study evaluating the efficacy, tolerability and safety of [x,x]-reboxetine (PNU-165442G) for stress urinary incontinence in women. *J Urol* 179:569-570.

702. Greenland, J.E., Hvistendahl, J.J., Andersen, H., Jorgensen, T.M., McMurray, G., Cortina-Borja, M., Brading, A.F., and Frokiaer, J. 2000. The effect of bladder outlet obstruction on tissue oxygen tension and blood flow in the pig bladder. *BJU Int* 85:1109-1114.

703. Pessina, F., McMurray, G., Wiggin, A., and Brading, A.F. 1997. The effect of anoxia and glucose-free solutions on the contractile response of guinea-pig detrusor strips to intrinsic nerve stimulation and the application of excitatory agonists. *J Urol* 157:2375-2380.

704. Barendrecht, M.M., Chichester, P., Michel, M.C., and Levin, R.M. 2007. Effect of short-term outlet obstruction on rat bladder nerve density and contractility. *Autonomic & Autacoid Pharmacol* 27:47-53.

705. Rothrock, N.E., Lutgendorf, S.K., Hoffman, A., and Kreder, K.J. 2002. Depressive symptoms and quality of life in patients with interstitial cystitis. *J Urol* 167:1763-1767.

706. Melville, J.L., Walker, E., Katon, W., Lentz, G., Miller, J., and Fenner, D. 2002. Prevalence of comorbid psychiatric illness and its impact on symptom perception, quality of life, and functional status in women with urinary incontinence. *Am J Obstet Gynecol* 187:80-87.

707. van der Vaart, C.H., Roovers, J.P., de Leeuw, J.R., and Heintz, A.P. 2007. Association between urogenital symptoms and depression in community-dwelling women aged 20 to 70 years. *Urology* 69:691-696.

708. Fenton, B.W. 2007. Limbic associated pelvic pain: a hypothesis to explain the diagnostic relationships and features of patients with chronic pelvic pain. *Medical Hypotheses* 69:282-286.

709. Miczek, K.A. 1979. A new test for aggression in rats without aversive stimulation: differential effects of d-amphetamine and cocaine. *Psychopharmacol* 60:253-259.

Committee 4

Pathophysiology of Urinary Incontinence, Faecal Incontinence and Pelvic Organ Prolapse

Chair

H. Koelbl (Germany)

Members

Ty. Igawa (Japan),

S. Salvatore (Italy),

R.M. Laterza (Germany),

A. Lowry (Usa),

K-D. Sievert (Germany),

A. Sultan (U.K.)

CONTENTS

PREFACE

A. THE OVERACTIVE BLADDER

I. INTRODUCTION

II. MECHANISMS UNDERLYING INCREASED AFFERENT ACTIVITY

III. MECHANISMS INVOLVED IN ABNORMAL HANDLING OF THE AFFERENT SIGNALS IN THE BRAIN

B. PREGNANCY, CHILDBIRTH AND THE PELVIC FLOOR

I. DAMAGE TO FUNCTIONS SUSTAINED BY THE PELVIC FLOOR

II. EFFECT OF PREGNANCY ON PELVIC FLOOR FUNCTION

III. PATHOPHYSIOLOGICAL MECHANISM OF BIRTH INJURY TO THE PELVIC FLOOR

IV. PERINEAL TRAUMA

V. CONCLUSION AND RECOMMENDATION

C. PATHOPHYSIOLOGY OF STRESS INCONTINENCE IN WOMEN: URETHRAL STRUCTURE, SUPPORT AND FUNCTION

I. THE FEMALE UROGENITAL DIAPHRAGM: URETHRAL SPHINCTER LOCATION

II. EFFECT OF CHILDBIRTH, VAGINAL PROLAPSE AND URETHRAL POSITION ON URINARY CONTINENCE

III. EMERGING CONCEPTS OF URETHRA WEAKNESS AND ISD

IV. HYPERMOBILITY VS. ISD: FROM DICHOTOMY TO CONTINUUM

V. CONCLUSIONS

D. PELVIC ORGAN PROLAPSE

I. PATHOPHYSIOLOGY OF PELVIC ORGAN PROLAPSE

II. CONCLUSION AND RECOMMENDATIONS

E. PATHOPHYSIOLOGY OF FAECAL INCONTINENCE

I. STRUCTURE AND FUNCTION OF THE ANORECTUM

II. CONTINENCE MECHANISM

II. CONTINENCE MECHANISM

III.DEVELOPMENT OF INCONTINENCE

IV. RISK FACTORS FOR FECAL INCONTINENCE

V. SUMMARY AND RESEARCH RECOMMENDATIONS

F. CHILDBIRTH AND FAECAL INCONTINENCE

I. NEUROGENIC TRAUMA

II. MECHANICAL TRAUMA

III. INSTRUMENTAL VAGINAL DELIVERY

IV. EPISIOTOMY

V. DELIVERY TECHNIQUES

VI. TRAINING

VII. IRRITABLE BOWEL SYNDROME (IBS)

VIII. CONCLUSIONS AND RECOMMENDATIONS

G. PATHOPHYSIOLOGY OF INCONTINENCE IN MEN

I. CONTINENCE MECHANISM IN THE MALE

II. INCONTINENCE ASSOCIATED WITH BPH AND ITS TREATMENT

III. CONTINENCE ASSOCIATED WITH RADICAL PROSTATECTOMY

IV. INCONTINENCE RELATED TO RADIATION THERAPY FOR PROSTATE CANCER

V. CONCLUSIONS

H. CAUSE OF TRANSIENT INCONTINENCE IN OLDER ADULTS

I. URINARY INCONTINENCE

II. FAECAL INCONTINENCE

III. SUMMARY

IV. RECOMMENDATIONS

V. RESEARCH PRIORITIES

LIST OF ABBREVIATIONS

REFERENCES

Pathophysiology of Urinary Incontinence, Faecal Incontinence and Pelvic Organ Prolapse

H. Koelbl
Ty. Igawa, S. Salvatore, R.M. Laterza,
A. Lowry, K-D Sievert, A. Sultan

PREFACE

For this 5th International Consultation on Incontinence, the Committee on Pathophysiology has considered the causes of pelvic organ prolapse and urinary and faecal incontinence. Knowledge has increased in the recent years about childbirth and pregnancy, leading to urinary and faecal incontinence.

Special problems of the elderly have also been included for this ICI. We have also been 2asked to consider pathophysiological mechanisms underlying pelvic organ prolapse. These three areas (urinary incontinence, pelvic organ prolapse and faecal incontinence) are closely interconnected by virtue of similar location within the body. In the case of women, childbirth and pregnancy may contribute to one or all of these conditions. Yet there are also neurological factors, and gender specific factors which must be considered in the evaluation of any given patient. Thus, we have tried to provide a balanced overview of the subject, keeping in mind both the common and the distinct qualities of the various conditions, while organising them in a logical, narrative manner that make any one section of the chapter easy to read.

In the area of women's stress incontinence, intrinsic urethral function continues to receive increased attention. As newer pharmacological agents to provide neural stimulation of the striated sphincter appear, and the limits of vaginal suspensory operations for correction of urethral dysfunction are reported, considerations of pathophysiology have shifted from the 50 year old paradigm regarding urethral mobility associated with vaginal prolapse in the genesis of incontinence. However, these newer directions should be considered against the background of half a century of observation and practical clinical experience. We therefore continue to recommend a balanced approach.

In the area of men's incontinence, the greatest concern remains the problem of sphincter injury following radical pelvic surgery and brachytherapy. While many thousands of procedures are performed annually, our knowledge about sphincter anatomy and function has progressed little. Instead, empirical methods of treatment and hopefully prevention have been advanced to treat affected individuals, and insofar as prosthetic implants remain an effective method of treatment, enthusiasm for further basic research into male sphincter function remains limited. In contrast to this kind of sphincter injury, the causes of incontinence associated with bladder outlet obstruction and prostatic enlargement have been well characterised, and little new knowledge has appeared in recent years.

A. THE OVERACTIVE BLADDER

I. INTRODUCTION

The International Continence Society defines urgency as "the complaint of a sudden compelling desire to pass urine, which is difficult to defer" [1]. The "overactive bladder" (OAB) is a symptom syndrome which is defined by the presence of urgency, with or without urgency incontinence, but usually with frequency and nocturia in the absence of infection or other obvious pathology [1]. Therefore, urgency is the pivotal symptom of the OAB syndrome. A better understanding of the genesis of urgency and its relationship to other aspects of bladder function is required to unravel the pathophysiology of OAB and to develop more effective treatments [2].

OAB symptoms are suggestive of urodynamically demonstrable detrusor overactivity (DO; involuntary detrusor contractions) during the filling phase which may be spontaneous or provoked [1]. However, OAB is not interchangeable with DO regardless of whether they are associated with reported urgency. Only about half of all patients with DO experience

urgency [3], whereas among patients with urgency 44–69% exhibit DO during cystometric studies [4-7].

The definition of urgency as a complaint implies that it can only be measured in cognitively intact patients [2, 8]. Quantifiable and objective demonstration of urgency is difficult, and thus surrogate measures are often used as outcome measures in OAB, leading to inconsistency between clinical trials. Urgency is a pathological sensation and does not necessarily involve the same mechanisms as those underlying the physiologic desire to void upon bladder filling. Therefore, comparisons between urge in healthy people and urgency in patients may help our understanding of the mechanisms involved in the latter but, in fact, may be misleading [8].

The emphasis on urgency, rather than DO, as the defining element of OAB gives the condition a subjective foundation which renders derivation of basic science insights challenging. The subjective nature of urgency makes development of animal models impossible. Despite these limitations, most studies on mechanisms related to urgency/OAB have employed the use of isolated tissues and experimental animals. Non-voiding contraction remains the most frequently used surrogate parameter in such experimetal animal studies [8]. The pathophysiology of the OAB syndrome and DO is still incompletely known, but most probably multifactorial. Against the background mentioned above, this section focuses on pathophysiology of OAB and reviews studies that have provided insight into the mechanisms underlying OAB symptoms and DO.

DO may be further characterised as neurogenic when there is a relevant neurological condition. The dependence of lower urinary tract (LUT) functions on complex central neural networks makes these functions susceptible to a variety of neurological disorders. Non-neurogenic aetiologies may be related to outflow obstruction, aging and female anatomical incontinence, but most cases are idiopathic. There may be two possible origins of OAB symptoms; 1) decreased capacity to handle the afferent signals in the brain, and 2) abnormally increased afferent signals from the bladder and /or urethra (**Figure 1**).

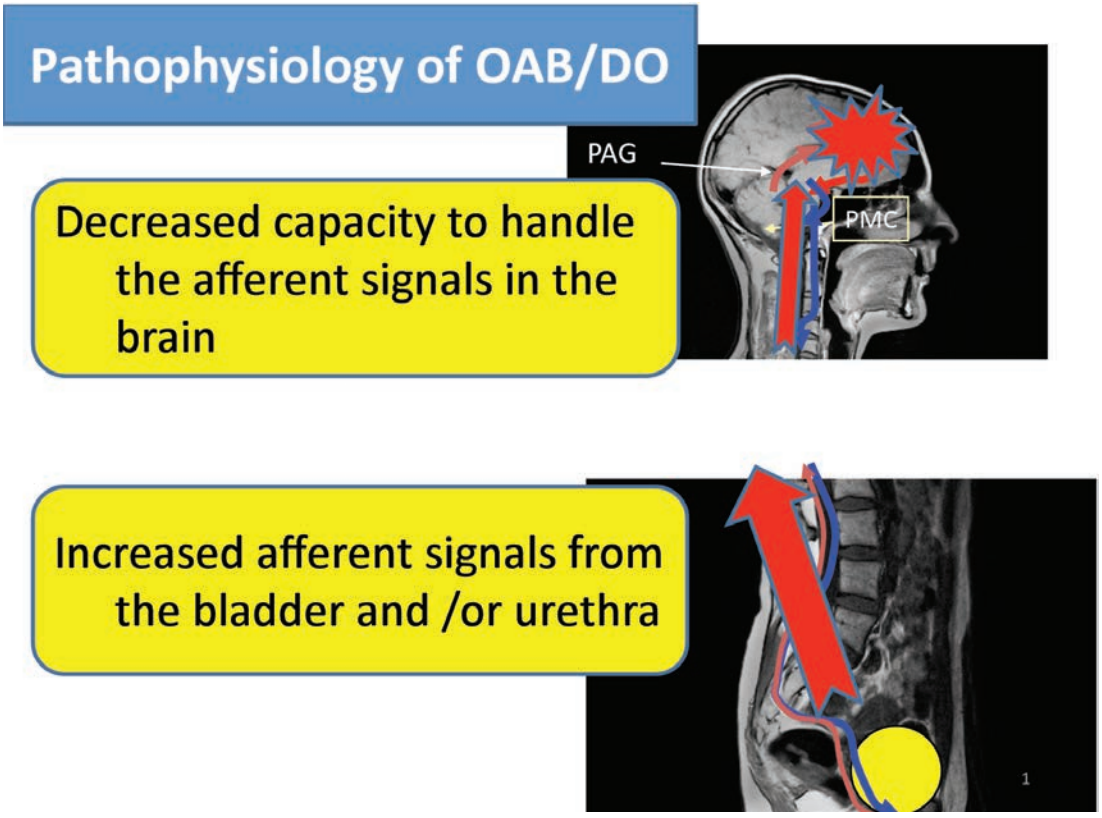


Figure 1. Two possible origins of OAB symptoms; 1) decreased capacity to handle the afferent signals in the brain, and 2) abnormally increased afferent signals from the bladder and /or urethra.

II. MECHANISMS UNDERLYING INCREASED AFFERENT ACTIVITY

Two theories probably contribute in varying proportion to the complex mechanisms underlying the genesis of DO and the associated storage symptoms comprising OAB, have been put forward (**Figure 2**):

- The urothelium-based hypothesis: changes in urothelial receptor function and neurotransmitter release as well as in the sensitivity and coupling of the suburothelial interstitial cell network lead to enhancement of involuntary contractions [9, 10].
- The myogenic hypothesis: changes to the excitability and coupling of smooth muscle cells with other myocytes or interstitial cells lead to the generation of uninhibited contractions [11, 12].

1. THE UROTHELIUM-BASED HYPOTHESIS

There is increasing evidence that urothelial cells play an important role in modulation of bladder activity by responding to local chemical and mechanical stimuli and then sending chemical signals to bladder afferent nerves. It has been shown that urothelial cells express various "sensor molecules" such as receptors of bradykinin, neurotrophins, purines (P2X and P2Y), norepinephrine (NE) (α and β), ACh (nicotinic and muscarinic), epithelial Na + channels (ENaC), and a number of transient receptor potential (TRP) channels. These sensor molecules respond to mechanical as well as chemical stimuli and in turn release chemicals such as ATP, prostaglandins (PG), nerve growth factor (NGF), ACh, and NO. These agents are known to have excitatory or inhibitory actions on afferent nerves, which are located close to or in the urothelium (**Figure 3**) [10].

The urothelium interacts closely with the underlying suburothelial layer, in particular the interstitial cell network contained within it, so that the whole structure can be regarded as a functional unit [9]. The suburothelium is an area composed of nerves, blood vessels, and connective tissue in intimate contact with the urothelium. Recently, the roles of the urothelium and suburothelial myofibroblasts in afferent activation have become the focus of intense interest. The C-fibre afferents generally have endings in the suburothelial layer of the bladder wall, but in some cases, they also penetrate the urothelium [13].

ATP was the first neurotransmitter demonstrated to be released directly from the urothelium [14]. Non-vesicular ATP release is evoked by chemical stimuli or by stretch proportional to the extent of bladder distension [15-19]. Both P2X and P2Y purinergic receptor subtypes have been identified in the bladder urothelium. It is now thought that these may respond to urothelial-derived adenosine triphosphate (ATP) release in autocrine and paracrine signalling [15, 16, 20-23]. By acting on structures such as nerves [24] and interstitial cells in the suburothelial space, it is thought to trigger the underlying afferent signalling bladder fullness and pain and possibly even to activate the micturition reflex [25].

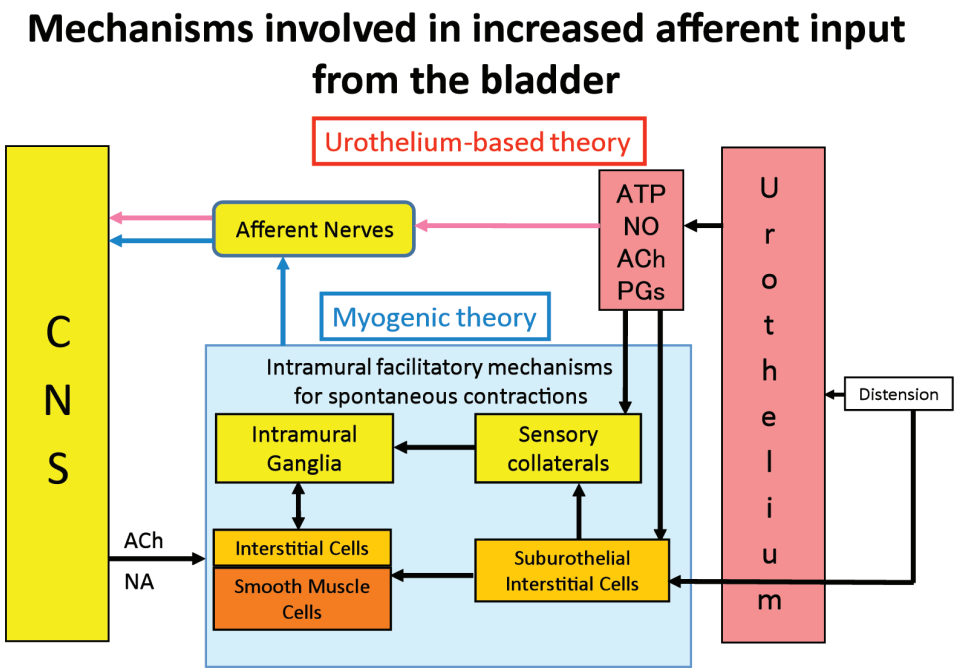


Figure 2. Mechanisms involved in increased afferent input from the bladder: the urothelium-based and myogenic theories

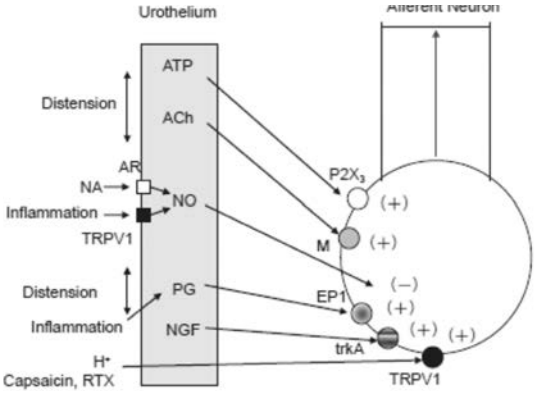


Figure 3. The urothelial afferent transduction system (modified from Yoshida M et al. 2010 [10])

After successful treatment with botulinum toxin injection, a reduced immunoreactivity correlated well with a reduction in urgency [26]. Pathologically increased amounts of urothelially released ATP in rats with spinal cord injury can be reduced on treatment with botulinum toxin [27]. Sugaya et al [28] recently reported that improvement of OAB symptoms with antimuscarinic treatment was significantly correlated with a decrease in urinary ATP level in female patients with OAB.

The presence and localisation of muscarinic receptor protein and mRNA in the human [29-34] and mouse [35] urothelium have been studied. All five muscarinic subtypes are expressed throughout the urothelial layers with a specific localisation of the M2 subtype to the umbrella cells and M1 to the basal layer, with M3 receptors more generally distributed. Release of ACh from human urothelial and suburothelial sites increases with age, as well as during bladder stretch, and represents a functional, non-neuronal, alternative cholinergic system [31]. At therapeutic doses, antimuscarinics act mainly during the filling phase and exert little effect on detrusor contraction during emptying [36-38]. This lends support to the suggestion that urothelial muscarinic receptors might be involved in the generation of afferent impulses.

Urothelial cells express both α and β adrenoceptor subtypes, stimulation of which has been shown to trigger the release of ATP and nitric oxide (NO), respectively [39, 40]. Stimulation of urothelial β adrenoceptors also triggers an urothelially-derived inhibitory factor [41]. Catecholamines could be released from nerves adjacent to the urothelium; however, neither a role for catecholamines nor an altered adrenoceptor profile has yet been shown in pathological conditions.

In addition to the changes in ACh-release mentioned above, several specific alterations in urothelial function and ultrastructure have been demonstrated in OAB. Expression of the mechanosensitive ENaC is increased significantly in human obstructed bladders in comparison to unobstructed controls and correlates significantly with storage symptom scores [42]. It is possible that increased expression of mechanosensitive channels such as ENaC in the urothelium enhances substance release upon bladder stretch. Levels of PG, which is locally synthesised in bladder muscle and mucosa, and levels of NGF are increased in subjects with OAB in comparison to controls; and in symptomatic patients, levels of PGE 2 are positively correlated with voiding behaviour and maximum cystometric capacity [43, 44]. Bladder biopsies from patients with both idiopathic detrusor overactivity (IDO) [45] and neurogenic detrusor overactivity (NDO) [46] have shown increased urothelial TRPV1 expression. This may be in accordance with the fact that intravesical vanilloids (resineferatoxin) have been shown to improve OAB symptoms in patients with idiopathic detrusor overactivity as well as with hypersensitivity disorders [47, 48].

This sensory process is more complex than originally thought. A suburothelial layer of myofibroblasts (interstitial cells) that or a functional syncitium through connexin 43 gap junction can be identified in the bladder wall [49, 50]. These myofibroblasts make close apposition to unmyelinated nerves (afferent C-fibre nerves) [51]. The studies investigating human myofibroblasts show that the cells can respond to ATP by generating an intracellular Ca2+ transient, which is mediated by a P2Y receptor, most likely including a P2Y6 [52]. On the basis of these observations, it has been hypothesised that the close relation between nerves and myofibroblasts allows for an amplification of the afferent system in its response to stimulatory mediators such as ATP.

Overall, up-regulation of urothelial function and increased release of various chemical mediators and known neurotransmitters may influence afferent nerve activity to generate OAB symptoms, although the precise mechanism by which these processes interact with neural tissue to achieve signal transduction remains to be clarified.

2. MYOGENIC HYPOTHESIS

Brading and Turner [11, 12] have emphasised that myogenic changes (regardless of aetiology) may contribute to the pathophysiology of idiopathic detrusor overactivity. On the basis of observation that denervation is consistently found in detrusor biopsy specimens from patients with various forms of non-neurogenic detrusor overactivity, it has been proposed that partial denervation of the detrusor may alter the properties of smooth muscle, leading to increased excitability and increased coupling between cells [53]. Thus, local contraction (activity) that occurs somewhere in the detrusor will spread throughout the bladder wall, resulting in coordinated myogenic contraction of the whole bladder. In addition, this local contraction in the bladder wall has been shown to generate afferent discharge [54, 55]. Recently,

localised bladder activity was assessed by the micromotion detection method, demonstrating that women with increased bladder sensation on filling cystometry had a significantly higher prevalence of localised activity than the control group [56]. This observation suggests that localized distortion of the bladder wall simulates afferent activity, which would precipitate a feeling of urgency and detrusor overactivity [57, 58] (**Figure 4**).

Although the relationships between intercellular communication and spontaneous mechanical activity and the degree of involvement of different types of connexins (Cxs) need further study, Cx45 and Cx43 appear to be the most prominent Cxs expressed in human detrusor smooth muscle tissue and cultured cells. Observations in tissue biopsies from patients with neurogenic DO and urgency symptoms clearly demonstrated an increase in the presence of Cx43-derived gap junction channels in detrusor muscle [59].

In addition, another population of cells in the bladder known as interstitial cells has been proposed for a pacemaking role in spontaneous activity of the bladder [60, 61]. Because it has been reported that the number of interstitial cells is increased in a guinea-pig model of BOO [62] and that c-kit tyrosine kinase inhibitors, which inhibit interstitial cell activity, decreased the amplitude of spontaneous contractions in the guinea-pig and human bladder [63, 64], interstitial cells may also be involved in the emergence of detrusor overactivity because of enhanced autonomous detrusor muscle activity.

3. OTHER LOCAL FACTORS

a) Ischaemia

Ischaemia/reperfusion has been proposed as a pathophysiological factor of OAB/DO. Recent studies suggest that arterial obstructive disease, such as atherosclerosis, may cause OAB in both men and women via ischaemia, hypoxia and oxidative stress in the bladder [65-68]. DO associated mitochondrial stress may have a central role in epithelial damage, smooth muscle cell injury and neurodegeneration. Superoxide dismutase and aldose reductase up-regulation in the overactive bladder imply intrinsic defensive reaction against free radicals that apparently fails to prevent oxidative damage and neurodegeneration [67]. HIF, TGF-β, VEGF and NGF up-regulation in the ischaemic bladder was accompanied by the loss of mitochondrial structural integrity, fibrosis, and the degeneration of microvasculature and nerve fibres [69]. These observations may suggest the role of ischaemia in the overactive bladder with impaired contraction, as reported in elderly patients without obstruction. Ischaemia may be a key factor in aging associated LUTS.

b) Inflammation

Recent studies have noted signs of inflammation in bladder biopsy specimens from OAB patients [69, 70]. Increases in cytokines, chemokines, and growth factors have been reported in the urine of OAB patients [71]. Consistent association of increasing serum CRP levels and OAB has been also demonstrated [72, 73]. All together, these results support the hypothesis for the role of inflammation in the development of OAB.

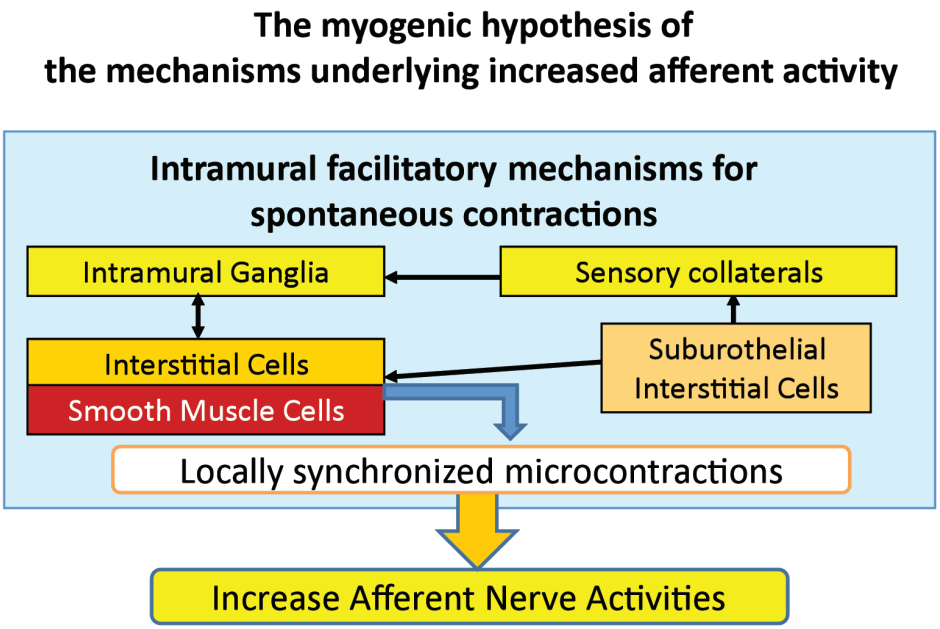


Figure 4. The myogenic hypothesis of the mechanisms involved in increased afferent input from the bladder

III. MECHANISMS INVOLVED IN ABNORMAL HANDLING OF THE AFFERENT SIGNALS IN THE BRAIN

The 'neurogenic hypothesis' suggests that damage to the central inhibitory pathways, or sensitisation of afferent nerves, leads to the unmasking of primitive voiding reflexes which trigger overactive detrusor contraction [74, 75]. Plasticity both in the peripheral innervation and within the CNS may have a pathophysiological role in DO [76], and increased release of nerve growth factor has been reported, which may alter the neural regulation of detrusor muscle [77-79]. Peripherally, neurological diseases might cause a sensitisation of C fibres that are silent under normal circumstances, thereby leading to the emergence of a C-fibre-mediated reflex.

1. NEUROGENIC DETRUSOR OVERACTIVITY

Recent advances in functional brain imaging have made it possible to directly study the supraspinal control system operating during bladder filling. Comparisons between brain response in subjects with normal bladder function and those with OAB may give us a neural correlate of urgency and possible origins of OAB symptoms [80-82].

While many neurological diseases predispose patients to neurogenic detrusor overactivity (NDO), the only populations that have been systematically studied are adults with multiple sclerosis, adults with spinal cord injury (SCI) and children and young adults with myelodysplasia [73]. As a sensation it can be affected by neurological disorders and may, therefore, be perceived differently in patients with neurological lesions.

a) Suprapontine lesions

It is generally accepted that suprapontine lesions such as cerebrovascular disease and Parkinson's disease produce DO. The patient with a suprapontine lesion loses voluntary inhibition of micturition, which corresponds to uninhibited overactive bladder according to a classification by Fall et al. [83, 84] .

Higher brain centres provide an additional level of urinary control, which is responsible for conscious sensation, volition and emotional response. Key higher centres include the prefrontal cortex, insular cortex and anterior cingulate gyrus, and functional brain imaging has shown changes in higher CNS activity in OAB [75, 80, 81]. Although such observations have been made infrequently, they do point to some key areas for consideration. For example, the participation of several brain areas in urinary control may explain why brain diseases and senile cerebral atrophy are risk factors for lower urinary tract dysfunction [75]. Variation in observations between individuals implicates a diversity of processes in the mechanisms that underlie OAB, although these are expressed clinically in the common manifestation of OAB. The increased activity observed in certain regions of the brain in patients with OAB may actually be compensatory, to counteract urgency, rather than being responsible for the symptom [75]. This confounds interpretation of function, and there are many questions that still need to be answered.

Brain transection studies in animals with an intact neuroaxis showed that suprapontine areas generally exert a tonic inhibitory influence on the pontine micturition centre (PMC) [85, 86]. In humans, the cerebral cortex (medial frontal lobes) and the basal ganglia are thought to suppress the micturition reflex. Thus, damage to the brain induces DO by reducing suprapontine inhibition.

1. Stroke (Cerebral infarction)

The mechanism of DO induced by cerebral infarction or Parkinson's disease has been further studied using animal models [87, 88]. In the central nervous system, a glutamatergic pathway is known to play a role in both excitatory and inhibitory regulation of micturition [88-90]. It has been demonstrated that in the rat cerebral infarction model, bladder overactivity is mediated by NMDA glutamatergic and D2 dopaminergic excitatory mechanisms [88], suggesting that cerebral infarction may alter a balance between the facilitatory and inhibitory mechanism that results in up-regulation of an excitatory pathway and down-regulation of a tonic inhibitory pathway.

2. Parkinson's disease

Parkinson's disease (PD) is characterised by the degeneration of dopamine-producing cells in the substantia nigra of the midbrain and Lowy body formation. PD is the most common cause of parkisonnism which is the neurological syndrome bearing the hallmarks, hypokinaesia and postural instability. Urgency occurs in 33-54% of patients with PD. Neurogenic DO was seen in 45-93% of PD patients [91]. The most widely accepted theory of pathophysiology of DO in PD is that basal ganglia inhibits the micturion reflex in the normal situation via D1 receptors, and that cell depretion in the substantia nigra in PD results in loss of D1-mediated inhibition and consequently DO [91, 92]. The absence of dopaminergic tone via D1 receptors may cause a dysfunction in GABA regulation in the periaqueductal gray (PAG) and DO [93]. Kitta et al [94] demonstrated an increased activation in the PAG, supplementary motor area, cerebellar vermis, insula, putamen and thalamus during DO in male patients with PD. Compared with previous results in healthy volunteers the periaqueductal gray, insula, putamen and thalamus were common activation sites responding to bladder filling, while the pons was not activated during DO, suggesting alteration in brain activation sites in response to bladder filling may be related to the pathophysiology of DO in patients with PD.

b) Spinal cord lesions

A spinal cord lesion above the lumbosacral level eliminates voluntary and supraspinal control of micturition,

leading to DO mediated by spinal reflex pathways [85]. Disruption below the level of the pons leads to unsustained and uncoordinated detrusor contractions often associated with uncoordinated sphincter overactivity (detrusor-sphincter dyssynergia, DSD). Impairment or loss of bladder sensation is a typical feature.

Electrophysiological studies of the effect of capsaicin on voiding reflexes have shown that the afferent limb of the micturition reflex in chronic spinal cats, consists of unmyelinated C-fibre afferents, whereas in normal cats it consists of myelinated A-delta afferents [85, 95, 96]. Since C-fibre bladder afferents in the cat do not usually respond to bladder distension [97], a considerable reorganisation of reflex connections takes place in the spinal cord following the interruption of descending pathways from the brain. In humans with spinal cord lesions, NDO is likely to be mediated by capsaicin-sensitive C-fibre afferents. Clinical experience with capsaicin supports the role of these C-fibre afferents in the pathophysiology of NDO. Capsaicin has been used for the treatment of NDO in patients with spinal cord injury or multiple sclerosis. When administered intravesically, capsaicin increases bladder capacity, reduces micturition contraction pressure, decreases autonomic dysreflexia and reduces the frequency of incontinence [98-100]. More recently, resineferatoxin, an ultra-potent analogue of capsaicin, has also been used [101-103].

Increased TRPV1, P2X3 and pan-neuronal marker (PGP9.5) staining in suburothelial nerves and increased TRPV1 staining in the basal layer of the urothelium have been observed in patients with neurogenic bladder due to SCI and multiple sclerosis [26]. Treatment of NDO patients with intravesical capsaicin or resiniferatoxin reduces the density of TRPV1, P2X3 and PGP9.5 immunoreactive nerve fibres and urothelial TRPV1 immunoreactivity in those patients exhibiting symptomatic improvement [104]. Injections into the bladder wall of botulinum neurotoxin type A (BoNT/A), an agent that blocks the release of neurotransmitters from afferent and efferent nerves, and from urothelial cells, also reduces NDO and the density of TRPV1- and P2X3-immunoreactive nerves [105]. These results indicate that an abnormality of the C-fibre afferent innervation contributes to NDO.

Upregulation of TRPA1 protein and mRNA levels, in bladder and in dorsal root ganglion (DRG; L6-S1) has been reported in rats with SCI. Moreover, HC-030031 (TRPA1 antagonist) treatment decreased the number and the amplitude of DO, suggesting that the TRPA1 activation and upregulation seem to exert an important role in DO following SCI [106].

Following SCI changes in the electrophysiological properties of bladder afferent neurons have also been observed consisting in multiple action potentials (tonic firing) in response to long depolarizing current pulses [107]. In addition, A-type K+ channels are suppressed in parallel with an increased expression of TTX-sensitive Na+ currents, thereby increasing excitability of C-fibre bladder afferent neurons[108]. These electrophysiological changes contribute to the emergence of the C-fibre-mediated spinal micturition reflex following SCI.

B. PREGNANCY, CHILDBIRTH AND THE PELVIC FLOOR

Despite the great achievements made in modern obstetric practice in developed countries during the last 100 years, delivery remains the most stressful and dangerous event the female pelvic diaphragm is submitted to during a woman's lifespan.

Reduction in both perinatal and maternal mortality rates in recent decades has allowed us to focus increasingly on maternal morbidity and the long-term sequelae of childbirth. Due to improved investigative techniques available over the past decade, the incidence and mechanisms of obstetric injury to the pelvic floor have come under scrutiny.

However, the controversial debate on whether and how pregnancy and vaginal delivery are responsible for pelvic floor damage is still wide open.

During pregnancy, muscular, connective and nervous pelvic structures are already subjected to anatomical, morphological, functional and hormonal changes. During vaginal delivery, the pelvic floor undergoes an enormous amount of stretching to allow the passage of the newborn through it.

During the pregnancy and just after delivery, the functions sustained by the pelvic floor (urinary and faecal continence, pelvic organ containment and sexual function) often begin to fail. Evident or hidden injuries of the pelvic floor may manifest themselves through symptoms of urinary and faecal incontinence, prolapse or sexual dysfunction, with a considerable impact on quality of life.

If several mechanisms of birth trauma have already been investigated, a lot needs to be understood regarding the role of pregnancy on the pelvic floor.

The growing knowledge of the consequences of childbirth and pregnancy on the pelvic floor, offers the chance to develop prevention and treatment strategies. It is important that contributing obstetric factors are identified and their occurrence minimised, in order to focus efforts on preventable risk factors.

I. DAMAGE TO FUNCTIONS SUSTAINED BY THE PELVIC FLOOR

1. POSTPARTUM URINARY INCONTINENCE

A recent systematic review of 33 studies reported a 33% prevalence of any type postpartum urinary incontinence (UI) in the first 3 months postpartum, with a prevalence of weekly and daily incontinence of 12% and 3% respectively. The prevalence in the

vaginal delivery group (31%) was double that of the caesarean section group (15%). Long-term studies in the first year postpartum showed small changes in prevalence over time [109]. Cesarean section seems to decrease the risk of postpartum UI [110, 111], but its protective effect seems to diminish over time and disappears after multiple deliveries [111, 112].

In a recent cohort study extracted by the national Swedish Medical Birth Registry between 1973 and 1982, two groups were identified: 30,880 women who had their first and all subsequent deliveries by cesarean vs. an age-matched sample of 60,122 women who delivered vaginally only. Stress urinary incontinence (SUI) surgery was observed in 0.4% of the cesarean group and 1.2% of the vaginal group (follow-up time 26.9 years), and the risk of SUI is estimated to be 2.9 times higher after vaginal delivery compared with women after cesarean section. Among women with vaginal deliveries, rates of SUI surgery increased with the number of births, whereas in the cesarean delivery cohort it slightly decreased with a higher number of births. Compared with cesarean delivery, the risk of SUI was more than doubled for vaginal delivery with vacuum extraction and tripled for a vaginal non-instrumental delivery, but this lower risk for a vacuum extraction delivery has been in part explained by an overall lower birth rate in this subset of patients. After vaginal delivery, the incidence rates for SUI surgery steadily increased, reaching a peak close to 3 decades after the first delivery. For cesarean delivery, the incidence of SUI increased more slowly and started to diverge from the curve for vaginal delivery very early during follow-up (**Figure 5 A**) [113].

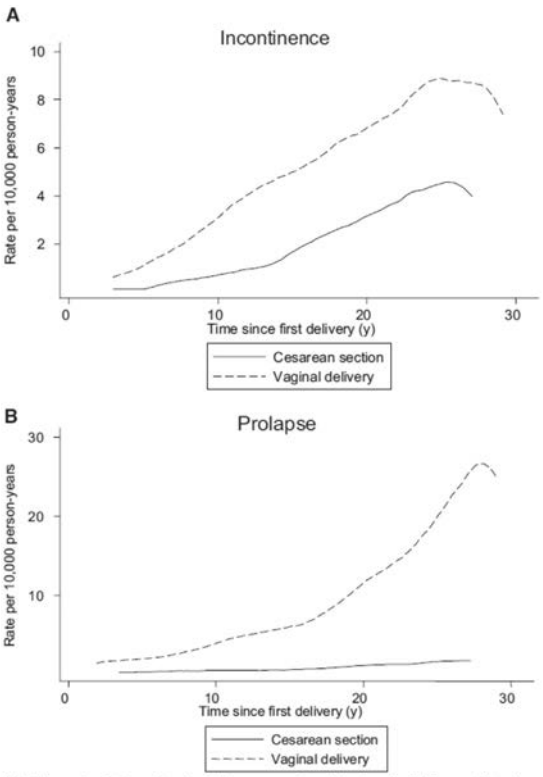
After the first delivery, women who delivered vaginally seem to have at least a two-fold greater risk of urinary incontinence than those who delivered by cesarean. However, data for the rates of incontinence after elective and emergency cesarean section are mixed; therefore meaning that the information as to whether cesarean done before labour confers greater protection than cesarean done after labour is lacking.

To understand the true impact of cesarean delivery on urinary incontinence, future studies must compare incontinence by planned (not actual) delivery modes, consider a woman's entire reproductive career, focus on leakage severe enough to be problematic, consider other bladder symptoms as well as incontinence, and take into account other risk factors, particularly antepartum urinary incontinence [114].

2. ANAL INCONTINENCE

De-novo anal incontinence symptoms after childbirth are reported as up to 26-38% between 6 weeks-6 months postpartum [115-120].

In a population-based survey estimating the postpartum incidence of faecal incontinence, Guise et al. [116] reported that 29% of 8,774 women reported faecal incontinence (defined as recurring episodes of involuntary loss of stool or flatus since delivery) within 3-6 months postpartum: almost half (46%) of them reported incontinence of stool, and 38% reported incontinence of flatus only. Approximately 46% reported the onset of incontinence after the delivery of their first child. Higher body mass index, longer pushing, forceps-assisted delivery, third or fourth-degree tears and smoking were associated with severe faecal incontinence. The authors conclude that in this population-based study, more than one in four women reported faecal incontinence within 6 months of childbirth, with almost half reporting the onset of symptoms after delivery of their first child. Four in ten women reported loss of flatus or stool during intercourse. Given the burden of this condition, both in number and social impact, coupled with the hesitancy of women in initiating this conversation, providers should ask women about symptoms of faecal incontinence during postpartum examinations. Additionally, these data suggest that there may be a benefit to extending postpartum follow-up visits beyond the typical 6-8 weeks to provide surveillance for potential incontinence. LEVEL OF EVIDENCE: II.



A, Incidence rates of stress urinary incontinence surgery in relation to mode of delivery and time since first childbirth; **B**, Incidence rates of pelvic organ prolapse surgery in relation to mode of delivery and time since first childbirth.

Figure 5 [113] Incidence rates in relation to mode of delivery and time since first childbirth
From: Leijonhufvud et al. Incontinence and prolapse surgery after childbirth. Am J Obstet Gynecol 2011[113]

In comparison to cesarean section, vaginal delivery seems to be associated with an increased risk of anal incontinence. In a population-based study, Guise et al. [115], reported that vaginal delivery has a greater risk of FI compared to cesarean (OR 1.45; 95%CI: 1.29-1.64) 3-6 months postpartum. However, a vaginal delivery without a tear or instrument assistance did not create a higher risk of FI than the risk with cesarean delivery. Being overweight (body mass index >/=30 kg/m(2)), pushing for greater than 2 h, and constipation were independently associated with postpartum FI ($p < 0.05$) regardless of route of delivery.

A self-administered survey of faecal incontinence symptoms and delivery events administered to 50 women at 6 weeks postpartum, showed that vaginal delivery was associated with an increased risk of any faecal incontinence symptom in comparison with cesarean section (43% vs. 20%) [117].

3. PELVIC ORGAN PROLAPSE

The occurrence rate of pelvic organ prolapse stage ≥2 in the first 3-6 months postpartum has been described in literature between 18.1-56% [121-123].

In a cross-sectional study of 382 primigravid women, pelvic organ support was explored 6 months postpartum: POP-Q stage ≥II was present in 7.7, 18.1 and 29.0% of women who delivered by cesarean section, spontaneous and instrumental vaginal delivery, respectively. Spontaneous vaginal delivery increased the risk by more than three times (OR 3.19) while instrumental vaginal delivery increased it more than five-fold (OR 5.52) in comparison with cesarean section. Instrument-assisted delivery did not increase the risk of prolapse in women who delivered vaginally. The authors concluded that cesarean section is associated with a lower prevalence of pelvic organ prolapse after delivery and instrument assisted delivery is not associated with an increased risk of postpartum prolapse among women who delivered vaginally [121].

In the cohort study extracted by the nationwide Swedish Medical Birth Registry [113], POP surgery was recorded in 2.2% of vaginal deliveries and 0.2% of cesarean sections (follow-up time 25.9 years). Among women who had only had vaginal deliveries, rates of POP surgery increased with number of deliveries. In the cesarean delivery cohort, rates of POP surgery slightly decreased with increasing parity. Compared with a cesarean delivery, the risk of POP surgery was increased nine-fold both after non-instrumental vaginal delivery and after vacuum extraction, whereas among women with forceps delivery a twenty-fold increase in risk was observed. The incidence rate of POP in women with cesarean deliveries showed very little variation over time, but started to diverge more notably from the vaginal delivery cohort 10 years after the first birth (**Figure 5B**).

The association between cesarean section and POP was investigated by Larsson et al. [124]: the Swedish Hospital Discharge Registry was used to identify women with an inpatient diagnosis of pelvic organ prolapse, and the data were linked to the Swedish Medical Birth Registry. A total of 1.4 million women were investigated. A strong and statistically significant association between cesarean section and pelvic organ prolapse was found (Adjusted OR 0.18 [95% CI: 0.16-0.20] and overall hazard ratio=0.20 [95% CI: 0.18-0.22]). The authors concluded that cesarean section is associated with a lower risk of pelvic organ prolapse than vaginal delivery.

The incidence rate of urinary incontinence (UI) and anal incontinence during pregnancy in previously continent women has been reported as 39.1% and 10.3% respectively. Age, baseline body mass index, and family history of UI were significantly associated with the occurrence of UI during pregnancy, while age and excess weight gain during pregnancy were associated with the occurrence of anal incontinence during pregnancy. The identified risk factors for both incontinences postpartum were incontinence during pregnancy and vaginal delivery. LEVEL OF EVIDENCE II [125].

About half of all women develop transient urinary incontinence during pregnancy [114]; SUI in pregnancy was a significant predictor for postpartum incontinence. The weight of the women and duration of their labour were also significantly associated with the development of SUI postpartum [126].

Women with incontinence before pregnancy were nearly three times more likely to have postpartum incontinence [127].

Among 272 eligible women attending follow-up at 2 years postpartum, 26 (9.5%) women reported persistent SUI since pregnancy. A higher BMI in pregnant women at term was recognised as an independent risk factor for the persistence of SUI from pregnancy to 2 years post partum [128].

Fear of birth is a frequent cause of cesareans demanded by the patient [129, 130]. A recent cross-sectional study based on the Norwegian Mother and Child Cohort Study (n=58.881), reported that 6% of the sample preferred cesarean over vaginal delivery in week 30 of pregnancy; 16% reported “fear of giving birth” as the reason for cesarean preference [131]. A general fear of pelvic floor trauma was cited as the most common reason for this choice [132]. Despite being based on incomplete prognostic data, this feeling may be echoed increasingly among obstetric patients and may lead to an unselected, and even misguided, increase in cesarean delivery rates.

However, so far, there is no evidence from randomised controlled trials, upon which to base any practice recommendations regarding planned cesarean section for non-medical reasons at term. This has been demonstrated by Lavender et al. [133]: their aim was to find out, from randomised trials, the effects on perinatal and maternal morbidity and

mortality, and on maternal psychological morbidity, of planned cesarean delivery versus planned vaginal birth in women with no clear clinical indication for cesarean section. A search of the Cochrane Pregnancy and Childbirth Group's Trials Register (December 2005), MEDLINE (1974 to April 2005), EMBASE (1974 to April 2005), CINAHL (1982 to April 2005) and PsycINFO (1887 to April 2005) was carried out. The selection criteria were the following: comparisons of intention to perform cesarean section and intention for women to give birth vaginally; random allocation to treatment and control groups; adequate allocation concealment; women at term with a single fetus with cephalic presentation and no clear medical indication for cesarean section. No studies were identified that met the inclusion criteria [133].

To our knowledge, scientific data are insufficient to justify an elective cesarean section in order to avoid pelvic floor symptoms in a woman without previous disorders [134], considering that pregnancy itself may be involved in the development of such problems.

A recent systematic review of Cochrane assessed the ability of cesarean delivery (CD), in comparison to vaginal delivery (VD), to preserve anal continence: 21 reports have been found eligible for inclusion, encompassing 31,698 women having had 6,028 CDs and 25,170 VDs, as the index event prior to anal continence assessment. Only one report randomised women (with breech presentation) to CD or VD, but because of extensive cross-over, 52.1% after randomisation, it was analysed along with the other 20 studies as treated, i.e. as a non-randomized trial. Only one of these reports demonstrated a significant benefit of CD in the preservation of anal continence, a report in which the incidence of incontinence was extremely high, 39% in CD and 48% in VD, questioning, relative to other reports, the timing and nature of continence assessment. The authors did not find any difference in continence preservation in women who had an emergency versus elective CD. They concluded that without demonstrable benefit, preservation of anal continence should not be used as a criterion for choosing elective primary CD [135].

Despite the great advances that have been made in many areas of obstetric care, the effect of pregnancy on the morphology and function of the pelvic floor is still mostly unknown. Prospective data assessing the severity of urinary and anal incontinence during pregnancy are scarce.

II. EFFECT OF PREGNANCY ON PELVIC FLOOR FUNCTION

1. EFFECT ON THE COLLAGEN

During pregnancy, hormones affect the biochemical composition of the solid matrix and hydration phases constituting all pelvic floor tissue. Remodelling mechanisms lead to changes in the organisation, orientation, and diameter of the collagen fibres as well as the crimp structure of the collagen fibrils reinforcing each tissue. Such effects can significantly affect the short and long-term viscoelastic properties of the vaginal wall, the pubovisceral muscles, and the perineal body, for example. They will largely determine (a) the extent and rate at which these structures can be stretched by an expulsive force acting cyclically on the fetal head, and (b) the resistance to stretch provided by those structures. The more a tissue exhibits creep behaviour, the further it will stretch under a constant load. And the more it exhibits relaxation behaviour, the more the stress in a tissue will decrease over time when held at a constant length, thereby helping to lower the risk of rupture in the next loading cycle. Were a tissue to exhibit viscoplasticity, it would behave as a solid below a critical level of stress, but above that level, it would flow like a viscous liquid. There is evidence that tensile failure in some soft tissues can be predicted by the product of the stress times the strain extent in the tissue, so mechanisms that lower one or both these variables will reduce the risk of rupture. Pregnancy is known to significantly affect the instantaneous stiffness and relaxation behaviour of vaginal tissues in rats. However, accurate data are lacking for pregnant human pelvic floor tissues, and the effects of pregnancy on injury at any tissue level, and on structural failure, are as yet largely unknown [136].

Changes in collagen may result in greater mobility of the bladder neck resulting in stress incontinence. In a study of 116 primigravidae, perineal ultrasound was used to assess bladder neck mobility. Women with antenatal bladder neck mobility of more than 5mm on linear movement (equivalent to >108° rotation) were found to be at higher risk of developing postpartum stress incontinence. Approximately 50% of this group reported stress incontinence at 3 months postpartum [137].

There may be a group of women at an inherent increased risk of developing incontinence due to abnormalities in collagen [138], as the collagenous component of the connective tissue contributes to structural support of the bladder neck. In pregnancy, the tensile properties of the connective tissue are reduced, with a reduction in total collagen content and increase in glycosaminoglycans [139].

2. NATURAL HISTORY

Distinguishing the time of onset, severity, and persistence of urinary and anal incontinences during and after pregnancy may provide an insight into the natural history of incontinence, and hence in the differences between transient incontinence due to the hormonal and mechanical effects of pregnancy and the damage that may occur as a result of delivery [125].

Solans-Domenech et al. [125] have brought to light the high incidence of urinary incontinence and anal incontinence over the three trimesters of pregnancy, and particularly in the second trimester. In this cohort study, an incidence rate of urinary incontinence

during pregnancy of 39.1% and 10.3% of anal incontinence was found.

Figure 6 shows the evolution of severity of UI by data collection time, as well as the changes in trends between slight and moderate UI, with a tendency for slight to become moderate UI. The correlation between the severity of UI and level of interference in daily living was moderate but statistically significant in all periods of data collection with correlation coefficients of 0.35, 0.13, 0.46, and 0.47 for the first, second, and third trimesters and postpartum, respectively.

Ten percent of women presented anal incontinence at some point during pregnancy: the evolution of the prevalence of anal incontinence in this study cohort is 2.3%, 6.8% and 7.4% in the first, second and third trimesters. The presence of anal incontinence was characterised by loss of flatus in more than 90% of cases and common to all periods LEVEL OF EVIDENCE: II [125].

The prevalence of urinary and anal incontinence in a subgroup African American of pregnant adolescents (age: 14-19 years) in the third trimester, resulted even higher: 44% of patients complained of urinary urgency incontinence and 43% of stress incontinence; 12% complained of faecal and 41% of flatal incontinence [140].

Incontinence during pregnancy has been linked to age [141], body mass index [142], strenuous physical exercise [143] and smoking history [142].

The risk of UI increases in pregnant women aged more than 35 years, in women who are overweight or obese at baseline, and in those with a family history of UI, while the risk of anal incontinence rises with age and excessive weight gain during pregnancy [125]. Weight gain greater than the 50th percentile during weeks 0–15 of pregnancy was weakly associated with a higher incidence of UI at week 30 compared with weight gain less than or equal to the 50th percentile [144].

The recent data regarding the relationship between urinary incontinence during pregnancy and its persistence or worsening condition postpartum are controversial: the results of Solans-Domenech et al. [125] showed that the occurrence of UI and anal incontinence during pregnancy is related to the presence of incontinence in the postpartum period, and vaginal delivery increases the risk of persistent incontinence. On the other hand Wesnes et al [145] conclude that the association between incontinence postpartum and mode of delivery is not substantially influenced by incontinence status in pregnancy and the prediction of a group with high risk of incontinence according to mode of delivery cannot be based on continence status in pregnancy.

3. FAMILIAL PREDISPOSITION

A familial predisposition in the evaluation of the aetiology of urinary incontinence has also been considered, but the results are still controversial. Buchsbaum et al. [146] investigated the role of vaginal delivery and familial factors in the development of urinary incontinence by comparing the prevalence of this condition in nulliparous women and their parous sisters. Among this sample of biological sisters, urinary incontinence was reported by 47.6% of nulliparous women and by 49.7% of parous women (P =0.782). Considering the high concordance in continence status between sister pairs, and considering that the majority of parous women are continent, an underlying familial predisposition toward the development of urinary incontinence may be present. LEVEL OF EVIDENCE II-2.

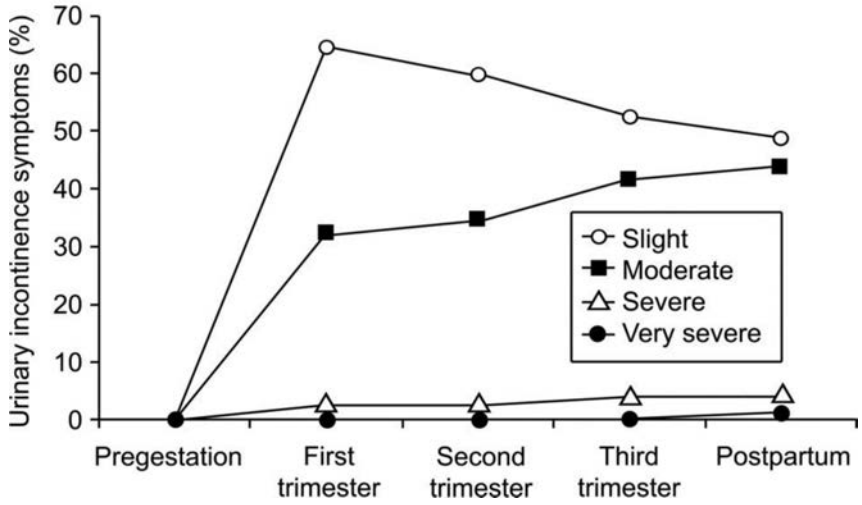


Figure 6. Evolution of the severity of urinary incontinence symptoms by time of data collection. From: Solans-Domenech. Incontinence During Pregnancy and Postpartum. Obstet Gynecol 2010 [125].

A recent article of Nguyen et al. [147], analysed a large population comprising 1530 identical and 234 non-identical female twins (mean age 41.3 years), who answered a specific questionnaire focusing on symptoms of SUI. The two groups were comparable in terms of age, race, parity, BMI, menopausal status, tobacco use, mode of delivery and prior pelvic surgery. The authors demonstrated that environmental factors contributed significantly to the occurrence of SUI (shared environmental factors contribute 77.6% of the variance, unique environmental factors contribute to 20.9% of the variance; p<0.001). The heritability of SUI was not statistically significant for the contribution of the phenotypic variance (1.49%; p=0.46). Additional analyses were performed on the subgroup of women without prior incontinence or prolapse surgery (638 twin pairs) and in the subgroup of twins with "pure stress urinary incontinence" (458 twin pairs): the results in this cohort of patients showed no genetic influence. The authors underscore that environmental factors (in particular obstetric events) play a dominant role in middle-aged women; genetics contributed more toward the development of stress urinary incontinence in elderly women, as reported by Rohr et al. [148]: "nurture" before menopause and "nature" during aging. LEVEL OF EVIDENCE II.

III. PATHOPHYSIOLOGICAL MECHANISM OF BIRTH INJURY TO THE PELVIC FLOOR

Strong epidemiological evidence links vaginal childbirth and the development of postpartum incontinence and prolapse.

There would seem to exist three major mechanisms by which vaginal delivery might contribute to the pelvic floor trauma: a) muscle trauma, b) connective tissue damage, c) nerve injury, d) vascular damage.

1. MUSCLE TRAUMA

The effect of delivery on muscular structure has been widely investigated, either with computer models, MRI and ultrasound. In a three-dimensional computer model Lien et al. [149] predicted levator ani muscle stretch during vaginal birth. Serial magnetic resonance images from a healthy nulliparous 34-year-old woman, and engineering graphics software, were used to construct a structural model of the levator ani muscles along with related passive tissues. The model was used to quantify pelvic floor muscle stretch induced during the second stage of labour as a model in which the fetal head progressively engaged and then stretched the iliococcygeus, pubococcygeus and puborectalis muscles. The largest tissue strain reached a stretch ratio (tissue length under stretch/ original tissue length) of 3.26 in the medial pubococcygeus muscle, the shortest, most medial and ventral levator ani muscle. Regions of the ileococcygeus, pubococcygeus, and puborectalis muscles reached a maximal stretch ratio of 2.73, 2.50, and 2.28, respectively. Tissue stretch ratios were proportional to fetal head size: for example, increasing fetal head diameter by 9% increased medial pubococcygeus stretch by the same amount. The authors demonstrated that the medial pubococcygeus muscles undergo the largest stretch of any levator ani muscles during vaginal birth and it is therefore at the greatest risk of stretch-related injury [149] (**Figure 7**).

Svabik et al. [150] showed that the area of the levator hiatus needs a distension of between 25% and 245% to allow the passage of the fetal head, considering as average a cross-sectional fetal head area of 68 cm2, based on Caucasian biometric data.

The occurrence rate of postpartum levator avulsion in primiparae, diagnosed with 3D-4D ultrasound between 24 hours and 9 months after vaginal delivery, is reported between 15-39.5% [151-157]. The incidence of levator trauma evaluated with MRI is reported between 17.7%-19.1% 6-12 months postpartum [158-161].

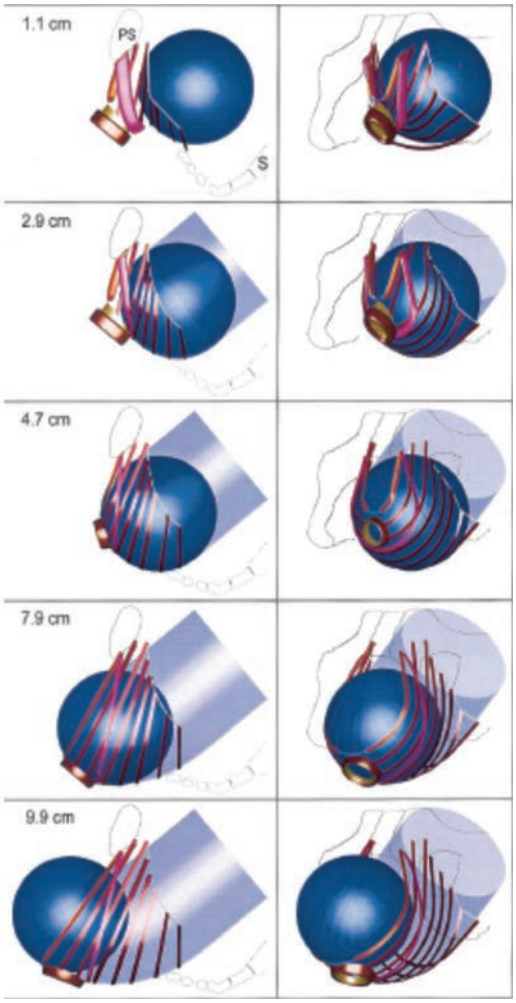


Figure 7. Simulated effect of fetal head descent on the levator ani muscles in the second stage of labour. From Lien et al, Obstet Gynecol 2004 [149].

A study published by Novellas et al. [158], reported an occurrence of 19.1% levator abnormalities diagnosed with MRI in primiparae who underwent a caesarean section and they found that patients who underwent emergency cesarean sections had 2.7 times more abnormalities than patients who underwent elective cesarean. Only a study reported 4 cases of levator defect diagnosed with 3D ultrasound following emergency cesarean section [156].

Avulsion of the pubovisceral muscle seems to occur more frequently after forceps delivery than after spontaneous vaginal delivery: 1-12 months postpartum the occurrence rate of levator avulsion after forceps reaches the incidence rate of 59-72% [151, 162].

Kearney et al. [163] compared levator ani muscle injury rates in primiparous women who had a forceps delivery owing to fetal distress, with women delivered by forceps for second stage arrest; they compared these injury rates with a historical control group of women who delivered spontaneously. The major defect rates were 42% for women who delivered by forceps with a short second stage; 63% for women who delivered by forceps and had a prolonged second stage; and 6% for spontaneous delivery. The odds ratios for major injury were: 11.0 for forceps and short second stage compared with spontaneous delivery; 25.9 for forceps and second stage arrest compared to spontaneous delivery; and 2.3 for forceps and second stage arrest compared with short second stage (P=0.07). These authors also confirmed that women delivered by forceps have a higher rate of levator ani injury compared with spontaneous delivery controls, but the length of the second stage of labour does not influence the effect of the forceps on the levator ani muscle.

Several obstetrical factors associated with the occurrence of levator avulsion have been investigated: Valsky et al. [153] reported that a fetal head circumference ≥35.5 cm and a second stage of labour ≥110 min, increased odds of LAM trauma by a factor of 5.32. DeLancey´s group [161] demonstrated that injuries to the levator ani muscles in women after their first vaginal delivery are associated with forceps use (OR 14.7 [95% CI: 4.9-44.3]), anal sphincter rupture (OR 8.1 [95% CI: 3.3-19.5]) and episiotomy (OR 3.1 [95% CI: 1.4-7.2]); vacuum delivery (OR 0.9 [95% CI: 0.19-4.3]), epidural use (OR 0.9 [95% CI: 0.4-2.0]) and oxytocin use (OR 0.8 [95% CI: 0.3-1.8]) seem instead to have a protective effect against the occurrence of pubovisceral avulsion after delivery. LEVEL OF EVIDENCE II-3.

The levator ani muscle plays an independent role in pelvic organ support. The levator hiatus is the “hernial portal” through which female pelvic organ prolapse develops and damage to the levator ‘plate’ leads to a weakening of muscular supports to the pelvic organs and an increase in load carried by connective tissue and fascia.

It has been demonstrated that increasing pelvic organ prolapse is associated with increasing urogenital hiatus size [164].

The results published by Dietz and Simpson [165] in a retrospective study of the urogynecological population, showed that prolapse was seen in 150/181 (83%) women with avulsion and in 265/600 (44%) women without avulsion, giving a RR of 1.9 (95% CI: 1.7-2.1). The association was strongest for cystocele (RR 2.3, 95% CI: 2.0-2.7) and uterine prolapse (RR 4.0, 95% CI: 2.5-6.5). The authors conclude that women with levator avulsion defects were about twice as likely to have pelvic organ prolapse of stage II or higher than those without.

Chen et al. [166] used a biomechanical model to explore how the impairment of the pubovisceral portion of the levator ani muscle, of the apical vaginal suspension complex, or both might interact to affect anterior vaginal wall prolapse severity. The authors stated that once a certain degree of pubovisceral impairment was reached, the genital hiatus opened and a prolapse developed; the larger the pubovisceral impairment, the larger the anterior wall prolapse became. A 90% impairment of apical support led to an increase in anterior wall prolapse from 0.3 cm to 1.9 cm (a 530% increase) at 60% pubovisceral muscle impairment, and from 0.7 cm to 2.4 cm (a 240% increase) at 80% pubovisceral muscle impairment.

The aetiological role of LAM integrity in bladder dysfunction is still not completely clear. A weakly significant association between levator avulsion and worsening or de novo urinary incontinence has been reported 3 months postpartum, through the use of ultrasound [155]. Recent evidence questions this link, reporting that women with major levator defect diagnosed by MRI are less likely to experience SUI [167], and that puborectalis trauma evaluated by ultrasound is not associated with an increased risk of SUI or urodynamic stress incontinence [168].

The involvement of the urethral function in the presence of levator avulsion has been approached recently, considering that it is often assumed that SUI may be due to abnormal pelvic floor muscle function or anatomy. Brincat et al [169], found no significant association between maximal urethral closure pressure (MUCP) and urethral closure pressure with a pelvic floor contraction or Kegel (KUCP) in women with or without LA defects ($p = 0.94$, $p = 0.95$). Additionally, there was no correlation between MUCP and vaginal closure force ($r = 0.06$, $p = 0.41$), and there was a weak correlation between KUCP and vaginal closure force ($r = 0.20$, $p = 0.01$). They conclude that urethral pressure profiles are unrelated to LA defect status after vaginal birth, indicating that the mechanism responsible for LA damage spares the urethra. Shek et al. [157], demonstrated that except at the bladder neck, there was no significant association between urethral mobility and avulsion.

With regard to anorectal function, Heilbrun et al. [159] showed a weak trend towards more faecal incontinence in women with LAM avulsion and anal sphincter tears, but the interpretation of these results must take into account that this is a rather select group, with a special set of risk factors.

One might speculate as to how 85–90% of first time mothers can undergo vaginal birth without the fetal head overstretching and rupturing the U-shaped loop of pubovisceral muscle tissue. One possibility is that the structure that lies in series with this muscle could protect it by stretching more than the muscle itself, just as a fusible link protects the wiring harness of an automobile against an electrical short. That structure, the perineal body, located between the vagina and rectum and comprised of relatively soft connective tissue, has material properties that do appear to change in late pregnancy, but these remain to be quantified [136].

2. NERVE INJURY

A geometric model has been used to predict the stretch ratios in the nerves innervating the levator ani, urethra, and anal sphincter during the second stage of vaginal labour [170]. The results showed that the inferior rectal branch exhibited the maximum strain, 35%, and this strain varied by 15% from the scenario with the least perineal descent to that with the most perineal descent. The strain in the perineal nerve branch innervating the anal sphincter reached 33%, whereas the branches innervating the posterior labia and urethral sphincter reached values of 15% and 13%, respectively. It was concluded that during the second stage (a) nerves innervating the anal sphincter are stretched beyond the 15% strain threshold known to cause permanent damage in the nonpregnant appendicular nerve, and (b) the degree of perineal descent is shown to influence pudendal nerve strain.

Pudendal nerve lesions usually result in demyelination of the fibres; axonal breaks may occur in severe cases where there is no recovery of the tissues [171]. c-Fos expression (an early reactive nerve injury marker) in the L6 to S1 spinal cord segments was observed in rats after simulated birth trauma, indicating acute nerve injury or irritation in spinal neurons. Also, histological studies have revealed a marked decrease of ganglion cells in the neural plexuses posterolateral to the vagina in rats after simulated birth [172].

Neuromuscular abnormal pelvic floor activation patterns may also contribute to the development of postpartum pelvic floor disorders [173-175]. Electroneuromyography studies have shown that 80% of primigravidae developed evidence of partial denervation with signs of reinnervation and increase in the density of nerve fibres in the postpartum period after vaginal delivery [176, 177]. The latency time of pudendal nerve motor fibres increased after 2 to 3 days following vaginal delivery, but values normalised after 6 months in 66% [177]. Most nerve lesions spontaneously recover within a year by regenerative processes [171]. However, pudendal nerve damage, even with partial reinnervation of the external anal sphincter muscle, may persist and become more marked in the long term [178]. Neurophysiological tests revealed nerve damage in 36% of women with persistent SUI at 3 months postpartum. Compared with nulliparous control subjects, patients with SUI and POP had changes in the levator ani and external anal sphincter consistent with either motor unit loss or failure of central activation, or both [179].

IV. PERINEAL TRAUMA

1. EPIDURAL ANALGESIA DURING LABOUR

Regional anesthesia for the relief of labour pain has become more popular during the past 20 years. Despite interest in its possible obstetric consequences, little attention has been paid to its potential effects on the pelvic floor and perineal injury.

The available published data describe controversial results. Some studies suggest that epidural analgesia, by enabling relaxation of the pelvic floor, leads to greater control of crowning of the fetal head and consequently fewer perineal tears [180], but prolongation of the second stage may also increase the incidence of pudendal nerve damage [181, 182].

Robinson et al. [183] examined whether epidural analgesia is associated with differences in rates of severe perineal trauma during vaginal deliveries. Among women who had epidurals, 16.1% (221/1376) had severe perineal tears compared with 9.7% (55/ 566) women who did not have epidurals ($P < .001$; OR 1.8, 95% CI: 1.3-2.4). When controlling for birth weight, use of oxytocin, and maternal age in logistic regression analysis, epidural remained a significant predictor of severe perineal injury (OR 1.4, 95% CI: 1.0-2.0). Epidural use is consistently associated with increased operative vaginal deliveries and consequent episiotomies, so the authors constructed a logistic regression model to evaluate whether the higher rates of those procedures were responsible for the effect of epidurals on severe perineal trauma. With operative vaginal delivery and episiotomy in the model, epidural was no longer an independent predictor of perineal injury (OR 0.9, 95% CI: 0.6-1.3). They concluded that epidural analgesia is associated with an increase in the rate of severe perineal trauma because of the more frequent use of operative vaginal delivery and episiotomy.

Carroll et al. [184], evaluated whether epidural analgesia was an independent risk factor for severe perineal tears. Among women who had epidural analgesia, 10.25% (65 of 634) had severe perineal tears compared with 5.22% (111 of 2,125) of the women who did not have epidural analgesia. After controlling for major variables in a logistic regression

analysis, epidural analgesia remained a significant predictor of severe perineal injury (OR 1.5, 95% CI = 1.0-2.1). A logistic regression model examining predictors of instrument use found that epidural analgesia does significantly increase instrument use (OR 3.01, 95% CI: 2.2-4.0). The author concluded that epidural analgesia is associated with an increase in severe perineal trauma as a result of an associated three-fold increased risk of instrument use. Instrument use in vaginal delivery more than triples the risk of severe perineal tears.

No significant association between anal sphincter injury and the use of epidural anesthesia was observed in 91 women in the retrospective study published by Christianson et al. [185]. On the other hand, Fitzgerald et al. [186] demonstrated that epidural was significantly associated with anal sphincter tear when the analysis was adjusted for maternal age, race, and gestational age.

In a study of 82 women, Meyer et al. [187] assessed the effects of epidural analgesia on pelvic floor function. Eighty-two primiparous women (consisting of 41 given an epidural and 41 not given an epidural) were investigated during pregnancy and at 2 and 10 months after delivery by a questionnaire, clinical examination, and assessment of bladder neck behaviour, urethral sphincter function and intravaginal/intra-anal pressures. Ten months after spontaneous delivery, there were no significant differences in the prevalence of SUI and decreased sexual vaginal response, or in bladder neck behaviour, urethral sphincter function and pelvic floor muscle strength between women who had or had not had epidural analgesia.

Sartore et al. [188] concluded that the use of epidural analgesia is not associated with symptoms related to perineal trauma and pelvic floor muscle weakness 3 months after vaginal delivery.

In a prospective observational study of 488 primiparae, Shek et al. [189], demonstrated with 3D ultrasound that intrapartum epidural appeared to have a protective effect (P=0.03; OR 0.42; 95% CI: 0.19-0.93) against levator trauma at the time of first delivery. Also Kearney et al. [161], using MRI, confirmed that epidural reduce the risk of developing a levator defect during vaginal delivery.

2. ROLE OF EPISIOTOMY

The episiotomy, a surgical incision in the perineum made to enlarge the vaginal opening and facilitate delivery, was originally introduced on the assumption that it would improve maternal and neonatal outcomes and rapidly became a part of standard obstetric care. However, since the 1980s, routine use of episiotomy has been challenged, based on the lack of evidence of benefits of the procedure [190] and the publication of multiple studies reporting increased blood loss at delivery, perineal scar breakdown and infection, postpartum pelvic pain, and dyspareunia [191-194].

Nowadays routine episiotomy is not recommended any more. Various types of episiotomy have been described in the past (median, modified median, J-shaped episiotomy, mediolateral, lateral, radical lateral and anterior) in papers and text-books (**Figure 8**). The description of mediolateral episiotomy (the most frequently used in Europe) in standard obstetrics textbooks differs widely: some publications provide only descriptive terms, the angle of incision varies between 31° and 63°, suggesting the wide potential variation in the practice of episiotomy worldwide.

Some studies deal with the different use of various episiotomies in different countries (e.g. UK, Finland and Greece) [196-199]. However randomised trials comparing alternative methods or position of episiotomy are lacking, resulting in Level 2b or Level 3 of evidence, only. To ensure Level 1 evidence from randomised trials, there needs to be standardisation of the practice and reporting of the episiotomy incision. However, a standardised classification system has not been introduced yet, making it difficult to compare the various techniques. Even in the recent Cochrane review of episiotomy, an exact classification or definition of episiotomies is lacking [200].

Some studies have demonstrated increased incidence of third and fourth-degree lacerations associated with the use of midline episiotomy [201, 202]. The resulting damage to the internal and external anal sphincters can lead to devastating long-term sequelae, including faecal incontinence and recto-vaginal fistulae [203].

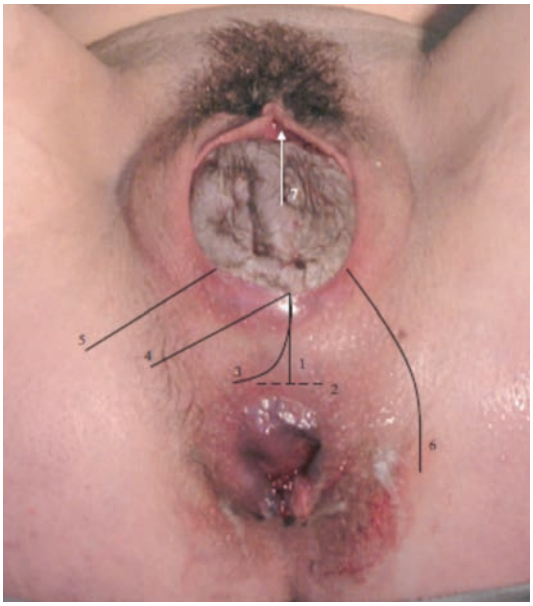


Figure 8. Types of episiotomy. 1: median episiotomy, 2: modified median episiotomy, 3. 'J'- shaped episiotomy, 4: mediolateral episiotomy, 5. lateral episiotomy, 6: radical lateral (Schchardt incision), 7: anterior episiotomy (white arrow). From Kalis et al. Classification of episiotomy: towards a standardization of terminology. BJOG 2012 [195].

To support the benefits of episiotomy, some clinicians have claimed that meticulous repair of a surgical episiotomy yields improved wound healing when compared with an unpredictable spontaneous tear [191]. This assertion, however, has not been substantiated by empirical evidence [204].

Kalis et al. [205] evaluated the results of mediolateral episiotomy with an incision angle of 60°: the study group comprised 60 consecutively recruited primiparous women who required an episiotomy during delivery. The results showed that the angles differed significantly among the incision (60°), repair (45°), and 6-month (48°) measurements ($P < 0.001$). There was a poor correlation between the suture angle and the angle measured at 6 months postpartum. No severe perineal tear was diagnosed in the cohort. At 6 months postpartum, only one woman reported mild symptoms of de novo anal incontinence, whereas 7 women reported perineal pain related to episiotomy.

Many institutions and individual obstetric practitioners have decreased their performance of episiotomy over the past 20 years, most likely as a result of practicing evidence-based medicine.

An electronic audit of the medical procedures database at Thomas Jefferson University Hospital from 1983 to 2000 was completed to determine if practice patterns have been altered by the large body of literature strongly advocating the selective use of episiotomy. Overall episiotomy rates in 34,048 vaginal births showed a significant reduction from 69.6% in 1983 to 19.4% in 2000. Significantly decreased risk of episiotomy was seen based upon year of childbirth (OR 0.87, 95% CI: 0.86-0.87), black race (OR 0.29, 95% CI: 0.28-0.31), and spontaneous vaginal delivery (OR 0.40, 95% CI: 0.36-0.45). Increased association with episiotomy was seen in forceps deliveries (OR 4.04, 95% CI: 3.46-4.72), and with third or fourth-degree lacerations (OR 4.87, 95% CI: 4.38-5.41). This study demonstrates a statistically significant reduction in the overall episiotomy rate between 1983 and 2000. White women consistently underwent episiotomy more frequently than black women, even when controlling for age, parity, insurance status, and operative vaginal delivery [194].

A population-based register of 514,741 women with singleton vaginal deliveries recorded in the Finnish Medical Birth Register was reviewed. Primiparous and multiparous women who had undergone episiotomy were compared to women who had not undergone episiotomy, for possible risk factors. The rise of episiotomy decreased from 71.5% in 1997-1999 to 54.9% in 2006-2007 among primiparous women, and from 21.5% in 1997-2001 to 9.2% in 2006-2007 among multiparous women. The use of episiotomy decreased in not only low-risk but also high-risk women who had operative vaginal or breech deliveries, macrosomic newborns, and oxytocin augmentation. The ratio of episiotomy use remained relatively unchanged in different subgroups even though episiotomy policy became increasingly restrictive over time. The authors concluded that the spectrum of indications for episiotomy has not changed over time, and use of episiotomy has declined arbitrarily to a similar extent among high and low-risk women [206].

To identify the risk factors for obstetric anal sphincter rupture (OASR), a retrospective population-based register study was carried out. A total of 514,741 women with singleton pregnancy and vaginal delivery between 1997 and 2007 in Finland were recruited. Episiotomy decreased the likelihood of OASR for the primiparous [OR 0.83, 95% CI: 0.75-0.92], but not the multiparous women (OR 2.01, 95% CI: 1.67-2.44). Episiotomy was associated with decreased risks for obstetric anal sphincter rupture in vacuum assisted deliveries (OR 0.70, 95% CI: 0.57-0.85). These results support the restrictive use of episiotomy, since 909 episiotomies appear to be needed to prevent one OASR among primiparous women. The equivalent estimate in vacuum assisted deliveries among primiparous women was 66, favouring routine use of episiotomy in such cases [198].

Robinson et al. [207], carried out a study to identify factors associated with the use of episiotomy at spontaneous vaginal delivery. They studied 1576 consecutive term, singleton, spontaneous vaginal deliveries; the association of demographic variables and obstetric factors with the rate of episiotomy use were examined. The overall rate of episiotomy was 40.6% (640 of 1576). Midwives performed episiotomies at a lower rate (21.4%) than faculty (33.3%) and private providers (55.6%) ($P = 0.001$). After controlling for confounding factors with logistic regression, private practice provider was the strongest predictor of episiotomy use (OR 4.1, 95% CI: 3.1-5.4) followed by faculty provider (OR 1.7; 95% CI: 1.1-2.5), prolonged second stage of labour (OR 1.8; 95% CI: 1.2-2.7), fetal macrosomia (OR 1.6; 95% CI: 1.1-2.5), and epidural analgesia (OR 1.4 95% CI: 1.1-1.8). The authors conclude that the strongest factor associated with episiotomy at delivery was the category of obstetric provider. Obstetric and demographic factors evaluated did not readily explain this association.

A study was carried out to lower the episiotomy rate through physician education and to document the indication when episiotomy was performed. The intervention consisted of an evidence-based lecture recommending limited usage of episiotomy and requesting documentation of any indication for episiotomy. Data 3 months prior to the intervention were compared to those of the following year. For all vaginal deliveries, there was a 17% decrease in the rate of episiotomy, from 46.9% to 38.8%. For spontaneous vaginal deliveries, there was a 25% decrease in the episiotomy rate, from 40.8% to 30.8%. The most common indications for episiotomy reported were routine/elective, 41.0%; vacuum, 18.6%; forceps, 16.4%; and nonreassuring fetal heart tracing, 10.9% [208].

A review was conducted of women with consecutive vaginal deliveries at Magee-Women's Hospital

between 1995 and 2005 to evaluate the episiotomy exposure at first vaginal delivery. A total of 6,052 patients were included, of whom 47.8% had episiotomy at first delivery. Spontaneous second-degree tears at the time of second delivery occurred in 51.3% of women with history of episiotomy at first delivery, compared to 26.7% without history of episiotomy (P<0.001). Severe tears (third or fourth- degree) occurred in 4.8% of women with history of episiotomy at first delivery compared with 1.7% without history of episiotomy (P<0.001). Previous episiotomy remained a significant risk factor for second-degree (OR 4.47, 95% CI: 3.78-5.30) and severe obstetric lacerations (OR 5.25, 95% CI: 2.96-9.32) in the second vaginal delivery after controlling for confounders. Based on these findings, for every four episiotomies not performed, one second-degree tear would be prevented. To prevent one severe tear, performing 32 fewer episiotomies is required. Episiotomy at first vaginal delivery increases the risk of spontaneous obstetric trauma in the subsequent delivery. This finding should encourage obstetric providers to further restrict the use of episiotomy. LEVEL OF EVIDENCE II [209].

V. CONCLUSION AND RECOMMENDATION

1. Prevalence of UI after vaginal delivery is double that after caesarean section [109]. Cesarean section seems to decrease the risk of postpartum UI [110, 111], but its protective effect seems to diminish over time and disappears after multiple deliveries [111, 112]. Risk of SUI is estimated to be 2.9 times higher after vaginal delivery compared with women after cesarean section [113]. Information regarding whether cesarean done before labour confers greater protection than cesarean done after labour is lacking. To understand the true impact of cesarean delivery on urinary incontinence, future studies must compare incontinence by planned delivery modes.
2. De-novo anal incontinence symptoms after childbirth are described as up to 26-38% between 6 weeks-6 months postpartum [115-120]. Vaginal delivery has a greater risk of FI compared to cesarean 3-6 months postpartum [115] [117]. It is recommended extending postpartum follow-up visits beyond the typical 6-8 weeks to provide surveillance for potential incontinence. **LEVEL OF EVIDENCE: II**.
3. Pelvic organ prolapse rate in the first 3-6 months postpartum is reported between 18.1-56% [121-123]. Spontaneous vaginal delivery increased the risk by more than three times while instrumental vaginal delivery increased it more than five-fold in comparison with cesarean section [121]. Cesarean section has a protective effect on the occurrence of pelvic organ prolapse [124].
4. The occurrence of UI and anal incontinence during the postpartum period is related to the presence of incontinence in pregnancy, and vaginal delivery increases the risk of persistent incontinence. **LEVEL OF EVIDENCE II** [125].
5. So far, there is no evidence from randomised controlled trials, upon which to base any practice recommendations regarding planned cesarean section for non-medical reasons at term or to avoid pelvic floor symptoms in a woman without previous disorder, considering that pregnancy itself may be involved in the development of such dysfunction [133] [134] [135].
6. Obstetrics factors associated with the occurrence of LAM trauma postpartum: forceps use, fetal head circumference ≥ 35.5 cm, second stage of labour ≥110 min, anal sphincter rupture, episiotomy. **LEVEL OF EVIDENCE II-3**. Levator ani avulsion is associated with the occurrence of pelvic organ prolapse later in life, but the role of LAM integrity in bladder and anorectal dysfunction are still not completely clear.
7. Epidural analgesia during labour: controversial results regarding its potential effect on the pelvic floor and perineal injury. There is a lack of prospective, randomized trials, requiring further research and development in order to draw recommendations.
8. Randomised trials comparing alternative methods or position of episiotomy are lacking, resulting in Level IIb or Level III of evidence, only. To ensure Level 1 evidence from randomized trials, it needs a standardisation of the practice and reporting of the episiotomy incision. The actual evidence shows that episiotomy is associated with 3rd-4th degree of perineal tears and with an increased risk of spontaneous obstetrics trauma in the subsequent delivery. These findings encourage restriction of routine use of episiotomy. **LEVEL OF EVIDENCE II**.

C. PATHOPHYSIOLOGY OF STRESS INCONTINENCE IN WOMEN: URETHRAL STRUCTURE, SUPPORT AND FUNCTION

The factors necessary for the urethra to remain closed at rest and during increased abdominal pressure have been well characterised, but their functional inter-relationships are still not fully understood. These factors include: 1) healthy, functioning striated sphincter controlled by pudendal innervation, 2) well vascularised urethral mucosa and sub- mucosa, 3) properly aligned and functioning intrinsic urethral smooth muscle, and 4) intact vaginal wall support.

I. THE FEMALE UROGENITAL DIAPHRAGM: URETHRAL SPHINCTER LOCATION

Detailed descriptions of the urogenital diaphragm have been made by Max Brodel working with Howard Kelly [210], Oelrich [211] and further expanded by DeLancey [212]. These reports have provided clear descriptions of the urethral rhabdosphincter. The proximal one-third of the urethra is shown surrounded by a sleeve of striated muscle continuous with a longer ascending cone which extends to the vaginal introitus. Manometric and electrophysiological recordings from this proximal one-third of the urethra have shown that it generates the highest level of resting pressure and electromyographic activity.

This portion of the urethra is an intra-pelvic structure located immediately posterior to the pubic bone. In the past, much has been made of the loss of this intra-pelvic position in stress incontinence. It had been suggested that when the urethra descended away from its intra-abdominal position, intra-abdominal forces no longer constricted it during straining. This concept has survived and been modified into the "hammock hypothesis" [213] which suggests that the posterior position of the vagina provides a backboard against which increasing intra-abdominal forces compress the urethra. Data supporting this hypothesis are drawn from urethral pressure transmission studies showing that continent patients experience an increase in intra-urethral pressures during coughing. This pressure increase is lost in stress incontinence and may be restored following successful operations designed to stabilize or elevate the sub-urethral vaginal wall [214-223].

The urethra is supported posteriorly and inferiorly by the anterior vaginal wall. The superior vaginal sulcus, most clearly found in nullipara, exists at this junction of the lower and middle third of the vaginal wall. This point represents the two lateral insertion points of the vaginal "hammock ". Portions of the pubococcygeus muscle attach to these sulci within the pelvis and can produce elevation during voluntary contraction.

Immediately anterior to the proximal urethra are found the reflections of the endopelvic fascia are found. The most prominent of these, the pubo-urethral ligaments, are sufficiently condensed to form distinct and recognisable ligaments on either side of the pubis. Although these structures form one continuous complex, they are distinguished by their names, as posterior and anterior pubo-urethral ligaments. The posterior pubo-urethral ligaments, which can be seen at the time of retropubic surgery, are the more familiar of these. These are strong fascial condensations which most likely maintain their characteristics throughout life. Previous investigators, however, have suggested that elongation of these structures may be responsible for the loss of urethral support seen in stress incontinence.

Different authors have described the striated external urethral sphincter (EUS), both in foetuses [224, 225] and adults [226] as a superior horseshoe structure covering the urethra and an inferior one surrounding the anterolateral aspect of the urethra and the lateral part of the vagina (**Figure 9**).

The LAM is an important element in maintaining urinary continence. Wallner at al. [227] investigated the topographical relationship between the EUS and the LAM (**Figure 10**), showing that in female foetuses, but not in male, the inferior part of the EUS is firmly attached to the LAM by a tendinous connection. This determines an anterior bending of the midurethral zone when a simultaneous contraction of the LAM and EUS occurs, closing the urethral lumen and maintaining continence. The functional integrity of this connection between the EUS and the LAM is therefore crucial to avoid urinary incontinence.

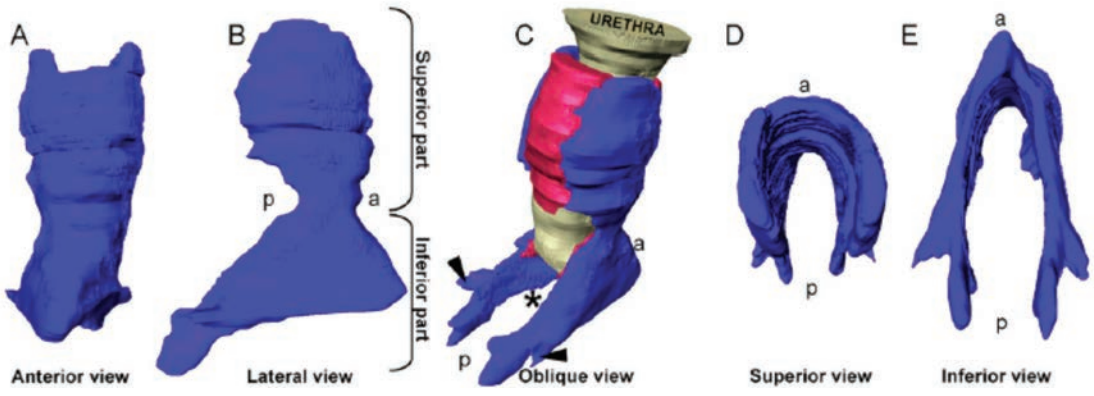


Figure 9. EUS in 18 weeks female foetus: A anterior view, B lateral view, C oblique view, D superior view, E inferior view - From Wallner et al., Eur Urol 2009 [227].

The striated external urethral sphincter (EUS), both in foetuses and adults, has a superior horseshoe structure covering the urethra and an inferior one surrounding the anterolateral aspect of the urethra and the lateral part of the vagina.

Moreover, while the lower one-third of the vagina is oriented more vertically in the nullipara, the upper two-thirds of the vagina deviate horizontally. This orientation is due: 1) to the posterior attachments of the cervix by the cardinal and utero-sacral ligaments and 2) to the anterior position of the levator hiatus. Barium vaginograms have demonstrated this horizontal angulation of the upper two-thirds of the vagina, and show that during coughing and stressful manoeuvres, the levator hiatus is shortened in an anterior direction by the contraction of the pubococcygeus muscles Thus, the pelvic organs receive support from the shape and active contraction of the levator muscles.

Modifications of the genital hiatus determining an increase in the genitohiatal distance can be associated with urodynamic stress incontinence. In a retrospective study of 396 women with urodynamic stress incontinence [228], pelvic floor ultrasound revealed a negative association of the genitohiatal distance to urodynamic functional urethral parameters such as the functional profile length, the maximum urethral closure pressure and a low Valsalva leak-point pressure ($r = -0.148$, $P = 0.018$ and $r = -0.227$, $P = 0.009$, $r = -0.199$, $P = 0.02$ respectively).

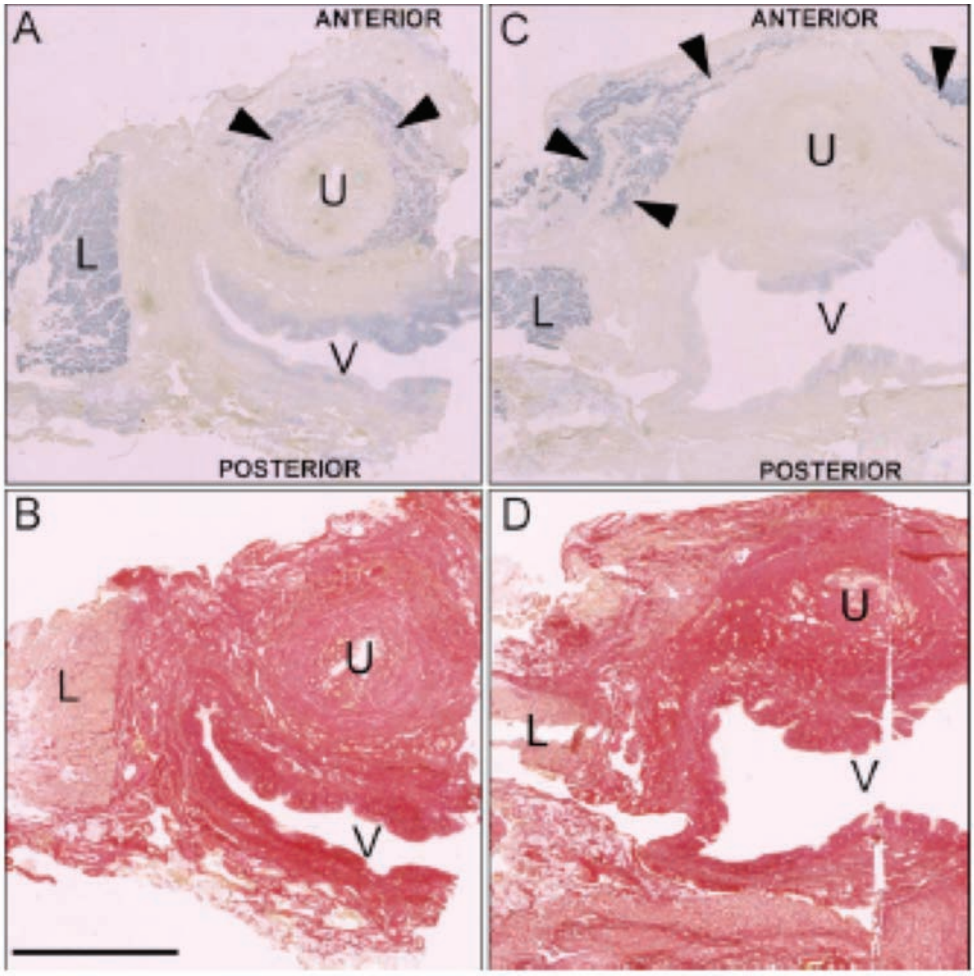


Figure 10: The anatomical relationship of the EUS to the LAM in adults. Panels (A) through (D) show transverse sections through the EUS and the LAM of an adult female (54 yr): (A) superior part of the EUS (arrowheads), section stained immunohistochemically for striated muscle; (B) sequential section stained with sirius red for connective tissue; (C) inferior part of the EUS (arrowheads), section stained immunohistochemically for striated muscle; (D) sequential section stained with sirius red for connective tissue. Note in (C) that in the adult, the anatomical relationship between the inferior part of the EUS and the LAM is still maintained. The contrast of images (A) and (C) was increased digitally. L = levator ani muscle; U = urethra; V = vagina. From Wallner et al Eur Urol 2009 [227].

II. EFFECT OF CHILDBIRTH, VAGINAL PROLAPSE AND URETHRAL POSITION ON URINARY CONTINENCE

Labour and delivery alter vaginal and pelvic anatomy and innervation in several ways as has been discussed in other sections of this chapter. Each of these may contribute to the eventual development of urinary incontinence:

1. PUDENTAL NERVE

Direct crushing or traction on the pudendal nerve has been discussed above and has previously been suggested as a primary cause of sphincter incompetence in stress incontinence. The pudendal nerve, which projects from Onuf's nucleus and traverses Alcock's canal before entering the ischiorectal fossa and innervating the EUS, can be injured during vaginal delivery, particularly in the area between the sacrospinous and sacrotuberous ligaments. Two different mechanisms of pudendal nerve damage during delivery have been described: 1) nerve compression and stretching which may cause an elongation of the 13% of its motor branch innervating the EUS [229]; 2) a reduced at 8% stretch and complete ischemia at 15% stretch of the nerve as shown in a tibial nerve rat model [230]. Thus, pudendal nerve ischemia likely occurs during vaginal delivery as a result of both stretch and compression [231].

2. CARDINAL AND UTERO-SACRAL LIGAMENTS

Cardinal and utero-sacral ligaments may be stretched or torn, resulting in anterior displacement of the uterus during straining or under the influence of gravity.

3. THE VAGINA

The vagina itself may be torn away from its intrapelvic attachments with subsequent loss of the superior vaginal sulcus. There may be direct attenuation of the vaginal wall itself, manifested by loss of vaginal rugae and a thin appearance. Cullen Richardson has suggested four distinct kinds of vaginal injuries: paravaginal, central, distal, and cervical, the first two being the most commonly seen in women with stress incontinence. These defects have been identified by sonographic examination [232].

4. LEVATOR MUSCLES

Finally, stretching, tearing and avulsion of the levator muscles result in a longer and wider levator hiatus. Consequently, the perineum is displaced anteriorly and posteriorly under stress and temporarily fails to support the pelvic organs. These changes in the levator hiatus with or without associated relaxation of cervical support result in chronic anterior displacement of pelvic organs with a loss of both active and passive organ support during rest and especially during straining.

In the patient with SUI these changes typically give rise to a rotational descent of the proximal urethra away from its retropubic position.

Radiographic images of stress urinary incontinence in women have noted this and generated our earliest concepts of this condition. Jeffcoate and Roberts [233], using lateral cystourethrograms, concluded: "…the most common characteristic anatomical change, present in four out of five cases of incontinence, is loss of the posterior urethro-vesical angle so that the urethra and trigone tend to come into line."

In 2002, fifty years later, perineal sonographic studies of urethrovesical angle differences in incontinent and normal patients have found excellent correlation identified between angle and degree of incontinence, supporting these original observations [234].

Hodgkinson, using a suspension of barium paste placed in the bladder and a small bead chain in the urethra, produced images of the urethra at rest and during maximum straining in women with stress urinary incontinence [235, 236]. He concluded: "… it is clear that the distinguishing topographic pathological feature is depression of the urethrovesical junction to the lowest level of the bladder during the peak of the straining effort. It is also clear that the spatial relationships of the bladder and urethra to the symphysis make no difference in either the incidence or severity of stress incontinence."

These kinds of radiographic studies, however, cannot distinguish between lateral or central defects in vaginal wall support. Therefore, while urethral movement can be identified as an important finding in stress incontinence, one cannot determine the exact location of the vaginal defect. Because the proximal urethra rotates out of the focal plane of ultrasonograhic probes or MRI, coronal images of vaginal relaxation have not yet shown anatomical detail at the moment of incontinence. They cannot distinguish central from paravaginal defects. For this, an examination of the patient is required.

Although we have considerable knowledge about anatomical defects in the majority of patients with urodynamic stress incontinence (USI), less is understood about the exact effect of these defects, and indeed, vaginal position itself, on urethral closure. Early experience with operations for stress incontinence showed that not all women with stress urinary incontinence had vaginal prolapse, that correction of vaginal relaxation did not always correct stress incontinence, and that women who redeveloped stress incontinence symptoms after apparently successful surgery did not necessarily show a recurrence of their prolapse [237].

The effect on the urethral mechanism of anatomical defects induced by vaginal delivery has been recently investigated. In a rat model birth trauma has been simulated by inducing vaginal distension by balloon catheter inflation [238]. Sneeze

induced stress urinary incontinence was caused by decreased active closure mechanisms at the mid urethra without affecting the passive transmission of abdominal pressure in the proximal urethra.

The greater involvement of the urethral mechanism in the occurrence of post-partum stress incontinence was confirmed in a case control study evaluating urethral closure pressure and bladder neck movement assessed with ultrasound [239]. Eighty primiparous women complaining of de-novo stress incontinence 9-12 months after delivery were compared with 80 primiparous continent and 80 nulliparous continent women. Lower maximal urethral closure pressure was the closest association with de novo stress incontinence after first vaginal birth followed by vesical neck mobility.

III. EMERGING CONCEPTS OF URETHRA WEAKNESS AND ISD

The idea that primary urethral weakness could cause urinary incontinence independent of vaginal weakness appeared in a proposed classification by Blaivas et al [240]. In their classification, they named this Type III incontinence to distinguish it from Types I and II, each of which showed movement, while Type III did not. This term still remains in the contemporary literature, although it has now been largely replaced by the term intrinsic sphincter deficiency (ISD), focusing attention on urethral elements which appear to be independent of vaginal position and mobility. These elements include pudendal innervation, striated sphincter mass and function, and urethral smooth muscle, mucosa and submucosal cushions.

When ISD was first introduced as a concept to explain surgical failures and the presence of stress incontinence in the absence of vaginal mobility, the diagnostic tendency was to consider the cause of stress incontinence as a dichotomy, due either to hypermobility (displacement, or prolapse of the vaginal wall) or ISD. The typical patient with ISD was described as having low urethral closure pressures, a “stovepipe” appearance on cystoscopy, and opening or funnelling of the urethra under resting or minimal increases in intra-abdominal pressures on radiographic images. The common causes were thought to be surgical injury, ischemia following previous pelvic or vaginal surgery or radiation damage.

It appears now, that these examples of ISD may represent the most advanced or extreme forms.

IV. HYPERMOBILITY VS. ISD: FROM DICHOTOMY TO CONTINUUM

Currently, these appear to be a shift away from this simple categorisation of stress incontinence as being due either to hypermobility or ISD. This has arisen in part because of the development of the concept of Valsalva Leak Point Pressure (VLPP) [241, 242] and more recent analyses of long term results of stress incontinence surgery [243].

VLPP emerged as an alternative method to study urethral closure during stress for studies of urethral bulking with collagen. Investigators recognised that improvements in continence following urethral bulking did not correlate with urethral closure pressures, but did correlate with the amount of pressure required to produce leakage in the absence of intrinsic detrusor contraction. Although VLPP still lacks specific anatomic or theoretical grounding and many uncertainties related to standardisation of recording methods and associated prolapse remain, low VLPP (without specified or established values) has been widely embraced as an indicator of ISD.

Just as the concept of VLPP blurred the previous distinction between simple ISD and simple hypermobility, long term outcome studies of correction of hypermobility have suggested that there may be more urethral weakness among patients with hypermobility than had been previously considered.

Long term outcome studies of stress incontinence surgery have shown that there is a much greater failure rate of many of the commonly performed stress incontinence operations than had been generally appreciated, and that slings providing direct sub-urethral support seemed to give the greatest long term protection against recurrence of incontinence [243]. Since slings had traditionally been the procedure of choice for recurrent incontinence or “Type III” (now ISD) incontinence, the possibility that ISD was more common than previously thought was more widely considered. Recently, Horbach and Ostergaard have found that age is a significant, independent predictor of ISD in the setting of urodynamic stress incontinence [244], suggesting that age-related reduction in muscle mass, slowed reflexes or repeated episodes of prolapse may all contribute to the condition.

In two interesting studies Perucchini et al [245, 246] showed that aging can cause a decrease in the number and density of urethral striated muscle fibres at the bladder neck and along the ventral wall of the urethra [246].

These two developments have led to a growing clinical impression that some degree of ISD may exist in many patients who, until recently, were thought to have only hypermobility as the cause of their incontinence. Atypical expression of this approach can be found in the conclusion of Kayigil et al. [247] following examination of 50 patients; “The high rate of intrinsic sphincter deficiency in patients with urethral hypermobility indicates that the incidence with stress incontinence may be greater than previously believed, and may influence the apparently higher failure rates after bladder neck suspension.” In contemporary clinical practice, this impression has given rise to a growing tendency to recommend suburethral sling surgery as a form of primary surgical treatment for all women with stress incontinence, where as formerly

this approach was reserved almost exclusively for patients with recurrent stress incontinence or significant ISD [248, 249].

1. DIRECT STUDIES OF URETHRAL FUNCTION

As recognition of the importance of urethral function has increased, so too have the number of investigations of urethral position, urethral closure and transmission pressure profiles, Valsalva leak point pressure measurements and electromyographic examinations of the pudendal nerve and the striated sphincter.

a) Studies of urethral position

Stress incontinence is frequently associated with loss of urethral position. This has been the primary pathophysiological paradigm since the observations of Hodgkinson and Jeffcoate and Roberts. Similar observations are still reported today [250, 251]. Even when some displacement is seen in continent nulliparous females, incontinent women show a greater degree of mobility [252].

This pathophysiological mechanism has been supported by different authors [172, 253, 254] using a rat model. Both (word missing) and induced trauma on structures supporting the urethra (such as the pubouretheral ligaments) and uretherolysis resulted in SUI in short and long term because of increased urethral mobility.

Successful suspensory operations, whether by sling or paraurethral suspension stabilise urethral position [237] and, when studied, increase pressure transmission during stress. It is not clear if the active contraction of urethral support seen in the female is restored after surgery, nor is it known if it is necessary for continence. It has been suggested that passive support alone is what restores continence after suspension.

b) Studies of urethral pressure and resistance

Stress incontinence is generally thought to be characterised by a decrease in urethral transmission profiles and resting closure pressure. The correlation between low resting pressures and low leak point pressures is still controversial. With a bladder filled up to 200ml Almeida et al. [255] reported a significant correlation between MUCP and LPP. Patients with a LPP of 60 cm H2O or less also had shorter urethral functional length and lower sphincter activity. Moreover Sinha et al [256] showed that women with urodynamic stress incontinence were more likely to leak at cough leak point pressure than the Valsalva manoeuvre, with the opposite happening for women with detrusor overactivity. On the contrary Martan et al. [257] could not find any significant correlation between MUCP and VLPP.

Different urodynamic parameters have also been considered to assess urethral function and to correlate with women with stress incontinence. Digesu et al. [258] showed that urethral resistance pressure (URP) and pressure flow parameters were reduced in women with stress incontinence. Salvatore et al. [259] found that the opening vesical pressure is significantly correlated with ISD.

Sonographic studies have recently shown a relationship between low urethral resistance and decreased urethral smooth and skeletal muscle layers [260].

Improvement in transmission pressures is associated with successful outcomes after suspensory operations for SUI [214, 218, 221, 222, 261, 262]. The exact mechanism for this increase in transmission is not clear. Increased exposure to intra-abdominal forces has been suggested [223, 263, 264]. Compression against the pubis by the pelvic viscera has also been suggested [265]. The final position of the urethra, however, may not be the key variable [214].

c) Electrophysiological studies of urethral function

Snooks and Swash [266, 267] first brought attention to the importance of urethral denervation after its possible contribution to urinary and faecal incontinence. Stress incontinence is frequently associated with a decline in the electrophysiological function of the pudendal nerve [268], the striated urethral sphincter [269], and the pelvic floor muscles [174, 179]. Most recent studies continue to support the finding of prolonged pudendal nerve terminal motor latency in SUI [270].

With the use of animal models simulating intrinsic urethra deficit through periurethral cauterisation, urethral sphincterectomy or pudendal nerve transection, different authors reported a decrease of LPP lasting for weeks [271-273]. Injury of the pudendal nerve determined a dramatic decrease of urethral resistance causing urinary loss during an intrabdominal pressure increase.

Electromyographic studies of normal sphincter function show that in continent women, pressures begin to rise in the urethra before rising in the bladder, suggesting an active muscular component [274].

Women with stress incontinence have an altered pattern of pelvic floor muscle response during successive coughing efforts [275] with a sharp decrease in MUCP after repeated coughs [276]. EMG studies have also shown that women with persistent stress incontinence after previous surgery have poorer urethral neuromuscular function than naïve stress incontinent women [277]. Experimental studies of urethral function and the role of Onuf's nucleus in the sacral spinal cord have led to recent practical innovations in the development of serotonin uptake inhibitor agents in the treatment of stress incontinence [278]. Most electrophysiological studies have concentrated on motor rather than sensory innervation, however, and the role of urethral sensation in urodynamic stress incontinence is unknown.

d) Genetic factors

Recent research is now focusing on the identification of factors related to stress incontinence which

might be genetically determined. Chen et al. [279] reported that genes involved in elastin metabolism were differentially expressed in vaginal tissue from women with stress incontinence, suggesting that elastin remodelling may be important in the molecular aetiology of stress incontinence. Wen et al. [280] recently reported a decreased expression of alpha2-M mRNA and protein and protease inhibitor activity in the vaginal wall tissues of women with stress incontinence.

There is a need for a hypothesis which would integrate these various observations regarding hypermobility, ISD and pudendal nerve function, place them within the context of an abnormal pelvic floor and provide a model to guide research and studies of the natural history of the condition.

2. ROLE OF ADVANCED IMAGING IN UNDERSTANDING PATHOPHYSIOLOGY

Many imaging modalities have been used to improve our knowledge on pelvic floor dysfunction, such as: radiographic imaging, ultrasound, computed tomography and magnetic resonance imaging (MRI).

Radiographic imaging has provided considerable insight into the pathophysiology of stress incontinence, ever since the advent of bead chain cystograms and simple static and straining lateral cystograms.

MRI and real time ultrasonography, in addition to showing the events of stress incontinence on both a global pelvic and local urethral scale, have suggested a relationship between the proximal urethra to vaginal wall movement.

a) Magnetic resonance imaging

Dynamic fastscan MRI can visualise all compartments of the female pelvis during increased intraabdominal straining [281]. MRI is comparable to standard cystography in demonstrating cystocele defects [282].

Using the pubococcygeal line as a reference marker, the normal displacement of bladder base, cervix or cervical cuff, and the rectum can be identified and compared to women with prolapse. The urethra is shown in the context of global pelvic relaxation [283]. Although most MRI studies have been descriptive rather than quantitative, they still show far more soft tissue detail than earlier radiographic studies and continue to offer promising research opportunities. Recent studies have utilised an endovaginal coil to obtain higher resolution images of the urethra [284].

Dynamic MRI with cine-loop reconstruction produces vivid, intuitively appealing images which can show movement of all compartments of the relaxed pelvis during straining [283]. Static MRI shows details of urethral and peri-urethral anatomy and the striated sphincter can be clearly seen [285]. Pending further improvements in resolution, MRI remains a most promising tool for studying details of urethral movement [286].

Ultrasonography, however, is simpler and less expensive, and, for now, provides better visualisation of moving structures.

Functional MRI has recently been evaluated to assess the efficacy of pelvic floor muscle training with EMG- biofeedback in women with stress incontinence. After a 12-week training period a more focused activation in the primary motor and somatosensory cortical representation sites of the lower urogenital tract was found [287].

b) Real time ultrasonography

Several sonographic approaches have been used for the study of stress incontinence: suprapubic, translabial, transvaginal and transperineal.

As resolution of sonographic probes has improved, the detail previously best seen with the transrectal approach may now be seen by a transperineal approach. Earlier studies with a transrectal approach have shown that funnelling of the proximal urethra was the sonographic sign most-frequently associated with loss of urine [288].

In about half the patients with stress incontinence in the study of Schaer et al. [289], funnelling was seen only with straining. In the other half, some degree of funnelling was already present at rest, increasing with straining and present with actual leakage. Enhanced views of the urethra are possible with sonographic contrast material.

Most recently, 3-D reconstruction from translabial views of the urethra has been used to compare findings in normal volunteers and those with ISD [290].

The most recent sonographic study of women with stress urinary incontinence found funnelling at rest in 109 of 330 patients, and found that the degree of vaginal relaxation as well as the parameters of intrinsic urethral function, including VLPP and urethral closure pressures, were worse in patients with funnelling than without. The authors of this study concluded that: “In primary genuine stress incontinence, bladder neck funnelling on ultrasound cystourethrography implies the potential coexistence of poor anatomic support and an intrinsic sphincter defect [291].” Ghoniem et al. [292] also found that urethral funnelling was more likely to be associated with low closure pressures, low VLPPs, and a higher incidence of ISD in patients with stress urinary incontinence. However, recently, Tunn et al. [293] could not find an association between the ultrasound findings of urethral funnelling with stress incontinence using an introital approach, demonstrating it only in 59% of the patients with stress urinary incontinence.

Ultrasound has been used to identify paravaginal defects prior to Burch colposuspension to guide surgical modification, and then repeated after surgery to show correction of the defects [294].

Urethral movement and funnelling seen by ultrasound resemble the rotational descent previously described by Nichols and Randall [295]. It is also consistent with the previously cited descriptions of Jeffcoate and Roberts, and that of Hodgkinson. Improved soft tissue detail seen with ultrasound has permitted an extension of these original observations. The anterior and posterior walls of the proximal urethra appear to move differently during increases in intra-abdominal pressure. At first, they appear to move together: the urethra begins its descent as a single unit. At some point, however, the anterior urethra becomes arrested in its rotational movement and appears to move more slowly. The posterior portion of the urethra continues to descend along with the vaginal wall [288, 296].

This difference in movement suggests a shearing apart of the two walls, leading to the appearance of funnelling, which can be seen as urine leaks out of the urethra.

On Valsalva, the proximal urethra rotates in a postero-inferior direction approximating to the symphysis pubis. This movement can be measured by comparing the angle of inclination between the proximal urethra and any other fixed axis. No normal values of bladder neck descent have been defined but cutoffs of 20, 25 and 30 mm have been reported to classify urethral hypermobility [297, 298]. The anatomical and functional integrity of PFM have an important role in the urethral support system and, therefore, in the continence mechanism. It has been shown that women with UI, compared to continent subjects, have less effective PFM in terms of: strength, reduced endurance, reduced thickness, coordination of PFM and lower abdominal muscles, and altered electromyographic activity [299-301]. With transperineal ultrasound it is possible to evaluate the urethral displacement towards the pubic bone caused by pelvic floor muscle contractions [302]. This mechanism is involved in maintaining urinary continence by determining good efficacy in intraurethral pressure transmission [303].

Anatomic correlation suggests that the pubourethral ligaments may restrict the movement of the anterior urethral wall, facilitating downward traction by the prolapsing vagina during stress, contributing to the shear. At the level of the pubis, the posterior portion of the pubourethral ligament travels beneath the pubis to form an anterior portion, which supports the clitoris in women, and the corpora cavernosa in men. Milley and Nichols [304], Zacharin [305, 306] and Mostwin [307] have previously suggested that the posterior pubourethral ligaments might support the urethra, and their laxity could contribute to the descent of the urethra in stress incontinence. These studies, however, suggest a different interpretation. Longitudinal and cross-sectional views of the proximal urethra show that the ligaments travel along only the anterior portion of the urethra as they pass beneath the pubis to emerge as the anterior pubourethral ligaments.

The vagina and its bilateral attachments forming the lateral sulcus support the posterior part of the urethra. It is more likely that the vaginal wall and its attachments become weaker than the strong condensations of endopelvic fascia forming these ligaments. Therefore, the pubourethral complex, even if attenuated, probably remains stronger than the underlying vaginal wall. Sonographic examination of the prolapsing urethra therefore suggests arrest of anterior urethral wall movement by the pubourethral complex, while the vaginal wall continues to rotate, pulling the posterior wall of the urethra along with it.

These anatomical considerations, combined with current knowledge about pudendal nerve activity in normal, prolapse or stress incontinence, suggest an inter-relationship regarding urethral closure and vaginal movement. As intra-abdominal pressure increases, the proximal urethra experiences two kinds of forces, which may lead to opening. The first of these is a shearing force produced by the unequal separation of the anterior and posterior urethral walls from the pubis during straining. This is the effect of vaginal mobility on urethral closure. The second is an expulsive force, produced by the transmission of intra-abdominal forces to the bladder, which must be resisted by the urethra if opening is to be prevented.

The urethra resists this primarily by intrinsic closure of the pudendally innervated striated sphincter, aided by vaginal support.

3D ultrasound has recently introduced new insights into the image of urethral sphincters. Athanasiou et al. [308], using a transvaginal approach, reported a close correlation between the urethral sphincter volume and the degree of incontinence assessed on videocystourethrography ($r = .-65$; $P < 0.001$).

With the use of three-dimensional ultrasound Athanasiou et al. [308] evaluated the urethra and the urethral sphincter in women with stress incontinence. These authors reported that this group of women have urethral sphincters that are shorter, thinner, and smaller in volume compared to controls.

Urethral vasculature has also been postulated to play a role in the continence mechanism and different Doppler parameters have been studied to evaluate correlation with stress urinary incontinence.

However, Tsai et al [309] reported that urethral vasculature, and in particular the anterior branch of the middle urethral vessels is less likely to be seen after the menopause (89.1% vs. 79.2% pre- and postmenopause, $P = 0.030$). In the postmenopausal women hormone replacement therapy did not affect the appearance of the urethral vessels.

Results are controversial since some authors [280] reported less periurethral vessels and flow in women suffering from stress urinary incontinence whereas others [310] could not find any difference in the appearance of the urethral vasculature in subjects with or without stress urinary incontinence.

It is likely that these shearing and expulsive forces are generated simultaneously as intra-abdominal pressure rises. One can easily imagine that the urethra can be brought to a continence threshold beyond which urethral closure cannot be maintained. One can further imagine that repeated episodes of prolapse may eventually stretch, tear or attenuate sphincter mass and contribute to a chronically weakened urethra manifested by low VLPP or low urethral closure pressures, characteristic of ISD. After severe or prolonged untreated prolapse and stress incontinence, vaginal support alone may not be sufficient to correct the deficiencies of an exhausted sphincter. Although theoretical rather than evidence-based, such considerations may direct future research efforts towards a more integrated hypothesis regarding stress incontinence in women. The relative contributions of abnormal vaginal mobility and intrinsic urethral function should be considered as part of a continuum rather than a dichotomy. Current research and interest has concentrated mostly on ISD as the primary cause of SUI in women, but the relationship of the many factors affecting urethral support and function should remain a perspective in interpreting emerging findings.

V. CONCLUSIONS

We are approaching a new classification of stress incontinence which will integrate hypermobility and urethral dysfunction as inter-related elements on a spectrum of change. Certain concepts have stood the test of time, and they are included below, along with conclusions:

1. Many patients with urodynamic stress incontinence show urethral mobility (Level 2), although it is not yet known what it is about that mobility which permits urethral opening during stress.
2. Some patients who present with minimal mobility have primary or residual sphincter insufficiency.
3. Sphincter insufficiency is related to a decline in striated sphincter muscle mass and function as measured by electrophysiological studies of pudendal nerve and sphincter function, and MRI and sonographic estimates of muscle mass (Level 1). If repeated episodes of vaginal traction can be shown to enhance sphincter damage, then the effect of early treatment of stress incontinence and prolapse on future development of ISD should be investigated, since advanced ISD remains difficult to treat.
4. Successful operations can restore urethral position but do not restore urethral function. A good surgical outcome probably requires a certain reserve of urethral function. It is in the area of functional understanding of urethral anatomy that the greatest progress is likely to be made.

D. PELVIC ORGAN PROLAPSE

I. PATHOPHYSIOLOGY OF PELVIC ORGAN PROLAPSE

Anatomical support of pelvic viscera is mainly provided by the levator ani muscle complex and connective tissue attachments of the pelvic organs: vaginal support arises from the connective tissue attachments between the vagina and the pelvic sidewall, the vaginal wall, and the levator ani muscles [311, 312].

Two mechanical principles explain how the uterus and vagina are normally held in place. First, the uterus and vagina are attached to the walls of the pelvis by the endopelvic fascia that suspends the organs from the pelvic sidewalls. Second, the levator ani muscles constrict the lumens of these organs closed, forming an occlusive layer on which the pelvic organs may rest [313].

The levator ani complex consists of the pubococcygeus, the puborectalis, and iliococcygeus muscles [314]. These muscles are tonically contracted at rest and act to close the genital hiatus and provide a stable platform for the pelvic viscera. Decline of normal levator ani tone by denervation or direct muscle trauma, results in an open urogenital hiatus, weakening of the horizontal orientation of the levator plate, and a bowl-like configuration [315, 316].

The supportive connective tissues are a continuous, highly interdependent sheet in which all components interact to achieve support of the vagina and, therefore, of the pelvic organs. DeLancey has introduced the concept of dividing the connective tissue support of the pelvis into three levels, with level I, II and III representing apical, midvaginal and distal support respectively. The upper portion of the paracolpium (Level I) consists of a relatively long sheet of tissue that suspends the vagina by attaching it to the pelvic side wall, and it is responsible for suspending the apex of the vagina after hysterectomy. In the middle third of the vagina, the paracolpium attaches the vagina laterally, to the arcus tendineus and fascia of the levator ani muscles (Level II). This attachment stretches the vagina transversely between the bladder and the rectum. The structural layer that supports the bladder (pubocervical fascia) is composed of the anterior vaginal wall and its attachment through the endopelvic fascia to the pelvic side wall. Similarly, the posterior vaginal wall and endopelvic fascia (rectovaginal fascia) form the restraining layer that prevents the rectum from protruding forward. The vagina´s lower third (Level III) fuses with the perineal membrane, levator ani muscles and perineal body, without any intervening paracolpium (**Figure 11**) [313, 317]. Damage to the upper suspensory fibres of the paracolpium causes a different type of prolapse from damage to the mid-level supports of the vagina. Defects in

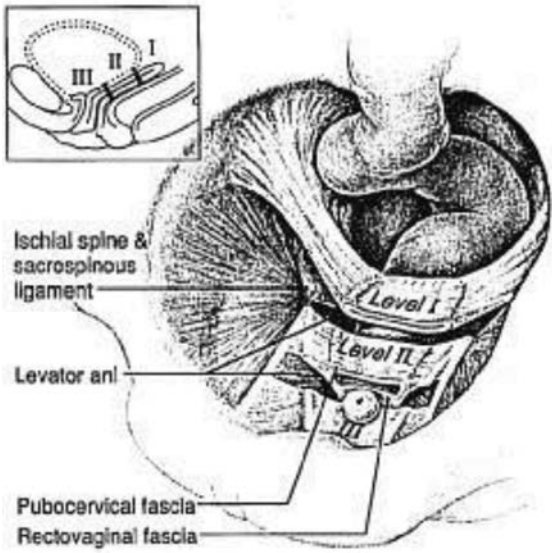


Figure 11. Level I (suspension) and level II (attachment). In level I the paracolpium suspends the vagina from the lateral pelvic walls. Fibers of level I extend both vertically and also posteriorly towards sacrum. In level II vagina is attached to arcus tendineus fasciae pelvis and superior fascia of levator ani. From DeLancey et al, Clin Obstet Gynecol,1993 [318].

the support provided by the mid-level vaginal supports (pubocervical and rectovaginal fascia) result in cystocele and rectocele, while loss of the upper suspensory fibres of the paracolpium and parametrium is responsible for the development of vaginal and uterine prolapse. These defects usually occur in varying combinations and this is responsible for the diversity of clinical problems encountered within the overall spectrum of pelvic organ prolapse [313].

For conceptual purposes the supportive connective tissue has been related to structural elements of the pelvic floor: the uterosacral ligaments (level I); the paravaginal attachments (endopelvic fascia) that connect the lateral vaginal walls to the arcus tendineous fascia pelvis (ATFP) and the fascia of the levator ani muscles (level II); the perineal membrane and the perineal body (level III) [317]. **Table 1** lists the structural elements of pelvic organ support, their possible damage and subsequent site of pelvic organ prolapse.

The integrity of muscular, connective and nerve structures is essential to guarantee normal pelvic organ support. If one of these factors fails, the other might be able to compensate to a certain degree.

In an American gynaecological clinic population (18-83 years), approximatively 3-6% of women had pelvic organ prolapse descending beyond the vaginal opening on routine pelvic examination [319]; an estimated 11% of women will undergo surgery for pelvic organ descent and urinary incontinence sometime in their lifespan [320].

The aetiology of pelvic organ prolapse is thought to be multifactorial with contributions from both environmental and genetic risk factors. Environmental factors that contribute to POP include vaginal delivery, chronic increases in intra-abdominal pressure, obesity, advanced age and oestrogen deficiency [321, 322]. Evidence for a genetic contribution to pelvic organ prolapse has been found in family-based studies, candidate gene association studies, expression studies and linkage studies [323]. **Table 2** lists anatomical and functional determinants of normal pelvic organ support. It also summarises the possible nature of failure and its potential causes as well as the established and theoretical risk factors.

Vaginal delivery has been considered the main causal factor in the development of pelvic organ prolapse for some years [112, 320, 324-327]. However, if it is true that all women undergo pelvic floor stretching during vaginal delivery, not all of them develop a further prolapse; moreover, pelvic floor dysfunction has also been described in women who gave birth by caesarean section only [112, 322] and in nulliparous women [328]. Therefore, vaginal delivery does not totally explain the origin and progression of pelvic floor descent in all women. This supports the hypothesis that other causes, besides obstetrics, are involved in the aetiology of pelvic organ prolapse: connective tissue deficiencies, genetic predisposition, sexual hormones, pregnancy, ageing, menopause, obesity, neuropathies, ethnicity and family history.

In the last decade, attention has increasingly focused on understanding the molecular basis of POP and the recognition of the potential molecular markers and their modulators in pelvic floor supportive tissues in order to identify women predisposed to develop POP.

1. INHERITANCE, GENETIC AND ETHNIC PREDISPOSITION

Several studies have recently focused their attention on the inheritable predisposition for pelvic organ prolapse.

In the large case-control study carried out by Chiaffarino et al. [329], a higher risk of prolapse was reported in women whose mother (OR: 3.2; 95% CI: 1.1-7.6) or sister (OR: 2.4; 95% CI: 1.0-5.6) were affected by the same condition; their data support that first-degree **family history** of prolapse is a risk factor for POP.

Jack et al. [330] demonstrated that the risk of POP among siblings of young women (average age: 37 years) with stage III and IV POP was five times higher than in the general population. Genetic analysis of the inheritance pattern within these families showed that pelvic organ prolapse segregated in a dominant fashion with incomplete penetrance.

Table 1. Structural elements of pelvic organ support, their possible damage and subsequent site of pelvic organ prolapse. The levels of support and anatomical defects are derived from the anatomical studies of DeLancey [313, 317].

	Structure	Failure/Defects	Anatomical results
Level 1	Uterosacral ligaments	- Disruption - Overdistension - Elongation	- Uterine prolapse - Vault prolapse
Level 2	- Anterior endopelvic fascia (pubocervical fascia) - Posterior endopelvic fascia (rectovaginal fascia)	- Central impairment of fascia - Lateral detachment of fascia from ATFP - Impairment of fascia	- Midline cystocele - Paravaginal defect-cystocele - Rectocele
Level 3	Perineum	- Disruption from endopelvic fascia - Disruption of bulbocavernosus muscles	- Excessive perineal descent - Rectocele

Table 2. Determinants of normal pelvic organ support. Possible sites of failure and possible causes, established and theoretical risk factors. LOE= LEVEL OF EVIDENCE

Normal support	Failure	Possible cause/risk factors
Normal connective tissue including normal tone (smooth muscle cells)	• Reduced tone • Pathological type and cross linking (LOE 2) • Disruption (LOE 2)	• Genetic (LOE 2) • Pregnancy (connective tissue remodelling) (LOE 3) • Vaginal birth (mechanical) (LOE2) • Chronic pelvic floor stress (straining, constipation, asthma) • Obesity
Normal attachment of connective tissue and pelvic floor musculature	• Disruption, detachment (LOE2)	• Vaginal birth (LOE 1) • Hysterectomy, pelvic operations (LOE3) • Chronic pelvic floor stress (LOE3) • Pelvic trauma (accidents, falls) (LOE3)
Normal tone of the pelvic floor muscle	• Hypotonic pelvic floor muscle (LOE4)	• Pregnancy, childbirth (ischemic, mechanical, hormonal) (LOE2) • Reduced connective tissue tone • Chronic pelvic floor stress
Normal, nearly horizontal, axis of the vagina	• Vertical course of the vagina (LOE3)	• Hysterectomy, pelvic operations including Burch colposuspension (LOE3) • Chronic pelvic floor stress • Vaginal birth (LOE2)
Normal innervations and pre-programming of abdominal capsule and pelvic floor muscle	• Denervation/re-innervation (LOE1) • Loss of pre-programming (LOE4)	• Vaginal birth (LOE1) • Pelvic trauma/pain • Delayed or lack of pelvic floor contraction during increased abdominal pressure (LOE3)

The recent findings of high concordance in the POP stage between nulliparous women and their parous sisters strongly support the hypothesis of a familial basis for POP. Buchsbaum et al. [331] investigated the role of familial factors in the development of pelvic organ prolapse by comparing the prevalence of this condition in nulliparous postmenopausal women and their parous sisters. By compartment, there was a 74.3% to 91.1% concordance in prolapse stage within sister pairs. In discordant sister pairs, the parous sister was found to have the more advanced prolapse 88% of the time. Based on these results, the authors conclude that a high concordance of pelvic organ prolapse in nulliparous and parous sister pairs suggests a familial predisposition toward developing this condition. However, vaginal delivery appeared to confer a risk for more advanced pelvic organ prolapse. LEVEL OF EVIDENCE: II-2.

Some studies have drawn attention to the incidence of pelvic organ prolapse amongst identical **twins**.

In the larger Swedish twin registry of 3,376 monozygotic and 5,067 dizygotic female twin pairs, a greater twin similarity among the monozygotic twins was found, indicating the influence of a genetic component to the aetiology of pelvic organ prolapse. Genetic and non-shared environmental factors seemed to contribute equally to the development of pelvic floor disorders in these women, about 40% for each factor [332].

Buchsbaum et al. [333] even reported that vaginal delivery was not associated with clinically relevant differences in relaxation of the pelvic support system within four sets of postmenopausal identical twins with different parity status.

Genetic variants that run in families with an increased incidence of pelvic organ prolapse have been documented.

A recent study provides strong scientific evidence for a genetic contribution to pelvic organ prolapse: using a genome-wide association study, Allen-Brady et al. [334], demonstrated that 6 single-nucleotide polymorphisms (SNPs) are significantly associated with POP in high-risk familial case group participants. LEVEL OF EVIDENCE: II. Their results showed that two of the six SNPs are located within the genes ZFAT and COL18A1, both with Mendelian inheritance in man. The ZFAT has been found to play a transcriptional regulator role for immune regulation and apoptosis and, hence, may affect development of the muscle and connective tissue of the pelvic floor. The COL18A1 gene (precursor of the collagen XVIII) may play a role in the structural organisation of basement membranes. The other four SNPs identified are intergenic, but one of them is close to the ANTXR2 gene, which binds intravenously to collagen and laminin, suggesting that it may be involved in extracellular matrix adhesion. The authors identified at least three strong candidate genes for POP that warrant follow-up.

Recent data suggest a role of genetic influence in early onset of POP. In a family in which three generations of female relatives suffered from prolapse at a very young age, a polymorphism in the promoter of LAMC1 gene has been found that seems to increase the susceptibility to early onset pelvic organ prolapse, as an autosomal dominant transmission [335].

One study examined gene expression of structural proteins that are related to actin and myosin in five women with, and five women without, pelvic organ prolapse in the pubococcygeal muscle. Several genetic differences between subjects and controls with gene under- and overexpression were found [336].

In mice, HOXA11 has been identified as an essential gene for the development of the uterosacral ligaments [337]. In HOXA11-null mice, the uterosacral ligaments were absent. Women with POP might have weakened connective tissue due to changes in a signalling pathway involving HOXA11 [337].

Increasing evidence supports a genetic aetiology of POP, also with respect to abnormal extracellular matrix remodelling [338]. A genetic predisposition to POP specific to elastin metabolism was noted in the rodent model, in which genetic mutation of the LOXL1 or the fibulin-5 gene in mice are involved in the altered elastic fibre assembly and then in the pathogenesis of the pelvic prolapse [339]. Altered gene expression of elastin has also been described in women with POP [340].

Genetic screening would certainly be an essential future tool for identifying the woman at risk of developing POP and for refining the counseling of women deemed to be increased risk. The primary prevention tool could be the adaptation of mode of delivery in at-risk groups. These patients could also benefit from changing their management such as whether surgery should be considered early or late in the woman´s lifespan.

Race is another demographic factor that seems to be associated with the development of POP. Some studies reported that Hispanic and European women appear to be at higher risk for POP than those of African, Asian or other descent [319, 322, 326, 341, 342]. This is also supported by evidence suggesting that women of Asian descent have reduced inherent pelvic organ mobility. In a cadaveric study, Zacharin [343] reported that Chinese women have stronger and thicker pubourethral ligaments, endopelvic fascia and endopelvic attachment to the obturator fascia compared to Caucasian women. More recently, Dietz et al. [342] confirmed these results using pelvic floor ultrasound, showing that Asian women have significantly less pelvic organ mobility than Caucasian women both antepartum and postpartum.

In cohort analysis of 27,342 women, Hendrix et al. [326], confirmed previously reported differences between white and African-American women. Hispanic

women had the highest rate of uterine prolapse (OR: 1.24, 95% CI: 1.01-1.54) and an increased risk for cystocele (OR: 1.20, 95% CI: 1.05-1.36) but not rectocele (OR: 0.95, 95% CI: 0.82-1.11).

The reasons for these ethnic differences are unclear; however, some evidence indicates that African-American women have smaller pelvic outlets than those of European descent [344].

Other connective tissue deficiencies such as **hernias** may share common pathophysiological mechanisms with POP. In a group of 60 women with advanced prolapse, the total prevalence of hiatal and inguinal hernias was significantly higher than in a control group of 60 women with mild or no prolapse (31.6% vs. 5%, p<0.001) [345].

A population-based, cross-sectional study of 5,489 Stockholm women found an OR of 1.8 for a positive association with symptomatic prolapse in women with a history of conditions suggestive of deficient connective tissue (varicose veins/hernia/haemorrhoids) [346].

McLennan et al. [347] demonstrated that the risk of prolapse was 1.4 (95% CI 1.2-1.8) times higher in women with a family history of prolapse and/or hernia, after adjusting for vaginal deliveries, hysterectomy and incontinence. The authors confirm that heredity is a risk factor for prolapse and suggest that history taking should include both male and female family members.

Taken together, this evidence suggests that there is a familial or genetic basis for POP in some women, and that heritable or genetic factor play a role in its development.

2. ALTERATION OF COLLAGEN, ELASTIN AND SMOOTH MUSCLE OF THE VAGINAL AND SUPPORTIVE TISSUE.

It has been demonstrated that young women with POP are more likely to have connective or neurological tissue diseases and congenital abnormalities [348].

Women with Marfan or Ehlers-Danlos syndrome have high rates of POP. Intrinsic joint hypermobility is another well recognised connective tissue disease that is associated with pelvic descent [349-352]. This finding supports the hypothesised aetiological role of connective tissue disorders as a factor in the pathogenesis of this conditions [353].

The vaginal wall is comprised of four layers: a superficial layer of non-keratinised stratified squamous epithelium; a subepithelial dense connective tissue layer composed primarily of collagen and elastin; a layer of smooth muscle referred to as the muscularis; and a layer of adventitia, composed of loose connective tissue. The subepithelium and muscularis together are thought to confer the greatest tensile strength to the vaginal wall. In the normally supported vagina, the supportive connective tissues pull the vagina up and back away from the vaginal introitus over the levator ani muscles. A normally supported vagina, in turn, provides support to the bladder, urethra, uterus and rectum. Disruptions of - or damage to - these connective tissue structures and injury to the vaginal wall are thought to be two important mechanisms causing prolapse.

The connective tissue of the vagina and supportive tissues contains a fibrillar component (collagen and elastin) and a non-fibrillar component (non-collagenous glycoproteins, hyaluronan, and proteoglycans). In addition, and with the exception of the arcus tendineous, these tissues contain a significant amount of smooth muscle. The fibrillar component is thought to contribute the most to the biomechanical behaviour of these tissues. The quantity and quality of collagen and elastin are maintained through a precise balance between synthesis, post-translational modification, and degradation.

Therefore, the integrity of the vagina and its supportive connective tissues are essential for keeping the pelvic organs in their normal anatomic position. Evaluation of these tissues from a biochemical perspective enables us to better discern the complex interplay between structural composition and supportive capacity.

Collagen types I, III and V are the main structural components of vaginal epithelium and endopelvic fascia and they are thought to be the principal determinants of tissue strength. Type I collagen confers strength to tissues while type III contributes to elasticity. Type III collagen is the primary collagen subtype in the vagina and its supportive structures. The ratio of collagen I to III is an indicator of tensile strength: the higher the amount of collagen type III, the lower is the mechanical strength. To our knowledge the role of type V collagen, which is found in small quantities in the vagina, is still unknown.

The turnover of connective tissues throughout the body is maintained by a family of highly conserved, zinc-dependent endopeptidases referred to as matrix metalloproteinases (MMPs). The MMPs are involved in both normal physiological and pathological proteolytic processes, which are an integral part of tissue remodelling in both women with and without prolapse. An excessive tendency towards connective tissue degradation may underlie the predisposition of some women to prolapse.

Interstitial collagens (types I, II and III) are cleaved by MMP-1, 8 and 13. The cleaved collagen fragments are susceptible to rapid gelatinase (MMP-2 and 9) degradation into amino acids. These gelatinases (MMP-2 and 9) also degrade elastin.

Reports of decreased total collagen in pelvic tissue from women with POP suggest that collagen degradation may contribute to POP. Collagen degradation depends on the activity of MMPs produced by connective tissue cells. MMP proteolytic activity is specifically regulated by their inhibitors, TIMPs, which

bind stoichiometrically to MMPs to inhibit their activity. The balance between MMPs and TIMPs defines the collagenolysis.

In women with prolapse, MMP-2 mRNA expression is increased with a concurrent decrease in the inhibitor TIMP-2 [354]. Recent data also indicate increased MMP-1 expression and decreased collagen I in the uterosacral ligaments of women with POP [355]. In contrast, collagen I and III mRNA expression was increased in vaginal tissue from women with POP [356]. Discrepancies in the literature can be due to the different methodological issues (different tissues targeted or a different method of protein quantification) used. Mismatches between mRNA and protein data are often found when examining proteins in the extracellular matrix. Thus, gene expression should always be confirmed with protein expression. These issues contribute to significant variations in the reported data and underscore the importance of careful research methodology. These discrepancies also suggest the possibility that different pathways in the extracellular matrix may be activated depending on injury type and severity, mechanical load and environmental factors [338].

Despite discrepancies in the precise MMP/TIMP or collagen type, the reported data and numerous other publications indicate that women with POP show an abnormal pelvic extracellular matrix metabolism with increased collagen remodelling.

Takano et al. [357] demonstrated that the general amount of collagen in the parametria is reduced in pre- and postmenopausal women with pelvic organ prolapse compared with women without prolapse. Moalli et al. [358] showed that collagen III is increased in vaginal subepithelium and muscularis in patients with prolapse relative to patients without prolapse, independent of age and parity. LEVEL OF EVIDENCE II-2. Increase in collagen III has also been reported in the uterosacral and cardinal ligaments of women with prolapse [359, 360]. The Moalli's group [361] demonstrated that collagen III is the primary subtype in the arcus tendineus fascia pelvis; a decrease in the ratio of collagen I/(III+V) is associated with menopause in the absence of hormone therapy and a restoration of this ratio to premenopausal levels with hormone therapy. From these data the authors suggested that sex steroid hormones may improve the biomechanical properties of the supportive tissues of the vagina.

As all studies involving the procurement of human tissue are by necessity cross-sectional, it is impossible to determine whether the increase in collagen III reflects the causes or effects of prolapse. In either case, the increased flexibility and distensibility plus the decreased tensile strength associated with an increase in collagen III are likely to contribute to the progression of POP.

Elastin is primarily laid down during fetal development and rarely synthesised in adult tissues. In contrast to the other tissues in which elastin fibres do not experience a turnover in a lifespan, there is cyclical remodelling of elastin fibres in the reproductive tract. A massive degradation of elastin occurs at the time of parturition, followed by postpartum resynthesis, allowing recovery of reproductive tissues to their pre-pregnancy state [362]. Mice deficient in LOX (lysyl oxidase) fail to replenish mature elastin fibres in the reproductive tract following parturition and develop spontaneous prolapse [363]. Yamamoto et al. [340] found a marked decrease in elastin mRNA and tropoelastin protein in the cardinal ligaments of women with pelvic organ prolapse relative to women without prolapse. Chen et al. [364] demonstrated a significant decrease in the endogenous inhibitors of elastases with increase in elastolytic activity in vaginal tissue from women with stress urinary incontinence and pelvic organ prolapse compared with control subjects. Therefore, these data suggest that the proper degradation, synthesis, and regeneration of elastic fibres are essential for maintaining pelvic organ support.

If damaged or destroyed, metabolically repaired elastin frequently results in malformed and dysfunctional repair products. Proteolytic enzymes capable of degrading elastin include the serine proteases, such as neutrophil elastase, the cysteine proteases, and MMP-2, 9 and 12. Marked decreases in elastin gene transcripts and elastin synthesis in pelvic fibroblasts were noted in women with POP [340], suggesting that altered elastin metabolism may contribute to prolapse. In rodent models with genetic disruption to LOXL1 or fibulin-5 gene, prolapse develops due to failure to synthesise and assemble functional elastic fibres [363]. Elastin content was decreased in the uterosacral ligaments of women with POP, as were LOX, and LOXL1 and LOXL2 gene expression [365].

A recent study by Moon et al. [366], evaluated the alteration of elastin metabolism in women with pelvic organ prolapse in a prospective case-control study: their results showed that expression of neutrophil elastase and matrix metalloproteinase-2 mRNA was higher in women with than in those without POP. Compared to before menopause, neutrophil elastase and matrix metalloproteinase-2 showed a significant decrease in postmenopausal women without POP, although they remained increased in postmenopausal women with POP. Alpha-1-antitrypsin was significantly lower in postmenopausal women with pelvic organ prolapse than in postmenopausal women without. The activities of neutrophil elastase, matrix metalloproteinase-2 and matrix metalloproteinase-9 were increased in women with POP, and these trends were similar to neutrophil elastase and matrix metalloproteinase-2 expression even after adjusting for age, parity and menopausal status. This study demonstrates that after menopause increased elastolytic protease has a significant role in the development of POP.

The strongly heritable connective tissue diseases, in which pelvic organ prolapse predominates as a result of an elastinopathy, highlight the importance of elastic fibres for maintaining vaginal support. Marfan's syndrome, characterised by mutations in the fibrillin-1 gene, and cutis laxa with mutations in the elastin and fibulin-5 genes, are notable for an increased incidence of POP in affected women [367-370].

Childbirth is an important risk factor for POP, not only for the mechanical trauma that the pelvic floor is submitted to: inflammatory pathways are activated during the complex process of tissue healing after birth trauma. During healing proteinases, growth factors such as TGF-β, cytokines and chemokines are secreted into the extracellular matrix by surrounding cells. TGF-β is one of a family of 25 kDa polypeptide growth factors that is currently viewed as the most important fibrosis promoting cytokine. It is responsible for extracellular matrix synthesis in fibroblasts, the differentiation of fibroblasts to myofibroblasts and the inhibition of matrix degradation by inhibiting MMP expression and upregulating TIMP expression. Thus, it is important in extracellular matrix metabolism and affects tissues or organs in various ways. There is sparse but growing evidence of TGF-β modulation in pelvic connective tissue. Large quantities of TGF-β1 are stored in readily available form in the extracellular matrix. Release and activation of stored latent TGF-β1 by proteases can generate rapid, highly localised signals. Therefore, the modulation of TGF-β1 activity by extracellular proteases provides faster signal transduction than alterations in gene expression. This is important for tissue remodelling during pregnancy and repair after birth trauma [338].

3. NEUROLOGICAL FACTORS

Integrity of the pelvic innervation is essential for normal pelvic function. The changes in neurophysiological parameters seen after childbirth were interpreted to reflect neuromuscular injury caused by forces exerted on the sacral plexus, pudendal nerves, and pelvic floor muscles.

Abnormal findings have also been found in women with prolapse or stress incontinence. Histologically, there were smaller and fewer nerve bundles in women with posterior vaginal wall prolapse compared with women without prolapse [371]. It has been demonstrated that the density of peptide-containing nerves in the periurethral tissue and in the levator ani muscle in women with prolapse is reduced [372, 373].

Between 1985 and 1987, Allen et al. [177] found that 80% of primigravidae developed evidence of partial denervation of the pelvic floor following delivery. However, evidence of reinnervation and increased fibre density 2 months after vaginal delivery has been detected [177, 374]. Snooks et al. investigated 14 multiparous women from their previous studies [176, 374] 5 years after first vaginal delivery and demonstrated that pelvic floor striated sphincter musculature denervation progressed, indicating that age is a contributory factor [178]. Similarly, progressive denervation with time up to 15 years postpartum was found in another prospective study, corroborating the ageing factor [375].

The pudendal nerve innervates the voluntary urethral and anal sphincters, but it does not innervate the levator ani muscles, which receive their own nerve supply from the sacral plexus. Therefore, there is currently no clear evidence whether the neurological damage is responsible, together with the mechanical damage of stretching, for the visible levator defects.

Information from electrodiagnostic studies has demonstrated that birth causes changes in mean motor unit duration after vaginal birth and changes in pudendal nerve conduction patterns [177, 178, 376-378]. Prolongation of the pudendal nerve terminal motor latency (PNTML) is thought to be a result of pudendal nerve damage during vaginal delivery. Significantly prolonged mean PNTML´s have been found in women two to three days after vaginal delivery, compared to a multiparous [176] and a nulliparous control group [374]. At follow-up five years later, prolongation of PNTML persisted [178]. Two prospective analyses demonstrated a prolongation of PNTML antenatally to six to eight weeks after vaginal delivery, particularly after the first delivery [379, 380]. But, again, many of these changes seem to be temporary, as two-thirds of the women with an abnormally prolonged PNTML after delivery had normal measurement six months later [379].

Little recent electrophysiological work has been added to the literature, probably due to the technical difficulty of the nerve function tests in clinical practice.

Although it has not been proved in studies, it is reasonable to assume that periods of pain and discomfort after childbirth (e.g., perineal tears and episiotomy) and especially pain related to attempted PFM contraction could lead to a temporary nonactivation of the PFM. This could be the origin of disturbances in behavioural patterns, which would need to be readjusted. In combination with a particularly vulnerable pelvic floor neural control, whose complexity only evolved phylogenetically after the attainment of the upright stance, such a temporary disturbance of neural control after childbirth may persist, although the pelvic tear(s) resulting from vaginal delivery would have fully recovered.

Therefore, the effects of vaginal delivery on pelvic floor nerves are still controversial. While it seems logical that vaginal delivery causes some neuromuscular injury which would predictable to the development of pelvic organ dysfunction, many details are uncertain.

4. PREGNANCY AND PELVIC FLOOR MUSCLE REMODELLING

Several of the changes occurring prior to delivery are in all likelihood normal physiological changes and may be secondary to hormone-induced collagen alterations. Hormonal alterations are essential to prepare the body and to adjust the musculature and connective tissue for vaginal birth.

The high progesterone levels during pregnancy influence the pelvic floor structures: progesterone has smooth muscle-relaxing and oestrogen-antagonising effects, reducing the tone in the ureters, bladder and urethra [381].

Relaxin, increases markedly during pregnancy and it modifies the connective tissue: its collagenolytic effect, that allows appropriate stretching during vaginal birth, has been demonstrated in guinea pigs [382]. As a likely result of connective tissue remodelling in preparation for birth, Landon and colleagues found that the connective tissue of the rectus sheath fascia and the obturator fascia could be stretched to greater length during pregnancy, but it is also much weaker. In some women, these changes may be irreversible and further stretching beyond physiological limits may result in permanent dysfunction [383].

Recently, several studies have focused on the effect of pregnancy on the pelvic floor and on the development of prolapse.

Rahn et al. [384] identified pregnancy-induced changes in biomechanical properties of the vaginal wall and compared these with fibulin-5 knockout mice (Fbln5−/−) with and without prolapse. Compared to nonpregnant mice, vaginas of pregnant and Fbln5−/− (with prolapse) mice exhibited decreased maximal stress, increased distensibility and strain, plus decreased stiffness. Tissues from Fbln5−/− mice without prolapse were similar to non-pregnant animals. The authors concluded that pregnancy confers remarkable changes to the vaginal wall that include increased distensibility, decreased stiffness and maximal stress. Elastinopathy alone is insufficient to cause significant changes in these properties, but prolapse confers additional alterations in distensibility and stiffness that are similar to those changes that have been observed in pregnancy. These changes may contribute to the poor durability of many restorative surgical procedures for prolapse.

The effect of pregnancy on the development of pelvic organ prolapse was evaluated by O'Boyle et al. [385]: in a series of 135 nulliparous pregnant women, POPQ stage appears to increase during pregnancy and does not change significantly following delivery. POPQ stage assignments and POPQ component measurements were compared for first-, second- and third-trimester examinations. Overall, POPQ stage was significantly higher in the third trimester than in the first. These findings probably represent normal physiological changes of the pelvic floor during pregnancy, but suggest that significant changes may be objectively demonstrated prior to delivery. In nulliparous women, pregnancy is associated with increased POPQ stage compared with non-pregnant control subjects [386].

Sze reported that 46% of 94 nulliparous women had pelvic organ prolapse at their 36-week antepartum visit. Of them, 26% had a stage II prolapse [387].

5. CHILDBIRTH

Undoubtedly, vaginal delivery constitutes a traumatic event for the pelvic floor: it may affect the pelvic nerves, the pubococcigeus-puborectalis muscle complex, the pelvic fascial structures or the anal sphincter. However, all women sustain trauma to their pelvic floor during vaginal birth, but only some experience long term injury.

Several attempts have been made to define fascial trauma after vaginal delivery. In the anterior compartment, childbirth may result in disruption of the 'endopelvic fascia', in particular of paraurethral and paravaginal structures. Analogous to increased bladder descent after childbirth, there is a highly significant increase in caudal displacement of the rectal ampulla after childbirth [388]. The rectovaginal septum and Denonviller's fascia are the connective structures involved in the posterior compartment damage that appears as a rectocele. It has recently been shown that vaginal childbirth also results in an increased prevalence of true rectocele, i.e. presumpted defects of the rectovaginal septum [389]. Such defects are strongly associated with symptoms of pelvic organ prolapse and obstructed defaecation [390].

Specific features of injury during vaginal birth influence whether a woman develops prolapse later in life. Several factors, that can be grouped together as descriptors of difficult vaginal delivery, are associated with increased occurrence of prolapse: forceps delivery, a prolonged second stage of labour, and large infant birth weight. Unfortunately, because of the overlapping nature of these different factors, it is difficult to determine which of them is causal and which of them is associated (e.g., forceps delivery is used when there has been a prolonged second stage of labour, and both of these factors increase in large-sized infants).

The role of childbirth in causing damage to the levator ani muscle (LAM), which is associated with both vaginal delivery and with pelvic organ prolapse, is probably the mediating mechanism in these injuries. Recent investigations using techniques such as magnetic resonance imaging (MRI) and three-four dimensional ultrasound have focused on the morphology of the levator ani complex and its integrity after delivery.

The occurrence of levator trauma postpartum is reported to be between 15-39.5% with ultrasound [151-157] (**Figure 12**) and between 17.7%-19.1% with MRI [159-161].

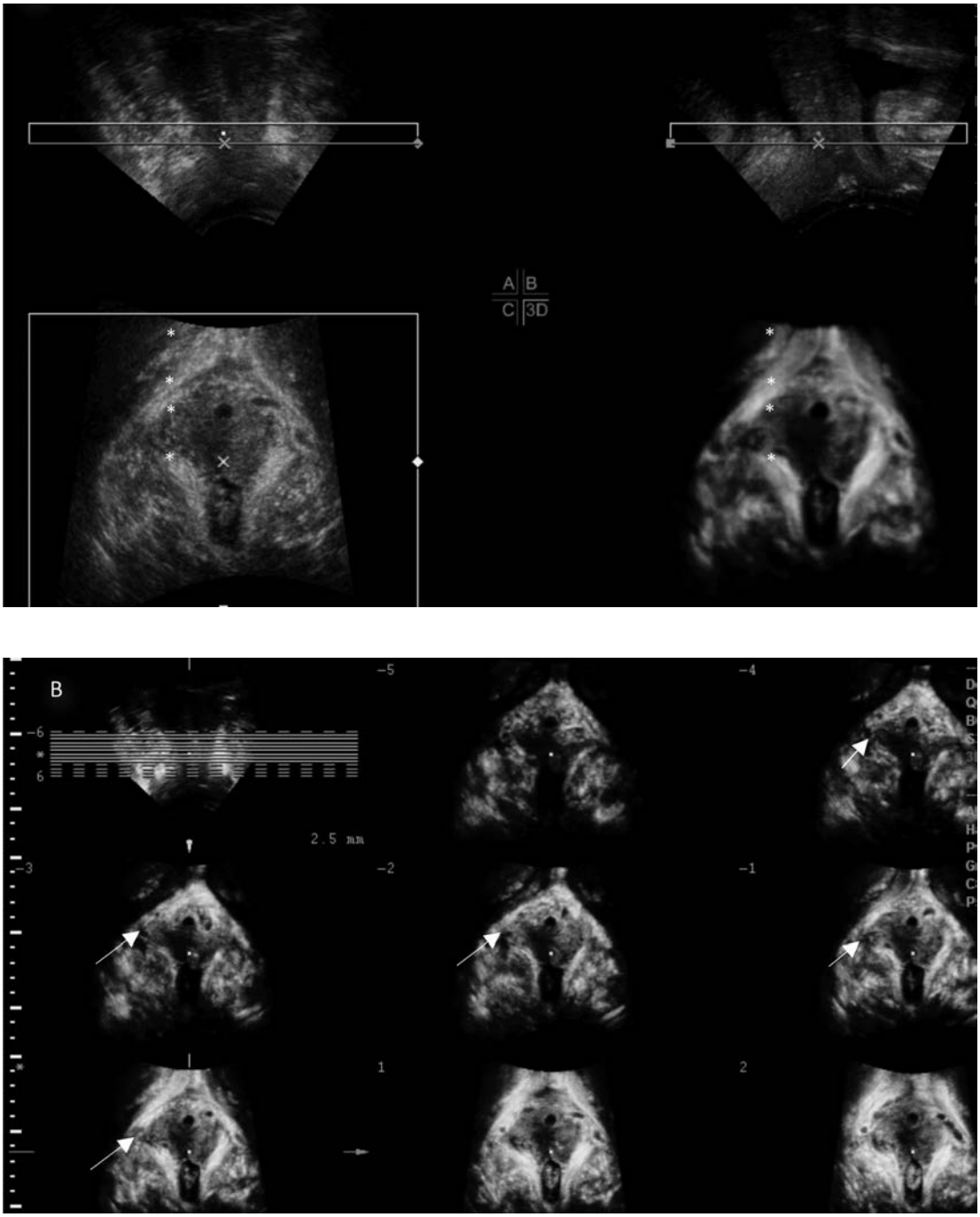


Figure 12. Levator ani defect early postpartum in a patient had spontaneous vaginal delivery (acquisition screen GE Voluson-e ® System).

A. In the multiplanar mode, the axial plane (lower left) and the rendered image (lower right) show an unilateral levator discontinuity (**) on the right side of pubococcigeal-puborectalis muscle.

B. Eight slices obtained with TUI in coronal-C plane in the same patients: the discontinuity (arrow) is demonstrated in at least three consecutive slices at and above the plane of minimal hiatal dimension (frames *,-1,-2,-3).

From Albrich et al, BJOG 2011 [156]

An observational study in women 2–4 weeks before and 2–6 months after vaginal childbirth provided direct proof for the hypothesis that childbirth is responsible for certain morphologic abnormalities of LAM observed in parous women and suggests that older age at first delivery is a risk factor for such trauma. LEVEL OF EVIDENCE II-3 [155].

To estimate the risk of prolapse associated with levator avulsion injury among a urogynaecological clinic population, Dietz et al. [165] retrospectively considered 781 women, with a mean age 53 years (range 15-89 years), and a median parity of 2 (range 0-12). Significant prolapse (stage II or higher) was diagnosed in 415 (53%) women, and 181 (23%) women were found to have levator avulsion defects. Prolapse was seen in 150/181 (83%) women with avulsion and in 265/600 (44%) women without avulsion, giving a RR of 1.9 (95% CI: 1.7-2.1). The association was strongest for cystocele (RR 2.3, 95% CI: 2.0-2.7) and uterine prolapse (RR 4.0, 95% CI: 2.5-6.5). The authors concluded that women with levator avulsion defects were about twice as likely to show pelvic organ prolapse of stage II or higher than those without, with an increased risk of cystocele and uterine prolapse.

Pelvic organ prolapse seems considerably lower after caesarean section [112, 344] but it has been described in prospective study in 35% of 26 women after caesarean section during active labour compared to 32% of 41 women who had spontaneous vaginal deliveries [387]. On the other hand, one epidemiological study using validated questionnaires negated the influence of labour versus no-labour caesarean delivery on pelvic organ prolapse [391] LEVEL OF EVIDENCE: II-2. Recent studies [156, 158] reported cases of early levator abnormalities after emergency caesarean section, and hypothesised a possible role of active labour in the occurrence of lesions damage to the pelvic floor muscle.

A recent study by Leijonhufvud et al. [113] considered a cohort of women having their first and all subsequent caesarean delieveries (n = 33,167), and an age-matched sample of women having only vaginal deliveries (n = 63,229). Women who had only vaginal deliveries had an overall increased risk for prolapse surgery (HR, 9.2; 95% CI: 7.0-12.1) compared with women who only had cesarean deliveries. They concluded that having only vaginal deliveries was associated with a significantly increased risk of pelvic organ prolapse surgery later in life compared to having caesarean deliveries.

There seems to be sufficient proof for the hypothesis that pelvic organ support can be impaired by vaginal delivery. It is unclear whether this effect is due to stretching or avulsion of structures and whether the observed changes are primary (i.e. directly due to childbirth) or the medium-term or long-term consequence of levator impairment. Several mechanisms may well coexist in one individual [392].

Furthermore, it has been shown that any delivery-related changes occur against the background of marked variations in pelvic organ support in young nulliparous women [393]. As the most significant changes are observed in those with the least organ mobility antenatally [394], the effect of childbirth may be a partial equalisation of those inter-individual differences.

6. OBSTETRIC AND MATERNAL FACTORS

Increasing vaginal parity was the strongest risk factor for pelvic organ prolapse in women younger than 60 years in the Oxford Family Planning Study [325]. Compared with nulliparous individuals, the relative risk of developing prolapse was 8.4 for a woman who had delivered two children and 10.9 (95% CI: 4.7–33.8) for someone with four or more children [325]. The Women's Health Initiative reported that single childbirth was associated with raised odds of uterine prolapse (OR 2.1;95% CI: 1.7–2.7), cystocele (OR 2.2; 95% CI: 1.8–2.7), and rectocele (OR 1.9; 95% CI: 1.7–2.2) [326]. Every additional delivery up to five births increased the risk of worsening prolapse by 10–20% [326]. Similarly, the Progetto Menopausa Italia study showed that the risk of pelvic organ prolapse rose with increasing parity [395].

Caesarean section seems to protect against prolapse development whereas forceps delivery increases the risk [391, 396]. Findings of a cross-sectional study of 3050 women randomly selected from a large southern California Health Maintenance Organisation showed that women who had undergone one or more vaginal deliveries had a significantly greater risk of developing symptomatic pelvic organ prolapse than did those who had only caesarean sections (OR 3.21; 95% CI: 1.96–5.26), after adjusting for age, parity, and obesity [391]. The attributable risk of vaginal delivery for development of symptomatic prolapse, or the proportion that could have been prevented with a policy of routine elective caesarean section, was 46% in this population. LEVEL OF EVIDENCE: II-2 [391].

Other obstetric factors that have been associated with an increased risk of pelvic organ prolapse, albeit less consistently, are high infant birth weight (>4500 g), vaginal delivery of a macrosomic infant, prolonged second stage of labour, and age <25 years at first delivery [396, 397]. Somewhat more controversial is whether pregnancy itself, distinct from mode of delivery, alters the risk of pelvic organ prolapse. In a small case-control study, pregnancy was associated with worsening prolapse compared with non-pregnant controls matched for age and ethnic origin [386]. A substantial proportion of pregnant nulliparous women show progression from stage 0 or I support in the first trimester to stage I or II in the third trimester [385]. This loss of vaginal support does not seem to return to baseline in the postpartum period.

To date, the studies are controversial considering younger age (25 versus 28 years of age) [396] as well as older age (more than 30 years) [398] at first delivery as a risk factor for the development of pelvic organ prolapse. Another large study did not reveal an association at all [322].

Despite the strong relationship between obstetric factors and pelvic organ prolapse, most cases of symptomatic cases arise a long time after vaginal childbirth, and most women who bear children do not have symptomatic prolapse [399].

7. AGE

Both incidence and prevalence of pelvic organ prolapse increase with advancing age. In a cross-sectional study of 1004 women (age 18–83 years) who attended for their yearly examination, the relative prevalence of this disorder rose by about 40% with every decade of life [319]. In the Women's Health Initiative, American women aged 60–69 years (OR 1.2; 95% CI: 1.0–1.3) and 70–79 years (OR 1.4; 95%CI: 1.2–1.6) had a higher risk of prolapse than did those aged 50–59 [326]. Similarly, findings of a cross-sectional study of 21449 menopausal Italian women showed an augmented risk of pelvic organ prolapse in women aged 52–55 years (OR 1.3; 95% CI:1.1–1.5) and those 56 years or older (OR 1.7; 95% CI: 1.5–2.0) compared with those younger than 51 years [395]. Surgery for prolapse is uncommon in women younger than 30 and older than 80 years; for women between these ages, the incidence rises steadily [320].

8. HORMONES

As age has been clearly shown to affect the prevalence and progression of POP, it is intuitive to believe that declining sex hormone levels observed with ageing may contribute to biochemical changes observed within tissue. However, several researchers studying hormonal status and prolapse have failed to find an association between oestrogen status and prolapse [325, 329, 344, 395].

The female lower urinary tract is a target organ for the action of the two sex steroid hormones, oestrogen and progesterone.

Steroidal hormones exert their effect on tissue through an interaction with specific intracellular receptors. Hormone receptor affinity may be at the root of the differences between women with pelvic floor diseases and normal controls. Progesterone receptors have been found to have greater expression in women with POP than in women without POP [400]. Several polymorphisms are present in the progesterone receptor gene that can alter its expression. A specific genotype (PGR rs484389) was significantly associated with the risk of having POP in a multivariate analysis [401]. Similarly, the oestrogen receptor β gene also contains multiple single nucleotide polymorphisms that affect its expression. A case-control study of 69 women with POP and 141 control subjects found that a specific haplotype for the oestrogen receptor β gene was associated with an increased risk of POP [402].

Studies have shown lower serum oestradiol (E2) levels in premenopausal women with SUI, with [403] and without concurrent POP [404], compared to control subjects. The impact of oestrogen on tissue may be related to its systemic or local levels, or altered sensitivity from a decreased number of receptors noted in genitourinary tissues [403, 405].

Skala et al. [406], evaluated the expression of oestrogen receptor (ER) alpha (α) and beta (β) and progesterone receptor (PR) in vaginal and periurethral tissue in women with genital prolapse. The expression of PR and ER varied with the extent of prolapse. For patients with prolapse >stage 1 (n=32), there was a significantly greater amount of PR in periurethral tissue (p=0.007) and a significantly lower expression of ER β in vaginal tissue (p=0.008) compared to patients with a low stage prolapse (n=15). Patients with stage II and III prolapse did not differ in their receptor expression. The authors concluded that the expression of PR in periurethral and ER in vaginal tissue varied with the extent of prolapse .

The current status of the literature suggests a hormonal impact on pelvic floor disorders, although the weak level of evidence emphasises the necessity for future research endeavours in this field to elucidate these complex relationships.

9. OBESITY

Increasing body-mass index also seems to have a role in the development of pelvic organ prolapse. An high BMI increases the risk of prolapse [319, 325, 396, 407, 408] and specifically for progressive rectoceles [409]. Increased waist circumference was associated with more pelvic organ prolapse in some studies [344, 409]. Handa et al. [409] demonstrated this for cystoceles. Women who are overweight (body mass index 25–30 kg/m²) and obese (>30 kg/m²) are at high risk of developing pelvic organ prolapse [326, 397]. Similarly, women with a body mass index of more than 26 kg/m² are more likely (OR 3.0; 95%CI: 1.6–5.7) to undergo surgery for prolapse than are those with a lower value [396].

10. CONSTIPATION

Repetitive straining, such as that seen in patients with chronic constipation or workers whose jobs entail heavy lifting, has also been associated with pelvic organ prolapse. Spence-Jones et al. [410] reported that straining at stool as a young adult was more typical in women with prolapse than in those without the disorder (61% vs 4%; p<0.001). Individuals with stage II or greater pelvic organ prolapse had an increased risk of constipation (OR 3.9; 95% CI: 1.4–11.9) compared to women with stage 0 or 1 prolapse [411]. However, findings of larger studies have disputed this association, and several groups have shown that neither overall stage of prolapse nor stage of the posterior vaginal wall correlate with bowel function [412-414]. Additionally, women with only urinary incontinence and no prolapse seem to meet Rome II criteria for constipation with the same frequency as those with advanced pelvic organ prolapse [414].

11. CHRONIC PELVIC FLOOR STRESS

Low socioeconomic status [415] and a labour-intensive occupation [329, 415, 416] are two demographic factors identified as risk factors for the development of POP.

Housewives, who perform more physically demanding work seem more likely to have prolapse (OR: 3.1; 95% CI: 1.6–8.8) than do professional managerial women [329]. Similarly, people with occupations involving heavy lifting might have a higher chance of undergoing surgery for pelvic organ prolapse [416].

12. PREVIOUS OPERATIONS

Although hysterectomy might increase the risk of subsequent POP, prolapse symptoms typically develop many years after this procedure [320, 325, 396, 417, 418]. In the Oxford Family Planning Study, surgical incidence for prolapse in women who had undergone a previous hysterectomy was 29 per 1000 women-years versus 16 per 1000 women-years for the entire cohort [325]. The cumulative risk of surgery for pelvic organ prolapse rose from 1% at 3 years after hysterectomy to 5% at 15 years. Risk was highest in women who had undergone a previous hysterectomy for prolapse (158 per 1000 women-years). In a retrospective cohort study of 149.554 women aged 20 and older, the mean interval between hysterectomy and surgery for pelvic organ prolapse in those who developed the disorder was 19.3 years [320, 419]. Contrary to findings of many other studies, the prevalence of prolapse in women with a uterus in the Women's Health Initiative was slightly higher than for those who had undergone hysterectomy, suggesting that previous prolapse of pelvic organs might have been repaired at the time of the procedure in this study population [326]. The surgical technique performed during hysterectomy, including performance of prophylactic culdoplasty, can lessen the development of a subsequent prolapse [420].

13. THE BONY PELVIS

There is evidence from several case control studies that variations in axial and pelvic skeletal structure can be associated with increased POP risks. These include increasing severity of thoracic kyphosis, a decrease in lumbar lordosis and in vertical orientation of the pelvic inlet, and an increase in the transverse diameter of the pelvic inlet [421-423]. In a case control study, Handa [424] compared 59 women with pelvic floor disorders with controls using standardised pelvimetry techniques during MRI. After controlling for age, race and parity and using a multiple logistic regression analysis, pelvic floor disorders were significantly associated with a wider transverse inlet (OR 3.4) and a shorter obstetrical conjugate (OR 0.23). The association between young age, advanced stage POP and severe disruption of pubic bone and pelvic muscle structure in women with bladder exstrophy is well recognised [425].

14. ASSOCIATED PELVIC FLOOR CONDITIONS

During a woman's lifespan, the pelvic floor is responsible for urinary and the faecal continence as well as for sexual function. If the anatomy of the pelvic floor is altered, each one of these functions may be compromised. Pelvic organ prolapse is a common condition that often leads to lower urinary tract symptoms (LUTS) and may require surgical intervention to alleviate those symptoms. Therefore, the clinical evaluation of women with POP symptoms also requires the assessment of urinary and faecal incontinence symptoms as well as of sexual disorders. Physicians, who examine women seeking care for one condition, should inquire about symptoms of other disorders.

The relationship between LUTS and pelvic organ descent however, is not completely understood.

In a recent study, Costantini et al. [426] evaluated the correlation between LUTS and POP. They retrospectively reviewed 256 patients presented with POP and LUTS and underwent POP surgery. Most of 50% of patients reported two or more symptoms and only 4.2% had no LUTS. 73.8% patients had voiding symptoms, 15% urodynamic detrusor overactivity, 5% suffered from hydronephrosis. 57.8% had SUI. The authors concluded that urologists and gynaecologists should be aware of the high frequency of the association between POP and LUTS. POP repair my restore normal anatomy but LUTS may continue following surgery or develop "de novo."

a) Bladder function

In a large community-based questionnaire survey, 44% (104/239) of women who had prolapse symptoms (239/3799) also complained of SUI and 37% of overactive bladder [427].

SUI can be functionally masked by POP. SUI may be uncovered by POP surgery and clinically continent women are at risk of developing symptomatic postoperative SUI. Many agree on the importance of preoperative urodynamic assessment with the prolapse reduced to assess potential occult SUI and detrusor overactivity. Preoperative identification of occult (and overt) SUI will facilitate the decision making by the surgeon and counselling of the patient regarding the possibility of an anti-incontinence procedure after prolapse repair or, in some specific cases, even at the same time.

Evidence of reduced peptide-containing innervation of perineal and periurethral muscles in women with SUI and POP has emerged [364], suggesting a neural abnormality in their pathogenesis. Connective tissue alterations such as decreased a-1 antitrypsin expression and altered elastin metabolism [364], decreased collagen concentration [428], and decreased oestrogen receptors [405, 429] have been described in women with urinary incontinence and/or POP.

Failure of bladder, bladder neck, and urethral support is often part of a more extensive defective

pelvic organ support. Poor pelvic organ support can lead to pathological pelvic relaxation in one or more compartment(s). Marinkovic and Stanton [430] published a review of 97 articles regarding incontinence and voiding difficulties associated with POP: they described the incidence, pathophysiology, anatomical changes and resultant consequences, evaluation and imaging of cystocele, rectocele, enterocele, and uterine and vaginal vault prolapse in combination with urinary incontinence. The authors concluded that POP appears to have significant clinical effects on urethral and voiding function that should be quantified preoperatively to allow appropriate surgical intervention, with the aim of restoring vaginal function and correcting concurrent incontinence, whether overt or occult. Not uncommonly, POP can lead to bladder outlet obstruction, detrusor overactivity, and latent SUI that is unmasked only with reduction of the POP (potential, latent, or unmasked SUI) [431]. It is recognised that POP surgery can improve voiding dysfunction and unmask occult SUI by alleviating the urethral kinking causing outlet obstruction [432].

Burrows et al. [433] described symptoms of bladder, bowel, and sexual function in 330 women with POP, comparing different degrees of prolapse staged by the POP-Q system. Women with SUI symptoms had less advanced prolapse (median 5 cm less prolapse in the apical compartment) than those without SUI. Women who needed to manually assist micturition had more advanced prolapse (median 3.5 cm more prolapse in the most severe compartment) than those who did not. Women with urgency and urgency incontinence had less advanced prolapse (median 3 cm or less) but the differences were smaller than those for SUI. Severity of prolapse was not associated with bowel or sexual symptoms in this study. The most important finding was that there are few strong associations between specific symptoms and severity of prolapse. LEVEL OF EVIDENCE: II-2.

Women without anterior prolapse on POP-Q exam rarely (<10%) report urinary splinting (digitally reduction of prolapse to aid with voiding) but ranged between 23 and 36% for stage III and IV. Urinary splinting is 97% specific for anterior prolapse. Seventy-seven percent of women with stage II POP report a symptomatic bulge, and report of a bulge has an 81% positive predictive value and a 76% negative predictive value [434]. It seems therefore that if women present with symptoms of vaginal/perineal bulge, then careful assessment for POP is warranted. However a woman with SUI, presents with no symptoms of POP, then surgical treatment of asymptomatic and incidental anterior POP is not indicated.

The surgical management of women with POP and with latent SUI remains controversial and challenging. Maher et al. [435] aimed to determine the effects of surgery in the management of POP by searching the Cochrane Incontinence Group trials register (as of June 2004) for randomised or quasi-randomised controlled trials that included surgical procedures for POP. The metaanalysis on the impact of POP surgery on continence was 'limited and inconclusive', but they reported that 10% of women developed new incontinence symptoms postoperatively.

Levin et al. [436] prospectively evaluated 313 women who underwent a TVT procedure for overt (228 women) or occult (85 women) SUI. About 50% women also underwent POP surgery concurrently. Overall, for 241 women with at least a follow-up of 12 months, 6.6% had persistent mild SUI, an additional 7% had urodynamic evidence of asymptomatic sphincter incontinence, whereas 8% developed de-novo urgency incontinence.

Among 130 women who underwent surgical treatment for an enterocele (75% the vaginal wall protruded through the introitus), 77% presented with SUI or detrusor overactivity. Sixty-seven percent of patients underwent Burch colposuspension with enterocele repair. Postoperative SUI requiring further treatment occurred in 10% after a mean period of follow up of 10 months, and cystocele developed in 1.5% [437].

Urologists and urogynecologists are faced with the challenge of determining which women with POP associated with SUI will benefit from concurrent surgical intervention for the POP. A comprehensive and anatomic approach to pelvic floor reconstruction is recommended, but no high-level evidence-based studies exist in the contemporary literature.

The intended goal of surgical correction of SUI and POP is durable restoration of normal anatomy and function, with symptomatic relief and avoidance of morbidity. At present, few evidence-based conclusions can be drawn about when to surgically intervene for SUI in women who present with POP. The available contemporary studies are few with a small number of patients; however, it seems prudent to recommend repairing symptomatic POP in women who present with SUI. So far, routine performance of anti-incontinence procedures at the same time as reconstruction of the anterior compartment does not seem to be justified by the current evidence. In women with symptomatic SUI and incidental, asymptomatic POP, one must balance any potential treatment associated morbidity with the intended clinical/surgical outcome.

Recently, Ramanah et al [438] compared changes in urinary symptoms before and after POP surgery, using either laparoscopic sacrocolpopexy (LSC) or transvaginal porcine dermis hammock placement with sacrospinous ligament suspension (VS). Out of the 151 patients included, 87 patients underwent LSC, and 64 VS. Overall, after a median follow-up of 32.4 months, POP surgery improved urinary frequency ($P = 0.006$), voiding difficulty ($P = 0.001$), stress urinary incontinence ($P = 0.001$), but not urgency ($P = 0.29$). VS was more effective in treating SUI ($P < 0.001$ vs. 0.52) while LSC more effective for voiding difficulty ($P = 0.01$ vs. 0.08). Postoperative de novo symptoms were observed in 35.8%

of patients with no difference between the groups (P = 0.06). UDI (P = 0.04) and UIQ (P = 0.01) scores were significantly lower after surgery. However, LSC significantly improved UDI (P = 0.03) with no effect on UIQ (P =0.29) scores while VS significantly improved both scores (P=0.02 and 0.001, respectively). Using multivariate analysis, only the improvement in the impact of urinary symptoms on daily living was independently associated with VS (OR 5.45, P=0.01). The authors concluded that most preoperative urinary symptoms decreased after POP surgery with equivalent proportion of de novo symptoms after vaginal and laparoscopic approaches.

The prevalence of OAB symptoms in relation to signs and symptoms of POP is reported to be between 22.5-36.8% in community based studies [427, 439-441] and between 16-88% in hospital based studies [431, 442-444]. The prevalence of OAB with POP is greater in the hospital-based studies than in the community-based studies, which is not surprising, given the selected nature of the hospital samples. Only three studies, one community-based and two hospital-based, were identified that presented data specified per compartment and showed conflicting results: in the study by Miedel et al. [441], there is a clear relationship between anterior and posterior compartment prolapse and OAB symptoms in contrast to central compartment prolapse. In the studies by Bradley and Nygaard [445] and Sobhgol and Charandabee [446] such a relation could not be identified. In a study by Ellerkmann et al. [447] no correlation between worsening of the anterior compartment and urgency incontinence could be found. Data regarding the relationship between the stage of prolapse and OAB are very sparse. Burrows et al. [433] found that urgency and urgency incontinence occurred more often in women with a less advanced overall prolapse. Another study using ultrasound reached the same conclusion; women with a higher grade of bladder descent were less likely to suffer from urgency incontinence [448].

The pathophysiology of OAB in women with POP is unclear. Several theories exist: bladder outlet obstruction; release of various chemical factors (ATP, Ach, and P2X3) by bladder distension stimulating the detrusor receptors; traction on the urethra due to prominent cystocele resulting in an open urethra with urine entering the urethra that causes detrusor contractions. Bladder outlet obstruction is likely to be the most important mechanism by which POP induces OAB symptoms and DO signs. However, several other mechanisms might also play a role. However, strong indications show a causal relationship between OAB and POP [449].

b) Anorectal function

Prolapse of the posterior vaginal wall, alone or in combination with other compartment defects, can be challenging for the pelvic surgeon. Pelvic pressure, vaginal/ perineal splinting to defecate, difficult defaecation, faecal incontinence and impaired sexual function are some of the symptoms associated with posterior POP. Whether the prolapse is the cause of the symptoms or is a result of straining and stretching of support structures in women with defaecation disorders, remains unclear.

Bowel symptom like incontinence of flatus and obstructed defaecation are common in women with POP. In several surveys, the incidence of anal incontinence ranges from 15-50% [412, 427, 450-457]. Faecal incontinence was reported in 5-22% of women with prolapse [332, 450, 456] which was significantly more than bowel symptoms in a control group [456]. There were no associations found between the stage of the prolapse and symptoms after adjusting for age and BMI [412, 455].

Meschia et al. [452] reported that among 881 women with symptoms of urinary incontinence and pelvic organ prolapse, the prevalence of anal incontinence was 20%. Urinary incontinence and severe rectocele were found to be associated with anal incontinence.

Disparities have been shown between the degree of pelvic organ prolapse, pelvic floor symptoms and defecography results [332, 458]. Two series of defaecographies in consecutive patients with prolapse and/or evacuation disorders described defaecographic findings that changed the patients diagnosis (although not always the management) in 46 of 62 of cases and noted enteroceles that were not found on physical examination in approximately 50% of cases [459-461]. Sigmoidoceles are present in 4-11% of reported series, and are nearly always missed on physical examination [461, 462]. Their clinical impact and management remain unclear. Defaecography is not a routine investigation in women with POP and interpretation may be difficult in some cases since normal asymptomatic women may have focal defaecographic abnormalities [458]. The prevalence of abnormal colonic transit time is approximately 20% in patients presenting with evacuation disorders [463]. An abnormal preoperative colonic transit study is the most consistently cited risk factor for failure of rectocele repair to relieve evacuatory symptoms, regardless of the surgical technique [464-466]. Goh et al. [467] reviewed the management of rectocele and clearly described the complexity of clinical conditions resulting from the possible combination of various gynaecological and colorectal symptoms with anatomical abnormalities and the different surgical approaches.

Recently, Ramanah et al. [468] evaluated changes in anorectal symptoms before and after pelvic organ prolapse surgery, using laparoscopic sacrocolpoperineopexy. Preoperative and postoperative anorectal symptoms, colorectal-anal distress inventory (CRADI) and colorectal-anal impact questionnaire (CRAIQ) scores were prospectively compared from 90 consecutive women undergoing laparoscopic sacrocolpoperineopexy. After a median follow-up

of 30.7 months, laparoscopic surgery significantly worsened CRADI (p=0.02) with no effect on CRAIQ (p=0.37) scores. Post-operative and de novo straining (27%) and the need for digital assistance (17%) were the most frequent anorectal symptoms. No correlation was found between laparoscopic surgery and anorectal symptoms after multivariate analysis (OR 2.45, p=0.05). The authors conclude that anorectal symptoms are not improved after POP surgery by laparoscopic sacrocolpoperineopexy.

c) Sexual function

Patients who present with pelvic organ prolapse symptoms should be questioned about their sexual function. Surgical treatment in these patients may help their sexual disorders (e.g., by curing incontinence in patients with coital incontinence) but may also have undesired effects on sensation, blood flow, and anatomy. These effects can affect sexual arousal and orgasm or cause dyspareunia.

Dyspareunia, coital incontinence and vaginal dryness are common complaints in women with pelvic floor disorders [469, 470]. Although sexual dysfunction appears to be more frequently observed in these women, pelvic organ prolapse does not seem to negatively impact on sexual satisfaction when controlled for confounders like age [470-472].

Clinical populations are likely to have more severe pelvic floor symptoms and more advanced pelvic organ prolapse, with a greater potential for discernible impact on sexual function, whereas community populations may have mild symptoms and prolapse, with minimal impact. These conflicting results may also be the result of population differences in other related factors, such as age, menopause, or the woman's sexual relationships. Other challenges in studying the factors associated with sexual function in women with POP include a limited characterisation of female sexual function in some studies and difficulties assessing sexual function among women who do not have intercourse.

Handa et al. [473] reported that, with respect to anatomical prolapse, women with stage III–IV prolapse were more likely to report decreased libido and infrequent orgasm than women with stage 0 support. Adjustment for other characteristics attenuated the strength of these associations, although the association between prolapse and infrequent orgasm remained statistically significant. In the final adjusted model, the odds of infrequent orgasm were increased more than three times for women with stage III–IV prolapse (P=0.02). The authors concluded that women with anatomical prolapse stage III–IV were more likely to report infrequent orgasm but they were not at increased risk of other sexual problems. An important observation is that women with stage II support were not more likely to report any sexual complaint than women with stage 0 support. This suggests that the physical presence of stage II prolapse alone is not associated with sexual dysfunction. In contrast, women with prolapse symptoms (as reflected by a high score on the prolapse scale of the Pelvic Floor Distress Inventory) were much more likely to report sexual complaints. Thus, one can conclude that sexual function is worse in women with symptomatic prolapse. LEVEL OF EVIDENCE II.

In 305 women over 40 years seeking outpatient gynaecological care has been investigated the association between sexual complaints and perceived sexual distress. Women with sexual distress were also more likely to report sexual difficulty related to pelvic floor symptoms, sexual avoidance due to vaginal prolapse (13.9% vs. 1%, P=0.001) [474].

A better understanding of the anatomy of this area and of the sexual function will guide us in a more targeted approach to the management of these conditions.

II. CONCLUSION AND RECOMMENDATIONS

The aetiology of POP is thought to be multifactorial with contributions from both environmental and genetic risk factors. Undoubtedly vaginal delivery is the most traumatic event for the pelvic floor during a womans lifespan, recent growing evidence underlines the possible genetic influence in the aetiology of POP. High concordance in the stage of POP between nulliparous and parous sisters suggests a familial predisposition toward developing this condition [331]. **LEVEL OF EVIDENCE II-2.** Recent studies provided strong scientific evidence of a genetic contribution to pelvic organ prolapse: 6 single-nucleotide polymorphisms are significantly associated with POP in high-risk familial case group participants [334]. **LEVEL OF EVIDENCE II.**

Also with respect to abnormal extracellular matrix (difference in collagen type and metabolism, elastin turnover), increasing evidence supports the genetic aetiology of POP. **LEVEL OF EVIDENCE II**. This has been confirmed by severe inherited connective tissue disorders, in which POP predominates [367-370].

Hormonal and mechanical physiological changes during pregnancy affect the pelvic floor support, but it has still to be demonstrated whether this is a reversible factor.

Even though it has been demonstrated that vaginal delivery is the major traumatic event for the pelvic floor caesarean section does not seem to be completely protective (**LEVEL OF EVIDENCE II**). Forceps, vaginal parity, prolonged second stage of labour, infant birthweight >4500 g are obstetrics risk factors for development of POP. The neurological sequelae of vaginal delivery on the pelvic floor are still controversial.

Declining sex steroid hormone level, ageing, age, obesity, constipation, chronic pelvic floor stress are associated with pelvic organ prolapse.

Although it has been documented that most patients with POP experience, in addition to symptoms of prolapse, urinary, faecal and sexual symptoms, their anatomical and functional relationship remains unclear. Moreover, recent findings show that there are few strong associations between specific symptoms and severity of prolapse. **LEVEL OF EVIDENCE: II-2.**

It is important to have better understanding of the pathophysiology of concomitant SUI and POP, in order to decide on the surgical management of these patients.

The complexity of the anorectal function in patients with POP needs to be clarified, as well as sexual function, which seems to be worse in women with symptomatic prolapse but not with the physical presence of stage II prolapse alone.

New research focuses on the identification of at-risk populations to develop pelvic organ descent. Establishing the inheritance of POP may identify populations that can be targeted for primary and secondary prevention studies, such as elective caesarean delivery. If specific genes can be identified, we may understand why some patients do not respond to certain therapies. Moreover, biomarkers or novel proteins, are expected to be related to various POP phenotypes.

The research priorities in pelvic organ prolapse are:

- to understand the mechanical and functional aspects of the vaginal birth
- to clarify the effects of labour on the pelvic floor and consequently the benefits of the emergency caesarean section
- to quantify the importance of genetic information on POP using Twin Models
- to investigate racial and ethnic background with genetic studies
- to determine possible explanation for related conditions (e.g. hernia, bowel dysfunction)

E. PATHOPHYSIOLOGY OF FAECAL INCONTINENCE

Faecal continence is maintained by a complex, poorly elucidated process involving the structural and functional integrity of the anorectal unit, the central and peripheral nervous system and pelvic organs. Continence requires a closed anal canal at rest, sensory function to detect the presence of flatus or stool in the rectum, intact reflex response of the appropriate muscles, cognitive recognition of the sensory signal, adequate storage capacity in the rectum and adequate function of the puborectalis and sphincter muscles. In addition, other factors such as stool consistency and physical mobility play a role. Disruption of the normal anatomy or physiology in any of these areas may lead to incontinence. Often, multiple factors contribute in patients with significant faecal incontinence [475-479].

I. STRUCTURE AND FUNCTION OF THE ANORECTUM

The anus is a muscular tube 2 cm to 4 cm long consisting of the internal anal sphincter, conjoined longitudinal muscle, external anal sphincter and puborectalis muscle.

1. MUSCLES

a) Internal anal sphincter (IAS)

The internal anal sphincter (IAS), an involuntary smooth muscle, is a 0.3 cm to 0.5 cm thick expansion of the circular smooth muscle layer of the rectum. The IAS ends about 10 mm proximal to the distal end of the external sphincter. It is primarily responsible for closure of the anal canal at rest through both myogenic and sympathetic excitatory activity. Studies disagree about the relative contribution of myogenic and nerve induced activity to the resting tone [480, 481]. The IAS generates slow waves occurring 6-20 times per minute; about 10 % of asymptomatic people also have ultra-slow waves with pressures fluctuating between 20 mmHg and 50 mm Hg [482-484]. The significance of variations in recordings between controls and incontinent patients is not well understood [485]. The internal anal sphincter contains non-adrenergic, non-cholinergic (NANC) fibres which contribute to contraction of the muscle mediated by nitric oxide [486-488]. The possible roles of other neurotransmitters and of the interstitial cells of Cajal are currently being studied in animal models [489-493]. Other animal studies have focused on the cellular regulation of basal tone in the IAS. Up regulation of RhoA/Rho kinase in the smooth muscle cells of the IAS plays a significant role in the maintenance of the basal tone [494]. The RhoA/Rho kinase components are responsible for the inhibition of myosin light-chain phosphatase of resulting in high level of myosin regulatory light chain [495].

b) External anal sphincter (EAS)

The external anal sphincter, a 0.6 cm to 1.0 cm thick cylinder of striated muscle covers the whole length of the internal sphincter and extends more distally into the subcutaneous tissue. The external sphincter contributes to the resting tone. Its primary function, however, is to contract to preserve continence when stool or flatus is present in the rectum or intra-abdominal pressure increases. The contraction may be voluntary or reflex with increased abdominal pressure from coughing or distension [496]. The muscle also relaxes to facilitate evacuation. The separation of the external sphincter into sections is controversial [497]. Many authors describe three sections termed superficial, subcutaneous and deep but they have also been described as subcutaneous, main body

and deep winged portion based upon MRI imaging [498, 499]. On MRI images, the subcutaneous portion is visibly distinct from the other portions with less clear separation between the middle and deeper portions [498]. Others argue the EAS functions as a single muscle unit. The EAS is a predominantly slow-twitch, fatigue resistant muscle with a majority of Type I fibres although there are also Type II rapidly contracting fibres as well [500, 501].

c) Conjoined longitudinal muscle

The outer longitudinal muscle layer of the rectal wall joins with fibres of the levator ani muscle to become the conjoined longitudinal muscle. The muscle extends distally between the internal and external anal sphincter and then splits into extensions that traverse the superficial portion of the external sphincter to attach to the perianal skin and medially through the internal anal sphincter to join the submucosal smooth muscle [502]. Suggested roles for this muscle include provision of supporting meshwork for the anal sphincters and assistance in maintaining anal closure. A more functional role is suggested by the differential response of the longitudinal muscle to neurotransmitters when compared to the internal anal sphincter [488]. One suggested role is that contraction of the muscle flattens the anal cushions and shortens the anal canal [503].

d) Puborectalis muscle (PR)

The puborectalis muscle, the most medial portion of the levator ani muscle, is a U-shaped loop of striated muscle that encircles the anorectal junction and attaches to the posterior aspect of the pubis. The puborectalis muscle is a mixture of Type I and Type II fibres but has fewer Type II fibres than the EAS [504]. It functions to close the upper anal canal [505, 506]. It is situated immediately cephalad to the external sphincter. The configuration of the puborectalis muscle results in the anorectal angle between the distal rectum and anal canal. At rest, the anal canal forms an angle with the axis of the rectum of approximately 90°; during voluntary squeeze the angle becomes more acute, approximately 70°; during defaecation, the angle becomes more obtuse, about 110° to 130°. Some data support the concept that the puborectalis muscle is part of the levator ani muscle (embryology, in vitro stimulation studies, innervation) [507-513] while other information suggests that it is part of the external anal sphincter (anatomic dissection, function during cough and straining [514-516]. The puborectalis muscle responds to increased abdominal pressure (coughing or straining) and rectal distension by contraction.

e) Levator ani

The levator ani muscles are a pair of broad sheets of striated muscle lying below the pelvic organs. There are three major components with different attachments. The ileococcygeus muscle arises from the ischial spine and attaches to the lateral aspect of the lower sacrum and coccyx. The pubococcygeus muscle runs from the posterior aspect of the pubis, mixes with fibres from the contralateral muscle at the anococcygeal raphe and inserts at the distal sacrum and coccyx. The third component is the puborectalis muscle which is described above. The urethra, vagina and rectum pass through an opening between the levator ani muscles called the levator hiatus.

2. NERVE STRUCTURE AND SENSATION

The somatic nerve supply arises from the second, third and fourth sacral spinal segments. The lower motor neuronal cell bodies for those nerves are located in Onuf's nucleus of those sacral spinal segments. The primary nerve is the pudendal nerve which has both motor and sensory functions [517]. The pudendal nerve divides into three main branches. One branch, the inferior rectal nerve, supplies the external sphincter. The levator muscles including the puborectalis receive innervation directly from those spinal segments [510, 511, 513, 518]. However, the puborectalis muscle frequently receives an auxiliary supply from the inferior rectal and perineal branches of the pudendal nerve on its inferior aspect [519]. Both the EAS and levator ani muscles may be controlled voluntarily through corticospinal descending motor pathways [504]. They are also under reflex control through sacral reflex pathways. Pudendal nerve block creates a loss of sensation in the perianal and genital skin and weakness of the anal sphincter muscle, but it does not affect rectal sensation [520]. It also abolishes the rectoanal contractile reflexes, suggesting that pudendal neuropathy may affect the rectoanal contractile reflex response.

The anorectum also has a rich nerve supply through the enteric, sympathetic, parasympathetic and extrinsic spinal sensory neurons. Enteric motor neurons control most aspects of rectal motility; parasympathetic and sympathetic influence is mediated largely through modulation of the enteric neuronal circuits [521]. Within the myenteric plexuses there are motor, sensory and interneurons. The sympathetic supply of the rectum arises from the first three lumbar spinal segments. The innervation is carried through the preaortic plexus to the upper rectum and through the presacral nerves to the hypogastric plexus and then through the hypogastric nerves to the pelvic plexus. The parasympathetic fibres originate in the sacral parasympathetic nucleus in the sacral spinal cord and emerge through the sacral foramen as the nervi erigentes. They join the sympathetic fibres at the pelvic plexus and pass through rectal nerves to the rectal wall. The parasympathetic pathways have a role in propulsive activity of the colon and defaecation.

Extrinsic sensory innervation of the rectum seems to be responsible for sensory perception of rectal distension. Sacral afferents have cell bodies in the dorsal root ganglia of the sacral segments. Specialised sacral afferents have mechano-sensitive transduction sites within the myenteric ganglia of the rectum

[522, 523]. These sites are sensitive to distension and contraction of surrounding muscle layers. Both thinly myelinated A fibres and unmyelinated C fibres are present in the rectal mucosa, and the myenteric plexus [524-527] The C fibres are mostly present in the wall of the rectum while the A fibres predominate in the rectal mucosa [527]. These nerves most likely mediate the distension or stretch-induced sensory responses as well as the viscero-visceral, [528] the recto-anal inhibitory, and the recto-anal contractile reflexes [526]. The sensation of rectal distension is most likely transmitted along the S2, S3, and S4 parasympathetic nerves [526]. Clinical studies confirm that balloon distension is perceived in the rectum and that such perception plays a role in maintaining continence. [529, 530] Furthermore, sensory conditioning can improve hyposensitivity [531, 532] of the rectum.

Anal sensation is carried in the inferior rectal branch of the pudendal nerve. The upper anal canal particularly has a rich mixture of free and organised nerve endings such as the Krause end-bulbs, (cold) Goigi-Mazzoni bodies (pressure), genital corpuscles (friction), and the sparse Meissner's corpuscles (touch) [526, 533, 534]. Specialised afferent nerves may exist that transmit the sensations of touch, temperature, tension, and friction, but are incompletely understood [526]. The role of anorectal temperature sensation is subject to debate [535-539]. The likely role of anal sensation is to facilitate discrimination between flatus and faeces and the fine-tuning of the continence barrier, but its precise role needs to be characterised.

3. CEREBRAL CORTEX

Rectal distension produces bilateral activation in the secondary somatosensory cortex, sensory association cortex, the anterior cingulate cortex and insular cortex, as well as bilateral activation in the prefrontal cortex and extending from the peri-orbital cortex to the anterior temporal lobe [540-543]. Studies have identified activation in multiple areas of the cortex including those involved in spatial discrimination (secondary somatosensory cortex, sensory association cortex) and those that process affective and cognitive aspects of sensation (the anterior cingulate cortex, insula and prefrontal cortex.). While rectal and anorectal stimulation activated similar regions of the brain the locations within the regions varied [544]. Anal musculature is represented bilaterally on the superior motor cortex (Brodmann area 4); the degree of symmetry varies [545].

4. REFLEXES

Distension of the rectum results in contraction of the rectum, relaxation of the internal anal sphincter and contraction of the external anal sphincter.

a) Rectoanal inhibitory reflex (RAIR)

Rectal distension is associated with a fall in anal resting pressure known as the rectoanal inhibitory reflex. The amplitude and duration of this relaxation increases with the volume of rectal distension [546]. It has been suggested that bowel contents are periodically sensed by anorectal "sampling," [547-549] the process by which transient relaxation of the IAS allows the rectal contents from the rectum to come into contact with specialised sensory organs. This process allows discrimination between flatus and stool.

b) Cough reflex

Abrupt increases in intra-abdominal pressure, such as those caused by coughing or laughing, are associated with increases in anal sphincter pressure. [496, 550-553]. The increased pressure may be achieved through multiple mechanisms, including reflex contraction of the puborectalis [554]. The response is relative to the intensity of the cough [550]. It is unclear whether the response is a polysynaptic spinal reflex [496, 551] since it is preserved after spinal cord transection [555] or also requires central integrative centres [552].

c) Rectoanal contractile reflex (sensori-motor response)

The rectoanal contractile reflex (or rectal anal excitatory reflex or inflation reflex) is the contraction of the EAS in response to rectal distension [556-558]. The amplitude and duration of the rectoanal contractile reflex increases with rectal distension up to a maximum volume of 30 ml [546].

5. RECTUM

The rectum is a hollow muscular tube, 12 cm to 15 cm long, composed of a continuous layer of longitudinal muscle that interlaces with the underlying circular muscle. These muscles are a mixture of smooth muscle cells and several types of interstitial cell of Cajal [521]. A network of interstitial cells of Cajal joined by gap junction connections coupled to smooth muscle cells trigger mechanisms that give rise to large, slow repetitive depolarisation of the smooth muscle, the slow waves [559]. The proximal end is defined either as the sacral promontory, the third sacral vertebrae or the area where the colonic taenie splay out and end. The distal end is the dentate line or anorectal ring. The rectum serves as a reservoir for storage and a "pump" for evacuation of stool facilitated by several characteristics. The rectal walls are compliant maintaining a relatively low pressure with increasing volumes. Its innervation allows the sensation of increasing volume [475, 521].

6. ANAL ENDOVASCULAR CUSHIONS

The submucosa of the anal lining contains blood vessels, connective tissue, smooth muscle and elastic tissue. They typically form three separate complexes of smooth muscle fibres and vascular channels called the anal cushions [560, 561]. A recent study of women demonstrated the normal variation in size; the size did vary with posture and parity but not age, history of obstetrical trauma or mild hemorrhoid symptoms [562]. Their contribution to continence is poorly studied and controversial.

7. STOOL CONSISTENCY

Considerable evidence exists that evacuation of formed stool is more easily deferred than loose stool (discussed in detail under diarrhoea). While theories exist about the reason, physiological proof is not available.

8. PHYSICAL MOBILITY

The ability to defer evacuation until a socially acceptable time and place requires physical mobility to reach a bathroom in the required time frame. The contribution of physical mobility to continence is largely inferred from studies identifying lack of physical mobility as a risk factor for incontinence [563-565]. There is limited information about the relative role for mobility in continent patients.

II. CONTINENCE MECHANISM

Complete continence is most likely with normal transit of formed stool, anal closure at rest, sufficient reservoir capacity and sensation in the rectum, functional reflexes for sampling and sphincter contraction, adequate cognitive function to recognise the urge to defaecate and physical mobility to reach the bathroom in time.

The anus is normally closed by the tonic activity of the IAS with contribution from the EAS and PR at different levels of the anal canal [506, 566]. Studies of the relative contribution of the IAS to the resting tone yield results varying from 55-85 % [481, 520]. Some of that variation is likely to be related to the measurement technique utilised but it has also been found that resting pressure varies during the day [567] and with posture, increasing with the upright position [568]. The IAS contribution is also influenced by rectal distension [520, 569]. Some postulate that the anal cushions provide a tight seal based upon studies showing that the sphincter muscles in their circular configuration cannot contract sufficiently to provide complete closure [570, 571]. An in vitro study showed that even during maximal involuntary contraction, the internal sphincter ring was unable to close the anal orifice completely and a gap of approximately 7 mm was left open. This gap was filled by the anal cushions [572]. Anal cushions may exert pressures of up to 9 mmHg and thereby may contribute 10% to 20% of resting anal pressure [573]. These barriers are further augmented by the puborectalis muscle, which pulls the anal canal forward forming the anorectal angle. The extent to which the anorectal angle contributes to continence is controversial [566, 574-578]. One study suggests that it is important to the control of semi-solid material more than the control of liquid [579].

With rectal distension or increased intra-abdominal pressure, this barrier is reinforced by reflex or voluntary contraction of the EAS and PR. The contraction requires functional peripheral, spinal and cerebral function to sense and recognise the distension, activate the reflex and voluntary responses. In addition, adequate muscular contraction to increase the anal pressure is required. The rectal wall must distend to allow accommodation to the increased pressure. Finally, the mobility to reach an appropriate setting before the muscle fatigues is required.

III.DEVELOPMENT OF INCONTINENCE

Clearly there are a number of potential areas of injury or dysfunction in the complex mechanisms required for continence that might result in incontinence. Faecal incontinence occurs when one or more mechanisms that maintain continence is disrupted to an extent that other mechanisms are unable to compensate. Hence, faecal incontinence is often multi-factorial [475-479]. In a prospective study, 80% of patients with faecal incontinence had more than one pathogenic abnormality [476]. The interaction of those factors and when they result in clinical incontinence is poorly understood.

1. PASSIVE INCONTINENCE

Compromise of anal closure and loss of sensation may result in soiling or incontinence without awareness. Prolapsing tissue (either mucosal or full thickness rectal prolapse, rectal lesions) prevents closure of the anus. Some believe that resection of the anal cushions may result in passive incontinence [571]. Injury secondary to trauma, surgery or childbirth and weakness of the IAS are other causes. IAS atrophy occurs in systemic sclerosis and may contribute to a faecal incontinence [580, 581] although neuropathy appears to be a contributing factor as well [582]. Loss of sensation occurs from peripheral neuropathy, spinal cord and cerebral cortex events or after transection of the nerve supply by surgical or other trauma. Increasing evidence suggests that rectal hyposensitivity significantly contributes to passive incontinence [583-587]. Interestingly faecal seepage in men occurs despite normal anorectal physiology testing [583, 588, 589].

2. URGENCY INCONTINENCE

Incontinence occurs when the ability to hold stool or flatus is overwhelmed. If the rectum cannot distend to hold stool or the muscles do not contract adequately incontinence results. Changes in the reservoir function of the rectum from disease processes, radiation therapy or surgical resection. Pelvic floor muscle dysfunction may result from direct injury causing a defect or weakness. Iatrogenic or obstetrical trauma to the IAS is the most common cause of injury to that muscle. Direct injury to the EAS occurs most frequently from obstetrical injuries which are comprehensively presented elsewhere but may also occur from surgery or other trauma. The puborectalis and levator ani muscles may also be injured and the presence of defects appears to correlate with poor contractility and symptoms in

several studies [159, 590-593]. Major levator ani muscle injuries are more frequent in women with EAS obstetrical injuries and those with combined injures are more likely to be symptomatic [159]. However, other investigators found no relationship between the presence of levator ani injuries and faecal incontinence [456, 594].

Rectal hypersensitivity, a lower threshold for the urge to defaecate, also contributes to urgency incontinence [477, 478, 595-599] Complex, poorly understood mechanisms mediate rectal hypersensitivity. Variables include decreased compliance, increased sensitivity of extrinsic peripheral pathways or central afferent mechanisms [597].

IV. RISK FACTORS FOR FECAL INCONTINENCE

Many events and conditions impact on the mechanisms of continence often in multiple ways. The next section covers the conditions that most frequently contribute to incontinence.

1. AGING

Multiple studies document the increasing incidence of faecal incontinence with aging in both men and women [479, 600-606]. One study of women in a community found that 70% of incontinence developed after the age of 40 [607]. Another study of women in the United States documented an initial 15% prevalence of incontinence in women over 50 years old and onset rate of 7% over the next 10 years [608].

While the rising incidence is well documented, understanding of the physiological impact of aging is less clear. Conflicting evidence exists about the effect of aging on anal resting pressure. While a number of studies report decreased anal resting pressures in older continent and incontinent persons [598, 609-612], some found lower pressures in patients with incontinence but not asymptomatic older persons [613, 614]. Increased thickness of the internal anal sphincter is associated with aging [598, 615-618]; this finding is thought to represent increased fibrosis although that hypothesis is not proven. Animal studies of smooth muscle contraction demonstrate decreased contractility with aging [619]. Studies of the internal sphincters of aging animals found changes in translocation of signaling molecules as well association and phosphorylation of contractile proteins [619].

Most studies of the effect of aging on anal squeeze pressures found decreasing pressures with advanced age [610-614, 620, 621] but not all [598, 622, 623]. One report found decreasing anal squeeze pressures with age in women but not men [621]. The decrease in anal squeeze pressures does not correlate with easier fatigability of the external sphincter. Indeed, studies show no change with age [624] or that the external sphincter becomes more resistant to fatigue with age [625]. These findings are consistent with studies of skeletal muscle in general which show that reduction of muscle fibres with increasing age with a greater loss of Type II fibres which are less fatigue resistant [626]. The result is a weaker but more fatigue resistant muscle. Very little specific data about the external anal sphincter exist, however.

The decreased anal squeeze pressures might also be related to external sphincter atrophy. Thinning, presumed to be secondary to atrophy, of the external sphincter has been documented in both endoanal ultrasound and MRI studies [615-617, 627-629]. One study found excellent correlation between atrophy on imaging and the pathological changes of atrophy [630]. Some studies found that atrophy is related to aging [617, 628] but not all [598]. Faecal incontinence did correlate with external sphincter atrophy [598]. Data from studies of nerve injury in animals reveals that sphincter atrophy and decreased function develops after nerve injury [631-633]. It is known that muscle atrophy secondary to age related loss of anterior horn cell occurs [634]. Human studies demonstrate increased muscle fibre density suggesting reinnervation in the external sphincter with age [614, 635].

Finally several studies have shown a decrease in rectal sensitivity with increasing age [609, 620]. One study found that decrease only in women [612]. The relationship of this finding to faecal incontinence is not clear.

2. GENDER

Prevalence studies suggest that faecal incontinence occurs more frequently in young women but as people age, many studies report essentially equal incidence in men and women. [602, 604-606, 621, 636, 637] The mechanisms of faecal incontinence in men appear to differ from women [479, 583, 588, 589, 638, 639].

Oestrogen and progesterone receptors are found in the IAS and EAS. Because of this finding, some proposed that menopause is a factor for incontinence in women. However, since aging and menopause are closely related, an independent relationship is difficult to prove. Symptomatic improvement from oral oestrogen replacement supports the proposed relationship; however study of topical oestrogen compared to placebo showed no difference. In addition one study found a 30% increased risk of incontinence in patients currently taking oral oestrogens [640]. At the present, the role of the hormone receptors and relationship of menopause to the onset of incontinence is uncertain.

3. DIABETES

Diabetes is reported as a risk factor for faecal incontinence in several prevalence studies [605, 606, 640, 641]. One study reported a 40% increase in the risk of faecal incontinence [640]. Another population based study found that both occasional and frequent episodes of incontinence were more common in diabetic patients (OR 2.7) [642]. In a study of elderly

Korean patients, diabetes was associated with faecal incontinence in women but not men [643]. A review of incontinence in community dwelling men did identify diabetes as a risk factor, however [639]. A case control investigation found that diabetic patients had more frequent and severe episodes of faecal incontinence [644]. Several reports found that incontinence was more frequent in patients with other diabetic complications particularly neuropathy and retinopathy [644-646]. It is uncertain whether longer duration of disease increases the likelihood of incontinence as one study found an association [645] but two did not [644, 646]. Faecal incontinence was associated with poor glycemic control in one report, [644] but not another [646].

The underlying mechanism for faecal incontinence in diabetic patients is not clear. One likely contributor is oral medication taken for diabetic control. Metformin has been shown to be independently related to faecal incontinence in diabetic patients [647]. In addition, withdrawal of metformin was reported to eliminate the incontinence [648]. One confounding factor is that diarrhoea, a known risk factor for faecal incontinence, occurs in 5-35% of patients with diabetes [642, 645, 649, 650].

One hypothesis is that microvascular changes associated with diabetes result in damage to pelvic floor innervation and muscles [651]. A comparative study of anorectal physiology of controls, incontinent patients with diabetes and continent and incontinent patients with multiple sclerosis found that the incontinent, diabetic patients had higher sensory thresholds and lower resting and squeeze pressures [652]. An anal physiology study compared findings of patients with the diagnosis of diabetes for less than 10 years to those with the diagnosis for longer than 10 years [653]. Both groups of patients had lower resting and squeeze anal pressures ($P < 0.01$), impaired rectoanal inhibitory and anocutaneous reflexes, and reduced sensitivity to rectal distention. Although both groups had statistically significant differences from the control group, the patients with the longer duration of disease had lower sphincter pressures and more blunted sensation in addition to more frequent episodes of incontinence. The latter group also had more evidence of microvascular disease and neuropathy. Blunted rectal sensation and internal sphincter dysfunction were identified in diabetic patients in two separate studies [532, 654]. These findings would be consistent with underlying neurologic and/or microvascular changes. It is unclear how to reconcile that hypothesis, however, with the lack of association of incontinence with neuropathy in some epidemiology studies [649, 655].

4. GASTROINTESTINAL DISORDERS

a) Diarrhoea

Diarrhoea is consistently reported as a risk factor for faecal incontinence. For many patients symptoms of diarrhea include loose consistency of the stool and rectal urgency. Loose stool is an independent risk factor for incontinence and is additive to other risk factors such as obstetrical sphincter injury [479, 600, 602, 603, 608, 636, 639, 640, 656, 657]. Diarrhoea has a significant impact on the development of incontinence with OR 53 in one study [600]. Loose stool is also reported to result in incontinence after treatment with pelvic radiation [658].

b) Rectal urgency

Rectal urgency is reported as an independent risk factor for faecal incontinence [602, 659] as well as a factor in worsening symptoms in patients with incontinence [597]. It is unclear whether the aetiology is rapid transit into the rectum overwhelming the reservoir function or hypersensitivity or some combination of factors [602, 636]. Several investigators have shown that rectal hypersensitivity is a common finding but incontinence developed only in patients with associated sphincter weakness [477, 597]. Rectal hypersensitivity has also been found to be associated with an abnormal colonic motility pattern in the sigmoid colon in incontinent patients [660]. The relationship between this finding and irritable bowel syndrome remains to be clarified.

c) Constipation/impaction

Constipation and incomplete evacuation of the rectum are associated with faecal incontinence in several studies [601, 608]. A study of hospitalised elderly patients found that faecal impaction and diarrhoea were strongly associated with faecal incontinence [661]. Uncertainty exists regarding whether these two factors result in incontinence in patients with otherwise normal anorectal function. Overflow incontinence occurs in some patients with faecal impaction. The use of laxatives may exacerbate the problem [662]. One study of elderly patients with impaction, compared to controls, found that they had blunted rectal sensation and less frequent external sphincter contractions in response to rectal distension [663]. In addition the internal sphincter relaxed at lower levels of rectal distension. Studies of impacted patients without incontinence have not been reported.

d) Irritable bowel syndrome

A number of studies found irritable bowel syndrome to be a risk factor for faecal incontinence [600-602, 640, 664-666]. Proposed mechanisms include loose stool consistency, rapid colonic motility and rectal hypersensitivity [660, 667].

5. NEUROLOGICAL/PSYCHIATRIC CONDITIONS

a) Dementia

The prevalence of faecal incontinence is higher in patients with dementia compared to others of similar age. One study reported a prevalence of 32% in older patients with dementia [668]. Another study reported a rate of 34% in patients with dementia compared to 6.7% in those without dementia [669].

Although diarrhoea was the greatest risk factor for incontinence in a study of nursing home residents, dementia also contributed to the development of incontinence [670]. In the study of community-living older adults in the United States, the prevalence odds ratio of fecal incontinence decreased by 51% with each unit improvement in cognitive score [671]. A Japanese study of community dwelling older adults found dementia to be a risk factor for double incontinence [672]. There is limited information available about the relationship between intellectual disability and faecal incontinence [673]. Proposed mechanisms for the specific contribution of dementia include lack of recognition or understanding of the urge to defaecate and lack of ability to articulate the need for the bathroom.

b) Depression

Several studies identified depression as a risk factor for faecal incontinence [603, 605, 636, 639, 674]. Many assume that the association occurs because of the psychological burden of the symptoms while it is also possible that side effects of anti-depressant medication contribute to the symptoms. Recently, however, an editorial challenged investigators to "clarify the link between the cerebral impact of neurotransmitters and anorectal physiology" given the role of serotonin in depression and gastrointestinal function [675]. Depression and faecal incontinence are both associated with poor nutritional status in the elderly [676]; that association confounds understanding of any true causal relationship between any two of the conditions.

c) Spinal Cord Injury

Patients with spinal cord injuries frequently report difficulty with both constipation and incontinence [677, 678]. The level of the injury determines the effect on continence. Supraconal lesions lead to delayed colonic transit and exaggerated rectal contractions and anal relaxation in response to rectal distension. Cauda equina lesions interrupt the efferent limb of the reflex arc which results in loss of rectal sesation and tone as well as impaired sphincter function [679]. Paraplegics or people with sacral neuronal lesions may retain some degree of sensory function, but virtually no sensation is felt if lesions reach the higher spine [530, 555].

d) Stroke

In several large surveys, stroke has been identified as a risk factor for incontinence [605, 636, 639, 672]. Studies of stroke patients demonstrate fairly consistent rates of faecal incontinence from 30-40% on admission [668, 680-683]. The rates decreased to 20% by the time of discharge [680, 682] and 7-11% at 6-12 months [668, 681, 683]. The Copenhagen Stroke Study found that abnormalities in patients with incontinence were more likely to be hemorrhagic, larger in size and involve the cerebral cortex than stroke patients without incontinence [683].

6. NUTRITION

a) Obesity

Population based studies of faecal incontinence identify obesity as a significant risk factor [600, 601, 640]. In addition studies of pelvic floor symptoms in obese patients find a higher incidence of faecal incontinence than generally found in the non-obese population with rates ranging from 16-68% [684-691]. A non-significant trend towards worsening incontinence was found in another study [692]. Four studies investigated the relationship between the rate of incontinence to the BMI; two found increasing rates of incontinence with increasing BMI [640, 689, 693]. One did not [691]. The relationship is further supported by data that weight loss after bariatric surgery decreases the incidence of faecal incontinence [685, 689, 694, 695]. While the findings of these studies are quite consistent a recent systemic review of obesity and pelvic floor disorders found the number of studies to be limited, primarily focused upon women, and usually lacking control groups and physiology testing [696]. Two confounding factors were noted in studies of this relationship. One is that diarrhoea, an independent risk factor for incontinence, is also frequently associated with obesity [696]. The second is the association of faecal incontinence with low fibre intake in obese women raising the question of dietary contribution to the increased incidence of faecal incontinence with obesity [687]. Chronically elevated intra-abdominal pressure, known to be associated with obesity [697, 698], is typically proposed as the reason for pelvic floor dysfunction in obesity. Other factors including diabetes, neurological changes and intervertebral disc herniation which are common in the obese population may very well contribute.

b) Vitamin D

Vitamin D deficiency is associated with urinary incontinence in men and women [699, 700]. One small study of ten patients with faecal incontinence found that all had either vitamin D deficiency or relative vitamin D insufficiency [701]. These rates are much higher than the 36-57% rate of deficiency or relative insufficiency from historical data of the general population. In a large study of 1881women in the US, there was a non-significant trend towards an association between lower vitamin D levels and faecal incontinence [699]. It is known that vitamin D absorption and synthesis in the skin declines with age [702, 703]. Any association between lower levels of vitamin D and faecal incontinence may represent only the factor that both are common in the elderly; the significance is at present uncertain but potentially could represent a easily remediable factor.

7. OBSTETRICAL INJURY

The impact of pregnancy and vaginal delivery on continence is described in the section on obstetrical injury. While those injuries occur with reasonable

frequency, quite often the patient does not develop clinical incontinence until later in life. The reasons for the onset of symptoms and the required combination of factors are poorly understood. However the contribution of EAS defects to incontinence is supported by data demonstrating that clinical improvement after sphincteroplasty is more likely in patients with successful anatomical repair seen on ultrasound [627, 704-706]. The frequency of puborectalis or levator ani muscle injury as well as the degree to which it contributes to faecal incontinence is unclear but is being more actively investigated [591, 592, 594, 707].

8. PHYSICAL MOBILITY

Intuitively, adequate physical mobility to reach the toilet in a timely manner in response to the urge to defaecate is necessary for continence. Limited mobility was found to be a risk factor for incontinence in one population based study [636] and an investigation of nursing home residents [564]. In a study of urban dwelling older people, the odds of prevalent incontinence increased by 20% for each unit decrease in the physical performance measure [671]. In a study of long-term care patients, immobility was one of the strongest predictors of incontinence [708]. In another study, the use of physical restraints (maximal limitation of mobility) was found to be the most significant cause of incontinence when the data were adjusted for other risk factors [709].

9. RADIATION

Faecal incontinence occurs after pelvic irradiation for prostate, gynecological and rectal cancer [710-713]. Radiation therapy adds to the risk of incontinence associated with rectal resection [714-717]. It appears that short course radiotherapy carries a higher risk than long term irradiation [718]. Direct comparison trials powered to answer the question are currently in progress [719, 720]. In a study of the relationship of radiation dosage to symptoms after prostate radiotherapy, faecal incontinence was associated primarily with radiation to the EAS and PR [721]. The exact mechanism(s) by which radiation therapy causes incontinence is uncertain. The rectum may be stiffer and less compliant [722] and the anal pressures reduced either from muscle or nerve injury by the radiation [715, 723, 724].

10. RECTAL PROLAPSE

a) Mucosal, internal and full thickness rectal prolapse.

A significant proportion (48-63%) of patients with prolapsing haemorrhoids or mucosal prolapse report soiling [725, 726]. Symptoms resolve with successful treatment [725-728].

External rectal prolapse is associated with faecal incontinence in up to 66% of patients [729-732]. Diminished anal resting tone commonly accompanies rectal prolapse [555, 730, 733]; that finding suggests that internal sphincter dysfunction perhaps from repeated stretching is one mechanism for incontinence. Other considerations include the presence of neuropathy; it is unclear if the prolapse results in prolonged pudendal nerve latencies [734, 735] or if both share a common aetiology. The exact mechanism or combination of causes is uncertain. Other investigators, however, found that patients with rectal prolapse and persistent incontinence had evidence of sphincter defects either from surgical or obstetrical injury [736, 737].

Internal rectal prolapse is also associated with faecal incontinence [738, 739] and decreased anal pressures [733]. While surgical intervention for internal rectal prolapse is controversial, several studies report improvement in their incontinence after rectopexy [740-742].

11.SURGERY

a) Anorectal surgery

Lateral internal sphincterotomy, is the recommended surgical procedure for refractory anal fissures. The surgery involves the division of the internal sphincter and may result in incontinence of flatus and stool [743-748]. Quite variable rates of post-operative incontinence from none to 36 % are reported. The definition of incontinence, type of follow-up and length of sphincterotomy contribute to the variability. Some authors suggest that pre-existing sphincter injury might predispose to incontinence [749, 750]. Another author found evidence for increased sphincter asymmetry in patients with incontinence after sphincterotomy compared to continent post-operative patients but no differences in pre-existing sphincter defects [751]. A recent report suggests that the development of symptoms of incontinence may be delayed similar to women with obstetrical sphincter injuries [752].

Incontinence is reported in 0-14% of patients after hemorrhoidectomy [753-756]. In the limited studies available, increased risk of incontinence has been related to previous vaginal deliveries [754], number of hemorrhoids excised [755] and post-operative internal sphincter defects [754, 757]. Some have argued that excision of the anal cushions is the reason for incontinence [571].

Surgery for anal fistula may result in faecal incontinence. The frequency depends upon the anatomy of the fistula, baseline sphincter function and the surgical procedure performed. The reported rates of post-operative incontinence range from 0-50% [758-770]. The definition and measurement of incontinence varies among the studies. Treatment of high fistulas involving more sphincter muscle is more likely to be followed by incontinence [744, 758, 765, 770]. Injections of fibrin glue and endorectal advancement flaps have lower post-operative incontinence rates than other fistula procedures [761]. Age over 45 years old [758] and gender [760, 769] were found to increase the risk in some studies. The mechanism appears to be iatrogenic (and sometimes intentional) sphincter injury.

b) Rectal resection

In a recent meta-analysis of functional outcomes after resection for rectal cancer including studies reported between 1978 and 2004, faecal incontinence of any kind occurred in 3-79% of patients [713]. Rates of incontinence of solid stool ranged from 0-40%, liquid 0-60% and flatus 9-76%. The pooled proportion of incontinence of solid stool was 14 % and liquid stool 29%. The risk of incontinence appears to depend upon the tumor location and level of the anastomosis [771]. Theoretically loss of the rectal reservoir contributes to incontinence. The goal of replacing the reservoir function led to the development various types of reconstruction following resection (coloplasty, colonic J pouch, ileoanal reservoir). While long –term data are sparse, in the first 18 months post-operatively colonic J pouches result in lower rates of incontinence than straight anastomoses or coloplasty according to a recent Cochrane review [772]. Damage to the internal sphincter occurs during this type of resection presumably from transanal introduction of stapling devices and may contribute to incontinence as well [773, 774]. However a recent study comparing patients undergoing handsewn anastomoses to double stapled ones found no difference in faecal incontinence post-operatively or anorectal manometry results [775]. Diminished rectal sensation and changes in motility seen post-operatively indicate that nerve damage may also contribute [775-777]. Rectal sensation and the ability to defaecate can be abolished completely by resection of the nervi erigentes [778]. If parasympathetic innervation is absent, rectal filling is only perceived as a vague sensation of discomfort. Cadaver studies after total mesorectal excision reveal the close proximity of the levator ani nerve and pelvic splanchic nerves to the plane of dissection particularly for low rectal resections [779]. Damage to those nerves would impact on the function of the puborectalis muscle. It is likely that multiple factors contribute to incontinence after rectal resection and difficult to assign relative importance.

c) Hysterectomy

Several reports identified hysterectomy as a risk factor for faecal incontinence [600, 636]. However, another study found a decreased risk of incontinence [640]and one found no association [601]. In addition to conflicting results, the mechanism is not understood.

d) Cholecystectomy

Cholecystectomy results in diarrhoea in some patients. It is often assumed that incontinence occurring after cholecystectomy is related to the onset of diarrhoea. However, two studies identified cholecystecomy as a significant independent risk factor for incontinence [600, 780]. The underlying mechanism, if not associated loose stool, is uncertain but perhaps could be related to rectal urgency secondary to bile salt irritation.

12. SMOKING

A study from the Mayo Clinic reported an association between incontinence in older adults and current smoking with an odds ratio of 4.7 [600]. An earlier study reported the same finding in post-partum patients with faecal incontinence. The reason is unclear [116]. Chronic obstructive pulmonary disease has been associated with faecal incontinence [640] but in The Mayo Clinic study pulmonary disease was not found to be a factor. Other proposed mechanisms include the anti-oestrogen effect of nicotine [781] or accelerated colonic transit secondary to nicotine induced high amplitude contractions in the colon [782].

13. URINARY INCONTINENCE

Many studies report an association between urinary and faecal incontinence. It is likely that it is not a causative relationship but rather that the two conditions result from a common aetiology [414, 600, 603, 606, 636, 640, 657, 783, 784].

V. SUMMARY AND RESEARCH RECOMMENDATIONS

Multiple factors play a role in the development of faecal incontinence. More information is now available about the impact of aging on the sphincter muscles and pelvic nerves. The role of rectal urgency and hypersensitivity in the onset of incontinence, perhaps in conjunction with an underlying abnormality that alone did not result in symptoms, has received more attention. Recent work has also focused on remediable risk factors such as nutritional factors and lifestyle choices. However the complex interaction of the pelvic floor is not fully understood and requires more investigation. More information about the aging process including the potential for reversible changes would be of interest. In addition, little data exist to demonstrate whether changes in theoretically remediable risk factors will decrease incontinence.

F. CHILDBIRTH AND FAECAL INCONTINENCE

Pregnancy and childbirth have a significant impact on the emotional and physical wellbeing of a woman. It is reported that as many as 91% of women report at least one new symptom eight weeks post-partum [785]. A fall in maternal mortality accompanied by an increase in female life expectancy (86 years in Japan) has now shifted the focus of attention towards identification of factors that may minimise morbidity. Although pre-existing bowel symptoms may be aggravated during pregnancy and childbirth, the development of symptoms de novo is a more frequent occurrence. Obstetric trauma is the most common cause of faecal incontinence. However, the onset of symptoms may occur many years after delivery with a peak incidence in the perimenopausal years. This

may reflect the effect of contributory factors such as the process of aging, the effect of the menopause or progression of neuropathy. This section focuses on the association between obstetric trauma and faecal incontinence. The term 'anal incontinence' is used to include incontinence to flatus, liquid and solids.

Anal incontinence has been reported to occur between 5 [202, 786] to 26 [119] % of women during the first year following vaginal delivery. In a Canadian study [787] involving 949 consecutive women who delivered vaginally, 26% reported anal incontinence while 3% reported faecal incontinence. They identified forceps delivery and third/fourth degree tears as independent risk factors. In a population based study of 8774 women in Oregon, USA, more than 25% reported faecal incontinence within 6 months of childbirth [116].

I. NEUROGENIC TRAUMA

The mechanism that maintains continence is complex and affected by various factors such as mental function, lack of a compliant rectal reservoir, rectal hypersensitivity, enhanced colonic transit and changes in stool consistency and volume. However, the ultimate barrier is the anal sphincter. Anal incontinence may ensue if there is mechanical disruption to the anal sphincter muscles, disturbance in neurological function or a combination of both factors. In about 80% of women with presumed "idiopathic" anorectal incontinence there is histological evidence of denervation of the striated pelvic floor muscles, particularly the puborectalis and external anal sphincter (EAS) [788]. This feature has also been demonstrated electro-physiologically by means of an increased fibre density in patients with idiopathic faecal incontinence indicating re-innervation following denervation [789]. Another finding in these patients is a conduction delay in pudendal nerves as measured by pudendal nerve terminal motor latency (PNTML)[790].

Although Hertz in 1909 suggested that pelvic floor damage may result from a normal vaginal delivery, objective scientific evidence for this was only produced in 1984 [176] and a follow-up of 14 patients 5 years later [178]. These authors studied 122 women, 71 after delivery with manometry, perineometry, PNTML and EMG, and 51 before and after delivery with EMG. This study demonstrated an increase in anal sphincter striated muscle fibre density in the vaginal delivery group at 2 months post-partum indicating evidence of re-innervation following denervation. The fibre density was not altered following elective cesarean section. Thirty three percent of primiparae and 50% of multiparae had prolonged PNTML within 48 hours of delivery. However, by 2 months, the PNTML had returned to normal in 60% of these women, indicating that damage to pudendal nerve conduction is reversible. Multiparity, forceps delivery, increased duration of the second stage of labour, third degree perineal tears and high birth weight were important factors leading to pudendal nerve damage. In the five year follow-up study of 14 women, only multiparae who did not have a forceps delivery were selected; the denervating process was found to be progressive in the majority of women and 5 women suffered from stress urinary incontinence , 3 of whom were also incontinent to flatus.

In another prospective neurophysiological study, Allen et al. [177] studied 96 nulliparous women with EMG, PNTML and vaginal pressure measurements during pelvic floor contraction. They found evidence of re-innervation in the pelvic floor muscles of 80% of primiparae 2 months after vaginal delivery. The only obstetric factors associated with re-innervation were a high birth weight and a longer active stage of labour. Forty five of the original 96 women were studied again 6 years later and they concluded that changes in pelvic floor neurophysiology occur with time and do not appear to be related to further childbearing.

A third prospective study [791] measured anal pressures, anal sensation and the perineal plane in 72 antenatal women and repeated 72 hours post-partum and in 41 women 2 months postpartum. Anal sensation was unchanged. Cornes et al. [792] measured anal sensation in 96 primiparae within 10 days after delivery and measurements were repeated in 74 women 6 months after delivery. They found that at 6 months anal sensation had returned to normal. Anal sensation remained unchanged after cesarean section. In women who had a torn EAS, only impairment of sensation in the upper anal canal persisted at 6 months. More than half the women who admitted to persistent anal incontinence had normal anal sensation. Chaliha et al. [793] measured anal electro-sensitivity before and after childbirth and found it unchanged. Anal sensation in isolation therefore probably plays a minor role in the development of obstetric related faecal incontinence.

II. MECHANICAL TRAUMA

Until the advent of anal endosonography, mechanical trauma to the anal sphincters was only suspected when there was a history of third or fourth degree tears collectively known as obstetric anal sphincter injuries (OASIS). Consequently, when anal endosonography was performed in patients believed to be suffering from "neurogenic" faecal incontinence unsuspected internal anal sphincter (IAS) and EAS defects were identified [794]. The sonographic appearance of EAS defects has been verified histologically to represent fibrosis [795] while the appearance of IAS defects have been validated prospectively in patients undergoing lateral internal anal sphincterotomy [750]. Trauma as identified by ultrasound may represent unrecognised OASIS (previously referred to as occult) or the consequence of recognised and repaired OASIS.

1. UNRECOGNISED ("OCCULT") ANAL SPHINCTER TRAUMA

Sultan et al. [202] performed the first prospective study (before and after childbirth) to demonstrate

both “occult” anal sphincter trauma (**Figure 13**) and pudendal nerve damage during childbirth in both primiparous and multiparous women (n=150). In 35% of primiparous and 44% of multiparous women anal sphincter defects were identified at 6 weeks postpartum by anal endosonography that were not present before vaginal delivery. Thirteen percent and 23% respectively developed defecatory symptoms (faecal urgency and/or anal incontinence) after delivery. Only two of the 150 women (both primiparous) had recognised tears of the anal sphincter at the time of delivery. A strong association was demonstrated between the presence of any defect and the development of symptoms. Only 4% of multiparous women sustained new sphincter damage following a subsequent delivery. The single independent factor associated with anal sphincter damage was forceps delivery. The 23 women delivered by cesarean section remained asymptomatic and none developed sphincter defects. No relationship was demonstrated between PNTML measurements and defecatory or urinary symptoms.

Donnelly et al. [796] interviewed 219 nulliparae in the third trimester regarding bowel habits and performed anal vector manometry. At 6 weeks postpartum 184 women returned and the same bowel symptom questionnaire was completed and anal vector manometry plus PNTML measurements were performed. Anal endosonography was performed in 81 women with altered faecal continence or abnormal physiology. Instrumental vaginal delivery and a passive second stage of labour prolonged by epidural analgesia were significantly associated with the greatest risk of anal sphincter trauma and impaired faecal continence. As instrumental delivery is a known risk factor (8 fold increased risk of sphincter trauma), early use of oxytocin was recommended to shorten the second stage. A continuation of the same study [797] reported that PNTML was prolonged and the squeeze pressure increment was reduced in women who had a cesarean section in the late first stage (>8cm cervical dilatation) or second stage.

Chaliha et al. [793] measured anal sensation and manometry in 286 nulliparae during the third trimester and repeated in 161 women postpartum when anal endosonography was also performed. Anal endosonography revealed sphincter defects in 38% of women and this was associated with the presence a lowering of anal squeeze and resting pressures. Threshold anal electrosensitivity remained unchanged and bore no relationship to symptoms. Postpartum sphincter defects were associated with perineal tears and vaginal delivery.

Abramowitz et al. [798] undertook a prospective study of 233 women who had anal endosonography performed before and 6 to 8 weeks after childbirth. Of the 233 women (118 primiparae), 202 had a vaginal delivery. Postpartum anal incontinence in the 233 women was reported by 13% of primiparae and 8.5% of multiparae and anal sphincter defects in 21% and 12% respectively. However, the prevalence of anal sphincter defects amongst those who had a vaginal delivery (n=202) was 26% and 13% respectively. Previous studies [799, 800] including others mentioned in **Table 1** and **2** have shown that the

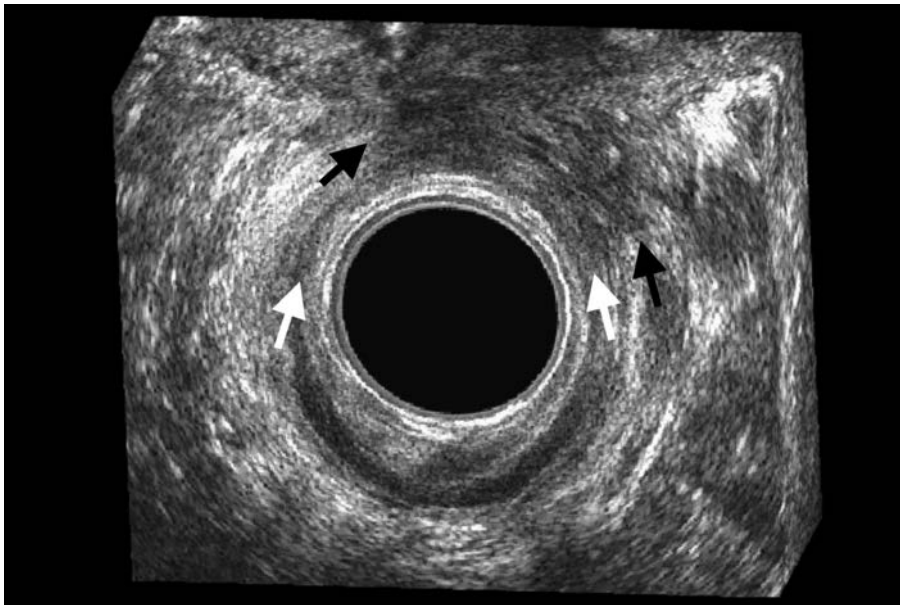


Figure 13. Anal ultrasound image of the mid anal canal

EAS = external anal sphincter. IAS = internal anal sphincter. The area between the black arrows at 11 and 2 o’clock represents an external anal sphincter defect while the area between the white arrows between 9 and 3 represent an internal sphincter defect

first delivery is most likely to be associated with anal sphincter trauma but this study is at variance as it claimed that secundiparous females have the same risk as primiparous women. However, this finding remains unsubstantiated and is further disputed by a subsequent prospective study [801].

Fynes et al. [800] undertook a prospective study of 59 previously nulliparous women through 2 successive pregnancies and found that 34% had anal sphincter injury after their first delivery but only 2 new injuries occurred after the second delivery confirming the findings in Sultan's study [202]. An important finding in this study was that 42% of women (5 of 12) who had a severe 'occult' sphincter injury during their first delivery (squeeze pressure increment < 20mmHg or anal sphincter defect > one quadrant) developed anal incontinence after the second delivery.

Willis et al. [802] performed anal vector manometry, endosonography, PNTML and rectal sensibility at the 32 weeks and 6 weeks postpartum. Using the Kelly-Holschneider score they reported anal incontinence in 5% and identified occult injuries in 19%. PNTML and rectal sensibility was unaffected by vaginal delivery.

Nazir et al. [803]performed vector manometry and endoanal ultrasound in 73 nulliparous woman at 25 weeks and 5 months postpartum (T**able 3**). There was no correlation between vector manometry and anal endosonography or clinical variables.

Belmonte-Montes [804] performed anal endosonography in 98 nulliparous women 6 weeks before and 6 weeks after delivery and after excluding 20 third degree tears found occult sphincter injuries in 13%. Seventy five percent of women with defects were symptomatic and there was a good correlation between defects and symptoms. However, it is not clear as to how many with 'occult' defects were symptomatic (**Table 3**).

In 3 further studies [805-807] anal ultrasound was performed only after delivery and defects were identified in 11.5 to 34% (**Table 4**). Varma et al [805] studied 159 postnatal women (105 primiparous and 54 secundiparous) and found occult anal sphincter defects in 11.5% of primiparous and 19% of secundiparous vaginal deliveries but 80% of forceps deliveries. None of their patients suffered faecal incontinence but only 72% of questionnaires were returned. However, their cohort was recruited before 1998 and had a high cesarean section rate (25%) and a low forceps rate (4%).

Williams et al [808] performed a prospective study

Table 3. Prospective studies before and after vaginal delivery of "occult" anal sphincter injury (using 2d ultrasound) and anal incontinence but excluding faecal urgency

Study	**Parity**	**Vaginal delivery** Numbers	FU in weeks postpartum	Sphincter Defects	Anal incontinence
Sultan et al 93 [2]	Primi Multi	79 48	6 6	33% 44%	5% 19%
*Donnelly et al 98 [20]	Primi	168	6	35%	25%
Rieger et al 98 [30]	Primi	37	6	41%	8%
Zetterstrom et al 99 [31]	Primi	38	9	20%	18%
*Fynes et al 99 [25]	Multi	59	6-12	37%	17%
Abramowitz et al 00 [22]	Primi Multi	202 including multi	8	26% 13%	15% 10%
Chaliha et al 01 [16]	Primi	130	12	19%	13%
Belmonte-Montes et al 01 [28]	Primi	78	6	13%	?
Nazir et al 02 [27]	Primi	73	20	19%	25%
Willis et al 02 [26]	Primi +Multi	42	12	10%	5%
MEAN (excluding Willis et al)	Primi Multi			28% 31%	16% 15%

*** modified continence score questionnaire used and may include urgency**

Table 4: Postnatal studies of "occult" anal sphincter injury (using 2d ultrasound) sustained during vaginal delivery and anal incontinence excluding faecal urgency

Study	**Parity**	**Vaginal delivery** Numbers	FU in weeks postpartum	Sphincter Defects	Anal incontinence
*Varma et al 99[29]	78 31	Primi Multi	4 weeks 4 weeks	11.5% 19%	0% 0%
Damon 00[32]	197	Primi	3 months	34%	6%
**Faltin 00[33]	150	Primi	3 months	28%	15%

*** Ultrasound performed < 1 week after delivery**
**** Anal ultrasound performed immediately after delivery before perineal repair**

in 45 nulliparous women before and after vaginal delivery using 3 dimensional endosonography. There was evidence of perineal trauma in 29% (external sphincter 11%, puboanalis 20%, transverse perineal muscle 7%). Sudoł-Szopińska et al. [809] performed 3 dimensional endoanal ultrasound in 112 primiparous women and found only 2.6% sonographic injuries. However, their obstetric practice was different in that they had a 77% episiotomy rate and a 59% epidural rate.

Oberwalder et al. [810] performed a meta-analysis of 717 vaginal deliveries and found a 26.9% incidence of anal sphincter defects in primiparous women and an 8.5% incidence of new sphincter defects in multiparous women. Although two thirds of these women with "occult" defects were asymptomatic in the postpartum period, the probability of faecal incontinence associated with a sphincter defect was 76.8 to 82.8%.

Some 15 years after having first coined the term "occult" OASIS based on anal endosonography, Sultan [202] began questioning whether the 28% sonographic anal sphincter defects (**Table 5**) identified some weeks after delivery were really genuine occult defects that were not identifiable clinically at delivery. They therefore conducted a prospective study [811] in which 241 women having their first vaginal delivery had their perineum re-examined by an experienced research fellow and endoanal ultrasound was performed immediately after delivery and repeated 7 weeks postpartum. When OASIS were identified by the research fellow, the injuries were confirmed and repaired by the duty registrar or consultant. The prevalence of clinically diagnosed OASIS increased from 11% to 25% (n=59). Every clinically diagnosed injury was identified by postpartum endoanal ultrasound. However, there were three women with sonographic defects in whom the injury was not identified clinically. Two of these had only small IAS defects that were not considered clinically significant. The other was a combined defect of both the IAS and EAS and while this could be classified as an occult tear, it is most probably a tear that was not recognised by the research fellow. At 7 weeks postpartum, no de novo defects were identified by ultrasound. This study concluded that virtually all sphincter defects that have previously been designated as "occult" injuries (**Table 5**) were in fact OASIS that could have been identified by a trained clinician [812] and that less than one percent are genuine occult OASIS (if indeed they exist). Interestingly, 87% of midwives and 27% of junior doctors failed to recognise OASIS clinically. Although it is likely that some of these injuries would have been detected at the time of suturing the tear, it is concerning that clinical recognition of OASIS is suboptimal [813]. However, this finding is not unique as Groom and Patterson [814] also found that the rate of third degree tears rose to 15% when all "2nd degree tears" were re-examined by a second experienced person.

These studies [811, 814] confirm the lack of adequate training as previously highlighted by Sultan et al. [815] who reported that 91% of doctors who had done at least 6 months of training in obstetrics and 60% of midwives indicated inadequate training in perineal anatomy and 84% and 61% respectively reported inadequate training in identifying 3rd degree tears. Another possible reason for under-diagnosis is that tears of the anal sphincter have been wrongly classified and therefore anal sphincter tears have been under-reported. Any involvement of the anal sphincter should be classified as a third degree tear. However 41% of doctors and 16% of midwives classified a torn anal sphincter as a 2nd degree tear [815]. Sultan and Thakar [816] reviewed every relevant text book (n=65) in the library of the Royal College of Obstetricians and Gynaecologists (RCOG) and found that there was a lack of consistency in classification and in about 40% the classification was omitted or wrong. Furthermore, previous classifications were incomplete because they did not

Table 5. Prevalence of anal incontinence following primary repair of obstetric anal sphincter rupture (fecal incontinence ie. excluding flatus incontinence only is shown in parentheses).

Authors (n=33)	Year	Country	N	Follow-up Months	Anal (Faecal) incontinence
Sangalli et al [45]	2000	Switzerland	177	13 years	15% (10%)
Wood J et al [55]	1998	Australia	84	31	17%* (7%)
Walsh et al [56]	1996	UK	81	3	20% (7%)
Sander et al [57]	1999	Denmark	48	1	21% (4%)
Pretlove et al [58]	2004	UK	41	?	22% (22%)
Crawford et al [59]	1993	USA	35	12	23% (6%)
Sorensen et al [53]	1993	Denmark	38	3	24% (?)
Mackenzie et al [60]	2003	UK	53	3	25% (7%)
Nichols et al [61]	2005	USA	56	3	25% (11%)
Nielsen et al [62]	1992	Denmark	24	12	29% (?)
Go & Dunselman [63]	1988	Netherland	2	6	30% (15%)
Fenner et al [64]	2003	USA	165	6	30% (?)
DeLeeuw et al [65]	2001	Netherland	125	14 years	31% (?)
Wagenius et al [66]	2003	Sweden	186	4 years	33% (25%)
Vaccaro & Clemons [80]	2008	USA	60	3	33% (12%)
Uustal Fornell et al [67]	1996	Sweden	51	6	40% (6%)
Poen et al [50]	1998	Netherland	117	56	40% (?)
Sultan et al [44]	1994	UK	34	2	41% (9%)
Zetterstrom et al [48]	1999	Sweden	46	9	41% (2%)
Sorensen et al [68]	1988	Denmark	25	78	42% (?)
Tetzschner et al [69]	1996	Denmark	72	24-48	42% (17%)
Williams et al [70]	2003	UK	124	?	42% (?)
Norderval et al [71]	2004	Norway	156	25	42% (17%)
Garcia et al [72]	2005	USA	26	3	42% (15%)
Kammerer-Doak et al [51]	1999	USA	15	4	43% (13%)
Haadem et al [54]	1988	Sweden	62	3	44% (?)
Rieger et al [73]	2004	Australia	51	3	45% (25%)
Bek & Laurberg [74]	1992	Denmark	121	?	50% (?)
Davis et al [75]	2003	UK	52	3.6	50% (?)
Fitzpatrick et al [46]	2000	Ireland	154	3	53% (6%)
Nazir et al [76]	2003	Norway	100	18	54% (17%)
Gjessing H et al [49]	1998	Norway	35	12-60	57% (23%)
Savoye-Collet et al [77]	2003	France	21	4	57% (29%)
Goffeng et al [51]	1998	Sweden	27	12	59% (11%)
Nygaard et al [78]	1997	USA	29	30 years	59% (28%)
Pinta et al [79]	2004	Finland	52	15	61% (10%)
+Sakse et al [81]	2009	Denmark	33	5	67% (42%)
Mean					**39% (15%)**

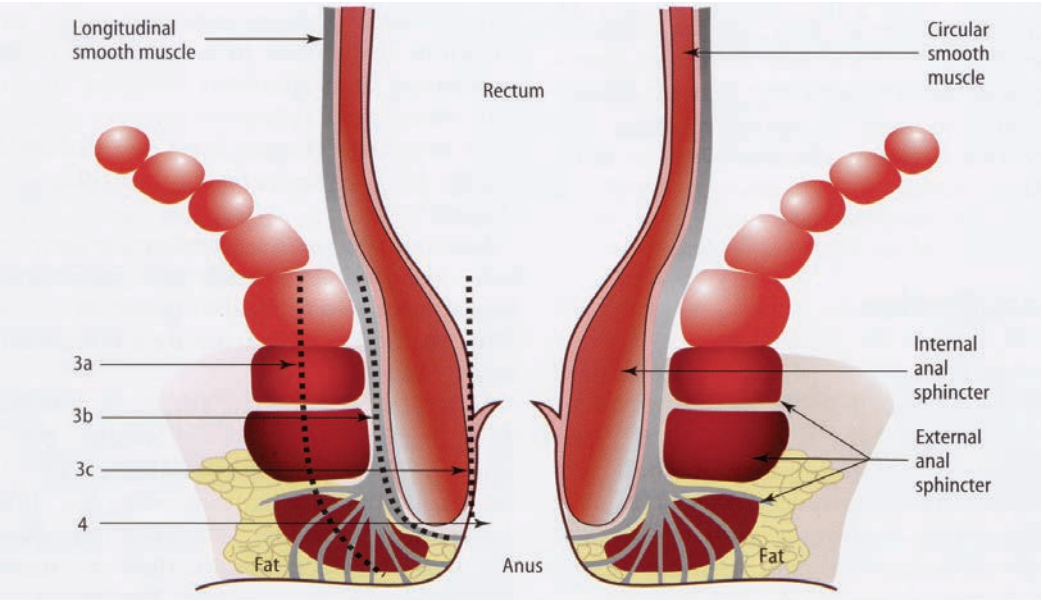
*Includes 2 with secondary sphincter repair
+ *Includes only 4th degree tears

incorporate depth of EAS rupture or involvement of the IAS. This therefore has epidemiological, clinical and medicolegal implications. If a third degree tear is incorrectly classified as second degree, then inappropriate repair could result in sub-optimal outcome (see below). Sultan [817] has therefore proposed the following classification (**Figure 14**)[813] that has been incorporated into the 29th RCOG green top guidelines [818] and the first edition of this book:

First degree: laceration of the vaginal epithelium or perineal skin only.

Second degree: involvement of the perineal muscles but not the anal sphincter.

Figure 14. Schematic representation of the classification of 3rd and 4th degree tears (with permission from Springer) [813]



Third degree: disruption of the anal sphincter muscles and this should be further subdivided into:

3a: <50% thickness of external sphincter torn.

3b: >50% thickness of external sphincter torn.

3c: internal sphincter torn also.

Fourth degree: a third degree tear with disruption of the anal epithelium.

An isolated rectal tear without involvement of the anal sphincter is rare and should not be included in the above classification.

2. RECOGNISED OBSTETRIC ANAL SPHINCTER INJURIES

Primary repair of OASIS are usually performed by obstetricians using the end-to-end repair technique [819]. However, as shown in **Table 3,** anal incontinence occurs in 39% (range15 to 67%) and in addition, urgency can affect a further 6 [819] to 28% [820]. Frank faecal incontinence affected 14% [819] (range 2 [821] to 29% [822]). The reasons for persistent symptoms are unclear but there are five studies [819, 820, 823-825] demonstrating anal sphincter defects following repair in 40 to 91% of women. Although the extent of the sphincter injury appears to be related to outcome of repair, in some studies (**Table 5**) the data were not interpretable, [826] incomplete [824] or inclusive of symptoms other than anal incontinence [203] Forceps delivery, first vaginal delivery, large baby, shoulder dystocia and a persistent occipito-posterior position have been identified as the main risk factors for the development of OASIS [798, 799, 817, 823].

The most popular method of EAS repair is the end-to-end technique but colorectal surgeons prefer the overlap technique for secondary repair because of better outcome [827]. It is now known that like other incontinence procedures, the outcome can deteriorate with time and one study has reported continence in 50% of women at 5-year follow-up. However, at least one third of women in this study had more than one attempt at sphincter repair and therefore these findings cannot be extrapolated to those following primary repair of acute injury [828]. In 1999, Sultan et al. [829] were the first to explore the feasibility of the overlap technique of repair for acute EAS rupture but more importantly advocated the identification and separate repair of the torn IAS. Until then, very little importance was given to the torn IAS during primary repair. However, subsequently in a study involving 500 consecutive women with OASIS it has been shown that sonographic evidence of IAS injury was predictive of faecal incontinence [830]. More recently Roos et al. [831] studied 531 consecutive women with OASIS and found that women who sustained an IAS tear were significantly more likely to suffer incontinence, have lower anal pressures, persistent IAS defects and a reduced quality of life. Increasing IAS defect size has also been shown to be related to symptoms of anal incontinence [832]. When a patient presents with faecal incontinence months or years after delivery, it is almost impossible to perform a successful IAS repair highlighting the importance of identification and repair immediately after delivery [813, 829]. Compared to matched historical controls [819] who had an end-to-end repair, Sultan et al. found that the rate of anal incontinence was reduced from 41% to 8% when the overlap technique was used for EAS repair with separate repair of the torn IAS [829] and therefore recommended the performance of a randomised controlled trial.

The first published randomised trial by Fitzpatrick et al. [820] reported no significant difference between end-to-end and overlap repair although there appeared to be trend towards more symptoms in the end-to-end group. However, there were methodological differences in that the torn IAS was not identified and repaired separately and they used a constipating agent for 3 days after the repair. Unfortunately, they included partial EAS tears in their randomised study. A true overlap [813, 828] is not possible if the sphincter ends are not completely divided and it would be expected that if an overlap is attempted, the residual intact sphincter muscle would have to curl up and hence there would be undue tension on the remaining torn ends of muscle that would be overlapped. This technique would therefore go against the general principles of surgery of deliberately placing tissue under avoidable tension [819].

Garcia et al. [833] also performed a randomised trial of the two techniques and took great care to include only complete ruptures of the EAS (full thickness 3b,3c and 4th degree tears). There were 23 women in the end-to-end group and 18 in the overlap group. Unfortunately, only 15 and 11 women respectively returned for follow-up which was only at 3 months. No significant difference was found between the groups in terms of symptoms of faecal incontinence or transperineal ultrasound findings. However, the authors acknowledged that the major limitations of their study were that randomisation was inaccurate and that their study was underpowered.

Williams et al. [834] performed a factorial randomised controlled trial (n=112) in which women were randomised into 4 groups: overlap with polyglactin (Vicryl; Ethicon, Edinburgh, UK); end-to-end repair with Vicryl; overlap repair with polydiaxanone (PDS; Ethicon, Edinburgh, UK); end-to-end repair with PDS. This trial was specifically designed to test the hypothesis regarding suture related morbidity (need for suture removal due to pain, suture migration or dyspareunia) using the two techniques. At six weeks, there were no differences in suture related morbidity. The authors claimed that there were no differences in outcome based on repair technique. Unfortunately, the majority of patients included in this trial were partial tears of the EAS (70% were 3a tears) and as mentioned above, a true overlap [812, 829] cannot be performed if the EAS is only partially torn. Furthermore, their follow up rate at 12 months was only 54%. These data therefore need to be interpreted with caution.

Fernando et al. [835] performed a randomised controlled trial of end-to-end vs overlap technique. The study had adequate power (n=64) and the primary outcome was faecal incontinence at one year. All repairs were performed by two trained operators and Grade 3a EAS were excluded. At 12 months (81% follow-up rate), 24% in the end-to-end and none in the overlap group reported faecal incontinence (p=0.009). Faecal urgency at 12 months was reported by 32% in the end-to-end and 3.7% in the overlap group (p=0.02). There were no significant differences in dyspareunia and quality of life between the groups. At 12 months 20% reported perineal pain in the end-to-end and none in the overlap group (p=0.04). During the 12 months period 16% in end-to-end and none in the overlap group reported deterioration of defaecatory symptoms (p=0.01). Further calculation

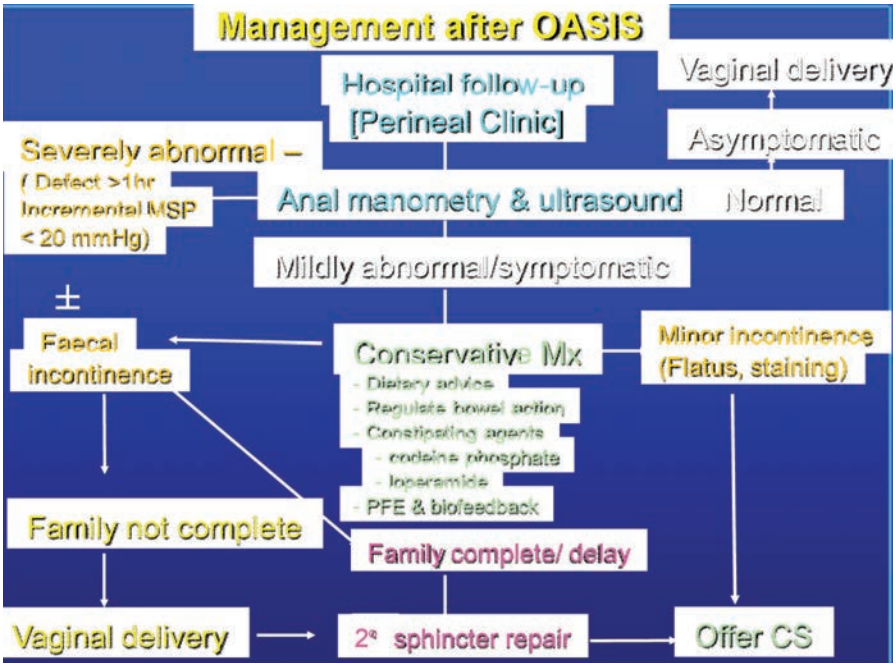


Figure 15. Flow chart demonstrating a pathway of the management of a subsequent pregnancy following OASIS (MSP= maximum squeeze pressure; CS =caesarean section)

revealed that four women need to be treated with the overlap technique to prevent one woman with OASIS developing faecal incontinence. On the basis of this randomised trial it would appear that the overlap technique of EAS repair accompanied by separate repair of the torn internal sphincter, performed by trained clinicians is associated with a good outcome. In 2006, the Cochrane review [836] concluded that as the surgeon's experience was not addressed in two of the three randomized studies, it would be inappropriate to recommend one type of repair over the other.

Farrell et al. [837] performed a randomised controlled trial with a 6 month follow-up of end-to-end (n=62) vs overlap (n=63) EAS repair in primiparous women. They reported significantly higher rates of flatal but not faecal incontinence in the overlap group. However, there were more 4th degree tears in the overlap group and therefore more IAS injury that could explain the increased flatal incontinence in this group [838]. At 3 year follow up there was no significant difference in anal incontinence between the groups [839]. This supports the findings of Fernando et al. [835, 836] who demonstrated a significantly higher risk of deterioration in anal incontinence over time in the end-to-end group and highlights the importance of longer term follow-up.

Rygh and Korner [840] performed another randomised controlled trial (n=101) with the primary outcome measure 'of at least weekly solid stool incontinence'. They concluded that the overlap technique was not superior to the end-to-end repair. However, there were more women with symptoms of anal incontinence with the end-to-end repair (34% vs 20%).

Therefore, until the Cochrane review is updated the current recommendation is that as the surgeon's experience was not fully assessed in all the studies, it would be inappropriate to recommend one type of repair in favour of another [836].

Management of subsequent pregnancy after OASIS

All women who sustained OASIS should be assessed in hospital by a senior obstetrician 6 to 12 weeks after delivery. Some centres have established dedicated multidiscliplinary perineal clinics. In 2010, 30% of UK hospitals had such a dedicated clinic (Sultan AH, unpublished data). It is important that a comprehensive history is taken regarding bowel, bladder and sexual function. As these symptoms are embarrassing, a structured questionnaire may be useful. A proper vaginal and rectal examination should be performed to check for complete healing, scar tenderness and sphincter tone [809, 813, 841]. Mild incontinence (faecal urgency, flatus incontinence, infrequent soiling) may be controlled with dietary advice, constipating agents (loperamide or codeine phosphate), physiotherapy or biofeedback. However, women who have severe incontinence should, in addition, be offered secondary sphincter repair by a colorectal surgeon. Asymptomatic women must be advised to return if symptoms develop [812].

There are no randomised studies to determine the most appropriate mode of delivery. Women who have had a successful secondary sphincter repair for faecal incontinence should be delivered by cesarean section [842]. Some women with faecal incontinence may choose to complete their family prior to embarking on anal sphincter surgery. It would appear that these women could be allowed a vaginal delivery as the damage to the sphincter has already occurred and risk of further damage is minimal and probably insignificant in terms of outcome of surgery. The risk of worsening or de novo neuropathy has not been quantified and in practice, does not appear to be clinically significant.

Until recently [821] the management of a subsequent pregnancy after OASIS has not been described in any detail [816].

It has been suggested that a cesarean section should be performed even after transient anal incontinence [843] but this has been questioned [844].

In order to counsel women with previous OASIS appropriately, Sultan et al [812] find it useful to have a symptom questionnaire, anal ultrasound (**Figure 7**) and manometry results (**Fig 3**). It has been shown that clinical assessment alone has a poor sensitivity for detecting anal sphincter defects [845] If vaginal delivery is contemplated then these tests should be performed during the current pregnancy unless performed previously and found to be normal. In a prospective study over a 5 year period, Scheer et al. [846] followed the protocol shown in **Figure 15** and found that when women who had no evidence of significant anal sphincter compromise based on anal endosonography and manometry were allowed a vaginal delivery (the others offered cesarean section) there was no deterioration in symptoms, anorectal function or quality of life. Although 11% of textbooks recommend a prophylactic episiotomy [816] there is limited evidence that an elective episiotomy prevents subsequent anal sphincter disruption [116] while other studies have indicated that episiotomy may increase the prevalence of anal sphincter disruption.

III. INSTRUMENTAL VAGINAL DELIVERY

Although only 4% of women delivered by forceps sustain a 3rd/4th degree tear, up to 50% of those that do tear have an instrumental delivery [819]. Vacuum extraction is associated with fewer OASIS than forceps and this view is supported by two large randomised studies [847, 848]. A UK study [847] where mediolateral episiotomy is practised reported severe vaginal lacerations in 17% of forceps compared to 11% of vacuum deliveries and a Canadian study [848] where midline episiotomy is practised reported OASIS in 29% of forceps compared to 12% of vacuum deliveries. In a Cochrane review [849], forceps were less likely than the vacuum extractor to fail to achieve a vaginal birth (risk ratio 0.65, 95% CI: 0.45-0.94).

However, with forceps there was a trend to more cesarean sections, and significantly more third- or fourth-degree tears (with or without episiotomy), vaginal trauma, use of general anaesthesia, and flatus incontinence or altered continence. Facial injury was more likely with forceps (RR 5.10, 95% CI: 1.12-23.25). Serious neonatal injury was uncommon with either instrument.

A 5 year follow-up of infants who participated in a randomised trial of forceps and vacuum delivery has confirmed that there is no difference in terms of neurological development and visual acuity with use of either instrument [850]. "Occult" trauma to the anal sphincter has also been identified more frequently in forceps delivery occurring in up to 80 percent [202, 805, 851]. A small randomised study (n=44) confirmed this by identifying occult anal sphincter defects in 79% of forceps compared to 40% of vacuum deliveries [851]. Trauma occurs more frequently when a second instrument is used to attempt vaginal delivery [851] and therefore if no descent of the head occurs following appropriate cup selection and application technique of vacuum extraction, one should resort to a cesarean section. Metal cups appear to be more suitable for 'occipito-posterior', transverse and difficult 'occipito-anterior' position deliveries [852]. The soft cups seem to be appropriate for straightforward deliveries as they are significantly more likely to fail to achieve vaginal delivery (OR 1.65, 95% CI 1.19-2.29). Although, they were associated with less scalp injury (OR 0.45, 95% CI 0.15-0.60), there was no difference between the two groups in terms of maternal injury. Farrell et al. [853] performed a prospective study of 690 primigravid women and found that forceps delivery was associated with a higher incidence of flatal incontinence (RR 2.6) compared to spontaneous vaginal delivery and a higher incidence of both flatal (RR 2.6) and faecal (RR 3.6) incontinence compared to cesarean delivery. Vacuum delivery did not increase the risk of flatus incontinence. MacArthur et al. [786] performed the largest questionnaire based multicentre study to establish the prevalence of faecal incontinence at 3 months post-partum. They reported a prevalence of 9.2%, with 4.2% reporting it more often than rarely. Compared to vacuum extraction, forceps delivery was associated with almost twice the risk of developing faecal incontinence. Thakar and Eason [854] performed a meta-analysis and demonstrated that one anal sphincter injury is avoided for every 18 women delivered by vacuum extraction instead of forceps.

IV. EPISIOTOMY

There is now considerable observational data to indicate that a reduction in episiotomy rate is not associated with an increase in OASIS [855]. The Cochrane database [200] shows that restricting the use of episiotomy is associated with less posterior trauma. Although there was an increase in anterior perineal trauma it had no effect on the development of urinary incontinence. Henrikssen et al. [856, 857] performed an observational study in which they noted that when midwives who previously had a high episiotomy rate reduced their rate, the prevalence of OASIS also reduced. However, this beneficial effect was abolished when midwives with a low rate of episiotomy attempted to reduce it even further. Based on this evidence, it was suggested that the ideal episiotomy rate should lie between 20 to 30% and no more. Midline episiotomies are more popular in North America as it is believed that they are more comfortable and recovery is less complicated. However Coats et al. [858] performed a quasi-randomised study of 407 primiparae and found 24% of midline episiotomies extended into the anal sphincter (partial or complete tears) compared to 9% of mediolateral episiotomies. Although the perineum was significantly less bruised in the midline group and sexual intercourse commenced earlier, pain and wound breakdown was similar in both groups. However, care needs to be taken to ensure that mediolateral episiotomies are performed correctly as Andrews et al [859] have shown that only 22% of doctors and no midwife made the incision commencing from the posterior fourchette with a 40 to 60 degree angle from the midline. Another study demonstrated that for every six degrees away from the midline there was a 50% reduction in OASIS [860]. It has also been shown that the angle of incision when the head is crowning is underestimated such that a 60 degree angle measures 45 degrees after delivery [205].

V. DELIVERY TECHNIQUES

Pirhonen et al. [861] compared the frequency of OASIS in low risk deliveries between two Scandinavian countries (26 541 vaginal deliveries) and found the risk to be 13 times higher in Sweden (Malmo) vs Finland (Turku). They speculated that the only explanation for this was a difference in manual support given to the baby's head during crowning and pushing the perineum under the chin. Jonsson et al. [862] performed a randomised trial between the Ritgen's manoeuvre and standard delivery but found no significant difference in OASIS rates. However, only 50% of the elligible women were assigned and almost 20% of the women randomised to the Ritgen's manoeuvre did not have this method of delivery. The following interventions with randomised controlled trials evidence regarding effectiveness demonstrated no effect on OASIS: antenatal perineal massage, pelvic floor exercises in pregnancy, water births, positions during labour and birth, epidural analgesia, early vs delayed pushing with epidural and second stage pushing advice [854]. Although one small randomised trial showed otherwise [788] other large observational studies, have shown that duration of the second stage of labour is an independent risk factor for the occurrence of OASIS [796, 799, 863, 864].

VI. TRAINING

McLennan et al. [865] who surveyed 1177 fourth year residents and found that the majority of residents had received no formal training in pelvic floor anatomy, episiotomy or perineal repair and supervision during perineal repair was limited. Stepp et al. [866] found that textbooks used in American practice offered little in terms of prevention and repair of perineal trauma. There is evidence from one study [815] that perineal anatomy is poorly understood by midwives and trainee doctors, who perform the bulk of deliveries in the UK. In this study 41% of trainees and 16% of midwives incorrectly classified a partial or complete tear of the EAS as 'second degree'. Inconsistency in classification of tears would allow many injuries to pass, unrecognised. In another study conducted in the USA, the majority of residents demonstrated substandard skill in repairing OASIS [867]. It has been shown that hands-on workshops on perineal repair (www.perineum.net) can change practice [868-870] and intensive and focused training in perineal anatomy and repair should therefore become an essential module in the programme for trainees and midwives. Hals et al. [871] provided the best available evidence to show how an interventional program in four Norwegian hospitals can reduce the frequency of OASIS. The program involved a 2-3 day course at the delivery suite of each hospital that included training on delivery with perineal support and delivery of the neonates chin. In addition, restrictive mediolateral/ lateral episiotomy was recommended. OASIS reduced from 4.16 -5.25% before intervention to 1.73% during the last year of intervention.

VII. IRRITABLE BOWEL SYNDROME (IBS)

IBS affects 3-17% in selected populations and the cause remains unknown. Donnelly et al. [872] recruited 312 primiparous women and reported that 11% of young primiparous women (n= 34 of 208) suffered from pre-existing IBS prior to their first pregnancy. Twenty four percent reported symptoms of impaired faecal continence in the puerperium but symptoms were found significantly more frequently in those with IBS compared to those with normal bowel habit (71% vs 18%). However, women suffering from IBS are no more likely to incur mechanical or neurological injury to the anal sphincter. Women with IBS delivered by cesarean section did not have altered continence postpartum. However, 6 months postpartum there were no symptomatic differences between those with IBS and those without but only 90 of the 107 women who had either impaired faecal continence or abnormal anal manometry were studied. Treatment is directed towards the predominant symptom and although antispasmodics such as hyoscine, mebeverine and dicyclomine are used widely to relax intestinal smooth muscle, they should be avoided during pregnancy.

VIII. CONCLUSIONS AND RECOMMENDATIONS

a) Compared to forceps the vacuum extractor is associated with less perineal and anal sphincter trauma. **(Level 1)**

b) Compared to midline episiotomy, mediolateral episiotomy is associated with a significantly lower risk of 3rd/4th degree tears. **(Level 1)**

c) Liberal use of episiotomy is not beneficial (Level 1) and restricting the rate of episiotomy to about 30% may reduce the risk of trauma to the anal sphincter. **(Level 4)**

d) A prolonged active second stage of labour is associated with denervation of the pelvic floor and one study has suggested that this also occurs with a prolonged passive second stage of labour with epidural analgesia. In these circumstances, early use of oxytocics in the second stage of labour may be useful. **(Level 4)**

e) Selective use of cesarean section may be beneficial particularly in those who have evidence of compromised anal sphincter function and those who have had previous successful continence or prolapse surgery. **(Level 4)**

f) Modification in techniques of delivery of the baby may reduce anal sphincter injury and further research is needed. **(Level 3)**

g) A more focused training program for doctors and midwives needs to implemented. There is a poor understanding of perineal and anal sphincter anatomy and hence identification of anal sphincter trauma, incorrect classification and poor outcome of repair. **(Level 4)**

h) There is increasing evidence supporting the identification and repair of the internal anal sphincter. Repair techniques of the external sphincter (overlap versus the end-to-end) are inconclusive and one technique cannot be recommended over the other. **(Level 1)**

G. PATHOPHYSIOLOGY OF INCONTINENCE IN MEN

Urinary incontinence (UI) in men, as in women, which is subdivided into three major groups as there is urgency, stress and mixed UI, may be caused by either an abnormality of the bladder (UUI), an abnormality of the bladder outlet (SUI) (bladder outlet which includes the internal (IUS) and distal to the prostate the external urethral sphincter (EUS)), or a combination of both (MUI) [873-875]. Changes in bladder ultrastructure and function that can occur as a result of neurological disease or aging (that can cause detrusor overactivity or underactivity) occur in men [876].

Many of these problems are associated with benign and/or malignant diseases of the prostate and their treatment. For example in men the prevalence of detrusor overactivity and impaired compliance causing incontinence is not associated with the bladder outlet obstruction caused by benign prostatic obstruction [876, 877].

Key outlet functions are; maintaining closure for urine storage, increased closure (guarding) during exertion, sustained opening for voiding, transient opening for territorial marking in animals and orthograde male ejaculation. These are coordinated by several spinal and higher CNS centres, with overlap of the somatic, sympathetic and parasympathetic nervous systems [878]. Also sphincter insufficiency resulting in stress urinary incontinence (SUI) does not generally occur as the result of aging, but rather as a side effect of surgery (for benign or malignant conditions) or radiation of the prostate followed by transurethral resection or neurological injury. Ectopic ureter in the male does not cause incontinence as its insertion into the lower urinary tract is always proximal to the external urethral sphincter. Extra-urethral incontinence in men is only known as a result of a fistula, where as it can occur in women because of congenital (developmental) abnormalities. Fistulae in men are most often iatrogenic (surgery, radiotherapy, cryotherapy, HIFU (High-intensity focused ultrasound)) or inflammatory (diverticulitis).

This section will focus on the pathophysiology of incontinence as it relates to prostatic obstruction and its treatment and the treatment of prostate cancer.

I. CONTINENCE MECHANISM IN THE MALE

The internal urethral sphincter (IUS) has its source at the urinary bladder's inferior neck (smooth muscle) continues through the prostatic urethra above the verumontanum and remains under autonomic control. The external urethral sphincter (EUS) located distal to the prostate at the level of the membranous urethra as the secondary sphincter to control the flow of urine. It contains mainly striated muscle and is therefore under voluntary control by the somatic nervous system. Opposite to the female sphincter (**Figure 16**), the male closing mechanism of the bladder is separated by the prostate.

At the boundary between the IUS and EUS, the striated and smooth muscle fibres intertwine to some extent. The external urethral sphincter (EUS) extends from the prostatic urethra below the verumontanum through the membranous urethra. EUS includes the rhabdosphincter (intrinsic skeletal and smooth muscle) and extrinsic paraurethral skeletal muscle. At the prostatic level, the superior part of the striated EUS is largely confined to the anterior side of the urethra and prostate. Inferior to the prostate, the EUS is horseshoe-shaped (although named as the rhabdosphincter, omega shaped) with the opening on the dorsal side. The dorsal muscle fibres of the left and right sides approach the midline and sometimes cross the prostate [227, 880, 881].

For simplicity, the normal male urinary sphincter mechanism may be divided into two functionally separate units, the internal urethral sphincter (IUS) and the external urethral sphincter (EUS) [882]. The IUS consists of the bladder neck, prostate and prostatic urethra to the level of the verumontanum. The IUS is innervated by autonomic parasympathetic and sympathetic fibres from the inferior hypogastric plexus (**Figure 17**). The EUS extending from the verumontanum to the proximal bulb and is comprised of a number of structures that help to maintain continence.

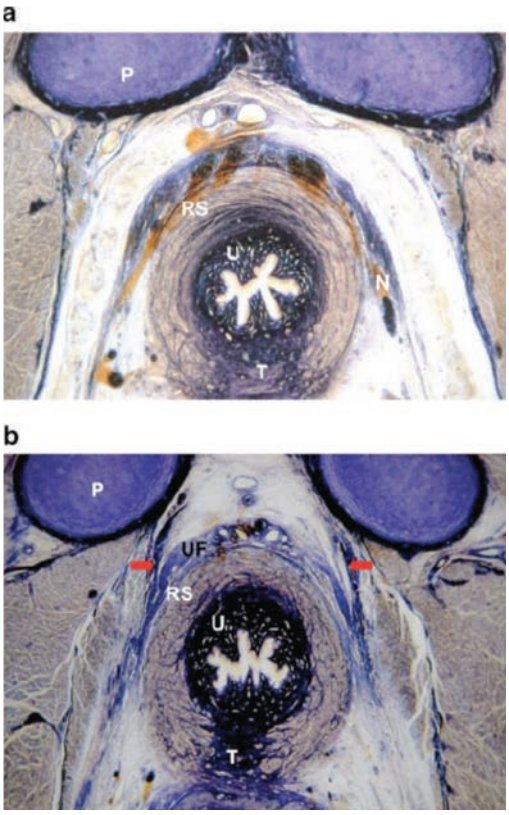


Figure 16. a: Rhabdosphincter and urethra of a female fetus (transverse section). Both ends of the omega-shaped rhabdosphincter (RS) and the urethra (U) are anchored in the ventral wall of the vagina by the help of a strong dorsal connective tissue raphe (T). Ventrally and laterally the rhabdosphincter and the urethra are surrounded by loose connective tissue (and vessels). P, pubic bone; N, nerves; b: Rhabdosphincter and urethra of the same fetal specimen as in (transverse section). The level of this section is more caudal than in (a). P, pubic bone; U, urethra; RS, rhabdosphincter; UF, ventral urethral fascia; T, strong dorsal connective tissue raphe (T); the tendinous arch of the pelvic fascia is marked with arrows.
From Fritsch et al. (2006) Neurourol Urodyn 25: 128 – 134 [879]

The male EUS complex is composed of the prosta-to-membranous urethra, cylindrical rhabdosphincter (external sphincter muscle) surrounding the prosta-to-membranous urethra, and extrinsic paraurethral musculature and connective tissue structures of the pelvis. The rhabdosphincter is a muscular structure consisting of longitudinal smooth muscle and slow-twitch (type I) skeletal muscle fibres, which can maintain resting tone and preserve continence [227, 883, 884]. The striated muscle of the rhabdosphincter is considerably thicker ventrally and thins dorsally. Striated muscle fibres of the rhabdosphincter have been shown to intermingle with smooth muscle fibres of the proximal urethra, suggesting a dynamic and coordinated interaction. The rhabdosphincter is invested in a facial framework, and supported below by a musculofascial plate that fuses with the midline raphe, which is also a point of origin for the rectourethralis muscle [885]. Superiorly, the fascial investments of the rhabdosphincter fuse with the puboprostatic ligaments [886]. This dorsal and ventral support probably contributes to the competence of the sphincter. The striated fibres of the extrinsic paraurethral muscle (levator ani complex), on the other hand, are of the fast-twitch (type II) variety [883]. During sudden increases in abdominal pressure, these fibers can contract rapidly and forcefully to provide continence. Continence maintains even after inducing paralysis of the striated sphincter [887] indicating that this structure is not solely responsible for continence. In addition, unlike in the female where urethral support can be compromised as a result of childbirth and aging [888], in the majority of the cases the male rhabdosphincter functions as a result of prostate surgery[889]. The striated muscle fibres of the rhabdosphincter intermingle with smooth muscle fibres of the proximal urethra and in fact have been shown to be inseparable from each other [880]. In the past related to the approach of radical prostatectomy the smooth muscle fibres inserting into the bladderneck (IUS) were resected, which interrupted innervation. It is worth noting that impaired detrusor contractility seems to be frequently associated with intrinsic sphincter deficiency. With increasing knowledge of the periprostatic nerves and the improvement of preservation of the bladder neck (IUS) the functional outcome has improved even further [890].

The EUS is innervated by the autonomic (via the pelvic nerve) and somatic (by the pudendal nerve) nervous systems. Nerve fibres are seen proximally ina dorsolateral position (5 to 7 o'clock), while more distally, they are located primarily laterally [885, 891]. The intrinsic smooth muscle of the proximal urethra receives parasympathetic innervation from pelvic nerve branches of the inferior hypogastric plexus [891, 892]. The rhabdosphincter may also receive somatic innervation. Hollabaugh et al. described the so-called "putative continence nerves" as branches of the pelvic nerve travelling under the endopelvic fascia picking up intrapelvic branches of the pudendal nerve, given off before it enters the pudendal canal, which was further verified by Castello et al. [891, 893]. It has also been proposed that somatic innervation from the pudendal nerve after it exits the pudendal canal is primarily sensory in origin, facilitating reflex contraction of the sphincter complex to maintain continence. [894] (**Figure 17**).

An elegant histological and immunohisto chemical-study with 3-D reconstruction in the male fetus has confirmed mixed autonomic and somatic innervation [880]. Unmyelinated (autonomic) nerve fibres destined for smooth muscle fibres run alongside of the myelinated (somatic) fibers. The majority of the unmyelinated fibres approach the smooth muscle layers at 5 and 7 o'clock while the majority of myelinated fibres penetrate the striated sphincter at 3 and 9 o'clock.

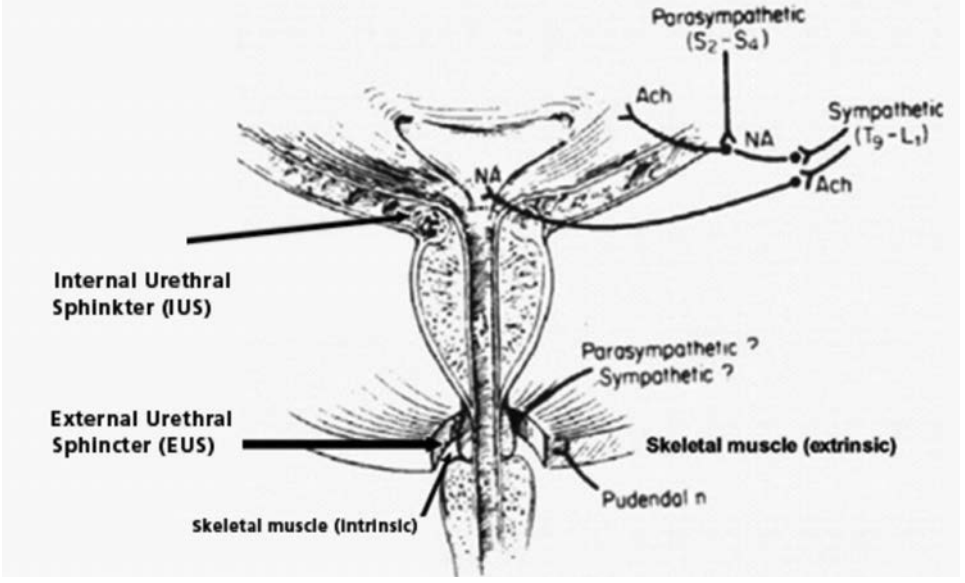


Figure 17. The innervation of the bladder outlet is better investigated with its internal urethral sphincter than the external sphincter, which is substantial for the continence.

Structure and innervation are important components of sphincter function. In addition, Tuygun et al. [895] have found a much higher incidence of periurethral (or peri-sphincter) fibrosis in incontinent vs. continent men after prostatectomy. Using MRI at least 6 months after prostatectomy they discovered that all 22 incontinent men had periurethral fibrosis while only 4/14 (29%) continent men did [896, 897]. This might lead to the importance of the corpus spongiosum, which surrounds the bulbar urethra and supports with its blood filling in addition to the sphincteric function.

In summary, sphincter continence in the male is dependent on the integrity of the IUS and/or EUS, its support structures and neural innervation and probably the prostate, as long it is not enlarged to cause obstruction. Following the removal of the IUS during radical prostatectomy, continence seems to be mainly maintained by the EUS mechanism, consisting of soft tissue supportive structures, smooth muscle, and striated muscle. This outcome has improved in relation to surgical techniques which preserve the IUS. The smooth muscle and slow twitch striated muscle of the rhabdosphincter (EUS) are probably mostly responsible for sphincter continence; however, striated muscle contractions of the periurethral and paraurethral muscles are likely to assist. Damage to the innervation (parasympathetic and somatic) of the smooth and striated muscle may indirectly contribute to post-prostatectomy incontinence. In addition compromise of the sphincter support mechanism or post operative changes such as fibrosis can compromise sphincter function (**Figure 18**).

II. INCONTINENCE ASSOCIATED WITH BPH AND ITS TREATMENT

Benign prostatic hyperplasia (BPH) and benign prostatic obstruction (BPO) and their treatments have long been associated with incontinence in men. Detrusor Overactivity (DO), impaired compliance and urgency incontinence are prevalent in men with BPO. The prevalence of OAB ranges in adult males from 10% to 26% and in adult females from 8% to 42%. It increases with age and is often associated with other LUTS [898]. In men undergoing urodynamic testing detrusor overactivity is present in 40-80% of patients with obstruction [899-901]. In addition, impaired compliance, another potential cause of incontinence, has been shown to have a high correlation with outlet obstruction in men [902, 903]. Thus even before treatment of BPH and BPO there is a notable incidence of bladder dysfunction and incontinence.

Incontinence after the treatment of BPH may be related to persistent bladder dysfunction, new onset bladder dysfunction or sphincter dysfunction (injury). However, one European survey of 840 men reported lower prevalence of UI after transvesical prostatectomy for BPH compared to other studies [904]. Turner-Warwick et al. [905] first directed attention to the relationship of bladder outlet obstruction, the symptoms of frequency, urgency and urgency incontinence (now commonly known as LUTS: Lower Urinary Tract Symptoms) and the correlation of these symptoms with detrusor overactivity seen on cystometry. They noted that in 75% of men, symptoms resolved after relief of the obstruction. Leng and McGuire [906] showed improvement in compliance after removal of obstruction in 7/9 men with severely impaired compliance (<5 ml/cmH^2O), but only one man regained “normal” bladder compliance. Several contemporary explanations for the cause of persistent overactivity after obstruction exist. These include denervation supersensitivity of the bladder muscle [11, 907, 908], alterations in collagen composition of the obstructed bladder [909], emergence of altered and increased sensory reflexes mediating the micturition reflex [910, 911] and physical changes in detrusor myocytes affecting electrical transmission [912] or even the remaining influence of CRP as investigated by Kupelian et al [73]. In addition, the bladder itself and particularly the trigone may be inadvertently resected during surgery, causing bladder dysfunction or even without prior surgical treatment. Causes of sphincter damage related to transurethral or open prostatectomy include direct damage because of surgical technique and electrocautery or thermal injury to the sphincter [913].

Recently, Han et al [914] conducted a retrospective data analysis using a managed care data set (Integrated Healthcare Information Services National Benchmark Database) from 1997 through 2003. They identified a cohort of men with BPH using International Classification of Diseases, Ninth Revision (ICD-9) codes. From a total of over 12 million men, 411,658 men with BPH (3.3%) were identified. The group then determined the nature of incontinence in these men with BPH focusing on its incidence, prevalence, and management. Furthermore they stratified patients into therapeutic subgroups of watchful waiting, alpha-blockers, 5-alpha-reductase inhibitors and surgery. Of the total cohort, 2.7% had a diagnosis of incontinence. Most of these men (87.5%) did not have prior BPH surgery, but those who did have surgery 12.5% were diagnosed with incontinence. The rates were almost identical whether the procedure was transurethral resection or incision, laser, transurethral needle ablation, transurethral microwave therapy. Newer data suggest that open prostatectomy might be more effective and safer than the transurethral approaches, which probably depends to the size of the prostate and the experience of the surgeon [915, 916]. The rate of incontinence after surgical treatment was 1.4% for both stress and mixed incontinence, 4.5% for urgency incontinence and 6.5% for unspecified incontinence whereas the incontinence rates for men on watchful-waiting, alpha-blockers, 5-alpha-reductase inhibitors and combination therapy were 6.4%,

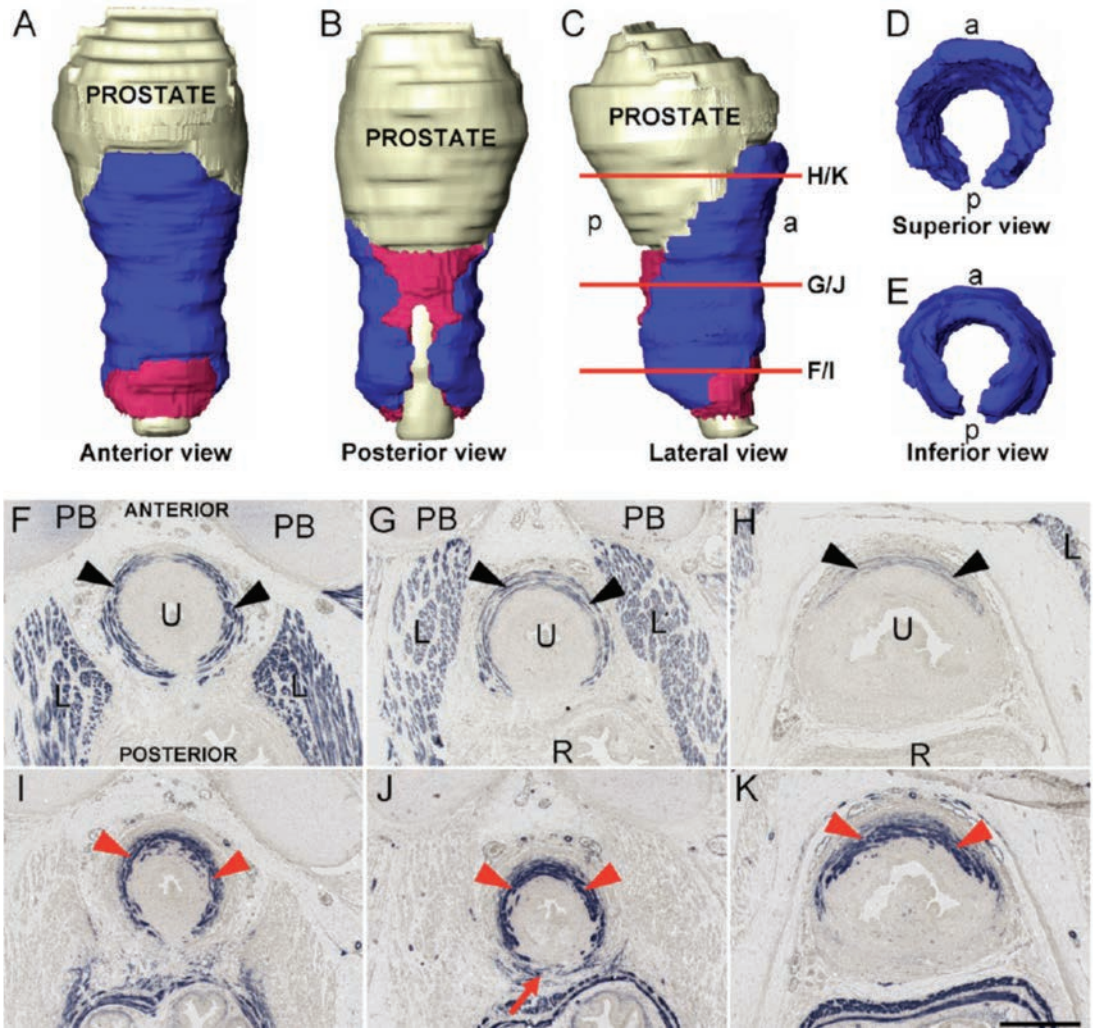


Figure 18. The external urethral sphincter (EUS) and internal urethral sphincter (IUS) in a male fetus (12 wk of gestation). Three- dimensional reconstruction in (A) anterior view, (B) posterior view, (C) right-lateral view, (D) superior view, and (E) inferior view. The EUS is shown in blue, and the IUS is shown in pink. The urethra and prostate are shown in light grey. Anterior and posterior directions are represented by the letters "a" and "p." Immunohistochemically stained sections: Sections from inferior (F) to superior (H) stained immunohistochemically for striated muscle, showing the EUS (black arrowheads). Panels (I) through (K) are from same level as sections (F) through (H), stained immunohistochemically for smooth muscle, showing the IUS (red arrowheads). Note the smooth muscle tissue at the dorsal side of the urethra, where the striated muscle of the external sphincter is lacking; see red arrow in (J). Red lines in (C) illustrate the level of the sections as seen in (F) through (H). L = levator ani muscle; PB = pubic bone; R = rectum; U = urethra; bar = 0.5 mm. From Wallner et al, Eur Urol 55(4):932-944, 2009 [227]

5.7%, 5.1%, and 6, 5% respectively [914]. This study provides some interesting data but must be interpreted with caution. The diagnosis of incontinence was limited by what the patient and provider considered to be incontinence and was not often confirmed by objective testing.

Nevertheless, the relationship between BPH and incontinence can clearly be inferred. Until the last decade, transurethral resection of the prostate and open prostatectomy accounted for the majority of surgical procedures to treat BPO. In 1989,the American Urological Association published two major series on TURP and its complications. The AUA cooperative study included 3,885 patients from 13 teaching centres and private practices [917], while the second consisted of a survey of all practicing urologists in the United States of whom 2,716 urologists responded [917]. Rates of post-TURP incontinence requiring a pad or collection device were 0.4% in the first and 3.3% in the second study. The AUA Cooperative study also reported mild stress

incontinence in 1.2% [918]. In 1994, the Agency for Health Care Policy and Research published clinical guidelines for the diagnosis and treatment of benign prostatic hyperplasia. The guidelines panel reviewed 27 articles about transurethral prostatectomy and 30 articles reporting open prostatectomy to analyse treatment outcomes. The panel reported that the risk of total incontinence, defined as complete loss of voluntary control over micturition was of great concern to patients facing a treatment decision for BPH. In an overall ranking of 15 different outcomes, the panel's proxy judges ranked total incontinence of urine as the fourth most important outcome influencing a treatment decision. After TURP, 2.1% of patients experienced stress incontinence, 1.9 % had urgency incontinence, and 1.0% reported total incontinence. The panel attempted to abstract data on urgency incontinence, but found very few studies reporting this particular outcome, therefore a statistical analysis was not performed. For open prostatectomy stress incontinence occurred in 1.9%, urgency incontinence in 0.5% and total incontinence in 0.5% of patients.

Most studies evaluating post TURP and open prostatectomy incontinence have found a significant incidence of sphincter and bladder dysfunction. The incidence of sphincter dysfunction ranges from 20-92% and bladder dysfunction from 56-97% [919-924]. The relatively high incidence of sphincter dysfunction may seem somewhat surprising as the incidence of DO before treatment is so high and it persists in 18-59% after surgery to relieve obstruction [900, 905]. Therefore one might expect that a large number of patients would have persistent detrusor overactivity and urgency incontinence. However, in large series, sphincter dysfunction appears to be the main cause of incontinence. The high incidence of sphincter dysfunction is likely to represent a selection bias, e.g. large numbers of patients referred to tertiary centres for treatment of stress incontinence. Nitti et al. [925] evaluated patients with voiding dysfunction after TURP and found that of those who had incontinence 75% had bladder dysfunction, while only 20% had sphincter dysfunction (the cause of incontinence could not be identified in 5%). Twenty-seven percent of incontinent patients with bladder dysfunction also had obstruction. In the past decade, alternatives to TURP for the treatment of BPH have emerged. Most notable are thermal therapies and laser resection/enucleation of the prostate. Thermal therapies are considered "less invasive" and outcomes in most series are not comparable to traditional TURP with respect to efficacy. However some laser treatments provide similar efficacy in well-selected patients, at least in the short term. Studies that have evaluated that holmium laser resection (HoLRP) and potassium titanyl phosphate (KTP) laser vaporisation of the prostate have shown a similar incidence of incontinence. Two randomised controlled trials of holmium laser versus TURP have shown rates of stress incontinence to be very similar. Westenberg, et al [926] showed the incidence of stress incontinence with or without urgency incontinence to be 7% for HoLRP versus 6.7% for TURP at a minimum of 4 years follow-up. Kuntz and colleagues [927] found just 1% stress incontinence in each group at 12 months. They also showed a similar rate of resolution of preoperative urge incontinence for both groups (81% versus 85%). Two other prospective non-randomised trials of HoLEP found 0.6% -2.5% incidence of stress [928]. Two randomised controlled trials of KTP (green light) laser versus TURP reported 0% and 1% stress incontinence in each group respectively [929, 930] while a third randomised trial did not mention incontinence [931]. Retrospective studies on Greenlight showed a 2-3.3% incidence of stress incontinence [932, 933]. Te, et al. [934] reported 1 year results of Green Light in the first US multicentre prospective trial. At 12 months 2 of 139 men had persistent new onset UII. They reported no stress incontinence. Others report no better outcome than standard management apart from length of hospitalisation [935].

In addition to the surgical treatment, it needs to be borne in mind that males with urinary tract infections (UTIs) had higher adjusted rates of UI with a pooled odds ratio of 3.5 (95% CI: 2.3; 5.2) [936-940]. Acute genitourinary toxicity, enuresis, incomplete urination (residual), and other urological conditions were associated with higher adjusted odds of UI in all studies that examined the relationship [936, 941-943].

III. CONTINENCE ASSOCIATED WITH RADICAL PROSTATECTOMY

1. INCIDENCE

The incidence of incontinence after radical prostatectomy has been a source of controversy over the past several decades as reported rates have varied greatly depending on the definition and methodology of data collection. The incidence has probably declined over the past two decades, owing to advances in surgical technique and to earlier recognition of lower stage disease in younger patients, however the prevalence of post-prostatectomy incontinence has risen; paralleling the increase in surgical procedures performed annually [944]. In 1991, Foote et al tabulated data from series published between 1977 and 1990, and reported a range of incontinence rates from 2.5 to 87% after radical prostatectomy [945]. In general, older single-institution studies utilizing physician assessments to determine incontinence rates report relatively low rates (5-8%) [946-951]. Another study with a follow-up of up to 5 years reported frequent leakage in 14% or no urinary control in men 60 months after diagnosis [952]. A variety of definitions of incontinence were used, making comparison of data difficult. Since then, validated patient questionnaires have been developed, which help to standardise definitions of incontinence, allow easier comparison between in-

stitutions, and assess the impact of incontinence on quality of life. This eliminates physician bias perhaps improving accuracy [953-955], although it introduces the cavee at that questionnaire-based data may reflect subjective urine leakage but does not correlate with bother or actual urine, especially for mild degrees of incontinence [956, 957]. As expected these studies show the incidence of incontinence to be significantly higher, 13-65%, depending upon the definition.

In the past few years robotic radical prostatectomy has gained popularity and now, probably the majority of radical prostatectomies are performed with the support of robot surgical assistance. This surgical approach (trans- vs. extraperitoneal) has been further developed so that even in this instance, the outcome related to the approach needs to be evaluated periodically by further developments [958]. Similar to what has been observed with open radical prostatectomy, the continence rates tend to increase with longer follow-up and may continue to improve even beyond 12 months [959]. The continence rates from several large recently published series ranged from 68 to 97% at 12 months post surgery [959-964], reaching the laprascopic data with longer experience (continence range 12 months post op: 84.9 – 94 (mean72)% [965], Jacobson et al reported in their prospective study that there were no differences in urinary functional outcomes one year after open radical retropubic prostatectomy or laparoscopic radical prostatectomy [966] with 20 - 27% reported to have achieved immediate continence following catheter removal [960, 962, 963]. Recently anterior vesicourethral reconstruction [967], posterior vesicourethral reconstruction [968] and total reconstruction [969] have been described to increase the continence rate and hasten time to recovery of continence. As in earlier open prostatectomy series, robotic series tend to be single institution studies with physician reported outcomes and continence status based on 0 or 0-1 pads.

In 1993, The American College of Surgeons Commission on Cancer reviewed the reported results of 2,122 patients treated by radical prostatectomy performed at 484 institutions in 1990 [970]. Only 58% reported complete continence, 23% reported occasional incontinence not requiring pads, 11.2% wore 2 or fewer pads per day, 4% wore more than 2 pads per day, and 3.6% were completely incontinent. Fowler et al [971] published the results of an outcomes study on a series of Medicare patients with less encouraging results. In this series patients age >65 surveyed by mail, telephone, and personal interview, over 30% reported currently wearing pads or clamps to deal with wetness; over 40% said they dripped urine on coughing or when the bladder was full; 23% reported daily wetting of more than a few drops. Six percent had surgery after the radical prostatectomy to treat incontinence.

There appear to be differences in physician vs. patient reported outcomes and centres of excellence versus community surgeons' outcomes [972]. When trying to interpret all of the data, it is clear that the varying definitions of incontinence make comparisons impossible. Even using the definition of pad free totally continence has its limitations. Rodriguez et al [964] found that 70% of men who attained "pad-free continence" after radical prostatectomy have occasional incontinence. Conversely, Lepor et al [973] asked the single question "Do you consider yourself continent?" at 3-24 months after surgery where 97.1% of men answered yes. They found that the best correlation of objective measures with a positive response were 0 or 1 pad, total control or occasional dribbling, and no or slight problem from incontinence on the UCLA/RAND questionnaire [973]. There is a wealth of good quality prospective studies evaluating incontinence after prostatectomy in an objective manner. One such study compared continence in patients undergoing open versus laparoscopic radical prostatectomy at one year, using a 24-hour pad test, symptom scores and quality of life measures [689]. Incontinence was defined as a pad weight of > 8 grams/24 hours. There were no differences in objective and subjective measures between the two groups. Urinary incontinence was present in 13% of open and 17% of laparoscopic cases. In practical terms incidence of incontinence that produces bother, no matter what its degree, is the true parameter of interest. However, because of the individual variability of bother and the way data have been collected, we must be aware of the limitations of the historical data in the literature.

2. RECOVERY OF CONTINENCE AFTER RADICAL PROSTATECTOMY

While the majority of patients experience incontinence immediately following RRP, for most this is transient with a gradual improvement over time. It needs to be kept in mind that there is even a group of about 4% who might be incontinent prior to surgery (≥8g) although they might not consider themselves as incontinent [974]. Most studies report progressive return of continence up to one year after surgery and in general intervention for incontinence is usually delayed until one year after surgery unless absolutely no progressive improvement is seen. Thus, most prostatectomy series report continence rates at 1 year. Lepor and Kaci [973] showed that continence may continue to improve up to 24 months based on objective and subjective measures. They showed modest improvements in bother (UCLA RAND questionnaire) pad usage and total control rates between 12 and 24 months. Pad weights were not determined so it is possible that some "improvement" could have been related to patient tolerance and expectations over time. Smither et al. [975] objectively assessed the natural history of post radical prostatectomy incontinence using a standardised I hour pad test. They showed a rapid improvement in urinary control during the first 18 weeks post-RRP with a flattening of the recovery

curve beyond that point. Minimal incontinence defined as < 1 g on a 1 hour pad test was as demonstrated in 3,37,66, 85, 87 and 91% of patients at 2, 6, 18, 30, 42, and 54 weeks. They concluded that the 18-week marker appears to be the time point after which the majority of patients have achieved urinary control, although a small percentage will have continued objective improvement. This estimation is echoed by Socco et al. reporting the progressive improvement of continence until 2 years following RRP but some patients may become incontinent even later [976] whereas others reported that the peak level of continence was already reached at 3 months [974].

3. RISK FACTORS

An increased risk of post-prostatectomy incontinence in older men is supported in theory by anatomical observations. With advancing age, there is evidence of atrophy of the rhabdosphincter [885] and neural degeneration [977]. Several studies have shown advancing age to be a risk factor for postoperative incontinence [946, 947, 949, 951, 978, 979]. Steiner, et al [950] found no correlation between age and continence status, but only 21 of the 593 patients were 70 years or older. Catalona et al. [946] reported that "Recovery of urinary continence occurred in 92% (1,223 of 1,325 men) and was associated with younger age ($p<0.0001$) which might be related to surgical approach (nerve sparing), which might be performed more in the younger than in the older patient, although they ultimately reach a similar outcome [980], Most large series have found no correlation between the stage of disease and incontinence rates [946, 947, 953, 957], whereas Loeb reported the benefit of the younger patient in the high risk group to maintain continence [981]. However, in certain cases, the stage of disease may affect the surgical technique (i.e. nerve sparing) and rates may be higher, but this appears to be a reflection on surgical technique and not disease stage [947].

Authors of several single-institution studies have argued that surgeon experience and surgical technique are important determinants of post-operative incontinence rates [891, 921, 947, 982, 983] and many have found that changes in their own technique have led to reduced rates of incontinence or a reduced time to continence recovery [891, 947, 969, 984-986].

This includes procedural modifications such as, nerve sparing (probably secondary to a more careful dissection [987, 988] bladder neck preservation, preservation of anterior urethral ligamentous attachments and urethrovesical junction reconstruction (**Figures 19, 20**).

Patients who have undergone previous irradiation for prostate cancer are at high risk of developing incontinence after radical prostatectomy with the possible need of a postoperative radiation therapy [981]. Rates of significant incontinence after salvage prostatectomy range from 57-64% [991, 992]. Sanderson and colleagues [993] reported that 45% of men underwent artificial urinary sphincter placement after salvage prostatectomy and another 31% without an artificial sphincter had incontinence greater than occasional dribbling. This has prompted some to recommend urinary diversion at the time of salvage radical prostatectomy [708].

4. AETIOLOGY AND PATHOPHYSIOLOGY OF POST RADICAL PROSTATECTOMY INCONTINENCE: SPHINCTER VS.BLADDER DYSFUNCTION

There is fairly extensive literature on urodynamic investigation of post prostatectomy incontinence. While it is well established that both bladder and sphincter dysfunction may be present after radical prostatectomy, most studies agree that sphincter dysfunction (stress incontinence) is the main cause [994]. In these series the incidence of sphincter dysfunction ranges from 88-98.5%, with associated bladder dysfunction (detrusor overactivity and less commonly impaired compliance) in 26-46%. Bladder dysfunction, on the other hand, was present in 34-45% of patients, but was the sole cause of incontinence in only 1.5-4%. Bladder dysfunction when present in association with sphincter dysfunction may not always be clinically significant. Ficazzola and Nitti [995] found that although 46% of patients had bladder dysfunction, incontinence on urodynamic study was demonstrated in only 27%. Even in those patients, sphincter dysfunction was the main cause of incontinence in the overwhelming majority. Groutz and colleagues [996] found a 33% incidence of bladder dysfunction, but found that it was the main cause of incontinence in only 7.25%. Two earlier series reported a higher incidence of bladder dysfunction [920, 921]. Some authors feel that in some patients with severe intrinsic sphincter deficiency, bladder dysfunction may occur as a result of filling the bladder to volumes that it is not accustomed to holding [995]. The study of Giannantoni et al. reported that after RRP a high proportion of patients (70.3%) were affected by DO and about the half of these patients complained of overactive bladder symptoms of which DO was also observed in 61.2% of patients before surgery, which indicates that the abnormality can be attributed to the surgical damage in a small percentage of patients. At the 36-month follow-up, the dysfunction persisted in 56.3% of 32 men, and about 40% of these presented with overactive bladder symptoms. At three year follow-up, the dysfunction persisted in 25% of cases. [997]. Filling to capacity may produce detrusor overactivity or decreased accommodation. Thus, bladder dysfunction is in a sense an artefact, but one possibility is partial de-

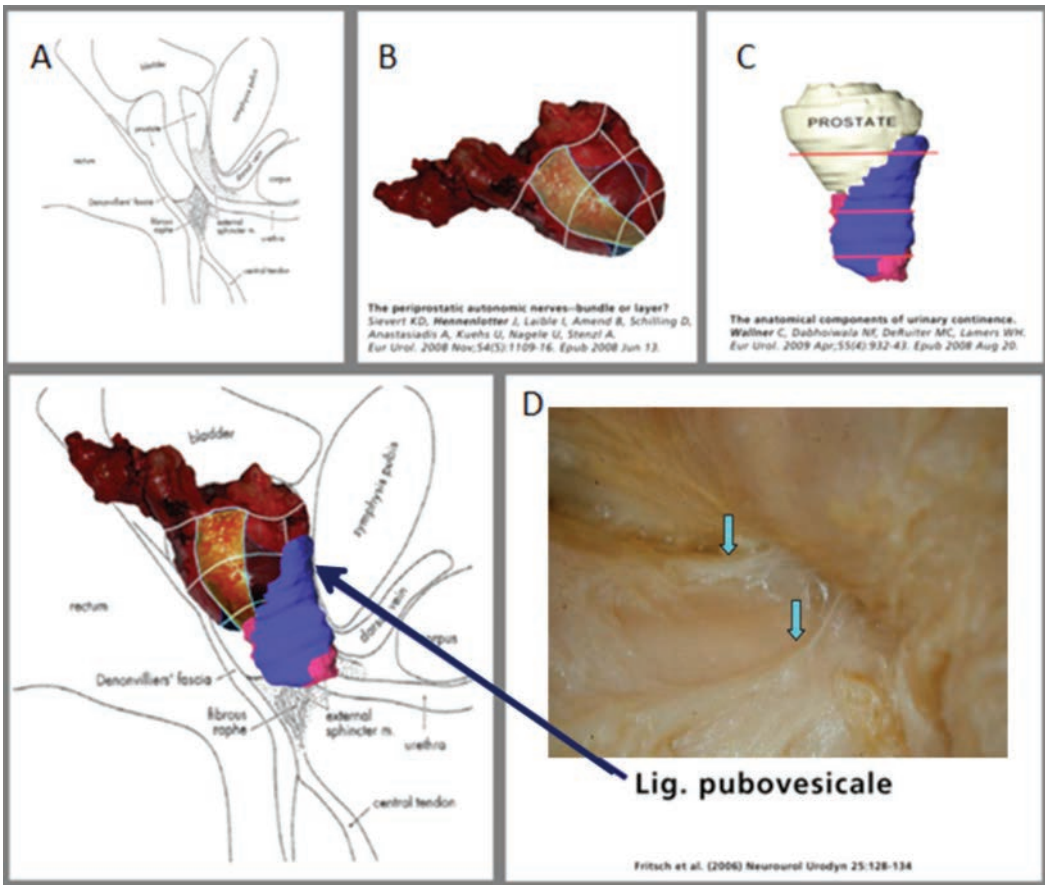


Figure 19: By projecting the found concourses of the periprostetic nerves (B, [989]) and the structure of the external urethral sphincter (C,[227]) in the common given anatomical knowledge (A) demonstrates the necessary protection of the periprostatic nerve concourses to ensure the postoperative fast recurrence of urinary continence (E,[888]). The extraprostetic innervation continues into the external urethral sphincter, surrounding the apex of the prostateal most completely. The external urethral sphincter function, and the related continence, is secured through the Lig. Pubovesicale, anchored by the tendinous arch and the detrusor ((D)[879]).

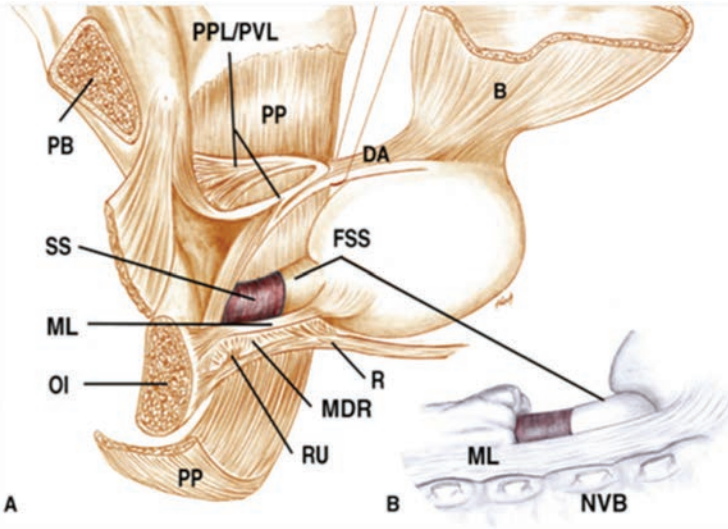


Figure 20. Surgical anatomy of the urethral sphincter complex. (A) Fixation of the urethral sphincter (modified from Luschka [16]). (B) Lateral aspect of the urethral sphincter after nerve sparing. PPL = puboprostatic ligament; PVL = pubovesicalis ligament; PP = puboperinealis muscle; DA = detrusor apron; B = bladder; FSS = fascia of the striated sphincter; ML = Mueller's ligaments (ischioprostatic ligaments); NVB = neurovascular bundle; R = rectum; MDR =medial dorsal raphe; RU = rectourethralis muscle; OI = Os ischiadicum; SS = striated sphincter (rhabdosphincter); PB = pubis bone.
From Schlomm et al, Eur Urol 2011 [990]

centralisation of the bladder as a result of its mobilisation during prostatectomy [996], combined with somatic denervation, because the branches of the pudendal nerves innervating the pelvic floor muscles and the striated urethral sphincter split before reaching the urogenital diaphragm [950]. This may explain why the outcomes for artificial urinary sphincters for the treatment of stress incontinence are not adversely affected by the presence of detrusor overactivity [998, 999]. In addition bladder dysfunction may be chronic and stem from obstructive uropathology present before prostatectomy. It must be emphasised that patient selection, urodynamic technique and timing of urodynamic evaluation maybe responsible for the differences seen among the different studies. It is also important to note that most of these studies are preformed in men seeking treatment for their incontinence. However, it appears that sphincter dysfunction is the primary cause of post-radical prostatectomy incontinence, but bladder dysfunction may be present in a significant number of men (though rarely alone) and must not be completely discounted when planning treatment.

The majority of evidence in the literature supports the conclusion that sphincter damage is the primary cause of incontinence after total prostatectomy. Direct exposure and manipulation of the sphincter during radical prostatectomy would suggest that sphincter damage is the most likely cause of incontinence. Successful treatment with the artificial urinary sphincter and male sling procedures also indirectly suggests that primary sphincter injury is the major cause of incontinence, since outcome is usually not complicated by bladder dysfunction. It might be helpful to include urodynamics and especially the urethral pressure profile as suggested by Bentzon et al. [1000]. They suggested that postoperative urodynamics after 6 months may be predictive for persistent incontinence at the bladder, sphincter, and both, that immediate intervention is more appropriate than watchful waiting. They found that sphincter insufficiency was diagnosed by stress incontinence with maximal urethral closure pressure below 30 cmH2O, decreased functional length and a distinctive profile. Bladder dysfunction after prostatectomy may have been present preoperatively, for example due to pre-existing outflow obstruction, may be caused by the operation itself, or may be due to age related changes in bladder function. Many patients who have prostate surgery have pre-existing bladder dysfunction, which may or may not be symptomatic. While it is more obvious how an overzealous TURP (with resection into the trigone) can cause detrusor overactivity, it is less apparent how radical prostatectomy affects detrusor function. Some have suggested that denervation of the urethra or the bladder may occur during radical prostatectomy. John et al [1001] studied trigonal innervation by biochemical markers and found that “urinary incontinence was associated with decreased trigonal innervation, a high sensory threshold and low maximal urethral closure pressure” which was evaluated differently by the same author slightly differently [877].

IV. INCONTINENCE RELATED TO RADIATION THERAPY FOR PROSTATE CANCER

Radiation therapy, whether external beam or brachytherapy, can be a cause of voiding dysfunction and incontinence [1002]. Sometimes this is a direct effect of the radiation or it can be related to the treatment of other sequelae such as urinary retention. The initial response to it is primarily oedema and then gradually degeneration, fibrosis and disorganisation overcome the bladder musculature. While radiation is primarily delivered to the prostate, portions of the bladder may also be affected. Perivascular fibrosis of blood vessels may then cause vascular occlusion followed by ischemia of the bladder wall, which can then progress to fibrosis within 6 to 12 months [1003]. Choo et al. [1004], found that urodynamic bladder capacity decreased by an average of 54 ml, 18 months after radiation therapy. Blaivas et al [1005] evaluated 47 men with symptomatic LUTS after brachytherapy and found that 71% were incontinent and 85% had detrusor overactivity. Similarly, radiation can cause damage to the distal urinary sphincter, which can result in incontinence. In addition there is a dose-effect relationship for individual pelvic floor muscles and anorectal complaints after prostate radiotherapy, which was related to incontinence-related complaints showing specific dose-dependent effects to individual pelvic floor muscles [721].

Urinary retention and increased obstructive LUTS are other common problems of radiation therapy,particularly brachytherapy resulting in urinary retention. The incidence of retention has been reported to range from 2% to 30% after brachytherapy [1006-1009]. Most patients with retention will have resolution of their obstruction within weeks while others may require surgical procedures. A retrospective review of over 2,100 Medicare patients who underwent brachytherapy for prostate cancer found that 8.3% required a surgical procedure to relieve bladder outlet obstruction post-brachytherapy [1010]. Flam, et al [1011] reported that 19 of 600 (3.1%) patients receiving brachytherapy required TURP. Kollmeier and colleagues [1012] reported a similar rate of 2% in 2050 men. Most authors have found significant rates of post TURP incontinence after radiation. Incontinence following TURP after brachytherapy has been reported in 0-70% and is often severe. [1011-1013]. External beam radiation is also a risk factor as Green et al [1014] reported a 33% incidence of incontinence following TURP in patients post-irradiation for prostate cancer. Some authors have emphasised that incontinence can be

minimised by performing a limited resection [1015] or by performing TURP within 2 years of brachytherapy [1012]. In the latter study, two of 24 patients (8%) that underwent TURP within 2 years of treatment were incontinent and 5 of 14 patients (36%) that underwent TURP 2 years or more after brachytherapy were incontinent (p=0.04). However, others suggest that delaying TURP until 5 years after radiation can actually reduce the risk of incontinence [1016-1018].

V. CONCLUSIONS

Incontinence in the male as in the female can be broadly divided into causes related to bladder and/or sphincter dysfunction. The pathophysiology of incontinence as it relates specifically to the male is fairly well described; however advances in science and anatomy will undoubtedly provide a more intricate understanding in the future. For example, the causes of sphincter insufficiency are known (i.e. damage to muscle, nerve and/or supporting structures) but clinicians are not able to accurately assess the exact cause of sphincter insufficiency in any given patient. Therefore much of our understanding of post treatment incontinence "pathophysiology" is derived from reports of incontinence (incidence/prevalence) after surgery or radiation. In addition investigators have not adequately defined the incidence of incontinence related to interventions for prostatic disease, whether benign or malignant. Some work has been undertaken to understand and discriminate the issue of pre- and post operative related incontinence, but because of the shortened hospitalization those prospective investigations, which are mandatory for the understanding of the physiological functioning and the pathophysiology, which might become clinically significant after the intervention. Problems have been two-fold: first in defining incontinence and what is bothersome/significant and second in accurately reporting data. New technologies for the treatment of BPH have provided us with Level 1 evidence regarding the incidence of incontinence in trials comparing new technology to TURP and **Level 2** evidence through meta-analysis and prospective series. Data regarding the incidence of post-radical prostatectomy and postradiation incontinence has been less robust and of a lower quality - **level 2-4.**

H. CAUSE OF TRANSIENT INCONTINENCE IN OLDER ADULTS

I. URINARY INCONTINENCE

Transient causes probably account for one-third of incontinent cases among community-dwelling older people (>65 years old), up to one-half of cases among acutely-hospitalised older people, and a significant proportion of cases among nursing home residents [1019-1023]. Transient urinary incontinence rises suddenly, lasts less than six months, and results from reversible causes [1024]. Most causes of transient incontinence in the older population lie outside the lower urinary tract but two points are worth emphasising. First, the risk of transient incontinence is increased if, in addition to physiologic changes of the lower urinary tract, the older person also suffers from pathological changes [1025, 1026]. Overflow incontinence is more likely to result from an anticholinergic agent in a person with a weak or obstructed bladder, just as urgency incontinence is more likely to result from a loop diuretic in someone with detrusor overactivity and/or impaired mobility [1027, 1028].

This fact may explain why some controversy persists regarding some causes of transient incontinence. It also emphasises that continence depends on the integrity of multiple domains-mental state, mobility, manual dexterity, medical factors, and motivation, as well as lower urinary tract function. Although in younger individuals incontinence usually results from lower urinary tract dysfunction alone, incontinence in older patients often results from deficits in multiple domains that together result in incontinence [1023, 1029]. Attention to any one or more of these risk factors can restore continence or at least improve it. Second, although termed "transient," these causes of incontinence may persist if left untreated, and so they cannot be dismissed merely because the incontinence is of long duration.

1. QUALITY OF DATA

In older people, continence status may not be absolute, especially in those who are frail. Infrequent leakage of small amounts may appear and disappear, and reporting accuracy varies as well [1030]. Sometimes the changing status of incontinence is the initial symptom of LUTS, neurological disorder (Parkinson's disease, MS etc.), cardiac changes or diabetes. Furthermore, ethical constraints and methodological issues preclude robust investigations of the conditions commonly impugned as causes of transient incontinence. Thus, it is not surprising that evidence supporting the association between these conditions and transient incontinence consists predominantly of case reports and case series.

2. RESULTS OF LITERATURE REVIEW

Transient causes of incontinence in older people are shown in **Table 6** and can be recalled using the mnemonic DIAPPERS (Delirium, Infection, Atrophic vaginitis, Pharmaceuticals, Psychological condition, Excess urine output, Reduced mobility, Stool impaction) [1024, 1031-1033].

Table 6: Transient Incontinence in Older Adult DIAPPERS

Delirium
Infection
Atrophic vaginitis
Pharmaceuticals
Psychological condition
Excess urine output
Reduced mobility
Stool impaction

a) Delirium

"D" is for delirium, a confusional state characterised by fluctuating inattentiveness and disorientation. Its onset occurs over hours to days, as contrasted with dementia, which develops over years. Delirium can result from almost any medication and from virtually any acute illness, including congestive heart failure, deep vein thrombosis, or infection. Many of these conditions may present atypically in older patients, and if the patient becomes confused because of them, incontinence may be the first abnormality detected [1034]. Delirium leads the list because, if unrecognised, it is associated with significant mortality [1035]. Thus, in this case, meticulous medical evaluation - not cystometry - is crucial [1036].

b) Urinary infection

Symptomatic urinary infection is another cause of incontinence, although it is supposing uncommon one [1022]. However, asymptomatic urinary infection, is much more common in older people [1037, 1038]. Women with recurrent urinary tract infection had the highest increase in UI by 230% for weekly UI [1039] and for monthly UI [1040], 220% for UI in the past year [936], and by 470% for ever having UI [1041]. In addition Arya at al. reported that women with recurrent UTIs have greater urinary frequency and increased perceived bladder sensation in the absence of an active infection than control women [1042].

c) Atrophic vaginitis

Atrophic vaginitis in older women is frequently associated with lower urinary tract symptoms, which occasionally include incontinence [1043]. As many as 80% of such women attending an incontinence clinic are reported to have physical evidence of atrophic vaginitis, characterised by vaginal mucosal atrophy, friability, erosions, and punctuate haemorrhages. While the evidence supporting the use of oestrogens in lower urinary tract dysfunction remains controversial there are considerable data to support their use in urogenital atrophy and the vaginal route of administration correlates with better symptom relief by improving vaginal dryness, pruritus and dyspareunia, greater improvement in cytological findings, and higher serum oestradiol levels [1044]. Atrophic vaginitis has been associated with urgency and occasionally a sense of "scalding" dysuria, but both symptoms may be relatively unimpressive. More recent epidemiological and clinical studies have called these beliefs into question since they have demonstrated an association with systemic oestrogen treatment and the onset of incontinence [Sievert et al ICI-RS paper 2012]. Unfortunately, limitations in their design allow for the possibility of both bias and confounding factors. Further research is warranted.

d) Medications

Pharmaceuticals are one of the most common causes of incontinence in older people, with several categories of drugs commonly implicated [1045, 1046]. Of note, many of these agents are also used in the treatment of incontinence, underscoring the fact that most medications used by older people are "double-edged swords." The first category of relevant drugs is the long-acting sedative/hypnotics, such as diazepam and flurazepam, which can cloud an older patient's memory. "Loop" diuretics, such as furosemide or bumetanide, by inducing a brisk diuresis, can also provoke leakage. Drugs with anticholinergic side effects are a particular problem and include major tranquilizers, antidepressants, anti-Parkinsonian agents (e.g., benztropine mesylate or trihexyphenidyl), first generation (sedating) antihistamines, antiarrhythmics (disopyramide), antispasmodics, and opiates. By decreasing detrusor contractility, they can cause urinary retention and overflow incontinence. They also can cause confusion. Anticholinergic agents are particularly important to ask the patient about for two reasons. First, older patients may often take more than one of them at a time. Second, they are contained in many non-prescription preparations that older people frequently take without consulting a physician.

Adrenergically-active agents have also been associated with incontinence. Many alpha-adrenoreceptor antagonists (used mainly for treatment of hypertension) block receptors at the bladder neck and may induce stress incontinence in women [1047]. Older women are particularly at risk because their urethral length and closure pressure normally decline with age. Thus, prior to considering other interventions for stress incontinence in a woman taking such a drug, substitution of an alternative agent should be tried and the incontinence re-evaluated. Calcium channel blockers can cause incontinence. As smooth muscle relaxants, they can increase residual volume, especially in older adults with impaired detrusor contractility. The increased residual urine may occasionally lead to stress incontinence in women with a weak urethral sphincter, or to overflow incontinence in men with concurrent urethral obstruction. Finally, angiotensin converting enzyme inhibitors, by inducing cough (the risk of which is age-related), may precipitate stress incontinence in older women whose urethra has shortened and sphincter weakened with age [1048].

e) Diuresis

Excess urinary output can also cause incontinence, especially in individuals with impaired mobility, mental state, or motivation, particularly if they also have detrusor overactivity. Causes of excess output include excess intake, diuretics (including theophylline-containing fluids and alcohol), and metabolic abnormalities (e.g., hyperglycemia and hypocalcaemia). Nocturnal incontinence can be caused or exacerbated by disorders associated with excess nocturnal excretion, such as congestive heart failure, peripheral venous insufficiency, hypoalbuminemia (especially in malnourished older people), and drug induced peripheral oedema associated with NSAIDs, thiazolidinediones, and some calcium channel blockers (e.g., dihydropyridines such as nifedipine, isradipine, and nicardipine). In addition certain foods are natural diuretics like asparagus, parsley, beetroot, grapes, green beans, leafy greens, pineapple, pumpkin, onion, leeks, and garlic, as well as juices such as orange juice. The role of caffeine and timing of drinking fluids (e.g. in the evening or before bedtime) is still not clear, but should nonetheless be considered a possible contributing cause for nocturia and nocturnal incontinence, whereas it is known to increase the bowel motility [1049-1051].

f) Restricted mobility

Restricted mobility is an easily understood but frequently overlooked cause of incontinence [1052]. In addition to obvious causes, restricted mobility may be associated with orthostatic or postprandial hypotension, poorly-fitting shoes, poor physical state, or fear of falling, all of which are common geriatric conditions. All of these reasons together with restricted mobility might be the cause of incontinence due to nocturia.

g) Nocturia

For frail/older people with bothersome nocturia, assessment should focus on identifying the potential underlying cause(s), including (GR: C):

- Nocturnal polyuria;
- Primary sleep problem (including sleep apnoea);
- Conditions resulting in a low voided volumes (e.g. elevated post-voiding residual) co-morbidity.

Post-void residual (PVR) volume

A post-void residual volume (PVR) is impractical to obtain in many care settings. However, there is compelling clinical experience for measuring PVR in selected frail/ older persons with:

- Diabetes mellitus (especially if longstanding);
- Previous episodes of urinary retention or history of high PVR;
- Recurrent UTIs;
- Medications that impair bladder emptying (e.g. anticholinergics);
- Chronic constipation;
- Persistent or worsening UI despite treatment with antimuscarinics;
- Previous urodynamic study demonstrating detrusor underactivity and/or bladder outlet obstruction (GR: C).

h) Faecal impaction

II. FAECAL INCONTINENCE

1. BACKGROUND

The prevalence of faecal incontinence in older adults ranges from 3.7-27% in community dwelling elderly persons to over 50% in nursing home residents [602, 603, 605, 606, 636, 637, 672, 709, 1053, 1054]. In addition faecal incontinence is a common reason for referral of elderly persons to a nursing home. [565, 1055] Underreporting is an issue with both urinary and faecal incontinence [656, 1054, 1056, 1057]; memory-loss and dementia exacerbate that the problem in the elderly. While the prevalence is fairly well documented, the percentage of those people who have transient as opposed to long-term incontinence is not well known. There is significant financial and social cost associated with management of faecal incontinence in the community and nursing homes [607, 656, 1058-1062]. Identifying transient and remediable causes would benefit patients, caregivers and the health care system. One confounding aspect in the discussion of transient incontinence is the largely unknown natural history of faecal incontinence. It is clear that the symptom is intermittent in some patients and spontaneously resolves in others. As noted earlier in this chapter, continence for stool is a complex mechanism involving the consistency and transit time of stool, rectal capacity and pelvic floor function. Rectal capacity and pelvic floor function are less likely to undergo transient changes but stool consistency, transit time of the intestinal tract and other medical conditions may change. It is well established that the prevalence of faecal incontinence increases with age, even if the mechanism is not completely understood; the increase in prevalence suggests progressive deterioration of some aspect of anorectal function [602-604, 606, 607, 636, 640, 656]. Theoretically, alternations in stool consistency, transit time and medical conditions would be more likely to result in incontinence in the elderly although that there is minimal confirmatory data.

The literature on transient faecal incontinence is limited with a dominance of case series and retrospective reports. Some information is inferred from data from large studies of prevalence and risk factors. Treatment recommendations are frequently based upon an empirical rather than evidence-based approach.

2. CAUSES

Faecal incontinence occurs when the propulsive forces in the colon and rectum overwhelm the resistant forces of the pelvic floor. Continence for stool requires the receipt and recognition of the urge to defaecate, mobility to reach the toilet in time, and the ability to postpone defaecation until reaching the bathroom.

Delaying defaecation requires sufficient rectal capacity and compliance and adequate neurologic and anal sphincter function.

a) Altered mental status

Acute medical illness, hospitalisation, surgery and medications such as opiates and sedatives may result in delirium or disorientation in the elderly. The reported rates of mental status changes to as high as 74% after surgery and from 11 to 42% during medical hospitalisation [1063, 1064]. In a systematic review of delirium associated with medication, opiods, benzodiazepines, and dihydropyridines were found to clearly increase the risk of delirium. There was uncertainty regarding antihistamines, tricyclic antidepressants, anti-Parkinson mediations, steroids and non-steroidal anti-inflammatory medication [1065]. Delirium, confusion and other transient changes in cognitive function may impair a patient's ability to recognise the urge to defaecate and/or their motivation to remain continent. The limited investigations of the relationship between delirium and incontinence studied patients with chronically altered mental status; any relationship of acute delirium and/or confusion with faecal incontinence is inferred from those data. Studies of the impact of delirium on continence show that delirium plays an important role in the development of incontinence [670, 708]. The impact of altered mental status on continence has also been inferred from studies showing improvement in continence with scheduled toileting programs [1066, 1067]. Ignoring the urge to defaecate combined with the effect of medications may result in faecal impaction followed by incontinence. Delirium may require the use of restraints. Need for a restraint has been reported as an independent factor in incontinence [709].

b) Impaired mobility

Lack of adequate mobility may prevent a patient from reaching the bathroom in time to avoid incontinence. In addition to the causes described in the urinary incontinence section, musculoskeletal ailments, such as arthritis and bone fractures, occur more commonly in the elderly and limit mobility. During the recovery phase from joint replacements ambulation may be slow and unsteady. Acute neurological conditions such as stroke may affect a patient's gait as well as debilitated states from other illness. Faecal incontinence is fairly common (up to 30% in first week) immediately after a stroke; with rehabilitation, the rate decreases [605, 681, 1068]. The use of anti-cholingeric medication and requiring assistance to reach the toilet were significant independent factors [681]. For patients temporarily requiring assistance to reach the bathroom, the timeliness of the assistant may affect their continence.

c) Stool consistency

Change in stool consistency affects continence; both constipation and diarrhoea may result in faecal incontinence.

d) Diarrhoea

Loose stool is clearly a risk factor for incontinence [606, 608, 636, 640, 674, 1054, 1068-1070]; one study identified loose stool as the most important independent risk factor [607]. Any condition or medication resulting in loose stools may also lead to incontinence including acute infection, intestinal inflammatory processes, medication and supplements (**Table 7)**. Medications with the side effects of diarrhoea and/or steatorrhea may result in faecal incontinence. **Table 8** lists the medications, which cause diarrhoea or steatorrhoea with reasonable frequency.[605, 1071, 1072] Laxatives and the medications used for bowel preparation for colonoscopy and surgery frequently result in temporary incontinence in older patients.

Although rarely described in the literature, intuitively cessation of the causative medication should decrease the incontinence. In a case report, withdrawal of the offending medication, metformin, resolved the incontinence.[648]

e) Constipation

Paradoxically faecal incontinence may occur in patients with faecal impaction. [641, 662, 1073-1075] Immobility, inadequate dietary and fluid intake, depression, metabolic disorders neurological conditions, connective tissue disorders and medications contribute to constipation.[641, 662] Impaction may result in overflow incontinence with loose stool leaking around the faecal bolus. [663] Evaluation of impacted patients compared to elderly controls revealed similar resting and squeeze pressures although both groups had lower pressures than younger healthy controls. However perianal and rectal sensation was impaired in 74% of the impacted patients.[613, 1076] The theory is the patients with impaired sensation do not experience the urge to defaecate with the typical volume of stool. The stool bolus causes the usual reflex relaxation of the internal anal sphincter but the lack of perception prevents the normal contraction of the external sphincter muscle. Incontinence is often aggravated by the use of laxatives to relieve constipation.

Table 7:Causes of Loose Stool

Infection
• Acute viral or bacterial gastroenteritis
• Clostridium difficile colitis
Inflammation
• Ischaemic colitis
• Inflammatory bowel disease flare (ulcerative colitis, Crohn's colitis)
• Microscopic colitis
Medications
• Supplements/dietary elements
• Caffeine
• Fructose
• High dose probiotics
• Magnesium
• Omega-3 fatty acids
• Orlistat
Tube feedings

Table 8: Medications causing diarrhoea

Alpha-glucosidase inhibitors
Antibiotics
Antiretroviral therapy
Biguanides (e.g. Metformin)
Bile acids
Chemotherapy agents
Cholinergic drugs
Colchicine
Diacerein
Digoxin
Immunosuppressive agents
Mesalamine
Metocopramide
Non-steroidal anti-inflammatory agents
Orlistat
Osmotic laxatives
Prostaglandins
Selective serotonin reuptake inhibitors
Ticlopidine
Tyrosine kinase inhibitors

III. SUMMARY

Apart from data for alpha-adrenergic agents (**Level of Evidence = 2**), the level of evidence for most of these causes is Level 3-4. Nonetheless, because many are easily addressed and contribute to morbidity beyond the lower urinary tract and perianal area, they are worth identifying even if the evidence is not strong.

IV. RECOMMENDATIONS

Despite the lack of robust data about the incidence and causes, transient urinary and faecal incontinence are clinically common problems. Since in most cases treatment is relatively straightforward, it is important to consider the causes discussed in this section when elderly patients present with new onset incontinence. Moreover, addressing them may improve the incontinence even if it does not eliminate it, and it may make the incontinence more amenable to subsequent therapy. (**Grade of recommendation C**)

V. RESEARCH PRIORITIES

Further research should be performed on the mechanisms, prevalence, incidence, and remission rates of each of the known causes of transient incontinence, and possible additional causes should be identified as well. Since the clinical circumstances of older people are heterogeneous, studies should be conducted among several subgroups, including independent and homebound and community-dwelling older people, bedbound and mobile institutionalised older people and acutely hospitalised older people.

LIST OF ABBREVIATIONS

ACS	American College of Surgeons
ANS	Autonomic Nervous System
ACh	Acetylcholine
AChE	Acetylcholinesterase
ASR	Anal Sphincter Rupture
ATP	Adenosine Triphosphate
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostatic Obstruction
CNS	Central Nervous System
CI	Confidence Interval
cAMP	Cyclic Adenosine Monophosphate
DO	Detrusor Overactivity
DM	Diabetes Mellitus
DSD	Detrusor Sphincter Dyssynergia
EMG	Electromyography
EAS	External Anal Sphincter
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IAS	Internal Anal Sphincter
ICI	International Consultation on Incontinence
IPSS	International Prostate Symptom Score
ISD	Intrinsic Sphincter Deficiency
LAM	Levator Ani Muscle
LUTS	Lower Urinary Tract Symptoms
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NGF	Nerve Growth Factor
OAB	Overactive Bladder
OR	Odds Ratio
PMC	Pontine Micturition Centre
PFD	Pelvic Floor Dysfunction
PFM	Pelvic Floor Muscle
POP	Pelvic Organ Prolapse
POP-Q	Pelvic Organ Prolapse Quantification
PNTML	Pudendal Nerve Motor Terminal Motor Latency
RRP	Radical Retropubic Prostatectomy
RCOG	Royal College of Obstetricians and Gynaecologists
RR	Relative Risk
SSRI	Selective Serotonin Re-uptake Inhibitor
SUI	Stress Urinary Incontinence
TURP	Transurethral Prostatectomy
TUIP	Transurethral Incision of the Prostate
TTX	Tetrodotoxin
VLPP	Valsalva Leak Point Pressure
UI	Urinary Incontinence
USI	Urodynamic Stress Incontinence

REFERENCES

1. Abrams, P., et al., *The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society.* Neurourol Urodyn, 2002. **21**(2): p. 167-78.
2. Michel, M.C. and C.R. Chapple, *Basic mechanisms of urgency: roles and benefits of pharmacotherapy.* World J Urol, 2009. **27**(6): p. 705-9.
3. Wyndaele, J.J., T.D. Van Meel, and S. De Wachter, *Detrusor overactivity. Does it represent a difference if patients feel the involuntary contractions?* J Urol, 2004. **172**(5 Pt 1): p. 1915-8.
4. Malone-Lee, J., D.J. Henshaw, and K. Cummings, *Urodynamic verification of an overactive bladder is not a prerequisite for antimuscarinic treatment response.* BJU Int, 2003. **92**(4): p. 415-7.
5. Rovner E, P.C., Yalla S *Response to fesoterodine in overactive bladder (OAB) patients is independent of the uryodynamic finding of detrusor overactivity. .*
6. Matharu, G., et al., *Relationship between urinary symptoms reported in a postal questionnaire and urodynamic diagnosis.* Neurourol Urodyn, 2005. **24**(2): p. 100-5.
7. Hashim, H. and P. Abrams, *Is the bladder a reliable witness for predicting detrusor overactivity?* J Urol, 2006. **175**(1): p. 191-4; discussion 194-5.
8. Michel, M.C. and C.R. Chapple, *Basic mechanisms of urgency: preclinical and clinical evidence.* Eur Urol, 2009. **56**(2): p. 298-307.
9. Andersson, K.E., *Bladder activation: afferent mechanisms.* Urology, 2002. **59**(5 Suppl 1): p. 43-50.
10. Yoshida, M., et al., *The forefront for novel therapeutic agents based on the pathophysiology of lower urinary tract dysfunction: pathophysiology and pharmacotherapy of overactive bladder.* J Pharmacol Sci, 2010. **112**(2): p. 128-34.
11. Brading, A.F., *A myogenic basis for the overactive bladder.* Urology, 1997. **50**(6A Suppl): p. 57-67; discussion 68-73.
12. Brading, A.F. and W.H. Turner, *The unstable bladder: towards a common mechanism.* Br J Urol, 1994. **73**(1): p. 3-8.
13. Maggi, C.A., *Tachykinins and calcitonin gene-related peptide (CGRP) as co-transmitters released from peripheral endings of sensory nerves.* Prog Neurobiol, 1995. **45**(1): p. 1-98.
14. Ferguson, D.R., I. Kennedy, and T.J. Burton, *ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes--a possible sensory mechanism?* J Physiol, 1997. **505 (Pt 2)**: p. 503-11.
15. Chopra, B., et al., *Expression and function of rat urothelial P2Y receptors.* Am J Physiol Renal Physiol, 2008. **294**(4): p. F821-9.
16. Wang, E.C., et al., *ATP and purinergic receptor-dependent membrane traffic in bladder umbrella cells.* J Clin Invest, 2005. **115**(9): p. 2412-22.
17. Kumar, V., C.C. Chapple, and R. Chess-Williams, *Characteristics of adenosine triphosphate [corrected] release from porcine and human normal bladder.* J Urol, 2004. **172**(2): p. 744-7.
18. Lewis, S.A. and J.R. Lewis, *Kinetics of urothelial ATP release.* Am J Physiol Renal Physiol, 2006. **291**(2): p. F332-40.
19. Rong, W., K.M. Spyer, and G. Burnstock, *Activation and sensitisation of low and high threshold afferent fibres mediated by P2X receptors in the mouse urinary bladder.* J Physiol, 2002. **541**(Pt 2): p. 591-600.
20. Vial, C. and R.J. Evans, *P2X receptor expression in mouse urinary bladder and the requirement of P2X(1) receptors for functional P2X receptor responses in the mouse urinary bladder smooth muscle.* Br J Pharmacol, 2000. **131**(7): p. 1489-95.
21. Elneil, S., et al., *Distribution of P2X(1) and P2X(3) receptors in the rat and human urinary bladder.* Pharmacology, 2001. **63**(2): p. 120-8.
22. Lee, H.Y., M. Bardini, and G. Burnstock, *Distribution of P2X receptors in the urinary bladder and the ureter of the rat.* J Urol, 2000. **163**(6): p. 2002-7.
23. Yu, W., et al., *Adenosine receptor expression and function in bladder uroepithelium.* Am J Physiol Cell Physiol, 2006. **291**(2): p. C254-65.
24. Vlaskovska, M., et al., *P2X3 knock-out mice reveal a major sensory role for urothelially released ATP.* J Neurosci, 2001. **21**(15): p. 5670-7.
25. Andersson, K.E., *LUTS treatment: future treatment options.* Neurourol Urodyn, 2007. **26**(6 Suppl): p. 934-47.
26. Apostolidis, A., et al., *Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity.* J Urol, 2005. **174**(3): p. 977-82; discussion 982-3.
27. Khera, M., et al., *Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury.* Neurochem Int, 2004. **45**(7): p. 987-93.
28. Sugaya, K., et al., *Relationship between lower urinary tract symptoms and urinary ATP in patients with benign prostatic hyperplasia or overactive bladder.* Biomed Res, 2009. **30**(5): p. 287-94.
29. Bschleipfer, T., et al., *Expression and distribution of cholinergic receptors in the human urothelium.* Life Sci, 2007. **80**(24-25): p. 2303-7.
30. Chess-Williams, R., *Muscarinic receptors of the urinary bladder: detrusor, urothelial and prejunctional.* Auton Autacoid Pharmacol, 2002. **22**(3): p. 133-45.
31. Yoshida, M., et al., *Non-neuronal cholinergic system in human bladder urothelium.* Urology, 2006. **67**(2): p. 425-30.
32. Mukerji, G., et al., *Localization of M2 and M3 muscarinic receptors in human bladder disorders and their clinical correlations.* J Urol, 2006. **176**(1): p. 367-73.
33. Mansfield, K.J., et al., *Muscarinic receptor subtypes in human bladder detrusor and mucosa, studied by radioligand binding and quantitative competitive RT-PCR: changes in ageing.* Br J Pharmacol, 2005. **144**(8): p. 1089-99.
34. Tyagi, S., et al., *Qualitative and quantitative expression profile of muscarinic receptors in human urothelium and detrusor.* J Urol, 2006. **176**(4 Pt 1): p. 1673-8.
35. Zarghooni, S., et al., *Expression of muscarinic and nicotinic acetylcholine receptors in the mouse urothelium.* Life Sci, 2007. **80**(24-25): p. 2308-13.
36. Andersson, K.E. and M. Yoshida, *Antimuscarinics and the overactive detrusor--which is the main mechanism of action?* Eur Urol, 2003. **43**(1): p. 1-5.
37. Finney, S.M., et al., *Antimuscarinic drugs in detrusor overactivity and the overactive bladder syndrome: motor or sensory actions?* BJU Int, 2006. **98**(3): p. 503-7.
38. Andersson, K.E., *Antimuscarinics for treatment of overactive bladder.* Lancet Neurol, 2004. **3**(1): p. 46-53.
39. Ishihama, H., et al., *Activation of alpha1D adrenergic receptors in the rat urothelium facilitates the micturition reflex.* J Urol, 2006. **175**(1): p. 358-64.
40. Birder, L.A., et al., *Beta-adrenoceptor agonists stimulate endothelial nitric oxide synthase in rat urinary bladder urothelial cells.* J Neurosci, 2002. **22**(18): p. 8063-70.
41. Masunaga, K., et al., *The beta3-adrenoceptor mediates the inhibitory effects of beta-adrenoceptor agonists via the urothelium in pig bladder dome.* Neurourol Urodyn, 2010. **29**(7): p. 1320-5.
42. Araki, I., et al., *Overexpression of epithelial sodium channels in epithelium of human urinary bladder with outlet obstruction.* Urology, 2004. **64**(6): p. 1255-60.

43. Kim, J.C., et al., *Nerve growth factor and prostaglandins in the urine of female patients with overactive bladder.* J Urol, 2006. **175**(5): p. 1773-6; discussion 1776.

44. Kim, D.K., et al., *The case for bladder botulinum toxin application.* Urol Clin North Am, 2006. **33**(4): p. 503-10, ix.

45. Liu, H.T. and H.C. Kuo, *Increased expression of transient receptor potential vanilloid subfamily 1 in the bladder predicts the response to intravesical instillations of resiniferatoxin in patients with refractory idiopathic detrusor overactivity.* BJU Int, 2007. **100**(5): p. 1086-90.

46. Apostolidis, A., et al., *Capsaicin receptor TRPV1 in urothelium of neurogenic human bladders and effect of intravesical resiniferatoxin.* Urology, 2005. **65**(2): p. 400-5.

47. Silva, C., M.J. Ribeiro, and F. Cruz, *The effect of intravesical resiniferatoxin in patients with idiopathic detrusor instability suggests that involuntary detrusor contractions are triggered by C-fiber input.* J Urol, 2002. **168**(2): p. 575-9.

48. Apostolidis, A., G.E. Gonzales, and C.J. Fowler, *Effect of intravesical Resiniferatoxin (RTX) on lower urinary tract symptoms, urodynamic parameters, and quality of life of patients with urodynamic increased bladder sensation.* Eur Urol, 2006. **50**(6): p. 1299-305.

49. Wiseman, O.J., C.J. Fowler, and D.N. Landon, *The role of the human bladder lamina propria myofibroblast.* BJU Int, 2003. **91**(1): p. 89-93.

50. Sui, G.P., et al., *Gap junctions and connexin expression in human suburothelial interstitial cells.* BJU Int, 2002. **90**(1): p. 118-29.

51. Sui, G.P., C. Wu, and C.H. Fry, *Characterization of the purinergic receptor subtype on guinea-pig suburothelial myofibroblasts.* BJU Int, 2006. **97**(6): p. 1327-31.

52. Fry, C.H., et al., *The function of suburothelial myofibroblasts in the bladder.* Neurourol Urodyn, 2007. **26**(6 Suppl): p. 914-9.

53. Mills, I.W., et al., *Studies of the pathophysiology of idiopathic detrusor instability: the physiological properties of the detrusor smooth muscle and its pattern of innervation.* J Urol, 2000. **163**(2): p. 646-51.

54. Coolsaet, B.L., et al., *New concepts in relation to urge and detrusor activity.* Neurourol Urodyn, 1993. **12**(5): p. 463-71.

55. Downie, J.W. and J.A. Armour, *Mechanoreceptor afferent activity compared with receptor field dimensions and pressure changes in feline urinary bladder.* Can J Physiol Pharmacol, 1992. **70**(11): p. 1457-67.

56. Drake, M.J., et al., *Localized contractions in the normal human bladder and in urinary urgency.* BJU Int, 2005. **95**(7): p. 1002-5.

57. Gillespie, J.I., *A developing view of the origins of urgency: the importance of animal models.* BJU Int, 2005. **96 Suppl 1**: p. 22-8.

58. Gillespie, J.I., et al., *On the origins of the sensory output from the bladder: the concept of afferent noise.* BJU Int, 2009. **103**(10): p. 1324-33.

59. Andersson, K.E., *Detrusor myocyte activity and afferent signaling.* Neurourol Urodyn, 2010. **29**(1): p. 97-106.

60. Andersson, K.E. and A. Arner, *Urinary bladder contraction and relaxation: physiology and pathophysiology.* Physiol Rev, 2004. **84**(3): p. 935-86.

61. Yoshimura N, C.M., *Physiology and pharmacology of the bladder and urethra*. Campbell-Walsh urology, ed. e. Wein AJ. Vol. Vol. 3. 2007, Philadelphia: PA: Saunders. p. 1922–1972.

62. Kubota Y, K.Y., Hayase M, Hirose M, Okada O, Sasaki S, et al, *Association between bladder overactivity and increased numbers of interstitial cells in the guinea pigs with partial bladder outlet obstruction.* J Urol, 2007. **177**(4 Suppl: 85).

63. Biers, S.M., et al., *The functional effects of a c-kit tyrosine inhibitor on guinea-pig and human detrusor.* BJU Int, 2006. **97**(3): p. 612-6.

64. Kubota, Y., et al., *Effects of imatinib mesylate (Glivec) as a c-kit tyrosine kinase inhibitor in the guinea-pig urinary bladder.* Neurourol Urodyn, 2006. **25**(3): p. 205-10.

65. Yamaguchi, O., et al., *Place of overactive bladder in male lower urinary tract symptoms.* World J Urol, 2009. **27**(6): p. 723-8.

66. Yoshida, M., et al., *The effects of chronic hyperlipidemia on bladder function in myocardial infarction-prone Watanabe heritable hyperlipidemic (WHHLMI) rabbits.* Neurourol Urodyn, 2010. **29**(7): p. 1350-4.

67. Azadzoi, K.M., et al., *Oxidative modification of mitochondrial integrity and nerve fiber density in the ischemic overactive bladder.* J Urol, 2010. **183**(1): p. 362-9.

68. Azadzoi, K.M., et al., *Molecular reactions and ultrastructural damage in the chronically ischemic bladder.* J Urol, 2011. **186**(5): p. 2115-22.

69. Comperat, E., et al., *Histologic features in the urinary bladder wall affected from neurogenic overactivity--a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A.* Eur Urol, 2006. **50**(5): p. 1058-64.

70. Apostolidis, A., et al., *Histological changes in the urothelium and suburothelium of human overactive bladder following intradetrusor injections of botulinum neurotoxin type A for the treatment of neurogenic or idiopathic detrusor overactivity.* Eur Urol, 2008. **53**(6): p. 1245-53.

71. Tyagi, P., et al., *Urine cytokines suggest an inflammatory response in the overactive bladder: a pilot study.* Int Urol Nephrol, 2010. **42**(3): p. 629-35.

72. Chung, S.D., et al., *Elevation of serum c-reactive protein in patients with OAB and IC/BPS implies chronic inflammation in the urinary bladder.* Neurourol Urodyn, 2011. **30**(3): p. 417-20.

73. Kupelian, V., et al., *Association of overactive bladder and C-reactive protein levels. Results from the Boston Area Community Health (BACH) Survey.* BJU Int, 2011.

74. de Groat, W.C., *A neurologic basis for the overactive bladder.* Urology, 1997. **50**(6A Suppl): p. 36-52; discussion 53-6.

75. Gulur, D.M. and M.J. Drake, *Management of overactive bladder.* Nat Rev Urol, 2010. **7**(10): p. 572-82.

76. Steers, W.D. and J.B. Tuttle, *Mechanisms of Disease: the role of nerve growth factor in the pathophysiology of bladder disorders.* Nat Clin Pract Urol, 2006. **3**(2): p. 101-10.

77. Liu, H.T., M.B. Chancellor, and H.C. Kuo, *Urinary nerve growth factor level could be a biomarker in the differential diagnosis of mixed urinary incontinence in women.* BJU Int, 2008. **102**(10): p. 1440-4.

78. Kuo, H.C., H.T. Liu, and M.B. Chancellor, *Can urinary nerve growth factor be a biomarker for overactive bladder?* Rev Urol, 2010. **12**(2-3): p. e69-77.

79. Kuo, H.C., H.T. Liu, and M.B. Chancellor, *Urinary nerve growth factor is a better biomarker than detrusor wall thickness for the assessment of overactive bladder with incontinence.* Neurourol Urodyn, 2010. **29**(3): p. 482-7.

80. Griffiths, D. and S.D. Tadic, *Bladder control, urgency, and urge incontinence: evidence from functional brain imaging.* Neurourol Urodyn, 2008. **27**(6): p. 466-74.

81. Drake, M.J., C. Tannenbaum, and A.J. Kanai, *Potential insights into lower urinary function derived from CNS imaging.* Neurourol Urodyn, 2010. **29**(4): p. 629-33.

82. Fowler, C.J. and D.J. Griffiths, *A decade of functional brain imaging applied to bladder control.* Neurourol Urodyn, 2010. **29**(1): p. 49-55.

83. Fall, M., G. Geirsson, and S. Lindstrom, *Toward a new classification of overactive bladders.* Neurourol Urodyn, 1995. **14**(6): p. 635-46.

84. Fall, M., B.L. Ohlsson, and C.A. Carlsson, *The neurogenic overactive bladder. Classification based on urodynamics.* Br J Urol, 1989. **64**(4): p. 368-73.

85. de Groat, W.C., Booth AM, Yoshimura N, *Neurophysiology of micturition and its modeification in animal models of human disease, in The Autonomic Nervous System: Nervous Control of the Urogenital System*, ed. E. C.A. Maggi. 1993: Harwood Academic Publishers: London.

86. Ruch, T.C. and P.C. Tang, *Localization of brain stem and diencephalic areas controlling the micturation reflex.* J Comp Neurol, 1956. **106**(1): p. 213-45.

87. Yoshimura, N., et al., *The dopamine D1 receptor agonist SKF 38393 suppresses detrusor hyperreflexia in the monkey with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).* Neuropharmacology, 1993. **32**(4): p. 315-21.

88. Yokoyama, O., et al., *Glutamatergic and dopaminergic contributions to rat bladder hyperactivity after cerebral artery occlusion.* Am J Physiol, 1999. **276**(4 Pt 2): p. R935-42.

89. Chen, S.Y., et al., *Glutamate activation of neurons in CV-reactive areas of cat brain stem affects urinary bladder motility.* Am J Physiol, 1993. **265**(4 Pt 2): p. F520-9.

90. Yoshiyama, M., J.R. Roppolo, and W.C. de Groat, *Effects of MK-801 on the micturition reflex in the rat--possible sites of action.* J Pharmacol Exp Ther, 1993. **265**(2): p. 844-50.

91. Campeau, L., R. Soler, and K.E. Andersson, *Bladder dysfunction and parkinsonism: current pathophysiological understanding and management strategies.* Curr Urol Rep, 2011. **12**(6): p. 396-403.

92. Sakakibara, R., et al., *Pathophysiology of bladder dysfunction in Parkinson's disease.* Neurobiol Dis, 2011.

93. Kitta, T., et al., *GABAergic mechanism mediated via D receptors in the rat periaqueductal gray participates in the micturition reflex: an in vivo microdialysis study.* Eur J Neurosci, 2008. **27**(12): p. 3216-25.

94. Kitta, T., et al., *Brain activation during detrusor overactivity in patients with Parkinson's disease: a positron emission tomography study.* J Urol, 2006. **175**(3 Pt 1): p. 994-8.

95. de Groat, W.C., et al., *Mechanisms underlying the recovery of urinary bladder function following spinal cord injury.* J Auton Nerv Syst, 1990. **30 Suppl**: p. S71-7.

96. de Groat, W.C., et al., *Organization of the sacral parasympathetic reflex pathways to the urinary bladder and large intestine.* J Auton Nerv Syst, 1981. **3**(2-4): p. 135-60.

97. Habler, H.J., W. Janig, and M. Koltzenburg, *Activation of unmyelinated afferent fibres by mechanical stimuli and inflammation of the urinary bladder in the cat.* J Physiol, 1990. **425**: p. 545-62.

98. Fowler, C.J., et al., *Intravesical capsaicin for neurogenic bladder dysfunction.* Lancet, 1992. **339**(8803): p. 1239.

99. Fowler, C.J., et al., *Intravesical capsaicin for treatment of detrusor hyperreflexia.* J Neurol Neurosurg Psychiatry, 1994. **57**(2): p. 169-73.

100. Geirsson, G., M. Fall, and L. Sullivan, *Clinical and urodynamic effects of intravesical capsaicin treatment in patients with chronic traumatic spinal detrusor hyperreflexia.* J Urol, 1995. **154**(5): p. 1825-9.

101. Cruz, F., et al., *Suppression of bladder hyperreflexia by intravesical resiniferatoxin.* Lancet, 1997. **350**(9078): p. 640-1.

102. Silva, C., M.E. Rio, and F. Cruz, *Desensitization of bladder sensory fibers by intravesical resiniferatoxin, a capsaicin analog: long-term results for the treatment of detrusor hyperreflexia.* Eur Urol, 2000. **38**(4): p. 444-52.

103. Silva, C., et al., *Urodynamic effect of intravesical resiniferatoxin in patients with neurogenic detrusor overactivity of spinal origin: results of a double-blind randomized placebo-controlled trial.* Eur Urol, 2005. **48**(4): p. 650-5.

104. Brady, C.M., et al., *P2X3-immunoreactive nerve fibres in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin.* Eur Urol, 2004. **46**(2): p. 247-53.

105. Apostolidis, A. and C.J. Fowler, *The use of botulinum neurotoxin type A (BoNTA) in urology.* J Neural Transm, 2008. **115**(4): p. 593-605.

106. Andrade, E.L., et al., *TRPA1 receptor modulation attenuates bladder overactivity induced by spinal cord injury.* Am J Physiol Renal Physiol, 2011. **300**(5): p. F1223-34.

107. Steers, W.D., *Pathophysiology of overactive bladder and urge urinary incontinence.* Rev Urol, 2002. **4 Suppl 4**: p. S7-S18.

108. Yoshimura, N. and W.C. de Groat, *Plasticity of Na+ channels in afferent neurones innervating rat urinary bladder following spinal cord injury.* J Physiol, 1997. **503 (Pt 2)**: p. 269-76.

109. Thom, D.H. and G. Rortveit, *Prevalence of postpartum urinary incontinence: a systematic review.* Acta Obstet Gynecol Scand, 2010. **89**(12): p. 1511-22.

110. Persson, J., P. Wolner-Hanssen, and H. Rydhstroem, *Obstetric risk factors for stress urinary incontinence: a population-based study.* Obstet Gynecol, 2000. **96**(3): p. 440-5.

111. Rortveit, G., et al., *Urinary incontinence after vaginal delivery or cesarean section.* N Engl J Med, 2003. **348**(10): p. 900-7.

112. MacLennan, A.H., et al., *The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery.* BJOG, 2000. **107**(12): p. 1460-70.

113. Leijonhufvud, A., et al., *Risks of stress urinary incontinence and pelvic organ prolapse surgery in relation to mode of childbirth.* Am J Obstet Gynecol, 2011. **204**(1): p. 70 e1-7.

114. Nygaard, I., *Urinary incontinence: is cesarean delivery protective?* Semin Perinatol, 2006. **30**(5): p. 267-71.

115. Guise, J.M., et al., *Does cesarean protect against fecal incontinence in primiparous women?* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(1): p. 61-7.

116. Guise, J.M., et al., *Incidence of fecal incontinence after childbirth.* Obstet Gynecol, 2007. **109**(2 Pt 1): p. 281-8.

117. Hall, W., et al., *Frequency and predictors for postpartum fecal incontinence.* Am J Obstet Gynecol, 2003. **188**(5): p. 1205-7.

118. Borello-France, D., et al., *Fecal and urinary incontinence in primiparous women.* Obstet Gynecol, 2006. **108**(4): p. 863-72.

119. Zetterstrom, J.P., et al., *Anal incontinence after vaginal delivery: a prospective study in primiparous women.* Br J Obstet Gynaecol, 1999. **106**(4): p. 324-30.

120. Brown, S.J., et al., *Effects of prolonged second stage, method of birth, timing of caesarean section and other obstetric risk factors on postnatal urinary incontinence: an Australian nulliparous cohort study.* BJOG, 2011. **118**(8): p. 991-1000.

121. Diez-Itza, I., et al., *Influence of mode of delivery on pelvic organ support 6 months postpartum.* Gynecol Obstet Invest, 2011. **72**(2): p. 123-9.

122. Diez-Itza, I., et al., *Postpartum impairment of pelvic floor muscle function: factors involved and association with prolapse.* Int Urogynecol J, 2011.

123. Wai, C.Y., et al., *Urodynamic indices and pelvic organ prolapse quantification 3 months after vaginal delivery in primiparous women.* Int Urogynecol J, 2011. **22**(10): p. 1293-8.

124. Larsson, C., K. Kallen, and E. Andolf, *Cesarean section and risk of pelvic organ prolapse: a nested case-control study.* Am J Obstet Gynecol, 2009. **200**(3): p. 243 e1-4.

125. Solans-Domenech, M., E. Sanchez, and M. Espuna-Pons, *Urinary and anal incontinence during pregnancy and postpartum: incidence, severity, and risk factors.* Obstet Gynecol, 2010. **115**(3): p. 618-28.

126. Groutz, A., et al., *Cesarean section: does it really prevent the development of postpartum stress urinary incontinence? A prospective study of 363 women one year after their first delivery.* Neurourol Urodyn, 2004. **23**(1): p. 2-6.

127. Farrell, S.A., V.M. Allen, and T.F. Baskett, *Parturition and urinary incontinence in primiparas.* Obstet Gynecol, 2001. **97**(3): p. 350-6.

128. Arrue, M., et al., *Factors involved in the persistence of stress urinary incontinence from pregnancy to 2years post partum.* Int J Gynaecol Obstet, 2011.

129. Wiklund, I., et al., *Expectation and experiences of childbirth in primiparae with caesarean section.* BJOG, 2008. **115**(3): p. 324-31.

130. Waldenstrom, U., I. Hildingsson, and E.L. Ryding, *Antenatal fear of childbirth and its association with subsequent caesarean section and experience of childbirth.* BJOG, 2006. **113**(6): p. 638-46.

131. Fuglenes, D., et al., *Why do some pregnant women prefer cesarean? The influence of parity, delivery experiences, and fear.* Am J Obstet Gynecol, 2011.

132. Sjogren, B., *Reasons for anxiety about childbirth in 100 pregnant women.* J Psychosom Obstet Gynaecol, 1997. **18**(4): p. 266-72.

133. Lavender, T., et al., *Caesarean section for non-medical reasons at term.* Cochrane Database Syst Rev, 2006. **3**: p. CD004660.

134. Fritel, X., *[Pelvic floor and pregnancy].* Gynecol Obstet Fertil, 2010. **38**(5): p. 332-46.

135. Nelson, R.L., et al., *Cesarean delivery for the prevention of anal incontinence.* Cochrane Database Syst Rev, 2010(2): p. CD006756.

136. Ashton-Miller, J.A. and J.O. Delancey, *On the biomechanics of vaginal birth and common sequelae.* Annu Rev Biomed Eng, 2009. **11**: p. 163-76.

137. King, J.K. and R.M. Freeman, *Is antenatal bladder neck mobility a risk factor for postpartum stress incontinence?* Br J Obstet Gynaecol, 1998. **105**(12): p. 1300-7.

138. Keane, D.P., et al., *Analysis of collagen status in premenopausal nulliparous women with genuine stress incontinence.* Br J Obstet Gynaecol, 1997. **104**(9): p. 994-8.

139. Lavin JM, S.A., Anderson J,, *The effect of pregnancy on the connective tissue rectus sheath.* Neurourol Urodyn 1997. **16**: p. 381-382.

140. Lewicky-Gaupp, C., D.C. Cao, and S. Culbertson, *Urinary and anal incontinence in African American teenaged gravidas during pregnancy and the puerperium.* J Pediatr Adolesc Gynecol, 2008. **21**(1): p. 21-6.

141. Rortveit, G. and S. Hunskaar, *Urinary incontinence and age at the first and last delivery: the Norwegian HUNT/EPINCONT study.* Am J Obstet Gynecol, 2006. **195**(2): p. 433-8.

142. Hannestad, Y.S., et al., *Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study.* BJOG, 2003. **110**(3): p. 247-54.

143. Eliasson, K., et al., *Influence of physical activity on urinary leakage in primiparous women.* Scand J Med Sci Sports, 2005. **15**(2): p. 87-94.

144. Wesnes, S.L., et al., *Urinary incontinence and weight change during pregnancy and postpartum: a cohort study.* Am J Epidemiol, 2010. **172**(9): p. 1034-44.

145. Wesnes, S.L., et al., *The effect of urinary incontinence status during pregnancy and delivery mode on incontinence postpartum. A cohort study.* BJOG, 2009. **116**(5): p. 700-7.

146. Buchsbaum, G.M., et al., *Urinary incontinence in nulliparous women and their parous sisters.* Obstet Gynecol, 2005. **106**(6): p. 1253-8.

147. Nguyen, A., et al., *Nongenetic factors associated with stress urinary incontinence.* Obstet Gynecol, 2011. **117**(2 Pt 1): p. 251-5.

148. Rohr, G., et al., *Genetic and environmental influences on urinary incontinence: a Danish population-based twin study of middle-aged and elderly women.* Acta Obstet Gynecol Scand, 2004. **83**(10): p. 978-82.

149. Lien, K.C., et al., *Levator ani muscle stretch induced by simulated vaginal birth.* Obstet Gynecol, 2004. **103**(1): p. 31-40.

150. Svabik, K., K.L. Shek, and H.P. Dietz, *How much does the levator hiatus have to stretch during childbirth?* BJOG, 2009. **116**(12): p. 1657-62.

151. Cassado Garriga, J., et al., *Tridimensional sonographic anatomical changes on pelvic floor muscle according to the type of delivery.* Int Urogynecol J, 2011. **22**(8): p. 1011-8.

152. Shek, K.L. and H.P. Dietz, *The effect of childbirth on hiatal dimensions.* Obstet Gynecol, 2009. **113**(6): p. 1272-8.

153. Valsky, D.V., et al., *Fetal head circumference and length of second stage of labor are risk factors for levator ani muscle injury, diagnosed by 3-dimensional transperineal ultrasound in primiparous women.* Am J Obstet Gynecol, 2009. **201**(1): p. 91 e1-7.

154. Dietz, H.P. and K.L. Shek, *Tomographic ultrasound imaging of the pelvic floor: which levels matter most?* Ultrasound Obstet Gynecol, 2009. **33**(6): p. 698-703.

155. Dietz, H.P. and V. Lanzarone, *Levator trauma after vaginal delivery.* Obstet Gynecol, 2005. **106**(4): p. 707-12.

156. Albrich, S., et al., *Impact of mode of delivery on levator morphology: a prospective observational study with three-dimensional ultrasound early in the postpartum period.* BJOG, 2011.

157. Shek, K.L., A. Pirpiris, and H.P. Dietz, *Does levator avulsion increase urethral mobility?* Eur J Obstet Gynecol Reprod Biol, 2010. **153**(2): p. 215-9.

158. Novellas, S., et al., *MR features of the levator ani muscle in the immediate postpartum following cesarean delivery.* Int Urogynecol J, 2010. **21**(5): p. 563-8.

159. Heilbrun, M.E., et al., *Correlation between levator ani muscle injuries on magnetic resonance imaging and fecal incontinence, pelvic organ prolapse, and urinary incontinence in primiparous women.* Am J Obstet Gynecol, 2010. **202**(5): p. 488 e1-6.

160. Branham, V., et al., *Levator ani abnormality 6 weeks after delivery persists at 6 months.* Am J Obstet Gynecol, 2007. **197**(1): p. 65 e1-6.

161. Kearney, R., et al., *Obstetric factors associated with levator ani muscle injury after vaginal birth.* Obstet Gynecol, 2006. **107**(1): p. 144-9.

162. Krofta, L., et al., *Pubococcygeus-puborectalis trauma after forceps delivery: evaluation of the levator ani muscle with 3D/4D ultrasound.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(10): p. 1175-81.

163. Kearney, R., et al., *Levator ani injury in primiparous women with forceps delivery for fetal distress, forceps for second stage arrest, and spontaneous delivery.* Int J Gynaecol Obstet, 2010. **111**(1): p. 19-22.

164. Delancey, J.O. and W.W. Hurd, *Size of the urogenital hiatus in the levator ani muscles in normal women and women with pelvic organ prolapse.* Obstet Gynecol, 1998. **91**(3): p. 364-8.

165. Dietz, H.P. and J.M. Simpson, *Levator trauma is associated with pelvic organ prolapse.* BJOG, 2008. **115**(8): p. 979-84.

166. Chen, L., et al., *Interaction among apical support, levator ani impairment, and anterior vaginal wall prolapse.* Obstet Gynecol, 2006. **108**(2): p. 324-32.

167. Morgan, D.M., et al., *Levator ani defect status and lower urinary tract symptoms in women with pelvic organ prolapse.* Int Urogynecol J, 2010. **21**(1): p. 47-52.

168. Dietz, H.P., et al., *Does avulsion of the puborectalis muscle affect bladder function?* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(8): p. 967-72.

169. Brincat, C.A., J.O. Delancey, and J.M. Miller, *Urethral closure pressures among primiparous women with and without levator ani muscle defects.* Int Urogynecol J, 2011.

170. Martins, J.A., et al., *Finite element studies of the deforma-*

tion of the pelvic floor. Ann N Y Acad Sci, 2007. **1101**: p. 316-34.

171. Fitzpatrick, M. and C. O'Herlihy, *The effects of labour and delivery on the pelvic floor.* Best Pract Res Clin Obstet Gynaecol, 2001. **15**(1): p. 63-79.
172. Lin, A.S., et al., *Effect of simulated birth trauma on the urinary continence mechanism in the rat.* Urology, 1998. **52**(1): p. 143-51.
173. Deindl, F.M., et al., *Pelvic floor activity patterns: comparison of nulliparous continent and parous urinary stress incontinent women. A kinesiological EMG study.* Br J Urol, 1994. **73**(4): p. 413-7.
174. Gunnarsson, M. and A. Mattiasson, *Female stress, urge, and mixed urinary incontinence are associated with a chronic and progressive pelvic floor/vaginal neuromuscular disorder: An investigation of 317 healthy and incontinent women using vaginal surface electromyography.* Neurourol Urodyn, 1999. **18**(6): p. 613-21.
175. Vodusek, D.B., *The role of electrophysiology in the evaluation of incontinence and prolapse.* Curr Opin Obstet Gynecol, 2002. **14**(5): p. 509-14.
176. Snooks, S.J., et al., *Injury to innervation of pelvic floor sphincter musculature in childbirth.* Lancet, 1984. **2**(8402): p. 546-50.
177. Allen, R.E., et al., *Pelvic floor damage and childbirth: a neurophysiological study.* Br J Obstet Gynaecol, 1990. **97**(9): p. 770-9.
178. Snooks, S.J., et al., *Effect of vaginal delivery on the pelvic floor: a 5-year follow-up.* Br J Surg, 1990. **77**(12): p. 1358-60.
179. Weidner, A.C., et al., *Pelvic muscle electromyography of levator ani and external anal sphincter in nulliparous women and women with pelvic floor dysfunction.* Am J Obstet Gynecol, 2000. **183**(6): p. 1390-9; discussion 1399-401.
180. Abitbol, M.M., *Birth and human evolution:anatomical and obstetrical mechanics in primates.* , ed. C.B.G. Westport. 1996, London.
181. Rortveit, G., et al., *Vaginal delivery parameters and urinary incontinence: the Norwegian EPINCONT study.* Am J Obstet Gynecol, 2003. **189**(5): p. 1268-74.
182. Moerman, M.L., *Growth of the birth canal in adolescent girls.* Am J Obstet Gynecol, 1982. **143**(5): p. 528-32.
183. Robinson, J.N., et al., *Episiotomy, operative vaginal delivery, and significant perinatal trauma in nulliparous women.* Am J Obstet Gynecol, 1999. **181**(5 Pt 1): p. 1180-4.
184. Carroll, T.G., et al., *Epidural analgesia and severe perineal laceration in a community-based obstetric practice.* J Am Board Fam Pract, 2003. **16**(1): p. 1-6.
185. Christianson, L.M., et al., *Risk factors for perineal injury during delivery.* Am J Obstet Gynecol, 2003. **189**(1): p. 255-60.
186. Fitzgerald, M.P., et al., *Risk factors for anal sphincter tear during vaginal delivery.* Obstet Gynecol, 2007. **109**(1): p. 29-34.
187. Meyer, S., et al., *Effects of epidural analgesia on pelvic floor function after spontaneous delivery: a longitudinal retrospective study.* Int Urogynecol J Pelvic Floor Dysfunct, 2002. **13**(6): p. 359-64; discussion 364-5.
188. Sartore, A., et al., *Effects of epidural analgesia during labor on pelvic floor function after vaginal delivery.* Acta Obstet Gynecol Scand, 2003. **82**(2): p. 143-6.
189. Shek, K.L. and H.P. Dietz, *Intrapartum risk factors for levator trauma.* BJOG, 2010. **117**(12): p. 1485-92.
190. Thacker, S.B. and H.D. Banta, *Benefits and risks of episiotomy: an interpretative review of the English language literature, 1860-1980.* Obstet Gynecol Surv, 1983. **38**(6): p. 322-38.
191. Carroli, G. and J. Belizan, *Episiotomy for vaginal birth.* Cochrane Database Syst Rev, 2000(2): p. CD000081.
192. Woolley, R.J., *Benefits and risks of episiotomy: a review of the English-language literature since 1980. Part I.* Obstet Gynecol Surv, 1995. **50**(11): p. 806-20.
193. Woolley, R.J., *Benefits and risks of episiotomy: a review of the English-language literature since 1980. Part II.* Obstet Gynecol Surv, 1995. **50**(11): p. 821-35.
194. Goldberg, J., et al., *Has the use of routine episiotomy decreased? Examination of episiotomy rates from 1983 to 2000.* Obstet Gynecol, 2002. **99**(3): p. 395-400.
195. Kalis, V., et al., *Classification of episiotomy: towards a standardisation of terminology.* BJOG, 2012.
196. Tincello, D.G., et al., *Differences in episiotomy technique between midwives and doctors.* BJOG, 2003. **110**(12): p. 1041-4.
197. Laine, K., M. Gissler, and J. Pirhonen, *Changing incidence of anal sphincter tears in four Nordic countries through the last decades.* Eur J Obstet Gynecol Reprod Biol, 2009. **146**(1): p. 71-5.
198. Raisanen, S.H., et al., *Lateral episiotomy protects primiparous but not multiparous women from obstetric anal sphincter rupture.* Acta Obstet Gynecol Scand, 2009. **88**(12): p. 1365-72.
199. Raisanen, S., et al., *High episiotomy rate protects from obstetric anal sphincter ruptures: a birth register-study on delivery intervention policies in Finland.* Scand J Public Health, 2011. **39**(5): p. 457-63.
200. Carroli, G. and L. Mignini, *Episiotomy for vaginal birth.* Cochrane Database Syst Rev, 2009(1): p. CD000081.
201. Klein, M.C., et al., *Relationship of episiotomy to perineal trauma and morbidity, sexual dysfunction, and pelvic floor relaxation.* Am J Obstet Gynecol, 1994. **171**(3): p. 591-8.
202. Sultan, A.H., et al., *Anal-sphincter disruption during vaginal delivery.* N Engl J Med, 1993. **329**(26): p. 1905-11.
203. Haadem, K., et al., *Anal sphincter function after delivery rupture.* Obstet Gynecol, 1987. **70**(1): p. 53-6.
204. Eason, E., et al., *Preventing perineal trauma during childbirth: a systematic review.* Obstet Gynecol, 2000. **95**(3): p. 464-71.
205. Kalis, V., et al., *Evaluation of the incision angle of mediolateral episiotomy at 60 degrees.* Int J Gynaecol Obstet, 2011. **112**(3): p. 220-4.
206. Raisanen, S., et al., *A population-based register study to determine indications for episiotomy in Finland.* Int J Gynaecol Obstet, 2011. **115**(1): p. 26-30.
207. Robinson, J.N., et al., *Predictors of episiotomy use at first spontaneous vaginal delivery.* Obstet Gynecol, 2000. **96**(2): p. 214-8.
208. Goldberg, J., et al., *The Philadelphia Episiotomy Intervention Study.* J Reprod Med, 2006. **51**(8): p. 603-9.
209. Alperin, M., M.A. Krohn, and K. Parviainen, *Episiotomy and increase in the risk of obstetric laceration in a subsequent vaginal delivery.* Obstet Gynecol, 2008. **111**(6): p. 1274-8.
210. Kelly, H.A.a.C.F.B., *Diseases of kidneys, ureters and bladder.* Vol. 2v. 1922, New York and London: D. Appleton and company.
211. Oelrich, T.M., *The striated urogenital sphincter muscle in the female.* Anat Rec, 1983. **205**(2): p. 223-32.
212. DeLancey, J.O., *Functional anatomy of the female lower urinary tract and pelvic floor.* Ciba Found Symp, 1990. **151**: p. 57-69; discussion 69-76.
213. DeLancey, J.O., *Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis.* Am J Obstet Gynecol, 1994. **170**(6): p. 1713-20; discussion 1720-3.
214. Athanassopoulos, A., et al., *Stamey endoscopic vesical neck suspension in female urinary stress incontinence: results and changes in various urodynamic parameters.* Int Urol Nephrol, 1994. **26**(3): p. 293-9.

215. Bump, R.C., J.A. Fantl, and W.G. Hurt, *Dynamic urethral pressure profilometry pressure transmission ratio determinations after continence surgery: understanding the mechanism of success, failure, and complications.* Obstet Gynecol, 1988. **72**(6): p. 870-4.

216. Bunne, G. and A. Obrink, *Influence of pubococcygeal repair on urethral closure pressure at stress.* Acta Obstet Gynecol Scand, 1978. **57**(4): p. 355-9.

217. Hilton, P. and S.L. Stanton, *Urethral pressure measurement by microtransducer: the results in symptom-free women and in those with genuine stress incontinence.* Br J Obstet Gynaecol, 1983. **90**(10): p. 919-33.

218. Masuda, H., et al., *[Analysis of continence mechanisms by stress urethral pressure profiles].* Nihon Hinyokika Gakkai Zasshi, 1994. **85**(3): p. 434-9.

219. Obrink, A., G. Bunne, and A. Ingelman-Sundberg, *Pressure transmission to the pre-urethral space in stress incontinence.* Urol Res, 1978. **6**(3): p. 135-40.

220. Penttinen, J., et al., *Successful colposuspension in stress urinary incontinence reduces bladder neck mobility and increases pressure transmission to the urethra.* Arch Gynecol Obstet, 1989. **244**(4): p. 233-8.

221. Penttinen, J., K. Kaar, and A. Kauppila, *Effect of suprapubic operation on urethral closure. Evaluation by single cough urethrocystometry.* Br J Urol, 1989. **63**(4): p. 389-91.

222. Rottenberg, R.D., et al., *Urodynamic and clinical assessment of the Lyodura sling operation for urinary stress incontinence.* Br J Obstet Gynaecol, 1985. **92**(8): p. 829-34.

223. van Geelen, J.M., et al., *The clinical and urodynamic effects of anterior vaginal repair and Burch colposuspension.* Am J Obstet Gynecol, 1988. **159**(1): p. 137-44.

224. Sebe, P., et al., *Fetal development of the female external urinary sphincter complex: an anatomical and histological study.* J Urol, 2005. **173**(5): p. 1738-42; discussion 1742.

225. Yucel, S. and L.S. Baskin, *An anatomical description of the male and female urethral sphincter complex.* J Urol, 2004. **171**(5): p. 1890-7.

226. Ludwikowski, B., et al., *The development of the external urethral sphincter in humans.* BJU Int, 2001. **87**(6): p. 565-8.

227. Wallner, C., et al., *The anatomical components of urinary continence.* Eur Urol, 2009. **55**(4): p. 932-43.

228. Huang, W.C., S.H. Yang, and J.M. Yang, *Anatomical and functional significance of urogenital hiatus in primary urodynamic stress incontinence.* Ultrasound Obstet Gynecol, 2006. **27**(1): p. 71-7.

229. Lien, K.C., et al., *Pudendal nerve stretch during vaginal birth: a 3D computer simulation.* Am J Obstet Gynecol, 2005. **192**(5): p. 1669-76.

230. Diao E, A.A., Diao J, *Animal models of peripheral nerve injury.* Oper Tech Orthop, 2004. **14**: p. 153-162.

231. Sajadi, K.P., B.C. Gill, and M.S. Damaser, *Neurogenic aspects of stress urinary incontinence.* Curr Opin Obstet Gynecol, 2010. **22**(5): p. 425-9.

232. Martan, A., et al., *[Ultrasonic evaluation of paravaginal defects before and after surgical treatment in women with urinary stress incontinence].* Ceska Gynekol, 2000. **65**(3): p. 152-6.

233. Jeffcoate, T.N. and H. Roberts, *Observations on stress incontinence of urine.* Am J Obstet Gynecol, 1952. **64**(4): p. 721-38.

234. Pregazzi, R., et al., *Perineal ultrasound evaluation of urethral angle and bladder neck mobility in women with stress urinary incontinence.* BJOG, 2002. **109**(7): p. 821-7.

235. Hodgkinson, C.P., *Relationships of the female urethra and bladder in urinary stress incontinence.* Am J Obstet Gynecol, 1953. **65**(3): p. 560-73.

236. Hodgkinson, C.P., *Stress urinary incontinence--1970.* Am J Obstet Gynecol, 1970. **108**(7): p. 1141-68.

237. Wall, L.L., et al., *Bladder neck mobility and the outcome of surgery for genuine stress urinary incontinence. A logistic regression analysis of lateral bead-chain cystourethrograms.* J Reprod Med, 1994. **39**(6): p. 429-35.

238. Kamo, I., et al., *Functional analysis of active urethral closure mechanisms under sneeze induced stress condition in a rat model of birth trauma.* J Urol, 2006. **176**(6 Pt 1): p. 2711-5.

239. DeLancey, J.O., et al., *Vaginal birth and de novo stress incontinence: relative contributions of urethral dysfunction and mobility.* Obstet Gynecol, 2007. **110**(2 Pt 1): p. 354-62.

240. Blaivas, J.G. and C.A. Olsson, *Stress incontinence: classification and surgical approach.* J Urol, 1988. **139**(4): p. 727-31.

241. McGuire, E.J., R.D. Cespedes, and H.E. O'Connell, *Leak-point pressures.* Urol Clin North Am, 1996. **23**(2): p. 253-62.

242. McGuire, E.J., *Diagnosis and treatment of intrinsic sphincter deficiency.* Int J Urol, 1995. **2 Suppl 1**: p. 7-10; discussion 16-8.

243. Leach, G.E., et al., *Female Stress Urinary Incontinence Clinical Guidelines Panel summary report on surgical management of female stress urinary incontinence. The American Urological Association.* J Urol, 1997. **158**(3 Pt 1): p. 875-80.

244. Horbach, N.S. and D.R. Ostergard, *Predicting intrinsic urethral sphincter dysfunction in women with stress urinary incontinence.* Obstet Gynecol, 1994. **84**(2): p. 188-92.

245. Perucchini, D., et al., *Age effects on urethral striated muscle. I. Changes in number and diameter of striated muscle fibers in the ventral urethra.* Am J Obstet Gynecol, 2002. **186**(3): p. 351-5.

246. Perucchini, D., et al., *Age effects on urethral striated muscle. II. Anatomic location of muscle loss.* Am J Obstet Gynecol, 2002. **186**(3): p. 356-60.

247. Kayigil, O., S. Iftekhar Ahmed, and A. Metin, *The coexistence of intrinsic sphincter deficiency with type II stress incontinence.* J Urol, 1999. **162**(4): p. 1365-6.

248. Chaikin, D.C., J. Rosenthal, and J.G. Blaivas, *Pubovaginal fascial sling for all types of stress urinary incontinence: long-term analysis.* J Urol, 1998. **160**(4): p. 1312-6.

249. Bemelmans, B.L. and C.R. Chapple, *Are slings now the gold standard treatment for the management of female urinary stress incontinence and if so which technique?* Curr Opin Urol, 2003. **13**(4): p. 301-7.

250. Kiilholma, P.J., et al., *Perineal ultrasound: an alternative for radiography for evaluating stress urinary incontinence in females.* Ann Chir Gynaecol Suppl, 1994. **208**: p. 43-5.

251. Karan, A., et al., *Hypermobility syndrome in 105 women with pure urinary stress incontinence and in 105 controls.* Arch Gynecol Obstet, 2004. **269**(2): p. 89-90.

252. Meyer, S., et al., *The assessment of bladder neck position and mobility in continent nullipara, mulitpara, forceps-delivered and incontinent women using perineal ultrasound: a future office procedure?* Int Urogynecol J Pelvic Floor Dysfunct, 1996. **7**(3): p. 138-46.

253. Pauwels, E., S. De Wachter, and J.J. Wyndaele, *Evaluation of different techniques to create chronic urinary incontinence in the rat.* BJU Int, 2009. **103**(6): p. 782-5; discussion 785-6.

254. Kefer, J.C., G. Liu, and F. Daneshgari, *Pubo-urethral ligament injury causes long-term stress urinary incontinence in female rats: an animal model of the integral theory.* J Urol, 2009. **181**(1): p. 397-400.

255. Almeida, F.G., H. Bruschini, and M. Srougi, *Correlation between urethral sphincter activity and Valsalva leak point pressure at different bladder distentions: revisiting the urethral pressure profile.* J Urol, 2005. **174**(4 Pt 1): p. 1312-5; discussion 1315-6.

256. Sinha, D., V. Nallaswamy, and A.S. Arunkalaivanan, *Value of leak point pressure study in women with incontinence.* J Urol, 2006. **176**(1): p. 186-8; discussion 188.

257. Martan, A., et al., *Weak VLPP and MUCP correlation and their relationship with objective and subjective measures of severity of urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(3): p. 267-71.

258. Digesu, G.A., et al., *The relationship of urethral resistance pressure and pressure flow parameters in women with lower urinary tract symptoms.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(5): p. 493-7.

259. Salvatore, S., et al., *Opening vesical pressure: a new test to discriminate urethral sphincter deficiency?* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(12): p. 1435-8.

260. Heit, M., *Intraurethral ultrasonography: correlation of urethral anatomy with functional urodynamic parameters in stress incontinent women.* Int Urogynecol J Pelvic Floor Dysfunct, 2000. **11**(4): p. 204-11.

261. Kauppila, A., J. Penttinen, and V.M. Haggman, *Six-microtransducer catheter connected to computer in evaluation of urethral closure function of women.* Urology, 1989. **33**(2): p. 159-64.

262. Behr, J., M. Winkler, and U. Schwiersch, *[Urodynamic observations on the Marshall-Marchetti-Krantz operation].* Geburtshilfe Frauenheilkd, 1986. **46**(9): p. 649-53.

263. Vanderschot, E.L., M.L. Chafik, and F.M. Debruyne, *Has the suprapubic suspension operation any influence on the urethral pressure profile?* Br J Urol, 1979. **51**(2): p. 140-3.

264. Langer, R., et al., *Continence mechanism after colpo-needle suspension for stress urinary incontinence.* J Reprod Med, 1995. **40**(10): p. 699-702.

265. Hertogs, K. and S.L. Stanton, *Lateral bead-chain urethrocystography after successful and unsuccessful colposuspension.* Br J Obstet Gynaecol, 1985. **92**(11): p. 1179-83.

266. Snooks, S.J., P.R. Barnes, and M. Swash, *Damage to the innervation of the voluntary anal and periurethral sphincter musculature in incontinence: an electrophysiological study.* J Neurol Neurosurg Psychiatry, 1984. **47**(12): p. 1269-73.

267. Swash, M., S.J. Snooks, and M.M. Henry, *Unifying concept of pelvic floor disorders and incontinence.* J R Soc Med, 1985. **78**(11): p. 906-11.

268. Ismael, S.S., et al., *Postpartum lumbosacral plexopathy limited to autonomic and perineal manifestations: clinical and electrophysiological study of 19 patients.* J Neurol Neurosurg Psychiatry, 2000. **68**(6): p. 771-3.

269. Takahashi, S., et al., *Electromyographic study of the striated urethral sphincter in type 3 stress incontinence: evidence of myogenic-dominant damages.* Urology, 2000. **56**(6): p. 946-50.

270. Bakas, P., et al., *Pudendal nerve terminal motor latency in women with genuine stress incontinence and prolapse.* Gynecol Obstet Invest, 2001. **51**(3): p. 187-90.

271. Chermansky, C.J., et al., *A model of intrinsic sphincteric deficiency in the rat: electrocauterization.* Neurourol Urodyn, 2004. **23**(2): p. 166-71.

272. Eberli, D., et al., *A canine model of irreversible urethral sphincter insufficiency.* BJU Int, 2009. **103**(2): p. 248-53.

273. Jiang, H.H., et al., *Dual simulated childbirth injuries result in slowed recovery of pudendal nerve and urethral function.* Neurourol Urodyn, 2009. **28**(3): p. 229-35.

274. Pieber, D., F. Zivkovic, and K. Tamussino, *Timing of urethral pressure pulses before and after continence surgery.* Neurourol Urodyn, 1998. **17**(1): p. 19-23.

275. Deffieux, X., et al., *Pelvic floor muscle activity during coughing: altered pattern in women with stress urinary incontinence.* Urology, 2007. **70**(3): p. 443-7; discussion 447-8.

276. Deffieux, X., et al., *Decrease in urethral pressure following repeated cough efforts: a new concept for pathophysiology of stress urinary incontinence.* Int J Urol, 2007. **14**(11): p. 1019-24.

277. Kenton, K., et al., *Recurrent stress incontinence is associated with decreased neuromuscular function in the striated urethral sphincter.* Am J Obstet Gynecol, 2006. **194**(5): p. 1434-7.

278. Thor, K.B., *Serotonin and norepinephrine involvement in efferent pathways to the urethral rhabdosphincter: implications for treating stress urinary incontinence.* Urology, 2003. **62**(4 Suppl 1): p. 3-9.

279. Chen, B., et al., *Microarray analysis of differentially expressed genes in vaginal tissues from women with stress urinary incontinence compared with asymptomatic women.* Hum Reprod, 2006. **21**(1): p. 22-9.

280. Wen, Y., et al., *Is alpha2-macroglobulin important in female stress urinary incontinence?* Hum Reprod, 2008. **23**(2): p. 387-93.

281. Yang, A., et al., *Pelvic floor descent in women: dynamic evaluation with fast MR imaging and cinematic display.* Radiology, 1991. **179**(1): p. 25-33.

282. Gufler, H., et al., *Comparison of cystourethrography and dynamic MRI in bladder neck descent.* J Comput Assist Tomogr, 2000. **24**(3): p. 382-8.

283. Yang, A., et al, *Patterns of Prolapse Demonstrated With Dynamic Fastscan MRI; Reassessment of Conventional Concepts of Pelvic Floor Weaknesses.* Neurourol Urodyn, 1993. **12**(4): p. 4.

284. Kim, J.K., et al., *The urethra and its supporting structures in women with stress urinary incontinence: MR imaging using an endovaginal coil.* AJR Am J Roentgenol, 2003. **180**(4): p. 1037-44.

285. Yang, A.e.a., *High Resolution Magnetic Resonance Imaging of Urethra and Periurethral Structures Using Intravaginal Surface Coil and Quadrature Phased Array Surface Coil.* Neurourol Urodyn, 1993. **12**(4): p. 15.

286. Perez, N., et al., *Dynamic magnetic resonance imaging of the female pelvis: radio-anatomy and pathologic applications. Preliminary results.* Surg Radiol Anat, 1999. **21**(2): p. 133-8.

287. Di Gangi Herms, A.M., et al., *Functional imaging of stress urinary incontinence.* Neuroimage, 2006. **29**(1): p. 267-75.

288. Masata, J., et al., *[Ultrasonography of the funneling of the urethra].* Ceska Gynekol, 2000. **65**(2): p. 87-90.

289. Schaer, G.N., et al., *Improvement of perineal sonographic bladder neck imaging with ultrasound contrast medium.* Obstet Gynecol, 1995. **86**(6): p. 950-4.

290. Siracusano, S., et al., *The feasibility of urethral color ultrasound imaging in the diagnosis of female intrinsic sphincter deficiency: preliminary results.* Spinal Cord, 2002. **40**(4): p. 192-5.

291. Huang, W.C. and J.M. Yang, *Bladder neck funneling on ultrasound cystourethrography in primary stress urinary incontinence: a sign associated with urethral hypermobility and intrinsic sphincter deficiency.* Urology, 2003. **61**(5): p. 936-41.

292. Ghoniem, G.M., et al., *Grades of intrinsic sphincteric deficiency (ISD) associated with female stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2002. **13**(2): p. 99-105; discussion 105.

293. Tunn, R., et al., *Pathogenesis of urethral funneling in women with stress urinary incontinence assessed by introital ultrasound.* Ultrasound Obstet Gynecol, 2005. **26**(3): p. 287-92.

294. Martan, A., et al., *Ultrasound imaging of paravaginal defects in women with stress incontinence before and after paravaginal defect repair.* Ultrasound Obstet Gynecol, 2002. **19**(5): p. 496-500.

295. Nichols, D.H., Randall C.L., *Vaginal surgery*. 3rd ed. 1989, Baltimore: Williams & Wilkins.

296. Mostwin, J.L., et al., *Radiography, sonography, and magnetic resonance imaging for stress incontinence. Contributions, uses, and limitations.* Urol Clin North Am, 1995. **22**(3): p. 539-49.

297. Martan, A., et al., *Ultrasound imaging of the lower urinary*

system in women after Burch colposuspension. Ultrasound Obstet Gynecol, 2001. **17**(1): p. 58-64.

298. Orno, A.K. and H.P. Dietz, *Levator co-activation is a significant confounder of pelvic organ descent on Valsalva maneuver.* Ultrasound Obstet Gynecol, 2007. **30**(3): p. 346-50.

299. Oliveira, E., et al., *Ultrasonographic and Doppler velocimetric evaluation of the levator ani muscle in premenopausal women with and without urinary stress incontinence.* Eur J Obstet Gynecol Reprod Biol, 2007. **133**(2): p. 213-7.

300. Devreese, A., et al., *Clinical evaluation of pelvic floor muscle function in continent and incontinent women.* Neurourol Urodyn, 2004. **23**(3): p. 190-7.

301. Morin, M., et al., *Pelvic floor muscle function in continent and stress urinary incontinent women using dynamometric measurements.* Neurourol Urodyn, 2004. **23**(7): p. 668-74.

302. Dietz, H.P., S.K. Jarvis, and T.G. Vancaillie, *The assessment of levator muscle strength: a validation of three ultrasound techniques.* Int Urogynecol J Pelvic Floor Dysfunct, 2002. **13**(3): p. 156-9; discussion 159.

303. Constantinou, C.E., *Dynamics of female pelvic floor function using urodynamics, ultrasound and Magnetic Resonance Imaging (MRI).* Eur J Obstet Gynecol Reprod Biol, 2009. **144 Suppl 1**: p. S159-65.

304. Milley, P.S. and D.H. Nichols, *The relationship between the pubo-urethral ligaments and the urogenital diaphragm in the human female.* Anat Rec, 1971. **170**(3): p. 281-3.

305. Zacharin, R.F., *The anatomic supports of the female urethra.* Obstet Gynecol, 1968. **32**(6): p. 754-9.

306. Zacharin, R.F., *The Suspensory Mechanism of the Female Urethra.* J Anat, 1963. **97**: p. 423-7.

307. Mostwin, J.L., et al., *Stress incontinence observed with real time sonography and dynamic fastscan magnetic resonance imaging--insights into pathophysiology.* Scand J Urol Nephrol Suppl, 2001(207): p. 94-9; discussion 106-25.

308. Athanasiou, S., et al., *Imaging the urethral sphincter with three-dimensional ultrasound.* Obstet Gynecol, 1999. **94**(2): p. 295-301.

309. Tsai, E., et al., *Bladder neck circulation by Doppler ultrasonography in postmenopausal women with urinary stress incontinence.* Obstet Gynecol, 2001. **98**(1): p. 52-6.

310. Yang, J.M., S.H. Yang, and W.C. Huang, *Functional correlates of Doppler flow study of the female urethral vasculature.* Ultrasound Obstet Gynecol, 2006. **28**(1): p. 96-102.

311. Norton, P.A., *Pelvic floor disorders: the role of fascia and ligaments.* Clin Obstet Gynecol, 1993. **36**(4): p. 926-38.

312. Goh, J.T., *Biomechanical and biochemical assessments for pelvic organ prolapse.* Curr Opin Obstet Gynecol, 2003. **15**(5): p. 391-4.

313. DeLancey, J.O., *The anatomy of the pelvic floor.* Curr Opin Obstet Gynecol, 1994. **6**(4): p. 313-6.

314. Kearney, R., R. Sawhney, and J.O. DeLancey, *Levator ani muscle anatomy evaluated by origin-insertion pairs.* Obstet Gynecol, 2004. **104**(1): p. 168-73.

315. Singh, K., et al., *Three-dimensional magnetic resonance imaging assessment of levator ani morphologic features in different grades of prolapse.* Am J Obstet Gynecol, 2003. **188**(4): p. 910-5.

316. DeLancey, J.O., et al., *The appearance of levator ani muscle abnormalities in magnetic resonance images after vaginal delivery.* Obstet Gynecol, 2003. **101**(1): p. 46-53.

317. DeLancey, J.O., *Anatomic aspects of vaginal eversion after hysterectomy.* Am J Obstet Gynecol, 1992. **166**(6 Pt 1): p. 1717-24; discussion 1724-8.

318. DeLancey, J.O., *Anatomy and biomechanics of genital prolapse.* Clin Obstet Gynecol, 1993. **36**(4): p. 897-909.

319. Swift, S., et al., *Pelvic Organ Support Study (POSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects.* Am J Obstet Gynecol, 2005. **192**(3): p. 795-806.

320. Olsen, A.L., et al., *Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence.* Obstet Gynecol, 1997. **89**(4): p. 501-6.

321. Brown, J.S., et al., *Pelvic organ prolapse surgery in the United States, 1997.* Am J Obstet Gynecol, 2002. **186**(4): p. 712-6.

322. Rortveit, G., et al., *Symptomatic pelvic organ prolapse: prevalence and risk factors in a population-based, racially diverse cohort.* Obstet Gynecol, 2007. **109**(6): p. 1396-403.

323. Norton, P. and I. Milsom, *Genetics and the lower urinary tract.* Neurourol Urodyn, 2010. **29**(4): p. 609-11.

324. Samuelsson, E.C., et al., *Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors.* Am J Obstet Gynecol, 1999. **180**(2 Pt 1): p. 299-305.

325. Mant, J., R. Painter, and M. Vessey, *Epidemiology of genital prolapse: observations from the Oxford Family Planning Association Study.* Br J Obstet Gynaecol, 1997. **104**(5): p. 579-85.

326. Hendrix, S.L., et al., *Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity.* Am J Obstet Gynecol, 2002. **186**(6): p. 1160-6.

327. Scherf, C., et al., *Epidemiology of pelvic organ prolapse in rural Gambia, West Africa.* BJOG, 2002. **109**(4): p. 431-6.

328. Harris, R.L., et al., *Urinary incontinence and pelvic organ prolapse in nulliparous women.* Obstet Gynecol, 1998. **92**(6): p. 951-4.

329. Chiaffarino, F., et al., *Reproductive factors, family history, occupation and risk of urogenital prolapse.* Eur J Obstet Gynecol Reprod Biol, 1999. **82**(1): p. 63-7.

330. Jack, G.S., et al., *Familial transmission of genitovaginal prolapse.* Int Urogynecol J Pelvic Floor Dysfunct, 2006. **17**(5): p. 498-501.

331. Buchsbaum, G.M., et al., *Pelvic organ prolapse in nulliparous women and their parous sisters.* Obstet Gynecol, 2006. **108**(6): p. 1388-93.

332. Altman, D., et al., *Genetic influence on stress urinary incontinence and pelvic organ prolapse.* Eur Urol, 2008. **54**(4): p. 918-22.

333. Buchsbaum, G.M. and E.E. Duecy, *Incontinence and pelvic organ prolapse in parous/nulliparous pairs of identical twins.* Neurourol Urodyn, 2008. **27**(6): p. 496-8.

334. Allen-Brady, K., et al., *Identification of six loci associated with pelvic organ prolapse using genome-wide association analysis.* Obstet Gynecol, 2011. **118**(6): p. 1345-53.

335. Nikolova, G., et al., *Sequence variant in the laminin gamma1 (LAMC1) gene associated with familial pelvic organ prolapse.* Hum Genet, 2007. **120**(6): p. 847-56.

336. Visco, A.G. and L. Yuan, *Differential gene expression in pubococcygeus muscle from patients with pelvic organ prolapse.* Am J Obstet Gynecol, 2003. **189**(1): p. 102-12.

337. Connell, K.A., et al., *HOXA11 is critical for development and maintenance of uterosacral ligaments and deficient in pelvic prolapse.* J Clin Invest, 2008. **118**(3): p. 1050-5.

338. Chen, B. and J. Yeh, *Alterations in connective tissue metabolism in stress incontinence and prolapse.* J Urol, 2011. **186**(5): p. 1768-72.

339. Drewes, P.G., et al., *Pelvic organ prolapse in fibulin-5 knockout mice: pregnancy-induced changes in elastic fiber homeostasis in mouse vagina.* Am J Pathol, 2007. **170**(2): p. 578-89.

340. Yamamoto, K., et al., *Decrease in elastin gene expression and protein synthesis in fibroblasts derived from cardinal ligaments of patients with prolapsus uteri.* Cell Biol Int, 1997. **21**(9): p. 605-11.

341. Kim, S., M.A. Harvey, and S. Johnston, *A review of the epidemiology and pathophysiology of pelvic floor dysfunction: do racial differences matter?* J Obstet Gynaecol Can, 2005. **27**(3): p. 251-9.

342. Dietz, H.P., *Do Asian women have less pelvic organ mobility than Caucasians?* Int Urogynecol J Pelvic Floor Dysfunct, 2003. **14**(4): p. 250-3; discussion 253.

343. Zacharin, R.F., *Abdominoperineal urethral suspension: a ten-year experience in the management of recurrent stress incontinence of urine.* Obstet Gynecol, 1977. **50**(1): p. 1-8.

344. Nygaard, I., C. Bradley, and D. Brandt, *Pelvic organ prolapse in older women: prevalence and risk factors.* Obstet Gynecol, 2004. **104**(3): p. 489-97.

345. Segev, Y., et al., *Are women with pelvic organ prolapse at a higher risk of developing hernias?* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(12): p. 1451-3.

346. Miedel, A., et al., *Nonobstetric risk factors for symptomatic pelvic organ prolapse.* Obstet Gynecol, 2009. **113**(5): p. 1089-97.

347. McLennan, M.T., et al., *Family history as a risk factor for pelvic organ prolapse.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(8): p. 1063-9.

348. Strohbehn, K., J.A. Jakary, and J.O. Delancey, *Pelvic organ prolapse in young women.* Obstet Gynecol, 1997. **90**(1): p. 33-6.

349. ZS, A.L.-R. and Z.T. Al-Rawi, *Joint hypermobility in women with genital prolapse.* Lancet, 1982. **1**(8287): p. 1439-41.

350. Bai, S.W., et al., *Pelvic organ prolapse and connective tissue abnormalities in Korean women.* J Reprod Med, 2002. **47**(3): p. 231-4.

351. Marshman, D., et al., *Rectal prolapse: relationship with joint mobility.* Aust N Z J Surg, 1987. **57**(11): p. 827-9.

352. Norton, P.A., et al., *Genitourinary prolapse and joint hypermobility in women.* Obstet Gynecol, 1995. **85**(2): p. 225-8.

353. Carley, M.E. and J. Schaffer, *Urinary incontinence and pelvic organ prolapse in women with Marfan or Ehlers Danlos syndrome.* Am J Obstet Gynecol, 2000. **182**(5): p. 1021-3.

354. Liang, C.C., et al., *Expression of matrix metalloproteinase-2 and tissue inhibitors of metalloproteinase-1 (TIMP-1, TIMP-2 and TIMP-3) in women with uterine prolapse but without urinary incontinence.* Eur J Obstet Gynecol Reprod Biol, 2010. **153**(1): p. 94-8.

355. Vulic, M., et al., *Difference in expression of collagen type I and matrix metalloproteinase-1 in uterosacral ligaments of women with and without pelvic organ prolapse.* Eur J Obstet Gynecol Reprod Biol, 2011. **155**(2): p. 225-8.

356. Mosier, E., V.K. Lin, and P. Zimmern, *Extracellular matrix expression of human prolapsed vaginal wall.* Neurourol Urodyn, 2010. **29**(4): p. 582-6.

357. Takano, C.C., et al., *Analysis of collagen in parametrium and vaginal apex of women with and without uterine prolapse.* Int Urogynecol J Pelvic Floor Dysfunct, 2002. **13**(6): p. 342-5; discussion 345.

358. Moalli, P.A., et al., *Remodeling of vaginal connective tissue in patients with prolapse.* Obstet Gynecol, 2005. **106**(5 Pt 1): p. 953-63.

359. Gabriel, B., et al., *Uterosacral ligament in postmenopausal women with or without pelvic organ prolapse.* Int Urogynecol J Pelvic Floor Dysfunct, 2005. **16**(6): p. 475-9.

360. Ewies, A.A., F. Al-Azzawi, and J. Thompson, *Changes in extracellular matrix proteins in the cardinal ligaments of post-menopausal women with or without prolapse: a computerized immunohistomorphometric analysis.* Hum Reprod, 2003. **18**(10): p. 2189-95.

361. Moalli, P.A., et al., *Regulation of matrix metalloproteinase expression by estrogen in fibroblasts that are derived from the pelvic floor.* Am J Obstet Gynecol, 2002. **187**(1): p. 72-9.

362. Liu, X., et al., *Failure of elastic fiber homeostasis leads to pelvic floor disorders.* Am J Pathol, 2006. **168**(2): p. 519-28.

363. Liu, X., et al., *Elastic fiber homeostasis requires lysyl oxidase-like 1 protein.* Nat Genet, 2004. **36**(2): p. 178-82.

364. Chen, B., Y. Wen, and M.L. Polan, *Elastolytic activity in women with stress urinary incontinence and pelvic organ prolapse.* Neurourol Urodyn, 2004. **23**(2): p. 119-26.

365. Klutke, J., et al., *Decreased endopelvic fascia elastin content in uterine prolapse.* Acta Obstet Gynecol Scand, 2008. **87**(1): p. 111-5.

366. Moon, Y.J., et al., *Alteration of elastin metabolism in women with pelvic organ prolapse.* J Urol, 2011. **185**(5): p. 1786-92.

367. Judge, D.P. and H.C. Dietz, *Marfan's syndrome.* Lancet, 2005. **366**(9501): p. 1965-76.

368. Gupta, P.A., et al., *Ten novel FBN2 mutations in congenital contractural arachnodactyly: delineation of the molecular pathogenesis and clinical phenotype.* Hum Mutat, 2002. **19**(1): p. 39-48.

369. Milewicz, D.M., Z. Urban, and C. Boyd, *Genetic disorders of the elastic fiber system.* Matrix Biol, 2000. **19**(6): p. 471-80.

370. Lewis, K.G., et al., *Acquired disorders of elastic tissue: Part II. decreased elastic tissue.* J Am Acad Dermatol, 2004. **51**(2): p. 165-85; quiz 186-8.

371. Boreham, M.K., et al., *Morphometric properties of the posterior vaginal wall in women with pelvic organ prolapse.* Am J Obstet Gynecol, 2002. **187**(6): p. 1501-8; discussion 1508-9.

372. Busacchi, P., et al., *Abnormalities of somatic peptide-containing nerves supplying the pelvic floor of women with genitourinary prolapse and stress urinary incontinence.* Urology, 2004. **63**(3): p. 591-5.

373. Busacchi, P., et al., *A histological and immunohistochemical study of neuropeptide containing somatic nerves in the levator ani muscle of women with genitourinary prolapse.* Acta Obstet Gynecol Scand, 1999. **78**(1): p. 2-5.

374. Snooks, S.J., et al., *Risk factors in childbirth causing damage to the pelvic floor innervation.* Int J Colorectal Dis, 1986. **1**(1): p. 20-4.

375. Dolan, L.M., et al., *Stress incontinence and pelvic floor neurophysiology 15 years after the first delivery.* BJOG, 2003. **110**(12): p. 1107-14.

376. Shafik, A. and O. El-Sibai, *Study of the levator ani muscle in the multipara: role of levator dysfunction in defecation disorders.* J Obstet Gynaecol, 2002. **22**(2): p. 187-92.

377. Marshall, K., D.M. Walsh, and G.D. Baxter, *The effect of a first vaginal delivery on the integrity of the pelvic floor musculature.* Clin Rehabil, 2002. **16**(7): p. 795-9.

378. Gregory, W.T., et al., *Quantitative electromyography of the anal sphincter after uncomplicated vaginal delivery.* Obstet Gynecol, 2004. **104**(2): p. 327-35.

379. Sultan, A.H., M.A. Kamm, and C.N. Hudson, *Pudendal nerve damage during labour: prospective study before and after childbirth.* Br J Obstet Gynaecol, 1994. **101**(1): p. 22-8.

380. Tetzschner, T., et al., *Pudendal nerve damage increases the risk of fecal incontinence in women with anal sphincter rupture after childbirth.* Acta Obstet Gynecol Scand, 1995. **74**(6): p. 434-40.

381. Miodrag, A., C.M. Castleden, and T.R. Vallance, *Sex hormones and the female urinary tract.* Drugs, 1988. **36**(4): p. 491-504.

382. Wahl, L.M., R.J. Blandau, and R.C. Page, *Effect of hormones on collagen metabolism and collagenase activity in the pubic symphysis ligament of the guinea pig.* Endocrinology, 1977. **100**(2): p. 571-9.

383. Landon, *Mechanical properties of fascia during pregnancy: a possible factor in the development of stress incontinence of urine.* Contemp Rev Obstet Gynaecol, 1990. **2**: p. 40-46.

384. Rahn, D.D., et al., *Biomechanical properties of the vaginal wall: effect of pregnancy, elastic fiber deficiency, and pelvic organ prolapse.* Am J Obstet Gynecol, 2008. **198**(5): p. 590 e1-6.

385. O'Boyle, A.L., et al., *The natural history of pelvic organ support in pregnancy.* Int Urogynecol J Pelvic Floor Dysfunct, 2003. **14**(1): p. 46-9; discussion 49.

386. O'Boyle, A.L., et al., *Pelvic organ support in nulliparous pregnant and nonpregnant women: a case control study.* Am J Obstet Gynecol, 2002. **187**(1): p. 99-102.

387. Sze, E.H., G.B. Sherard, 3rd, and J.M. Dolezal, *Pregnancy, labor, delivery, and pelvic organ prolapse.* Obstet Gynecol, 2002. **100**(5 Pt 1): p. 981-6.

388. Dietz, H.P. and M.J. Bennett, *The effect of childbirth on pelvic organ mobility.* Obstet Gynecol, 2003. **102**(2): p. 223-8.

389. Dietz, H.P. and A.B. Steensma, *The role of childbirth in the aetiology of rectocele.* BJOG, 2006. **113**(3): p. 264-7.

390. Dietz, H.P. and A. Korda, *Which bowel symptoms are most strongly associated with a true rectocele?* Aust N Z J Obstet Gynaecol, 2005. **45**(6): p. 505-8.

391. Lukacz, E.S., et al., *Parity, mode of delivery, and pelvic floor disorders.* Obstet Gynecol, 2006. **107**(6): p. 1253-60.

392. Dietz, H.P., *Pelvic floor trauma following vaginal delivery.* Curr Opin Obstet Gynecol, 2006. **18**(5): p. 528-37.

393. Dietz, H.P., et al., *Pelvic organ descent in young nulligravid women.* Am J Obstet Gynecol, 2004. **191**(1): p. 95-9.

394. Dietz, H.P. and A.B. Steensma, *Which women are most affected by delivery-related changes in pelvic organ mobility?* Eur J Obstet Gynecol Reprod Biol, 2003. **111**(1): p. 15-8.

395. *Risk factors for genital prolapse in non-hysterectomized women around menopause. Results from a large cross-sectional study in menopausal clinics in Italy. Progetto Menopausa Italia Study Group.* Eur J Obstet Gynecol Reprod Biol, 2000. **93**(2): p. 135-40.

396. Moalli, P.A., et al., *Risk factors associated with pelvic floor disorders in women undergoing surgical repair.* Obstet Gynecol, 2003. **101**(5 Pt 1): p. 869-74.

397. Swift, S.E., S.B. Tate, and J. Nicholas, *Correlation of symptoms with degree of pelvic organ support in a general population of women: what is pelvic organ prolapse?* Am J Obstet Gynecol, 2003. **189**(2): p. 372-7; discussion 377-9.

398. Dietz, H.P. and J.M. Simpson, *Does delayed child-bearing increase the risk of levator injury in labour?* Aust N Z J Obstet Gynaecol, 2007. **47**(6): p. 491-5.

399. Bump, R.C. and P.A. Norton, *Epidemiology and natural history of pelvic floor dysfunction.* Obstet Gynecol Clin North Am, 1998. **25**(4): p. 723-46.

400. Ewies, A.A., J. Thompson, and F. Al-Azzawi, *Changes in gonadal steroid receptors in the cardinal ligaments of prolapsed uteri: immunohistomorphometric data.* Hum Reprod, 2004. **19**(7): p. 1622-8.

401. Chen, H.Y., et al., *Progesterone receptor polymorphism is associated with pelvic organ prolapse risk.* Acta Obstet Gynecol Scand, 2009. **88**(7): p. 835-8.

402. Chen, H.Y., et al., *Estrogen receptor beta gene haplotype is associated with pelvic organ prolapse.* Eur J Obstet Gynecol Reprod Biol, 2008. **138**(1): p. 105-9.

403. Xie, Z., et al., *Alterations of estrogen receptor-alpha and -beta in the anterior vaginal wall of women with urinary incontinence.* Eur J Obstet Gynecol Reprod Biol, 2007. **134**(2): p. 254-8.

404. Lang, J.H., et al., *Estrogen levels and estrogen receptors in patients with stress urinary incontinence and pelvic organ prolapse.* Int J Gynaecol Obstet, 2003. **80**(1): p. 35-9.

405. Bai, S.W., et al., *The role of estrogen receptor, progesterone receptor and p53 in development of stress urinary incontinence.* Yonsei Med J, 2004. **45**(5): p. 885-90.

406. Skala, C.E., et al., *The effect of genital and lower urinary tract symptoms on steroid receptor expression in women with genital prolapse.* Int Urogynecol J, 2011. **22**(6): p. 705-12.

407. Dietz, H.P. and B. Clarke, *Prevalence of rectocele in young nulliparous women.* Aust N Z J Obstet Gynaecol, 2005. **45**(5): p. 391-4.

408. Bradley, C.S., et al., *Natural history of pelvic organ prolapse in postmenopausal women.* Obstet Gynecol, 2007. **109**(4): p. 848-54.

409. Handa, V.L., et al., *Progression and remission of pelvic organ prolapse: a longitudinal study of menopausal women.* Am J Obstet Gynecol, 2004. **190**(1): p. 27-32.

410. Spence-Jones, C., et al., *Bowel dysfunction: a pathogenic factor in uterovaginal prolapse and urinary stress incontinence.* Br J Obstet Gynaecol, 1994. **101**(2): p. 147-52.

411. Arya, L.A., et al., *Pelvic organ prolapse, constipation, and dietary fiber intake in women: a case-control study.* Am J Obstet Gynecol, 2005. **192**(5): p. 1687-91.

412. Weber, A.M., et al., *Posterior vaginal prolapse and bowel function.* Am J Obstet Gynecol, 1998. **179**(6 Pt 1): p. 1446-9; discussion 1449-50.

413. Kahn, M.A., et al., *Pelvic Organ Support Study (POSST) and bowel symptoms: straining at stool is associated with perineal and anterior vaginal descent in a general gynecologic population.* Am J Obstet Gynecol, 2005. **192**(5): p. 1516-22.

414. Jelovsek, J.E., et al., *Functional bowel and anorectal disorders in patients with pelvic organ prolapse and incontinence.* Am J Obstet Gynecol, 2005. **193**(6): p. 2105-11.

415. Woodman, P.J., et al., *Prevalence of severe pelvic organ prolapse in relation to job description and socioeconomic status: a multicenter cross-sectional study.* Int Urogynecol J Pelvic Floor Dysfunct, 2006. **17**(4): p. 340-5.

416. Jorgensen, S., H.O. Hein, and F. Gyntelberg, *Heavy lifting at work and risk of genital prolapse and herniated lumbar disc in assistant nurses.* Occup Med (Lond), 1994. **44**(1): p. 47-9.

417. Karasick, S. and C.M. Spettell, *The role of parity and hysterectomy on the development of pelvic floor abnormalities revealed by defecography.* AJR Am J Roentgenol, 1997. **169**(6): p. 1555-8.

418. Swift, S.E., T. Pound, and J.K. Dias, *Case-control study of etiologic factors in the development of severe pelvic organ prolapse.* Int Urogynecol J Pelvic Floor Dysfunct, 2001. **12**(3): p. 187-92.

419. Clark, A.L., et al., *Epidemiologic evaluation of reoperation for surgically treated pelvic organ prolapse and urinary incontinence.* Am J Obstet Gynecol, 2003. **189**(5): p. 1261-7.

420. Cruikshank, S.H. and S.R. Kovac, *Randomized comparison of three surgical methods used at the time of vaginal hysterectomy to prevent posterior enterocele.* Am J Obstet Gynecol, 1999. **180**(4): p. 859-65.

421. Lind, L.R., V. Lucente, and N. Kohn, *Thoracic kyphosis and the prevalence of advanced uterine prolapse.* Obstet Gynecol, 1996. **87**(4): p. 605-9.

422. Nguyen, J.K., et al., *Lumbosacral spine and pelvic inlet changes associated with pelvic organ prolapse.* Obstet Gynecol, 2000. **95**(3): p. 332-6.

423. Sze, E.H., et al., *A retrospective comparison of abdominal sacrocolpopexy with Burch colposuspension versus sacrospinous fixation with transvaginal needle suspension for the management of vaginal vault prolapse and coexisting stress incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 1999. **10**(6): p. 390-3.

424. Handa, V.L., et al., *Architectural differences in the bony pelvis of women with and without pelvic floor disorders.* Obstet Gynecol, 2003. **102**(6): p. 1283-90.

425. Blakeley, C.R. and W.G. Mills, *The obstetric and gynaecological complications of bladder exstrophy and epispadias.* Br J Obstet Gynaecol, 1981. **88**(2): p. 167-73.

426. Costantini, E., M. Lazzeri, and M. Porena, *[Pelvic organ prolapse and lower urinary tract symptoms: experience from a high-volume uro-gynecologic center.].* Urologia, 2012: p. 0.

427. Lawrence, J.M., et al., *Prevalence and co-occurrence of pelvic floor disorders in community-dwelling women.* Obstet Gynecol, 2008. **111**(3): p. 678-85.

428. Soderberg, M.W., et al., *Young women with genital prolapse have a low collagen concentration.* Acta Obstet Gynecol Scand, 2004. **83**(12): p. 1193-8.

429. Zhu, L., et al., *Estrogen receptor in pelvic floor tissues in patients with stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2004. **15**(5): p. 340-3.

430. Marinkovic, S.P. and S.L. Stanton, *Incontinence and voiding difficulties associated with prolapse.* J Urol, 2004. **171**(3): p. 1021-8.

431. Romanzi, L.J., D.C. Chaikin, and J.G. Blaivas, *The effect of genital prolapse on voiding.* J Urol, 1999. **161**(2): p. 581-6.

432. Romanzi, L.J., *Management of the urethral outlet in patients with severe prolapse.* Curr Opin Urol, 2002. **12**(4): p. 339-44.

433. Burrows, L.J., et al., *Pelvic symptoms in women with pelvic organ prolapse.* Obstet Gynecol, 2004. **104**(5 Pt 1): p. 982-8.

434. Tan, J.S., et al., *Predictive value of prolapse symptoms: a large database study.* Int Urogynecol J Pelvic Floor Dysfunct, 2005. **16**(3): p. 203-9; discussion 209.

435. Maher, C., et al., *Surgical management of pelvic organ prolapse in women.* Cochrane Database Syst Rev, 2004(4): p. CD004014.

436. Levin, I., et al., *Surgical complications and medium-term outcome results of tension-free vaginal tape: a prospective study of 313 consecutive patients.* Neurourol Urodyn, 2004. **23**(1): p. 7-9.

437. Cronje, H.S., J.A. De Beer, and R. Bam, *The pathophysiology of an enterocele and its management.* J Obstet Gynaecol, 2004. **24**(4): p. 408-13.

438. Ramanah, R., et al., *Effects of pelvic organ prolapse repair on urinary symptoms: A comparative study between the laparoscopic and vaginal approach.* Neurourol Urodyn, 2012. **31**(1): p. 126-31.

439. Tegerstedt, G., et al., *Prevalence of symptomatic pelvic organ prolapse in a Swedish population.* Int Urogynecol J Pelvic Floor Dysfunct, 2005. **16**(6): p. 497-503.

440. Fritel, X., et al., *Symptomatic pelvic organ prolapse at midlife, quality of life, and risk factors.* Obstet Gynecol, 2009. **113**(3): p. 609-16.

441. Miedel, A., et al., *Symptoms and pelvic support defects in specific compartments.* Obstet Gynecol, 2008. **112**(4): p. 851-8.

442. Long, C.Y., et al., *Abnormal clinical and urodynamic findings in women with severe genitourinary prolapse.* Kaohsiung J Med Sci, 2002. **18**(12): p. 593-7.

443. Digesu, G.A., et al., *The relationship of vaginal prolapse severity to symptoms and quality of life.* BJOG, 2005. **112**(7): p. 971-6.

444. Schimpf, M.O., et al., *Anterior vaginal wall prolapse and voiding dysfunction in urogynecology patients.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(7): p. 721-5.

445. Bradley, C.S. and I.E. Nygaard, *Vaginal wall descensus and pelvic floor symptoms in older women.* Obstet Gynecol, 2005. **106**(4): p. 759-66.

446. Sobhgol, S.S. and S.M. Charandabee, *Related factors of urge, stress, mixed urinary incontinence and overactive bladder in reproductive age women in Tabriz, Iran: a cross-sectional study.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(3): p. 367-73.

447. Ellerkmann, R.M., et al., *Correlation of symptoms with location and severity of pelvic organ prolapse.* Am J Obstet Gynecol, 2001. **185**(6): p. 1332-7; discussion 1337-8.

448. Dietz, H.P. and B. Clarke, *Is the irritable bladder associated with anterior compartment relaxation? A critical look at the 'integral theory of pelvic floor dysfunction'.* Aust N Z J Obstet Gynaecol, 2001. **41**(3): p. 317-9.

449. de Boer, T.A., et al., *Pelvic organ prolapse and overactive bladder.* Neurourol Urodyn, 2010. **29**(1): p. 30-9.

450. Jackson, S.L., et al., *Fecal incontinence in women with urinary incontinence and pelvic organ prolapse.* Obstet Gynecol, 1997. **89**(3): p. 423-7.

451. Khullar, V., et al., *Prevalence of faecal incontinence among women with urinary incontinence.* Br J Obstet Gynaecol, 1998. **105**(11): p. 1211-3.

452. Meschia, M., et al., *Prevalence of anal incontinence in women with symptoms of urinary incontinence and genital prolapse.* Obstet Gynecol, 2002. **100**(4): p. 719-23.

453. Soligo, M., et al., *Double incontinence in urogynecologic practice: a new insight.* Am J Obstet Gynecol, 2003. **189**(2): p. 438-43.

454. Gordon, D., et al., *Anal incontinence: prevalence among female patients attending a urogynecologic clinic.* Neurourol Urodyn, 1999. **18**(3): p. 199-204.

455. Bradley, C.S., et al., *Bowel symptoms in women planning surgery for pelvic organ prolapse.* Am J Obstet Gynecol, 2006. **195**(6): p. 1814-9.

456. Morgan, D.M., et al., *Symptoms of anal incontinence and difficult defecation among women with prolapse and a matched control cohort.* Am J Obstet Gynecol, 2007. **197**(5): p. 509 e1-6.

457. de Mello Portella, P., et al., *Prevalence of and quality of life related to anal incontinence in women with urinary incontinence and pelvic organ prolapse.* Eur J Obstet Gynecol Reprod Biol, 2012. **160**(2): p. 228-31.

458. Goei, R., *Anorectal function in patients with defecation disorders and asymptomatic subjects: evaluation with defecography.* Radiology, 1990. **174**(1): p. 121-3.

459. Altringer, W.E., et al., *Four-contrast defecography: pelvic "floor-oscopy".* Dis Colon Rectum, 1995. **38**(7): p. 695-9.

460. Kelvin, F.M., et al., *Female pelvic organ prolapse: diagnostic contribution of dynamic cystoproctography and comparison with physical examination.* AJR Am J Roentgenol, 1999. **173**(1): p. 31-7.

461. Agachan, F., J. Pfeifer, and S.D. Wexner, *Defecography and proctography. Results of 744 patients.* Dis Colon Rectum, 1996. **39**(8): p. 899-905.

462. Lopez, A., et al., *Cystodefecoperitoneography in patients with genital prolapse.* Int Urogynecol J Pelvic Floor Dysfunct, 2002. **13**(1): p. 22-9.

463. Karasick, S. and S.M. Ehrlich, *Is constipation a disorder of defecation or impaired motility?: distinction based on defecography and colonic transit studies.* AJR Am J Roentgenol, 1996. **166**(1): p. 63-6.

464. van Dam, J.H., W.C. Hop, and W.R. Schouten, *Analysis of patients with poor outcome of rectocele repair.* Dis Colon Rectum, 2000. **43**(11): p. 1556-60.

465. Karlbom, U., et al., *Does surgical repair of a rectocele improve rectal emptying?* Dis Colon Rectum, 1996. **39**(11): p. 1296-302.

466. Mellgren, A., et al., *Results of rectocele repair. A prospective study.* Dis Colon Rectum, 1995. **38**(1): p. 7-13.

467. Goh, J.T., J.J. Tjandra, and M.P. Carey, *How could management of rectoceles be optimized?* ANZ J Surg, 2002. **72**(12): p. 896-901.

468. Ramanah, R., et al., *Anorectal symptoms before and after laparoscopic sacrocolpoperineopexy for pelvic organ prolapse.* Int Urogynecol J, 2012.

469. Handa, V.L., et al., *Sexual function among women with urinary incontinence and pelvic organ prolapse.* Am J Obstet Gynecol, 2004. **191**(3): p. 751-6.

470. Rogers, G.R., et al., *Sexual function in women with and without urinary incontinence and/or pelvic organ prolapse.* Int Urogynecol J Pelvic Floor Dysfunct, 2001. **12**(6): p. 361-5.

471. Barber, M.D., et al., *Sexual function in women with urinary*

incontinence and pelvic organ prolapse. Obstet Gynecol, 2002. **99**(2): p. 281-9.

472. Weber, A.M., et al., *Sexual function in women with uterovaginal prolapse and urinary incontinence.* Obstet Gynecol, 1995. **85**(4): p. 483-7.

473. Handa, V.L., et al., *Female sexual function and pelvic floor disorders.* Obstet Gynecol, 2008. **111**(5): p. 1045-52.

474. Knoepp, L.R., et al., *Sexual complaints, pelvic floor symptoms, and sexual distress in women over forty.* J Sex Med, 2010. **7**(11): p. 3675-82.

475. Rao, S.S., *Diagnosis and management of fecal incontinence. American College of Gastroenterology Practice Parameters Committee.* Am J Gastroenterol, 2004. **99**(8): p. 1585-604.

476. Rao, S.S. and R.S. Patel, *How useful are manometric tests of anorectal function in the management of defecation disorders?* Am J Gastroenterol, 1997. **92**(3): p. 469-75.

477. Sun, W.M., T.C. Donnelly, and N.W. Read, *Utility of a combined test of anorectal manometry, electromyography, and sensation in determining the mechanism of 'idiopathic' faecal incontinence.* Gut, 1992. **33**(6): p. 807-13.

478. Bharucha, A.E., et al., *Relationship between symptoms and disordered continence mechanisms in women with idiopathic faecal incontinence.* Gut, 2005. **54**(4): p. 546-55.

479. Lam, T.J., D.J. Kuik, and R.J. Felt-Bersma, *Anorectal function evaluation and predictive factors for faecal incontinence in 600 patients.* Colorectal Dis, 2012. **14**(2): p. 214-23.

480. Frenckner, B. and T. Ihre, *Influence of autonomic nerves on the internal and sphincter in man.* Gut, 1976. **17**(4): p. 306-12.

481. Penninckx, F., B. Lestar, and R. Kerremans, *The internal anal sphincter: mechanisms of control and its role in maintaining anal continence.* Baillieres Clin Gastroenterol, 1992. **6**(1): p. 193-214.

482. Mularczyk, A., P.A. Bianchi, and G. Basilisco, *Effect of continuous rectal distention on anal resting pressure.* Dis Colon Rectum, 2001. **44**(5): p. 672-6.

483. Rao, S.S., et al., *Anorectal contractility under basal conditions and during rectal infusion of saline in ulcerative colitis.* Gut, 1988. **29**(6): p. 769-77.

484. Schouten, W.R. and J.D. Blankensteijn, *Ultra slow wave pressure variations in the anal canal before and after lateral internal sphincterotomy.* Int J Colorectal Dis, 1992. **7**(3): p. 115-8.

485. Zbar, A.P. and M. Khaikin, *Should we care about the internal anal sphincter?* Dis Colon Rectum, 2012. **55**(1): p. 105-8.

486. Burleigh, D.E., *Non-cholinergic, non-adrenergic inhibitory neurons in human internal anal sphincter muscle.* J Pharm Pharmacol, 1983. **35**(4): p. 258-60.

487. Cook, T.A., A.F. Brading, and N.J. Mortensen, *Differences in contractile properties of anorectal smooth muscle and the effects of calcium channel blockade.* Br J Surg, 1999. **86**(1): p. 70-5.

488. O'Kelly, T.J., A. Brading, and N.J. Mortensen, *In vitro response of the human anal canal longitudinal muscle layer to cholinergic and adrenergic stimulation: evidence of sphincter specialization.* Br J Surg, 1993. **80**(10): p. 1337-41.

489. Goyal, R.K. and A. Chaudhury, *Mounting evidence against the role of ICC in neurotransmission to smooth muscle in the gut.* Am J Physiol Gastrointest Liver Physiol, 2010. **298**(1): p. G10-3.

490. McDonnell, B., et al., *Functional evidence for purinergic inhibitory neuromuscular transmission in the mouse internal anal sphincter.* Am J Physiol Gastrointest Liver Physiol, 2008. **294**(4): p. G1041-51.

491. Mills, K. and R. Chess-Williams, *Pharmacology of the internal anal sphincter and its relevance to faecal incontinence.* Auton Autacoid Pharmacol, 2009. **29**(3): p. 85-95.

492. Opazo, A., et al., *Specific and complementary roles for nitric oxide and ATP in the inhibitory motor pathways to rat internal anal sphincter.* Neurogastroenterol Motil, 2011. **23**(1): p. e11-25.

493. Rattan, S. and J. Singh, *Basal internal anal sphincter tone, inhibitory neurotransmission, and other factors contributing to the maintenance of high pressures in the anal canal.* Neurogastroenterol Motil, 2011. **23**(1): p. 3-7.

494. Patel, C.A. and S. Rattan, *Spontaneously tonic smooth muscle has characteristically higher levels of RhoA/ROK compared with the phasic smooth muscle.* Am J Physiol Gastrointest Liver Physiol, 2006. **291**(5): p. G830-7.

495. Patel, C.A. and S. Rattan, *Cellular regulation of basal tone in internal anal sphincter smooth muscle by RhoA/ROCK.* Am J Physiol Gastrointest Liver Physiol, 2007. **292**(6): p. G1747-56.

496. Meagher, A.P., D.Z. Lubowski, and D.W. King, *The cough response of the anal sphincter.* Int J Colorectal Dis, 1993. **8**(4): p. 217-9.

497. Dalley, A.F., 2nd, *The riddle of the sphincters. The morphophysiology of the anorectal mechanism reviewed.* Am Surg, 1987. **53**(5): p. 298-306.

498. Hsu, Y., et al., *Magnetic resonance imaging and 3-dimensional analysis of external anal sphincter anatomy.* Obstet Gynecol, 2005. **106**(6): p. 1259-65.

499. Guo, M., et al., *MRI anatomy of the anal region.* Dis Colon Rectum, 2010. **53**(11): p. 1542-8.

500. Johnson, M.A., et al., *Data on the distribution of fibre types in thirty-six human muscles. An autopsy study.* J Neurol Sci, 1973. **18**(1): p. 111-29.

501. Salmons, S. and G. Vrbova, *The influence of activity on some contractile characteristics of mammalian fast and slow muscles.* J Physiol, 1969. **201**(3): p. 535-49.

502. Lunniss, P.J. and R.K. Phillips, *Anatomy and function of the anal longitudinal muscle.* Br J Surg, 1992. **79**(9): p. 882-4.

503. Shafik, A., *A new concept of the anatomy of the anal sphincter mechanism and the physiology of defecation. III. The longitudinal anal muscle: anatomy and role in anal sphincter mechanism.* Invest Urol, 1976. **13**(4): p. 271-7.

504. Azpiroz, F., et al., *The puborectalis muscle.* Neurogastroenterol Motil, 2005. **17 Suppl 1**: p. 68-72.

505. Liu, J., et al., *Functional correlates of anal canal anatomy: puborectalis muscle and anal canal pressure.* Am J Gastroenterol, 2006. **101**(5): p. 1092-7.

506. Raizada, V., et al., *Functional morphology of anal sphincter complex unveiled by high definition anal manometery and three dimensional ultrasound imaging.* Neurogastroenterol Motil, 2011. **23**(11): p. 1013-9, e460.

507. Levi, A.C., F. Borghi, and M. Garavoglia, *Development of the anal canal muscles.* Dis Colon Rectum, 1991. **34**(3): p. 262-6.

508. Percy, J.P., et al., *Electrophysiological study of motor nerve supply of pelvic floor.* Lancet, 1981. **1**(8210): p. 16-7.

509. Wallner, C., *Is the puborectalis muscle part of the levator ani muscle?* Dis Colon Rectum, 2008. **51**(7): p. 1165-6; author reply 1167.

510. Wallner, C., et al., *Evidence for the innervation of the puborectalis muscle by the levator ani nerve.* Neurogastroenterol Motil, 2006. **18**(12): p. 1121-2.

511. Wallner, C., et al., *Innervation of the pelvic floor muscles: a reappraisal for the levator ani nerve.* Obstet Gynecol, 2006. **108**(3 Pt 1): p. 529-34.

512. Wallner, C., et al., *The contribution of the levator ani nerve and the pudendal nerve to the innervation of the levator ani muscles; a study in human fetuses.* Eur Urol, 2008. **54**(5): p. 1136-42.

513. Matzel, K.E., R.A. Schmidt, and E.A. Tanagho, *Neuroanatomy of the striated muscular anal continence mechanism. Implications for the use of neurostimulation.* Dis Colon Rectum, 1990. **33**(8): p. 666-73.

514. Lawson, J.O., *Pelvic anatomy. II. Anal canal and associated sphincters.* Ann R Coll Surg Engl, 1974. **54**(6): p. 288-300.

515. Oh, C. and A.E. Kark, *Anatomy of the external anal sphincter.* Br J Surg, 1972. **59**(9): p. 717-23.

516. Shafik, A., *A new concept of the anatomy of the anal sphincter mechanism and the physiology of defecation. The external anal sphincter: a triple-loop system.* Invest Urol, 1975. **12**(5): p. 412-9.

517. Gunterberg, B., et al., *Anorectal function after major resections of the sacrum with bilateral or unilateral sacrifice of sacral nerves.* Br J Surg, 1976. **63**(7): p. 546-54.

518. Percy, J.P. and A.G. Parks, *The nerve supply of the pelvic floor.* Schweiz Rundsch Med Prax, 1981. **70**(15): p. 640-2.

519. Roberts WH, H.C., Mitchell, Jr. DA, Fischer HF, *The Levator Ani Muscle and the Nerve Supply of Its Puborectalis Component.* Clinical Anatomy, 1988. **1**: p. 267-273.

520. Frenckner, B. and C.V. Euler, *Influence of pudendal block on the function of the anal sphincters.* Gut, 1975. **16**(6): p. 482-9.

521. Brookes, S.J., P.G. Dinning, and M.A. Gladman, *Neuroanatomy and physiology of colorectal function and defaecation: from basic science to human clinical studies.* Neurogastroenterol Motil, 2009. **21 Suppl 2**: p. 9-19.

522. Lynn, P.A., et al., *Rectal intraganglionic laminar endings are transduction sites of extrinsic mechanoreceptors in the guinea pig rectum.* Gastroenterology, 2003. **125**(3): p. 786-94.

523. Zagorodnyuk, V.P., et al., *Mechanisms of mechanotransduction by specialized low-threshold mechanoreceptors in the guinea pig rectum.* Am J Physiol Gastrointest Liver Physiol, 2005. **289**(3): p. G397-406.

524. Goligher, J.C. and E.S. Hughes, *Sensibility of the rectum and colon. Its role in the mechanism of anal continence.* Lancet, 1951. **1**(6654): p. 543-7.

525. Ness, T.J. and G.F. Gebhart, *Visceral pain: a review of experimental studies.* Pain, 1990. **41**(2): p. 167-234.

526. Rogers, J., *Testing for and the role of anal and rectal sensation.* Baillieres Clin Gastroenterol, 1992. **6**(1): p. 179-91.

527. Sengupta, J.N. and G.F. Gebhart, *Characterization of mechanosensitive pelvic nerve afferent fibers innervating the colon of the rat.* J Neurophysiol, 1994. **71**(6): p. 2046-60.

528. Bharucha, A.E., et al., *Viscoelastic properties of the human colon.* Am J Physiol Gastrointest Liver Physiol, 2001. **281**(2): p. G459-66.

529. Read, M.G. and N.W. Read, *Role of anorectal sensation in preserving continence.* Gut, 1982. **23**(4): p. 345-7.

530. Sun, W.M., N.W. Read, and T.C. Donnelly, *Anorectal function in incontinent patients with cerebrospinal disease.* Gastroenterology, 1990. **99**(5): p. 1372-9.

531. Rao, S.S., K.D. Welcher, and J. Happel, *Can biofeedback therapy improve anorectal function in fecal incontinence?* Am J Gastroenterol, 1996. **91**(11): p. 2360-6.

532. Wald, A. and A.K. Tunuguntla, *Anorectal sensorimotor dysfunction in fecal incontinence and diabetes mellitus. Modification with biofeedback therapy.* N Engl J Med, 1984. **310**(20): p. 1282-7.

533. Duthie, H.L. and F.W. Gairns, *Sensory nerve-endings and sensation in the anal region of man.* Br J Surg, 1960. **47**: p. 585-95.

534. Goligher, J.C., *The functional results after sphincter-saving resections of the rectum.* Ann R Coll Surg Engl, 1951. **8**(6): p. 421-38.

535. Chan, C.L., et al., *Contribution of the pudendal nerve to sensation of the distal rectum.* Br J Surg, 2005. **92**(7): p. 859-65.

536. Miller, R., et al., *Anorectal temperature sensation: a comparison of normal and incontinent patients.* Br J Surg, 1987. **74**(6): p. 511-5.

537. Miller, R., et al., *Sensory discrimination and dynamic activity in the anorectum: evidence using a new ambulatory technique.* Br J Surg, 1988. **75**(10): p. 1003-7.

538. Rogers, J., et al., *Temperature gradient between the rectum and the anal canal: evidence against the role of temperature sensation as a sensory modality in the anal canal of normal subjects.* Br J Surg, 1988. **75**(11): p. 1083-5.

539. Salvioli, B., et al., *Rectal compliance, capacity, and rectoanal sensation in fecal incontinence.* Am J Gastroenterol, 2001. **96**(7): p. 2158-68.

540. Mayer, E.A., et al., *Brain imaging approaches to the study of functional GI disorders: a Rome working team report.* Neurogastroenterol Motil, 2009. **21**(6): p. 579-96.

541. Mayer, E.A., B.D. Naliboff, and A.D. Craig, *Neuroimaging of the brain-gut axis: from basic understanding to treatment of functional GI disorders.* Gastroenterology, 2006. **131**(6): p. 1925-42.

542. Moisset, X., et al., *Anatomical connections between brain areas activated during rectal distension in healthy volunteers: a visceral pain network.* Eur J Pain, 2010. **14**(2): p. 142-8.

543. Tillisch, K., E.A. Mayer, and J.S. Labus, *Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome.* Gastroenterology, 2011. **140**(1): p. 91-100.

544. Hobday, D.I., et al., *A study of the cortical processing of ano-rectal sensation using functional MRI.* Brain, 2001. **124**(Pt 2): p. 361-8.

545. Turnbull, G.K., et al., *The cortical topography of human anorectal musculature.* Gastroenterology, 1999. **117**(1): p. 32-9.

546. Martelli, H., et al., *Some parameters of large bowel motility in normal man.* Gastroenterology, 1978. **75**(4): p. 612-8.

547. Bajwa, A. and A. Emmanuel, *The physiology of continence and evacuation.* Best Pract Res Clin Gastroenterol, 2009. **23**(4): p. 477-85.

548. Duthie, H.L. and R.C. Bennett, *The relation of sensation in the anal canal to the functional anal sphincter: a possible factor in anal continence.* Gut, 1963. **4**(2): p. 179-82.

549. Miller, R., et al., *Anorectal sampling: a comparison of normal and incontinent patients.* Br J Surg, 1988. **75**(1): p. 44-7.

550. Amarenco, G., et al., *Cough anal reflex: strict relationship between intravesical pressure and pelvic floor muscle electromyographic activity during cough. Urodynamic and electrophysiological study.* J Urol, 2005. **173**(1): p. 149-52.

551. Chan, C.L., S. Ponsford, and M. Swash, *The anal reflex elicited by cough and sniff: validation of a neglected clinical sign.* J Neurol Neurosurg Psychiatry, 2004. **75**(10): p. 1449-51.

552. Deffieux, X., et al., *External anal sphincter contraction during cough: not a simple spinal reflex.* Neurourol Urodyn, 2006. **25**(7): p. 782-7.

553. Duthie, H.L. and J.M. Watts, *Contribution of the External Anal Sphincter to the Pressure Zone in the Anal Canal.* Gut, 1965. **6**: p. 64-8.

554. Dubrovsky, B., *Effects of rectal distension on the sphincter ani externus and levator ani muscles in cats.* Am J Physiol, 1988. **254**(1 Pt 1): p. G100-6.

555. Frenckner, B., *Function of the anal sphincters in spinal man.* Gut, 1975. **16**(8): p. 638-44.

556. F.C., G., *The response to stimluation of the caudal end of the large bowel in the cat. .* J. Physiol, 1933. **78**(2): p. 208-24.

557. Gaston, E.A., *The physiology of fecal continence.* Surg Gynecol Obstet, 1948. **87**(3): p. 280-90.

558. Kumar, D., et al., *Prolonged anorectal manometry and external anal sphincter electromyography in ambulant human subjects.* Dig Dis Sci, 1990. **35**(5): p. 641-8.

559. Smith, T.K., J.B. Reed, and K.M. Sanders, *Origin and propagation of electrical slow waves in circular muscle of canine proximal colon.* Am J Physiol, 1987. **252**(2 Pt 1): p. C215-24.

560. Thomson, W.H., *The nature of haemorrhoids.* Br J Surg, 1975. **62**(7): p. 542-52.

561. Thomson, H., *The anal cushions--a fresh concept in diagnosis.* Postgrad Med J, 1979. **55**(644): p. 403-5.

562. Thekkinkattil, D.K., et al., *Measurement of anal cushions in continent women.* Colorectal Dis, 2011. **13**(9): p. 1040-3.

563. AlAmeel, T., M.K. Andrew, and C. MacKnight, *The association of fecal incontinence with institutionalization and mortality in older adults.* Am J Gastroenterol, 2010. **105**(8): p. 1830-4.

564. Aslan, E., et al., *The prevalence of and the related factors for urinary and fecal incontinence among older residing in nursing homes.* J Clin Nurs, 2009. **18**(23): p. 3290-8.

565. Burge, E., A. Berchtold, and A. von Gunten, *Gender-related ADL performance of old people recently admitted to a Swiss nursing home. A cross-sectional study.* Swiss Med Wkly, 2011. **141**: p. w13183.

566. Jung, S.A., et al., *Closure mechanism of the anal canal in women: assessed by three-dimensional ultrasound imaging.* Dis Colon Rectum, 2008. **51**(6): p. 932-9.

567. Enck, P., et al., *Spontaneous variation of anal "resting" pressure in healthy humans.* Am J Physiol, 1991. **261**(5 Pt 1): p. G823-6.

568. Thekkinkattil, D.K., et al., *Contribution of posture to anorectal manometric measurements: are the measurements in left-lateral position physiologic?* Dis Colon Rectum, 2007. **50**(12): p. 2112-9.

569. Bouchoucha, M., et al., *Anal sphincter response to distension.* Int J Colorectal Dis, 2001. **16**(2): p. 119-25.

570. Gibbons, C.P., et al., *An analysis of anal sphincter pressure and anal compliance in normal subjects.* Int J Colorectal Dis, 1986. **1**(4): p. 231-7.

571. Gibbons, C.P., et al., *Role of anal cushions in maintaining continence.* Lancet, 1986. **1**(8486): p. 886-8.

572. Lestar, B., et al., *The internal anal sphincter can not close the anal canal completely.* Int J Colorectal Dis, 1992. **7**(3): p. 159-61.

573. Lestar, B., F. Penninckx, and R. Kerremans, *The composition of anal basal pressure. An in vivo and in vitro study in man.* Int J Colorectal Dis, 1989. **4**(2): p. 118-22.

574. Bannister, J.J., C. Gibbons, and N.W. Read, *Preservation of faecal continence during rises in intra-abdominal pressure: is there a role for the flap valve?* Gut, 1987. **28**(10): p. 1242-5.

575. Bartolo, D.C., et al., *Flap-valve theory of anorectal continence.* Br J Surg, 1986. **73**(12): p. 1012-4.

576. Kerremans, R.P., *A new method of objective examination in proctology.* Gut, 1968. **9**(2): p. 243-5.

577. Padda, B.S., et al., *Effects of pelvic floor muscle contraction on anal canal pressure.* Am J Physiol Gastrointest Liver Physiol, 2007. **292**(2): p. G565-71.

578. Parks, A.G., N.H. Porter, and J. Hardcastle, *The syndrome of the descending perineum.* Proc R Soc Med, 1966. **59**(6): p. 477-82.

579. Hajivassiliou, C.A., K.B. Carter, and I.G. Finlay, *Anorectal angle enhances faecal continence.* Br J Surg, 1996. **83**(1): p. 53-6.

580. Engel, A.F., M.A. Kamm, and I.C. Talbot, *Progressive systemic sclerosis of the internal anal sphincter leading to passive faecal incontinence.* Gut, 1994. **35**(6): p. 857-9.

581. Thoua, N.M., et al., *Internal anal sphincter atrophy in patients with systemic sclerosis.* Rheumatology (Oxford), 2011. **50**(9): p. 1596-602.

582. Thoua, N.M., et al., *Fecal Incontinence in Systemic Sclerosis Is Secondary to Neuropathy.* Am J Gastroenterol, 2011.

583. Burgell, R.E., et al., *Fecal incontinence in men: coexistent constipation and impact of rectal hyposensitivity.* Dis Colon Rectum, 2012. **55**(1): p. 18-25.

584. Gladman, M.A., et al., *Rectal hyposensitivity: prevalence and clinical impact in patients with intractable constipation and fecal incontinence.* Dis Colon Rectum, 2003. **46**(2): p. 238-46.

585. Hoffmann, B.A., et al., *Fecal seepage and soiling: a problem of rectal sensation.* Dis Colon Rectum, 1995. **38**(7): p. 746-8.

586. Rao, S.S., R. Ozturk, and M. Stessman, *Investigation of the pathophysiology of fecal seepage.* Am J Gastroenterol, 2004. **99**(11): p. 2204-9.

587. Siproudhis, L., et al., *Fecal incontinence with normal anal canal pressures: where is the pitfall?* Am J Gastroenterol, 1999. **94**(6): p. 1556-63.

588. Qureshi, M.S., et al., *Male faecal incontinence presents as two separate entities with implications for management.* Int J Colorectal Dis, 2011. **26**(12): p. 1589-94.

589. Sentovich, S.M., et al., *Patterns of male fecal incontinence.* Dis Colon Rectum, 1995. **38**(3): p. 281-5.

590. Dietz, H.P., M. Erdmann, and K.L. Shek, *Reflex contraction of the levator ani in women symptomatic for pelvic floor disorders.* Ultrasound Obstet Gynecol, 2012.

591. Fernandez-Fraga, X., F. Azpiroz, and J.R. Malagelada, *Significance of pelvic floor muscles in anal incontinence.* Gastroenterology, 2002. **123**(5): p. 1441-50.

592. Lewicky-Gaupp, C., et al., *Fecal incontinence in older women: are levator ani defects a factor?* Am J Obstet Gynecol, 2010. **202**(5): p. 491 e1-6.

593. Steensma, A.B., et al., *Prevalence of major levator abnormalities in symptomatic patients with an underactive pelvic floor contraction.* Int Urogynecol J, 2010. **21**(7): p. 861-7.

594. Chantarasorn, V., K.L. Shek, and H.P. Dietz, *Sonographic detection of puborectalis muscle avulsion is not associated with anal incontinence.* Aust N Z J Obstet Gynaecol, 2011. **51**(2): p. 130-5.

595. Andrews, C., et al., *Rectal sensorimotor dysfunction in women with fecal incontinence.* Am J Physiol Gastrointest Liver Physiol, 2007. **292**(1): p. G282-9.

596. Chan, C.L., et al., *Rectal sensorimotor dysfunction in patients with urge faecal incontinence: evidence from prolonged manometric studies.* Gut, 2005. **54**(9): p. 1263-72.

597. Chan, C.L., et al., *Rectal hypersensitivity worsens stool frequency, urgency, and lifestyle in patients with urge fecal incontinence.* Dis Colon Rectum, 2005. **48**(1): p. 134-40.

598. Lewicky-Gaupp, C., et al., *Anal sphincter structure and function relationships in aging and fecal incontinence.* Am J Obstet Gynecol, 2009. **200**(5): p. 559 e1-5.

599. Siproudhis, L., et al., *Low rectal volumes in patients suffering from fecal incontinence: what does it mean?* Aliment Pharmacol Ther, 2005. **22**(10): p. 989-96.

600. Bharucha, A.E., et al., *Bowel disturbances are the most important risk factors for late onset fecal incontinence: a population-based case-control study in women.* Gastroenterology, 2010. **139**(5): p. 1559-66.

601. Boreham, M.K., et al., *Anal incontinence in women presenting for gynecologic care: prevalence, risk factors, and impact upon quality of life.* Am J Obstet Gynecol, 2005. **192**(5): p. 1637-42.

602. Kalantar, J.S., S. Howell, and N.J. Talley, *Prevalence of faecal incontinence and associated risk factors; an underdiagnosed problem in the Australian community?* Med J Aust, 2002. **176**(2): p. 54-7.

603. Melville, J.L., et al., *Fecal incontinence in US women: a population-based study.* Am J Obstet Gynecol, 2005. **193**(6): p. 2071-6.

604. Pretlove, S.J., et al., *Prevalence of anal incontinence according to age and gender: a systematic review and*

meta-regression analysis. Int Urogynecol J Pelvic Floor Dysfunct, 2006. **17**(4): p. 407-17.

605. Quander, C.R., et al., *Prevalence of and factors associated with fecal incontinence in a large community study of older individuals.* Am J Gastroenterol, 2005. **100**(4): p. 905-9.

606. Whitehead, W.E., et al., *Fecal incontinence in US adults: epidemiology and risk factors.* Gastroenterology, 2009. **137**(2): p. 512-7, 517 e1-2.

607. Bharucha, A.E., et al., *Prevalence and burden of fecal incontinence: a population-based study in women.* Gastroenterology, 2005. **129**(1): p. 42-9.

608. Rey, E., et al., *Onset and risk factors for fecal incontinence in a US community.* Am J Gastroenterol, 2010. **105**(2): p. 412-9.

609. Bannister, J.J., L. Abouzekry, and N.W. Read, *Effect of aging on anorectal function.* Gut, 1987. **28**(3): p. 353-7.

610. Fox, J.C., et al., *Effect of aging on anorectal and pelvic floor functions in females.* Dis Colon Rectum, 2006. **49**(11): p. 1726-35.

611. Ryhammer, A.M., S. Laurberg, and F.H. Sorensen, *Effects of age on anal function in normal women.* Int J Colorectal Dis, 1997. **12**(4): p. 225-9.

612. Gundling, F., et al., *Influence of gender and age on anorectal function: normal values from anorectal manometry in a large caucasian population.* Digestion, 2010. **81**(4): p. 207-13.

613. Barrett, J.A., et al., *Anal function in geriatric patients with faecal incontinence.* Gut, 1989. **30**(9): p. 1244-51.

614. Laurberg, S. and M. Swash, *Effects of aging on the anorectal sphincters and their innervation.* Dis Colon Rectum, 1989. **32**(9): p. 737-42.

615. Beets-Tan, R.G., et al., *Measurement of anal sphincter muscles: endoanal US, endoanal MR imaging, or phased-array MR imaging? A study with healthy volunteers.* Radiology, 2001. **220**(1): p. 81-9.

616. Burnett, S.J. and C.I. Bartram, *Endosonographic variations in the normal internal anal sphincter.* Int J Colorectal Dis, 1991. **6**(1): p. 2-4.

617. Frudinger, A., et al., *Female anal sphincter: age-related differences in asymptomatic volunteers with high-frequency endoanal US.* Radiology, 2002. **224**(2): p. 417-23.

618. Huebner, M., et al., *Age effects on internal anal sphincter thickness and diameter in nulliparous females.* Dis Colon Rectum, 2007. **50**(9): p. 1405-11.

619. Bitar, K.N., *Aging and Gi smooth muscle fecal incontinence: Is bioengineering an option.* Exp Gerontol, 2005. **40**(8-9): p. 643-9.

620. Akervall, S., et al., *The effects of age, gender, and parity on rectoanal functions in adults.* Scand J Gastroenterol, 1990. **25**(12): p. 1247-56.

621. McHugh, S.M. and N.E. Diamant, *Effect of age, gender, and parity on anal canal pressures. Contribution of impaired anal sphincter function to fecal incontinence.* Dig Dis Sci, 1987. **32**(7): p. 726-36.

622. Jameson, J.S., et al., *Effect of age, sex and parity on anorectal function.* Br J Surg, 1994. **81**(11): p. 1689-92.

623. Rao, S.S., et al., *Manometric tests of anorectal function in healthy adults.* Am J Gastroenterol, 1999. **94**(3): p. 773-83.

624. Bilali, S. and J. Pfeifer, *Anorectal manometry: are fatigue rate and fatigue rate index of any clinical importance?* Tech Coloproctol, 2005. **9**(3): p. 225-8.

625. Nockolds, C.L., G.L. Hosker, and E.S. Kiff, *Fatigue rate of the external anal sphincter.* Colorectal Dis, 2011.

626. Chan, K.M., et al., *Age-related changes in muscle fatigue resistance in humans.* Can J Neurol Sci, 2000. **27**(3): p. 220-8.

627. Nielsen, M.B., et al., *Endosonography of the anal sphincter: findings in healthy volunteers.* AJR Am J Roentgenol, 1991. **157**(6): p. 1199-202.

628. Rociu, E., et al., *Normal anal sphincter anatomy and age- and sex-related variations at high-spatial-resolution endoanal MR imaging.* Radiology, 2000. **217**(2): p. 395-401.

629. Cazemier, M., et al., *Atrophy and defects detection of the external anal sphincter: comparison between three-dimensional anal endosonography and endoanal magnetic resonance imaging.* Dis Colon Rectum, 2006. **49**(1): p. 20-7.

630. Briel, J.W., et al., *Relationship between sphincter morphology on endoanal MRI and histopathological aspects of the external anal sphincter.* Int J Colorectal Dis, 2000. **15**(2): p. 87-90.

631. Healy, C.F., et al., *Experimental models of neuropathic fecal incontinence: an animal model of childbirth injury to the pudendal nerve and external anal sphincter.* Dis Colon Rectum, 2008. **51**(11): p. 1619-26; discussion 1626.

632. Salcedo, L., et al., *Long-term effects on pressure and electromyography in a rat model of anal sphincter injury.* Dis Colon Rectum, 2010. **53**(8): p. 1209-17.

633. Voyvodic, F., et al., *Delayed pudendal nerve conduction and endosonographic appearance of the anal sphincter complex.* Dis Colon Rectum, 2000. **43**(12): p. 1689-94.

634. Tomlinson, B.E., J.N. Walton, and J.J. Rebeiz, *The effects of ageing and of cachexia upon skeletal muscle. A histopathological study.* J Neurol Sci, 1969. **9**(2): p. 321-46.

635. Percy, J.P., et al., *A neurogenic factor in faecal incontinence in the elderly.* Age Ageing, 1982. **11**(3): p. 175-9.

636. Goode, P.S., et al., *Prevalence and correlates of fecal incontinence in community-dwelling older adults.* J Am Geriatr Soc, 2005. **53**(4): p. 629-35.

637. Perry, S., et al., *Prevalence of faecal incontinence in adults aged 40 years or more living in the community.* Gut, 2002. **50**(4): p. 480-4.

638. Christoforidis, D., et al., *Faecal incontinence in men.* Colorectal Dis, 2011. **13**(8): p. 906-13.

639. Shamliyan, T.A., et al., *Prevalence and risk factors of fecal incontinence in community-dwelling men.* Rev Gastroenterol Disord, 2009. **9**(4): p. E97-110.

640. Varma, M.G., et al., *Fecal incontinence in females older than aged 40 years: who is at risk?* Dis Colon Rectum, 2006. **49**(6): p. 841-51.

641. Nelson, R.L., *Epidemiology of fecal incontinence.* Gastroenterology, 2004. **126**(1 Suppl 1): p. S3-7.

642. Bytzer, P., et al., *Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults.* Arch Intern Med, 2001. **161**(16): p. 1989-96.

643. Joh, H.K., M.K. Seong, and S.W. Oh, *Fecal incontinence in elderly Koreans.* J Am Geriatr Soc, 2010. **58**(1): p. 116-21.

644. Abid, S., et al., *Poor glycaemic control is the major factor associated with increased frequency of gastrointestinal symptoms in patients with diabetes mellitus.* J Pak Med Assoc, 2007. **57**(7): p. 345-9.

645. Oh, J.H., et al., *The prevalence of gastrointestinal symptoms in patients with non-insulin dependent diabetes mellitus.* Korean J Intern Med, 2009. **24**(4): p. 309-17.

646. Talley, N.J., et al., *Predictors of turnover of lower gastrointestinal symptoms in diabetes mellitus.* Am J Gastroenterol, 2002. **97**(12): p. 3087-94.

647. Bytzer, P., et al., *Oral hypoglycaemic drugs and gastrointestinal symptoms in diabetes mellitus.* Aliment Pharmacol Ther, 2001. **15**(1): p. 137-42.

648. Gerstel, C., M. Zarate Lagunes, and U.M. Vischer, *Fecal incontinence resolved using metformin withdrawal.* J Am Geriatr Soc, 2011. **59**(4): p. 756-7.

649. Enck, P., et al., *Prevalence of gastrointestinal symptoms in diabetic patients and non-diabetic subjects.* Z Gastroenterol, 1994. **32**(11): p. 637-41.

650. Janatuinen, E., et al., *Gastrointestinal symptoms in middle-aged diabetic patients.* Scand J Gastroenterol, 1993. **28**(5): p. 427-32.

651. Russo, A., et al., *Effects of acute hyperglycaemia on anorectal motor and sensory function in diabetes mellitus.* Diabet Med, 2004. **21**(2): p. 176-82.

652. Caruana, B.J., et al., *Anorectal sensory and motor function in neurogenic fecal incontinence. Comparison between multiple sclerosis and diabetes mellitus.* Gastroenterology, 1991. **100**(2): p. 465-70.

653. Epanomeritakis, E., et al., *Impairment of anorectal function in diabetes mellitus parallels duration of disease.* Dis Colon Rectum, 1999. **42**(11): p. 1394-400.

654. Schiller, L.R., et al., *Pathogenesis of fecal incontinence in diabetes mellitus: evidence for internal-anal-sphincter dysfunction.* N Engl J Med, 1982. **307**(27): p. 1666-71.

655. Clouse, R.E. and P.J. Lustman, *Gastrointestinal symptoms in diabetic patients: lack of association with neuropathy.* Am J Gastroenterol, 1989. **84**(8): p. 868-72.

656. Dunivan, G.C., et al., *Fecal incontinence in primary care: prevalence, diagnosis, and health care utilization.* Am J Obstet Gynecol, 2010. **202**(5): p. 493 e1-6.

657. Markland, A.D., et al., *Correlates of urinary, fecal, and dual incontinence in older African-American and white men and women.* J Am Geriatr Soc, 2008. **56**(2): p. 285-90.

658. Dunberger, G., et al., *Loose stools lead to fecal incontinence among gynecological cancer survivors.* Acta Oncol, 2011. **50**(2): p. 233-42.

659. Bharucha, A.E., et al., *Functional anorectal disorders.* Gastroenterology, 2006. **130**(5): p. 1510-8.

660. Rodger, C.J., et al., *Abnormal colonic motility: a possible association with urge fecal incontinence.* Dis Colon Rectum, 2010. **53**(4): p. 409-13.

661. Kinnunen, O., et al., *Diarrhea and fecal impaction in elderly long-stay patients.* Z Gerontol, 1989. **22**(6): p. 321-3.

662. Madoff, R.D., et al., *Faecal incontinence in adults.* Lancet, 2004. **364**(9434): p. 621-32.

663. Read, N.W. and L. Abouzekry, *Why do patients with faecal impaction have faecal incontinence.* Gut, 1986. **27**(3): p. 283-7.

664. Drossman, D.A., et al., *Urgency and fecal soiling in people with bowel dysfunction.* Dig Dis Sci, 1986. **31**(11): p. 1221-5.

665. O'Keefe, E.A., et al., *Bowel disorders impair functional status and quality of life in the elderly: a population-based study.* J Gerontol A Biol Sci Med Sci, 1995. **50**(4): p. M184-9.

666. Talley, N.J., et al., *Epidemiology of colonic symptoms and the irritable bowel syndrome.* Gastroenterology, 1991. **101**(4): p. 927-34.

667. Kanazawa, M., M. Hongo, and S. Fukudo, *Visceral hypersensitivity in irritable bowel syndrome.* J Gastroenterol Hepatol, 2011. **26 Suppl 3**: p. 119-21.

668. Brocklehurst, J., E. Dickinson, and J. Windsor, *Laxatives and faecal incontinence in long-term care.* Elder Care, 1998. **10**(4): p. 22-5.

669. Hellstrom, L., et al., *The influence of dementia on the prevalence of urinary and faecal incontinence in 85-year-old men and women.* Arch Gerontol Geriatr, 1994. **19**(1): p. 11-20.

670. Johanson, J.F., F. Irizarry, and A. Doughty, *Risk factors for fecal incontinence in a nursing home population.* J Clin Gastroenterol, 1997. **24**(3): p. 156-60.

671. Quander, C.R., et al., *Association of fecal incontinence with physical disability and impaired cognitive function.* Am J Gastroenterol, 2006. **101**(11): p. 2588-93.

672. Nakanishi, N., et al., *Urinary and fecal incontinence in a community-residing older population in Japan.* J Am Geriatr Soc, 1997. **45**(2): p. 215-9.

673. de Winter CF, J.A., Evenhuis HM, *Physical conditions and challenging behaviour in people with intellectual disability: a systematic review.* J Intellect Disabil Res., 2011. **55**(7): p. 6750698.

674. Markland, A.D., et al., *Incidence and risk factors for fecal incontinence in black and white older adults: a population-based study.* J Am Geriatr Soc, 2010. **58**(7): p. 1341-6.

675. Bailey, N. and D. Pares, *Faecal incontinence and depression: cause or effect?* Colorectal Dis, 2010. **12**(5): p. 397-8.

676. Saka, B., et al., *Malnutrition in the elderly and its relationship with other geriatric syndromes.* Clin Nutr, 2010. **29**(6): p. 745-8.

677. Glickman, S. and M.A. Kamm, *Bowel dysfunction in spinal-cord-injury patients.* Lancet, 1996. **347**(9016): p. 1651-3.

678. Krogh, K., et al., *Colorectal function in patients with spinal cord lesions.* Dis Colon Rectum, 1997. **40**(10): p. 1233-9.

679. Preziosi, G. and A. Emmanuel, *Neurogenic bowel dysfunction: pathophysiology, clinical manifestations and treatment.* Expert Rev Gastroenterol Hepatol, 2009. **3**(4): p. 417-23.

680. Brittain, K.R., S.M. Peet, and C.M. Castleden, *Stroke and incontinence.* Stroke, 1998. **29**(2): p. 524-8.

681. Harari, D., et al., *New-onset fecal incontinence after stroke: prevalence, natural history, risk factors, and impact.* Stroke, 2003. **34**(1): p. 144-50.

682. Kovindha, A., et al., *Prevalence of incontinence in patients after stroke during rehabilitation: a multi-centre study.* J Rehabil Med, 2009. **41**(6): p. 489-91.

683. Nakayama, H., et al., *Prevalence and risk factors of incontinence after stroke. The Copenhagen Stroke Study.* Stroke, 1997. **28**(1): p. 58-62.

684. Chen, C.C., et al., *Obesity is associated with increased prevalence and severity of pelvic floor disorders in women considering bariatric surgery.* Surg Obes Relat Dis, 2009. **5**(4): p. 411-5.

685. Cuicchi, D., et al., *Clinical and instrumental evaluation of pelvic floor disorders before and after bariatric surgery in obese women.* Surg Obes Relat Dis, 2011.

686. Fysekidis, M., et al., *Prevalence and Co-occurrence of Upper and Lower Functional Gastrointestinal Symptoms in Patients Eligible for Bariatric Surgery.* Obes Surg, 2011.

687. Markland, A.D., et al., *Fecal incontinence in obese women with urinary incontinence: prevalence and role of dietary fiber intake.* Am J Obstet Gynecol, 2009. **200**(5): p. 566 e1-6.

688. Richter, H.E., et al., *Urinary and anal incontinence in morbidly obese women considering weight loss surgery.* Obstet Gynecol, 2005. **106**(6): p. 1272-7.

689. Sileri, P., et al., *Prevalence of defaecatory disorders in morbidly obese patients before and after bariatric surgery.* J Gastrointest Surg, 2012. **16**(1): p. 62-7.

690. Uustal Fornell, E., G. Wingren, and P. Kjolhede, *Factors associated with pelvic floor dysfunction with emphasis on urinary and fecal incontinence and genital prolapse: an epidemiological study.* Acta Obstet Gynecol Scand, 2004. **83**(4): p. 383-9.

691. Wasserberg, N., et al., *Morbid obesity adversely impacts pelvic floor function in females seeking attention for weight loss surgery.* Dis Colon Rectum, 2007. **50**(12): p. 2096-103.

692. Altman, D., et al., *The risk of anal incontinence in obese women.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(11): p. 1283-9.

693. Erekson, E.A., V.W. Sung, and D.L. Myers, *Effect of body mass index on the risk of anal incontinence and defecatory dysfunction in women.* Am J Obstet Gynecol, 2008. **198**(5): p. 596 e1-4.

694. Foster, A., et al., *Gastrointestinal symptomatic outcome after laparoscopic Roux-en-Y gastric bypass.* J Gastrointest Surg, 2003. **7**(6): p. 750-3.

695. Potoczna, N., et al., *Bowel habits after bariatric surgery.* Obes Surg, 2008. **18**(10): p. 1287-96.

696. Poylin, V., et al., *Obesity and bariatric surgery: a*

systematic review of associations with defecatory dysfunction. Colorectal Dis, 2011. **13**(6): p. e92-103.

697. Lambert, D.M., S. Marceau, and R.A. Forse, *Intra-abdominal pressure in the morbidly obese.* Obes Surg, 2005. **15**(9): p. 1225-32.

698. Noblett, K.L., J.K. Jensen, and D.R. Ostergard, *The relationship of body mass index to intra-abdominal pressure as measured by multichannel cystometry.* Int Urogynecol J Pelvic Floor Dysfunct, 1997. **8**(6): p. 323-6.

699. Badalian, S.S. and P.F. Rosenbaum, *Vitamin D and pelvic floor disorders in women: results from the National Health and Nutrition Examination Survey.* Obstet Gynecol, 2010. **115**(4): p. 795-803.

700. Vaughan, C.P., et al., *Vitamin D and lower urinary tract symptoms among US men: results from the 2005-2006 National Health and Nutrition Examination Survey.* Urology, 2011. **78**(6): p. 1292-7.

701. Alkhatib, A.A. and A.K. Tuteja, *High prevalence of vitamin D deficiency among patients with fecal incontinence.* Dig Dis Sci, 2010. **55**(12): p. 3632-3.

702. Lanske, B. and M.S. Razzaque, *Vitamin D and aging: old concepts and new insights.* J Nutr Biochem, 2007. **18**(12): p. 771-7.

703. Perry, H.M., 3rd, et al., *Longitudinal changes in serum 25-hydroxyvitamin D in older people.* Metabolism, 1999. **48**(8): p. 1028-32.

704. Engel, A.F., et al., *Anterior anal sphincter repair in patients with obstetric trauma.* Br J Surg, 1994. **81**(8): p. 1231-4.

705. Karoui, S., et al., *Results of sphincteroplasty in 86 patients with anal incontinence.* Dis Colon Rectum, 2000. **43**(6): p. 813-20.

706. Sitzler, P.J. and J.P. Thomson, *Overlap repair of damaged anal sphincter. A single surgeon's series.* Dis Colon Rectum, 1996. **39**(12): p. 1356-60.

707. Thomas, C., I. Etienney, and P. Atienza, *Evaluation of the role of the puborectal part of the levator ani muscle in anal incontinence: a prospective study of 78 female patients with anal incontinence.* Dis Colon Rectum, 2011. **54**(9): p. 1129-33.

708. Borrie, M.J. and H.A. Davidson, *Incontinence in institutions: costs and contributing factors.* CMAJ, 1992. **147**(3): p. 322-8.

709. Nelson, R.L. and S.E. Furner, *Risk factors for the development of fecal and urinary incontinence in Wisconsin nursing home residents.* Maturitas, 2005. **52**(1): p. 26-31.

710. Hazewinkel, M.H., et al., *Long-term cervical cancer survivors suffer from pelvic floor symptoms: a cross-sectional matched cohort study.* Gynecol Oncol, 2010. **117**(2): p. 281-6.

711. Putta, S. and H.J. Andreyev, *Faecal incontinence: A late side-effect of pelvic radiotherapy.* Clin Oncol (R Coll Radiol), 2005. **17**(6): p. 469-77.

712. Maeda, Y., et al., *Faecal incontinence following radiotherapy for prostate cancer: a systematic review.* Radiother Oncol, 2011. **98**(2): p. 145-53.

713. Scheer, A.S., et al., *The long-term gastrointestinal functional outcomes following curative anterior resection in adults with rectal cancer: a systematic review and meta-analysis.* Dis Colon Rectum, 2011. **54**(12): p. 1589-97.

714. Bosset, J.F., et al., *Chemotherapy with preoperative radiotherapy in rectal cancer.* N Engl J Med, 2006. **355**(11): p. 1114-23.

715. Pollack, J., et al., *Long-term effect of preoperative radiation therapy on anorectal function.* Dis Colon Rectum, 2006. **49**(3): p. 345-52.

716. Peeters, K.C., et al., *Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study.* J Clin Oncol, 2005. **23**(25): p. 6199-206.

717. Dahlberg, M., et al., *Preoperative irradiation affects functional results after surgery for rectal cancer: results from a randomized study.* Dis Colon Rectum, 1998. **41**(5): p. 543-9; discussion 549-51.

718. Bujko, K., et al., *Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer.* Br J Surg, 2006. **93**(10): p. 1215-23.

719. Protocol, S. *The Stockholm III Trial on Different Preoperative Radiotherapy Regimens in Rectal Cancer*. [cited 2012 February 4]; Preoperative radiotherapy (RT) is recommended to many patients with localised rectal cancer, not previously treated with pelvic RT. However, the optimum fractionation, the timing of surgery and the best use of concomitant chemotherapy remains controversial. Short-course, preoperative RT may induce both acute and late morbidity and has been claimed to cause more morbidity than long-course preoperative RT. There are theoretical reasons to believe that RT given in larger fractions during a shorter period of time might result in more late side effects than giving a conventional, more protracted RT. In addition, the optimum timing of surgery after RT, with respect to postoperative morbidity, mortality and potential downsizing of the tumour is not known.]. Available from: http://clinicaltrials.gov/ct2/show/NCT00904813?term=radiation+therapy+and+rectal+cancer&cond=rectal+cancer&intr=radiation+therapy&cntry1=EU%3ASE&rank=1.

720. Siegel, R., et al., *Preoperative short-course radiotherapy versus combined radiochemotherapy in locally advanced rectal cancer: a multi-centre prospectively randomised study of the Berlin Cancer Society.* BMC Cancer, 2009. **9**: p. 50.

721. Smeenk, R.J., et al., *Dose-Effect Relationships for Individual Pelvic Floor Muscles and Anorectal Complaints After Prostate Radiotherapy.* Int J Radiat Oncol Biol Phys, 2011.

722. Varma, J.S., A.N. Smith, and A. Busuttil, *Correlation of clinical and manometric abnormalities of rectal function following chronic radiation injury.* Br J Surg, 1985. **72**(11): p. 875-8.

723. Da Silva, G.M., et al., *Histologic analysis of the irradiated anal sphincter.* Dis Colon Rectum, 2003. **46**(11): p. 1492-7.

724. Petersen, S., et al., *Radiation-induced sequelae affecting the continence organ: incidence, pathogenesis, and treatment.* Dis Colon Rectum, 2007. **50**(9): p. 1466-74.

725. Johannsson, H.O., L. Pahlman, and W. Graf, *Randomized clinical trial of the effects on anal function of Milligan-Morgan versus Ferguson haemorrhoidectomy.* Br J Surg, 2006. **93**(10): p. 1208-14.

726. Murie, J.A., A.J. Sim, and I. Mackenzie, *The importance of pain, pruritus and soiling as symptoms of haemorrhoids and their response to haemorrhoidectomy or rubber band ligation.* Br J Surg, 1981. **68**(4): p. 247-9.

727. Rasmussen, O.O., *Anorectal function.* Dis Colon Rectum, 1994. **37**(4): p. 386-403.

728. Read, M.G., et al., *A prospective study of the effect of haemorrhoidectomy on sphincter function and faecal continence.* Br J Surg, 1982. **69**(7): p. 396-8.

729. Broden, G., A. Dolk, and B. Holmstrom, *Recovery of the internal anal sphincter following rectopexy: a possible explanation for continence improvement.* Int J Colorectal Dis, 1988. **3**(1): p. 23-8.

730. Farouk, R. and G.S. Duthie, *Rectal prolapse and rectal invagination.* Eur J Surg, 1998. **164**(5): p. 323-32.

731. Kairaluoma, M.V. and I.H. Kellokumpu, *Epidemiologic aspects of complete rectal prolapse.* Scand J Surg, 2005. **94**(3): p. 207-10.

732. Williams, J.G., et al., *Incontinence and rectal prolapse: a prospective manometric study.* Dis Colon Rectum, 1991. **34**(3): p. 209-16.

733. Harmston, C., et al., *The relationship between internal rectal prolapse and internal anal sphincter function.* Colorectal Dis, 2011. **13**(7): p. 791-5.

734. Neill, M.E., A.G. Parks, and M. Swash, *Physiological studies of the anal sphincter musculature in faecal incontinence and rectal prolapse.* Br J Surg, 1981. **68**(8): p. 531-6.

735. Roig, J.V., et al., *Anorectal function in patients with complete rectal prolapse. Differences between continent and incontinent individuals.* Rev Esp Enferm Dig, 1998. **90**(11): p. 794-805.

736. Siproudhis, L., et al., *Overt rectal prolapse and fecal incontinence.* Dis Colon Rectum, 2008. **51**(9): p. 1356-60.

737. Woods, R., et al., *Anal sphincter tears in patients with rectal prolapse and faecal incontinence.* Colorectal Dis, 2003. **5**(6): p. 544-8.

738. Felt-Bersma, R.J. and M.A. Cuesta, *Rectal prolapse, rectal intussusception, rectocele, and solitary rectal ulcer syndrome.* Gastroenterol Clin North Am, 2001. **30**(1): p. 199-222.

739. Ihre, T. and U. Seligson, *Intussusception of the rectum-internal procidentia: treatment and results in 90 patients.* Dis Colon Rectum, 1975. **18**(5): p. 391-6.

740. Collinson, R., et al., *Laparoscopic ventral rectopexy for internal rectal prolapse: short-term functional results.* Colorectal Dis, 2010. **12**(2): p. 97-104.

741. Lazorthes, F., et al., *Is rectal intussusception a cause of idiopathic incontinence?* Dis Colon Rectum, 1998. **41**(5): p. 602-5.

742. Portier, G., et al., *The effect of abdominal ventral rectopexy on faecal incontinence and constipation in patients with internal intra-anal rectal intussusception.* Colorectal Dis, 2011. **13**(8): p. 914-7.

743. Arroyo, A., et al., *Surgical versus chemical (botulinum toxin) sphincterotomy for chronic anal fissure: long-term results of a prospective randomized clinical and manometric study.* Am J Surg, 2005. **189**(4): p. 429-34.

744. Garcia-Aguilar, J., et al., *Open vs. closed sphincterotomy for chronic anal fissure: long-term results.* Dis Colon Rectum, 1996. **39**(4): p. 440-3.

745. Khubchandani, I.T. and J.F. Reed, *Sequelae of internal sphincterotomy for chronic fissure in ano.* Br J Surg, 1989. **76**(5): p. 431-4.

746. Kiyak, G., et al., *Results of lateral internal sphincterotomy with open technique for chronic anal fissure: evaluation of complications, symptom relief, and incontinence with long-term follow-up.* Dig Dis Sci, 2009. **54**(10): p. 2220-4.

747. Nyam, D.C. and J.H. Pemberton, *Long-term results of lateral internal sphincterotomy for chronic anal fissure with particular reference to incidence of fecal incontinence.* Dis Colon Rectum, 1999. **42**(10): p. 1306-10.

748. Sileri, P., et al., *Conservative and surgical treatment of chronic anal fissure: prospective longer term results.* J Gastrointest Surg, 2010. **14**(5): p. 773-80.

749. Kement, M., et al., *Mild and severe anal incontinence after lateral internal sphincterotomy: risk factors, postoperative anatomical findings and quality of life.* Eur Surg Res, 2011. **47**(1): p. 26-31.

750. Sultan, A.H., et al., *Prospective study of the extent of internal anal sphincter division during lateral sphincterotomy.* Dis Colon Rectum, 1994. **37**(10): p. 1031-3.

751. Zbar, A.P., et al., *Fecal incontinence after minor anorectal surgery.* Dis Colon Rectum, 2001. **44**(11): p. 1610-9; discussion 1619-23.

752. Levin, A., et al., *Delayed fecal incontinence following surgery for anal fissure.* Int J Colorectal Dis, 2011. **26**(12): p. 1595-9.

753. Ganchrow, M.I., et al., *Hemorrhoidectomy revisited--a computer analysis of 2,038 cases.* Dis Colon Rectum, 1971. **14**(2): p. 128-33.

754. Lindsey, I., et al., *Patterns of fecal incontinence after anal surgery.* Dis Colon Rectum, 2004. **47**(10): p. 1643-9.

755. Liu, B., Y. Zhang, and X.D. Zeng, *[Factors associated with incontinence following anorectal procedures].* Zhonghua Wei Chang Wai Ke Za Zhi, 2011. **14**(6): p. 452-4.

756. McConnell, J.C. and I.T. Khubchandani, *Long-term follow-up of closed hemorrhoidectomy.* Dis Colon Rectum, 1983. **26**(12): p. 797-9.

757. Abbasakoor, F., et al., *Anal endosonography in patients with anorectal symptoms after haemorrhoidectomy.* Br J Surg, 1998. **85**(11): p. 1522-4.

758. Abbas, M.A., C.H. Jackson, and P.I. Haigh, *Predictors of outcome for anal fistula surgery.* Arch Surg, 2011. **146**(9): p. 1011-6.

759. Athanasiadis, S., A. Kohler, and M. Nafe, *Treatment of high anal fistulae by primary occlusion of the internal ostium, drainage of the intersphincteric space, and mucosal advancement flap.* Int J Colorectal Dis, 1994. **9**(3): p. 153-7.

760. Garcia-Aguilar, J., et al., *Anal fistula surgery. Factors associated with recurrence and incontinence.* Dis Colon Rectum, 1996. **39**(7): p. 723-9.

761. Jacob, T.J., B. Perakath, and M.R. Keighley, *Surgical intervention for anorectal fistula.* Cochrane Database Syst Rev, 2010(5): p. CD006319.

762. Joy, H.A. and J.G. Williams, *The outcome of surgery for complex anal fistula.* Colorectal Dis, 2002. **4**(4): p. 254-261.

763. Miller, G.V. and P.J. Finan, *Flap advancement and core fistulectomy for complex rectal fistula.* Br J Surg, 1998. **85**(1): p. 108-10.

764. Ortiz, H. and J. Marzo, *Endorectal flap advancement repair and fistulectomy for high trans-sphincteric and suprasphincteric fistulas.* Br J Surg, 2000. **87**(12): p. 1680-3.

765. Ritchie, R.D., J.M. Sackier, and J.P. Hodde, *Incontinence rates after cutting seton treatment for anal fistula.* Colorectal Dis, 2009. **11**(6): p. 564-71.

766. Sangwan, Y.P., et al., *Is simple fistula-in-ano simple?* Dis Colon Rectum, 1994. **37**(9): p. 885-9.

767. Schouten, W.R., D.D. Zimmerman, and J.W. Briel, *Transanal advancement flap repair of transsphincteric fistulas.* Dis Colon Rectum, 1999. **42**(11): p. 1419-22; discussion 1422-3.

768. Sileri, P., et al., *Surgery for fistula-in-ano in a specialist colorectal unit: a critical appraisal.* BMC Gastroenterol, 2011. **11**: p. 120.

769. Vasilevsky, C.A. and P.H. Gordon, *Results of treatment of fistula-in-ano.* Dis Colon Rectum, 1985. **28**(4): p. 225-31.

770. Westerterp, M., et al., *Anal fistulotomy between Skylla and Charybdis.* Colorectal Dis, 2003. **5**(6): p. 549-51.

771. Denost, Q., et al., *Risk factors for fecal incontinence after intersphincteric resection for rectal cancer.* Dis Colon Rectum, 2011. **54**(8): p. 963-8.

772. Brown, C.J., D.S. Fenech, and R.S. McLeod, *Reconstructive techniques after rectal resection for rectal cancer.* Cochrane Database Syst Rev, 2008(2): p. CD006040.

773. Farouk, R., et al., *Endosonographic evidence of injury to the internal anal sphincter after low anterior resection: long-term follow-up.* Dis Colon Rectum, 1998. **41**(7): p. 888-91.

774. Ho, Y.H., et al., *Anal sphincter injuries from stapling instruments introduced transanally: randomized, controlled study with endoanal ultrasound and anorectal manometry.* Dis Colon Rectum, 2000. **43**(2): p. 169-73.

775. Matsuoka, H., et al., *Neurophysiologic investigation of anal function following double stapling anastomosis.* Dig Surg, 2010. **27**(4): p. 320-3.

776. Batignani, G., et al., *What affects continence after anterior resection of the rectum?* Dis Colon Rectum, 1991. **34**(4): p. 329-35.

777. Matzel, K.E., B. Bittorf, and U. Stadelmaier, *Anorectal function after low anterior resection.* Acta Chir Iugosl, 2004. **51**(2): p. 95-7.

778. Devroede, G. and J. Lamarche, *Functional importance of extrinsic parasympathetic innervation to the distal colon and rectum in man.* Gastroenterology, 1974. **66**(2): p. 273-80.

779. Wallner, C., et al., *Causes of fecal and urinary incontinence after total mesorectal excision for rectal cancer based on cadaveric surgery: a study from the Cooperative Clinical Investigators of the Dutch total mesorectal excision trial.* J Clin Oncol, 2008. **26**(27): p. 4466-72.

780. Markland, A.D., et al., *Factors impacting quality of life in women with fecal incontinence.* Dis Colon Rectum, 2010. **53**(8): p. 1148-54.

781. Baron, J.A., C. La Vecchia, and F. Levi, *The antiestrogenic effect of cigarette smoking in women.* Am J Obstet Gynecol, 1990. **162**(2): p. 502-14.

782. Coulie, B., et al., *Colonic motility in chronic ulcerative proctosigmoiditis and the effects of nicotine on colonic motility in patients and healthy subjects.* Aliment Pharmacol Ther, 2001. **15**(5): p. 653-63.

783. Manning, J., et al., *Is there an association between fecal incontinence and lower urinary dysfunction?* Dis Colon Rectum, 2001. **44**(6): p. 790-8.

784. Roberts, R.O., et al., *Prevalence of combined fecal and urinary incontinence: a community-based study.* J Am Geriatr Soc, 1999. **47**(7): p. 837-41.

785. Glazener, C.M., et al., *Postnatal maternal morbidity: extent, causes, prevention and treatment.* Br J Obstet Gynaecol, 1995. **102**(4): p. 282-7.

786. MacArthur, C., et al., *Obstetric practice and faecal incontinence three months after delivery.* BJOG, 2001. **108**(7): p. 678-83.

787. Eason, E., et al., *Anal incontinence after childbirth.* CMAJ, 2002. **166**(3): p. 326-30.

788. Beersiek, F., A.G. Parks, and M. Swash, *Pathogenesis of ano-rectal incontinence. A histometric study of the anal sphincter musculature.* J Neurol Sci, 1979. **42**(1): p. 111-27.

789. Neill, M.E. and M. Swash, *Increased motor unit fibre density in the external anal sphincter muscle in ano-rectal incontinence: a single fibre EMG study.* J Neurol Neurosurg Psychiatry, 1980. **43**(4): p. 343-7.

790. Kiff, E.S. and M. Swash, *Slowed conduction in the pudendal nerves in idiopathic (neurogenic) faecal incontinence.* Br J Surg, 1984. **71**(8): p. 614-6.

791. Small, K.A. and J.M. Wynne, *Evaluating the pelvic floor in obstetric patients.* Aust N Z J Obstet Gynaecol, 1990. **30**(1): p. 41-4, 45.

792. Cornes, H., D.C. Bartolo, and G.M. Stirrat, *Changes in anal canal sensation after childbirth.* Br J Surg, 1991. **78**(1): p. 74-7.

793. Chaliha, C., et al., *Anal function: effect of pregnancy and delivery.* Am J Obstet Gynecol, 2001. **185**(2): p. 427-32.

794. Law, P.J., M.A. Kamm, and C.I. Bartram, *Anal endosonography in the investigation of faecal incontinence.* Br J Surg, 1991. **78**(3): p. 312-4.

795. Sultan, A.H., et al., *Anal endosonography for identifying external sphincter defects confirmed histologically.* Br J Surg, 1994. **81**(3): p. 463-5.

796. Donnelly, V., et al., *Obstetric events leading to anal sphincter damage.* Obstet Gynecol, 1998. **92**(6): p. 955-61.

797. Fynes, M., et al., *Cesarean delivery and anal sphincter injury.* Obstet Gynecol, 1998. **92**(4 Pt 1): p. 496-500.

798. Abramowitz, L., et al., *Are sphincter defects the cause of anal incontinence after vaginal delivery? Results of a prospective study.* Dis Colon Rectum, 2000. **43**(5): p. 590-6; discussion 596-8.

799. de Leeuw, J.W., et al., *Risk factors for third degree perineal ruptures during delivery.* BJOG, 2001. **108**(4): p. 383-7.

800. Fynes, M., et al., *Effect of second vaginal delivery on anorectal physiology and faecal continence: a prospective study.* Lancet, 1999. **354**(9183): p. 983-6.

801. Buchhave, P., et al., *Risk factors for rupture of the anal sphincter.* Eur J Obstet Gynecol Reprod Biol, 1999. **87**(2): p. 129-32.

802. Willis, S., et al., *Childbirth and incontinence: a prospective study on anal sphincter morphology and function before and early after vaginal delivery.* Langenbecks Arch Surg, 2002. **387**(2): p. 101-7.

803. Nazir, M., E. Carlsen, and B.I. Nesheim, *Do occult anal sphincter injuries, vector volume manometry and delivery variables have any predictive value for bowel symptoms after first time vaginal delivery without third and fourth degree rupture? A prospective study.* Acta Obstet Gynecol Scand, 2002. **81**(8): p. 720-6.

804. Belmonte-Montes, C., et al., *Anal sphincter injury after vaginal delivery in primiparous females.* Dis Colon Rectum, 2001. **44**(9): p. 1244-8.

805. Varma, A., et al., *Obstetric anal sphincter injury: prospective evaluation of incidence.* Dis Colon Rectum, 1999. **42**(12): p. 1537-43.

806. Damon, H., et al., *Postdelivery anal function in primiparous females: ultrasound and manometric study.* Dis Colon Rectum, 2000. **43**(4): p. 472-7.

807. Faltin, D.L., et al., *Diagnosis of anal sphincter tears by postpartum endosonography to predict fecal incontinence.* Obstet Gynecol, 2000. **95**(5): p. 643-7.

808. Williams, A.B., et al., *Anal sphincter damage after vaginal delivery using three-dimensional endosonography.* Obstet Gynecol, 2001. **97**(5 Pt 1): p. 770-5.

809. Sudol-Szopinnska, I., et al., *Postpartum endoanal ultrasound findings in primiparous women after vaginal delivery.* Acta Radiol, 2010. **51**(7): p. 819-24.

810. Oberwalder, M., J. Connor, and S.D. Wexner, *Meta-analysis to determine the incidence of obstetric anal sphincter damage.* Br J Surg, 2003. **90**(11): p. 1333-7.

811. Andrews, V., et al., *Occult anal sphincter injuries--myth or reality?* BJOG, 2006. **113**(2): p. 195-200.

812. Sultan AH, K.C., *Sultan AH, Thakar R, Fenner D. Perineal and anal sphincter trauma*, ed. Springer. 2007, London.

813. Sultan AH, T.R., *Sultan AH, Thakar R, Fenner D. Perineal and anal sphincter trauma*. Third and Fourth degree tears., ed. Springer. 2007, London.

814. Groom KM, P.-B.S., *Third degree tears: are they clinically underdiagnosed?* Gastroenterology International, 2000. **13**(2): p. 76-7.

815. Sultan AH, K.M., Hudson CN, *Obstetric perineal tears: an audit of training.* . Journal of Obstetrics and Gynaecology, 1995. **15**: p. 19-23.

816. Sultan, A.H. and R. Thakar, *Lower genital tract and anal sphincter trauma.* Best Pract Res Clin Obstet Gynaecol, 2002. **16**(1): p. 99-115.

817. Sultan, *Obstetric perineal injury and anal incontinence.* Clinical Risk 1999. **5**(5): p. 193-6.

818. Gynaecologists, R.C.o.O.a., *Management of Third and Fourth Degree Perineal Tears Following Vaginal Delivery*. Vol. RCOG Guideline 2001, London RCOG Press.

819. Sultan, A.H., et al., *Third degree obstetric anal sphincter tears: risk factors and outcome of primary repair.* BMJ, 1994. **308**(6933): p. 887-91.

820. Fitzpatrick, M., et al., *A randomized clinical trial comparing primary overlap with approximation repair of third-degree obstetric tears.* Am J Obstet Gynecol, 2000. **183**(5): p. 1220-4.

821. Zetterstrom, J., et al., *Anal sphincter tears at vaginal delivery: risk factors and clinical outcome of primary repair.* Obstet Gynecol, 1999. **94**(1): p. 21-8.

822. Gjessing, H., B. Backe, and Y. Sahlin, *Third degree obstetric tears; outcome after primary repair.* Acta Obstet Gynecol Scand, 1998. **77**(7): p. 736-40.

823. Poen, A.C., et al., *Third-degree obstetric perineal tear: long-term clinical and functional results after primary repair.* Br J Surg, 1998. **85**(10): p. 1433-8.

824. Goffeng, A.R., et al., *Objective methods cannot predict anal incontinence after primary repair of extensive anal tears.* Acta Obstet Gynecol Scand, 1998. **77**(4): p. 439-43.

825. Kammerer-Doak, D.N., et al., *A prospective cohort study of women after primary repair of obstetric anal sphincter laceration.* Am J Obstet Gynecol, 1999. **181**(6): p. 1317-22; discussion 1322-3.

826. Sorensen, M., et al., *Sphincter rupture in childbirth.* Br J Surg, 1993. **80**(3): p. 392-4.

827. Sakse, A., et al., *Defects on endoanal ultrasound and anal incontinence after primary repair of fourth-degree anal sphincter rupture: a study of the anal sphincter complex and puborectal muscle.* Ultrasound Obstet Gynecol, 2009. **34**(6): p. 693-8.

828. Malouf, A.J., et al., *Long-term results of overlapping anterior anal-sphincter repair for obstetric trauma.* Lancet, 2000. **355**(9200): p. 260-5.

829. Sultan, A.H., et al., *Primary repair of obstetric anal sphincter rupture using the overlap technique.* Br J Obstet Gynaecol, 1999. **106**(4): p. 318-23.

830. Mahony, R., et al., *Internal anal sphincter defect influences continence outcome following obstetric anal sphincter injury.* Am J Obstet Gynecol, 2007. **196**(3): p. 217 e1-5.

831. Roos, A.M., R. Thakar, and A.H. Sultan, *Outcome of primary repair of obstetric anal sphincter injuries (OASIS): does the grade of tear matter?* Ultrasound Obstet Gynecol, 2010. **36**(3): p. 368-74.

832. Vaccaro, C. and J.L. Clemons, *Anal sphincter defects and anal incontinence symptoms after repair of obstetric anal sphincter lacerations in primiparous women.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(11): p. 1503-8.

833. Garcia, V., et al., *Primary repair of obstetric anal sphincter laceration: a randomized trial of two surgical techniques.* Am J Obstet Gynecol, 2005. **192**(5): p. 1697-701.

834. Williams, A., et al., *How to repair an anal sphincter injury after vaginal delivery: results of a randomised controlled trial.* BJOG, 2006. **113**(2): p. 201-7.

835. Fernando, R.J., et al., *Repair techniques for obstetric anal sphincter injuries: a randomized controlled trial.* Obstet Gynecol, 2006. **107**(6): p. 1261-8.

836. Fernando, R., et al., *Methods of repair for obstetric anal sphincter injury.* Cochrane Database Syst Rev, 2006. **3**: p. CD002866.

837. Farrell, S.A., et al., *Overlapping compared with end-to-end repair of third- and fourth-degree obstetric anal sphincter tears: a randomized controlled trial.* Obstet Gynecol, 2010. **116**(1): p. 16-24.

838. Sultan, A. and R. Fernando, *Overlapping compared with end-to-end repair of third- and fourth-degree obstetric anal sphincter tears: a randomized controlled trial.* Obstet Gynecol, 2011. **117**(2 Pt 1): p. 408; author reply 408-9.

839. Farell S, G.D., Turnbull G, Schmidt M, Baskett T, Flowerdew G, Fanning C, *Randomized trial of overlapping versus end-to-end repair of third or fourth degree EAS tears: three year follow –up of anal incontinence symptoms.* Neurol Urodynam, 2011. **2011**(30): p. 285.

840. Rygh, A.B. and H. Korner, *The overlap technique versus end-to-end approximation technique for primary repair of obstetric anal sphincter rupture: a randomized controlled study.* Acta Obstet Gynecol Scand, 2010. **89**(10): p. 1256-62.

841. Sultan AH, A.M., *The yearbook of obstetrics and gynaecology- Anal incontinence – the role of the obstetrician and gynaecologist*, ed. O.K. Sturdee D, Keane D (eds). 2001, LONDON: RCOG press.

842. Sultan, A.H. and S.L. Stanton, *Preserving the pelvic floor and perineum during childbirth--elective caesarean section?* Br J Obstet Gynaecol, 1996. **103**(8): p. 731-4.

843. Tetzschner, T., et al., *Anal and urinary incontinence in women with obstetric anal sphincter rupture.* Br J Obstet Gynaecol, 1996. **103**(10): p. 1034-40.

844. Sultan, A.H. and A.K. Monga, *Anal and urinary incontinence in women with obstetric anal sphincter rupture.* Br J Obstet Gynaecol, 1997. **104**(6): p. 754-5.

845. Roos, A.M., et al., *Predicting anal sphincter defects: the value of clinical examination and manometry.* Int Urogynecol J, 2011.

846. Scheer, I., R. Thakar, and A.H. Sultan, *Mode of delivery after previous obstetric anal sphincter injuries (OASIS)--a reappraisal?* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(9): p. 1095-101.

847. Johanson, R.B., et al., *A randomised prospective study comparing the new vacuum extractor policy with forceps delivery.* Br J Obstet Gynaecol, 1993. **100**(6): p. 524-30.

848. Bofill, J.A., et al., *A randomized prospective trial of the obstetric forceps versus the M-cup vacuum extractor.* Am J Obstet Gynecol, 1996. **175**(5): p. 1325-30.

849. O'Mahony, F., G.J. Hofmeyr, and V. Menon, *Choice of instruments for assisted vaginal delivery.* Cochrane Database Syst Rev, 2010(11): p. CD005455.

850. Johanson, R.B., et al., *Maternal and child health after assisted vaginal delivery: five-year follow up of a randomised controlled study comparing forceps and ventouse.* Br J Obstet Gynaecol, 1999. **106**(6): p. 544-9.

851. Sultan, A.H., R.B. Johanson, and J.E. Carter, *Occult anal sphincter trauma following randomized forceps and vacuum delivery.* Int J Gynaecol Obstet, 1998. **61**(2): p. 113-9.

852. Johanson RB, M.B., *Soft versus rigid vacuum extractor cups for assisted vaginal delivery; Vacuum extraction versus forceps for assisted vaginal delivery.The Cochrane Library*. 2001, Oxford: update software.

853. Farrell SA, A.V., Baskett TF, *Anal incontinence in primaparas.* J Soc Obstet Gynaecol Can, 2001. **23**(4): p. 321-6.

854. Thakar R, E.E., *Prevention of perineal trauma. In: Sultan AH, Thakar R, Fenner D. Perineal and anal sphincter trauma.*, ed. Springer. 2007, London. 52-64.

855. Woolley, R.J., *Benefits and risks of episiotomy: A review of the English language literature since 1980.* Obstet Gynecol Surv, 1980. **50**: p. 806-35.

856. Henriksen, T.B., et al., *Methods and consequences of changes in use of episiotomy.* BMJ, 1994. **309**(6964): p. 1255-8.

857. Henriksen, T.B., et al., *Episiotomy and perineal lesions in spontaneous vaginal deliveries.* Br J Obstet Gynaecol, 1992. **99**(12): p. 950-4.

858. Coats, P.M., et al., *A comparison between midline and mediolateral episiotomies.* Br J Obstet Gynaecol, 1980. **87**(5): p. 408-12.

859. Andrews, V., et al., *Are mediolateral episiotomies actually mediolateral?* BJOG, 2005. **112**(8): p. 1156-8.

860. Eogan, M., et al., *Does the angle of episiotomy affect the incidence of anal sphincter injury?* BJOG, 2006. **113**(2): p. 190-4.

861. Pirhonen, J.P., et al., *Frequency of anal sphincter rupture at delivery in Sweden and Finland--result of difference in manual help to the baby's head.* Acta Obstet Gynecol Scand, 1998. **77**(10): p. 974-7.

862. Jonsson, E.R., et al., *Modified Ritgen's maneuver for anal sphincter injury at delivery: a randomized controlled trial.* Obstet Gynecol, 2008. **112**(2 Pt 1): p. 212-7.

863. Handa, V.L., B.H. Danielsen, and W.M. Gilbert, *Obstetric anal sphincter lacerations.* Obstet Gynecol, 2001. **98**(2): p. 225-30.

864. Landy, H.J., et al., *Characteristics associated with severe perineal and cervical lacerations during vaginal delivery.* Obstet Gynecol, 2011. **117**(3): p. 627-35.

865. McLennan, M.T., et al., *Episiotomy and perineal repair. An*

evaluation of resident education and experience. J Reprod Med, 2002. **47**(12): p. 1025-30.

866. Stepp, K.J., et al., *Textbook recommendations for preventing and treating perineal injury at vaginal delivery.* Obstet Gynecol, 2006. **107**(2 Pt 1): p. 361-6.

867. Uppal, S., et al., *Resident competency in obstetric anal sphincter laceration repair.* Obstet Gynecol, 2010. **115**(2 Pt 1): p. 305-9.

868. Andrews, V., R. Thakar, and A.H. Sultan, *Structured hands-on training in repair of obstetric anal sphincter injuries (OASIS): an audit of clinical practice.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(2): p. 193-9.

869. Andrews, V., R. Thakar, and A.H. Sultan, *Outcome of obstetric anal sphincter injuries (OASIS)--role of structured management.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(8): p. 973-8.

870. Andrews V, T.R., Sultan AH, Kettle C, *Can hands-on perineal repair courses affect clinical practice.* Br J Midwifery, 2005. **13**(9): p. 562-5.

871. Hals, E., et al., *A multicenter interventional program to reduce the incidence of anal sphincter tears.* Obstet Gynecol, 2010. **116**(4): p. 901-8.

872. Donnelly, V.S., et al., *Postpartum fecal incontinence is more common in women with irritable bowel syndrome.* Dis Colon Rectum, 1998. **41**(5): p. 586-9.

873. Wein, A.J., *Classification of neurogenic voiding dysfunction.* J Urol, 1981. **125**(5): p. 605-9.

874. Blaivas, J.G., *Pathophysiology of lower urinary tract dysfunction.* Urol Clin North Am, 1985. **12**(2): p. 215-24.

875. Blaivas, J.G., et al., *Definition and classification of urinary incontinence: recommendations of the Urodynamic Society.* Neurourol Urodyn, 1997. **16**(3): p. 149-51.

876. Oelke, M., et al., *Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia.* Eur Urol, 2008. **54**(2): p. 419-26.

877. John, H., et al., *Ultrastructure of the trigone and its functional implications.* Urol Int, 2001. **67**(4): p. 264-71.

878. Sadananda, P., B. Vahabi, and M.J. Drake, *Bladder outlet physiology in the context of lower urinary tract dysfunction.* Neurourol Urodyn, 2011. **30**(5): p. 708-13.

879. Fritsch, H., et al., *What are the supportive structures of the female urethra?* Neurourol Urodyn, 2006. **25**(2): p. 128-34.

880. Karam, I., et al., *The structure and innervation of the male urethra: histological and immunohistochemical studies with three-dimensional reconstruction.* J Anat, 2005. **206**(4): p. 395-403.

881. Sebe, P., et al., *Fetal development of striated and smooth muscle sphincters of the male urethra from a common primordium and modifications due to the development of the prostate: an anatomic and histologic study.* Prostate, 2005. **62**(4): p. 388-93.

882. Hadley, H.R., P.E. Zimmermann, and S. Raz, *The treatment of male urinary incontinence*, in *Campbell's Urology*, M.F. Campbell and P.C. Walsh, Editors. 1986, Saunders: London. p. 2297-3039.

883. Gosling, J.A., et al., *A comparative study of the human external sphincter and periurethral levator ani muscles.* Br J Urol, 1981. **53**(1): p. 35-41.

884. Turner-Warwick, R.T., *The sphincter mechanisms: Their relation to prostatic enlargement and its treatment*, in *Benign prostatic hyperthrophy*, F. Hinman and S. Boyarsky, Editors. 1983, Springer: New York. p. 809.

885. Burnett, A.L. and J.L. Mostwin, *In situ anatomical study of the male urethral sphincteric complex: relevance to continence preservation following major pelvic surgery.* J Urol, 1998. **160**(4): p. 1301-6.

886. Steiner, M.S., *Anatomic basis for the continence-preserving radical retropubic prostatectomy.* Semin Urol Oncol, 2000. **18**(1): p. 9-18.

887. Krahn, H.P. and P.A. Morales, *The effect of pudendal nerve anesthesia on urinary continence after prostatectomy.* J Urol, 1965. **94**(3): p. 282-5.

888. Sievert, K.D., et al., *Can we prevent incontinence? ICI-RS 2011.* Neurourol Urodyn, 2012. **31**(3): p. 390-9.

889. Goldman, H.B., K.D. Sievert, and M.S. Damaser, *Will we ever use stem cells for the treatment of SUI? ICI-RS 2011.* Neurourol Urodyn, 2012. **31**(3): p. 386-9.

890. Amend, B., et al., *Prostatic peripheral nerve distribution may impact the functional outcome of nerve-sparing prostatectomy.* World J Urol, 2011.

891. Hollabaugh, R.S., Jr., et al., *Preservation of putative continence nerves during radical retropubic prostatectomy leads to more rapid return of urinary continence.* Urology, 1998. **51**(6): p. 960-7.

892. Gosling, J.A. and J.S. Dixon, *The structure and innervation of smooth muscle in the wall of the bladder neck and proximal urethra.* Br J Urol, 1975. **47**(5): p. 549-58.

893. Costello, A.J., M. Brooks, and O.J. Cole, *Anatomical studies of the neurovascular bundle and cavernosal nerves.* BJU Int, 2004. **94**(7): p. 1071-6.

894. Narayan, P., et al., *Neuroanatomy of the external urethral sphincter: implications for urinary continence preservation during radical prostate surgery.* J Urol, 1995. **153**(2): p. 337-41.

895. Tuygun, C., et al., *Significance of fibrosis around and/or at external urinary sphincter on pelvic magnetic resonance imaging in patients with postprostatectomy incontinence.* Urology, 2006. **68**(6): p. 1308-12.

896. El-Sakka, A.I., *Alleviation of post-radical prostatectomy cavernosal fibrosis: future directions and potential utility for PDE5 inhibitors.* Expert Opin Investig Drugs, 2011. **20**(10): p. 1305-9.

897. Sirad, F., et al., *Sildenafil promotes smooth muscle preservation and ameliorates fibrosis through modulation of extracellular matrix and tissue growth factor gene expression after bilateral cavernosal nerve resection in the rat.* J Sex Med, 2011. **8**(4): p. 1048-60.

898. Irwin, D.E., et al., *Overactive bladder is associated with erectile dysfunction and reduced sexual quality of life in men.* J Sex Med, 2008. **5**(12): p. 2904-10.

899. Abrams, P.H., *Investigation of postprostatectomy problems.* Urology, 1980. **15**(2): p. 209-12.

900. Abrams, P.H., et al., *The results of prostatectomy: a symptomatic and urodynamic analysis of 152 patients.* J Urol, 1979. **121**(5): p. 640-2.

901. Comiter, C.V., et al., *Urodynamic risk factors for renal dysfunction in men with obstructive and nonobstructive voiding dysfunction.* J Urol, 1997. **158**(1): p. 181-5.

902. Madersbacher, S., et al., *Interrelationships of bladder compliance with age, detrusor instability, and obstruction in elderly men with lower urinary tract symptoms.* Neurourol Urodyn, 1999. **18**(1): p. 3-15.

903. Smoger, S.H., T.L. Felice, and G.H. Kloecker, *Urinary incontinence among male veterans receiving care in primary care clinics.* Ann Intern Med, 2000. **132**(7): p. 547-51.

904. Van Kampen, M., et al., *Urinary incontinence following transurethral, transvesical and radical prostatectomy. Retrospective study of 489 patients.* Acta Urol Belg, 1997. **65**(4): p. 1-7.

905. Warwick, R.T., et al., *A urodynamic view of prostatic obstruction and the results of prostatectomy.* Br J Urol, 1973. **45**(6): p. 631-45.

906. Leng, W.W. and E.J. McGuire, *Obstructive uropathy induced bladder dysfunction can be reversible: bladder compliance measures before and after treatment.* J Urol, 2003. **169**(2): p. 563-6.

907. Speakman, M.J., et al., *Bladder outflow obstruction--a cause of denervation supersensitivity.* J Urol, 1987. **138**(6): p. 1461-6.

908. Brading, A.F., et al., *The role of smooth muscle and its possible involvement in diseases of the lower urinary tract.* Clin Sci (Lond), 1986. **70 Suppl 14**: p. 7s-13s.

909. Murakumo, M., et al., *Three-dimensional arrangement of collagen and elastin fibers in the human urinary bladder: a scanning electron microscopic study.* J Urol, 1995. **154**(1): p. 251-6.

910. Steers, W.D., et al., *Alterations in afferent pathways from the urinary bladder of the rat in response to partial urethral obstruction.* J Comp Neurol, 1991. **310**(3): p. 401-10.

911. Steers, W.D. and W.C. De Groat, *Effect of bladder outlet obstruction on micturition reflex pathways in the rat.* J Urol, 1988. **140**(4): p. 864-71.

912. Seki, N., O.M. Karim, and J.L. Mostwin, *The effect of experimental urethral obstruction and its reversal on changes in passive electrical properties of detrusor muscle.* J Urol, 1992. **148**(6): p. 1957-61.

913. Seaman, E.K., et al., *Persistence or recurrence of symptoms after transurethral resection of the prostate: a urodynamic assessment.* J Urol, 1994. **152**(3): p. 935-7.

914. Han, E., L.K. Black, and J.P. Lavelle, *Incontinence related to management of benign prostatic hypertrophy.* Am J Geriatr Pharmacother, 2007. **5**(4): p. 324-34.

915. Ou, R., et al., *A randomized trial of transvesical prostatectomy versus transurethral resection of the prostate for prostate greater than 80 mL.* Urology, 2010. **76**(4): p. 958-61.

916. Simforoosh, N., et al., *Open prostatectomy versus transurethral resection of the prostate, where are we standing in the new era? A randomized controlled trial.* Urol J, 2010. **7**(4): p. 262-9.

917. Mebust, W.K., et al., *Transurethral prostatectomy: immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients.* J Urol, 1989. **141**(2): p. 243-7.

918. Mebust, W., et al., *Scope of the problem. Indications for treatment and assessment of benign prostatic hyperplasia and its relationship to cancer.* Cancer, 1992. **70**(1 Suppl): p. 369-70.

919. Winters, J.C., R.A. Appell, and R.R. Rackley, *Urodynamic findings in postprostatectomy incontinence*. Neurourol Urodyn, 1998. **17**(5): p. 493-8.

920. Leach, G.E., et al., *Post-prostatectomy incontinence: urodynamic findings and treatment outcomes.* J Urol, 1996. **155**(4): p. 1256-9.

921. Goluboff, E.T., et al., *Urodynamics and the etiology of postprostatectomy urinary incontinence: the initial Columbia experience.* J Urol, 1995. **153**(3 Pt 2): p. 1034-7.

922. Yalla, S.V., L. Karah, and G. Kearney, *Post-prostatectomy incontinence: urodynamic assessment.* Neurourol Urodyn, 1982. **1**: p. 77-78.

923. Fitzpatrick, J.M., R.A. Gardiner, and P.H. Worth, *The evaluation of 68 patients with post-prostatectomy incontinence.* Br J Urol, 1979. **51**(6): p. 552-5.

924. Andersen, J.T. and J. Nordling, *Urinary-Incontinence after Transvesical Prostatectomy.* Urol Int, 1978. **33**(1-3): p. 191-198.

925. Nitti, V.W., Y. Kim, and A.J. Combs, *Voiding dysfunction following transurethral resection of the prostate: symptoms and urodynamic findings.* J Urol, 1997. **157**(2): p. 600-3.

926. Westenberg, A., et al., *Holmium laser resection of the prostate versus transurethral resection of the prostate: results of a randomized trial with 4-year minimum long-term followup.* J Urol, 2004. **172**(2): p. 616-9.

927. Kuntz, R.M., et al., *Transurethral holmium laser enucleation of the prostate versus transurethral electrocautery resection of the prostate: a randomized prospective trial in 200 patients.* J Urol, 2004. **172**(3): p. 1012-6.

928. Vavassori, I., et al., *Three-year outcome following holmium laser enucleation of the prostate combined with mechanical morcellation in 330 consecutive patients.* Eur Urol, 2008. **53**(3): p. 599-604.

929. Horasanli, K., et al., *Photoselective potassium titanyl phosphate (KTP) laser vaporization versus transurethral resection of the prostate for prostates larger than 70 mL: a short-term prospective randomized trial.* Urology, 2008. **71**(2): p. 247-51.

930. Montorsi, F., et al., *Holmium laser enucleation versus transurethral resection of the prostate: results from a 2-center, prospective, randomized trial in patients with obstructive benign prostatic hyperplasia.* J Urol, 2004. **172**(5 Pt 1): p. 1926-9.

931. Bouchier-Hayes, D.M., et al., *KTP laser versus transurethral resection: early results of a randomized trial.* J Endourol, 2006. **20**(8): p. 580-5.

932. Seki, N., K. Tatsugami, and S. Naito, *Holmium laser enucleation of the prostate: comparison of outcomes according to prostate size in 97 Japanese patients.* J Endourol, 2007. **21**(2): p. 192-6.

933. Sarica, K., et al., *Photoselective vaporization of the enlarged prostate with KTP laser: long-term results in 240 patients.* J Endourol, 2005. **19**(10): p. 1199-202.

934. Te, A.E., et al., *Photoselective vaporization of the prostate for the treatment of benign prostatic hyperplasia: 12-month results from the first United States multicenter prospective trial.* J Urol, 2004. **172**(4 Pt 1): p. 1404-8.

935. Biester, K., et al., *Systematic review of surgical treatments for benign prostatic hyperplasia and presentation of an approach to investigate therapeutic equivalence (non-inferiority).* BJU Int, 2011.

936. Bortolotti, A., et al., *Prevalence and risk factors for urinary incontinence in Italy.* Eur Urol, 2000. **37**(1): p. 30-5.

937. Landi, F., et al., *Potentially reversible risk factors and urinary incontinence in frail older people living in community.* Age Ageing, 2003. **32**(2): p. 194-9.

938. Nuotio, M., et al., *Urinary incontinence in a Finnish population aged 70 and over. Prevalence of types, associated factors and self-reported treatments.* Scand J Prim Health Care, 2003. **21**(3): p. 182-7.

939. Ueda, T., et al., *Urinary incontinence among community-dwelling people aged 40 years or older in Japan: prevalence, risk factors, knowledge and self-perception.* Int J Urol, 2000. **7**(3): p. 95-103.

940. Van Oyen, H. and P. Van Oyen, *Urinary incontinence in Belgium; prevalence, correlates and psychosocial consequences.* Acta Clin Belg, 2002. **57**(4): p. 207-18.

941. Liu, M., et al., *Urinary incontinence in prostate cancer patients treated with external beam radiotherapy.* Radiother Oncol, 2005. **74**(2): p. 197-201.

942. Roberts, R.O., et al., *Natural history of prostatism: high American Urological Association Symptom scores among community-dwelling men and women with urinary incontinence.* Urology, 1998. **51**(2): p. 213-9.

943. Sandhu, A.S., et al., *Long-term urinary toxicity after 3-dimensional conformal radiotherapy for prostate cancer in patients with prior history of transurethral resection.* Int J Radiat Oncol Biol Phys, 2000. **48**(3): p. 643-7.

944. Lu-Yao, G.L., et al., *An assessment of radical prostatectomy. Time trends, geographic variation, and outcomes. The Prostate Patient Outcomes Research Team.* JAMA, 1993. **269**(20): p. 2633-6.

945. Foote, J., S. Yun, and G.E. Leach, *Postprostatectomy incontinence. Pathophysiology, evaluation, and management.* Urol Clin North Am, 1991. **18**(2): p. 229-41.

946. Catalona, W.J., et al., *Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies.* J Urol, 1999. **162**(2): p. 433-8.

947. Eastham, J.A., et al., *Risk factors for urinary incontinence after radical prostatectomy.* J Urol, 1996. **156**(5): p. 1707-13.

948. Geary, E.S., et al., *Incontinence and vesical neck strictures following radical retropubic prostatectomy.* Urology, 1995. **45**(6): p. 1000-6.

949. Leandri, P., et al., *Radical retropubic prostatectomy: morbidity and quality of life. Experience with 620 consecutive cases.* J Urol, 1992. **147**(3 Pt 2): p. 883-7.

950. Steiner, M.S., R.A. Morton, and P.C. Walsh, *Impact of anatomical radical prostatectomy on urinary continence.* J Urol, 1991. **145**(3): p. 512-4; discussion 514-5.

951. Zincke, H., et al., *Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer.* J Urol, 1994. **152**(5 Pt 2): p. 1850-7.

952. Penson, D.F., et al., *5-year urinary and sexual outcomes after radical prostatectomy: results from the Prostate Cancer Outcomes Study.* J Urol, 2008. **179**(5 Suppl): p. S40-4.

953. Wei, J.T. and J.E. Montie, *Comparison of patients' and physicians' rating of urinary incontinence following radical prostatectomy.* Semin Urol Oncol, 2000. **18**(1): p. 76-80.

954. McCammon, K.A., et al., *Comparative quality-of-life analysis after radical prostatectomy or external beam radiation for localized prostate cancer.* Urology, 1999. **54**(3): p. 509-16.

955. McHorney, C.A., et al., *The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups.* Med Care, 1994. **32**(1): p. 40-66.

956. Donnellan, S.M., et al., *Prospective assessment of incontinence after radical retropubic prostatectomy: objective and subjective analysis.* Urology, 1997. **49**(2): p. 225-30.

957. Jonler, M., et al., *A prospective study of quantification of urinary incontinence and quality of life in patients undergoing radical retropubic prostatectomy.* Urology, 1996. **48**(3): p. 433-40.

958. Horstmann, M., et al., *Single-centre evaluation of the extraperitoneal and transperitoneal approach in robotic-assisted radical prostatectomy.* Scand J Urol Nephrol, 2011.

959. Zorn, K.C., et al., *Robotic-assisted laparoscopic prostatectomy: functional and pathologic outcomes with interfascial nerve preservation.* Eur Urol, 2007. **51**(3): p. 755-62; discussion 763.

960. Patel, V.R., R. Thaly, and K. Shah, *Robotic radical prostatectomy: outcomes of 500 cases.* BJU Int, 2007. **99**(5): p. 1109-12.

961. Borin, J.F., et al., *Impact of urethral stump length on continence and positive surgical margins in robot-assisted laparoscopic prostatectomy.* Urology, 2007. **70**(1): p. 173-7.

962. Menon, M., et al., *Vattikuti Institute prostatectomy: contemporary technique and analysis of results.* Eur Urol, 2007. **51**(3): p. 648-57; discussion 657-8.

963. Joseph, J.V., et al., *Robotic extraperitoneal radical prostatectomy: an alternative approach.* J Urol, 2006. **175**(3 Pt 1): p. 945-50; discussion 951.

964. Rodriguez, E., Jr., D.W. Skarecky, and T.E. Ahlering, *Post-robotic prostatectomy urinary continence: characterization of perfect continence versus occasional dribbling in pad-free men.* Urology, 2006. **67**(4): p. 785-8.

965. Rassweiler, J., et al., *Laparoscopic radical prostatectomy--the experience of the German Laparoscopic Working Group.* Eur Urol, 2006. **49**(1): p. 113-9.

966. Jacobsen, N.E., et al., *Open versus laparoscopic radical prostatectomy: a prospective comparison of postoperative urinary incontinence rates.* J Urol, 2007. **177**(2): p. 615-9.

967. Tewari, A.K., et al., *Anatomic restoration technique of continence mechanism and preservation of puboprostatic collar: a novel modification to achieve early urinary continence in men undergoing robotic prostatectomy.* Urology, 2007. **69**(4): p. 726-31.

968. Rocco, B., et al., *Posterior reconstruction of the rhabdosphincter allows a rapid recovery of continence after transperitoneal videolaparoscopic radical prostatectomy.* Eur Urol, 2007. **51**(4): p. 996-1003.

969. Tewari, A., et al., *Total reconstruction of the vesico-urethral junction.* BJU Int, 2008. **101**(7): p. 871-7.

970. Murphy, G.P., et al., *National patterns of prostate cancer treatment by radical prostatectomy: results of a survey by the American College of Surgeons Commission on Cancer.* J Urol, 1994. **152**(5 Pt 2): p. 1817-9.

971. Fowler, F.J., Jr., et al., *Patient-reported complications and follow-up treatment after radical prostatectomy. The National Medicare Experience: 1988-1990 (updated June 1993).* Urology, 1993. **42**(6): p. 622-9.

972. Peterson, A.C. and Y. Chen, *Patient reported incontinence after radical prostatectomy is more common than expected and not associated with the nerve sparing technique: Results from the center for prostate disease research (CPDR) database.* Neurourol Urodyn, 2011.

973. Lepor, H., L. Kaci, and X. Xue, *Continence following radical retropubic prostatectomy using self-reporting instruments.* J Urol, 2004. **171**(3): p. 1212-5.

974. Moore, K.N., et al., *Urinary incontinence after radical prostatectomy: can men at risk be identified preoperatively?* J Wound Ostomy Continence Nurs, 2007. **34**(3): p. 270-9; quiz 280-1.

975. Smither, A.R., et al., *Quantifying the natural history of post-radical prostatectomy incontinence using objective pad test data.* BMC Urol, 2007. **7**: p. 2.

976. Sacco, E., et al., *Urinary incontinence after radical prostatectomy: incidence by definition, risk factors and temporal trend in a large series with a long-term follow-up.* BJU Int, 2006. **97**(6): p. 1234-41.

977. Chao, R. and M.E. Mayo, *Incontinence after radical prostatectomy: detrusor or sphincter causes.* J Urol, 1995. **154**(1): p. 16-8.

978. Stanford, J.L., et al., *Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study.* JAMA, 2000. **283**(3): p. 354-60.

979. Horie, S., et al., *Urinary incontinence after non-nerve-sparing radical prostatectomy with neoadjuvant androgen deprivation.* Urology, 1999. **53**(3): p. 561-7.

980. Rogers, C.G., et al., *Age stratified functional outcomes after laparoscopic radical prostatectomy.* J Urol, 2006. **176**(6 Pt 1): p. 2448-52.

981. Loeb, S., et al., *Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer.* Urology, 2007. **69**(6): p. 1170-5.

982. Walsh, P., *Trends in Treatment of Localized Prostate-Cancer by Radical Prostatectomy - Observations from the Commission-on-Cancer National-Cancer-Database.* Urology, 1994. **43**(4): p. 492.

983. O'Donnell, P.D. and B.F. Finan, *Continence following nerve-sparing radical prostatectomy.* J Urol, 1989. **142**(5): p. 1227-8; discussion 1229.

984. Lowe, B.A., *Preservation of the anterior urethral ligamentous attachments in maintaining post-prostatectomy urinary continence: a comparative study.* J Urol, 1997. **158**(6): p. 2137-41.

985. Lowe, B.A., *Comparison of bladder neck preservation to bladder neck resection in maintaining postprostatectomy urinary continence.* Urology, 1996. **48**(6): p. 889-93.

986. Kaye, K.W., et al., *Urinary continence after radical retropubic prostatectomy. Analysis and synthesis of contributing factors: a unified concept.* Br J Urol, 1997. **80**(3): p. 444-501.

987. Nandipati, K.C., et al., *Nerve-sparing surgery significantly affects long-term continence after radical prostatectomy.* Urology, 2007. **70**(6): p. 1127-30.

988. Burkhard, F.C., et al., *Nerve sparing open radical retropubic prostatectomy--does it have an impact on urinary continence?* J Urol, 2006. **176**(1): p. 189-95.

989. Sievert, K.D., et al., *The periprostatic autonomic nerves--bundle or layer?* Eur Urol, 2008. **54**(5): p. 1109-16.

990. Schlomm, T., et al., *Full functional-length urethral sphincter preservation during radical prostatectomy.* Eur Urol, 2011. **60**(2): p. 320-9.

991. Tefilli, M.V., et al., *Salvage surgery or salvage radiotherapy for locally recurrent prostate cancer.* Urology, 1998. **52**(2): p. 224-9.

992. Stein, M., et al., *Biofeedback for the treatment of stress and urge incontinence.* J Urol, 1995. **153**(3 Pt 1): p. 641-3.

993. Sanderson, K.M., et al., *Salvage radical prostatectomy: quality of life outcomes and long-term oncological control of radiorecurrent prostate cancer.* J Urol, 2006. **176**(5): p. 2025-31; discussion 2031-2.

994. !!! INVALID CITATION !!!

995. Ficazzola, M.A. and V.W. Nitti, *The etiology of post-radical prostatectomy incontinence and correlation of symptoms with urodynamic findings.* J Urol, 1998. **160**(4): p. 1317-20.

996. Groutz, A., et al., *The pathophysiology of post-radical prostatectomy incontinence: a clinical and video urodynamic study.* J Urol, 2000. **163**(6): p. 1767-70.

997. Giannantoni, A., et al., *Bladder and urethral sphincter function after radical retropubic prostatectomy: a prospective long-term study.* Eur Urol, 2008. **54**(3): p. 657-64.

998. Perez, L.M. and G.D. Webster, *Successful outcome of artificial urinary sphincters in men with post-prostatectomy urinary incontinence despite adverse implantation features.* J Urol, 1992. **148**(4): p. 1166-70.

999. Thiel, D.D., et al., *Do clinical or urodynamic parameters predict artificial urinary sphincter outcome in post-radical prostatectomy incontinence?* Urology, 2007. **69**(2): p. 315-9.

1000. Bentzon, D.N., C. Graugaard-Jensen, and M. Borre, *Urethral pressure profile 6 months after radical prostatectomy may be diagnostic of sphincteric incontinence: preliminary data after 12 months' follow-up.* Scand J Urol Nephrol, 2009. **43**(2): p. 114-8.

1001. John, H., et al., *Evidence of trigonal denervation and reinnervation after radical retropubic prostatectomy.* J Urol, 2001. **165**(1): p. 111-3.

1002. Peinemann, F., et al., *Low-dose rate brachytherapy for men with localized prostate cancer.* Cochrane Database Syst Rev, 2011(7): p. CD008871.

1003. Marks, L.B., et al., *The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy.* Int J Radiat Oncol Biol Phys, 1995. **31**(5): p. 1257-80.

1004. Choo, R., et al., *Urodynamic changes at 18 months post-therapy in patients treated with external beam radiotherapy for prostate carcinoma.* Int J Radiat Oncol Biol Phys, 2002. **53**(2): p. 290-6.

1005. Blaivas, J.G., J.P. Weiss, and M. Jones, *The pathophysiology of lower urinary tract symptoms after brachytherapy for prostate cancer.* BJU Int, 2006. **98**(6): p. 1233-7; discussion 1237.

1006. Landis, D., *Anemia management of chronic renal insufficiency patients in a managed care setting.* Journal of the American Society of Nephrology, 2002. **13**: p. 639a.

1007. Merrick, G.S., et al., *Prophylactic versus therapeutic alpha-blockers after permanent prostate brachytherapy.* Urology, 2002. **60**(4): p. 650-5.

1008. Sacco, D.E., et al., *Corticosteroid use after prostate brachytherapy reduces the risk of acute urinary retention.* BJU Int, 2003. **91**(4): p. 345-9.

1009. Thomas, M.D., et al., *Identifying the predictors of acute urinary retention following magnetic-resonance-guided prostate brachytherapy.* Int J Radiat Oncol Biol Phys, 2000. **47**(4): p. 905-8.

1010. Benoit, R.M., M.J. Naslund, and J.K. Cohen, *Complications after prostate brachytherapy in the Medicare population.* Urology, 2000. **55**(1): p. 91-6.

1011. Flam, T.A., et al., *Post-brachytherapy transurethral resection of the prostate in patients with localized prostate cancer.* J Urol, 2004. **172**(1): p. 108-11.

1012. Kollmeier, M.A., et al., *Urinary morbidity and incontinence following transurethral resection of the prostate after brachytherapy.* J Urol, 2005. **173**(3): p. 808-12.

1013. Hu, K. and K. Wallner, *Urinary incontinence in patients who have a TURP/TUIP following prostate brachytherapy.* Int J Radiat Oncol Biol Phys, 1998. **40**(4): p. 783-6.

1014. Green, N., D. Treible, and H. Wallack, *Prostate cancer: post-irradiation incontinence.* J Urol, 1990. **144**(2 Pt 1): p. 307-9.

1015. Patel, H., et al., *Risk of incontinence with transurethral resection of the prostate after radiation therapy for prostate cancer.* J Surg Oncol, 1997. **64**(2): p. 127-9.

1016. Hirshberg, E.D. and L.H. Klotz, *Post transurethral resection of prostate incontinence in previously radiated prostate cancer patients.* Can J Urol, 1998. **5**(2): p. 560-563.

1017. Merrick, G.S., K.E. Wallner, and W.M. Butler, *Minimizing prostate brachytherapy-related morbidity.* Urology, 2003. **62**(5): p. 786-92.

1018. Budaus, L., et al., *Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature.* Eur Urol, 2012. **61**(1): p. 112-27.

1019. Baztan, J.J., et al., *New-onset urinary incontinence and rehabilitation outcomes in frail older patients.* Age Ageing, 2005. **34**(2): p. 172-5.

1020. Brandeis, G.H., et al., *The prevalence of potentially remediable urinary incontinence in frail older people: a study using the Minimum Data Set.* J Am Geriatr Soc, 1997. **45**(2): p. 179-84.

1021. Ouslander, J.G., et al., *Urinary incontinence in nursing homes: incidence, remission and associated factors.* J Am Geriatr Soc, 1993. **41**(10): p. 1083-9.

1022. Resnick, N.M., *Voiding dysfunction in the elderly*, in *Neurourology and Urodynamics. Principle and Practice.*, V. Yalla, et al., Editors. 1988, Macmillian Publishing Co.: New York. p. 303-330.

1023. DuBeau, C.E., et al., *Incontinence in the frail elderly: report from the 4th International Consultation on Incontinence.* Neurourol Urodyn, 2010. **29**(1): p. 165-78.

1024. Dowling-Castronovo, A. and J.K. Specht, *How to try this: Assessment of transient urinary incontinence in older adults.* Am J Nurs, 2009. **109**(2): p. 62-71; quiz 72.

1025. Anger, J.T., et al., *True prevalence of urinary incontinence among female nursing home residents.* Urology, 2006. **67**(2): p. 281-7.

1026. Herzog, A.R., et al., *Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults.* J Gerontol, 1990. **45**(2): p. M67-74.

1027. Diokno, A.C., M.B. Brown, and A.R. Herzog, *Relationship between use of diuretics and continence status in the elderly.* Urology, 1991. **38**(1): p. 39-42.

1028. Fantl, J.A., et al., *Urinary incontinence in community-dwelling women: clinical, urodynamic, and severity characteristics.* Am J Obstet Gynecol, 1990. **162**(4): p. 946-51; discussion 951-2.

1029. Resnick, N.M., M. Baumann, and M. Scott, *Risk factors for incontinence in the nursing home: a multivariate study.*. Neurourol Urodyn, 1988. **7**: p. 274-6.

1030. Resnick, N.M., et al., *Short-term variability of self report of incontinence in older persons.* J Am Geriatr Soc, 1994. **42**(2): p. 202-7.

1031. Resnick, N.M., *Urinary incontinence in the elderly* Medical Ground Rounds, 1984. **3**: p. 281-290.

1032. Doughty, D.B., *Urinary & fecal incontinence: Current management concepts*. 2006, St. Louis: Mosby.

1033. Dowling-Castronovo, A. and C. Bradway, *Urinary incontinence*, in *Geriatric nursing protocols for best practice*, E.

Capezuti, et al., Editors. 2008, Springer Publishing Company, Inc.: New York.

1034. Paillard, M. and N.M. Resnick, *Natural-History of Nosocomial Urinary-Incontinence*

Gerontologist, 1984. **24**(212).

1035. Griffiths, D., et al., *Brain control of normal and overactive bladder.* J Urol, 2005. **174**(5): p. 1862-7.

1036. Tadic, S.D., et al., *Abnormal connections in the supraspinal bladder control network in women with urge urinary incontinence.* Neuroimage, 2008. **39**(4): p. 1647-53.

1037. Boscia, J.A., et al., *Lack of association between bacteriuria and symptoms in the elderly.* Am J Med, 1986. **81**(6): p. 979-82.

1038. Ouslander, J.G. and J.F. Schnelle, *Incontinence in the nursing home.* Ann Intern Med, 1995. **122**(6): p. 438-49.

1039. Kocak, I., et al., *Female urinary incontinence in the west of Turkey: prevalence, risk factors and impact on quality of life.* Eur Urol, 2005. **48**(4): p. 634-41.

1040. Parazzini, F., et al., *Risk factors for stress, urge or mixed urinary incontinence in Italy.* BJOG, 2003. **110**(10): p. 927-33.

1041. Ozerdogan, N., N.K. Beji, and O. Yalcin, *Urinary incontinence: its prevalence, risk factors and effects on the quality of life of women living in a region of Turkey.* Gynecol Obstet Invest, 2004. **58**(3): p. 145-50.

1042. Arya, L.A., et al., *Evidence of bladder oversensitivity in the absence of an infection in premenopausal women with a history of recurrent urinary tract infections.* BJU Int, 2011.

1043. Suckling, J., A. Lethaby, and R. Kennedy, *Local oestrogen for vaginal atrophy in postmenopausal women.* Cochrane Database Syst Rev, 2006(4): p. CD001500.

1044. Cardozo, L., et al., *Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee.* Obstet Gynecol, 1998. **92**(4 Pt 2): p. 722-7.

1045. Holroyd-Leduc, J.M. and S.E. Straus, *Management of urinary incontinence in women: scientific review.* JAMA, 2004. **291**(8): p. 986-95.

1046. Longo, D.L., et al., *Harrison's Principles of Internal Medicine*. 18th ed. 2011, New York: Mcgraw-Hill Professional.

1047. Marshall, H.J. and D.G. Beevers, *Alpha-adrenoceptor blocking drugs and female urinary incontinence: prevalence and reversibility.* Br J Clin Pharmacol, 1996. **42**(4): p. 507-9.

1048. Clobes, A., J.O. DeLancey, and D.M. Morgan, *Urethral circular smooth muscle in young and old women.* Am J Obstet Gynecol, 2008. **198**(5): p. 587 e1-5.

1049. Grandjean, A.C., et al., *The effect of caffeinated, noncaffeinated, caloric and non-caloric beverages on hydration.* J Am Coll Nutr, 2000. **19**(5): p. 591-600.

1050. Armstrong, L.E., et al., *Fluid, electrolyte, and renal indices of hydration during 11 days of controlled caffeine consumption.* Int J Sport Nutr Exerc Metab, 2005. **15**(3): p. 252-65.

1051. Rao, S.S., et al., *Is coffee a colonic stimulant?* Eur J Gastroenterol Hepatol, 1998. **10**(2): p. 113-8.

1052. Johnson, M.F., et al., *Outcomes of older persons receiving rehabilitation for medical and surgical conditions compared with hip fracture and stroke.* J Am Geriatr Soc, 2000. **48**(11): p. 1389-97.

1053. Wald, A., *Faecal incontinence in the elderly : epidemiology and management.* Drugs Aging, 2005. **22**(2): p. 131-9.

1054. Alsheik, E.H., et al., *Fecal incontinence: prevalence, severity, and quality of life data from an outpatient gastroenterology practice.* Gastroenterol Res Pract, 2012. **2012**: p. 947694.

1055. Grover, M., et al., *Survey of geriatricians on the effect of fecal incontinence on nursing home referral.* J Am Geriatr Soc, 2010. **58**(6): p. 1058-62.

1056. Kuehn, B.M., *Silence masks prevalence of fecal incontinence.* JAMA, 2006. **295**(12): p. 1362-3.

1057. Johanson, J.F. and J. Lafferty, *Epidemiology of fecal incontinence: the silent affliction.* Am J Gastroenterol, 1996. **91**(1): p. 33-6.

1058. Sung, V.W., et al., *National trends and costs of surgical treatment for female fecal incontinence.* Am J Obstet Gynecol, 2007. **197**(6): p. 652 e1-5.

1059. Deutekom, M., et al., *Costs of outpatients with fecal incontinence.* Scand J Gastroenterol, 2005. **40**(5): p. 552-8.

1060. Morris, A.R., et al., *Costs of managing urinary and faecal incontinence in a sub-acute care facility: a "bottom-up" approach.* Neurourol Urodyn, 2005. **24**(1): p. 56-62.

1061. Farage, M.A., et al., *Psychosocial and societal burden of incontinence in the aged population: a review.* Arch Gynecol Obstet, 2008. **277**(4): p. 285-90.

1062. Mellgren, A., et al., *Long-term cost of fecal incontinence secondary to obstetric injuries.* Dis Colon Rectum, 1999. **42**(7): p. 857-65; discussion 865-7.

1063. Dyer, C.B., C.M. Ashton, and T.A. Teasdale, *Postoperative delirium. A review of 80 primary data-collection studies.* Arch Intern Med, 1995. **155**(5): p. 461-5.

1064. Siddiqi, N., A.O. House, and J.D. Holmes, *Occurrence and outcome of delirium in medical in-patients: a systematic literature review.* Age Ageing, 2006. **35**(4): p. 350-64.

1065. Clegg, A. and J.B. Young, *Which medications to avoid in people at risk of delirium: a systematic review.* Age Ageing, 2011. **40**(1): p. 23-9.

1066. Schnelle, J.F., et al., *Does an exercise and incontinence intervention save healthcare costs in a nursing home population?* J Am Geriatr Soc, 2003. **51**(2): p. 161-8.

1067. Ouslander, J.G., et al., *Effects of prompted voiding on fecal continence among nursing home residents.* J Am Geriatr Soc, 1996. **44**(4): p. 424-8.

1068. Shamliyan, T., et al., *Prevention of urinary and fecal incontinence in adults.* Evid Rep Technol Assess (Full Rep), 2007(161): p. 1-379.

1069. Roberson, E.N., J.C. Gould, and A. Wald, *Urinary and fecal incontinence after bariatric surgery.* Dig Dis Sci, 2010. **55**(9): p. 2606-13.

1070. Halland, M. and N.J. Talley, *Fecal incontinence: mechanisms and management.* Curr Opin Gastroenterol, 2012. **28**(1): p. 57-62.

1071. Abraham, B. and J.H. Sellin, *Drug-induced diarrhea.* Curr Gastroenterol Rep, 2007. **9**(5): p. 365-72.

1072. Lisi, D.M., *Fecal incontinence: possible role for drug-induced etiology.* J Am Geriatr Soc, 2011. **59**(1): p. 161-2; author reply 162-3.

1073. Gallagher, P. and D. O'Mahony, *Constipation in old age.* Best Pract Res Clin Gastroenterol, 2009. **23**(6): p. 875-87.

1074. Leung, F.W. and S.S. Rao, *Fecal incontinence in the elderly.* Gastroenterol Clin North Am, 2009. **38**(3): p. 503-11.

1075. Tariq, S.H., *Geriatric fecal incontinence.* Clin Geriatr Med, 2004. **20**(3): p. 571-87, ix.

1076. Read, N.W., et al., *Anorectal function in elderly patients with fecal impaction.* Gastroenterology, 1985. **89**(5): p. 959-66.

Committee 5

Initial Assessment of Urinary Incontinence in Adult Male and Female Patients (5A)

Patient-Reported Outcome Assessment (5B)

Chair

David Staskin (US)

Co-Chair

Con Kelleher (UK)

Members

Ruud Bosch (NL)

Nikki Cotterill (UK)

Karin Coyne (USA)

Con Kelleher (UK)

Zoe Kopp (USA)

Matthew Rosenberg (US)

David Staskin (US)

Tara Symonds (USA)

Cara Tannenbaum (Canada)

Masaki Yoshida (JP)

Consultants

Raman Basra (UK)

Praseetha Cherian (USA)

Committee 5A

Initial Assessment of Urinary Incontinence in Adult Male and Female Patients (5A)

CONTENTS

I. INTRODUCTION

II. GENERAL INFORMATION

III. INTIAL ASSESEMENT

IV. GENERAL POPULATIONS

V. SPECIFIC POPULATIONS: EVALUATION OF THE FEMALE PATIENT

VI. SPECIFIC POUPULATION: EVALUATION OF THE MALE PATIENT

REFERENCES

Committee 5B

Patient-Reported Outcome Assessment (5B)

CONTENTS

I. INTRODUCTION

II. THE MEASUREMENT OF PATIENT-REPORTED OUTCOMES (PROS) OF INCONTINENCE, OTHER LOWER URINARY TRACT SYMPTOMS, AND BOWEL PROBLEMS

III. RECOMMENDED PRO QUESTIONNAIRES

IV. INTERNATIONAL CONSULTATION ON INCONTINENCE MODULAR QUESTIONNAIRE (ICIQ): WHAT IS THE ICIQ?

V. PATIENT-REPORTED OUTCOME (PRO) QUESTIONNAIRES TO ASSESS THE IMPACT OF URINARY INCONTINENCE, OAB AND LOWER URINARY TRACT SYMPTOMS

VI. QUESTIONNAIRES TO ASSESS SYMPTOMS AND HEALTH-RELATED QUALITY OF LIFE IMPACT OF PELVIC ORGAN PROLAPSE

VII. QUESTIONNAIRES TO ASSESS SYMPTOMS AND HRQL IMPACT OF FAECAL INCONTINENCE

VIII. QUESTIONNAIRES TO ASSESS SEXUAL FUNCTION/SEXUAL HEALTH AND URINARY SYMPTOMS

IX. QUESTIONNAIRES FOR SPECIFIC PATIENT GROUPS

X. RECOMMENDATIONS FOR RESEARCH

REFERENCES

Committee 5A

Initial Assessment of Urinary Incontinence in Adult Male and Female Patients (5A)

David Staskin, Con Kelleher

Ruud Bosch, Nikki Cotterill, Karin Coyne, Con Kelleher, Zoe Kopp, Matthew Rosenberg, David Staskin, Tara Symonds, Cara Tannenbaum, Masaki Yoshida Craman Basra, Praseetha Cherian

I. INTRODUCTION

The aim of this report is to present an update of the evidence-based recommendations from the 4th ICI regarding the initial assessment of urinary incontinence (Committee 5A) and outcome measurements (Committee 5B) of UI for adult men and women.

II. GENERAL INFORMATION

1. TERMINOLOGY

A critical step in the evaluation of urinary incontinence (UI) is the use of up-to-date terminology to describe different types of UI and their associated lower urinary tract symptoms (LUTS). LUTS includes both storage and emptying symptoms in distinction to overactive bladder syndrome (OAB) which describes the subset of storage symptoms (e.g., urgency, frequency, nocturia), with or without the symptom of UI. The use of standardised terminology during the taking of the history of UI ensures an accurate characterisation of the type of UI experienced by each patient.

The ICS 2002 report [1] and the ICS /IUGA Joint Report [2] are recommended for reference, as well as an update of the terminology for nocturia [3]. Of note, a bibliometric and questionnaire analysis of the use of standardised terminology documents the low rate of acceptance of new terminology in both the literature and practice, and the slow abandonment of previously accepted common terms. [4]

The Standardisation Steering Committee (SSC) of the International Continence Society (ICS) "establishes terminology and methodology in the ICS's areas of activity, to underpin professional standards of clinical management and research. The value of the SSC is in promoting best standards when clinicians and allied professionals communicate with patients and colleagues, undertake diagnostic tests, proceed to therapeutic interventions and undertake research. Precise use of agreed terminology ensures clear understanding for collaborating centres and readers of publications. Adherence to the diagnostic testing standards gives patients and clinical colleagues confidence that conclusions on which important therapeutic decisions are based are reliable. Development of future insights into mechanisms and treatments of the disease areas relevant to the ICS is enhanced where research studies employ internationally standardised approaches." (http://www.icsoffice.org/ViewCommittee.aspx?ViewCommitteeID=7) The reports of the SSC are posted on the internet for reference (http://wiki.icsoffice.org).

The term "urinary incontinence" refers to the complaint of any involuntary loss of urine. The symptom of urinary incontinence can be volunteered by or elicited from the individual or may be described by the individual's caregiver. Urinary incontinence can be categorised into several distinct sub-types based on associated characteristics and circumstances surrounding episodes of urine leakage. Although defining the type of incontinence will not establish a definitive underlying diagnosis, it will ultimately guide investigation and treatment. The

following are the accepted ICS definitions of these conditions unless referenced [1].

a) Types of urinary incontinence

a) Stress (urinary) incontinence: Complaint of involuntary loss of urine on effort or physical exertion e.g., sporting activities), or on sneezing or coughing.(Sporting activities)

b) Urgency (urinary) incontinence: Complaint of involuntary loss of urine associated with urgency.

c) Postural (urinary) incontinence: Complaint of involuntary loss of urine associated with change of body position, for example, rising from a seated or lying position.

d) Mixed (urinary) incontinence: Complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing.

e) Incontinence associated with chronic retention of urine: Complaint of involuntary loss of urine which occurs in conditions where the bladder does not empty completely as indicated by a significantly high residual urine volume and/or a non-painful bladder which remains palpable or percussable after the individual has passed urine. (Note: The ICS no longer recommends the term overflow incontinence. A significant residual urine volume denotes a minimum volume of 300 mls, although this figure has not been well established.)

f) Nocturnal enuresis: Complaint of involuntary loss of urine which occurs during sleep.

g) Continuous (urinary) incontinence: Complaint of continuous involuntary loss of urine.

h) Insensible (urinary) incontinence: Complaint of urinary incontinence where the individual is unaware of how it occurred.

i) Coital incontinence (for women only): Complaint of involuntary loss of urine with coitus. This symptom can be further divided into that occurring with penetration or intromission and that occurring at orgasm.

j) Functional incontinence: Complaint of involuntary loss of urine that results from an inability to reach the toilet due to cognitive, functional or mobility impairments in the presence of an intact lower urinary tract system. (see Cmte. 11, Frail Elderly)

k) Multifactorial incontinence: Complaint of involuntary loss of urine related to multiple interacting risk factors, including factors both within and outside the lower urinary tract such as comorbidity, medication, age-related physiological changes and environmental factors. (see Cmte. 11, Frail Elderly).

Urinary incontinence can exist in isolation or may be associated with other lower urinary tract symptoms. The ICS classifies lower urinary tract symptoms (LUTS) into bladder storage, voiding and post-micturition, and pelvic organ prolapse symptoms. The following section summarises the definitions of LUTS described by the ICS-SSC.

b) Bladder storage symptoms

Bladder storage symptoms are experienced during the bladder filling phase:

a) Increased daytime urinary frequency: Complaint that micturition occurs more frequently during waking hours than previously deemed normal. Traditionally seven episodes of micturition during waking hours was considered as the upper limit of normal, although it may be higher in some populations.

b) Nocturia: Complaint of interruption of sleep one or more times because of the need to void. Each void is preceded and followed by sleep. (Note: The number of nocturia episodes and the degree of bother based on number has been questioned and the threshold of 2-3 per night has been suggested.) [5,6,7]

c) Urgency: Complaint of a sudden, compelling desire to pass urine which is difficult to defer. (Note: The 'all or none' nature of 'urgency' has been questioned) [8].

d) Overactive bladder syndrome (OAB): Urinary urgency, usually accompanied by increased urinary frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.

c) Bladder sensation

Asking patients about bladder sensory symptoms during bladder filling may be helpful in characterising certain types of incontinence.

a) Increased bladder sensation: Complaint that the desire to void during bladder filling occurs earlier or is more persistent to that previously experienced. This differs from urgency by the fact that micturition can be postponed despite the desire to void.

b) Reduced bladder sensation: Complaint that the definite desire to void occurs later than that previously experienced despite an awareness that the bladder is filling.

c) Absent bladder sensation: Complaint of both the absence of the sensation of bladder filling and a definite desire to void.

d) Voiding and postmicturition symptoms

Voiding symptoms are experienced during the voiding phase and post-micturition symptoms are experienced immediately after micturition.

a) Hesitancy: Complaint of a delay in initiating micturition.

b) Slow stream: The individual's perception of reduced urine flow, usually compared to previous performance or in comparison to others.

c) Intermittent stream (intermittency) Complaint of urine flow which stops and starts, on one or more occasions, during micturition.

d) Straining to void: Describes the muscular effort used to initiate, maintain or improve the urinary stream.

e) Spraying (splitting) of urinary stream: Complaint that the urine sprays or splits rather than coming out as a single, discrete stream.

f) Terminal dribble: is the term used when an individual describes a prolonged final part of micturition, when the flow has slowed to a trickle/dribble.

g) Feeling of incomplete bladder emptying: Complaint that the bladder does not feel empty after passing urine.

h) Need to immediately re-void: Complaint that further micturition is necessary soon after passing urine.

i) Postmicturition leakage: Complaint of a further involuntary passage of urine following the completion of micturition.

j) Position-dependent micturition: Complaint of having to take specific positions to be able to micturate spontaneously or to improve bladder emptying, for example, leaning forwards or backwards on the toilet seat or voiding in the semi-standing position.

k) Dysuria: Complaint of burning or other discomfort during micturition. Discomfort may be intrinsic to the lower urinary tract or external (vulvar dysuria in women).

l) (Urinary) retention: Complaint of the inability to pass urine despite persistent effort.

2. ASSESSMENT OF SUB-POPULATIONS REVIEWED BY OTHER COMMITTEES

The targeted assessments and specific outcome measures for conditions of UI in Children (Cmte 9), Neurogenic Patients (Cmte.10), Frail Elderly (Cmte.11), Painful Bladder Syndrome (Cmte.19) and Faecal Incontinence (Cmte.16) are presented separately in the respective reports. The requirements of specific sub-populations negate the ability to recommend a 'universal' initial evaluation. Within the initial assessment of UI, these sub-populations / subgroups are recognised because of the differences within patient groups or the interrelationship between the conditions. Congenital and maturational issues are critical considerations in children. Specific risks for combined storage and emptying abnormalities and upper urinary tract deterioration in the neurogenic population demand a more involved initial and complex evaluation. The effects of ageing on the lower urinary tract, altered toileting functions, and medical co-morbidities in the frail elderly group present unique challenges. These subgroups also include patients with LUTS with and without incontinence but the presence of pelvic pain or faecal incontinence.

The sub-sections in this report should be utilised in conjunction with other population or condition specific Committee Reports of the Consultation and with the final recommendations of the Consultation which are presented in simplified form in the Appendix (1.Definitions). Recommendations for initial evaluation have been developed by the International Scientific Committee and are also published in the Appendix (2.Evaluation). In addition, History and Symptom Assessment recommendations are further detailed as the initial steps in the evaluation of the index adult male (3. Initial Management, II. Male), and adult female (3. Initial Management, III. Female). The reader is encouraged to refer to these recommendations and algorithms in combination with this report.

3. EVIDENCE BASED RECOMMENDATIONS

The recommendations presented in this report are evidence-based and utilise the ICUD - EBM grades. A search of the available literature in English obtained from Medline© and Pubmed© up to January 2012 by the individual committee members employed multiple search terms related to the initial assessment of the patient with urinary incontinence and patient reported outcomes assessment.

III. INTIAL ASSESEMENT

1. PURPOSE OF INTIAL ASSESSMENT (EXPERT OPINION OF THE COMMITTEE)

As will be noted, especially in this committee report (5A), the amount and sophistication of the literature that is applicable for the development of evidence-based guidelines is limited. For this reason, the grade of recommendation in the area of "initial assessment" will often rely on 'expert opinion of the panel'. For the purpose of subsection 5A, the 'initial assessment' represents the components of the history, physical examination, laboratory tests, and basic office testing to:

1) Establish a presumptive or condition specific diagnosis, and exclude underlying organ-specific related or unrelated conditions that would require intervention.

2) Assess the level of bother and desire for intervention from information obtained from the

patient or caregivers, utilising objective measures or patient reported outcomes.

3) Prepare for the institution of empirical or disease specific primary therapy based on the risk and benefit of the untreated condition, the nature of the intervention and the alternative therapies – including Conservative (Cmte. 12) or Pharmacological (Cmte. 8) therapies.

4) Prompt the recommendation of additional more complex testing or specialist referral (when indicated).

5) Assess the level of improvement after intervention from information obtained from the patient or caregivers, utilising objective measures or patient reported outcomes (Cmte. 5B).

Once the type of UI with associated LUTS has been established, elaboration of a differential diagnosis can occur, and further investigations may be elected and an eventual treatment plan can be formulated to address or modify the effects of the underlying cause(s). The success of the treatment plan can be measured by patient-reported outcomes (from a simple "yes" or "no" to more complex questionnaires), and/or other objective measures of urinary leakage events (including bladder diaries, pad tests, or urodynamics studies).

The initial assessment must consider the degree of bother, and the costs of further evaluation, balanced against the consequences of a failure to diagnose an underlying condition, the risks and benefits of empirical conservative management or pharmacological therapy, and the need for an accurate diagnosis before more complex intervention or empirical therapy. The burden of these conditions and the availability of resources for individual patients, caregivers,, physicians, and health care systems requires that primary intervention strategies be formulated, when available, from evidence based findings and decisions emanating from the initial evaluation.

Of note, LUTS cannot be utilised with confidence to make a definitive diagnosis of a specific lower urinary tract condition or lower urinary tract disease (LUTD), as these symptoms may suggest and indicate pathologies such as urinary tract infection (UTI) or more serious underlying conditions. Basic laboratory tests, such as testing for UTI or blood (haematuria), and appropriate screening for malignancy should be considered before the decision is made to choose therapy for incontinence. Urinary retention with overflow voiding may present as urinary urgency, frequency, and nocturia with urinary loss mimicking OAB.

Concomitant pathology may affect urine production as a co-morbid contributory factor, by affecting fluid balance or renal function (fluid intake and output regulation) and may need to be addressed prior to or in combination with bladder or bladder outlet therapy. A thorough review of medications which alter fluid production or lower urinary tract function should be addressed. The physician should elicit a history of pelvic pathology or surgery and neurological symptoms and signs that may indicate alterations in the control of lower urinary tract function or be responsible for the cognitive, motivational, or physical factors that determine the ability to perform toileting functions effectively. The physical examination and the appropriate laboratory tests are necessary to refine the differential diagnosis and therapeutic course.

2. INTIAL ASSESSMENT – GENERAL RECOMMEDATIONS

1. Lower Urinary Tract Symptoms (LUTS) cannot be used to make a definitive diagnosis; they may also indicate pathologies other than Lower Urinary Tract Disease (LUTD). Specific to this report, LUTS includes Overactive Bladder (OAB) a syndrome which is associated with urgency incontinence (OAB-wet) or without incontinence (OAB-dry). (**Level 5 - Grade D**)

2. Urinary incontinence should be described by specifying relevant factors such as type, frequency, severity, precipitating factors, social impact, effect on hygiene and quality of life, the measures used to contain the leakage and whether or not the individual seeks or desires help. (**Level 5 - Grade D**)

3. Urinary incontinence should be categorised by symptoms into urgency incontinence, stress incontinence or mixed incontinence and conservative (non-invasive) therapies may then be started based on this classification to treat the most troublesome component, or either component of the incontinence. (**Level 5 - Grade D**) More sophisticated testing (e.g., urodynamic studies) is not required prior to the institution of conservative therapy (see indications for urodynamics in the Committee Report on Dynamic Testing Committee 6). (**Level 3 - Grade C**)

4. Both objective (bladder diary) and subjective (patient reported outcomes – PROs) are recommended for assessment and measurement of the degree of symptoms and bother of UI at baseline, and for the assessment of the impact of therapy. (**Level 3 – Grade D**).

5. Normal lower urinary tract function requires the ability of the bladder to adequately store urine at low pressure while the bladder outlet remains competent, and the bladder to contract until completely empty while the bladder outlet remains open . In addition to an evaluation of LUT function, a thorough evaluation for co-morbid conditions which affect fluid intake and output should be undertaken. Diseases of the nervous system and pelvic disorders, as well as medications

which may affect the LUT should be addressed. (**Level 5 - Grade D**).

6. Referral to a specialist is recommended for hematuria (visible or microscopic), urinary tract infection (persistent or recurrent), prolapse (symptomatic or below the introitus) , obstruction or retention (symptoms or findings of palpable bladder, hydronephrosis or obstructive renal insufficiency), suspected neurological disease, mass (urethral, bladder or pelvic - benign or malignant), fistula (urinary or bowel), faecal incontinence, a history of prior pelvic surgery or radiation (incontinence, oncologic) (**Level 5 - Grade D**).

3. INTIAL ASSESSEMENT – GENERAL RESEARCH RECOMMENDATIONS

1. Standardisation of the 'definition of symptoms' and the 'measurements of symptom frequency, severity and bother' are essential for patient care and research. Continued research into the appropriate scales and metrics should be accompanied by a significant attempt to establish best practice guidelines for their use and a consensus on the adoption of universal standards.

2. Recognition and resolution of the differences in common language usage and scientific utilisation of terms should continue. Resolution of the differences in definitions and metrics between recognised societies and regulatory agencies is essential for communicating data with respect to patient care, research, and treatment outcomes.

3. Research into the development of accurate measures to objectify subjective symptoms such as "urgency" and other bladder sensory symptoms.

4. Development, standardisation, and universal adoption of symptom assessment tools (questionnaires) to improve the diagnostic accuracy of lower urinary tract symptoms. (Refer to section 5B of this committee's report)

5. Validation of the accuracy of specific components of the history and physical findings to establish an accurate diagnosis and initiate non-invasive conservative or pharmacological therapy. In addition, to further identify components that would indicate the need for more invasive testing, complex therapeutic interventions, and indications prior to / or as a result of referral.

6. Creation and institution of evidence based guidelines for the referral of patients to a specialist are needed to improve the efficiency of the healthcare system in treating the large burden of disease. (See Epidemiology, Committee 1). The institution of conservative measures and pharmacology are in the domain of the primary caregiver. Further improvement in the ability to define the index patient, but more importantly the sub-groups of patients who will require more complex specialist therapy, will aid in counselling and referral at the primary level. In addition, refining the true risks for significant underlying disease noted while obtaining the history, or during the examination or laboratory findings will improve resource utilization.

IV. GENERAL POPULATIONS

1. INITIAL ASSESSMENT OF URINARY INCONTINENCE

Individuals with UI can be identified through routine screening, or the patient may initiate discussion about incontinence problems. The initial assessment of UI should help the health care provider understand the type of incontinence, while identifying potentially modifiable contributing factors. Most primary treatment options, such as lifestyle modifications and behavioral treatments, do not vary by type of UI. However, it is important to determine the type of UI since some treatment options do vary according to incontinence. Equally important, establishing the type of UI will lead the health care provider to a list of possible underlying causes, or differential diagnosis of the urinary symptoms. Most causes of UI are non-life threatening, however symptoms of incontinence may also herald life-threatening or more severe disease such as bladder cancer when associated with haematuria; when more specialised testing will be required immediately. Finally, assessing the level or bother and desire for intervention from information obtained from the patient or caregiver is essential for guiding the nature of the treatment plan.

a) History

The general history should include questions relevant to precipitating and aggravating factors of urinary loss, time of onset and duration of symptoms, and degree of bother. Acute symptoms can be defined by documenting patterns of fluid intake and output, acute infection, recent surgery or trauma. Chronic symptoms should prompt queries about a history of congenital abnormalities, neurological disease, relevant surgery or general health. Information should be obtained concerning medications with known or possible effects on the lower urinary tract. The general history in women should also include assessment of menstrual, obstetric, sexual and bowel function. The reader is referred to the report on Epidemiology (Cmte. 1) for specific risk factors to be considered during the medical history, and to the report on Frail Elderly (Cmte. 11) for a list of co-morbidities and medications that can cause or contribute to UI.

A later section of this Committee Report (5B) presents a complete review and evaluation of questionnaires that are applicable for clinical and research use in evaluating patient symptoms. Structured condition specific questionnaires may be utilised, and

may be either clinician or self-administered. Use of questionnaires may facilitate disclosure of embarrassing symptoms, ensure that symptoms are not omitted, and standardise information for audit and research. In the absence of questionnaire use, **Table 1** summarises key questions for the initial assessment of urinary incontinence based on the expert opinion of this committee. Note that the committee strongly encourages the use of standardised questions.

b) Diaries

The micturition time chart records the timing of voids in 24 hours; the frequency-volume chart (FVC) additionally includes the urinary volume voided, and the bladder diary which may include incontinence episodes, pad usage, fluid intake, and the degree of urgency and incontinence. Documentation of the frequency of an individual's lower urinary tract symptoms and the voided volume for at least 24 hours can be extremely helpful both in the initial assessment of urinary incontinence, may be therapeutic as it provides insight into bladder behaviour, can be utilised to monitor the effectiveness of treatment during follow-up. Two main methods of documenting this information are in use, and a sample frequency-volume chart and bladder diary are illustrated with the instructions for use in the appendix in Annex 1: Bladder Charts and Diaries. The frequency-volume chart is used to describe a chart that records the time of each micturition and the volume voided for at least 24 hours, although 2-3 days of recording generally provide more useful clinical data. The bladder diary refers to a more comprehensive instrument that may include the individual's daily type and volume of fluid intake, pad usage, incontinence episodes, and the degree of incontinence. Episodes of urgency and sensation might also be recorded, as might be the activities performed during or immediately preceding the involuntary loss of urine. A frequency-volume chart or bladder diary, if properly completed, can confirm all of the following information.

Table 1: Key questions in the initial assessment of urinary incontinence

Stress urinary incontinence: Do you sometimes leak urine when you cough or sneeze or when you exert yourself, such as when lifting a heavy object?*
Urgency urinary incontinence: Do you sometimes feel an urge to void that is so sudden and strong that you sometimes don't make it to the bathroom on time?*
How long have the symptoms been present?
How often do you leak urine and how much do you leak?
Circumstances surrounding urine leakage e.g. sexual activity, change in position, provocation by running water or 'key in the latch'?
Nocturnal symptoms or enuresis?
Association with other lower urinary tract or pelvic organ prolapse symptoms?
Impact on personal and social life?
Amount and type of fluid intake e.g. coffee, tea, alcohol?
Episodes of urinary tract infection or haematuria?
Previous treatment attempts (successful and unsuccessful)?
Mobility problems?
Cognitive deficits?
Neurological deficits?
Problems with constipation or faecal incontinence?
Number of pregnancies and the type of delivery, with complications?
Previous prostate, pelvic or abdominal surgeries or radiation treatment?
Coexisting diseases (diabetes, heart disease, neurological impairment)?
Types of medications consumed?

**Evidence regarding the reliability of these questions for diagnosing stress or urgency urinary incontinence is detailed below.*

a) Daytime urinary frequency: Number of voids by day (wakeful hours including last void before sleep and first void after waking and rising).

b) Nocturnal frequency/nocturia: Number of times sleep is interrupted by the need to micturate. Each void is preceded and followed by sleep.

c) Twenty-four-hour frequency: Total number of daytime voids and episodes of nocturia during a specified 24-hr period.

d) Twenty-four-hour urine production: Summation of all urine volumes voided in 24 hr.

e) Maximum voided volume: Highest voided volume recorded.

f) Average voided volume: Summation of volumes voided divided by the number of voids.

g) Median functional bladder capacity: Median maximum voided volume in everyday activities.

h) Polyuria: Excessive excretion of urine resulting in profuse and frequent micturitions, defined as over 40 ml/kg body weight during 24 hours or greater than 2.8 L of urine for an individual weighing 70 kg.

i) Nocturnal urine volume: Cumulative urine volume from voids after going to bed with the intention of sleeping to include the first void at the time of waking with the intention of rising (excludes last void before sleep).

j) Nocturnal polyuria: Excess (over 20–30% age dependent) proportion of urine excretion (nocturnal voided volume/total 24 hr voided volume x 100%) occuring at night (or when the patient is sleeping). [9]

However, it should be noted that there are some limitations to the use of a frequency-voiding chart or bladder diary. There is no evidence that the results of these charts provide a valid prediction of the type of urinary incontinence experienced by each patient.[10, 11] Some patients may have difficulty completing the diary in a reliable, meaningful or timely fashion, especially when increasing the complexity or the amount of time (days) required to complete the diary. [12] The bladder diary may not be helpful for gleaning information about the evolution of incontinence episodes that occurs less frequently than once per day. [12,13]

• Recommendations- Bladder Diary

1) A bladder diary is recommended in order to document and communicate both objective information and to objectify observations by the patient during the diary period. Although never completely diagnostic, diary patterns may characterise normal and abnormal states. (**Level 3 – Grade C**)

2) The ideal duration of a diary is not clear. (**Level 4**) A 1-day frequency volume chart (FVC) which includes the first morning void the following day is a reasonable tool to gain insight into voiding habits during normal daily routine. A 3-day FVC or diary is recommended for accurate assessment of LUTS and for confirming a consistent clinical pattern in day-to-day practice. (**Level 3 – Grade C**) For atypical clinical patterns or clinical research, a 7-day diary may be recommended (most pharmacological studies now employ a 3-day diary as a standard to improve patient compliance).

• Bladder Diaries - Future Research

1) The ideal duration of a bladder diary based on accuracy, compliance, and the utility of the diary for diagnosis, the selection of therapy, and improving the outcomes of therapy requires further investigation.

2) The utility of paper versus electronic methods of recording voiding patterns requires further research.

c) Urinalysis

"The urinalysis is a fundamental test that should be performed in all urological patients. Although in many instances a simple dipstick urinalysis provides the necessary information, a complete urinalysis includes both chemical and microscopic analysis." [14] Urine dipstick testing, as opposed to microscopy, is satisfactory for urinalysis in the diagnosis of acute uncomplicated cystitis. [15] In relation to urinary incontinence, dipstick urinalysis is not a diagnostic test, but a screening test, utilised to detect haematuria, glucosuria, pyuria and bacteriuria. Haematuria can indicate important pathology such as urothelial carcinoma in situ, leading to lower urinary tract storage symptoms including incontinence. [16] Glucosuria is relevant, as a potential indicator of diabetes mellitus. This can cause symptoms via several mechanisms including polyuria secondary to osmotic diuresis. Diabetic peripheral autonomic neuropathy affecting bladder innervation may be associated with impaired bladder emptying and chronic urinary infection[17] The examiner should note that a patient does not generally demonstrate glucose into the urine until the blood sugar is >180 mg/dl. Consequently, a dipstick urinalysis may fail to reveal intermittently high sugars or mild diabetics. [17] If diabetes is suspected, then a random or fasting blood sugar is preferred. [18]

Pyuria and bacteriuria, detected from urinary dipstick leukocyte esterase and nitrite tests respectively, are important signs of urinary tract infection. The specificity and sensitivity of these latter tests for UTI is increased when used together compared to either individual test. [19,20] Even in the absence

of controlled studies, there is general consensus that the benefits of urinalysis clearly outweigh the costs involved, although the use of urinalysis should always be associated with prognostic significance. [21] A positive dipstick urinalysis will prompt formal urine microscopy and culture to detect UTI prior to antibiotic treatment and/or the use of additional tests such as endoscopy and urinary tract imaging. In the evaluation of urinary incontinence and lower urinary tract symptoms, the value of urinalysis can be illustrated by the finding that 60% of women without detrusor overactivity will develop detrusor overactivity at the time of UTI. The importance of urinalysis in the basic assessment of patients with urinary incontinence and lower urinary tract symptoms is not dependent on gender, age or aetiology. Indeed, it has been recommended in the evaluation of geriatric patients including nursing home residents who are incontinent, [22,23] in peri- and postmenopausal women, [24] and in older women reporting urinary incontinence. [25] In the latter context, it has even been observed that clinically significant urine samples can even be obtained from disposable diapers in elderly incontinent women. [26] The clinical relevance of asymptomatic bacteriuria (without pyuria) and pyuria (without bacteriuria) in the elderly is controversial, as eradication of bacteruria appeared to have no effect on the resolution of incontinence, and may not deserve any treatment. [27,28].

• Urinalysis - Recommendation

1. It is considered standard to perform a urinalysis by either using a dipstick test or examining the spun sediment in incontinent patients. (**Level 5 - Grade D**)

2. If a dipstick test is used, it is recommended that a "multi-property" strip that includes fields for haematuria, glucose, leukocyte esterase and nitrite tests be chosen. (**Level 5 - Grade D**) Dipstick is not as accurate as urine culture, being specific for infection but not sensitive. (**Level 2 - Grade C**)

3. Additional tests available on urine dipstick strips, such a protein, bilirubin, ketones and pH, may be helpful in the broader medical management of patients. However, they are not essential in the context of evaluation of the patient with urinary incontinence or lower urinary tract symptoms. (**Level 5 - Grade D**)

d) Post Voiding Residual in the Female and Male Patient

1. General

The post voiding residual urine (PVR) is the volume of urine remaining in the bladder following a representative void. Both bladder outlet obstructionand low bladder contractility contribute to the development of PVR. PVR measurement can be accomplished within a few minutes of voiding either by catheterisation, or by calculation of bladder volume using a portable ultrasound scanner or formal ultrasonography.

It is difficult to determine the value of post-void residual determination in the initial assessment of urinary incontinence since most studies producing data on PVR have not been in patients with UI. However, the populations studied have included women with UI, and incontinent patients with neurogenic bladder disease.Several studies have compared volumes measured with portable ultrasound scanners versus catheterisation and found portable scanners to be 85-94% accurate [29,30]. A study has imaged the bladder volume after catheterisation and found that the volume of urine remaining in the bladder after catheterisation accounted for most of the difference between the two measurements [29]. Bimanual palpation cannot reliably estimate the post-void residual urine volume [31].

Since PVR may vary, one measurement of PVR may not be sufficient [32]. PVR should probably be measured several times to increase its reliability. Griffiths et al found a significant variability in PVR measurement depending on the time of the day, with the greatest volume occurring in the morning [33]. A non-representative PVR is particularly common if the patient's bladder is not full enough to yield an urge to void. Special consideration is required in male patients with incontinence and bladder outlet obstruction, in incontinent neurogenic patients who may demonstrate combined disorders of storage and emptying [34], and preoperatively in patients being considered for incontinence surgery.

An increased PVR alone is not necessarily a clinical problem, but if combined with high pressure storage pressures in the bladder it can lead to upper urinary tract problems. If the PVR is associated with urinary tract infections (UTIs), the PVR may need to be treated since UTIs may be more difficult to eradicate in the presence of an infected residual. A significant PVR also decreases the functional bladder capacity and contributes to urgency/frequency, urgency incontinence and nocturia. Of note, a Scandinavian study in nursing home residents found that an elevated PVR was not associated with bacteriuria and incontinence [35], Since recurrent UTI's [due to elevated PVR] can be associated with urinary incontinence it is suggestedthat PVR in incontinent patients with recurrent UTIs should be measured.

Review of the literature does not demonstrate an evidence-based specific maximum PVR that is considered normal, nor is there a minimum PVR that is considered abnormal. The amount of residual urine that precludes treatment by various therapies has not been determined. The AHCPR guidelines state that, in general, a PVR less than 50 ml is considered adequate bladder emptying and over 200 ml is considered inadequate emptying (expert opinion of the panel members – Level D) [36].

2. Post Voiding Residual (Specifics In The Female Patient)

"Normal values" of PVR have been determined in several groups of non-incontinent and incontinent women. Gehrich et al studied 96 women (mean age 60 ± 11 yrs) that were seen in a well-women clinic. These women had no history of incontinence, retention, symptomatic prolapse or neurologic disorders. Most (97%) had a minor (asymptomatic) degree of prolapse, 80% were post-menopausal and 30% had had a hysterectomy. The median PVR was 19 ml (range 0-145 ml; mean 24 ± 29 ml); only 5% had PVR > 100 ml. Only, age > 65 yrs was associated with higher PVR [37]. Tseng et al studied 107 women with urodynamic stress incontinence. They found a mean PVR of 62.5 ml by bladder scan and 38.5 ml by catheterisation. Only 15.9% had a PVR greater than 100 ml. The PVR determined by bladder scan offered a sensitivity of 64.7% and a specificity of 94.3% in detecting PVR greater than 100 ml [38]. Haylen et al studying women with lower urinary tract dysfunction found that 81% had a PVR of less than 30 ml [39]. Fitzgerald et al studied women with urgency, frequency and urgency incontinence: 10% had an elevated PVR of > 100ml. In these women with OAB, the following independent risk factors for increased PVR were found: vaginal prolapse, symptoms of voiding difficulty and abscence of stress-incontinence [40]. Lukacz et al found that only 11% of women with pelvic floor disorders had an elevated PVR [41]. Wu and Baguley studied 319 consecutive patients (196 women, 123 men) in a predominantly geriatric subacute general rehabilitation unit. Twenty two patients had been admitted with a catheter and were excluded. Of the 297 "asymptomatic" patients, 21.5% had PVR volumes of 150 mL or more. Patients with elevated PVR (> 150 ml) were significantly more likely to have a urinary tract infection at admission and have urinary incontinence on discharge [42]. Milleman et al retrospectively reviewed 201 women (mean age 55; range 20-90) who presented with complaints of urinary frequency, urgency and /or urgency incontinence. 19% had an elevated PVR of more than 100 ml (mean 211 ml; range 100-997 ml). On multivariate analysis the following independent predictors of raised PVR were identified: age > 55 yrs [OR 3.71], prior incontinence surgery [OR 4.32], a history of multiple sclerosis [OR 15.32] and pelvic organ prolapse grade 2 or greater [OR 3.61] [43]. In summary, an elevated PVR > 100 ml was found in 5% of women visiting a well-women clinic, in 10-19% of women with OAB, in 11% of women with pelvic floor disorders and in 15.9% of women with urodynamic SUI. Overall, incontinent women have a slightly higher risk of elevated PVR compared to asymptomatic subjects. There are insufficient data on incontinent men to draw conclusions.

Does a significant PVR have an impact on the outcome of treatment in patients with incontinence? Nager et al studied the predictive value of urodynamic measures on stress continence outcomes after surgery for stress urinary incontinence. They found that urodynamic measures do not predict outcomes. However, since women with PVR > 150 ml were excluded in this study, one can only conclude that PVR volumes < 150 ml did not have an adverse impact on stress continence outcome [44].

3. Post Voiding Residual (Specifics In The Male Patient)

A PVR measurement is especially recommended in men with symptoms suggestive of bladder outlet obstruction. A PVR less than 50ml is considered adequate bladder emptying and over 200ml is suggestive of obstruction. As in the female patient, PVR can be measured within a few minutes of voiding by catheterisation to confirm that the bladder is empty [45] or by ultrasonography [46]. A dedicated ultrasound system has been developed for automatic measurement of PVR, thereby improving the accuracy and increasing comfort in the male patient. The International Consultation on BPH defined a range of 50 to 100 ml as the lower threshold to define abnormal PVR [48]. Both the AUA and the EAU guidelines suggest a threshold of 300 ml to identify patients at risk of unfavorable outcome following LUTS / BPO treatment [49,50].

There is no consensus about the relation between PVR and UTI in the male patient. Although the negative role of large residuals has been reported, the evidence is controversial. Elevated residual urine volume has been considered a bad prognostic factor for disease progression. However, in the standard patients, renal failure, acute retention and UTIs are uncommon in men with large, chronic residuals [51]. No factors are available to identify patients, with significant residual urine, who are at risk of progression [52].Therefore, based on these trials, untreated LUTS may place the male patient at risk for potential clinical deterioration. Thus, periodical measurements of PVR are recommended in such patients.

• Post Voiding Residual - Recommendations

1. Varying degrees of decreased bladder emptying or urinary retention may be a cause of LUTS that are associated with symptoms of decreased urinary storage. The decision to perform a PVR in disease specific sub-groups of incontinent patients should be based on an association of the condition with poor bladder emptying (**Grade D**), whereas in individual patients this decision may be based on symptoms or physical findings. (**Grade C**).

2. Female patients who present with storage specific symptoms, with normal sensation and no complaints of decreased bladder emptying, and no anatomical, neurological, organ-specific, or co-morbid risk factors for retention may be assessed for

bladder emptying by history and physical examination alone, depending on the potential morbidity of the failure to diagnose and the nature of the intended therapy. (**Grade B**). Due to the increased possibility of bladder outlet obstruction due to prostatic obstruction is increased in the male patient, the threshold for investigating residual urine in the male is significantly lower (**Grade D**).

3. A PVR should be performed in incontinent patients when decreased bladder emptying is suspected, especially if treatments that decrease bladder contractility or increase outlet resistance are being considered. (**Grade D**)

4. A palpable bladder on physical examination is an indication for referral to a specialist (**Grade D**).

Residual urine determination by bladder scan is preferable to catheterisation due to the increased morbidity associated with instrumentation. (**Grade D**). Non-invasive ultrasound measurement of PVR is as accurate as measurement by catheterisation and is therefore the preferred method. (**Grade A**)

- **Post Voiding Residual - Future Research**

1. Development of more specific indications for PVR testing for diagnosis and prior to instituting therapy based on history, physical examination, and disease specific findings.

2. Further development of low cost, minimally invasive, and accurate means of measurement of PVR that do not require catheterisation.

3. Continued research in subsets of patients is required to determine the need for PVR assessment and the correlation between elevated PVR and treatment outcome, generally, to determine the effect of varying levels of PVR on the outcomes of observational, conservative, pharmacological and surgical interventions, and more specifically, the female patient prior to surgeries that increase outlet resistance, the male patient with bladder outlet obstruction where medications that can potentially decrease bladder contractility are considered, and the patient with elevated residual urine where intermittent catheterisation is not practical and where recurrent urinary tract infections and decreased functional bladder capacity are potential complicating factors.

V. SPECIFIC POPULATIONS: EVALUATION OF THE FEMALE PATIENT

1. ESTABLISHING THE TYPE OF URINARY INCONTINENCE IN WOMEN

a) The reliability of simple history questions for women

A meta-analysis was conducted by Holroyd-Leduc et al. using literature abstracted from 1960-2007 to determine the reliability of several questions for establishing the type of urinary incontinence in women. [53] An updated literature search was performed using the same search criteria from July 2007-January 2012 to determine whether new evidence was available to add to existing data. Among 794 new citations, no new relevant articles were found to contribute additional evidence. According to the results of the meta-analysis by Holroyd-Leduc et al, simple questions to diagnose stress or urgency urinary incontinence have high reliability in women (kappa=0.8; 95% CI, 0.3-0.9), with the percent agreement between repeated questioning estimated at 90% (95% CI, 84%-95%) for stress, urgency and mixed urinary incontinence sub-types. [54] The reader is referred to the systematic review for a list of all studies included in the analysis for each type of incontinence. In summary, if a woman responds “yes” to the question, “Do you lose urine during physical exertion, lifting, coughing, laughing or sneezing?” she is twice as likely to experience stress urinary incontinence compared to a woman who responds “no” to this question (positive likelihood ratio [LR], 2.2; 95% confidence interval [CI], 1.6-3.2; negative LR, 0.39; 95% CI, 0.25-0.61). The question to diagnose urgency urinary incontinence is even more reliable. A woman who responds “yes” when asked “Do you ever experience such a strong and sudden urge to void that you leak before reaching the toilet?” is four-times as likely to have urgency incontinence than a woman who does not experience feelings of urgency associated with urine leakage (positive LR, 4.2; 95% CI 2.3-7.6; negative LR, 0.48; 95% CI, 0.36-0.62). Positive answers to both these questions strongly suggest mixed urinary incontinence.

Martin et al performed a systematic review of methods of assessing urinary incontinence from 1996-2002, with findings similar to those reported by Holroyd-Leduc et al. [55] The clinical history alone in diagnosing stress urinary incontinence in women was found to have a sensitivity of 0.92 and specificity of 0.56, and for urgency urinary incontinence a sensitivity of 0.61 and specificity of 0.87. No evidence was provided by either review on the reliability of other questions to diagnose additional symptoms of incontinence.

Although positive answers to the questions noted by Holroyd-Leduc et al. increase the likelihood that a woman will have a certain type of urinary incontinence, the history alone is insufficient to establish diagnostic certainty. Sufficient diagnostic certainty has been defined as a positive likelihood ratio > 5 to confirm the diagnosis and a negative likelihood ratio <0.2 to exclude the diagnosis, which is greater than the values obtained in the meta-analysis. As such, diagnostic interviews need to be complemented by a targeted physical exam and sound clinical judgment to establish a probable diagnosis. According to the meta-analysis by Holroyd-Leduc

et al., comprehensive assessment including the history, physical exam and targeted investigation, still holds the most value for diagnosing stress urinary incontinence (positive LR, 3.7; 95% CI, 2.6-5.2; negative LR, 0.20; 95% CI 0.08-0.51) and urgency urinary incontinence (positive LR, 4.6; 95% CI, 1.7-12.6; negative LR, 0.11; 95% CI 0.04-0.33) in female patients.

b) Accuracy of the general physical examination in women

No studies were found that addressed the accuracy of components of the general physical examination for diagnosing the type of urinary incontinence in women. Nonetheless, it is recommended that a thorough physical examination, including but not restricted to the abdomen, rectum, gynaecological/ pelvic regions and neurological system be performed for ruling out certain risk factors as well as significant associated or underlying pathology, such as significant prolapse, obstruction, neurological disease and malignancy. Height and weight should be recorded so that the body mass index can be calculated (Kg/M2).

1. Abdominal examination

Observation of the abdomen may yield evidence of scars from previous surgeries or increased abdominal striae. Increased abdominal striae may be found in association with other markers of abnormal collagen metabolism, and are more likely in patients with prolapse and stress incontinence. [56] An attempt should be made to palpate the kidneys, particularly where a voiding dysfunction or neurogenic bladder dysfunction are suspected. A distended bladder may be identified by abdominal palpation or by suprapubic percussion. In one study designed to look at the clinical utility of basic assessment in elderly women, palpable enlargement indicated a post-void residual volume of at least 300ml. [57]

2. Neurological examination

A neurological examination should be performed with particular attention to the sacral neuronal pathways. Saddle anesthesia will occur with lesions affecting S2-S4. (See Cmte. 10, Neurogenic Patients) Assessment of gait, abduction and dorsiflexion of the toes (S3) and sensory innervation to the labia minora (L1-L2), sole and lateral aspect of the foot (S1), posterior aspects of the thigh (S2), and cutaneous sacral reflexes (bulbocavernosus and anal reflexes) are additional features of the neurological exam that may be assessed. A rectal examination will provide a subjective assessment of resting and voluntary anal tone (S2-S4). For patients with possible neurogenic lower urinary tract dysfunction, a more extensive neurological examination is required. In the elderly, full cognitive and mobility assessments are also recommended. An evaluation of hand dexterity should be performed when self-catheterisation is being considered as a treatment option for incontinence associated with chronic urinary retention.

3. Gynaecological examination

Gynaecological examination should include inspection of the perineal and genital regions as well as a digital vaginal examination to evaluate pelvic floor muscle strength. Inspection of the vulva and perineum allows a description of the skin and the presence of any abnormal anatomical features, of atrophy or excoriation, features of prolapse, and erythema due to incontinence and the wearing of pads.

Presently there are few scientific data documenting the parameters of a normal pelvic examination in women of various ages and with various obstetrical histories. The components of the examination have not been universally agreed upon. It seems intuitive that the examination should include an assessment of the bony architecture, pelvic floor muscle tone and muscle mass, connective tissue support, the epithelial lining of the vagina, the size, location, and mobility of the uterus, the adnexal structures, and innervation of the pelvic floor structures. It is important to establish the oestrogen status as oestrogen receptors are present within the lower urinary tract, [58] and have been shown to influence cell proliferation. [59] Women with oestrogen deficiency may complain of urgency and frequency and recurrent urinary tract infections may develop because of lossof urethral mucosal coaptation. In women of reproductive age, symptoms may vary with the menstrual cycle. [60]

The well-oestrogenised vagina has a thickened epithelium, with transverse rugae in its lower two-thirds. The poorly oestrogenised vagina has a thinned epithelium with loss of transverse rugae. Signs of moderate to severe vaginal atrophy include the presence of pale and dry vulvovaginal mucosa with petechiae. [61] A urethral caruncle, a small, soft, smooth friable red outgrowth along the edge of the urethra, may also develop. A thin watery yellow vaginal discharge may be observed. The appearance of thicker, white or other coloured vaginal secretions may suggest a vaginal infection; urine within the vagina suggests genitourinary fistula.

Urethral diverticula are occasionally congenital but most are acquired. They may have either a simple or a complex sacculation. Many patients with urethral diverticula are asymptomatic and need no treatment. Symptomatic patients report recurrent cystitis,frequency, dysuria, dyspareunia, urinary incontinence and voiding difficulties. On clinical examination a suburethralmass may be palpable; the urethra is usuallytender; and, if the sacculation communicates with the urethra, it may be possible to express a purulent exudate from the urethra. Occasionally, a stone may develop within the diverticulum. [62]

4. Specialised tests for diagnosis UI in Women

Three special manoeuvres can be performed during the initial assessment of urinary incontinence: the stress test, the Q-tip test, and the pad test. The post-void residual urine volume and use of a urinalysis in the initial assessment of women with urinary incontinence are also discussed.

• Stress Test

The stress test involves observation for urine loss with coughing or Valsalva maneouvre.

This procedure can be performed while the patient is in the lithotomy position or standing. Instantaneous urine leakage on coughing or during a Valsalvamaneouver is considered a positive test, and a sign of stress urinary incontinence. [2] Holroyd-Leduc et al. reviewed existing evidence on the diagnostic accuracy of the stress test for stress urinary incontinence. [53] Results from the meta-analysis revealed that a positive stress test increases the likelihood of a diagnosis of stress urinary incontinence (summary LR, 3.1; 95% CI, 1.7-5.5), while a negative test result decreases the likelihood (summary LR, 0.36; 95% CI, 0.21-0.60). The results obtained during a filled–bladder test are more accurate than the results obtained during an empty-bladder test. Doing a more complicated stress test that uses a step-wise approach to bladder filling and combines supine and standing testing does not further improve diagnostic accuracy for stress urinary incontinence. The stress test performed with coughing appears to be a reliable test. Reliability data are not available for tests performed using the Valsalva maneouvre. Price and Noblett recently compared the accuracy of the cough stress to the pad test for diagnosing stress urinary incontinence. [63] The cough stress test demonstrated superiority over the pad test with a sensitivity, specificity, and positive and negative predictive values of 90%, 80%, 98%, and 44% for diagnosing stress urinary incontinence.

• Q-tip test

The Q-tip test has traditionally been used to assess mobility of the urethro-vesical junction. The test involves placement of a lubricated cotton swab or Q-tip in the urethra to the level of the bladder neck while the woman is in the lithotomy position. Change in the axis of the free end of the swab is then measured while the woman performs a Valsalva maneouvre. The free end should remain horizontal if no anatomical defect is present. If the free end moves above the horizontal, urethral hypermobility is suspected, this can occur in patients with stress urinary incontinence. [64] In a meta-analysis by Holroyd-Leduc et al. that examined the accuracy of the Q-tip test for diagnosing stress urinary incontinence, only two relevant studies metthe inclusion criteria. [53] Results of the analysis suggested that a positive Q-tip test does not accurately predict the diagnosis of stress urinary incontinence in women. More specialised testing with pelvic floor ultrasound and other imaging techniques appears to be gradually replacing the Q-tip test for a more advanced assessment of bladder neck hypermobility. The reader is referred to the Report by the Committee on Imaging and Other Investigation (Cmte 7).

• Pad test

A pad test involves the continuous wearing of continence pads for a set period of time. The objective of pad testing is to quantify the volume of urine lost by weighing a perineal pad before and after some type of leakage provocation. This test has also been used in an attempt to distinguish continent from incontinent women, rather than for distinguishing the type of urinary incontinence. Holroyd-Leduc et al. reported that a positive pad test increases the likelihood of an incontinence problem (LR, 3.3; 95% CI, 2.0-5.4), while a negative pad test makes an incontinence problem much less likely (LR, 0.11; 95% CI, 0.05-0.27). [53] Pad tests can be divided into short-term tests, usually performed under standardised office conditions, and long-term tests, usually performed at home for 24–48 hours. Pad tests are generally performed with a full bladder or with a fixed known volume of saline instilled into the bladder before beginning the series of exercises. A pad weight gain >1 g is considered positive for a 1-hour test, and a pad weight gain >4 g is positive for a 24-hour test. There is wide variation in the pad weight gain in incontinent women participating in clinical trials. Although some studies have found high test-retest correlations in pad tests, [65, 66] other studies have reported low inter-subject and intra-subject reliability. [67, 68] The correlation coefficient between total leakage during two long-term tests appears to exceed of standard 1-hour tests. [69, 70]

2. PELVIC ASSESSMENT: PELVIC FLOOR STRENGTH AND PELVIC ORGAN PROLAPSE

a) Assessment of pelvic floor muscle strength

According to the recent 2010 joint guidelines published by IUGA/ICS in 2010, pelvic floor muscle strength is qualitatively defined by the tone at rest and the strength of a voluntary or reflex contraction as strong, normal, weak or absent, or by a validated grading symptom. [2] Voluntary pelvic floor muscle contraction should be evaluated during the initial assessment by vaginal digital palpation. Any or all of the following factors can be assessed including muscle strength (static and dynamic), voluntary muscle relaxation (absent, partial, complete), muscular endurance (ability to sustain maximal or near maximal force), repeatability (the number of times a contraction to maximal or near maximal force can be performed), duration, coordination, and displacement. If possible, it is desirable to document findings for each side of the pelvic floor separately to allow for any unilateral defects and asymmetry. The ICS report on the

standardisation of terminology of pelvic floor muscle function and dysfunction provides a fuller description of the assessment of pelvic floor muscle function including the following:[71]

a) Normal pelvic floor muscles: Pelvic floor muscles which can voluntarily and involuntarily contract and relax.

b) Overactive pelvic floor muscles: Pelvic floor muscles which do not relax, or may even contract when relaxation is functionally needed, for example, during micturition or defaecation.

c) Underactive pelvic floor muscles: Pelvic floor muscles which cannot voluntarily contract when this is appropriate.

d) Non-functioning pelvic floor muscles: Pelvic floor muscles where there is no action palpable.

b) Assessment of Pelvic Prolapse

Urinary incontinence and pelvic organ prolapse are separate clinical entities that often coexist. Significant protrusions of the vagina can obstruct voiding and defaecation. It is important to assess pelvic organ prolapse in a woman with incontinence, because repair of one pelvic support defect without repair of concurrent asymptomatic pelvic support defects can predispose to accentuation of unrepaired defects and new symptoms. The term stress incontinence on prolapse reduction (occult or latent stress incontinence) was recently introduced to describe the development of stress urinary incontinence after of reduction of co-existent prolapse by surgical repair or pessary insertion. [2]

Assessment of pelvic organ prolapse described in this section is in accordance with the recent 2010 joint guidelines produced by IUGA/ICS in 2010.[2] All examinations for pelvic organ prolapse should be performed with the woman's bladder empty (and if possible an empty rectum). [2] The patient should be examined in the position (for example, left lateral (Sims), supine, standing, or lithotomy) that best demonstrates prolapse according to the patient. The degree of prolapse may be worse later in the day (after a lengthy time in the erect position) than it is earlier in the day. The hymen always remains the fixed point of reference for prolapse description. Pelvic organ prolapse is defined as the descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix), or the apex of the vagina (vaginal vault or cuff scar after hysterectomy) at the level of the hymen or beyond. Most clinicians are generally comfortable with the terms cystocele, rectocele, vaginal vault prolapse, and enterocele, which have historically been used interchangeably with the terms anterior, posterior or apical vaginall prolapse. [2, 71]

a) Stage 0: No prolapse is demonstrated.

b) Stage I: Most distal portion of the prolapse is more than1 cm above the level of the hymen.

c) Stage II: Most distal portion of the prolapse is 1 cm or less proximal to or distal to the plane of the hymen.

d) Stage III: The most distal portion of the prolapse is more than 1 cm below the plane of the hymen.

e) Stage IV: Complete eversion of the total length of the lower genital tract is demonstrated.

1. Pelvic organ prolapse quantification (POP-Q)

Different systems have been used to describe pelvic organ prolapse (POP), however lack objectivity and validation [73, 74]. The need for an objective, site-specific method of quantifying and staging POP lead to the design and validation of the POP-Q system. The original description of the POP-Q was by Bump et al [72] in 1996 and is shown in **figures 1 and 2**. The POP-Q records defects relative to the hymenal remnants in centimetre gradients. These measurements are further staged according to the distal-most defect (F**igure 3**).

Anterior vaginal wall prolapse is defined as descent of the anterior vagina so that the urethra-vesical junction (a point 3cm proximal to the external urinary meatus) or any anterior point proximal to this is less than 3cm above the plane of the hymen. The well-supported anterior vaginal wall should not cross the longitudinal axis of the vaginal canal. Hypermobility of the urethro-vesical junction is demonstrated by having the patient perform a maximum Valsalva effort. In women with hypermobility, the increase in intra-abdominal pressure causes descent of the urethro-vesical junction (bladder neck).

On vaginal examination, there may be loss of the transverse crease between the lower and middle thirds of the anterior vaginal wall and descent of the anterior vaginal wall. Anterolateral protrusion into the vaginal canal may represent unilateral or bilateral detachment of the pubocervical fascia along the anterolateral vaginal sulcus from its attachment to the arcustendineus fascia pelvis (white line). Central protrusions of the anterior vaginal wall may represent defects in the pubocervical fascia below the trigone and base of the bladder. Advanced prolapse of the upper anterior vaginal wall may obstruct a well-supported bladder neck.

Prolapse of the apical segment of the vagina is defined as any descent of the vaginal cuff scar (after hysterectomy) or cervix, below a point that is 2cm less than the total vaginal length above the plane of the hymen. Descent of the cervix or of the vaginal apex following hysterectomy, below the level of the ischial spines is evidence of a defective vaginal suspension mechanism. In some women, the intravaginal portion of the cervix may become elongated and cause the cervix to extend into the lower vaginal canal, simulating prolapse; however the fundus may have good support. In other women, the uterus may prolapse fully outside the hymen as uterine procidentia. Following hysterectomy, the vaginal cuff

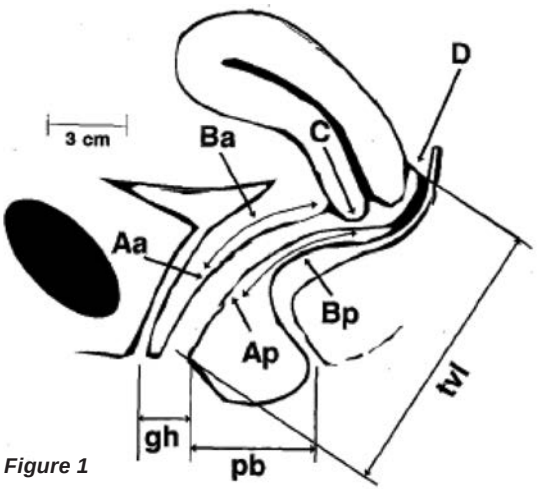


Figure 1

anterior wall **Aa**	anterior wall **Ba**	cervix or cuff **C**
genital hiatus **gh**	perineal body **pb**	total vaginal length **tvl**
posterior wall **Ap**	posterior wall **Bp**	posterior fornix **D**

Figure 2

Figure 1-2 Six sites (Aa, Ba, C, D, Bp, Ap), genital hiatus (gh), perineal body (pb) and total vaginal length (tvl) used for POP-Q and the three by three grid for recording quantitative description of pelvic organ support (72].

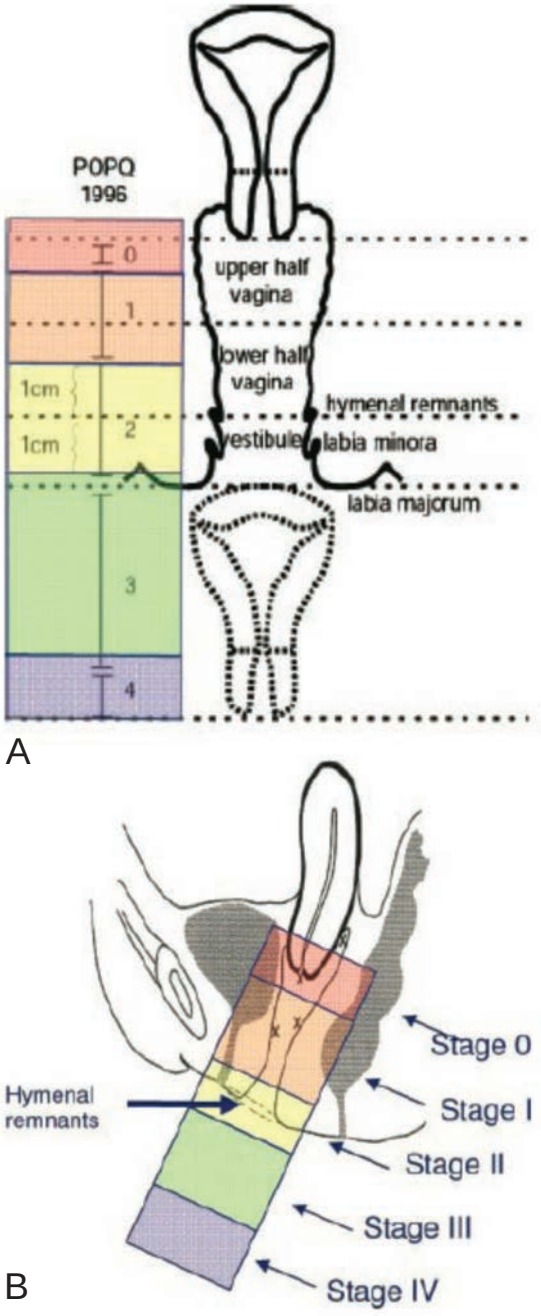


Figure 3A and B – POP-Q system [2]

may be well supported or may prolapse fully outside the hymen, along with other vaginal segments.

Posterior vaginal wall prolapse is defined as any descent of the posterior vaginal wall so that a midline point on the posterior vaginal wall 3cm above the level of the hymen or any posterior point proximal to this, less than 3cm above the plane of the hymen. The well-supported posterior vaginal wall should not cross the longitudinal axis of the vaginal canal. Posterior protrusions into the vaginal canal are most commonly caused by defects in the recto-vaginal fascia allowing protrusions of the small bowel (enterocoele) and/or rectum (rectocele). Normally, the anterior vaginal wall lies upon the posterior vaginal wall. Therefore, protrusions of the posterior vaginal wall can affect the function of the urethra and bladder that lie upon the anterior vaginal wall. For example, distal loss of support in the posterior segment may result in a bulge that compresses the urethra and affects voiding.

The system has not been widely adopted in clinical practice particularly by non-urogynaecologists; owing somewhat to difficulty in learning the assessment [75, 76]. A simplified version of the POP-Q was published by Swift in 2002, whereby the ordinal staging

system of the original scale was retained. Only four measurement points were suggested; i.e. the anterior and posterior vaginal walls, the cervix and the vaginal apex. Measuring the descent of a half-way point between the hymenal remnants and the vaginal wall, cervix or vaginal apex similar to the original POP-Q was described [77]. The inter-observer correlation of the simplified POP-Q was investigated in a secondary analysis of data from a large multicentre study. Weighted kappa statistics for the four POP-Q sites ranged from 0.53 (indicating poor agreement) to 1.0 (denoting excellent agreement) [78].

A review of the POP-Q with the aim of simplifying the assessment tool is underway by the standardisation committees of the International Continence Society (ICS) and International Urogynaecology Association (IUGA) [2].

Despite the difficulties highlighted with the adoption of the POP-Q, reproducibility and reliability of the assessment system have been demonstrated [75, 79, 80]. Hall et al demonstrated that the examination could be completed within four minutes by new learners and two minutes by clinicians experienced with the assessment [81]. With experienced practitioners, POP-Q staging performed using the measurement technique and estimation based on clinical examination are not significantly different [82]. Parnell et al have described a POP-Q model in order to teach the POP-Q examination [83].The POP-Q has gained popularity in the quantification of POP in clinical research protocols and is quoted in 80% of articles on POP [84].

A retrospective study by Collins et al showed that a point Bp value of >-.5 on the POP-Q was found to be strongly correlated with defaecatory dysfunction with symptoms of stool trapping and incomplete evacuation; leading to the need for perineal splinting in women with POP [85]. The POP-Q has been used for the linguistic validation of condition specific health related quality of life questionnaires such as the Pelvic Floor Distress Inventory, Pelvic Floor Impact Questionnaires [86], Prolapse Quality of Life questionnaire [87-89], Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ12) [90] and validation of the Patient Global Impression of Improvement (PGI-i) for urogenital prolapse [91].

The POP-Q measurements have been validated in the dorsal lithotomy, standing and upright positions. Digesu et al. investigated the reliability of the POP-Q in the left lateral position in a sample of 218 patients. Compared with digital examination, the POP-Q system showed a higher degree of reliability (Kappa coefficients of 0.54 and 0.88 respectively) [92].

The POP-Q has been used to define improvement in POP after surgical interventions in a number of studies; including novel laparoscopic techniques such as uterine suspension to the anterior abdominal wall [93], colpocleisis[94), sacrospinous fixation [95, 96], vaginal mesh or abdominal mesh [97-124], animal derived mesh [125-128] and collagen coated mesh repairs [129]. An advantage of the widespread adoption of the POP-Q system is the ability to compare results and surgical outcomes of different studies.

A recent study involving 311 women with symptomatic prolapse aimed to investigate the influence of increasing age, body mass index(BMI) and parity on POP-Q measurements [130]. The results of the study showed no correlation between BMI and POP-Q measurements. Increasing parity was associated with greater scores on point Aa. Aging was associated with worsening global POP-Q scores. The correlation between POP-Q measurements and symptoms of prolapse were found to be poor in a study of 64 patients with stage ?or greater prolapse [131]. This study reported that higher BMI was associated with experiencing fewer symptoms of prolapse.

An observational study of 94 women underwent POP-Q and pelvic ultrasound assessment of their type of cystocele [132]. The aim of the study was to investigate the agreement between physical POP-Q and the Green radiological classification of cystocele. Kappa co-efficients ranged between 0.56-0.54 and 0.32-0.79 for clinical and ultrasound diagnosis respectively. The clinical utility of these findings has not been established. The quantification of POP using the POP-Q was compared with dynamic MRI and perineal ultrasonographic imaging; the results showed that correlations of the anterior compartment were good to moderate, compared with central and posterior compartment that were poor to moderate. Correlations were independent of the Pop-Q staging measurements [133].

Sexual function in women with prolapse before and after treatment has been investigated in a number of studies, using the POP-Q as an objective measure of prolapse. One study of 68 women undergoing transvaginal mesh repair found improvement in POP-Q scores postoperatively, however dyspareunia was a significant factor for pre-menopausal women [134]. Another study looking at sexual function in women after pelvic floor surgery found significant improvement in both POP-Q scores and sexual satisfaction in women after surgery – interestingly, none of the women had undergone mesh repair [135].

3. GENERAL RECOMMENDATIONS IN THE FEMALE PATIENT

1. In order to diagnose female incontinence, interviews need to be complemented by a targeted physical exam and sound clinical judgment to establish a probable diagnosis. **LEVEL 1, Grade B.**

    a) A positive response to the question “Do you lose urine during physical exertion, lifting, coughing, laughing, or sneezing?”, increases

the ratio to 2.2 times that a woman has stress incontinence than to the woman who responds negatively.

b) A positive response to the question " Do you ever experience such a strong and sudden urge to void that you leak before reaching the toilet?, increases the ratio to 4 times as likely that a woman has urgency incontinence than to the woman who responds negatively.

c) Positive answers to the questions in (a) and (b) strongly suggest mixed incontinence.

d) Of note, a response ratio of 5 times as likely is generally accepted as a positive likelihood ratio.

2. There are no studies which address the components of the general physical examination for diagnosing the type of urinary incontinence in women. **LEVEL 1 Grade B**.

a) Urinary leakage with a cough or Valsalva maneover increases the likelihood by 3.1 times over a stress test that demonstrates no leakage.

b) The cough test is more reliable than a pad test for diagnosing stress incontinence.

3. An assessment of pelvic floor anatomy and strength should be performed during a routine pelvic examination. **LEVEL 5 Grade D**.

a) A simple description of the relationship of the anterior, superior and posterior walls at rest and with straining is recommended.

b) The degree of prolapse has not been correlated with the presence or degree of urinary loss.

c) Although the POP-Q examination has been reviewed by this committee on Initial Assessment and has been shown to be reproducible and reliable, this committee does not recommend the routine use of the POP-Q by primary caregivers.

4. RESEARCH RECOMMENDATIONS IN THE FEMALE PATIENT

1. Investigations to correlate the accuracy of the history (simple questions) and physical examination (stress test, pelvic anatomy, and pelvic strength) for the diagnosis of stress (effort), urgency (compelling urge), and mixed (combined) incontinence are recommended.

2. Investigations which correlate the accuracy of combining the history and physical findings for predicting the treatment response to empiric therapies involving conservative and pharmacological intervention are recommended.

3. A simplified, accurate and reproducible system for grading anatomic changes, and establishing the likelihood or presence of stress (effort) incontinence are needed. Investigations into the development of specific maneouvers which involve the reduction of prolapse and the "unmasking" of leakage and the reliability of these maneouvers in both the diagnosis of stress incontinence, and response to empiric conservative therapy should be undertaken.

VI. SPECIFIC POUPULATION: EVALUATION OF THE MALE PATIENT

1. CHARACTERISTICS OF MALE INCONTINENCE

In the male patients, lower urinary tract dysfunction, and obstruction from benign prostatic enlargement presents a multi-factorial paradigm for assessing symptom aetiology. Lower urinary tract symptoms (LUTS: voiding, storage and post-micturition symptoms) in men have a significant effect on quality of life (QOL), as compared with the unaffected general population [136]. The aetiology of voiding symptoms may vary, from benign prostatic hyperplasia (BPH), urethral stricture, primary bladder neck dysfunction, or abnormal voiding dynamics of the detrusor. Several epidemiological reports have demonstrated that storage symptoms (including urgency and urgency incontinence) defined as OAB syndrome also increases with age in men [137,138]. In men with bladder outlet obstruction and idiopathic detrusor overactivity, older age and a higher grade of obstruction has been reported [139]. Chronic prostatic pain syndromes (e.g. non-bacterial chronic prostatitis) and other pelvic floor dysfunctions can also present with a component of symptoms compatible with storage symptoms. In younger men, primary bladder neck dysfunction is a common cause of LUTS, with or without pelvic pain [140]. Functional abnormalities of striated sphincter relaxation may also occur in young men [141]. The complexity of the presenting symptoms and the various differential diagnoses mandate a thorough basic assessment of the lower urinary tract in men to plan optimal therapeutic intervention.

a) Prevalance of OAB (male)

In the NOBLE study, a different sex-specific pattern emerged for OAB with or without urgency incontinence [142]. The prevalence of OAB with urgency incontinence displays a steeper age-related increase among women than among men and the gender difference is statistically significant. In women, OAB with urgency incontinence increased more than nine-fold from 2.0% in those 18-24 years of age to 19.1% among those 65-74 years of age. In contrast, a substantial increase in prevalence of OAB with urgency incontinence among men did not occur until 65 years of age, reaching 8.2% for ages 65-74 years and 10.2% for those 75 years and older. In men, OAB without urgency incontinence increased approximately three-fold, from 8.5% below 45 years

of age to 21.8% after 55 years of age, whereas OAB without urgency incontinence gradually increased in women less than 44 years of age and reached a plateau in women over the age of 44 years.

Prevalence ratios for OAB with urgency incontinence and for OAB without incontinence were significantly elevated for men who self-reported with a history of prostate problems. Thus, the evaluation of men with symptoms of OAB syndrome depends on the identification and assessment of lower urinary tract obstruction that may be a cause (in part or in entirety) of the presenting symptoms.

Recently, Markland et al. estimated trends in the prevalence of urinary incontinence in the adult population of the United States from 2001 through 2008 before and after adjusting for other potential associated factors. They analyzed data on 17,850 adults 20 years or older who participated in the 2001 to 2008 cycles of the National Health and Nutrition Examination Survey. The age-standardised prevalence of urinary incontinence in the combined surveys was 13.9% in men, and 51.1% in women. Prevalence in women increased from 49.5% in 2001 to 2002, to 53.4% in 2007 to 2008 (Ptrend =0.01) and in men from 11.5% to 15.1%, respectively (Ptrend = 0.01). In women, the increased prevalence was explained in part, by differences in age, race/ethnicity, obesity, diabetes and select chronic diseases across the survey periods. In men, an adjustment for possible associated factors did not explain the increasing prevalence of urinary incontinence [142].

Recent epidemiological surveys have demonstrated a significant association between metabolic syndrome (MS) and life style factors, and LUTS, including incontinence. Well known life style factors, such as food; meat, fat for example, are widely known high risk factor of BPH. It has been revealed that lifestyle factors associated with metabolism – including obesity, blood glucose, exercise, and diet – also contribute substantially to the development of these conditions [143]. In the Third National Health and Nutrition Examination Survey conducted on men older than 60 yr, the odds of having LUTS increased significantly in men with three or more components of MS when compared with their control counterparts [odds ratio (OR) 1.80; 95%confidence interval (CI) 1.11–2.94] [144]. Patients with MS also had an increasing rate of prostate growth, which might account for the increasing prevalence of LUTS [145].

Boston Area Community Health (BACH) survey is a population based epidemiological survey of a broad range of urological symptoms and risk factors in a randomly selected 1,899 men [146]. Using ATP III guideline to characterise MS and AUA symptom index (AUASI) to assess LUTS, it showed that there is a significant association between MS and voiding symptoms rather than storage symptoms of LUTS. The overall prevalence of MS in this study was 29% and demonstrated the association of each LUTS and individual components of MS. Statistically significant associations between LUTS and type 2 diabetes and/or increased blood sugar were observed. Recent studies [147, 148] showed that administration of statins, which are medications currently prescribed for prevention of coronary heart disease, stroke, and peripheral artery diseases, may help prevent common urological problems in aging men.

b) Prevalance of Incontinence after surgery (male – the prostate)

Another important issue in male patients is incontinence after surgery or intervention for BPO and prostate cancer. A survey in England of 5276 patients who had undergone TURP found that one-third of men (n=1759 men) who were continent before surgery reported some incontinence 3 months post TURP [149]. Recently, a systematic review of the literature revealed that many minimally invasive techniques and surgeries for management of BPO result in urinary incontinence, which was observed more often following TURP (1.4%). The rate of urinary incontinence after other techniques are as follows: HIFU; 0.0%, ILCP: 0.1%, TUMT: 0.1%, TUNA: 0.0%, TUVP: 0.9%, VLAP: 0.2%, HoLEP: 1.2% [150]. (All these abbreviations need to be spelt out in full first) Carson et al. reported that incontinence occurs in 0.5 to 1.0% of all patients undergoing open prostatectomy for benign prostatic disease [151].

Urinary incontinence after radical prostatectomy continues to be a widespread and difficult problem for urologists to treat. After radical prostatectomy, Donnellan et al. reported that 6% of men were mildly incontinent, 6% were moderately incontinent and 4% were severely incontinent at 1 year after surgery [152]. Wei et al reported rates of 6% to 69% [153]. Flynn et al. reported that the rate of post-radical prostatectomy urinary incontinence ranges greatly in the published literature, from 3% to 74% after surgery, with varying definitions. Long-term incontinence after radical prostatectomy that significantly affects quality of life and requires surgical treatment occurs in approximately 5% of cases [154]. Catalona et al. showed that incontinence after prostate surgery was primarily dependent on the age of the patient. The older the patient, the more likely he is to be incontinent and to never regain urinary control. For 40-49 year olds, permanent incontinence is 8% (4/53) 50-59 year olds 3% (12/358) 60-69 year olds 8% (48/632) while after 70 it is 13% (or 38/282) making an overall 7.7% (102/1325) [155]. Laparoscopic and robotic prostatectomies have been reported to have lower rates of urinary incontinence [156]. After permanent prostate brachytherapy, urinary incontinence was reported in 0-19% of patients [157].

Although radical prostatectomy has a clinically significant beneficial effect on LUTS with significant

improvements of AUA symptom index and flow rate, [158,159] urinary leakage can have a major impact on QOL. Greater degrees of urinary loss have been correlated with greater bother and more significant life-style changes [162]. A Medicare survey by Fowler showed that in 1072 patients, more than half of the patients with urinary leakage considered it to be a medium or large problem [160]. In spite of these findings, many investigators have been encouraged by overall patient satisfaction with surgery and patients' willingness to undergo surgery again, if faced with the same situation [160].

In the immediate postoperative period, stress and urgency incontinence are common. These symptoms have been attributed to varying degrees of oedema and inflammation that may be present in the healing prostatic urethra. The majority of men achieve continence without invasive intervention following radical prostatectomy. Final continence status should be measured using self-administrated disease specific instruments at 24 months after operation [160]. No factors (age, severity of LUTS, Gleason score, bilateral nerve sparing surgery and estimated blood loss) were identified that predicted early return of continence [1152].

Post-prostatectomy incontinence may be caused by sphincter malfunction and/or bladder dysfunction [161, 162]. Urinary control in the adult male depends on integrity of both the internal and external sphincters. Even during TURP, the internal sphincter mechanism is virtually destroyed, and in some cases, the external sphincter is also damaged. Thus post-prostatectomy stress incontinence may result.

In a recent study of patients undergoing radical prostatectomy that specifically evaluated detrusor dysfunction [163] de novo detrusor underactivity and impaired or poor compliance, presumed to be a consequence of bladder denervation, occurred in a limited proportion of patients (28.6% and 18.4% respectively). However, it may cause urgency and urgency incontinence, which may be resolved in the majority within 8 months. Detrusor underactivity and decreased bladder compliance are also preexisting conditions in about 30% and 20% of patients. The conditions relate to the presence of BOO, and they do not appear to be influenced by prostatectomy. Persistent detrusor overactivity after obstruction relief is probably related to concomitant sphincter deficiency and stress urinary incontinence, which increase afferent nerve activity of the proximal urethra and induce involuntary detrusor contractions [164].

Obstruction after prostatectomy, resulting from an anastomotic stricture or residual prostatic tissue (post TUR-P), may also play an important role in the development of post-prostatectomy incontinence. Obstructing stricture often causes increase in post-void residual urine, resulting in urinary leakage and/or a weak urinary stream. It has been reported that the anastomotic stricture treatment rates after radical prostatectomy are 16% to 33% [165,166].

2. GENERAL MEDICAL HISTORY (MALE)

The medical history should focus on the urinary tract, previous surgical and radiation therapy history, medical condition and symptoms that may cause to bladder dysfunction, familial history of prostate diseases (BPH and cancer), and a review of sexual and bowel habits. If the patient has experienced prostatic surgery, surgical history, current stage of the prostatic cancer, co-morbid conditions, and typeof prostatic surgery (retropubic, perineal, laparoscopic, or robotic) should be assessed. Radiation therapy types are also assessed.

Urinary incontinence is rare in men without a history of previous trauma or prostatic or pelvic surgery; therefore, neurogenic bladder dysfunction (neurogenic bladder) must be considered in men with no history of surgery or trauma.

A critical assessment of current medications is recommended to exclude the effects of any pharmacological agents on lower urinary tract function. For example, angiotensin-converting enzyme inhibitors cause chronic cough, which can exacerbate activity-related (stress) incontinence. Alpha-adrenergic blockers cause decreased urethral resistance. This can exacerbate activity-related (stress) incontinence. Alpha-adrenergic agonists cause increased urethral resistance, resulting in exacerbation of urinary retention. Anticholinergics cause detrusor relaxation, which can cause straining to void and possible urinary retention. Diuretics have no direct effect on detrusor function, but can cause an increase in urinary volume, leading to frequency and urgency. Calcium channel blockers relax smooth muscles, causing straining to void may contribute to urinary retention. Psychotropic medications relax smooth muscles of detrusor, causing straining to void and may contribute to urinary retention. Sedatives have no direct affecton the bladder but can contribute to sedation and delirium [167]. All this is relevant to women as well as men so should not be in the male section

3. SYMPTOM ASSESSMENT (MALE)

Symptom assessment in men with incontinence should aim to identify and exclude patients with complicated incontinence that need to be referred for specialised management. Complicated incontinence comprises patients with recurrent incontinence after failed previous surgery, with total urinary incontinence, and/or with associated symptoms such as pain, haematuria, recurrent urinary tract infection, voiding symptoms, and/or a history of previous pelvic radiotherapy or radical pelvic surgery [168].

Because the occurrence of LUTS in men does not necessarily indicate concomitant prostate enlargement and/or obstruction, specific modalities should be

utilised to ascertain the potential for the aetiological role of these entities. A variety of symptom scores has been described to assess male patients with LUTS. In men, the American Urological Association symptom score for BPH (AUA-7) is most commonly used in North America for assessment of subjective symptoms. However, equally reproducible data can be obtained from the International Prostate Symptom Score (IPSS), the ICSmale questionnaire (now renamed the ICIQMLUTS, long and short forms, as part of the ICIQ modular questionnaire: www.iciq.net).

The IPSS has been the most widely used (in many countries and languages), but neglects the symptom of urgency incontinence, a symptom that produces significant bother. The ICIQMLUTS (ICSmale-SF) is slightly longer, but takes into account the symptom of urgency incontinence, and in fact may be divided into voiding and incontinence sub-scores. To date, it has not been as widely used as the IPSS, but may see more use that is widespread as part of the ICIQ Modular Questionnaire.

Overactive bladder symptom scores are also very useful for male patients with storage symptoms including urgency incontinence [169,170].

Among LUTS, urgency, nocturia, and hesitancy are most bothersome, whereas weak stream, urgency, and frequency are the most prevalent in pooled populations being evaluated for BPH [171]. Postmicturition dribbling is often provoked by an obstructing disease such as BPH or urethral stricture but can also be a symptom of a urethral diverticulum.

Many studies have stressed the lack of the reliability of symptoms and emphasized the important role of urodynamics testing in order to determine the cause of post-prostatectomy incontinence, [172,173]. Nevertheless, valuable information can be gained from a careful history with regard to incontinence, especially when related to sphincter dysfunction. The symptom of stress incontinence is highly predictive of the presence of sphincter dysfunction. Chao and Mayo found that 67 of 71 men with post-prostatectomy incontinence secondary to sphincter dysfunction complained of the symptom of stress incontinence [174]. Similarly, Ficazzola and Nitti found 95% positive predictive value and a 100 % negative predictive value for symptom of stress incontinence [161]. Urgency incontinence as a predictor of bladder dysfunction does not seem to be as valuable, and the presence of bladder dysfunction cannot be determined accurately without urodynamics testing [161, 174].

An important aspect of the assessment of male incontinence should be a description of the type and severity of incontinence and precipitating events, Severity may be determined by the number of episodes per day, the need for protection (e.g., pads, penile clamp, external catheter), and the impact of incontinence on activities of daily living. Bladder diaries and pad tests can quantify severity.

A bladder diary (or frequency volume chart) kept for 3 to 5 days may be useful in almost all male patients, especially in those with OAB. (refer to section VII, A, 1,a frequency-volume chart and bladder diary, and the Appendix Annex 1). The time and voided volume are recorded for each micturition during several 24-hour periods. Bladder diary completion by the patient provides useful evidence about the normal urinary habits of the patient, including giving some estimate of bladder capacity and diurnal and nocturnal frequency, urgency and stress incontinence. It also helps to identify patients with nocturnal polyuria or excessive fluid intake that are common in the aging male. The data obtained from a frequency-volume chart provide a strong correlation to cystometric capacities and are reasonably immune to the effect of detrusor overactivity in men with LUTS [175].

The 24-hour pad test is an excellent test to quantify the amount of urine leakage in men. Since most patients use different size and type of pad, it is difficult to compare number of pad/day per patient. Furthermore, some patients are very disturbed by any leakage at all and change the pads very frequently, before they are saturated. The other distinction is between a safety pad and true urinaryincontinence. In general,the each 1g weight equals 1ml urine loss. A cut-off value of 250gm of urine has been proposed to categorise minor from more troublesome or severe leakage [176] Recently, Machold et al. suggested that the technical feasibility of the 20-min pad test to evaluate post-prostatectomy incontinence was excellent. The results correlated significantly with both the self-assessment via questionnaire ($r = 0.63$; $p<0.001$) and the 1-hour pad test (ICS; $r = 0.66$; $p<0.001$). Moreover, it was highly reliable ($r = 0.74$; $p<0.0005$) with excellent patient acceptance. [177]

4. PHYSICAL EXAMINATION (MALE)

The assessments focus on general physical examination, digital rectal examination (DRE) and neurological testing of the perineum and lower extremities. **In general a physical examination should include a specific evaluation of the surgical wound, the presence or absence of a distended bladder, or excoriation of the genitals secondary to urinary incontinence.** Abdominal palpation to evaluate bladder distension, especially in elderly incontinent men, who may have overflow leakage due to obstruction, is recommended. A post-void residual volume should be measured in patients suspected of urinary retention.The examination should also include external genitalia, location of the urethral meatus, a retractable foreskin and evidence of congenital malformation. The evidence of urethral discharge after abdominal straining (a Valsalva manoeuvre) or coughing in either the supine or upright position should be performed so that the presence of stress incontinence can be ascertained.

A focused neurological examination is also highly recommended. In a patient suspected of neurogenic bladder, evaluation of perineal sensation and lower extremity neuromuscular function, and anal sphincter tone, which is often decreased in neurogenic patients [178] is important. A focused neurological examination should also assess the patient's general mental status and ambulatory status.

A DRE should include palpation of the prostate to assess size, symmetry and consistency of the gland and its relation to the pelvic sidewall and the rectum. An enlarged, indurated and painful prostate may imply BPH, prostate cancer and prostatitis, respectively. Locally advanced prostate cancer can also produce OAB-like symptoms. DRE may exclude prostatic cancer, although its specificity and sensitivity is low [179]. DRE tends to underestimate the true prostatic size: if the prostate feels large by DRE, it usually also is found to be enlarged by ultrasound or other measurement technique [180,181]. Prostate volume has been associated with the risk of BPH progression [182] and response to treatment [183]. It has been reported that men with BPH with idiopathic detrusor overactivity showed a significantly higher incidence (54%) of intravesical protrusion of the prostate [184]. This finding suggests that intravesical protrusion may in some way increase afferent impulses from the prostate and alter the stability status of the bladder. Occasionally tumours of the anal canal can be diagnosed while performing DRE of the prostate.

5. URINALYSIS AND URINE CYTOLOGY (MALE).

Bladder cancer, carcinoma in situ of the bladder, urinary tract infections, urethral strictures, and bladder stones can cause OAB-like symptoms in aged men. Although haematuria or pyuria is not universally present in those conditions, urinalysis is important to rule out these diseases. Urinalysis is not a single test; complete urinalysis includes physical, chemical, and microscopic examinations. Dipstick urinalysis is certainly convenient but false-positive and false negative results may occur. It is considered an inexpensive diagnostic test able to identify patients with urinary tract infection as indicated by the presence of leucocyte esterases and nitrites. A substantial proportion of older patients with chronic OAB-like symptoms have significant bacteriuria, sometimes accompanied by pyuria. In men, recent urinary tract infections were associated with OAB without urgency incontinence (prevalence ration=2.9; 95% CI: 1.6-5.0) [138]. However, infection may exist in the absence of pyuria and, in the elderly population, pyuria may develop in the absence of urinary tract infection. Microscopic haematuria can be easily identified by dipsticking because of the presence of haemoglobin. The detection of haematuria is important because the condition is associated with a 4-5% risk of diagnosing urological disorder or malignancy within 3 years. Because of the high prevalence of urinary tract infection and the increase of LUTS in the presence of urinary tract infection, all guidelines on the management of patients with LUTS suggestive of BPO, and urinary incontinence, endorse the use of urinalysis in primary care management [185,186]].

Urine cytology is also recommended in male patients with haematuria and a predominance of storage symptoms, especially with a history of smoking or other factors, to aid in the diagnosis of bladder carcinoma in situ and bladder cancer This applies to both men and women. [185,186]].

6. MEASUREMENT OF THE SERUM CREATININE (MALE)

Epidemiological studies in community dwelling men have shown the absence of any association between BPO/BPE/BPO and chronic kidney disease [187] suggesting that screening for renal function is not justified in male patients. Recently, data from the MTOPS study showed that the risk of developing de novo renal failure in men with LUTS is low (less than 1%) suggesting that is not necessary to monitor renal function in patients with LUTS / BPO [188].

7. MEASUREMENT OF THE SERUM PROSTATESPECIFIC ANTIGEN (PSA) (MALE)

In most patients, a normal DRE may be sufficient to exclude locally advanced cancer as a cause of LUTS or OAB. There is no consensus as to the measurement of prostate specific antigen (PSA) in patients with LUTS. The rationale for measuring PSA is twofold: to screen for prostate cancer [189] and to measure a parameter with prognostic value for the progression of BPH and the response to treatment [192, 193]. Because prostatic cancer is one of the potential causes of LUTS or OAB in men, PSA (together with DRE) is a relatively sensitive way to exclude prostatic cancer as a diagnosis [190, 191]. PSA measurement is recommended in men with LUTS and a life expectancy of over 10 years in whom the diagnosis of prostate cancer would change the management of patient's symptoms. Given the uncertainties, surroundingprostate cancer detection physicians must use clinical judgment in determining which patients should or should not undergo transrectal ultrasonography and prostate biopsy in response to a particular PSA [192].

However, it is important to understand that about 25% of men with BPH have a serum PSA greater than 4 ng/ml. Because of the overlap between serum PSA values in men with BPH and those with clinically localised prostate cancer, other parameters (PSA velocity, free/total PSA ratio, complexed PSA and PSA density) will assist diagnostic specificity [193, 194]. It has been suggested that a relationship between initial PSA level and subsequent prostate cancer detection with a stepwise increase in cancer detection rate (from <1% to 58%) in patients with

<1.0 ng/ml, 1.1-2.5, 2.6-4.0, 4-1-10.0 and >10 ng/ml PSA value in over 26.000 patients enrolled in a screening programme [156]. In addition, Thompson reported data on prostate cancer prevalence from the prostate cancer prevention trial [157]. This trial confirmed a stepwise increase in the risk of having a prostate cancer in patients with serum PSA from 0.5 to 4.0 ng/ml, but showing the limitation of the current threshold of 4.0 ng/ml. Change of PSA threshold from 4.0 to 2.0 ng/ml has been proposed but currently no consensus exists [197].

In addition, serum PSA is a reasonable predictor of prostate volume in men with LUTS and may be utilised in this capacity in making clinical decisions [192]. The role of the IPSS score in the assessment of BOO is questionable, and that the grade of obstruction correlates better with prostate volume, PVR, and Qmax [198]. Moderate-to-severe LUTS in men can result in urinary retention. The incidence of retention in men with untreated LUTS in community-based trials is 6.8 per 1000 during longitudinal follow-up of 4 years [199]. If only patients with moderate-to-severe symptoms are considered, the rate of retention increases to 25 per 1000 [200]. In a meta-analysis of predictors of retention in pooled groups of placebo patients from clinical trials of men with LUTS undergoing active interventions (4300 patients), Roehrborn et al. found PSA and prostate volume to be strong independent predictors of urinary retention and the need for surgery in men with LUTS followed up longitudinally in clinical trials [181, 201].

Laniado et al [202] have also tested the hypothesis that PSA level be utilised to predict the presence or absence of BOO, evaluated by pressure flow studies. In patients with LUTS, those with a PSA more than 4 ng/ml are significantly more likely to have some degree of BOO. Conversely, patients with PSA less than 2 ng/ml have a 33% risk of BOO.

8. RECOMMENDATIONS

1. Male patients differ from female patients in the presentation of LUTS. The incidence of OAB wet is lower until the 7th decade. (Level 2)
2. Stress urinary incontinence is primarily associated with surgery of the prostate in male patients. (Level 2)
3. Disorders of bladder emptying from benign prostatic enlargement should be considered before treating male patients for OAB symptoms. (Level 2) (Grade B).
4. In addition to DRE, PSA measurement is recommended in selected male patients with OAB.

9. FUTURE RESEARCH

1. Improve the understanding of the underlying pathophysiology and contributory clinical factors involved in the development and treatment of detrusor overactivity in the male patient, especially in differentiating the condition from female patients.
2. Develop simple, non-invasive, cost-effective methods to determine the contribution of bladder storage and bladder emptying abnormalities in male patients.

REFERENCES

1. Abrams P, Cardozo L, Fall M et al. The standardization of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167-178.
2. Haylen BT, de Ridder D, Freeman RM et al. An international urogynecological association (IUGA)/International continence society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29:4-20.
3. Weiss JP, Wein AJ,van Kerrebroeck P et al. Nocturia: new directions. Neurourol Urodyn 2011; 30:700–703.
4. Cartwright R, Cardozo L. Usage of International Continence Society standardized terminology: a bibliometric and questionnaire study. Neurourol Urodyn 2010;29:1373-1379.
5. Tikkinen KAO, Johnson TM, Tammela RLJ, et al. NocN turia frequency, bother and quality of life: How often is too often? A population-based study in Finland. Eur Urol 2010;57:488–98
6. Impact of nocturia on health-related quality of life and medical outcomes study sleep score in men. Kim SO, Choi HS, Kim YJ, Kim HS, Hwang IS, Hwang EC, Oh KJ, Jung SI, Kang TW, Kwon D, Park K, Ryu SB. Int Neurourol J. 2011 Jun;15(2):82-6
7. Self-rated sleep characteristics and bother from nocturia. Vaughan CP, Eisenstein R, Bliwise DL, Endeshaw YK, Nagamia ZJ, Wolf RA, Johnson TM 2nd. Int J Clin Pract. 2012 Apr;66(4):369-73
8. De Wachter S, Hanno P.Urgency: all or none phenomenon? Neurourol Urodyn. 2010;29:616-7
9. van Kerrebroeck P, Abrams P, Chaikin D et al. The standardization of terminology in nocturia: report from the standardization sub-committee of the International Continence Society. Neurourol Urodynam 2002;21:179-183.
10. Holroyd-Leduc JM, Tannenbaum C, Thorpe KE, Strauss SE. What type of urinary incontinence does this woman have? JAMA 2008;299:1446-1456.
11. Bright E, Drake MJ, Abrams P. Urinary diaries: evidence for the development and validation of diary content, format, and duration. Neurourol Urodyn. 2011 Mar;30(3):348-52.
12. Tannenbaum C, Corcos J. Outcomes in urinary incontinence: reconciling clinical relevance with scientific rigour. Eur Urol. 2008 Jun;53(6):1151-61.
13. Homma Y, Ando T, Yoshida M, et al. Voiding and incontinence frequencies: variability of diary data and required diary length. Neurourol Urodyn 2002;21:204–9.
14. Gerber GS, Brendler CB. Evaluation of the urologic patient: history, physical examination, and urinalysis. In: Walsh PC, editor. Campbell's Urology. 8 ed. Philadelphia: Saunders; 2002. p. 83-110.
15. Bradbury, SM. Collection of urine specimens in general practice, to clean or not to clean? JR Coll Gen Pract 1988 Aug;38(313):363-5. Lifshitz E, Kramer L. Outpatient urine culture: does dry collection technique matter? Arch Intern Med 2000 Sept 11; 160(16):2537-40.
16. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol 2000;163(2):524-7.

17. Roehrborn CG, McConnell JD, Barry MJ. Guidelines on the Management of Benign Prostatic Hyperplasia. Linthicum, MD: American Urological Association, Education and Research, Inc.,2003.)

18. Rosenberg MT, Staskin DR, Kaplan SA et al. A practical guide to the evaluation and treatment of male lower urinary tract symptoms in the primary care setting. Int J Clin Pract 2007; 61: 1535–46.)

19. Al-Daghistani HI, Abdel-Dayem M. Diagnostic value of various urine tests in the Jordanian population with urinary tract infection. Clin Chem Lab Med 2002;40(10):1048-51.

20. Semeniuk H, Church D. Evaluation of the leukocyte esterase and nitrite urine dipstick screening tests for detection of bacteriuria in women with suspected uncomplicated urinary tract infections. Journal of Clinical MIcrobiol 1999;37(9):3051-3052.

21. European Urinalysis Guidelines. Summary. Scand J Clin Lab Invest 2000;60:1-96.

22. Ouslander JG. Geriatric urinary incontinence. Dis Mon 1992;38(2):65-149.

23. Ouslander JG, Schnelle JF. Incontinence in the nursing home. Ann Int Med 1995;122(6):438-449.

24. Young SB, Pingeton DM. A practical approach to perimenopausal and postmenopausal urinary incontinence. Obstet Gynecol Clin N Am 1994;21(2):357-379.

25. McIntosh LJ, Richardson DA. 30-minute evaluation of incontinence in the older woman. Geriatrics 1994;49(2):35-8, 43-4.

26. Belmin J, Hervias Y, Avellano E, Oudart O, Durand I. Reliability of sampling urine from disposable diapers in elderly incontinent women. J Am Geratr Soc 1993;41(11):1182-1186.

27. DuBeau CE, Resnick NM. Evaluation of the causes and severity of geriatric incontinence. A critical appraisal. Urol Clin North Am 1991;18(2):243-256.

28. Ouslander JG, Schapira M, Schnelle JF, Fingold S. Pyuria among chronically incontinent but otherwise asymptomatic nursing home residents. J Am Geratr Soc 1996;44(4):420-423.

29. Goode PS, Locher JL, Bryant RL, Roth DL, Burgio KL. Measurement of postvoid residual urine with portable transabdominal bladder ultrasound scanner and urethral catheterization. Int Urogynecol J Pelvic Floor Dysfunct 2000; 11: 296-300

30. Ouslander JG, Simmons S, Tuico E, Nigam JG, Fingold S, Bates-Jensen B, Schnelle JF. Use of a portable ultrasound device to measure post-void residual volume among incontinent nursing home residents. J Am Geriatr Soc 1994; 42: 1189-1192.

31. Nygaard IE. Postvoid residual volume cannot be accurately estimated by bimanual examination. Int Urogynecol J Pelvic Floor Dysfunct 1996; 7: 74-6

32. Hall AF, Theofrastus JP, Cundiff GW, Harris RL, Hamilton LF, Swift SE et al. Interobserver and intraobserver reliability of the proposed International Continence Society, Society of Gynecologic Surgeons and American Urogynecologic Society, pelvic organ prolapse classification system. Am J Obstet Gynecol 1996; 175: 1467-1470

33. Griffiths DJ, Harrison G, Moore K, McCracken P: Variability of post-void residual urine volume in the elderly. Urol Res 1996; 24: 23.

34. Fowler CJ, Panicker JN, Drake M, et al. A UK consensus on the management of the bladder in multiple sclerosis. J Neurol Neurosurg Psychiatry 2009;80(5):470-7.

35. Barabas G, Mölstad S. No association between elevated post-void residual volume and bacteriuria in residents of nursing homes. Scand J Prim Health Care 2005; 23: 52-56.

36. Agency for Health Care Policy and Research. Clinical practice guideline: urinary incontinence in adults. AHPCR Pub. No. 96-0682. Rockville, MD: Dept of Health and Human Services (US), Agency for Health Care Policy and Research; 1996.

37. Gehrich A, Stany MP, Fischer JR, Buller J, Zahn CM. Establishing a mean postvoid residual volume in asymptomatic perimenopausal and postmenopausal women. Obstet Gynecol 2007; 110: 827-832.

38. Tseng LH, Liang CC, Chang YL, Lee SJ, Lloyd LK, Chen CK. Postvoid residual urine in women with stress incontinence. Neurourol Urodyn 2008; 27: 48-51.

39. Haylen BT, Law MG, Frazer M. Urine flow rates and residual urine volumes in urogynecology patients. Int Urogynecol J 1999; 10: 378-383.

40. Fitzgerald MP, Jaffar J, Brubaker L. Risk factors for an elevated postvoid residual urine volume in women with symptoms of urinary urgency, frequency and urge incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2001; 12: 237-239.

41. Lukacz ES, Duhamel E, Menefee SA et al. Elevated postvoid residual in women with pelvic floor disorders: prevalence and associated risk factors. Int Urogynecol J Pelvic Floor Dysfunct 2007; 18: 397-400.

42. Wu J, Baguley IJ. Urinary retention in a general rehabilitation unit: prevalence, clinical outcome, and the role of screening. Arch Phys Med Rehabil 2005; 86: 1772-1777.

43. Milleman M, Langenstroer P, Guralnick ML. Post-void residual urine volume in women with overactive bladder symptoms. J Urol 2004; 172(5 Pt 1): 1911-1914.

44. Nager CW, FitzGerald M, Kraus SR, Chai TC, Zyczynski H, Sirls L, Lemack GE, Lloyd LK, Litman HJ, Stoddard AM, Baker J, Steers W, Urinary Incontinence Treatment Network. Urodynamic measures do not predict stress continence outcomes after surgery for stress urinary incontinence in selected women. J Urol 2008; 179: 1470-147417.

45. Stoller, M. L. and Millard, R. J. The accuracy of a catheterized residual urine. J Urol. 1989; 141: 15-16.

46. Holmes, J. H. Ultrasonic studies of the bladder. J Urol. 1967; 97: 654-663.

47. Marks, L. S., Dorey, F. J., Macairan, M. L., et al. Three-dimensional ultrasound device for rapid determination of bladder volume. Urology.1997; 50: 341-348.

48. Abrams, P., Griffiths, D., Hoefner, K., Liao, L., Schafer, W., Tubaro, A., and Zimmern, P. The Urodynamic assessment of lower urinary tract symptoms. In: Benign Prostatic Hyperplasia. Eds. Chatelain, C., Denis, L., Foo, K., Khoury, S., and McConnell, J. Health Publication Ltd., Plymouth, 2001, pp:227-281.

49. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. J Urol. 2003; 170: 530-547.

50. Madersbacher, S., Alivizatos, G., Nordling, J., et al. EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). Eur.Urol. 2004; 46: 547-554.

51. Bates, T. S., Sugiono, M., James, E. D., Stott, M. A., and Pocock, R. D. Is the conservative management of chronic retention in men ever justified? BJU.Int. 2003; 92: 581-583.

52. Vesely S, Knutson T, Fall M, Damber JE, Dahlstrand C. Clinical diagnosis of bladder outlet obstruction in men with lower urinary tract symptoms: reliability of commonly measured parameters and the role of idiopathic detrusor overactivity. Neurourol Urodyn 2003;22(4):301-305.

53. Holroyd-Leduc J, Tannenbaum C, Thorpe H, etal. What Type of Urinary incontinence Does This Woman Have? JAMA, 2008 299(12): 1446-1456

54. Rohr G, Christensen K, Ulstrup K, Kragstrup J. Reproducibility and validity of simple questions to identify urinary incontinence in elderly women. Acta Obstet Gynecol Scand. 2004;83(10):969-972.

55. Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, Assassa RP, Shaw C, Cheater F. Systematic review and evaluation of methods of assessing urinary incontinence. Health Technol Assess. 2006;10(6):1-132.

56. Norton PA. Pelvic floor disorders: the role of fascia and ligaments. Clin Obstet Gynecol 1993;35(4):926-938.

57. Hilton P, Stanton SL. Algorithmic method for assessing urinary incontinence in elderly women. Brit Med J 1981;282(6268):940-942.

58. Blakeman PJ, Hilton P, Bulmer JN. Oestrogen andprogesterone receptor expression in the female lower urinary tract, with reference to oestrogen status. Brit J Urol Int 2000;86(1):32-38.

59. Blakeman PJ, Hilton P, Bulmer JN. Cellular proliferation inthe female lower urinary tract with reference to oestrogen status. Brit J Obstet Gynaecol 2001;108(8):813-816.

60. Hextall A, Bidmead J, Cardozo L, Hooper R. The impact of the menstrual cycle on urinary symptoms and the results of urodynamic investigation. Brit J Obstet Gynaecol 2001;108(11):1193-1196.

61. Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. .Mayo Clin Proc. 2010 Jan;85(1):87-94.

62. Fortunato P, Schettini M, Gallucci M. Diverticula of the female urethra. British Journal of Urology 1997;80(4):628-632.

63. Price DM, Noblett K. Comparison of the cough stress test and 24-h pad test in the assessment of stress urinary incontinence. Int Urogynecol J. 2011 Nov 16.

64. Crystle CD, Charme LS, Copeland WE. Q-tip test in stress urinary incontinence. Obstet Gynecol. 1971; 38(2):313-315.

65. Kinn AC, Larsson B. Pad test with fixed bladder volume in urinary stress incontinence. Acta Obstetricia et Gynecologica Scandinavica 1987;66(4):369-371.

66. Fantl JA, Harkins SW, Wyman JF, Choi SC, Taylor JR. Fluid loss quantitation test in women with urinary incontinence: a test-retest analysis. Obstetrics & Gynecology 1987;70(5):739-743.

67. Sutherst J, Brown M, Shawer M. Assessing the severity of urinary incontinence in women by weighing perineal pads. Lancet 1981;1(8230):1128-30.

68. Klarskov P, Hald T. eproducibility and reliability of urinary incontinence assessment with a 60 min test. Scand J Urol Nephrol 1984;18(4):293-8.

69. Victor A, Larsson G, Asbrink AS. A simple patient administered test for objective quantitation of the symptom of urinary incontinence. Scand J Urol Nephrol 1987;21(4):277-9.

70. Jorgensen L, Lose G, Thunedborg P. Diagnosis of mild stress incontinence in females: 24-hour pad weighing test versus the one-hour test. Neurourol Urodyn 1987;6:165-166.

71. Messelink B, Benson T, Berghmans B, et al. Standardization of terminology of pelvic floor muscle function and dysfunction: Report from the Pelvic Floor Clinical Assessment Group of the International Continence Society. Neurourol Urodyn 2005;24:374–80.

72. Bump RC, Mattiasson A, Bo K, et al. The standardization of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10–11.

73. Baden WF, Walker TA. Physical diagnosis in the evaluation of vaginal relaxation. Clin Obstet Gynecol 1972;15(4):1055-1069.

74. Porges R. A practical system of diagnosis and classification of pelvic relaxations. Surgery, Gynecology & Obstetrics 1963;117:761-773.

75. Kobak WH, Rosenberger K, Walters MD. Interobserver variation in the assessment of pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 1996;7(3):121-4.

76. Auwad W, Freeman RM, Swift S. Is the pelvic organ prolapse quantification system (POPQ) being used? A survey of members of the International Continence Society (ICS) and the American Urogynecologic Society (AUGS). Int Urogynecol J Pelvic Floor Dysfunct 2004 Sep;15(5):324-7.

77. Swift S. Current opinion on the classification and definition of genital tract prolapse. Curr Opin Obstet Gynecol 2002 Oct;14(5):503-7.

78. Lemos N, Korte JE, Iskander M, Freeman R, Arunkalaivanan A, Rizk D, et al. Center-by-center results of a multicenter prospective trial to determine the inter-observer correlation of the simplified POP-Q in describing pelvic organ prolapse. Int Urogynecol J 2011 Nov 15.

79. Barber MD, Cundiff GW, Weidner AC, Coates KW, Bump RC, Addison WA. Accuracy of clinical assessment of paravaginal defects in women with anterior vaginal wall prolapse. Am J Obstet Gynecol 1999 Jul;181(1):87-90.

80. Stark D, Dall P, Abdel-Fattah M, Hagen S. Feasibility, inter- and intra-rater reliability of physiotherapists measuring prolapse using the pelvic organ prolapse quantification system. Int Urogynecol J 2010 Jun;21(6):651-6.

81. Hall AF, Theofrastous JP, Cundiff GW, Harris RL, Hamilton LF, Swift SE, et al. Interobserver and intraobserver reliability of the proposed International Continence Society, Society of Gynecologic Surgeons, and American Urogynecologic Society pelvic organ prolapse classification system. Am J Obstet Gynecol 1996 Dec;175(6):1467-70.

82. Karp DR, Peterson TV, Jean-Michel M, Lefevre R, Davila GW, Aguilar VC. «Eyeball» POP-Q examination: shortcut or valid assessment tool? Int Urogynecol J 2010 Aug;21(8):1005-9.

83. Parnell BA, Dunivan GC, Geller EJ, Connolly A. A novel approach to teaching the pelvic organ prolapse quantification (POP-Q) exam. Int Urogynecol J 2011 Mar;22(3):367-70.

84. Treszezamsky AD, Rascoff L, Shahryarinejad A, Vardy MD. Use of pelvic organ prolapse staging systems in published articles of selected specialized journals. Int Urogynecol J 2010 Mar;21(3):359-63.

85. Collins SA, O'Sullivan DM, Lasala CA. Correlation of POP-Q posterior compartment measures with defecatory dysfunction. Int Urogynecol J 2012 Jan 17.

86. Manchana T, Bunyavejchevin S. Validation of the Prolapse Quality of Life (P-QOL) questionnaire in Thai version. Int Urogynecol J 2010 Aug;21(8):985-93.

87. Chan SS, Cheung RY, Yiu AK, Li JC, Lai BP, Choy KW, et al. Chinese validation of Pelvic Floor Distress Inventory and Pelvic Floor Impact Questionnaire. Int Urogynecol J 2011 Oct;22(10):1305-12.

88. Claerhout F, Moons P, Ghesquiere S, Verguts J, De RD, Deprest J. Validity, reliability and responsiveness of a Dutch version of the prolapse quality-of-life (P-QoL) questionnaire. Int Urogynecol J 2010 May;21(5):569-78.

89. de Oliveira MS, Tamanini JT, de Aguiar CG. Validation of the Prolapse Quality-of-Life Questionnaire (P-QoL) in Portuguese version in Brazilian women. Int Urogynecol J Pelvic Floor Dysfunct 2009 Oct;20(10):1191-202.

90. Cam C, Sancak P, Karahan N, Sancak A, Celik C, Karateke A. Validation of the short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) in a Turkish population. Eur J Obstet Gynecol Reprod Biol 2009 Sep;146(1):104-7.

91. Srikrishna S, Robinson D, Cardozo L. Validation of the Patient Global Impression of Improvement (PGI-I) for urogenital prolapse. Int Urogynecol J 2010 May;21(5):523-8.

92. Digesu GA, Athanasiou S, Cardozo L, Hill S, Khullar V. Validation of the pelvic organ prolapse quantification (POP-Q) system in left lateral position. Int Urogynecol J Pelvic Floor Dysfunct 2009 Aug;20(8):979-83.

93. Chen G, Wu D, Zhao W, Hu W, Li J, Ling B. Modified laparoscopic extraperitoneal uterine suspension to anterior abdominal wall: the easier way to treat uterine prolapse. Int Urogynecol J 2012 Jan 17.

94. Marrero C, Aponte A, Torres R, Santos F, Rivera J. A preliminary report on pelvic floor reconstruction through col-

pocleisis from 2001 to 2007 at the University Hospital of the Puerto Rico Medical Center. P R Health Sci J 2010 Dec;29(4):394-6.

95. Peng P, Zhu L, Lang JH, Wang WY, Shi HH. Unilateral sacrospinous ligament fixation for treatment of genital prolapse. Chin Med J (Engl) 2010 Aug 5;123(15):1995-8.

96. de TR, Boileau L, Fara JF, Monneins F, Raini C, Costa P. Bilateral anterior sacrospinous ligament suspension associated with a paravaginal repair with mesh: short-term clinical results of a pilot study. Int Urogynecol J 2010 Mar;21(3):293-8.

97. Yang X, Li H. A modified anterior compartment reconstruction and Prolift-a for the treatment of anterior pelvic organ prolapse: a non-inferiority study. Arch Gynecol Obstet 2011 Dec 31.

98. Sayer T, Lim J, Gauld JM, Hinoul P, Jones P, Franco N, et al. Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device. Int Urogynecol J 2011 Dec 6.

99. Grgic O, Oreskovic S, Grsic HL, Kalafatic D, Zupic T, Maurac I. Outcome and efficacy of a transobturator polypropylene mesh kit in the treatment of anterior pelvic organ prolapse. Int J Gynaecol Obstet 2012 Jan;116(1):72-5.

100. Antosh DD, Iglesia CB, Vora S, Sokol AI. Outcome assessment with blinded versus unblinded POP-Q exams. Am J Obstet Gynecol 2011 Nov;205(5):489-4.

101. Chu LC, Chuang FC, Kung FT, Huang KH. Comparison of short-term outcomes following pelvic reconstruction with Perigee and Apogee systems: hysterectomy or not? Int Urogynecol J 2012 Jan;23(1):79-84.

102. Nair R, Nnochiri A, Barnick C, Roberts C. Transvaginal mesh (Prolift) repair: 2-year anatomic outcomes. Eur J Obstet Gynecol Reprod Biol 2011 Oct;158(2):358-60.

103. Palma P, Riccetto C, Prudente A, Dalphorno F, Delroy C, Castro R, et al. Monoprosthesis for anterior vaginal prolapse and stress urinary incontinence: midterm results of an international multicentre prospective study. Int Urogynecol J 2011 Dec;22(12):1535-41.

104. Khandwala S, Jayachandran C. Transvaginal mesh surgery for pelvic organ prolapse--Prolift+M: a prospective clinical trial. Int Urogynecol J 2011 Nov;22(11):1405-11.

105. Simon M, Debodinance P. Vaginal prolapse repair using the Prolift kit: a registry of 100 successive cases. Eur J Obstet Gynecol Reprod Biol 2011 Sep;158(1):104-9.

106. Brocker KA, Alt CD, Corteville C, Hallscheidt P, Lenz F, Sohn C. Short-range clinical, dynamic magnetic resonance imaging and P-QOL questionnaire results after mesh repair in female pelvic organ prolapse. Eur J Obstet Gynecol Reprod Biol 2011 Jul;157(1):107-12.

107. Sergent F, Resch B, Al-Khattabi M, Ricbourg A, Schaal JP, Marpeau L. Transvaginal mesh repair of pelvic organ prolapse by the transobturator-infracoccygeal hammock technique: long-term anatomical and functional outcomes. Neurourol Urodyn 2011 Mar;30(3):384-9.

108. McDermott CD, Terry CL, Woodman PJ, Hale DS. Surgical outcomes following total Prolift: colpopexy versus hysteropexy. Aust N Z J Obstet Gynaecol 2011 Feb;51(1):61-6.

109. Alcalay M, Cosson M, Livneh M, Lucot JP, Von TP. Trocarless system for mesh attachment in pelvic organ prolapse repair--1-year evaluation. Int Urogynecol J 2011 May;22(5):551-6.

110. Lee YS, Han DH, Lim SH, Kim TH, Choo MS, Seo JT, et al. Efficacy and Safety of «Tension-free» Placement of Gynemesh PS for the Treatment of Anterior Vaginal Wall Prolapse. Int Neurourol J 2010 Apr;14(1):34-42.

111. Sergent F, Resch B, Al-Khattabi M, Ricbourg A, Schaal JP, Marpeau L. Transvaginal mesh repair of pelvic organ prolapse by the transobturator-infracoccygeal hammock technique: Long-term anatomical and functional outcomes. Neurourol Urodyn 2010 Nov 11.

112. Lo TS, Ashok K. Combined anterior trans-obturator mesh and sacrospinous ligament fixation in women with severe prolapse--a case series of 30 months follow-up. Int Urogynecol J 2011 Mar;22(3):299-306.

113. Zhu L, Lang J, Sun Z, Ren C, Liu X, Li B. Pelvic reconstruction with mesh for advanced pelvic organ prolapse: a new economic surgical method. Menopause 2011 Mar;18(3):328-32.

114. Stanford EJ, Mattox TF, Pugh CJ. Outcomes and complications of transvaginal and abdominal custom-shaped light-weight polypropylene mesh used in repair of pelvic organ prolapse. J Minim Invasive Gynecol 2011 Jan;18(1):64-7.

115. Fayyad AM, North C, Reid FM, Smith AR. Prospective study of anterior transobturator mesh kit (Prolift) for the management of recurrent anterior vaginal wall prolapse. Int Urogynecol J 2011 Feb;22(2):157-63.

116. Huang WC, Lin TY, Lau HH, Chen SS, Hsieh CH, Su TH. Outcome of transvaginal pelvic reconstructive surgery with Prolift after a median of 2 years' follow-up. Int Urogynecol J 2011 Feb;22(2):197-203.

117. Jacquetin B, Fatton B, Rosenthal C, Clave H, Debodinance P, Hinoul P, et al. Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 3-year prospective follow-up study. Int Urogynecol J 2010 Dec;21(12):1455-62.

118. Withagen MI, Vierhout ME, Mannaerts GH, van der Weiden RM. Laparoscopic sacrocolpopexy with bone anchor fixation: short-term anatomic and functional results. Int Urogynecol J 2011 Nov 16.

119. Shveiky D, Sokol AI, Gutman RE, Kudish BI, Iglesia CB. Vaginal mesh colpopexy for the treatment of concomitant full thickness rectal and pelvic organ prolapse: a case series. Eur J Obstet Gynecol Reprod Biol 2011 Jul;157(1):113-5.

120. Sergent F, Resch B, Loisel C, Bisson V, Schaal JP, Marpeau L. Mid-term outcome of laparoscopic sacrocolpopexy with anterior and posterior polyester mesh for treatment of genito-urinary prolapse. Eur J Obstet Gynecol Reprod Biol 2011 Jun;156(2):217-22.

121. Onol FF, Kaya E, Kose O, Onol SY. A novel technique for the management of advanced uterine/vault prolapse: extraperitoneal sacrocolpopexy. Int Urogynecol J 2011 Jul;22(7):855-61.

122. Tate SB, Blackwell L, Lorenz DJ, Steptoe MM, Culligan PJ. Randomized trial of fascia lata and polypropylene mesh for abdominal sacrocolpopexy: 5-year follow-up. Int Urogynecol J 2011 Feb;22(2):137-43.

123. Price N, Slack A, Jackson SR. Laparoscopic sacrocolpopexy: an observational study of functional and anatomical outcomes. Int Urogynecol J 2011 Jan;22(1):77-82.

124. Chen G, Ling B, Li J, Xu P, Hu W, Zhao W, et al. Laparoscopic extraperitoneal uterine suspension to anterior abdominal wall bilaterally using synthetic mesh to treat uterovaginal prolapse. J Minim Invasive Gynecol 2010 Sep;17(5):631-6.

125. Dahlgren E, Kjolhede P. Long-term outcome of porcine skin graft in surgical treatment of recurrent pelvic organ prolapse. An open randomized controlled multicenter study. Acta Obstet Gynecol Scand 2011 Dec;90(12):1393-401.

126. Sung VW, Rardin CR, Raker CA, Lasala CA, Myers DL. Porcine subintestinal submucosal graft augmentation for rectocele repair: a randomized controlled trial. Obstet Gynecol 2012 Jan;119(1):125-33.

127. Goldstein HB, Maccarone J, Naughton MJ, Aguirre OA, Patel RC. A multicenter prospective trial evaluating fetal bovine dermal graft (Xenform(R) Matrix) for pelvic reconstructive surgery. BMC Urol 2010;10:21.

128. Feldner PC, Jr., Castro RA, Cipolotti LA, Delroy CA, Sartori MG, Girao MJ. Anterior vaginal wall prolapse: a randomized controlled trial of SIS graft versus traditional colporrhaphy. Int Urogynecol J 2010 Sep;21(9):1057-63.

129. Cervigni M, Natale F, La PC, Saltari M, Padoa A, Agostini M. Collagen-coated polypropylene mesh in vaginal prolapse surgery: an observational study. Eur J Obstet Gynecol Reprod Biol 2011 Jun;156(2):223-7.

130. Shalom DF, Lin SN, St LS, Winkler HA. Effect of age, body mass index, and parity on Pelvic Organ Prolapse Quantification system measurements in women with symptomatic pelvic organ prolapse. J Obstet Gynaecol Res 2012 Feb;38(2):415-9.

131. Groenendijk AG, Birnie E, Roovers JP, Bonsel GJ. Contribution of primary pelvic organ prolapse to micturition and defecation symptoms. Obstet Gynecol Int 2012;2012:798035.

132. Chantarasorn V, Peter DH. Diagnosis of Cystocele type by clinical examination and pelvic floor ultrasound. Ultrasound Obstet Gynecol 2011 Nov 28.

133. Broekhuis SR, Kluivers KB, Hendriks JC, Futterer JJ, Barentsz JO, Vierhout ME. POP-Q, dynamic MR imaging, and perineal ultrasonography: do they agree in the quantification of female pelvic organ prolapse? Int Urogynecol J Pelvic Floor Dysfunct 2009 Feb 17.

134. Long CY, Hsu CS, Wu MP, Lo TS, Liu CM, Tsai EM. Comparison of the changes in sexual function of premenopausal and postmenopausal women following transvaginal mesh surgery. J Sex Med 2011 Jul;8(7):2009-16.

135. Srikrishna S, Robinson D, Cardozo L, Gonzalez J. Can sex survive pelvic floor surgery? Int Urogynecol J 2010 Nov;21(11):1313-9.

136. Welch G, Weinger K, Barry M. Quality-of-life impact of lower urinary tract symptom severity: results from the Health Professionals Follow up Study. Urol 2002;59:245-250.

137. Milsom I, Abrams P, Cardozo L, Roberts R, Thuroff J, Wein A. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJ U Int 2001; 87:760-766.

138. Stewart W, van Rooyen J, Cundiff G, Abrams P, Herzig A, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World Journal of Urology 2003; 20: 327-336.

139. Knutson T, Edlund C, Fall M, Dahlstrand C. BPH with coexisting overactive bladder-An everday urological dilemma. Neurourol Urodyn 2001;20:237-247.

140. Kaplan S, Te A, Jacobs B. Urodynamic evidenceof vesical neck obstruction in men with misdiagnosed chronic nonbacterial prostatitis and the therapeutic role of endoscopic incision of the bladder neck. J Urol 1994;152:2063-2065.

141. Yalla S, Gabilondo F, Blunt K, Fam B, Castello A, Kaufman J. Functional striated sphincter component at the bladder neck: clinical implications. J Urol 1977; 118(3): 408-411.

142. Markland AD, Goode PS, Redden DT, Lori G. Borrud LG, Kathryn L. Burgio KL Prevalence of Urinary Incontinence in Men: Results From the National Health and Nutrition Examination Survey. J Urol, 2010;184: 1022-102.

143. Parsons JK. Lifestyle factors, benign prostatic hyperplasia, and lower urinary tract symptoms. Curr Opin Urol 2011; 21: 1–4.

144. Rohrmann S, Smit E, Giovannucci E, Platz EA. Association between markers of the metabolic syndrome and lower urinary tract symptoms in the Third National Health and Nutrition Examination Survey (NHANES III). Int J Obest 2005; 29:310–316.

145. Ozden C, Ozdal OL, Urgancioglu G, Koyuncu H, Gokkaya S, Memis A. The correlation between metabolic syndrome and prostatic growth in patients with benign prostatic hyperplasia. Eur Urol 2007; 51:199–206

146. Kupelian V, McVary KT, Kaplan SA, et al. Association of lower urinary tract symptoms and the metabolic syndrome: results from the Boston Area Community Health Survey. J Urol 2009; 182:616-25.

147. Hall SA, Chiu GR, LINK CL, Steers WD, Kupelian V, McKinlay JB: Are statin medications associated with lower urinary tract symptoms in men and women? Results from the Boston area community health (BACH) survey Ann Epidemiol 2011; 21: 149-155

148. St Sauver JL, Jacobsen SJ, Jacobson DJ, McGree ME, Girman CJ, Nehra A, Roger VL, Lieber MM: Statin use and decreased risk of benign prostatic enlargement and lower urinary tract symptoms. BJU int 2011; 107, 443 – 450.

149. Emberton M, Neal DE, Black N, Fordham M, Harrison M, McBrien MP, et al. The effect of prostatectomy on symptom severity and quality of life. BJU int 1996; 77(2): 233-247.

150. De La Rosette, J., Baba S., Baldani G., Elhilali S., Gravas R., Muschter R., Naito S., Netto N.R. New minimally invasive and surgical developments in the management of BPO. Male lower urinary tract dysfunction. Evaluation and management. Eds: MaConnel J. et al., Health Publication Ltd., Plymouth, pp197-233, 2006

151. Carlson KV, Nitti VW. Prevention and management of incontinence following radical prostatectomy. Urol Clin North Am 2001;28(3):595-612.

152. Donnellan SM, Duncan HJ, MacGregor RJ, Russell JM. Prospective assessment of incontinence after radical retropubic prostatectomy: objective and subjective analysis. Urology 1997;49(2):225-230.

153. Wei JT, Dunn RL, Marcovich R et al: Prospective assessment of patient reported urinary continence radical prostatectomy. J Urol 2000; **164:** 744.

154. Flynn BJ, Peterson AC and Webster GD: Evaluation and management of intrinsic sphincter deficiency after radical prostatectomy. AUA Update Series 2007; 26: lesson 15.

155. Calalona WJ, Carvahal GF, Mager DE, Smith DS: Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies J Urol. 1999:162(2):433-8

156. Kaul S, Savera A, Badani K, Fumo M, Bhandari A, Menon M: Functional outcomes and oncological efficacy of Vattikuti Institute prostatectomy with Veil of Aphrodite nerve-sparing: an analysis of 154 consecutive patients BJU Int 2006: 97(3):467-472.

157. Stone N.N., Stock R.G. Complications following permanent prostate brachytherapy. Eur. Urol: 2002; 41: 427-433

158. Lepor H, Kaci L. The impact of open radical retropubic prostatectomy on continence and lower urinary tract symptoms: a prospective assessment using validated selfadministered outcome instruments. J Urol 2004;171(3):1216-1219.

159. Masters JG, Rice ML. Improvement in urinary symptoms after radical prostatectomy: a prospective evaluation of flow rates and symptom scores. Brit J Urol Int 2003;91(9):795-797.

160. Fowler FJ, Jr., Barry MJ, Lu-Yao G, Wasson J, Roman A, Wennberg J. Effect of radical prostatectomy for prostate cancer on patient quality of life: results from a Medicare survey. Urology 1995;45(6):1007-1013.

161. Ficazzola MA, Nitti VW. The etiology of post-radical prostatectomy incontinence and correlation of symptoms with urodynamic findings. J Urol 1998; 160(4): 1317-1320.

162. Groutz A, Blaivas JG, Chaikin DC, Weiss JP, Verhaaren M. The pathophysiology of post-radical prostatectomy incontinence: a clinical and video urodynamic study. J Urol 2000;163(6):1767-1770.

163. Giannantoni A, Mearini E, Di Stasi SM, Mearini L, Bini V, Pizzirusso G, et al. Assessment of bladder and urethral sphincter function before and after radical retropubic prostatectomy. J Urol 2004;171(4):1563-1566.

164. Jung SY, Fraser MO, Ozawa H, Yokoyama O, Yoshiyama M, De Groat WC, et al. Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. J Urol 1999: 162(1): 201-212.

165. Hu JC, Gold KF, Pashos CL, Mehta SS, Litwin MS. Temporal trends in radical prostatectomy complications from 1991 to 1998. J Urol 2003;169(4):1443-1448.

166. Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. J Am Med Assoc 2000;283(3):354-360.

167. Crestodina LR: Assessment and management of urinary incontinence in the Elderly male. The nurse Practitioner 2007; 32: 27-35.

168. Thüroff JW, Paul Abrams P, Andersson K-E, Artibani W, Chapple CR , Drake MJ, Hampel C, Neisius A, Schröder A, Tubaro A: EAU Guidelines on Urinary Incontinence. Eur Urol 2011; 59, 387-400.

169. Blaivas JG, Panagopoulos G, Weiss JP, Somaroo C. Validation of the overactive bladder symptom score. J Urol. 2007:178(2):543-7

170. Homma Y, Yoshida M, Seki N, Yokoyama O, Kakizaki H, Gotoh M, Yamanishi T, Yamaguchi O, Takeda M, Nishizawa O. Symptom assessment tool for overactive bladder syndrome--overactive bladder symptom score. Urology. 2006;68(2):318-23.

171. Eckhardt MD, van Venrooij GE, van Melick HH, Boon TA. Prevalence and bothersomeness of lower urinary tract symptoms in benign prostatic hyperplasia and their impact on well-being. J Urol 2001;166(2):563-568.

172. Hammerer P, Huland H. Urodynamic evaluation of changes in urinary control after radical retropubic prostatectomy. J Urol 1997;157(1):233-236.

173. Winters JC, Appell RA, Rackley RR. Urodynamic findings in postprostatectomy incontinence. Neurourol Urodyn 1998;17(5):493-498.

174. Chao R, Mayo ME. Incontinence after radical prostatectomy: detrusor or sphincter causes. J Urol 1995;154(1):16-18.

175. van Venrooij GE, Eckhardt MD, Gisolf KW, Boon TA. Data from frequency-volume charts versus filling cysotmetric estimated capacities and prevalence of instability in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Neurourol Urodyn 2002;21(2):106-111.

176. Brandes SB, Bullock AD: Update on male urinary stress incontinence. Missouri Medicine 2007; 104: 425-429.

177. Machold S, Olbert PJ, Hegele A, Kleinhans G, Hofmann R, Schrader AJ: Comparison of a 20-min pad test with the 1-hour pad test of international continence society to evaluate post prostatectomy incontinence. Urol Int 2009; 83 27-32.

178. Agarwal, P. and Rosenberg, M. L. Neurological evaluation of urinary incontinence in the female patient. Neurologist. 2003; 9: 110-117.

179. Chodak, G. W., Keller, P., and Schoenberg, H. Routine screening for prostate cancer using the digital rectal examination. Prog.Clin.Biol.Res. 1988; 269: 87-98.

180. Roehrborn C, Girman C, Rhodes T, Hanson K, Collins G, Sech S, et al. Correlation between prostate size extimated by digital rectal examination and measured by transrectal ultrasound. Urology 1997;49:548-557.

181. Roehrborn C, Sech S, Montoya J, Rhodes T, Girman C. Interexamner reliability and validity of a three dimensional model to asses prostate volume by digital examination. Urology 2001;57:1087-1092.

182. McConnell J, Roehrborn C, Bautista OM, et al. The long term effects of doxazosin, finasteride and combination therapy on the clinical progression of benign prostatic hyperplasia. NEJM 2003; 349:2387-2398

183. Boyle, P., Gould, A. L., and Roehrborn, C. G. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. Urology. 1996; 48: 398-405.

184. Tong YC, Lin YM, Yang WH, Tzai TS, Lin JS. Correlation of transrectal ultrasonographic findings of the prostate with the occurrence of detrusor instability in patients with benign prostatic hyperplasia. Urol Int 1995;55(3):154-157.

185. Gerber, G. S., Goldfischer, E. R., Karrison, T. G., and Bales, G. T. Serum creatinine measurements in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. Urology. 1997; 49: 697-702.

186. Roehrborn, C. G., Bartsch, G., Kirby, Ret al. Guidelines for the diagnosis and treatment of benign prostatic hyperplasia: a comparative, international overview. Urology. 2001; 58: 642-650.

187. Rule, A. D., Jacobson, D. J., Roberts, R. O., Girman, C. J., et al. The association between benign prostatic hyperplasia and chronic kidney disease in community-dwelling men. Kidney Int. 2005; 67: 2376-2382.

188. McConnell J, Roehrborn C, Bautista OM, et al. The long term effects of doxazosin, finasteride and combination therapy on the clinical progression of benign prostatic hyperplasia. NEJM 2003; 349:2387-239

189. Noel, G. Prostate-specific antigen (PSA) best practice policy. American Urological Association (AUA). Oncology (Huntingt). 2000; 14: 267-8, 280.

190. Catalona WJ, Richie JP, Ahmann FR, Hudson MA, ScardinoPT, Flanigan RC, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol 1994;151(5):1283-1290.

191. Carvalhal GF, Smith DS, Mager DE, Ramos C, Catalona WJ. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng./ml. or less. J Urol 1999;161(3):835-839.

192. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, Foster HE, Jr, Chris M. Gonzalez CM, Kaplan SA, Penson DF, Ulchaker JC, Wei JT. Update on AUA Guideline on the Management of Benign Prostatic Hyperplasia. J Urol 2011; 185, 1793-1803.

193. Polascik TJ, Oesterling JE, Partin AW. Prostate specific antigen: a decade of discovery—what we have learned and where we are going. J Urol 1999;162(2):293-306.

194. Mikolajczyk SD, Marks LS, Partin AW, Rittenhouse HG. Free prostate-specific antigen in serum is becoming more complex. Urology 2002;59(6):797-802.

195. Antenor, J. A., Han, M., Roehl, K. A., Nadler, R. B., and Catalona, W. J. Relationship between initial prostate specific antigen level and subsequent prostate cancer detection in a longitudinal screening study. J Urol. 2004; 172: 90-93.

196. Thompson, I. M., Pauler, D. K., Goodman, P. J., et al. Prevalence of prostate cancer among men with a prostatespecific antigen level < or =4.0 ng per milliliter. N.Engl.J Med. 2004; 350: 2239-2246.

197. Wilson, S. S. and Crawford, E. D. Screening for prostate cancer: current recommendations. Urol Clin.North Am. 2004; 31: 219-226.

198. Vesely S, Knutson T, Fall M, Damber JE, Dahlstrand C. Clinical diagnosis of bladder outlet obstruction in men with lower urinary tract symptoms: reliability of commonly measured parameters and the role of idiopathic detrusor overactivity. Neurourol Urodyn 2003;22(4):301-305

199. Jacobsen SJ, Girman CJ, Guess HA, Oesterling JE, Lieber MM. New diagnostic and treatment guidelines for benign prostatic hyperplasia. Potential impact in the United States. Arch Intern Med 1995;155(5):477-481.

200. Barry MJ, Fowler FJ, Jr., Bin L, Pitts JC, 3rd, Harris CJ, Mulley AG, Jr. The natural history of patients with benign prostatic hyperplasia as diagnosed by North American urologists. J Urol 1997;157(1):10-14.

201. Roehrborn CG, Boyle P, Bergner D, Gray T, Gittelman M, Shown T, et al. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. Urology 1999;54(4):662-669.

202. Laniado, M. E., Ockrim, J. L., Marronaro, A., et al. Serum prostate- specific antigen to predict the presence of bladder outlet obstruction in men with urinary symptoms. BJU. Int. 2004; 94: 1283-1286.

Committee 5B

Patient-Reported Outcome Assessment

Con Kelleher, David Staskin,
Praseetha Cherian, Nikki Cotterill, Karin Coyne, Zoe Kopp, Tara Symonds

I. INTRODUCTION

The last update of the International Consultations on Incontinence reports broadened the scope of this review to include all patient-reported outcomes, not just health-related quality of life. This update will continue in the same vein to extend and update the prior literature reviews of PROs, for lower urinary tract symptoms (LUTS) and bowel incontinence outcome measures, and provide recommendations for questionnaire selection for use in clinical practice and research. In addition, this summary will review the purpose and content of the ICI questionnaire (ICIQ) modules. The expansion in scope of this review to include all types of patient reported outcomes (PRO) is an important step in recogniesing the inherent conceptual differences of various PROs each with different assessment goals. A PRO is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"([1], page 2). PROs measure different aspects of disease and therapeutic impact such as: symptom frequency or symptom bother, health-related quality of life (HRQL), treatment satisfaction, or work productivity measures (**Figure 1**). An essential component of selecting a PRO for use is to ensure that the selected PRO is consistent with the objective of the study or clinical purpose. For example, if the goal is to assess treatment satisfaction, then a treatment satisfaction measure should be incorporated into the study design or as a clinical outcome. The matching of appropriate PRO selection with one's desired outcomes is critical to success when assessing PRO's and will be reviewed further in this chapter.

Ultimately, the last decade has been one of tremendous growth in the area of PROs with influences from scientific and regulatory communities. As such, the ICI will endeavour to continually update the recommendations it offers on the basis of emerging data and published evidence based on the sound and rigid recommendations of the prior reviews.

1. SELECTING PRO MEASURES FOR CLINICAL TRIALS AND CLINICAL PRACTICE

How does a researcher choose which instruments are most appropriate for a particular research study and/or clinical assessment? The following section provides general guidelines for use in conducting PRO assessments in clinical trials or other research investigations related to urinary or faecal incontinence.

As there are many available PROs, it is of utmost importance to select the PRO measure that is relevant and applicable to one's desired outcome. If an intervention is designed to reduce symptom bother, then a relevant PRO would be a symptom bother measure. Multiple PROs can be included in clinical practice or in a research study; however the designation of the PRO as a primary, co-primary, secondary,

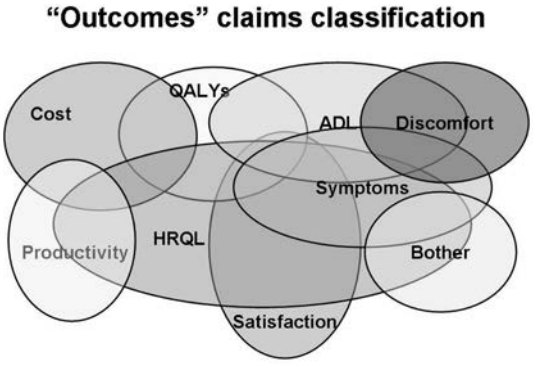


Figure 1. Patient-Reported Outcomes Assessment Areas. *Burke L, Evidence Review Branch DDMAC, FDA; DIA Workshop on Pharmacoeconomic and Quality of Life Labelling and Marketing Claims New Orleans October 3, 2000*

tertiary or exploratory endpoint must be noted. In addition, issues of staff and participant burden, time constraints, and resources should be considered in the selection of a PRO measure. Once it has been decided which outcomes are to be assessed it is important to choose a questionnaire that has been scientifically developed and validated. Principles of validation and questionnaires that have been validated are presented in this chapter.

2. SELECTING PRO MEASURES FOR RESEARCH STUDIES

a) Study Design

There are several protocol concerns that must be taken into account when using PRO measures in research studies, including the length of the study, the frequency of contact with the study participants, the timing of clinical assessments, the complexity of the study design, the number of participants enrolled, and participant and staff burden. The goal of the PRO assessment is to "fit" the PRO measures to the protocol without compromising either the study objective or design. For example, if the study design is complex with frequent participant contacts and multiple clinical measures, it may be necessary to keep the PRO measures at a minimum or to reduce the number of times the PRO is assessed (e.g. baseline and end of study rather than during all participant contacts) to minimise participant and staff burden. At the same time, however, PROs must be viewed as an important variable in the overall trial design and cannot be devalued in the data collection process. Consequently, PRO measures cannot be altered or reduced to accommodate study design as such alterations may yield less reliable measures or may seriously diminish the integrity of the overall study design and yield useless information. Having well developed research goals and questions regarding PROs will help to guide you in the selection of measures for a study. The aim is to develop a conceptually adequate, yet practical PRO battery given the study population, the specific intervention, and the study design.

The frequency with which PRO will need to be assessed in a research study will depend upon the nature of the condition or intervention being investigated and the expected effects (both positive and negative) of treatment. At a minimum, as with all measurements collected in a research study, a baseline and end of study assessment should be completed. In addition, PRO assessments should be timed to match expected changes in functioning due to either the intervention or the condition or the disease itself. Timing follow-up assessments to coincide with typical patient follow-up visits, if appropriate, may also reduce the costs involved in follow-up PRO assessments.

b) Study Population

It is critical to specify key population demographics that could influence the choice of instruments, the relevant dimensions of the PRO to be assessed, and the mode of administration. Thus, age, gender, educational level, the language(s) spoken, and cultural diversity should be carefully considered prior to selecting PRO measures. For example, a cohort of patients over the age of 70 may have more vision problems than middle-aged persons, making self-administered questionnaires potentially inadvisable. Ethnically diverse groups also require measures that have been validated across different cultures and/or languages.

In clinical trials, it is also as important to consider how the disease or condition will progress and affect the outcomes of patients in the control group as it is to understand the effects of the study treatment. For example, in patients with incontinence assigned to a placebo-control arm of a study, one might expect a symptom to worsen and thus have an effect on daily functioning. The point is to select PRO measures that are sufficiently sensitive to detect changes in both the treatment and the control group patients. Use of the same measures for both groups will ensure an unbiased and comparable assessment.

c) Intervention

There are three major factors related to the intervention that are relevant to PRO assessment, and therefore require careful consideration: 1) the positive and adverse effects of treatment; 2) the time course of the effects; and 3) the possible synergism of the treatment with existing medications and conditions. It is crucial to understand how a proposed treatment can affect patient outcomes in both positive and negative ways. For example, some drug therapies may relieve LUTS but produce side effects like dry mouth or sexual dysfunction.

In addition, the time course of an intervention's effects on PROs is also critical both in terms of the selection of measures and the timing of when PRO measures are administered to study participants. For example, in a trial comparing coronary artery bypass graft (CABG) surgery to angioplasty, an assessment of PRO one week post-intervention might lead to an interpretation that the surgical arm had worse outcomes than angioplasty for PRO since the individuals in this arm of the trial would still be suffering the effects of the surgical procedure (for instance, sore muscles and surgical site discomfort) which could overwhelm any benefits associated with CABG. However, at six months post-intervention, the benefits of CABG surgery such as, relief from angina might be more profound than the benefits received from angioplasty. Thus, when PROs are assessed could influence how one interprets the benefits (or negative effects) of the interventions.

Finally, it is important to have a clear understanding of the current medications the patient population is likely to be taking prior to randomisation to the study treatment, and how these medications might

interact with the trial intervention, (either a pharmacological or behavioural intervention), to influence patient outcomes.

3. TYPES OF PRO MEASURES

There are two types of PRO measures: generic and condition-specific. Generic measures are designed to assess outcomes in a broad range of populations (e.g., both healthy as well as ill individuals). These instruments are generally multidimensional, and assess at least the physical, social and emotional dimensions of life. An example of this type of instrument is the Medical Outcomes Study SF-36 Health Status Profile [2]. A second type of measure is condition-specific (e.g., instruments designed to assess the impact of specific diseases, conditions, age groups, or ethnic groups). Condition-specific measures can be similar to generic instruments in that they assess multiple outcome dimensions, but condition-specific measures also include items more specific to the particular condition or population being studied. Examples of condition specific instruments in urology include the Incontinence Impact Questionnaire [3], the King'sHealth Questionnaire [4], and the OAB-q [5].

In general, the growing trend has been to include condition-specific outcome measures in clinical trials due to their enhanced sensitivity to change and the need to minimise participant burden. Importantly, the type of instruments selected for inclusion in a research study will depend on the goals of the intervention and the specific research questions to be addressed. In practice, clinical trials that include PROs usually incorporate a combination of PRO measures most relevant to the study population and intervention, if applicable, being mindful of resource constraints and staff and participant burden.

Quality-adjusted Life Year (QALY)

Increasingly HRQL outcome measures are being used in the development of quality-adjusted life year (QALY) measures. A QALY is a universal health outcome measure applicable to all individuals and all diseases, which combines gains or losses in both life quantity (mortality) and life quality (morbidity) and enables comparisons across diseases and programs. QALYs are widely used for cost-utility analysis[6]. In the past decades, economic evaluation has been increasingly important for the decision maker to decide which treatment or intervention is more cost-effective, in order to allocate limited healthcare resources soundly. Economic evaluation aims to compare interventions in terms of their costs and benefits, including their patient outcome impact. Health benefits can be quantified as QALYs (pronounced "qualies"), which have become a standard measure and are now recommended in most of health economics guidelines as the method of choice [7]. The economic chapter contains additional information regarding QALYs, as do the following references: [8, 9].

4. LITERATURE SEARCH STRATEGY

For the current version of this chapter the previous literature search was updated. A number of databases were accessed, electronically, with specific search criteria, such as validation work from the period January 2006 through August, 2011. Age and gender limits were not specified. Databases used included Pub-Med/MEDLINE, and websites accessed included oab.com, proqolid.com, ncbi.nlm.nih.gov and mapi-institute.com. The following keywords were used separately and/or in combination: "urinary incontinence", "urinary symptoms", "urgency", "overactive bladder", "stress incontinence," "incontinence," "questionnaire," "epidemiology," "prostate," "prolapse(d)," "faecal," "bowel," "anal," "quality of life," "sexual," "geriatric," "paediatric," "satisfaction," "symptom bother," "goal attainment", "screener," and "generic." Questionnaires evaluated in this chapter were updated with any new information if new validation work was found. New questionnaires not in the previously updated resource tool were added to appropriate sections if they were validated and relevant with regard to the search terms specified above. Grades were evaluated for correctness, based on previous and new validation work, and modified if and when necessary to demonstrate any changes with respect to instrument validation.

II.THE MEASUREMENT OF PATIENT-REPORTED OUTCOMES (PROS) OF INCONTINENCE, OTHER LOWER URINARY TRACT SYMPTOMS, AND BOWEL PROBLEMS

Incontinence and other lower urinary tract symptoms (LUTS) as well as bowel problems and their impact on patients and their lives can be assessed in a number of ways. Traditionally, the clinical history has been used to gain a summary view of the symptoms experienced by patients and in some cases the impact on their lives. Increasingly however, patient-completed methods of measuring incontinence and LUTS are being used, including voiding diaries and questionnaires.

Patient self-completed questionnaires or patient reported outcomes (PROs) represent the most important clinical review of symptom impact and treatment benefit from a patient perspective. PROs provide a method for the standardised collection of data, or an objective assessment of subjective phenomena, from patients relating to incontinence, other LUTS, and bowel problems. Clinicians' assessments of patients' outcomes have often been shown to underestimate the degree of bother perceived by patients, and to focus on issues of lesser importance to patients [10].

1. PRO QUESTIONNAIRE DEVELOPMENT AND VALIDATION

PRO questionnaires can be used to record the presence and severity of urinary and bowel symptoms,

as well as the impact of symptoms on everyday activities and health-related quality of life (HRQL) and satisfaction with treatment, etc. To ensure that the results obtained with PROs are clinically useful, data must be gathered using valid and reliable instruments. Questionnaire design and development is not a simple process. Developing such instruments requires a multistep, structured process that incorporates cognitive psychology, psychometric theory, and patient and clinician input. The process begins by determining the intent and purpose of the PRO and culminates in studies that demonstrate the measure's validity, reliability, and responsiveness. The specific steps required for developing a PRO questionnaire are outlined in the following section and are shown in **Figure 2**.

The development of a PRO is a rigorous, scientific process to provide confidence that the PRO is measuring what it is intended to measure, that it does this reliably, and is appropriate for use in the patient or population group under investigation. The final instrument must have demonstrated validity and reliability in the intended target population. PROs need to be developed with patient and clinician input and have the psychometric, or measurement, properties of the PRO evaluated to determine that it is a valid outcome measure. To be a useful measurement tool, a PRO instrument must also be easy to administer, reliable, and valid. Only PROs that have undergone this process and have published validation data are discussed in this chapter.

Food & Drug Administration [1]. Guidance for industry - patient-reported outcome measures: Use in medical product development to support labelling claims. Silver Spring, MD: FDA; 2009.

a) Determining Questionnaire Intent and Purpose

The first task in developing a PRO measure is to determine why the instrument is needed. Given the current number of disease-specific questionnaires available in the field of incontinence and related pelvic disorders, a new PRO measure must fill a need that has not already been met by an existing instrument. Once the need for the measure is recognised, its purpose and clinical usefulness need to be considered because the purpose dictates the validation design process. For example, a symptom- and a treatment-satisfaction measure would be developed and validated differently because the outcome is different.

The development stage would focus on the outcome of interest (e.g., symptoms patients experience and the significance of each symptom, or what issues patients consider when determining how satisfied they are with treatment) with the items derived from the patient perspective and relating to the outcome

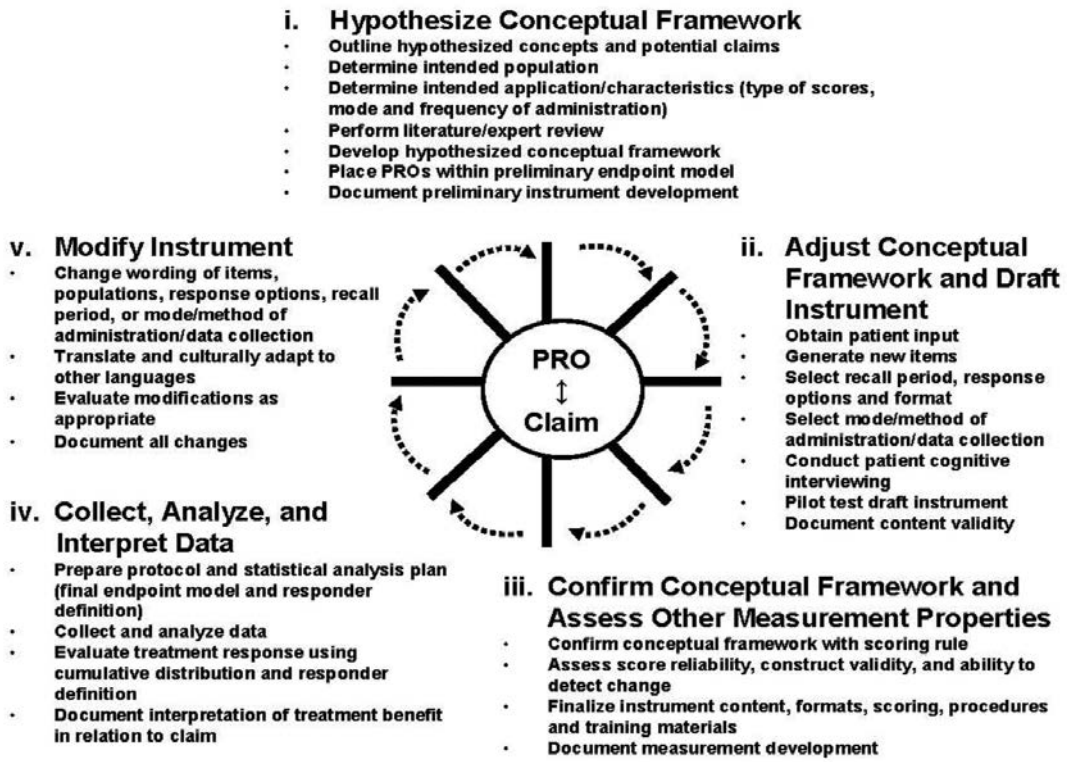


Figure 2. The development of a patient reported outcome is a multistep process

of interest. Validation efforts would include designing a study focused on the outcome of interest with the appropriate patient inclusion/exclusion criteria to enhance generalisability while maintaining internal consistency and providing opportunities to test—at a minimum—reliability and validity.

b) Developing the Items

Designing a clinically useful PRO measure involves more than just developing a series of questions. In addition to clinician input and literature review, questionnaire items must be generated from a patient perspective and include the patient voice. This is obtained through focus groups or one-on-one interviews to provide qualitative data on issues pertinent to patients and to identify the words patients use to describe their symptoms or disease impact. Focus groups and one-on-one interviews should be carefully planned to address the goals of the questionnaire being developed. For example, if a measure is intended to assess symptom bother, interview questions should pertain to the patient's symptom experience. Importantly, rather than using clinical terminology which patients may not comprehend, the words used during the focus groups or interviews should be common to patients. The results of the qualitative patient interviews lead to item generation. After items are generated, the newly drafted questionnaire should be reviewed by other patients and experts to ensure its readability and content validity.

An alternative approach to questionnaire development is to adapt an existing measure to meet the needs of the desired questionnaire. Patients need to be involved in the questionnaire adaptation to ensure that the revised measure is pertinent to the population of interest. The adapted questionnaire must be validated on its own in the target population as the validity of the original questionnaire does not apply to an adapted measure.

For newly developed and adapted questionnaires, think-out-loud interviews or cognitive interviews should be used to ascertain the correctness and validity of the revised questionnaire. In a think-out-loud interview, patients are asked to review a question and describe what they are thinking as they cognitively process the question; the patients think out loud about what the question means to them and how they think through their response to the question. For a cognitive interview approach, patients review and respond to the questionnaire items, and then they are interviewed about what each item meant to them as they completed the questionnaire. Both approaches provide information about what patients consider when responding to each question.

c) Determining the Mode of Administration of a Questionnaire

When generating the PRO items, the mode of administration must be considered. Will the measure be completed by the patient (i.e., self-administered) or administered by an interviewer (i.e., interviewer-administered)? How the questionnaire will be completed needs to be determined before the validation stage because mode of administration can affect patient responses. For highly personal or intimate questions, a self-administered questionnaire is recommended to avoid response bias. Questionnaires that are self-administered are preferable to interviewer-administered questionnaires because the data collection burden is reduced and patients are more likely to provide unbiased information on self-administered questionnaires. Importantly, if a questionnaire has been validated for a particular mode of administration (self-administered pen and paper), this does not make the questionnaire valid for all modes of administration (e.g. electronic administration via web or hand held device). Should the mode of administration change from the original validation, processes must be undertaken to ensure no change in meaning or content have occurred with the format change. Guidelines for this type of adaptation are clearly outlined by Coons et al (2009) [11].

d) Questionnaires' Psychometric Properties

All PRO measures must demonstrate reliability, validity, and responsiveness, which are described in detail below. This can be accomplished in several ways:

(1) Perform a stand-alone cross-sectional study to validate the questionnaire in the patient population for which it was designed;

(2) Administer the untested questionnaire in a clinical study and use the baseline data to perform psychometric validation (the end-of-study data can also be used to evaluate responsiveness); or

(3) Perform a stand-alone longitudinal study with an intervention to determine the instrument's psychometric performance and responsiveness in a non-clinical trial setting.

The following psychometric properties must be tested for and demonstrated in a validated questionnaire.

Reliability refers to the ability of a measure to produce similar results when assessments are repeated (i.e., is the measure reproducible?). Reliability is critical to ensure that change detected by the measure is due to the treatment or intervention and not due to measurement error [12]. One measure of reliability is the questionnaire's internal consistency, which indicates how well individual items within the same domain (or subscale) correlate. Cronbach's alpha coefficient is used to assess internal consistency reliability, with higher alphas indicating greater correlation. Typically, Cronbach's alpha should be greater than 0.70 to indicate good internal consistency reliability [12, 13]. If the item-to-total alpha is less than 0.20, the question should be removed or rewritten.

T**est-retest reliability**, or **reproducibility**, indicates how well results can be reproduced with repeated

testing. To assess test-retest reliability, the same patient completes the questionnaire more than once, at baseline and again after a period of time during which the impact of symptoms is unlikely to change (e.g., a few days or weeks) [12, 13]. The Spearman's correlation coefficient and intraclass correlation coefficient are used to demonstrate reproducibility. For group data, a Spearman's correlation coefficient or an intraclass correlation coefficient of at least 0.70 demonstrate good test-retest reliability [12, 13].

Interrater reliability indicates how well scores correlate when a measure is administered by different interviewers or when multiple observers rate the same phenomenon [12]. Demonstration of interrater reliability is not necessary for self-administered questionnaires but is necessary for instruments based on observer ratings or using multiple interviewers. A correlation of 0.80 or higher between raters indicates good interrater reliability [12].

Validity refers to the ability of an instrument to measure what it was intended to measure [12, 13]. A measure should be validated for each specific condition or outcome for which it will be used. For example a measure designed to assess stress incontinence would not be valid for OAB unless it were specifically validated in patients with OAB symptoms.

Content validity, convergent validity, discriminant validity and **criterion validity** typically are required to validate a questionnaire [12, 13]. Content validity is a qualitative assessment of whether the questionnaire captures the range of the concept it is intended to measure [12, 13]. For example, does a measure of symptom severity capture all the symptoms that patients with a particular condition have, and if so, is the measure capturing the items in a manner meaningful to patients in language patients can understand? To obtain content validity, patients review the measure and provide feedback as to whether the questions are clear, unambiguous, and comprehensive.

Convergent validity is a quantitative assessment of whether the questionnaire measures the theoretical construct it was intended to measure [12, 13]. Convergent validity indicates whether a questionnaire has stronger relationships with similar concepts or variables. Stronger relationships should be seen with the most closely related constructs and weaker relationships seen with less-related constructs [12, 13].

Discriminant validity indicates whether the questionnaire can differentiate between known patient groups (e.g., those with mild, moderate, or severe disease) [12, 13]. Generally, measures that are highly discriminative are also highly responsive.

Criterion validity reflects the correlation between the new questionnaire and an accepted reference, or gold standard [12, 14]. One difficulty in establishing criterion validity is that a gold-standard measure might not be available [12, 14]. When criterion validity can be established with an existing measure, the correlation should be 0.40 to 0.70; correlations approaching 1.0 indicate that the new questionnaire may be too similar to the gold-standard measure and therefore redundant [12, 14].

Responsiveness indicates whether the measure can detect change (for better or worse) in a patient's condition [15]. An aspect of responsiveness is determining not only whether the measure detects change but whether the change is meaningful to the patient. This can be done by determining the minimal important difference (MID) of the measure. The MID is the smallest change in a PRO questionnaire score that would be considered meaningful or important to a patient [16]. A treatment that is statistically significantly better than another may not necessarily have made a meaningful difference to the patient; the MID indicates whether the treatment made such a difference from a patient perspective.

Unfortunately, there is no scientific test for MID as it is an iterative process that involves two methodologies to determine the MID of a questionnaire: an anchor-based approach and a distribution-based approach [17, 18]. With the anchor-based approach, the MID is determined by comparing the measure to other measures (or "anchors") that have clinical relevance [17]. With the distribution-based approach, the MID can be determined by the statistical distributions of the data [17], using analyses such as effect size, one-half standard deviation, and standard error of measurement [17-19].

Another methodology to evaluate treatment benefit is to examine the cumulative distribution function (CDF) of responses between treatment groups. The CDF provides plots to examine the treatment effect and mean improvements by treatment group to see if the mean improvement varies by patient subsets [1, 19].

e) Linguistic and Cultural Validation

Increasingly, PRO questionnaires are required to be used in a number of different populations and settings, however, questionnaires and their psychometric properties are not necessarily transferable [20, 21]. A measure that is valid and reliable for a particular language and culture may not prove to be so after translation. Linguistic and cultural adaptation of a questionnaire can occur during the development phase before validation, or it can be done after the questionnaire is validated in the language in which it was initially developed, with the latter being the more common approach. Ensuring the linguistic and cultural validity of a questionnaire is especially important for measures used in multinational clinical trials [20, 21].

The principal steps in adapting a measure for different languages and cultures are as follows:

(1) two forward translations of the original instrument into the new language;

(2) quality-control procedures that may include a backward translation (translating the instrument back into the original language) [21];

(3) adjudication of all translated versions;

(4) discussion by an expert panel to ensure clarity of the translated questionnaire; and

(5) testing the translated instrument in monolingual or bilingual patients to ensure that it measures the same concepts as the original instrument [21, 22].

However, if a backward translation of the measure does not produce a semantically equivalent instrument, then the instrument may need to be developed in the target language, rather than just translated [21].

After cultural and linguistic validation, PROs should also be psychometrically validated within the target language. Thus, reliability, validity, and responsiveness need to be assessed with each language translation to confirm the same measurement properties are present in the translated language(s) to ensure psychometric equivalence. If psychometric equivalence is not present (e.g., not achieving similar or better results in new language translation), the cultural and linguistic translations need to be re-evaluated and perhaps a new instrument may need to be developed.

The ICIQ questionnaires and many of the other questionnaires discussed in this chapter have multiple linguistically validated versions making them useful for International implementation. It is also important to note that the step after linguistic validation, demonstrating psychometric equivalence, should also be demonstrated to ensure that the PRO performs equivalently in different languages and cultures (e.g., Coyne et al. 2008 [23]).

f) Regulatory Oversight

As clinicians and scientists have begun to appreciate and accept PROs as appropriate outcome measures, regulatory authorities have issued guidance documents on current best practices in the development and implementation of PRO in clinical trial settings [1, 24, 25]. For PROs to be acceptable outcome measures for regulatory authorities, documentation of measurement properties must be present as well as evidence of inclusion of the patient perspective and understanding of the PRO and a cohesive conceptual framework that stipulates how the PRO is related to the intervention. While PROs within this document may have a "recommended" status, they may not meet all of the required regulatory guidelines and may require additional validation work either from a qualitative or quantitative perspective. It is strongly suggested that regulatory authorities be contacted early in the process of selecting a PRO for clinical trials to ensure regulatory acceptance of the PRO.

g) Questionnaire Development - A Conclusion

PROs are the most suitable method for assessing the patient's perspective of their lower urinary tract, vaginal and bowel symptoms [26]. Questionnaires may be long and detailed for use in research, but need to be short and easy to use to be relevant for clinical practice. In addition to being valid and reliable, they need to be easy to complete, and, if they are being used to measure outcome, sensitive to change. Developing a new questionnaire and testing it thoroughly takes a great deal of time and is only necessary if there is not an existing instrument available.

There are many questionnaires currently available for use and these have been reviewed and described with recommendations from the Committee for their use in the last three ICI reports.

The major purpose of the ICI has been to provide a definitive international review and consultative opinion regarding the recommended measures to assess patient reported outcomes within the area of urinary incontinence and LUTS. To this end since the First Consultation, the ICI has worked to develop a modular format for the various patient reported outcomes allowing clinicians and researchers to select internationally recommended questionnaires for the assessment of their patients in both clinical practice and clinical trials. In this fifth ICI review, the ICIQ modular questionnaires (supported by the International Consultation) are presented in detail and their use evaluated. Whilst some of the modular questionnaires are still currently under full evaluation their content and format are presented within this chapter.

III. RECOMMENDED PRO QUESTIONNAIRES

Grades of Recommendation for Questionnaires 2012

As with previous Consultations, the Committee continues to use three grades of recommendation. However, we have added a + sign to indicate when published content validity is available for an instrument:

- Questionnaires were 'highly recommended' and given a **Grade A** if the Committee found "Published data indicating that the questionnaire is valid, reliable and responsive to change following standard psychometric testing. Evidence must be published on all three aspects and questionnaires must be relevant for use with persons with incontinence. **Grade A + indicates there is additional evidence of *published* content validity."**

- Questionnaires were "recommended" and given a **Grade B** if the Committee found "Published data

indicating that the questionnaire is valid and reliable following standard psychometric testing. Evidence must be published on two of the three main aspects (usually validity and reliability). **Grade B + indicates there is additional evidence of *published* content validity."**

- Questionnaires were considered to have "potential" and given **Grade C** if the Committee found "Published data (including abstracts) indicating that the questionnaire is valid or reliable or responsive to change following standard psychometric testing. **Grade C + indicates there is additional evidence of *published* content validity."**

The Committee decided that evidence published in abstracts or posters could be used to indicate a developing questionnaire's potential, but was not sufficiently peer-reviewed to provide the basis for a stronger recommendation.

As decided in the Fourth Consultation the recommendation will be to preferably utilise questionnaires from the ICIQ modules described in detail below. Many, but not all, of these questionnaires are Grade A or A+ questionnaires by previously stipulated criteria. Within the description of the ICIQ modules below the grade assigned to each module is indicated.

Should none of the modular questionnaires be deemed appropriate for specific research or clinical purposes, ICI's recommendation is to use a Grade A+ or A questionnaire as previously recommended. When no suitable instrument exists a Grade B or C questionnaire, performing additional validation as indicated prior to use if feasible, should be used.

For UI and UI/LUTS, the Committee examined the quality of the psychometric evidence. Only where published data were scientifically sound was the label 'with rigor' allowed. Where the Committee had concerns about the quality of evidence, this is noted in the descriptions of the questionnaires below. The Committee considered that the number of high quality questionnaires means that there are now sufficient questionnaires for most purposes and it is not necessary to encourage the development of new questionnaires, except for particular patient groups (see below).

IV. INTERNATIONAL CONSULTATION ON INCONTINENCE MODULAR QUESTIONNAIRE (ICIQ): WHAT IS THE ICIQ?

The ICIQ modular questionnaire was developed to meet the need for a universally applicable standard guide for the selection of questionnaires for use in clinical practice and clinical research [27, 28]. The decision to develop standard questionnaire modules was taken by the Committee after the first ICI meeting in 1998, and resulted in the development of the ICIQ core questionnaire discussed in this section. It was recognised at that time that there were many good validated questionnaires each developed for a specific purpose and each subtly different. Although developers of the questionnaires were familiar with their content and use, the increasing number of questionnaires made appropriate selection difficult and limited the ability to compare similar clinical and research data due to different data collection methods.

An international advisory board was established to continue the development of the modular ICI questionnaire outside the limits imposed by triennial convening of the ICI Committee. Early discussions with the advisory board resulted in the decision to expand the concept to include wider urinary symptoms, bowel symptoms and vaginal symptoms. The advisory board consisted of clinicians and researchers with experience in the design and use of questionnaires representing the major societies involved in the assessment and research of lower genital tract, lower urinary tract and bowel function. The members of the advisory board of the ICI can be seen on the ICIQ website at www.iciq.net. The ICIQ modular questionnaire was then established. Researchers who have developed questionnaires that they would like to be reviewed by the advisory board for inclusion should send the questionnaires and relevant publications to www.iciq.net. The project is a series of living documents that will be continually updated.

1. AIMS AND OBJECTIVES

The ICIQ's objective is to provide international consensus on the use of patient completed questionnaires for the assessment of lower pelvic symptoms and their impact on patient's lives. Three aims underpin the ICIQ in order to achieve clarity over questionnaire use:

- To recommend high quality self-completion questionnaires according to evidence of validation as stipulated by the three prior ICI Committees;
- To promote wider use of questionnaires to standardise assessment of lower urinary tract and pelvic dysfunction and its impact on patients' lives, in order to;
- Facilitate communication in different patient settings and different patient groups both in clinical practice and wider clinical research.

The ICIQ recognised that many high quality published questionnaires already existed and, with permission from the authors, those instruments were adopted into the modular project. It was not possible to adopt all available questionnaires and where more than one option existed, the most appropriate questionnaire for the purpose was included. Where high quality questionnaires were not available, the need to develop a new questionnaire/s was acknowledged. Collaborative efforts to develop new questionnaires are welcome and encouraged.

The ICIQ's international nature requires that linguistically validated translations are available. More than 50 language versions of various modules have been validated to date, conducted according to established protocol.

Fourteen ICIQ modules/questionnaires are currently available for use, with further modules in development (discussed in detail below). Clinicians or researchers are able to select module(s) to meet the particular requirements of their study or clinical practice. In order to simplify this selection process, modules have been categorised as shown in **Table 1**. It must be stressed that although multiple questionnaires can and probably should be used they must be used in the format in which they were originally designed and the questionnaires cannot be merged together.

In recent years, increasing advances have been made in the area of electronic documentation, particularly with regard to patient care. It is recognised that questionnaires requiring written completion by hand may lack versatility and therefore prevent uptake of the ICIQ, hampering

Table 1. The ICIQ Modular Structure

		RECOMMENDED MODULES	OPTIONAL MODULES	RECOMMENDED ADD-ON MODULES			
	CONDITION	Symptoms		HRQL	Generic HRGL	Sexual Matters	Post-treatment
Core modules	Urinary symptoms	Males: ICIQ-MLUTS Females: ICIQ-FLUTS	Males: ICIQ-MLUTS LF Females: ICIQ-FLUTS LF	ICIQ-LUTSqol	SF-12	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	ICIQ-Satisfaction*
	Vaginal symptoms and sexual matters	ICIQ-VS		ICIQ-VSqol*	SF-12		
	Bowel symptoms and quality of life	ICIQ-B			SF-12	Males: ICIQ-Bsex* Females: ICIQ-Bsex*	
	Urinary Incontinence	ICIQ-UI Short Form	ICIQ-UI LF*	ICIQ-LUTSqol	SF-12	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	
	CONDITION	B) Specific patient groups		HRQL	Generic HRQL	Sexual Matters	Post-treatment
Specific patient groups	Nocturia	ICIQ-N		ICIQ-Nqol	SF-12	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	ICIQ-Satisfaction*
	Overactive Bladder	ICIQ-OAB		ICIQ-OABqol	SF-12	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	
	Neurogenic	ICIQ-Spinal Cord Disease*			SF-12		
	Long-term catheter users	ICIQ-LTC*			SF-12		
	Children	ICIQ-CLUTS*		ICIQ-CLUTS qol*			

Gray: In development; black: Grade A

attempts to promote standardisation of evaluation. Evaluations of electronic ICIQ modules are currently underway. Cognitive interviewing is being conducted among the potential populations of interest to ensure the appropriateness of these formats, for example, adults with varied lower urinary tract symptoms [11]. Quantitative comparison studies of equivalence are also planned to ensure the robustness of their measurement capabilities is not compromised.

In this chapter, questionnaires forming part of the ICIQ modular format are referred to as those preferred for usage. Although many of the modules are Grade A or A+ questionnaires, others are still under various phases of development and are graded appropriately. Questionnaires that are in early stages of development and have yet to reach Grade C are described as "in development". Where an ICIQ module is not available it is recommended that a Grade A or B or C questionnaire is used.

2. ICIQ MODULES

a) Core Modules

Questionnaires to assess the core symptoms and impact on health related quality of life (HRQL) of lower pelvic dysfunction are contained in this section, in addition to impact on sexual matters. Core modules (**Table 2**) provide evaluation of:

- Lower urinary tract symptoms
- Urinary incontinence
- Vaginal symptoms
- Bowel symptoms

Each symptom module is intended for the comprehensive yet succinct measurement of symptoms and associated 'bother'. The bother item attached to each symptom enables the individual to indicate areas that cause the greatest negative impact on HRQL as perceived by them. This can be a more sensitive indicator of treatment goals than frequency of symptoms alone. The HRQL questionnaires cover specific issues that are a consequence of symptoms, such as life limitations and emotional impact.

b) Specific Patient Group Modules

Questionnaires to assess specific conditions or symptom complexes such as nocturia and overactive bladder are contained in this section along with HRQL modules for these specific symptom complexes. This category also includes specific patient groups, for example, children. These instruments contain only question items characteristic of the symptom complex or have been developed specifically for use in a diverse group making the items/questionnaire only utilisable in that population.

- Nocturia
- Overactive bladder
- Patients with spinal cord disease
- Patients using long term catheters
- Lower urinary tract symptoms in children

c) Optional Modules

This category lies within the core symptoms and includes lengthier questionnaires for more in-depth (maybe in-depth evaluation is more accurate) evaluation of lower pelvic dysfunction. Whilst these questionnaires are suitable for use in clinical practice, they have not been shortened for clinical efficiency and are therefore more widely used in research studies where exploration of broader associated symptoms may be desired.

- Lower urinary tract symptoms
- Urinary incontinence

d) Post-treatment Module

The ICIQ module for post-treatment satisfaction is in the early stages of development. Assessment of a patient's satisfaction with treatment (behavioural, surgical or medication) provides information on treatment impact on their condition and life and includes their perception of effectiveness, tolerability and convenience. It is not yet clear if satisfaction following treatment can be characterised by a set of common question items that are applicable to all lower pelvic health conditions. As with HRQL, there are generic and disease specific questionnaires that assess satisfaction. Ongoing studies will provide further evidence on which to make suggestions regarding post treatment evaluation but it is likely that this will encompass both generic and condition specific measures. Ultimately, the development of post treatment modules will also rely on advice from regulatory authorities (e.g. FDA, EMA) to ensure that measures capture a recognised multidimensionality of satisfaction.

3. GUIDANCE FOR USE OF THE ICIQ

The ICIQ recommends the use of a symptom and HRQL module that match the intended purpose of a study in order to provide a comprehensive evaluation of these two perspectives. The extent of burden placed on the respondent and the study or clinical outcomes must be considered however and ultimately guide questionnaire selection. The characteristics of each module are summarised below, although more extensive information can be found on the project website, www.iciq.net. Modules currently under development are summarised in **Table 3**.

Table 2. ICIQ Module Description

Name	Scope of assessment	Domains	Items	Grade
ICIQ-MLUTS [29] (ICS*male*SF)	Male lower urinary tract symptoms and associated bother.	• Voiding • Incontinence • Individual items evaluating frequency and nocturia	13	A
ICIQ-FLUTS [30] (BFLUTS SF)	Female lower urinary tract symptoms and associated bother.	• Filling • Voiding • Incontinence	12	A
ICIQ-VS [31]	Vaginal symptoms including prolapsed and associated bother.	• Vaginal symptoms • Sexual matters • Quality of life	14	A
ICIQ-B [32, 33]	Bowel symptoms including anal incontinence and associated bother	• Bowel pattern • Bowel control • Quality of life	21	A+
ICIQ-UI Short Form [28]	Urinary incontinence.	• Urinary incontinence frequency, overall interference • Perceived cause of incontinence	4	A
ICIQ-LUTSqol[4, 34] (King'sHealth Questionnaire))	HRQL issues associated with urinary symptoms and associated bother.	• Life restrictions • Emotional aspects • Preventive measures	22	A+
ICIQ-MLUTSsex[35] (ICS*male*)	Male sexual matters associated with urinary symptoms and associated bother.	• Erection and ejaculation issues • Overall interference	4	A
ICIQ-FLUTSsex[36] (BFLUTS)	Female sexual matters associated with urinary symptoms and related bother.	• Pain and leakage with sexual intercourse • Overall interference	4	A
ICIQ-FLUTS Long Form (BFLUTS)	Detailed assessment of female lower urinary tract symptoms and associated bother.	• Varied lower urinary tract symptoms	18	A
ICIQ-MLUTS Long Form (ICS*male)*	Detailed assessment of male lower urinary tract symptoms and associated bother.	• Varied lower urinary tract symptoms	23	A
ICIQ-N	Comprehensive assessment of symptoms of nocturia and associated bother.	• Frequency • Nocturia.	2	A
ICIQ-OAB	Comprehensive assessment of symptoms of overactive bladder and associated bother.	• Frequency • Nocturia • Urgency • Urgency incontinence	4	A
ICIQ-OABqol (OAB-q) [5]	Detailed assessment of health-related quality of life issues associated with overactive bladder.	• Coping • Concern/Worry • Sleep • Social Interaction	25	A
ICIQ-Nqol (NQOL) [37, 38]	Detailed assessment of HRQL issues associated with nocturia.	• Issues associated with sleep disturbance • Life restrictions • Preventive measures	13	A+

Table 3. ICIQ Description of modules in Development.

Name	Purpose	Current status
ICIQ-CLUTS [39]	Assessment of urinary symptoms in children.	Validitytesting published awaiting reliability and responsiveness evaluation.
ICIQ-LTCqol	Assessment of HRQL associated with long term catheter use	Validity and reliability underway but yet to be published. Requires responsiveness evaluation.
ICIQ-Bladder diary [40]	Daily diary regarding bladder pattern including frequency, volume, intake and incontinence episodes.	Validity and reliability established. Requires responsiveness evaluation.
ICIQ-Spinal cord disease	Assessment of urinary symptoms and impact on HRQL associated with specific management **devices** and related bother.	Initial qualitative development completed. Requires quantitative evaluation.
ICIQ-VSqol	Detailed assessment of HRQL issues associated with vaginalsymptoms and related bother.	Initial qualitative development completed. Quantitative evaluation underway.
ICIQ-Satisfaction	Generic assessment of post-treatment satisfaction for lower pelvic dysfunction including surgical and conservative intervention.	Initial qualitative development completed. Quantitative evaluation underway.
eICIQ	Evaluation of altered administration of ICIQ modules.	Initial qualitative evaluation completed. Quantitative evaluation of psychometric equivalence underway.

4. ICIQ QUESTIONNAIRE IMPLEMENTATION

The ICIQ modular questionnaire has attracted considerable attention from both clinicians and researchers worldwide since its structure was finalised in 2004. More than 1200 requests for use of the various modules have been documented and over 180 published studies were identified up to March 2012. The most widely applied module is the ICIQ-UI Short Form, particularly to evaluate female urinary incontinence. Reports on further validation and translations of the ICIQ and related educational projects are growing in number. This is essential in order to achieve standardised evaluation of pelvic floor dysfunction, which is a primary aim of the initiative.

The ICIQ has also been applied to clinical and general practice settings, and has been adopted in national guidelines for the management of urinary incontinence in primary care by the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/pdf/sign79.pdf) and in a primary care resource pack by the British Society of Urogynaecology.

5. CONCLUSION

The ICIQ modular questionnaire project (www.iciq.net) provides a series of standardized questionnaires for the patient reported assessment of lower pelvic dysfunction symptoms and their impact on patients lives. The ICIQ provides clarity over the selection of questionnaires by recommending only those with evidence of high quality and robust psychometric validation including validity, reliability and sensitivity to change. This assurance provides the user with confidence in the results obtained, which is important in clinical practice and research where treatment decisions or trial outcomes depend on this evidence. Increasing awareness of the ICIQ aims to promote increased use of standardised questionnaires, thereby facilitating communication between clinicians and researchers and enable more widespread comparisons between different treatments and patient groups worldwide. Collaboration with the ICIQ is encouraged among clinicians and researchers in order to conduct further evaluation and provide further translations of ICIQ modules.

V. PATIENT-REPORTED OUTCOME (PRO) QUESTIONNAIRES TO ASSESS THE IMPACT OF URINARY INCONTINENCE, OAB AND LOWER URINARY TRACT SYMPTOMS

There are a variety of PRO measures available for use in clinical practice and research that assess a range of concepts (e.g. HRQL, patient satisfaction, symptom bother, etc). This section and table series at the end of the chapter provides an overview and assessment of those measures. Importantly, clinical practitioners and researchers need to clearly determine their clinical and research objectives before selecting a PRO as it is these objectives and the target patient population that will help determine which validated PRO is appropriate to use. **Appendixed Tables 4 through 8** provide a brief overview of all current PRO measures for urinary incontinence and LUTS, their purpose, psychometric properties, translation availability, and recommended ICI grade.

Please note, as instrument development and validation is an ongoing process, the tables below contain publications through August, 2011. As additional work may have been performed on an in-

strument, it is always prudent to conduct a further literature search and/or contact the instrument developer prior to selecting an outcome measure for your clinical practice or study.

One trend that has become more apparent since the previous Consultations is the modification of more established urinary incontinence questionnaires for use in selected patient groups (e.g., pelvic organ prolapse; males; different cultural/language groups). When using a questionnaire in a patient group other than the group in which it was initially developed, cognitive interviews with the new patient population should be held to review the applicability of the questionnaire to the new patient group. Several of the main questionnaires to be discussed below have now had modified versions published in the literature. The Committee's view is that although it may be appropriate to modify established questionnaires for use with some populations, it is advisable to keep such modifications to a minimum, and to use the original versions whenever possible. Any modifications of established questionnaires may result in changes (sometimes substantial) in the psychometric performance of the instrument, and thus all modified instruments should be subjected to the same psychometric testing as that employed in developing a completely new instrument. Specifically, modified instruments should report information regarding the instrument's construct validity, reliability, and test-retest reliability, at a minimum, and sensitivity to change, in intervention studies.

For some of the more widely used instruments listed below, several modified, shortened versions have been published. Information regarding the modified versions is provided under the original source versions of the questionnaires, but the modified versions are evaluated and graded separately, based on the available information regarding their psychometric properties and performance.

1. HEALTH-RELATED QUALITY OF LIFE MEASURES

Health-related quality of life (HRQL) measures help to assess the impact of disease and treatment on those aspects of quality of life related to health. UI is a symptomatic condition that has been shown to affect many aspects of a patient's life - physical, emotional, and social relations and cause concern and burden. As such, it is important to assess HRQL in clinical research and practice. **Appendixed Table 4** at the end of the chapter provides a quick overview of the variety of HRQL measures available and their validity and characteristics to determine which measure is suitable for your objectives.

2. PATIENT SATISFACTION AND GOAL ATTAINMENT SCALING

Patient satisfaction and Goal Attainment Scaling are two important but separate types of PROs that allow for individualised assessment of disease impact and treatment. Patient satisfaction is the subjective, individual evaluation of treatment effectiveness and/or the service provided by the healthcare system. Goal attainment scaling (GAS) is a method developed to ascertain individual patient treatment goals and using those to facilitate patient-provider interaction and tailor the treatment plan based on those individual's goals [41].

Measures of patient satisfaction can include evaluation of accessibility/convenience, availability of resources, continuity of care, efficacy, finances, humaneness, information gathering and giving processes, pleasantness of surroundings and perceived quality/competence of health care personnel [42]. At its most basic level, satisfaction is a comprehensive evaluation of several dimensions of health care based on patient expectations and provider and treatment performance. As an outcomes measure, patient satisfaction allows health care providers to assess the appropriateness of treatment according to patient expectations. In chronic diseases, where patients must live with treatment, patient satisfaction may be the distinguishing outcome among treatments with comparable efficacy [43].

Two patient satisfaction methods of promise with Grade B criteria are the BSW and OAB-S [44, 45]. Generally responsiveness cannot be assessed as there is no baseline assessment of patient satisfaction with treatment as no treatment has been given. **Appendixed Table 5** at the end of the chapter presents a summary of satisfaction instruments identified in UI, OAB and other LUTS.

GAS has been used to measure clinically important change in several therapeutic areas. Although it was originally developed to assess health outcomes in mental health settings, it has recently been expanded to include evaluations in urogynecology[46-50]. GAS has been linked to several possible benefits compared with traditional outcome measures, such as improved clarity concerning treatment objectives for both the healthcare provider and the patient, active involvement of the patient in problem-solving efforts, establishment of realistic patient and healthcare provider expectations of treatment, and increased motivation of patients toward improving their health condition [41]. The end result of GAS is to clarify patients' expectations for their treatment, document goal achievement, and eventually increase patient satisfaction and improve therapeutic outcomes.

One GAS instrument for lower urinary tract symptoms has been well-developed, the Self Assessment Goal Attainment (SAGA) questionnaire. The development and pilot testing of the SAGA questionnaire has been published [46]. SAGA was developed in 3 phases: (1) a preparatory phase in which preliminary information on goal setting and attainment was gathered; (2) a goal elicitation phase that included qualitative interviews with 41 patients with OAB symptoms and/or other LUTS; and (3) cog-

nitive debriefing interviews during which the draft questionnaire was administered to 11 patients with OAB and/or other LUTS. Numerous linguistically validated translations are available at: http://www.pfizerpatientreportedoutcomes.com [51].

3. SCREENING TOOLS

In order to improve the detection of incontinence, OAB and other LUTS, several screening tools have been developed (**Appendixed Table 6**). These tools help patients self-describe symptoms and facilitate diagnosis of LUTS by the clinician. Only the B-SAQ has been designed to screen for general lower urinary tract symptoms (LUTS) rather than solely symptoms of one condition. The majority of patients with LUTS have mixed urinary symptoms, and therefore a questionnaire which can detect more than one symptom complex may be more functional as a screening tool in clinical practice than a highly specific questionnaire. The Leiscester Impact Scale (LIS), OAB-V8, OAB-SS and QUID are all Grade A, short, simple to understand and complete, and easy to interpret. However the LIS is interviewer, not patient administered. Importantly, with screeners, responsiveness is not assessed, however the sensitivity and specificity of each tool is critical.

4. ASSESSING SYMPTOM BOTHER AND OVERALL BOTHER

Measures that can be used to assess how bothered patients are by urinary symptoms are included in **Appendixed Table 7**. The Patient Perception of Bladder Condition [52] and the Urogenital Distress Inventory are the only Grade A recommend instrument.There are several Grade B and C measures which assess bother for incontinence and LUTS.

5. ASSESSING THE IMPACT OF URGENCY

Several instruments have been developed specifically to assess urinary urgency, which is defined by the International Continence Society as “the complaint of a sudden compelling desire to pass urine which is difficult to defer”[53]. Urgency is the hallmark symptom of OAB [54], thus assessing the effect of treatment on this symptom and its impact on HRQL is important. With any measure designed to evaluate urgency, patients must be able to distinguish between the normal desire to urinate (urge) and the difficult-to-postpone need to urinate (urgency) [55, 56]. Wording thus becomes critical in the development of urgency assessment measures. Chapple and Wein[57] make a case for describing urgency as a “compelling desire to void in which patients fear leakage of urine” as a means of distinguishing this abnormal sensation from the normal need to void. However, some patients may have a sensation of urgency without fear of leakage, further complicating attempts to define urgency. Importantly, with some of these scales, patients have the option of indicating that they experienced UUI (an event) rather than the strongest feeling of urgency (a sensation) itself. Several instruments have been developed to assess urinary urgency these are summarised in **Appendixed Table 8**.

VI.QUESTIONNAIRES TO ASSESS SYMPTOMS AND HEALTH-RELATED QUALITY OF LIFE IMPACT OF PELVIC ORGAN PROLAPSE

Many women with lower urinary tract and bowel symptoms have pelvic organ prolapse (POP). The clinical assessment, standardized measurement, conservative and surgical treatment of POP is covered in Chapters 5A and 15. Increasingly with new surgical techniques for the treatment of POP standardised objective and subjective assessments are required. This chapter will review the standardised symptom assessment tools for POP. These tools do not allow the clinical staging or planning of prolapse treatment, nor do they assess the correction of prolapse following conservative or surgical treatments. As with many of the other sections in this chapter, it is apparent that clinical conditions affect patients differently. Ultimately, the decision to seek and offer therapy for POP and the evaluation of its success will best be measured by the patient and not necessarily by the physician assessed clinical findings. Whilst not as advanced as the assessment tools to evaluate LUTS, there has been progress in the development of POP specific assessment tools since the last triennial ICI report.

It is important to remember that where specific problems of the patient with POP require assessment (e.g., lower urinary tract symptoms, sexual function) it may be preferable to use one of the questionnaires designed specifically for that purpose.

In general questionnaires for POP tend to focus more on the symptoms related to the lower bowel and prolapse probably because of the wider availability of questionnaires to assess LUTS. The broad three categories of instruments for POP are:

1. Presence of symptoms and their severity;

2. HRQL

3. sexual function.

As prolapse is almost always multidimensional, selecting questionnaires in the modular format of the ICIQ (see above) may well be preferable for many clinical and research applications

For POP, the Committee examined the quality of the psychometric evidence and only where published data were scientifically sound was the label ‘with rigor’ allowed. The Committee noted that this is a developing area and therefore three grades of recommendation were established (**Table 9**).

VII.QUESTIONNAIRES TO ASSESS SYMPTOMS AND HRQL IMPACT OF FAECAL INCONTINENCE

A range of PROs have been developed to identify the severity of anal (AI) or faecal incontinence (FI) and its impact on HRQL. By comparison with the last triennial review, questionnaires are now being incorporated into research trials on a more regular basis recognising the importance of capturing the patient's perspective. Less is reported regarding clinical assessment. Due to the close overlap between faecal incontinence and other pelvic floor disorders (in particular urinary incontinence), some of those questionnaires used for other pelvic disorders also include items to cover faecal incontinence. For similar reasons, items relating to faecal incontinence have often been included in questionnaires addressing general gastro-intestinal and colo-rectal function, as well as condition specific instruments in such areas as irritable bowel syndrome and inflammatory bowel disease, conditions which are commonplace in colorectal practice as well as in other specialties dealing with pelvic floor disorders [66, 67].It is also important to remember that the normal range of bowel function is broad, that bowel function may be highly variable within individuals without significant pathology. Consequently instruments in this field are likely to lack a degree of sensitivity or specificity for the specific bowel disorders such as IBS, IBD evacuation disorder and constipation.

Anal/faecal incontinence and bowel evacuation are intrinsically related to pelvic floor function and it may be inappropriate to consider bowel function purely in terms of continence and constipation. Evacuatory dysfunction may result from a variety of underlying pathologies including outlet obstruction, slow transit or other mechanical, pharmacological, metabolic, endocrine and neurogenic abnormalities [68]. Anal incontinence occurs in both sexes and it is unclear whether there is any difference between genders in terms of prevalence. Studies to date suggest that in different age groups prevalence varies, with unique risk factors attributable at these stages of life [69]. Symptoms are considered crucial to diagnosis as specific symptoms are thought to reflect the underlying pathophysiology [70]. Thus, urgency (the inability to defer defaecation) and urgency faecal incontinence are thought to indicate loss of voluntary control due to impaired external anal sphincter function, whereas passive faecalincontinence is thought to indicate impairment of the smooth muscle of the internal sphincter.

Table 9: Recommended questionnaires for the evaluation of symptoms and health-related quality of life impact of pelvic organ prolapse

Grade A (recommended)
Pelvic Floor Distress Inventory (PFDI) [58]
PelvicFloor Impact Questionnaire (PFIQ) [58]
Prolapse quality of life questionnaire P-QOL [59]
Grade B
The Australian Pelvic floor Questionnaire (APFQ) [60]
Pelvic floor symptom bother questionnaire (PFBQ) [61]
PelvicOrganProlapseUrinary incontinence Sexual questionnaire (PISQ) (PISQ-12) [62]
ICIQ vaginal symptoms questionnaire (ICIQ – VS) [62]
The electronic Personal Assessment Questionnaire – Pelvic Floor (ePAQ-PF) [63]
Grade C (with potential)
Pelvic Floor Dysfunction Questionnaire [64]
Danish Prolapse Questionnaire [65]

For AI/FI, the Committee examined the scope of available measures and quality of the psychometric evidence. While this remains a developing area, the publication of the ICIQ-B questionnaire for the assessment of anal incontinence and associated impact on quality of life means that a questionnaire is now available that reaches the highest level of recommendation, including the qualitative development phase [32, 33]. Further evaluation of existing measures such as the Faecal Incontinence Quality of Life index (FIQL) has also resulted in an improved grade of recommendation [71].

The grades of recommendation are as outlined in previous sections and below. **Table 10** summarises the questionnaires reviewed and grades of recommendation accordingly.

Appendixed **Tables 11 through 13** at the end of the chapter provide details of the specific psychometric properties and development of each questionnaire.

VIII. QUESTIONNAIRES TO ASSESS SEXUAL FUNCTION/SEXUAL HEALTH AND URINARY SYMPTOMS

Sexual function may be regarded as a dimension or aspect of overall HRQL, for which a number of dimension-specific measures have been developed and validated. There is a wide choice of available instruments, the selection of which will depend on the clinical or research setting where the instrument is to be employed. Established and widely used measures that have been shown to be valid, reliable and responsive are clearly desirable, however the feasibility and appropriateness of using a particular instrument in a particular setting must also be considered. A large number of different instruments exist in this field, which aim to evaluate specific aspects of sexual function and sexual health. A number have been specifically developed or adapted to examine sexual function in patients with pelvic floor disorders such as incontinence.

Table 10: Recommended questionnaires for the evaluation of symptoms and quality of life impact of faecal incontinence

Grade A+
ICIQ-B [32, 33]
Grade A
Faecal Incontinence Quality of Life Scale [71]
Birmingham Bowel and Urinary Symptom Questionnaire [72, 73]
Questionnaire for assessment of Faecal Incontinence and Constipation [74]
Grade B
Colorectal Functional Outcome Questionnaire [75]
Manchester Health Questionnaire [76]
Bowel Control Self Assessment Questionnaire [77]
Pelvic Floor Bother Questionnaire [61]
Elderly Bowel Symptom Questionnaire [78]
Faecal Incontinence and Constipation Assessment [79]
Grade C
Faecal Incontinence Questionnaire [80]
Ungraded (require formal validation, evidence of progress published)
Postpartum Flatal and Faecal Incontinence Quality of Life Scale [81]
Bowel Function Questionnaire [82]
Surgical Outcome Tool for Faecal Incontinence [83]

Clinicians who treat sexual problems often prefer to use unstructured rather than structured interviews or questionnaires in clinical practice as an unstructured approach allows the tailoring of questions to suit the couple or the individual being assessed. Unstructured interviews enable the clinician to support patients who feel vulnerable and encourage discussion. The experienced clinician hopes to have an appreciation of the information required to make the correct diagnosis and institute appropriate treatment. In this setting, vocabulary can be modified, as can the level of assertiveness and the depth of questioning to suit the needs of the individual. This flexibility is not readily achievable with questionnaires which individuals may also find difficult to complete due their impersonal nature or because of physical or mental impairment, cultural or language differences. However, some patients find the discussion of intimate issues with clinicians very difficult and questionnaires may allow these issues to be measured in private, at ease and more effectively before subsequently exploring questionnaire responses in the clinical interview itself.

Appendixed Table 14 at the chapter's end outlines a number of sexual health measures with a Grade A or B rating based on the criteria provided above. Three measures are of particular note, obtaining an A+ rating, having demonstrated not only reliability and validity but also that content was derived with patient input and responsiveness to treatment has been shown: GRISS [84], FSFI [85], and IIEF [86]. Most of the identified measures are self-reported, easy and quick to administer and many have various language versions available. The majority have also been previously used in incontinence populations. There are various others measures that would be given a rating of C (e.g., Sexual Behaviour Inventory [87, 88], McCoy Female Sexuality Questionnaire [89]), but given the breadth of measures available with an A or B rating, researchers are encouraged to use these for assessing sexual function/sexual quality of life. Specific choice of measure will be dependent on research hypothesis. For instance, if you wanted to assess impact of OAB on sexual function e.g. arousal in women then you would want to use the FSFI rather than the SQOL-F [90] because the FSFI has a specific arousal domain whereas the SQOL-F assesses sexual quality of life.

IX. QUESTIONNAIRES FOR SPECIFIC PATIENT GROUPS

Most studies and questionnaires have been developed for use with members of the general population or urology/gynaecology patients with incontinence or POP. However, some specific patient groups may experience particular problems with incontinence (for example, children, frail elderly or those who are severely disabled), which may require independent investigation and potentially the development of more specific measures or the addition of a new subset of items on already developed instruments. The Committee advises that researchers should use existing highly recommended or recommended questionnaires if possible as this aids comparison and to reduce the increasing proliferation of questionnaires. Many of the questionnaires developed below for particular conditions (e.g. prostate cancer) pre-dated the development of highly recommended questionnaires, and highly recommended questionnaires should be used preferentially.

1. OLDER PEOPLE

Urinary incontinence symptoms play an influential role on the overall HRQL in older people (>65) and causes a significant decrease in HRQL, as severe as that of many chronic disease states. Since the elderly commonly have a number of associated comorbid conditions, it may be difficult to measure the impact of urinary incontinence with generic HRQL measures. The use of incontinence specific tools to measure patient-reported outcomes in the elderly, therefore, is of considerable importance. Validated incontinence-specific PRO questionnaires, such as IIQ, I-QOL or KHQ, are used for clinical trials or research on urinary incontinence including elderly people, but their validity has not been specifically assessed in this age group. Okamura assessed symptoms and HRQL in older people (men and women)

with lower urinary tract symptoms including incontinence, using the KHQ and IPSS. They demonstrated that symptoms and HRQL in the elderly with LUTS could be assessed by IPSS and KHQ and that urinary incontinence appeared to be more associated with a decreased HRQL in elderly women [91].

On the other hand, there are a variety of factors affecting older people, including physical, social, mental, economic or environmental conditions, which are different from those of the young. In frail elderly people with dementia or physical impairment, it may be difficult to assess the impact of urinary incontinence alone. Questionnaires specifically developed for the elderly may be of great importance in this respect. However, there is little relating to the development or validation of particular questionnaires for older people with urinary incontinence. Two questionnaires dealing with older people were found and are described below. No questionnaires dealing with patient outcomes specifically for frail older incontinent people were found.

a) The Urge Impact Scale (URIS) [Grade B]

The Urge Impact Scale (URIS) was designed and tested specifically for older persons with urgency incontinence. The URIS was developed and validated by DuBeau et al. (1999) [92] and included 32 items, reduced to 24 items (URIS-24). The URIS-24 was psychometrically assessed for validity and reliability in community-dwelling older (>65y) men and women with urgency incontinence. Cronbach's alpha was 0.84 for the URIS-32 and 0.94 for the URIS-24. In assessment of test-retest reliability, interclass coefficient (ICC) was 0.88. The URIS-24 had modest but nearly significant correlation with the number of urgency incontinence episodes (rho=-0.39, p=0.05). Factor analysis revealed 3 component structures corresponding to physiological burden, perception of personal control and self-concept. There was no analysis for responsiveness. They showed that the URIS-24 is an internally consistent, highly reproducible tool for the assessment of the QOL impact of urgency incontinence on older persons.

b) Caregivers

The Overactive Bladder Family Impact (OAB-FIM) scale was developed to assess the impact of OAB on family members of patients with OAB. This 19-item tool consists of 6 subscales [93]. Four subscales (Irritation, Activities, Travel, Concern) could be used for all family members; however 2 additional subscales (Sleep, Sex) should only be administered to spouses/significant others. The OAB-FIM was highly discriminating between OAB and control family members, with all OAB family members indicating significant impact (all $p<0.0001$). Internal consistency reliability (Cronbach's alpha >0.71) and 2-week test-retest reliability (intraclass correlation coefficients >0.73) were high for all subscales. Concurrent validity of the OAB-FIM was demonstrated through statistically significant ($p < 0.001$) Spearman correlations with the OAB-q (coefficients ranging from 0.35 to 0.58) and the PPBC (0.31 to 0.56). No differences were noted on the OAB-FIM by patient incontinence status (none, urge vs. mixed). OAB-FIM scores also discriminated by family member perceptions of OAB severity, particularly among the Irritation, Activities and Travel subscales. Correlational analyses among the OAB-FIM and relationship quality measures suggest that greater OAB symptom impact on the family member was associated with increased problems in the patient–family member relationship. The responsiveness of the OAB-FIM is yet to be assessed. This measure can be found at www.pfizerpatientreportedoutcomes.com.

2. CHILDREN

Some questionnaires have been developed specifically to address issues for children, particularly enuresis. See Chapter 9 (Children) and section on ICIQ modular questionnaire.

3. SPINAL CORD INJURED/NEUROLOGICAL IMPAIRMENT

Individuals who have a spinal cord injury or are neurologically damaged can experience particular difficulties with incontinence and the use of various devices. It would be useful to investigate whether Grade A questionnaires, developed for people without neurological damage, can be used in this group, or whether additional modules or instruments are required. This is an area where a small number of questionnaires are being developed with the Qualiveen being a notable exception (Also see section on the ICIQ questionnaire and below).

Qualiveen: Quality of Life Related to Urinary Problems in Spinal Cord Injury [Grade A]

The Qualiveen was developed to evaluate the specific impact of urinary dysfunction on the quality of life of spinal cord injury patients in France [94]. The initial items were developed following patient interviews, and were then assessed for validity and reliability in 281 spinal cord injury patients with urinary difficulties. The Qualiveen contains 30 items and has demonstrated good reliability and validity [94]. Further validation of the Qualiveen has occurred in multiple sclerosis patients [95] and it has been translated and validated into English [96], German [97], and Portuguese [98]. The Qualiveen has demonstrated responsiveness in multiple sclerosis patients and has a suggested MID of 0.5 [99].

4. PROSTATE/BLADDER CANCER

Many PRO questionnaires are available for assessment in this area: Post-radical prostatectomy questionnaire [100, 101], Cancer Rehabilitation Evaluation System - Short Form (CARES-SF) [102], Prostate Cancer Treatment Outcome Questionnaire (PCTO-Q) [103],PROSQOLI [104], Modified Southwest Oncology Group (SWOG) [105], Functional Assessment of Cancer Therapy - (FACT-G), Bladder form (FACT-B) and Prostate form (FACT-P) [106],

Functional Assessment of Cancer Therapy Vanderviet Cystectomy Index (FACT-VCI) [107], EORTC metastatic prostate cancer [103], Changes in Urinary Function [108], Prostate-targeted Health Related Quality of Life [109]. While it is beyond the scope of this chapter to review and recommend PROs in this area, the principles and guidelines discussed herein apply to selecting a PRO related to prostate and bladder cancer.

5. LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATE DISEASE

Many questionnaires have been developed to assess LUTS and benign prostate disease; however, most do not contain a full evaluation of UI. Perhaps the most widely known urology PRO is the AUA Symptom Index [110], I-PSS (International Prostate Symptom Score) [110, 111]. The IPSS has been utilitised internationally to assess symptoms of prostate disease with documented reliability, validity and responsiveness. Additional PRO measures for BPH are as follows: Patient-completed modification of the Boyarsky[112], BPH Impact Index [113], and BPH Health-related QoL survey [114].

6. SUMMARY

In summary, some general points to consider in selecting PRO measures for urology studies:

- Ensure that the PRO research questions and study endpoints are clearly defined. Determine the PROs that are most critical to assess and which are most likely to be affected by a particular condition and/or its treatment.
- Make good use of prior literature searches in identifying past research in the area(s) of interest, as well as in identifying the types of PRO measures other researchers have used in past work. This information can provide valuable information on how particular outcome measures have performed in previous populations, as well as provide additional information to assist in defining research questions/issues regarding the PRO components of any given study.
- Consider the characteristics of the population in selecting measures. For example, are the study subjects to be children or older adults, well educated vs. those with limited education, or persons with low literacy? Ensure that the mode of data collection is appropriate for use with the study population. Furthermore, do not assume that an instrument validated for use with Caucasian, middle-class individuals in the U.S. will be appropriate for use in other countries, and/or those of a lower socio-economic status or of different educational backgrounds. This chapter has indicated, where possible, the extent to which specific PRO measures have been validated, and used reliably with different populations.
- Use the questionnaires recommended in this chapter whenever possible. Do not “reinvent the wheel.” Developing new PROs is a time-consuming and complicated process. If a new scale needs to be developed, ensure that the guidelines proposed by the FDA and EMEA on developing PROs are followed and that the appropriate expertise in questionnaire development and psychometrics is available to your research team in order to guide the questionnaire development process.
- Know the strengths and weaknesses of different types of PRO measures. In general, generic measures are useful in providing information on multiple patient outcome dimensions that can be compared across different populations. They may lack sensitivity, however, in addressing concerns of specific patient populations (e.g., OAB, UI, faecal incontinence). Condition-specific instruments, in contrast, do address areas of function more specific to the condition, and tend to be more responsive to changes in clinic status, due to their increased specificity in addressing the conditions of their patient populations. Weaknesses of condition-specific instruments, however, are that they are often not appropriate for use with multiple populations, and cannot be used to make direct comparisons across different patient groups.
- Know how to score your selected PRO measures and how to interpret the scores. Specifically, ensure that the scoring method of a measure provides you with the information you need to answer your research question?
- Finally, train and certify your staff to administer PRO measures using either patient interview and/or self-administration techniques, depending on the method to be used in the study. The administration process needs to be standardised and completely similarly across all participants.

X. RECOMMENDATIONS FOR RESEARCH

1.The selection of a PRO questionnaire must reflect study purpose and objectives

2. Grade A recommended questionnaires should be used in all clinical trials evaluating treatments

3. The inclusion of the ICIQ modules is preferred in all studies to standardise outcome assessment

4. Continued PRO development, refinement, and use should accurately and adequately report on the methods, samples, statistical analyses and psychometric properties of questionnaires in scientific journals (i.e. validity, reliability and responsiveness), so the quality of each study can be assessed

Researchers are encouraged to use existing questionnaires and refine for specific populations when needed (e.g. frail elderly, children)

5.Researchers are encouraged to collaborative with the ICIQ project on the development and refinement of modules and translations.

Table 4: Health-related Quality of Life measures for Lower Urinary Tract Symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
BFLUTS (Bristol Female Lower Urinary Tract Symptoms Questionnaire). Currently the ICIQ-FLUTS (ICIQ-Female Lower Urinary Tract Symptoms); Grade A [30]	34-question tool used to assess female LUTS, particularly urinary incontinence, measure impact on quality of life and evaluate treatment outcome	Women, inconti-nence	√	√	√		√		None	www.iciq.net
Contilife® (Quality of Life Assessment Questionnaire Concerning Urinary Inconti-nence); Grade B [115]	28-intem tool used to assess the impact of urinary incontinence on HRQL. Originally developed in French and designed for women with UI (urge, stress and mixed UI)	Women, SUI	√	√ (ICC = 0.96)			√		√	www.proqolid.org
DAN-PSS-1(Danish Prostatic Symptom Score); Grade A [116]	15-item tool used to evaluate males with LUTS suggestive of uncomplicated BPH	Men, BPH	√	√	√		√			www.proqolid.org
EPIQ (Epidemiology of Prolapse and Incontinence Questionnaire); Grade B [117]	49-item tool developed and validated in English and Spanish to assess the presence or absence of AI, OAB, SUI, and pelvic organ prolapse in female population	women, PFD	√	√	√	√	√	√		contact developer
ICIQ-UI Short Form (International Consultation on Incontinence Questionnaire - Urinary Inconti-nence Short Form (ICIQ-UI Short Form); Grade A[28]	4-item tool used to assess the symptoms and impact of urinary incontinence in clinical practice and research	men and women, Urinary symptoms	√	√	√		√	√	√ (8 weeks)	www.proqolid.org

Table 4: Health-related Quality of Life measures for Lower Urinary Tract Symptoms (continued)

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
ICSmale (ICIQ-MLUTS) (International Continence Society - Male); Grade A [35]	23-item tool used to provide a thorough evaluation of the occurrence and bothersomeness of lower urinary tract symptoms and their impact on the lives of men with benign prostatic disease	men with LUTS and possible BPH	√	√	√		√		√	www.proqolid.org
ICSQoL (International Continence Society-Benign Prostatic Hyperplasia study quality-of-life); Grade A [118]	8-item tool used to assess impact of lower urinary tract symptoms on the lives of men with LUTS	men with LUTS and possible BPH	√	√	√		√			www.proqolid.org
IIQ (Incontinence Impact Questionnaire); Grade A [119]	30-item tool developed to describe the severity of incontinence in a population. It was validated in a group of women aged 45 and over attending two continence clinics for SUI primarily. Used to assess the impact of urinary incontinence on HRQL.	Women, UI		√	√		√		√ (12Weeks)	contact developer
IIQ-7 (Incontinence Impact Questionnaire - short form); Grade A [120]	7-item tool used to assess the impact of urinary incontinence on HRQL	*validation study on men after radical prostatectomy who had UI	√ (Cronbach's Alpha = 0.93)	√ (Spearman's Rho = 0.99; ICC = 0.75)	√	√	√	√		contact developer

Table 4: Health-related Quality of Life measures for Lower Urinary Tract Symptoms (continued)

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
IOQ (Incontinence Outcome Questionnaire); Grade B [121]	27 question tool developed for assessing quality of life after surgery for stress urinary incontinence	Women SUI	√ (Cronbach's Alpha = 0.83)		√	√			√	contact developer
I-QOL (ICIQ-Uqol) (Urinary Incontinence-Specific Quality of Life Instrument); Grade A [122, 123]	22-item tool used to assess quality of life of women with UI	women, UI	√	√	√			√	√	www.proqolid.org
ISI (Incontinence Severity Index); Grade C [124]	2-item severity measure recommended by the World Health Organization for studying the epidemiology of incontinence and other LUTS; Developed in an epidemiologic study of 28,000 women in Norway.	Women, SUI				√	√			contact developer
ISQ (Incontinence Stress Index: ISQ-P [Patient]; ISQ-SOPS [Staff Observation of Patient Stress]; ISQ-SR [Staff Reaction to UI]); Grade C [125]	40-item tool (20-items in short form) used to assess psychological stress associated with urinary incontinence	Women	√	√						www.proqolid.org
ISS (Incontinence Symptom Severity Index); Grade A [126]	8-item instrument used for the self-assessment of severity of female urinary storage and voiding symptoms, rather than symptom bother or effects of on quality of life	Females		√ (ICC = 0.62 - 0.91)			√		√ (Duration not specified)	contact developer

Table 4: Health-related Quality of Life measures for Lower Urinary Tract Symptoms (continued)

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
KHQ (ICIQ-LUTSqol) (King's Health Questionnaire); Grade A+ [4, 34]	21-item tool used to assess the symptoms impact of LUTS including urinary incontinence on HRQL. Developed in a clinical perspective to evaluate incontinence in women.	UI, OAB, men and women	√ (all domains except severity measure (Cronbach's Alpha = 0.60) demonstrated excellent IC)	√	√	√	√	√	√ (12Weeks)	www.proqolid.org
LIS (The Leicester Impact Scale); Grade A [127]	21-item tool used as a quality of life measure for males and females with urinary storage symptoms of urgency, frequency, nocturia and incontinence.	men and women, LUTS	√	√	√		√		√	contact developer
MUDI (Male UrogenitalDistress Inventory); Grade B+ [128, 129]	27-item tool used to address the dimension of physical health, focusing on bother from multiple symptoms associated with UI in men. Created by eliminating four gender specific items from UDI and IIQ.	Men with LUTS following a radical prostatectomy for prostate cancer	√		√		√			www.proqolid.org
MUSIQ (Male Urinary Symptom Impact Questionnaire); Grade B+ [128, 129]	32-item tool used to capture mental/psychological health, social health, and global perceptions of function and well-being in men with urinary incontinence. Created by eliminating four gender specific items from UDI and IIQ.	Men, UI	√		√		√			www.proqolid.org

Table 4: Health-related Quality of Life measures for Lower Urinary Tract Symptoms (continued)

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
N-Qol(Nocturia Quality of Life Questionnaire); Grade A+[37, 130]	13-item tool used to assess the impact of nocturia on the quality of life of patients	men and women	√	√	√		√	√	√	www.pfizerpatientreportedoutcomes.com
OAB – q SF (OAB-q Short Form); Grade A [5]	19-item tool (shortened version of the OAB-q) used to evaluate both continent and incontinent symptoms of OAB and their impact on HRQL	OAB, men and women	√	√	√		√	√	√ (12 Weeks)	www.pfizerpatientreportedoutcomes.com
OAB-q (ICIQ-OABqol) (OveractiveBladder Questionnaire); Grade A [5, 38]	33-item tool used to evaluate both continent and incontinent symptoms of OAB and their impact on HRQL. Developed from focus groups of men and women, clinician opinion, and a thorough literature review	Continent and incontinent OAB	√	√ (ICC = 0.93 for 4-week recall period)	√	√	√	√	√ (12 Weeks)	www.pfizerpatientreportedoutcomes.com
PFDI (Pelvic Floor Distress Inventory); Grade A [58]	46-item tool used to assess presence of symptoms and HRQL in women with POP; 3 Scales (Urinary-28; Colorectal-17 Prolapse-16)	Females with symptomatic POP, UI	√ (Cronbach's Alpha = 0.88)	√ (ICC = 0.87)	√			√	√	contact developer
PFDI-20 (Pelvic Floor Distress Inventory Short Form); Grade A [58]	20-item short form of the PFDI (Urinary-6; Colorectal-8; Prolapse-6)	Females with symptomatic POP, UI		√ (ICC = 0.93)	√			√	√	www.mapi-institute.com
PFIQ (PelvicFloor Impact Questionnaire); Grade A [58]	93-item functional status tool used to assess presence of symptoms and HRQL in women with POP; 3 Scales (Urinary-31, Colorectal-31, Prolapse-31)	Females with symptomatic POP, UI	√ (Cronbach's Alpha = 0.98)	√ (ICC = 0.86)	√			√	√	contact developer

Table 4: Health-related Quality of Life measures for Lower Urinary Tract Symptoms (continued)

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
PFIQ-7 (Pelvic Floor Impact Questionnaire Short Form); Grade A [58]	21-item short form of the PFIQ used to assess presence of symptoms and QOL in women with POP; 3 Scales (Urinary-7, Colorectal-7, Prolapse-7)	Females with sympto-matic POP, UI		√ (ICC = 0.77)	√			√	√	www.mapi-institute.com
PRAFAB (Protection, Amount, Frequency, Adjustment, Body image); Grade A [131]	5 item questionnaire widely used in the Netherlands by physiotherapists and researchers used to evaluate treatment effects for UI in women	women with UI	√	√	√		√	√	√	contact developer
UIHI (Urinary Incontinence Handicap Inventory); Grade C [132]	17-item tool used to identify difficulties patients may be experiencing because of their incontinence	Elderly women, UI due to detrusor instability	√ (Cronbach's Alpha = 0.87)	√				√		www.proqolid.org
UISS (Urinary Incontinence Severity Score); Grade A [133]	10-item tool to assess symptom severity and impact of urinary incontinence	Women, UI		√	√	√	√		√	contact developer
Urolife (BPHQoL9) (Benign Prostatic Hypertrophy Health-Related Quality of Life Questionnaire); Grade A [134]	9-item tool used to assess the impact of BPH and its treatment on the quality of life of patients	Men, BPH	√	√	√		√		√	www.proqolid.org
YIPS (York Incontinence Perceptions Scale); Grade B [135]	8-item tool used to measure the psychosocial aspects of urinary incontinence and its management	Women, UI	√	√	√		√		√	www.proqolid.org

Table 5: Patient Satisfaction Measures for Lower Urinary Tract Symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
BSW (Benefit, Satisfaction with treatment, and Willingness); Grade B [45]	3 single-item tool used to capture patients' perceived benefit, satisfaction with treatment, and the willingness to continue treatment	men and women, OAB					√	√	√	www.pfizerpatientreportedoutcomes.com
EPI (Estimated Percent Improvement); Grade C [136]	Single-item tool used to gain a patient's improvement in a percent scale	Women, UI,SUI, MUI						√	√ (2-4 Weeks)	contact developer
GPI (Global Perception of Improvement); Grade C [136]	Single-item tool used to assess patient's improvement	Women, UI,SUI, MUI						√		contact developer
OAB-S (Overactive Bladder Satisfaction measure); Grade B [44]	51-items to assess following domains: expectations, control impact on daily living, medication tolerability, satisfaction and 5 overall assessments	men and women, OAB	√	√	√		√	√		contact developer
OAB-SAT-q OAB Satisfaction questionnaire; Grade B [137]	10-item tool used to assess patients' satisfaction with overactive bladder treatment including medication or non-pharmaceutical options such as physical therapy or biofeedback. The pre-medication module is designed assess the patient's expectations with medication and impact on OAB on patient's day to day life	Men and women, OAB	√	√	√		√	√		contact developer
PSQ (Patient Satisfaction Questionnaire); Grade C [136]	Single-item tool used to measure how satisfied a subject was with a program	Women, UI, SUI, MUI						√		contact developer
TBS (Treatment Benefit Scale); Grade B [138]	Single-item tool used to assess the patient-reported benefits of treatment of OAB	Men and Women OAB					√	√	√	contact developer
SAGA (Self-Assessment Goal Achievement Questionnaire); GAS; Grade C [46]	9-item tool on Goal Attainment related to lower urinary tract symptoms and the establishment of patients' goals concerning their treatment for lower urinary tract symptoms (LUTS),	Men and Women aged ≥18 years with OAB	Not Assessed	Not Assessed	√	√ (low to moderate)	√			www.pfizerpatientreportedoutcomes.com

Table 6: Screening Tools for Lower Urinary Track Symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
3IQ (Three Incontinence Questions Questionnaire); Grade C [139]	3-item tool used to classify urge and stress incontinence	Women, UI						√	N/A	None Found
B-SAQ (Bladder Self-Assessment Questionnaire) or Bladder Control Self-Assessment Questionnaire (BCSQ); Grade A [140]	8-item screening tool used for the presence of bothersome LUTS in Women	Women	√	√		√	√	√	N/A	www.mapi-institute.com
CLSS (Core Lower Urinary Tract Symptom Score) Questionnaire; Grade C [141]	10-item tool used in the overall assessment of lower urinary tract symptoms	Men & Women		√						contact developer
ISQ (Incontinence Screening Questionnaire); Grade B [142]	5-item tool developed to screen for incontinence in women	Women, UI		√				√	N/A	contact developer
MESA (Medical, Epidemiological, and Social Aspects of Aging Questionnaire); Grade C [143]	15-item screening tool used for urinary incontinence in female pelvic medicine and reconstructive surgery patients	Women, UI		√					N/A	www.ncbi.nlm.nih.gov
OAB-SS (Overactive Bladder Symptom Score); Grade A [144]	7-item tool used to measure overall symptom severity due to the four index symptoms of OAB	Men and women, LUTS with or without OAB	√	√	√			√	√	contact developer

Table 6: Screening Tools for Lower Urinary Track Symptoms (continued)

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
OAB-V8 (OAB Awareness Tool); Grade A [145]	8-item screening tool for use in a primary care setting to identify patients who may have OAB	Men and women, OAB	√		√	√	√	√	N/A	www.pfizerpatientreportedoutcomes.com
OAB - V3 (OAB short form) A [146]	3-Item awareness tool & shortened version of the OAB-q/OAB-V8	Men and women, OAB, UUI	√		√	√	√	√	n/a	www.pfizerpatientreportedoutcomes.com
PUF patient symptom scale (Pelvic Pain, Urgency, and Frequency); Grade C [147]	8-item tool used to evaluate of patients with suspected IC/PBS	Women and women, IC/PBS						√	√	www.ncbi.nlm.nih.gov
QUID (Questionnaire for Urinary Incontinence Diagnosis); Grade A [148]	6-item tool used to diagnose stress and/or urge types of urinary incontinence	Women with UI and SUI	√	√	√	√		√	√	contact developer
USP (Urinary Symptom Profile); Grade B [149]	13-item tool used to assess urinary symptoms in male and female with stress, urge, frequency or urinary obstructive symptoms for use in clinical practice to complement clinical measures and diagnosis	Men and women stress UI, urge UI, frequency, low stream, combined symptoms	√	√	√		√	√	N/A	www.mapi-institute.com

Table 7: Symptom Bother Measures for Lower Urinary Tract Symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
I-PSS (International Prostate Symptom Score); Grade B [110]	8-item tool used to capture the severity of urinary symptoms related to benign prostatic hyperplasia. Originally developed from the American Urological Association Symptom Index.	Men	√	√			√	√	√	www.proqolid.org
LUSQ (Leicester UrinarySymptom Questionnaire); Grade A [150]	10-item tool used to measure the presence and severity of storage abnormality symptoms of incontinence, urgency, frequency and nocturia	Men and women	√	√	√	√	√		√ (12Weeks)	contact developer
PGI-I and PGI-S (Patient Global Impression of Severity and of Improvement); Grade A [151, 152]	Two single-item global indices used to measure symptom bother related to urinary incontinence	Women with SUI	√	√			√	√	√ (12Weeks)	contact developer
PMSES (Broome Pelvic Muscle Exercise Self-Efficacy Scale); Grade C [153]	23-item tool used to measure self-efficacy for the performance of pelvic muscle exercises in females and males	Men and women					√	√		contact developer
POSQ (Primary OAB Symptom Questionnaire); Grade C [154]	5-item tool used to assess which symptom of OAB is the most bothersome to patients	OAB, men and women		√	√					contact developer
PPBC (Patient Perception of Bladder Condition); Grade A [52]	Single-item tool used to assess patients' subjective impression of their current urinary problems. Developed as a global assessment of bladder condition	Men and women		√			√		√	www.pfizerpatientreportedoutcomes.com

Table 7: Symptom Bother Measures for Lower Urinary Tract Symptoms (continued)

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
PFBQ (Pelvic Floor Bother Questionnaire); Grade B [61]	9-item global instrument used to assess female patients over the age of 18 years with symptoms of urinary incontinence, urinary urgency, and frequency, urge incontinence, faecal incontinence, obstructed defecation, dyspareunia and pelvic organ prolapse	Women, Urinary Inconti-nence, UUI, SUI	√	√	√	√		√		contact developer
SPI (Symptom Problem Index); Grade B [113]	7-item tool used to measure how troublesome the patients find their urinary symptoms	Male, BPH	√	√	√					www.proqolid.org
SSI and SII (Symptom Severity Index and Symptom Impact Index for stress incontinence in women); Grade B [155]	3-item tool used to measure stress incontinence severity and impact or bothersome of symptoms. This question-naire was developed and administered to women undergoing stress inconti-nence surgery	Women, SUI		√	√		√			www.proqolid.org
UI-4 (Urinary Incontinence -4 Questionnaire); Grade C [156]	4-item tool used to assess how patients are bothered by urinary incontinence	Women, UI					√			www.ncbi.nlm.nih.gov
UDI (UrogenitalDistres s Inventory); Grade A [119]	19-item tool used to asses symptom bother related to urinary incontinence. UDI is a complement to the IIQ	Women, UI, SUI	√	√	√		√	√		contact developer
UDI-6 (UrogenitalDistres s Inventory -6); Grade A [157]	6-item tool used to assess LUTS, including inconti-nence, in women.	Women	√	√	√	√	√	√	√	contact developer

Table 8: Urinary Urgency Measures for Lower Urinary Tract Symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
IUSS (Indevus Urgency Severity); Grade A [158]	Single-item tool used to quantify the level of urgency associated with each toilet void as measured during standard voiding diaries.	OAB with urgency inconti-nence, men and women		√		√	√	√	√ (12 Weeks)	contact developer
PPIUS (Patients' Perception of Intensity of Urgency Scale); Grade B [159]	Single-item tool used to assess female patient perception of urgency intensity in those women with UUI	Women, UUI		√					√	contact developer
SUIQ (Stress/Urge Incontinence Questionnaire); Grade B [160]	2-item tool used to differenti-ate between symptoms of stress and urge urinary incontinence	Women, UI		√			√			contact developer
U-IIQ (Urge Incontinence Impact Question-naire); Grade A [161]	32-item tool used to assess the interference of urine leakage and bladder problems Developed for use in patients with all types of incontinence.	MUI, UUI	√	√			√	√	√ (12Weeks)	contact developer
UPS (Urgency Perception Score); Grade B [162]	5-item OAB tool used for grading the urge to void and assessing the reason why individuals usually void	Men and women	√	√			√	√		contact developer
UPS (Urgency Perception Scale); Grade B [163]	Single-item tool used to assess the severity of urgency – whether or not urgency, the sudden and compelling desire to urinate should have a severity measure is debated.	OAB, men and women			√		√	√	√	contact developer

Table 8: Urinary Urgency Measures for Lower Urinary Tract Symptoms (continued)

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
UQ (Urgency Questionnaire); Grade B [154]	15-Likert Scale Item & 4-VAS tool used o assess the severity and impact of urinary urgency symptoms on HRQL. VAS scale is used to measure the impact of urinary urgency on overall HRQL, the severity, the intensity, and the discomfort of urgency.	Women, OAB	√	√	√		√	√	√ (10 Days)	contact developer
URIS-24 (Urge Impact Scale); Grade B [92]	24-item tool used to assess of the impact of the most common form of UI in older persons	Older persons, UI	√	√	√		√			contact developer
USIQ-QOL (Urgency Severity & Intensity Questionnaire: Symptom Severity); Grade B [164]	To measure severity impact from urinary urgency	Females, POP, UI	√			√		√		contact developer
USIQ-S (Urgency Severity & Intensity Questionnaire: Quality of Life); Grade B [164]	To measure quality of life impact from urinary urgency	Females, POP, UI	√ (Cronbach's Alpha = 0.85)			√		√		contact developer
USS (Urinary Sensation Scale); Grade B [165, 166]	5-point scale used to assess the impact of urgency with patients with OAB derivation from EMA's recommended 5-point scale	Urologists or urogy-necologists, Survey respondents with OAB symptoms	√ (Cronbach's Alpha = 0.85)		√		√	√	√	contact developer
UU Scale (10-item Scale to Measure Urinary Urgency); Grade A [167]	10-item tool use to measure urinary urgency	Men and women		√			√		√	contact developer
U-UDI (Urge-Urogenital distress inventory); Grade A [161]	9-item tool used to assess the extent to which the patient is bothered by the symptoms of urge urinary incontinence or mixed urinary incontinence with a primary urge component.	Men and women		√	√		√		√	www.mapi-institute.com

Table 11: Summary of PRO Measures for Faecal incontinence and other bowel symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsive-ness (Treatment Duration)	Psycho-metric Validation inOther Languages	Available Languages
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discri-minant			
Questionnaire for assessment of FI and constipation [74] **Grade A**	47-item general question-naire for constipation and anal incontinence, also including abdominal and urinary symptoms and medical history	Men and women		√		√			√	√	Contact www.iciq.net
Bowel function questionnaire [83] **Ungraded**	28-item bowel specific questionnaire including 10 anal incontinence-specific items	Men and women									
Faecal Incontinence Questionnaire [80] **Grade C**	63-item general questionnaire for bowel habits including faecal incontinence, also urinary symptoms and medical history	Men and women		√							
BBUSQ (Birmingham Bowel and Urinary Symptom Questionnaire [72, 73] **Grade A**	22-item questionnaire for bowel and urinary symptoms including 4 faecal incontinence-specific items	women	√	√		√			√		
FICA (Faecal incontinence and constipation assessment) [79] **Grade B**	98-item general questionnaire for constipation and faecal incontinence, also including abdominal and urinary symptoms and medical history	women		√		√					
PFBQ (Pelvic floor bother questionnaire) [61] **Grade B**	9-item symptom and bother questionnaire for pelvic floor disorders	women	√	√		√	√				

Table 12: Summary of PRO Measures for Faecal incontinence and HRQL associated specifically

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsive-ness (Treatment Duration)	Psycho-metric Validation inOther Languages	Available Languages
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discri-minant			
ICIQ-B [32, 33] **Grade A+**	19-item anal incontinence symptoms and HRQL questionnaire	Men and women	√	√	√	√	√		√	√	Contact www.iciq.net
FIQL (Faecal Incontinence Quality of life Index) [71] **Grade A**	29-item faecal incontinence HRQL questionnaire	Men and women	√	√			√		√	√	Contact author
MHQ (Manchester Health Question-naire) [76] **Grade B**	31-item anal incontinence HRQL questionnaire	Women	√	√			√				
Bowel control self-assessment questionnaire [77] **Grade B**	5-item faecal incontinence symptom and HRQL questionnaire	Men and women	√	√		√	√				

Table 13: Summary of PRO Measures for Faecal incontinence in specific patient groups

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsive-ness (Treatment Duration)	Psycho-metric Validation inOther Languages	Available Languages
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discri-minant			
Postpartum flatal and faecal inconti-nence quality of life scale [81] **Ungraded**	68-item anal incontinence HRQL questionnaire (adaptation of FIQL for postpartum females)	Women			√						
Surgical outcome tool for faecal incontinence[83] **Ungraded**	10-item anal incontinence symptoms and HRQL questionnaire for evaluation of incontinence surgery	Women									
COREFO (Colorec-tal functionalout-come question-naire) [75] **Grade B**	27-item anal incontinence symptom and HRQL questionnaire for evaluation of colorectal surgery	Men and women	√	√	√		√				
EBSQ (Elderly Bowel Symptom Questionnaire) [78] **Grade B**	56-item general questionnaire for gastrointestinal function including faecal incontinence, also including and medical history and HRQL	Men and women		√		√					

Table 14. Sexual Health and Quality of Life Measures

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Instrument Access & Translation(s)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
FSFI (Female Sexual Function Index); Grade B [85]	19-item tool used to assess the effects of incontinence on multiple dimensions of sexual function in sexually active, adult women	Women, OAB; SUI, MUI	√ (Cronbach's Alpha >/= 0.82)	√ (r = 0.79 - 0.86)				√		contact developer
ICIQ-VS (International Consultation on Incontinence Questionnaire -Vaginal Symp-toms); Grade B [31]	14-item tool used to assess effects of vaginal symptoms and associated sexual matter on sexual quality of life for sexually active females	Women	√ (Cronbach's Alpha = 0.81-0.88)	√	√			√ (all items except 'leakage during intercourse')		contact developer
PISQ (PelvicOrganProlapse/Urinary Incontinence Sexual Question-naire); Grade B [62]	31-item tool to assess sexual function after surgery in women with Pelvic Floor Dysfunction	Females with Pelvic Floor Dysfunc-tion	√ (Cronbach's Alpha = 0.85)	√ (k = 0.56 - 0.93)		√		√		contact developer
SFQ (SexualFunction Questionnaire); Grade C [168]	Generic Instrument used to assess the impact of OAB on sexual health/function in the male & female population	men& women with OAB								www.pfizerpatientreportedoutcomes.com
SQoL-F (Sexual Quality of Life–Female); Grade B [90]	To assess the impact of female sexual dysfunction on quality of life	women	√	√			√	√		www.pfizerpatientreportedoutcomes.com

REFERENCES

1. Food and Drug Administration (FDA): Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Federal Register, 2009. 74(235): p. 65132-65133.

2. Ware JE, Jr., Kosinski M, Bayliss MS, et al.: Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care, 1995. 33(4 Suppl): p. AS264-79.

3. Wyman JF, Harkins SW, Choi SC, Taylor JR, Fantl JA: Psychosocial impact of urinary incontinence in women. Obstet Gynecol, 1987. 70(3 Pt 1): p. 378-81.

4. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S: A new questionnaire to assess the quality of life of urinary incontinent women. Br J Obstet Gynaecol, 1997. 104(12): p. 1374-9.

5. Coyne K, Revicki D, Hunt T, et al.: Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. Qual Life Res, 2002. 11(6): p. 563-74.

6. Berger M, et al.: Health care cost, quality and outcomes, in ISPOR Book of Terms. 2003. p. 195-97.

7. Ingolf G, Joanna C, Jackie B: Quality-Adjusted Life-Year Lack Quality in Pediatric Care: A Critical Reiew of Published Cost-Utility Studies in Child Health. Pediatrics, 2005. 115(5): p. e600.

8. Karen B, Magnus J: Incorporating quality of life changes into economic evaluations of health care: an overview. Health Policy, 1996. 36: p. 155-66.

9. Rasanen P, Roine E, Sintonen H, et al.: Use of quality-adjusted life years for the estimation of effectiveness of health care: A systematic literature review. Int J Technol Assess Health Care, 2006. 22(2): p. 235-41.

10. Rodriguez LV, Blander DS, Dorey F, Raz S, Zimmern P: Discrepancy in patient and physician perception of patient's quality of life related to urinary symptoms. Urology, 2003. 62(1): p. 49-53.

11. Coons SJ, Gwaltney CJ, Hays RD, et al.: Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. Value Health, 2009. 12(4): p. 419-29.

12. Streiner DL NG: Health Measurement Scales. 1989: Oxford: OUP.

13. Revicki DA, Osoba D, Fairclough D, et al.: Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. Qual Life Res, 2000. 9(8): p. 887-900.

14. Kerlinger F, Lee H: Foundations of Behavioral Research. 4th ed. 1999: Wadsworth Publishing.

15. Murawski MM, Miederhoff PA: On the generalizability of statistical expressions of health related quality of life instrument responsiveness: a data synthesis. Qual Life Res, 1998. 7(1): p. 11-22.

16. Jaeschke R, Singer J, Guyatt GH: Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials, 1989. 10(4): p. 407-15.

17. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS: Interpreting treatment effects in randomised trials. Bmj, 1998. 316(7132): p. 690-3.

18. Kazis LE, Anderson JJ, Meenan RF: Effect sizes for interpreting changes in health status. Med Care, 1989. 27(3 Suppl): p. S178-89.

19. Wyrwich KW, Norquist JM, Lenderking WR, Acaster S: Methods for interpreting change over time in patient-reported outcome measures. Qual Life Res, 2012.

20. Acquadro C, Conway K, Hareendran A, Aaronson N: Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. Value Health, 2008. 11(3): p. 509-21.

21. Herdman M, Fox-Rushby J, Badia X: A model of equivalence in the cultural adaptation of HRQoL instruments: the universalist approach. Qual Life Res, 1998. 7(4): p. 323-35.

22. Wild D, Grove A, Martin M, et al.: Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health, 2005. 8(2): p. 94-104.

23. Coyne KS, Margolis MK, Thompson C, Kopp Z: Psychometric equivalence of the OAB-q in Danish, German, Polish, Swedish, and Turkish. Value Health, 2008. 11(7): p. 1096-101.

24. European Agency for the Evaluation of Medicinal Products CfPMP: Note for guidance on the clinical investigation of medicinal productsfor the treatment of urinary incontinence. . December 2002, London.

25. European Medicines Agency: Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products, Committee for Medicinal Products for Human Use (CHMP), Editor. 2005, EMEA: London.

26. Aaronson NK: Quality of life assessment in clinical trials: methodologic issues. Control Clin Trials, 1989. 10(4 Suppl): p. 195S-208S.

27. Abrams P, Avery K, Gardener N, Donovan J: The International Consultation on Incontinence Modular Questionnaire: www.iciq.net. J Urol, 2006. 175(3 Pt 1): p. 1063-6; discussion 1066.

28. Avery K, Donovan J, Peters TJ, et al.: ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn, 2004. 23(4): p. 322-30.

29. Donovan JL, Peters TJ, Abrams P, et al.: Scoring the short form ICSmaleSF questionnaire. International Continence Society. J Urol, 2000. 164(6): p. 1948-55.

30. Brookes ST, Donovan JL, Wright M, Jackson S, Abrams P: A scored form of the Bristol Female Lower Urinary Tract Symptoms questionnaire: data from a randomized controlled trial of surgery for women with stress incontinence. Am J Obstet Gynecol, 2004. 191(1): p. 73-82.

31. Price N, Jackson SR, Avery K, Brookes ST, Abrams P: Development and psychometric evaluation of the ICIQ Vaginal Symptoms Questionnaire: the ICIQ-VS. Bjog, 2006. 113(6): p. 700-12.

32. Cotterill N, Norton C, Avery KN, Abrams P, Donovan JL: A patient-centered approach to developing a comprehensive symptom and quality of life assessment of anal incontinence. Dis Colon Rectum, 2008. 51(1): p. 82-7.

33. Cotterill N, Norton C, Avery KN, Abrams P, Donovan JL: Psychometric evaluation of a new patient-completed questionnaire for evaluating anal incontinence symptoms and impact on quality of life: the ICIQ-B. Dis Colon Rectum, 2011. 54(10): p. 1235-50.

34. Margolis MK, Vats V, Coyne KS, Kelleher C: Establishing the content validity of the King's Health Questionnaire in men and women with overactive bladder in the US. Patient, 2011. 4(3): p. 177-87.

35. Donovan JL, Brookes ST, de la Rosette JJ, et al.: The responsiveness of the ICSmale questionnaire to outcome: evidence from the ICS-'BPH' study. BJU Int, 1999. 83(3): p. 243-8.

36. Jackson S, Donovan J, Brookes S, et al.: The Bristol Female Lower Urinary Tract Symptoms questionnaire: development and psychometric testing. Br J Urol, 1996. 77(6): p. 805-12.

37. Abraham L, Hareendran A, Mills IW, et al.: Development and validation of a quality-of-life measure for men with nocturia. Urology, 2004. 63(3): p. 481-6.

38. Coyne KS, Gelhorn H, Thompson C, Kopp ZS, Guan Z: The psychometric validation of a 1-week recall period for the OAB-q. Int Urogynecol J, 2011. 22(12): p. 1555-63.

39. De Gennaro M, Niero M, Capitanucci ML, et al.: Validity of the international consultation on incontinence questionnaire-pediatric lower urinary tract symptoms: a screening questionnaire for children. J Urol, 2010. 184(4 Suppl): p. 1662-7.

40. Bright E, Cotterill N, Drake M, Abrams P: Developing a validated urinary diary: Phase 1. Neurourol Urodyn, 2012. 31(5): p. 625-33.

41. Kiresuk T, Sherman R: Goal attainment scaling: a general method of evaluating comprehensive community mental health programs. Community Ment Health J, 1968. 4: p. 443-453.

42. Krowinski W, Steiber S: Measuring patient satisfacion. 2nd ed. 1996: American Hospital Publishing.

43. Weaver M, Patrick DL, Markson LE, et al.: Issues in the measurement of satisfaction with treatment. Am J Manag Care, 1997. 3(4): p. 579-94.

44. Piault E, Evans CJ, Espindle D, et al.: Development and validation of the Overactive Bladder Satisfaction (OAB-S) Questionnaire. Neurourol Urodyn, 2008. 27(3): p. 179-90.

45. Pleil AM, Coyne KS, Reese PR, et al.: The validation of patient-rated global assessments of treatment benefit, satisfaction, and willingness to continue--the BSW. Value Health, 2005. 8 Suppl 1: p. S25-34.

46. Brubaker L, Khullar V, Piault E, et al.: Goal attainment scaling in patients with lower urinary tract symptoms: development and pilot testing of the Self-Assessment Goal Achievement (SAGA) questionnaire. Int Urogynecol J, 2011. 22(8): p. 937-46.

47. Fianu-Jonasson A, Brubaker L, Kelleher C, et al.: Understanding Swedish patients' expectations for treatment of their urinary symptoms. in Nordic Urogynecological Association. 2009. Reykjavik, Iceland.

48. Hullfish KL, Bovbjerg VE, Gibson J, Steers WD: Patient-centered goals for pelvic floor dysfunction surgery: what is success, and is it achieved? Am J Obstet Gynecol, 2002. 187(1): p. 88-92.

49. Mahajan ST, Elkadry EA, Kenton KS, Shott S, Brubaker L: Patient-centered surgical outcomes: the impact of goal achievement and urge incontinence on patient satisfaction one year after surgery. Am J Obstet Gynecol, 2006. 194(3): p. 722-8.

50. Payne C, Allee T: Goal achievement provides new insights into interstitial cystitis/painful bladder syndrome symptoms and outcomes. Neurourol Urodyn, 2009. 28(1): p. 13-7.

51. Piault E, Doshi S, Brandt BA, et al.: Linguistic validation of translation of the Self-Assessment Goal Achievement (SAGA) questionnaire from English. Health Qual Life Outcomes, 2012. 10: p. 40.

52. Coyne KS, Matza LS, Kopp Z, Abrams P: The validation of the patient perception of bladder condition (PPBC): a single-item global measure for patients with overactive bladder. Eur Urol, 2006. 49(6): p. 1079-86.

53. Abrams P, Cardozo L, Fall M, et al.: The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology, 2003. 61(1): p. 37-49.

54. Brubaker L: Urgency: the cornerstone symptom of overactive bladder. Urology, 2004. 64(6 Suppl 1): p. 12-6.

55. Staskin DR: The urge to define urgency: a review of three approaches. Curr Urol Rep, 2004. 5(6): p. 413-5.

56. Brubaker L: Urinary urgency and frequency: what should a clinician do? Obstet Gynecol, 2005. 105(3): p. 661-7.

57. Chapple CR, Wein AJ: The urgency of the problem and the problem of urgency in the overactive bladder. BJU Int, 2005. 95(3): p. 274-5.

58. Barber MD, Kuchibhatla MN, Pieper CF, Bump RC: Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders. Am J Obstet Gynecol, 2001. 185(6): p. 1388-95.

59. Digesu GA, Santamato S, Khullar V, et al.: Validation of an Italian version of the prolapse quality of life questionnaire. Eur J Obstet Gynecol Reprod Biol, 2003. 106(2): p. 184-92.

60. Baessler K, O'Neill SM, Maher CF, Battistutta D: A validated self-administered female pelvic floor questionnaire. Int Urogynecol J, 2010. 21(2): p. 163-72.

61. Peterson TV, Karp DR, Aguilar VC, Davila GW: Validation of a global pelvic floor symptom bother questionnaire. Int Urogynecol J, 2010. 21(9): p. 1129-35.

62. Rogers RG, Coates KW, Kammerer-Doak D, Khalsa S, Qualls C: A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Int Urogynecol J Pelvic Floor Dysfunct, 2003. 14(3): p. 164-8; discussion 168.

63. Radley SCJ, G. L. Kubwalo, B. E. Stevens, V. Leathard, A. Tanguy, E: Feasibility and acceptability of electronic interviewing in urogynaecology. International Urogynecology Journal, 2003. 14(SUPP/1): p. 239

64. Ellerkmann RM, Cundiff GW, Melick CF, et al.: Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol, 2001. 185(6): p. 1332-7; discussion 1337-8.

65. Mouritsen L, Larsen JP: Symptoms, bother and POPQ in women referred with pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct, 2003. 14(2): p. 122-7.

66. Mann CH, Radley SC, Begum G, et al.: Constipation, faecal incontinence and urinary symptoms in women awaiting hysterectomy. J Obstet Gynaecol, 2000. 20(5): p. 530-2.

67. Radley S, Keighley MR, Radley SC, Mann CH: Bowel dysfunction following hysterectomy. Br J Obstet Gynaecol, 1999. 106(11): p. 1120-5.

68. Jorge JM WS: Etiology and management of fecal incontinence. Dis Colon Rectum. , 1993. 36(1): p. 77-97.

69. Norton C, Whitehead WE, Bliss D, Harari D, Lang J: Conservative and pharmacological management of faecal incontinence in adults. in Incontinence: Proceedings of the Fourth International Consultation on Incontinence. 2008. Paris, France: Health Publication Ltd.

70. Engel AF, Kamm MA, Bartram CI, Nicholls RJ: Relationship of symptoms in faecal incontinence to specific sphincter abnormalities. Int J Colorectal Dis, 1995. 10(3): p. 152-5.

71. Rockwood TH, Church JM, Fleshman JW, et al.: Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. Dis Colon Rectum, 2000. 43(1): p. 9-16; discussion 16-7.

72. Hiller L, Bradshaw HD, Radley SC, Radley S: A scoring system for the assessment of bowel and lower urinary tract symptoms in women. Bjog, 2002. 109(4): p. 424-30.

73. Hiller L, Radley S, Mann CH, et al.: Development and validation of a questionnaire for the assessment of bowel and lower urinary tract symptoms in women. Bjog, 2002. 109(4): p. 413-23.

74. Osterberg A, Graf W, Karlbom U, Pahlman L: Evaluation of a questionnaire in the assessment of patients with faecal incontinence and constipation. Scand J Gastroenterol, 1996. 31(6): p. 575-80.

75. Bakx R, Sprangers MA, Oort FJ, et al.: Development and validation of a colorectal functional outcome questionnaire. Int J Colorectal Dis, 2005. 20(2): p. 126-36.

76. Bug GJ, Kiff ES, Hosker G: A new condition-specific health-related quality of life questionnaire for the assessment of women with anal incontinence. Bjog, 2001. 108(10): p. 1057-67.

77. Krysa J, Lyons M, Williams AB: A simple quality of life questionnaire for patients with faecal incontinence. Int J Colorectal Dis, 2009. 24(10): p. 1213-7.

78. O'Keefe EA, Talley NJ, Tangalos EG, Zinsmeister AR: A bowel symptom questionnaire for the elderly. J Gerontol, 1992. 47(4): p. M116-21.

79. Bharucha AE, Locke GR, 3rd, Seide BM, Zinsmeister AR: A new questionnaire for constipation and faecal incontinence. Aliment Pharmacol Ther, 2004. 20(3): p. 355-64.

80. Reilly WT, Talley NJ, Pemberton JH, Zinsmeister AR: Validation of a questionnaire to assess fecal incontinence and associated risk factors: Fecal Incontinence Questionnaire. Dis Colon Rectum, 2000. 43(2): p. 146-53; discussion 153-4.

81. Cockell SJ, Oates-Johnson T, Gilmour DT, Vallis TM, Turnbull GK: Postpartum flatal and Fecal Incontinence Quality-of-Life Scale: a disease- and population-specific measure. Qual Health Res, 2003. 13(8): p. 1132-44.

82. Hallbook O, Sjodahl R: Surgical approaches to obtaining optimal bowel function. Semin Surg Oncol, 2000. 18(3): p. 249-58.

83. Hull TL, Floruta C, Piedmonte M: Preliminary results of an outcome tool used for evaluation of surgical treatment for fecal incontinence. Dis Colon Rectum, 2001. 44(6): p. 799-805.

84. Rust J, Golombok S: The Golombok-Rust Inventory of Sexual Satisfaction (GRISS). Br J Clin Psychol, 1985. 24 (Pt 1): p. 63-4.

85. Rosen R, Brown C, Heiman J, et al.: The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther, 2000. 26(2): p. 191-208.

86. Clayton AH, McGarvey EL, Clavet GJ: The Changes in Sexual Functioning Questionnaire (CSFQ): development, reliability, and validity. Psychopharmacol Bull, 1997. 33(4): p. 731-45.

87. Trudel G, Ravart M, Matte B: The use of the multiaxial diagnostic system for sexual dysfunctions in the assessment of hypoactive sexual desire. J Sex Marital Ther, 1993. 19(2): p. 123-30.

88. Tubaro A, Polito M, Giambroni L, et al.: Sexual function in patients with LUTS suggestive of BPH. Eur Urol, 2001. 40 Suppl 1: p. 19-22.

89. McCoy N: The McCoy Female Sexuality Questionnaire Quality of Life Research, 2000. 9(Supplement 6): p. 739-745.

90. Symonds T, Boolell M, Quirk F: Development of a questionnaire on sexual quality of life in women. J Sex Marital Ther, 2005. 31(5): p. 385-97.

91. Okamura K, Usami T, Nagahama K, Maruyama S, Mizuta E: "Quality of life" assessment of urination in elderly Japanese men and women with some medical problems using International Prostate Symptom Score and King's Health Questionnaire. Eur Urol, 2002. 41(4): p. 411-9.

92. DuBeau CE, Levy B, Mangione CM, Resnick NM: The impact of urge urinary incontinence on quality of life: importance of patients' perspective and explanatory style. J Am Geriatr Soc, 1998. 46(6): p. 683-92.

93. Coyne KS, Matza LS, Brewster-Jordan J, Thompson C, Bavendam T: The psychometric validation of the OAB family impact measure (OAB-FIM). Neurourol Urodyn, 2010. 29(3): p. 359-69.

94. Costa P, Perrouin-Verbe B, Colvez A, et al.: Quality of life in spinal cord injury patients with urinary difficulties. Development and validation of qualiveen. Eur Urol, 2001. 39(1): p. 107-13.

95. Bonniaud V, Bryant D, Parratte B, Gallien P, Guyatt G: Qualiveen: a urinary disorder-specific instrument for use in clinical trials in multiple sclerosis. Arch Phys Med Rehabil, 2006. 87(12): p. 1661-3.

96. Bonniaud V, Jackowski D, Parratte B, et al.: Quality of life in multiple sclerosis patients with urinary disorders: discriminative validation of the English version of Qualiveen. Qual Life Res, 2005. 14(2): p. 425-31.

97. Pannek J, Mark R, Stohrer M, Schurch B: [Quality of life in German-speaking patients with spinal cord injuries and bladder dysfunctions. Validation of the German version of the Qualiveen questionnaire]. Urologe A, 2007. 46(10): p. 1416-21.

98. D'Ancona CA, Tamanini JT, Botega N, et al.: (2008 June 5 [Epub ahead of print]) Quality of life of neurogenic patients: translation and validation of the Portuguese version of Qualiveen. Int Urol Nephrol.

99. Bonniaud V, Bryant D, Parratte B, Guyatt G: Qualiveen, a urinary-disorder specific instrument: 0.5 corresponds to the minimal important difference. J Clin Epidemiol, 2008. 61(5): p. 505-10.

100. Fowler FJ, Jr., Barry MJ, Lu-Yao G, et al.: Patient-reported complications and follow-up treatment after radical prostatectomy. The National Medicare Experience: 1988-1990 (updated June 1993). Urology, 1993. 42(6): p. 622-9.

101. Fowler FJ, Jr., Barry MJ, Lu-Yao G, et al.: Effect of radical prostatectomy for prostate cancer on patient quality of life: results from a Medicare survey. Urology, 1995. 45(6): p. 1007-13; discussion 1013-5.

102. Schag CA, Ganz PA, Heinrich RL: CAncer Rehabilitation Evaluation System--short form (CARES-SF). A cancer specific rehabilitation and quality of life instrument. Cancer, 1991. 68(6): p. 1406-13.

103. da Silva F RE, Costa T, Denis L: Quality of life in patients wtih prostatic cancer. Cancer, 1993. 71(3): p. 113-1142.

104. Stockler MR, Osoba D, Goodwin P, Corey P, Tannock IF: Responsiveness to change in health-related quality of life in a randomized clinical trial: a comparison of the Prostate Cancer Specific Quality of Life Instrument (PROSQOLI) with analogous scales from the EORTC QLQ-C30 and a trial specific module. European Organization for Research and Treatment of Cancer. J Clin Epidemiol, 1998. 51(2): p. 137-45.

105. Clark JA, Inui TS, Silliman RA, et al.: Patients' perceptions of quality of life after treatment for early prostate cancer. J Clin Oncol, 2003. 21(20): p. 3777-84.

106. Cella D: Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. Version 4 ed. 1997, Evanston IL: Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University.

107. Cookson MS, Dutta SC, Chang SS, et al.: Health related quality of life in patients treated with radical cystectomy and urinary diversion for urothelial carcinoma of the bladder: development and validation of a new disease specific questionnaire. J Urol, 2003. 170(5): p. 1926-30.

108. Watkins-Bruner D, Scott C, Lawton C, et al.: RTOG's first quality of life study--RTOG 90-20: a phase II trial

of external beam radiation with etanidazole for locally advanced prostate cancer. Int J Radiat Oncol Biol Phys, 1995. 33(4): p. 901-6.

109. Litwin MS, Hays RD, Fink A, et al.: Quality-of-life outcomes in men treated for localized prostate cancer. Jama, 1995. 273(2): p. 129-35.

110. Barry MJ, Fowler FJ, Jr., O'Leary MP, et al.: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol, 1992. 148(5): p. 1549-57; discussion 1564.

111. Cockett AT, Aso Y, Chatelain C, et al. : The international consultation on benign prostatic hyperplasia (BPH). 1991, Paris.

112. Boyarsky S, Jones G, Paulson DF, Prout GR, Jr.: A new look at bladder neck obstruction by the food and drug administration regulators: guide lines for investigation of benign prostatic hypertrophy. Trans Am Assoc Genitourin Surg, 1976. 68: p. 29-32.

113. Barry MJ, Fowler FJ, Jr., O'Leary MP, et al.: Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. Med Care, 1995. 33(4 Suppl): p. AS145-55.

114. Epstein RS, Deverka PA, Chute CG, et al.: Urinary symptom and quality of life questions indicative of obstructive benign prostatic hyperplasia. Results of a pilot study. Urology, 1991. 38(1 Suppl): p. 20-6.

115. Amarenco G, Arnould B, Carita P, et al.: European psychometric validation of the CONTILIFE: a Quality of Life questionnaire for urinary incontinence. Eur Urol, 2003. 43(4): p. 391-404.

116. Hansen BJ, Flyger H, Brasso K, et al.: Validation of the self-administered Danish Prostatic Symptom Score (DAN-PSS-1) system for use in benign prostatic hyperplasia. Br J Urol, 1995. 76(4): p. 451-8.

117. Lukacz ES, Lawrence JM, Buckwalter JG, et al.: Epidemiology of prolapse and incontinence questionnaire: validation of a new epidemiologic survey. Int Urogynecol J Pelvic Floor Dysfunct, 2005. 16(4): p. 272-84.

118. Donovan JL, Kay HE, Peters TJ, et al.: Using the ICSOoL to measure the impact of lower urinary tract symptoms on quality of life: evidence from the ICS-'BPH' Study. International Continence Society--Benign Prostatic Hyperplasia. Br J Urol, 1997. 80(5): p. 712-21.

119. Hagen S, Hanley J, Capewell A: Test-retest reliability, validity, and sensitivity to change of the urogenital distress inventory and the incontinence impact questionnaire. Neurourol Urodyn, 2002. 21(6): p. 534-9.

120. Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fantl JA: Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group. Neurourol Urodyn, 1995. 14(2): p. 131-9.

121. Bjelic-Radisic V, Dorfer M, Tamussino K, et al.: The Incontinence Outcome Questionnaire: an instrument for assessing patient-reported outcomes after surgery for stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct, 2007. 18(10): p. 1139-49.

122. Bushnell DM, Martin ML, Summers KH, et al.: Quality of life of women with urinary incontinence: cross-cultural performance of 15 language versions of the I-QOL. Qual Life Res, 2005. 14(8): p. 1901-13.

123. Wagner TH, Patrick DL, Bavendam TG, Martin ML, Buesching DP: Quality of life of persons with urinary incontinence: development of a new measure. Urology, 1996. 47(1): p. 67-71; discussion 71-2.

124. Murphy M, Culligan PJ, Arce CM, et al.: Construct validity of the incontinence severity index. Neurourol Urodyn, 2006. 25(5): p. 418-23.

125. Yu LC, Kaltreider DL: Stressed nurses dealing with incontinent patients. J Gerontol Nurs, 1987. 13(1): p. 27-30.

126. Twiss C, Triaca V, Anger J, et al.: Validating the incontinence symptom severity index: a self-assessment instrument for voiding symptom severity in women. J Urol, 2009. 182(5): p. 2384-91.

127. Shaw C, Matthews RJ, Perry SI, et al.: Validity and reliability of a questionnaire to measure the impact of lower urinary tract symptoms on quality of life: the Leicester Impact Scale. Neurourol Urodyn, 2004. 23(3): p. 229-36.

128. Robinson JP, Avi-Itzhak T, McCorkle R: Psychometric properties of the Male Urogenital Distress Inventory (MUDI) and Male Urinary Symptom Impact Questionnaire (MUSIQ) in patients following radical prostatectomy. Urol Nurs, 2007. 27(6): p. 512-8.

129. Robinson JP, Shea JA: Development and testing of a measure of health-related quality of life for men with urinary incontinence. J Am Geriatr Soc, 2002. 50(5): p. 935-45.

130. Mock LL, Parmelee PA, Kutner N, Scott J, Johnson TM, 2nd: Content validation of symptom-specific nocturia quality-of-life instrument developed in men: issues expressed by women, as well as men. Urology, 2008. 72(4): p. 736-42.

131. Hendriks EJ, Bernards AT, Berghmans BC, de Bie RA: The psychometric properties of the PRAFAB-questionnaire: a brief assessment questionnaire to evaluate severity of urinary incontinence in women. Neurourol Urodyn, 2007. 26(7): p. 998-1007.

132. Rai GS, Kiniors M, Wientjes H: Urinary incontinence handicap inventory. Arch Gerontol Geriatr, 1994. 19(1): p. 7-10.

133. Stach-Lempinen B, Kujansuu E, Laippala P, Metsanoja R: Visual analogue scale, urinary incontinence severity score and 15 D--psychometric testing of three different health-related quality-of-life instruments for urinary incontinent women. Scand J Urol Nephrol, 2001. 35(6): p. 476-83.

134. Lukacs B, Comet D, Grange JC, Thibault P: Construction and validation of a short-form benign prostatic hypertrophy health-related quality-of-life questionnaire. BPH Group in General Practice. Br J Urol, 1997. 80(5): p. 722-30.

135. Lee PS, Reid DW, Saltmarche A, Linton L: Measuring the psychosocial impact of urinary incontinence: the York Incontinence Perceptions Scale (YIPS). J Am Geriatr Soc, 1995. 43(11): p. 1275-8.

136. Burgio KL, Goode PS, Richter HE, Locher JL, Roth DL: Global ratings of patient satisfaction and perceptions of improvement with treatment for urinary incontinence: validation of three global patient ratings. Neurourol Urodyn, 2006. 25(5): p. 411-7.

137. Margolis MK, Fox KM, Cerulli A, et al.: Psychometric validation of the overactive bladder satisfaction with treatment questionnaire (OAB-SAT-q). Neurourol Urodyn, 2009. 28(5): p. 416-22.

138. Colman S, Chapple C, Nitti V, et al.: Validation of treatment benefit scale for assessing subjective outcomes in treatment of overactive bladder. Urology, 2008. 72(4): p. 803-7.

139. Brown JS, Bradley CS, Subak LL, et al.: The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. Ann Intern Med, 2006. 144(10): p. 715-23.

140. Basra R, Artibani W, Cardozo L, et al.: Design and validation of a new screening instrument for lower urinary tract dysfunction: the bladder control self-assessment questionnaire (B-SAQ). Eur Urol, 2007. 52(1): p. 230-7.

141. Homma Y, Yoshida M, Yamanishi T, Gotoh M: Core Lower Urinary Tract Symptom score (CLSS) questionnaire: a reliable tool in the overall assessment of lower urinary tract symptoms. Int J Urol, 2008. 15(9): p. 816-20.

142. Gunthorpe W, Brown W, Redman S: The development and evaluation of an incontinence screening questionnaire for female primary care. Neurourol Urodyn, 2000. 19(5): p. 595-607.

143. Diokno AC, Brock BM, Brown MB, Herzog AR: Prevalence of urinary incontinence and other urological symptoms in the noninstitutionalized elderly. J Urol, 1986. 136(5): p. 1022-5.

144. Blaivas JG, Panagopoulos G, Weiss JP, Somaroo C: Validation of the overactive bladder symptom score. J Urol, 2007. 178(2): p. 543-7; discussion 547.

145. Coyne KS, Zyczynski T, Margolis MK, Elinoff V, Roberts RG: Validation of an overactive bladder awareness tool for use in primary care settings. Adv Ther, 2005. 22(4): p. 381-94.

146. Coyne KS, Margolis MK, Bavendam T, Roberts R, Elinoff V: Validation of a 3-item OAB awareness tool. Int J Clin Pract, 2011. 65(2): p. 219-24.

147. Parsons CL, Dell J, Stanford EJ, et al.: Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. Urology, 2002. 60(4): p. 573-8.

148. Bradley CS, Rovner ES, Morgan MA, et al.: A new questionnaire for urinary incontinence diagnosis in women: development and testing. Am J Obstet Gynecol, 2005. 192(1): p. 66-73.

149. Haab F, Richard F, Amarenco G, et al.: Comprehensive evaluation of bladder and urethral dysfunction symptoms: development and psychometric validation of the Urinary Symptom Profile (USP) questionnaire. Urology, 2008. 71(4): p. 646-56.

150. Shaw C, Matthews RJ, Perry SI, et al.: Validity and reliability of an interviewer-administered questionnaire to measure the severity of lower urinary tract symptoms of storage abnormality: the Leicester Urinary Symptom Questionnaire. BJU Int, 2002. 90(3): p. 205-15.

151. Srikrishna S, Robinson D, Cardozo L: Validation of the Patient Global Impression of Improvement (PGI-I) for urogenital prolapse. Int Urogynecol J, 2010. 21(5): p. 523-8.

152. Yalcin I, Bump RC: Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol, 2003. 189(1): p. 98-101.

153. Broome BA: Psychometric analysis of the Broome Pelvic Muscle Self-Efficacy Scale in African-American women with incontinence. Urol Nurs, 2001. 21(4): p. 289-97.

154. Matza LS, Thompson CL, Krasnow J, et al.: Test-retest reliability of four questionnaires for patients with overactive bladder: the overactive bladder questionnaire (OAB-q), patient perception of bladder condition (PPBC), urgency questionnaire (UQ), and the primary OAB symptom questionnaire (POSQ). Neurourol Urodyn, 2005. 24(3): p. 215-25.

155. Black N, Griffiths J, Pope C: Development of a symptom severity index and a symptom impact index for stress incontinence in women. Neurourol Urodyn, 1996. 15(6): p. 630-40.

156. Badia Llach X CDD, Perales Cabañas L, Pena Outeriño JM, Martínez-Agulló E, Conejero Sugrañés J, Arañó Beltrán P, Marqués Queimadelos A, Roset Gamisans M, Perulero Escobar N: [The development and preliminary validation of the IU-4 questionnaire for the clinical classification of urinary incontinence]. Actas Urol Esp., 1999. 23(7): p. 565-72.

157. Lemack GE, Zimmern PE: Predictability of urodynamic findings based on the Urogenital Distress Inventory-6 questionnaire. Urology, 1999. 54(3): p. 461-6.

158. Nixon A, Colman S, Sabounjian L, et al.: A validated patient reported measure of urinary urgency severity in overactive bladder for use in clinical trials. J Urol, 2005. 174(2): p. 604-7.

159. Cartwright R, Panayi D, Cardozo L, Khullar V: Reliability and normal ranges for the Patient's Perception of Intensity of Urgency Scale in asymptomatic women. BJU Int, 2010. 105(6): p. 832-6.

160. Bent AE, Gousse AE, Hendrix SL, et al.: Validation of a two-item quantitative questionnaire for the triage of women with urinary incontinence. Obstet Gynecol, 2005. 106(4): p. 767-73.

161. Lubeck DP, Prebil LA, Peeples P, Brown JS: A health related quality of life measure for use in patients with urge urinary incontinence: a validation study. Qual Life Res, 1999. 8(4): p. 337-44.

162. Blaivas JG, Panagopoulos G, Weiss JP, Somaroo C, Chaikin DC: The urgency perception score: validation and test-retest. J Urol, 2007. 177(1): p. 199-202.

163. Cardozo L, Coyne KS, Versi E: Validation of the urgency perception scale. BJU Int, 2005. 95(4): p. 591-6.

164. Lowenstein L, FitzGerald MP, Kenton K, et al.: Evaluation of urgency in women, with a validated Urgency, Severity and Impact Questionnaire (USIQ). Int Urogynecol J Pelvic Floor Dysfunct, 2009. 20(3): p. 301-7.

165. Coyne KS, Harding G, Jumadilova Z, Weiss JP: Defining urinary urgency: patient descriptions of "gotta go". Neurourol Urodyn, 2012. 31(4): p. 455-9.

166. Coyne KS, Margolis MK, Hsieh R, Vats V, Chapple CR: Validation of the urinary sensation scale (USS). Neurourol Urodyn, 2011. 30(3): p. 360-5.

167. Al-Buheissi S, Khasriya R, Maraj BH, Malone-Lee J: A simple validated scale to measure urgency. J Urol, 2008. 179(3): p. 1000-5; discussion 1005.

168. Quirk FH, Heiman JR, Rosen RC, et al.: Development of a sexual function questionnaire for clinical trials of female sexual dysfunction. J Womens Health Gend Based Med, 2002. 11(3): p. 277-89.

Committee 6

Urodynamic Testing

Chair

Peter F.W.M. Rosier (The Netherlands)

Members

Hann-Chorng Kuo (Taiwan)

Mario De Gennaro (Italy)

Hidehiro Kakizaki (Japan)

Hashim Hashim (United Kingdom)

Tom David Van Meel (Belgium)

Philip Toosz Hobson (United Kingdom)

CONTENTS

I. INTRODUCTION

A. URODYNAMICS

I. WHAT IS URODYNAMICS?

II. WHAT SHOULD BE THE ROLE OF URODYNAMIC STUDIES IN CLINICAL PRACTICE?

III. THE TESTS OF CONVENTIONAL URODYNAMICS

IV. TECHNOLOGICAL INNOVATIONS IN URODYNAMICS

B. URODYNAMICS: NORMAL VALUES, RELIABILITY AND DIAGNOSTIC PERFORMANCE

I. REPRODUCIBILITY OF FILLING CYSTOMETRY AND AMBULATORY URODYNAMICS

II. CYSTOMETRY: NORMAL VALUES

III. REPRODUCIBILITY, RELIABILITY AND NORMAL VALUES OF URETHRAL PRESSURE MEASUREMENTS

IV. LEAK POINT PRESSURE

V. DIAGNOSTIC PERFORMANCE OF FILLING CYSTOMETRY AND AMBULATORY MONITORING

VI. THERAPEUTIC PERFORMANCE OF FILLING CYTOMETRY AND AMBULATORY MONITORING

C. CLINICAL APPLICATIONS OF URODYNAMIC STUDIES

I. PATIENT EVALUATION: WOMEN

II. PATIENT EVALUATION: MEN

III. NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

IV. PATIENT EVALUATION: CHILDREN

V. PATIENT EVALUATION: FRAIL ELDERLY

REFERENCES

LIST OF ABBREVIATIONS

ARM	anorectal malformation
AUS	artificial urinary sphincter
BOO	bladder outlet obstruction
BPH	benign prostatic hyperplasia
BPO	benign prostatic obstruction
CIC	Clean intermittent (self) catheterisation
DHIC	detrusor hyperactivity with impaired contractile function
DO	detrusor overactivity
DOI	detrusor overactivity incontinence
EMG	electromyogram/ electromyography
FDV	first desire to void
FSF	first sensation of filling
ICI	International Consultation on Incontinence
ICS	International Continence Society
IDO	idiopathic detrusor overactivity
IPSS	International Prostate Symptom Score
ISD	intrinsic sphincter deficiency
IWT	ice water test
LPP	leak point pressure
LUT	lower urinary tract
LUTD	lower urinary tract dysfunction
LUTS	lower urinary tract symptoms
MCC	maximum cystometric capacity
MS	multiple sclerosis
MUCP	maximum urethral closure pressure
NDV	normal desire to void
OAB	overactive bladder
POP	pelvic organ prolapse
PVR	post-void residual urine (volume)
QoL	quality of life
SCI	spinal cord injury
sd	standard deviation
SDV	strong desire to void
SUI	stress urinary incontinence
TOT	Trans Obturator -Tape
TURP	transurethral resection of the prostate
TVT	tension-free vaginal tape
UDS	urodynamic studies
UPP	urethral pressure profile/ profilometry
UPR	urethral pressure reflectometry
URP	urethral retro-resistance pressure
UI	urinary incontinence
USI	urodynamic stress urinary incontinence
UUI	urgency urinary incontinence
VV	voided volume

Urodynamic Testing

Peter f.w.m. Rosier,

Hann-Chorng Kuo, Mario De Gennaro, Hidehiro Kakizaki, Hashim Hashim, Tom David Van Meel, Philip Toosz Hobson

I. INTRODUCTION

The first two reports of the International Consultation on Incontinence (ICI) contained chapters on 'Urodynamic Testing' [Homma 1999; Homma 2002]. Urodynamics is the umbrella term used to describe measurements of the function of the lower urinary tract. These measurements can be used in the management of urinary incontinence (UI). The third and the fourth report of the ICI expanded the topic to include physiological measurements of the lower gastrointestinal tract in relation with faecal (or anal) incontinence. Consequently, the chapters were named 'Dynamic Testing.'[Griffiths 2005].

In this fifth consultation, ICI 2012, we have further updated the evidence for the technical performance, clinical utility and responsiveness to treatment of dynamic testing. However faecal incontinence is discussed in a separate committee for this 2012 consultation. Diagnosis of faecal incontinence and its measurement techniques is therefore not included in this chapter. Consequently, the chapters' name is Urodynamic Testing. We have used the chapter on 'Dynamic Testing' from the previous (2009) consultation as a template for this report; retaining some of the original text and tables where there has been no change since the previous consultation [Rosier 2010; Rosier 2010; Rosier 2010]. Nevertheless the use of the previous chapter as a template, this chapter is updated with more than 200 new references and ±300 outdated references have been removed. With the aim to use the 'test of time' we have however usually not included references of publications less than one year before the consultation. Also discussions of tests that have been presented as 'new' in the previous years, without follow-up o manuscripts from other centres, and or without manuscripts that describe the clinical use in comparative studies, have been reduced in length.

Treatment of (stress) urinary incontinence (SUI) has changed considerably in the last decade and that has had its consequence on diagnostic testing. One of the effects has been that the paragraphs that discuss urethral pressures and or leak point pressures are reduced in length.

The primary aim of the chapter is to present what tests might be performed to elucidate the mechanism that causes UI in the individual, but a more predominant aim has been to make recommendations, and to give the strength of the recommendation (A to D), for what tests could or should be performed for certain groups of patients. Thus we present an overview of the best scientific evidence with regard to the role of urodynamic testing in clinical practice. On the basis of this, we provide recommendations for the current state of assessment of the patient with UI, and recommendations for future scientific evaluation of dynamic testing. We present the overview of scientific evidence in paragraphs, with conclusion(s) (with a level of evidence that follows the Modified Oxfort Scale) from this evidence for each paragraph. Following on from that, we present our graded recommendation(s) and where deemed useful some topics(s) for research. These items are highlighted in the text and are therefore also suitable for 'express reading'.

The chapter considers urodynamics for patients with signs and symptoms of urinary incontinence. The tests are described with the clinical perspective as well as with normal values and reliability of the measured parameters in mind, followed by reviews of the literature regarding clinical urodynamic evaluation of different patient groups with UI; women, men, children, neurogenic lower urinary tract dysfunction (NLUTD), and the frail elderly. Urodynamics of micturition problems is not addressed specifically and only described where deemed relevant, when a combination with symptoms and signs of UI is present. Each section concludes with the committee's recommendations.

A. URODYNAMICS

I. WHAT IS URODYNAMICS?

The term 'Urodynamic studies' (UDS) was defined by the International Continence Society (ICS) in 1988 as to 'involve the assessment of the function and dysfunction of the urinary tract by any appropriate method' [Abrams 1988; Schafer 2002]. The report in

2002 which revised the 1988 standard did not alter the definition of 'urodynamic studies' or 'urodynamics' but did include new definitions of 'urodynamic observations' [Abrams 2002]. Another update that adds specific terms for female pelvic floor dysfunction and -female- lower urinary tract dysfunction (LUTD) restates the 2002 ICS terminology report in a descriptive manner [Haylen 2010; Haylen 2010] and includes elements from the ICS good urodynamic practice report [Schafer 2002] as well.

The conventional experts view, endorsed in the previous standardisations and consultations, is that urodynamics is a series of more or less agreed-upon clinical tests, such as flow studies, filling cystometry, pressure-flow studies and urethral (closure) -function measurements. These measurements can be combined with simultaneous electromyography (EMG) recording and/or with imaging by either X-rays or ultrasound. Also implicitly agreed upon is that urodynamics is the way to determine, in an objective manner, which dysfunction causes people to have lower urinary tract symptoms (LUTS) and or signs of UI.

The attempt to gain understanding of an individual's lower urinary tract (LUT) functioning, on the basis of test observations, in relation to what is known about normal, or expected abnormal, physiology, is what constitutes urodynamics.

Urodynamic studies can answer questions such as: 'What is the cause, or causes of increased voiding frequency in this patient' as well as: 'Why does this patient have urinary incontinence?' These questions not only can be posed for individual patients but also can form part of clinical or laboratory research [Toh 2006; Nager 2009; Gordon 2001; Gomes 2004].

Conventionally, UDS involves the patient being connected to equipment in the laboratory in order to measure physiological parameters, such as pressures, inside the patient. The data is monitored while the test is being carried out and adjustments can be made to prevent or correct for technical problems and artefacts as they arise. Ambulatory urodynamics may be employed in an attempt to answer the clinical (or fundamental or scientific) question [Pannek 2008]. In ambulatory urodynamics, pressures and other physiological parameters from the patient are fed into a data logger and the patient is free to move about and carry out normal activities. The advantage is that such tests can last for many hours in more 'natural' circumstances for the patient but the disadvantage is that prevention of, and control for artefacts and also integration of patients' activity, sensations or perceptions is much more difficult. Videourodynamics (or ultrasound combined) is a technique to combine anatomical morphological information of the lower urinary tract with functional (pressure and flow) measurements.

II. WHAT SHOULD BE THE ROLE OF URODYNAMIC STUDIES IN CLINICAL PRACTICE?

It is frequently quoted that that the aim of urodynamic testing is 'to reproduce the patients' symptom(s)'. This committee has a view that the 'symptoms' here referred to are the patients' (or caregivers') way of expressing that she or he notices UI and/or any other sign (or presumed sign) of LUTD. No evidence exists about the incidence of the presentation of the specific symptom 'urinary incontinence' in a referred population without that being true. It is the committees' opinion that this incidence is however probably very, very low. It is therefore not the primary task to 'solely' confirm UI as a symptom but it is the doctors' task to 'translate' the sign and or symptoms into a clinical diagnosis that leads to an effective treatment.

Urodynamic testing should be applied to objectively measure and document the entire lower urinary tract function and or dysfunction when it can have therapeutic consequences, bearing the individual patients' symptoms, and all other relevant circumstances, in mind. Urodynamic testing can show signs such as (significant) residual urine or underactive detrusor which is often not specifically noticed by the patient, even when neurologically unaffected. Especially, but not uniquely in patients with relevant neurological abnormalities, upper urinary tract signs (dilatation) can exist or develop without any (new) symptom. Furthermore the patient can present with symptoms such as, 'urinary frequency', 'nocturia' or 'recurrent urinary tract infections', which are difficult or impossible to reproduce in the usual UDS- laboratory. The importance of urodynamic testing is thus to reproduce the dysfunction of the lower urinary tract and to determine the cause of the signs and or symptoms of urinary tract functional disease. The implicit consequence of this is also that ideally at least one complete filling (storage) and pressure-flow (voiding) cycle, that adequately represents the patients problem (e.g. with regard to volumes) including post voiding features, (residual urine, or after contraction) should be tested, analysed, and documented, even if only storage or voiding signs or symptoms have been expressed by the patient.

The role of urodynamic studies in broad clinical perspective can be:

a) to identify all factors that contribute to the LUT symptoms (e.g. urinary incontinence) and assess their relative importance;

b) to obtain information about all other aspects of LUT function or dysfunction whether or not expressed as a symptom or recognisable as a sign;

c) to allow a prediction of the possible consequences of LUT dysfunction for the upper urinary tract;

d) to allow a prediction of the outcome, including undesirable side effects, of a contemplated treatment;

e) to confirm the effects of intervention or understand the mode of action of a particular type of treatment for a LUT dysfunction; especially a new and or experimental (pre-routine) one;

f) to understand the reasons for failure of previous treatments for urinary incontinence, or for LUT dysfunction in general (after unsatisfactory treatment).

Conclusion (level 1)

• Urodynamic testing in clinical practice is to evaluate a person's lower urinary tract function with at least one complete and representative filling-voiding-post voiding cycle by testing with relevant pressures and flowmetry. Urodynamic testing includes quality control, subsequent analysis, and documentation. Auxiliary testing of urethral (bladder outlet) closure function or simultaneous registration of pelvic floor muscle activity and or simultaneous addition of anatomical or morphological information with ultrasound, roentgen or other imaging can complete, or augment the value of, urodynamic testing for specific indications.

III. THE TESTS OF CONVENTIONAL URODYNAMICS

1. UROFLOWMETRY

This is the non-invasive measurement of urine flow rate. The patient voids into a flow meter in private ideally with a normal to strong (but not uncomfortable) desire to empty their bladder [Schafer 2002]. Urine flow rate is continuously measured and displayed graphically. Various parameters from the trace are automatically calculated and printed out together with the trace. After control for artefacts in automated calculations, the maximum flow rate, the volume voided and shape of the curve are usually the principal determinants of whether or not the patient is emptying their bladder in a normal way. If an abnormal voiding is obtained, it is good clinical practice to repeat the assessment to check that the result is reproduced, or not. Several factors, such as patient apprehension, can give an abnormal recording in patients who have no voiding difficulty. Asking the patient about what she or he thinks about the voiding; whether the voiding (including the volume) was an adequate representation of the real voiding (compare with voiding diary) and if necessary further explanation is absolutely relevant and must be regarded as standard (good urodynamic) practice. Repeating the assessment can eradicate the effect of such confounding factors and will confirm or refute the validity of earlier assessment(s). Unambiguous and careful instruction of the patient, privacy and a short meatus to flowmeter distance are all inherently relevant [Addla 2010].

2. FILLING CYTOMETRY

This is the measurement of the pressure inside the bladder to assess its storage capabilities. It is an invasive test which involves a catheter being placed into the bladder, usually transurethrally, and another catheter being placed rectally or vaginally (or sometimes through an abdominal stoma) to measure abdominal pressure. Subtracting the abdominal pressure, indirectly measured via vagina, rectum or stoma, from the pressure measured inside the bladder (intravesical pressure) gives a representation of pressure changes due to the action of the detrusor smooth muscle or due to the (lack of) viscoelasticity of the bladder to volume change, measured and expressed as bladder compliance.

During this assessment, the bladder is usually filled with normal saline solution, or x-ray contrast solution in the case of videourodynamics, either through a separate catheter placed transurethrally or through the filling channel of a dual lumen catheter if such is used to measure intravesical pressure. Usually the filling rate is much faster than physiological bladder filling so that, depending on the urodynamic capacity (and related to information from the voiding diary), the bladder is filled in about10 min.

The intravesical and abdominal pressure and the calculated ($p_{ves} - p_{pad}$) detrusor pressure are monitored as the bladder is filled and before the patient has been given 'permission to void'. The storage ability of the bladder is assessed in terms of the volumes required to elicit various sensations from the patient, its capacity, its compliance (passive muscle adaptation to volume stretch and detrusor muscle relaxation) as distinct from the absence of (phasic) detrusor pressure rises. The filling (storage) phase of cystometry is the method of demonstrating urodynamic stress incontinence (USI) by means of coughing or straining, on request of the clinician [Ward 2008]. Good urodynamic practice demands that abdominal pressure, and intravesical pressure, as well as subtracted detrusor pressure are evaluated to diagnose urinary bladder storage function.

3. PRESSURE-FLOW STUDIES (VOIDING CYSTOMETRY)

This is a measurement of the mechanics of micturition. When the filling (storage) phase of cystometry is complete, the patient is given 'permission to void' and will empty their bladder on a flow meter whilst intravesical, abdominal and detrusor pressures are being recorded. The simultaneous measurement of flow rate and pressure enables voiding to be assessed and pressure flow analysis can help determine whether slow urine stream is due to bladder outlet obstruction (BOO) or to an underactive detrusor contraction or to a combination of those.

4. URETHRAL PRESSURE PROFILOMETRY

This is a test to estimate the urethra and the surrounding (muscle and other-) structures' ability to maintain the bladder outlet closed allowing the body system to contain urine within the bladder. By concept, a catheter is placed transurethrally into the bladder and then withdrawn along the urethra (usually by a mechanical puller at a constant rate). The pressure along the length of the urethra is measured and interpreted relative to the pressure inside the bladder (and or abdomen). The maximum pressure measured in the urethra is assumed to give an indication of the urethral closure function.

5. ABDOMINAL LEAK POINT PRESSURE

This is another concept to estimate the urethra's (bladder outlet's) ability to contain urine within the bladder. Intra -abdominal pressure is measured whilst the patient is asked to increase their abdominal pressure by valsalva or by coughing. The abdominal pressure required to produce leakage from the bladder gives an indication of the closure function of the urethra since higher closure pressures ('better function') require higher abdominal pressure increments to cause leakage.

IV. TECHNOLOGICAL INNOVATIONS IN URODYNAMICS

1. AIR-CHANGED CATHETERS FOR PRESSURE MEASUREMENT

Single-use, air-charged catheters have been developed and used for intravesical, intra-urethral and abdominal pressure measurement in urodynamics (T-Doc, Wenonah, NJ). Initial reports, presented at a meeting, from a female cadaver -study showed that these catheters gave more reproducible measurements of MUCP compared to micro tip catheters, water filled catheters and fibre-optic catheters [McKinney 2000]. In a clinical study in 2004 on 45 women, their performance has been shown to be comparable to micro transducers in the measurement of maximum urethral closures pressure and Valsalva leak point pressure (VLPP) [Pollak 2004]. However, the same study showed a difference in functional urethral length which was attributed to the different diameters of the two catheters. Following on from that, a randomised comparison of these air charged catheters with micro tip catheters, in another 64 women, showed that measured maximum urethral closure pressure (MUCP) and functional urethral length were equally reliable. However, the air-charged catheter showed a systematically higher reading causing the conclusion that they cannot be used interchangeably [Zehnder 2008]. The measurement of VLPP by Pollak et al [Pollak 2004] suggests that they can be used to measure intravesical pressure [White 2009; Zehnder 2008]. To compare the response of two disposable clinical catheter systems: water-filled and air-charged, to controlled pressure signals in a laboratory set-up to assess their similarities and differences in pressure transduction using a transient step test and a sinusoidal frequency sweep test, has been carried out. Water-filled catheters were reported to act as an under damped system, and sensitive to (motion) artefacts, whilst air-charged catheters acted as an over damped system, were less sensitive to artefacts and slower in response [Cooper 2011]. Air-charged catheters have several practical advantages over fluid-filled pressure lines because there is no hydrostatic pressure effect to account for, so that there is no need to position external sensors at the level of the symphysis pubis. There is also no need to flush the system through to exclude air; a process that is essential in a fluid-filled pressure-sensing environment. Also, there are no fluctuation artefacts in pressure produced when the patients move [Kim 2010]. However, although air-charged catheters may make urodynamics easier to set up, the conduct and interpretation of a urodynamic study still requires an experienced, appropriately trained practitioner.

Conclusions (level 3)

- Air-charged catheters may provide an acceptable alternative to other techniques for measuring the pressure closing the female urethra.
- There have been no studies to show whether air-charged catheters provide a superior alternative to fluid-filled lines for measuring intravesical and intra-abdominal pressure in urodynamics.

Recommendation (grade C)

- Investigators planning to use air-charged catheters for intravesical and intra-abdominal pressure in urodynamics are advised to check for themselves that they have an equivalent performance to their current system for measuring pressure.
- Investigators planning to use air-charged catheters for intravesical and intra-abdominal pressure in urodynamics are advised to check for themselves how the performance of their system compares to the standard reference values for clinical relevant limits (of pressures obtained with the classical systems).

Topic for research

- A study to compare the performance of air-charged catheters with fluid-filled pressure lines in the measurement of intravesical and intra-abdominal pressure during filling and voiding cystometry, to include 'fast' events such as coughing.

2. OBJECTIVE ASSESSMENT OF BLADDER SENSATION

Bladder sensation during urodynamics is usually recorded by the simple expedient of asking the patient to inform the investigator when they experience

different sensations. This is an ICS standardised, but subjective measurement which can be confounded by the investigators inadvertently distracting the patient whilst bladder filling is being carried out. Investigators can also bias the measurement by inadvertent prompting, or by causing too much 'concentration' and unrepresentative awareness of the patient [Frenkl 2011]. Bladder (filling) sensation has received increasing attention since (urinary) urgency and 'early' filling sensation are clinically important and some treatments are believed to or initiated to influence LUT sensation [Wachter 2011; Heeringa,R.2011].

A patient-activated, keypad 'urge score' device to measure sensations during bladder filling was introduced [Craggs 2005] to enable patient perceptions of bladder filling and the successive stages of increasing bladder sensation to be recorded without prompting or intervention by the investigator. The device provided reliable and repeatable measures of different bladder sensations. In a controlled setting with 11 healthy volunteers of both sexes, bladder sensations were recorded during non-invasive rapid bladder filling and related to bladder filling sensations during cystometry in the same healthy volunteers: bladder sensation was reported to be continuously incremental [Heeringa 2011].

Filling sensations during conventional urodynamics were marked on a body map in another prospective study. Results from this study suggested that women's bladder sensations vary in relation to their bladder condition and suggested that this may provide clinicians with relevant information about bladder (dys)-function adding to the usual history and clinical examination [Digesu 2009].

Daily life bladder sensation can be evaluated by sensation related bladder diary and during cystometric bladder filling. 185 women with SUI, OAB or mixed UI filled out a 3-day bladder diary grading bladder sensation and measuring voided volume at each micturition. During UDS reported filling sensations were noted. The end -cystometric volumes were significantly larger than the diary voided volumes for corresponding bladder sensations, and this in all groups, leading to conclusion that symptoms relate more to the diary. [Naoemova 2009]

Imaging studies with regard to brain activity during bladder filling and emptying were reviewed [Fowler 2001]. Research, that started 1996 has provided the in vivo evidence for the existing indirect -neuro anatomical- knowledge of the brain areas involved in lower urinary tract function control and modulation, but cannot yet be regarded as a replacement of cystometry

Many studies consistently show that the correlation between objective and subjective features of detrusor adaptation to volume increment, bladder proprioception and the subjective interpretation of filling is weak [Chung 2011; Meel 2011; Clemens 2011; Tsunoyama 2011; Coyne 2011; Deffontaines 2010; Honjo 2010]. In fact these observations also demonstrate that urodynamic testing is adding new and objective diagnostic information to what has been gathered with history, voiding diary and clinical investigation. Both, UDI as well as signs and symptoms, are relevant, in combination, to select further treatment.

Conclusion (level 3-4)

- On the basis of published results, a significant variation exists in clinical practice to determine bladder filling sensation landmarks and maximum cystometric capacity, despite the standardisation of terms.
- Strategies to derive bladder filling sensation parameters in a more automated and objective way, have been published and show plausible and applicable results, however are not yet sufficiently tested with regard to reliability, relevance, investigator independency or test retest robustness.

Heart rate variability

The use of heart rate variability was studied during conventional cystometry [Mehnert 2009]. Heart rate variability was evaluated to serve as a monitor of the autonomic nervous system and an objective measure for bladder filling sensation. Heart rate variability showed to reflect sympathico -vagal balance and to correlate with bladder filling sensation in 11 healthy subjects.

Conclusions (level 3-4)

- Monocenter uncontrolled studies have provided evidence for an association of heart rate variability monitoring and urodynamic observations.
- None of the analysis or testing methods of the autonomic nerve system has, to date, shown any relevance for the diagnosis of lower urinary tract function or dysfunction in neurologically unaffected persons. No direct evidence exists for lower urinary tract dysfunction as a sign of – otherwise sub clinical- autonomic failure. No evidence exists that any analysis of autonomic function can be specific enough to monitor lower urinary tract function.

3. NON-INVASIVE PRESSURE (& FLOW) MEASUREMENTS

Over recent years, groups in UK and The Netherlands have been developing non-invasive techniques to measure pressure-flow in males. The UK group has developed a penile cuff device that was tested in various preclinical and clinical validation studies but has not been reported as a true replacement of pressure flow cystometry and has not been reported to be relevant for the diagnosis of UI [Griffiths 2002; Drinnan 2001; Griffiths 2005; Drin-

nan 2003; Clarkson 2008; Sajeel 2007; Harding,C. 2007]. The group in Rotterdam developed a condom catheter through which the patient voids into a urine flow meter. During flow, the stream is, via the condom episodically diverted to a transducer that records the bladder pressure at that time. Also this method has been carefully tested and compared with standard UDS [Pel 2002; Pel 2003; Huang 2004; van Mastrigt 2006].

Measurement of perineal noise during voiding as another way of non-invasively quantifying male BOO has been evaluated but the work has not yet progressed sufficiently beyond testing on models to determine the viability of this technique in vivo [Idzenga 2005; Idzenga 2006]. Both, noise analysis and condom pressure, have not demonstrated relevance for the diagnosis of (male) UI.

A subsequent technique, with automatic modulation of the flow rate by controlling pressure in a penile cuff, was recently introduced [Clarkson 2011] The prototype needs technical refinement but some feasibility has been shown in the determination of detrusor contraction properties in relation with the bladder outlet condition.

Transabdominal wall near-infrared spectroscopy was used to detect the haemodynamic changes that are associated with detrusor contractile activity. This has been demonstrable in a highly selective set of feasibility recordings and may lead the way for non invasive detection of detrusor activity [Farag 2011].

Conclusions (level 2)

- Non-invasive measurements of bladder pressure during voiding in men by the penile cuff or condom catheter have been shown to correlate with traditional invasive measurement of bladder pressure. None of these studies have however shown any applicability in the diagnosis of urinary incontinence.
- Near-infrared spectroscopy has in very selected recordings shown a relation with detrusor (over) activity and is reported to be applicable as a manner to detect detrusor overactivity.

Recommendation (grade B)

- The committee recommends that non-invasive measurements of bladder or detrusor 'voiding-pressure' are considered in order to evaluate voiding function in clinical experiments when the male patient is not required to undergo an invasive assessment of the storage function of the lower urinary tract.
- The committee does not recommend condom or penile cuff pressure, nor near infrared detrusor spectroscopy, for the diagnosis urinary incontinence, or of lower urinary tract dysfunction.

4. URETHRAL RETRO-RESISTANCE PRESSURE

In the measurement of urethral retro-resistance pressure (URP), a small meatal plug is inserted just inside the female urethra and saline is pumped into the urethra until the pressure reaches the value sufficient to overcome the resistance offered by the urethra when the fluid flows into the bladder. The pressure required to achieve and maintain an open bladder outlet is taken to be a measure of urethral closure function. The basic principle behind the technique has its origins in 1923 when Bonney made an attempt to measure the efficiency of urethral closure [Bonney 1923]. In his first clinical paper, Slack et al studied 258 SUI women with the URP technique in comparison with MUCP and Valsalva leak point pressure (VLPP). They found that URP measurements correlated well with both standard assessments and found that only URP measurements correlated with UI severity [Slack 2004]. The URP, in a group of 61 women, without symptoms of UI and who had negative standing SUI -tests, was significantly higher than in a group of women with SUI who had been tested previously [Slack 2004]. This study also provided some test-retest data which showed that URP measurements were consistent in individuals.

Measurements of URP on 165 women with various urodynamic diagnoses were published subsequently [Digesu 2006]. Women with USI had significantly lower URP than women with competent urethral sphincters. Women with mixed urodynamic incontinence had values of URP intermediate between women with DO and those with USI. In the mixed symptoms group, URP mean values were not significantly different from those with DO and competent sphincters, or those with USI. The authors concluded that whilst there are significantly different URP measurements between women with DO and those with USI, the URP is not a diagnostic tool.

An analysis of URP in 48 women with clinically and urodynamically proven SUI (USI) without pelvic organ prolapse (POP) before and after anti-incontinence surgery (colposuspension n = 8, tension-free vaginal tape n = 6, tension-free transobturator tape n = 34) and another study to compare URP with 'established measures of incontinence severity' showed that preoperative URP did not correlate with SUI in all women, had no predictive value and did not correlate with the outcome of anti-incontinence surgery [Tunn 2007; Roderick 2009].

Conclusion (level 2/3)

- After positive first reports of urethral retro-resistance pressure measurements it was shown that this measurement does not give any better information about urethral closure function than the urethral pressure profile or valsalva leak point pressure.

Recommendation (grade B/C)

- The committee recommends that urethral retro-resistance pressure measurements are not used in clinical routine as an alternative to (cystometry or) urethral pressure measurements made with conventional urodynamic equipment to diagnose the type of (female) urinary incontinence.

5. URETHRAL PRESSURE REFLECTOMETRY

In 2005, Klarskov et al reported on an in vitro study of pressure reflectometry for the simultaneous measurement of cross-sectional area and pressure in a collapsible biological tube and subsequently the technique of urethral pressure reflectometry (UPR), to assess the female urethra, was presented in 2007. The team postulated that these parameters had the potential to provide more physiological information about the urethra than could be obtained from conventional urethral studies.

In the same year these investigators compared UPR with urethral pressure profilometry (UPP) in 143 women (105 patients and 38 healthy volunteers) [Klarskov 2007]. UPR was measured supine, both while relaxed and during 'squeeze', and while upright and relaxed, and compared with UPP using the perfusion technique, with the patient supine and relaxed. All measures were done twice to evaluate short-term reproducibility and 17 patients were assessed with both methods on two different days (long-term reproducibility). The authors showed that UPR measured the same pressure as UPP but the UPR was more reproducible. Subsequently UPR parameters of in 30 SUI women and 30 volunteers (23 'continent' and 7 'nearly continent') were reported and compared with UPP [Klarskov 2008].

Conclusion (level 3)

- Preclinical measurements of urethral pressure reflectometry opening pressure and cross sectional area ('dynamics') have provided some insight into urethral closure function and dynamics, but, as yet have no clinical relevance in the diagnosis of (female) urinary incontinence.

Recommendation (grade C)

- The committee recommends that urethral pressure reflectometry is not used in clinical practice for the diagnosis of urinary incontinence before clinical relevance, non inferiority and or superiority over current urodynamic tests has been demonstrated.

6. ULTRASOUND IMAGING

Imaging and ultrasound in relation to UI will be discussed in a separate chapter. We will only give a short summary of ultrasound in relation with urodynamic observations.

The measurement of detrusor wall thickness has been used in a number of studies as a screening test for DO or BOO with a variety of measurement techniques using transvaginal, transabdominal or transperineal ultrasound. Different protocols were used and measured different parts of the bladder for example the dome, the trigone or the anterior bladder wall. This has resulted in contradictory data. Some data showed a smaller bladder capacity in overactive bladder (OAB) wet or DO, and an association between increased detrusor wall thickness and DO on urodynamic testing. Also, observations of an association of ultrasound detrusor wall thickness and BOO have been reported. Most researchers conclude that overlap of the results and the relatively low predictive value should be improved before bladder wall thickness is used in clinical practice [Lekskulchai 2008; Kuo 2009; Panayi 2009; Panayi 2010; Oelke 2009; Chung 2010; Ozawa 2010; Kuhn 2010; Almeida 2011; Serati 2010].

Conclusion (level 3)

- There is some evidence that detrusor wall thickness is related to bladder outlet obstruction as well as to detrusor overactivity.
- There is no evidence that ultrasound detrusor wall thickness analysis can discriminate between detrusor overactivity and bladder outlet obstruction and a relatively low predictive value to discriminate from normal lower urinary tract function.
- There is a large overlap between normal and abnormal values in detrusor wall thickness and a lack of standardisation in ultrasound detrusor wall thickness measurement.

Recommendation (grade C)

- The committee recommends that ultrasound detrusor wall thickness is not used in routine clinical practice for the diagnosis of lower urinary tract function related to urinary incontinence.

B. URODYNAMICS: NORMAL VALUES, RELIABILITY AND DIAGNOSTIC PERFORMANCE

I. REPRODUCIBILITY OF FILLING CYSTOMETRY AND AMBULATORY URODYNAMICS

1. INTER-OBSERVER, TEST-RETEST AND PRACTICE VARIATION

When different investigators judge urodynamic traces together with written clinical information in women, there is agreement between them regarding the final clinical diagnosis in about 80% of cases. In other words there is, depending on the diagnosis, some disagreement in 20% of cases when urodynamics is judged in combination with clinical

parameters [Whiteside 2006]. A few studies have concluded that there is good short time inter and intra–rater reliability. In a single centre series of 621 urodynamic pressure flow tracings of female patients, small average differences between parameters were observed by various investigators, which was interpreted as good inter -observer agreement [Digesu 2003]. Inter-observer variability has also been tested in other ways. In a study where 4 experienced practitioners, evaluated 17 paediatric urodynamic datasets, they failed to agree on aspects of detrusor function, including DO, in a quarter of the cases [Venhola 2003]. This result is reminiscent of a similar study of the interpretation of urodynamic recordings of male voiding function [Kortmann 2000].

To determine the reproducibility of same session repeated UDS in women with symptoms of UI, 152 women presenting with symptoms of UI underwent standardised UDS, which consisted of free uroflowmetry and two filling cystometries and pressure-flow studies. Overall, reproducibility of the urodynamic parameters were good to excellent (ICC range: 0.72-0.93), except for the bladder volume at FSF (ICC = 0.46) and the maximum Watt's factor (ICC = 0.68). The bladder volume at FSF and the MCC were systematically higher in the second run (mean difference (95% CI) = -45 (-73; -37) and -3 (-15; 10), respectively). Reproducibility of the diagnosis SUI and/or DO were good to excellent (median ICC = 0.76, p= 0.68 and p = 1.00, respectively). Reproducibility of the volume and amplitude at DO, however, were only poor (ICC = 0.18 and 0.25, respectively). The authors of this study concluded that reproducibility of same session repeated –standardised-UDS, in women with symptoms of UI was good to excellent [Broekhuis 2010].

In a survey to determine the variation in urodynamic practices in the United Kingdom 100 questionnaires were sent to units known to be performing urodynamic investigations. There was a significant variation in practices with only 51% of units having a protocol for what tests should be performed, under what circumstances and how [Adekanmi 2002]. Standardisation of urodynamic variables may result in a greater consistency of diagnosis, allowing easier comparisons of treatment regimes and outcomes, and is the conclusion of studies and reviews of this kind [Zimmern 2006; Ellis-Jones 2006]. Standardisation, education and training as well as auditing and evaluation are reported to be relevant in this regard [Ellis-Jones 2006; Singh 2010; Moore 2011].

In a review to examine the influence of position during (filling) cystometry with regard to the sensitivity for DO, sixteen relevant studies with good consistency were analysed. All but two showed a clear influence, with a higher incidence of DO in the vertical position (sitting or standing) or onset of DO when changing to a vertical position. Performing the UDS in a supine position would have missed a large proportion of DO diagnoses, ranging from 33% to 100%. The authors noticed a substantial practice variation in position during urodynamic investigation and suggested standardisation was needed [Al-Hayek 2008].

Some suggested that these findings are caused by difficulties of interpretation, included movement artefacts, and also criticise over-dependence on patients for suitable data recording without a medical assistant. This presumed lack of reliability has lead to the study of the additional value and reliability of ambulatory UDS, as it may improve diagnostic sensitivity and maybe specificity. The additional diagnostic value of ambulatory UDS in patients with LUTS was compared with conventional UDS [Koeveringe 2010]. A retrospective study was done in 108 patients between 2002 and 2007. Ambulatory UDS was shown to be useful in patients with OAB, or in patients with UI that was not demonstrated during conventional UDS, but the study is difficult to extrapolate to real values of amended diagnostic capability.

2. SHORT-TERM (WITHIN-SESSION) REPRODUCIBILITY

A number of authors have investigated the within-session reproducibility of cystometric measurements. Because such measurements are conducted within a short period of time, the possibility that the first measurement influences the second, for example through a direct effect on the mechanical properties of the bladder (hysteresis and/or viscoelasticity), has to be considered.

30 healthy women with a mean age of 52 years, underwent 2 consecutive medium fill rate (50 mL/min) cystometries in a single session [Brostrom 2002]. The volumes at first desire to void (FDV) and normal desire to void (NDV) increased significantly from the first to the second measurement, by 34 and 51 mL respectively. The MCC showed no difference. The proportion of these healthy subjects who showed DO changed from 4/30 (13%) in the first cystometry to 1/30 (3%) in the second; statistically insignificant.

In a similar study [Mortensen 2002] of short-term repeatability in 31 female patients aged 14-74 years, two consecutive cystometries were performed with body temperature liquid at a rate of 50 mL/min. On the first cystometry, FDV occurred at a median volume of 112 mL (range 26-503 mL). The cystometric capacity had a median value of 150 mL, with a range from 39-633 mL. The volume at FDV increased by 46 mL from the first to the second cystometogram, while the MCC increased by 35 mL. These changes are similar to those seen in normal volunteers, but, as the authors point out, they are not clinically important because they are much smaller than the random variability within subjects, as measured by the 95% confidence limits of ±130 and ±106 mL respectively.

Chin-Peuckert et al [Chin 2003] examined the variability between two consecutive cystometries in 32 male and 34 female children with a mean age of 7. Most suffered from spinal dysraphism. A smaller number showed DO on the second study than on the first ($p< 0.05$), and similarly the volume at which DO was first observed was larger on the second study ($p<0.05$). Interestingly, these results are similar to those obtained in children without overt neuropathy [Griffiths].

Hess et al [Hess 2002] did not perform repeated cystometries, but first measured the bladder pressure 'as is' at whatever volume was in the bladder initially, in 21 men and 1 woman with 'neurogenic bladder'. They then drained the bladder and refilled to the same volume and again measured the pressure. The second 'cystometric' pressures were higher than the initial 'physiological' ones by approx 6 cm H_2O ($p = 0.01$), although strongly correlated.

In another study where fifty consecutive individuals with spinal cord injury had 2 trials (trial 1 and trial 2) of UDS done 5 minutes apart, differences in MCC, opening pressure, maximum detrusor pressure, volume (leaked) voided, and post void residual (PVR) volume were evaluated. The variation observed was ± 100-150 mL for the volume parameters and ±10-20 cm H_2O for the mentioned pressure parameters, all in both directions between 1st and 2nd [Chou 2006].

Sixty men with LUTS and 35 with NLUTD after spinal cord injury (SCI) were assessed, with symptom scores and uroflowmetry obtained and filling and pressure-flow cystometry carried out three times in succession. In men with LUTS, a significant decrease in the number and pressure of detrusor contractions in consecutive filling cystometries resulted in a reduction of observed DO from 72% to 63% and 48%, in the three studies. In men with SCI, cystometric variables and DO remained consistent over sequential studies [Ockrim 2005].

Twenty asymptomatic women with a mean age of 42 years [30-55) agreed to undergo a urodynamic evaluation, repeated immediately without removing the catheters (a two-fill and void study) [Gupta 2004]. Sixteen women of this cohort returned for an identical assessment 1-5 months later. The short time variation was ± 5 mL/s for Q_{max} and ± 10 cm H_2O for $p_{det}Q_{max}$. Voided volume (VV) and first sensation of filling (FSF) differed ±50 mL in the test retest situation. The authors noted that the variation of parameters in these healthy women was larger than observed in other studies with patients.

3. INTERMEDIATE-TERM REPRODUCIBILITY

Homma et al [Homma 2000] found that, in 30 patients with DO, repeat cystometry carried out 2-4 weeks after initial testing showed a consistent shift towards normal. Bladder volumes increased by 10-13% ($p<0.01$), while DO disappeared in 10% of subjects and decreased in amplitude by an average of 18% in the remaining cases. The random variability of cystometric capacity was ± 57 mL (95% CI).

4. LONG-TERM REPRODUCIBILITY

10 healthy females (mean age 34 years), were investigated twice at an interval of 2 years in both, supine and sitting positions [Sorensen 1988]. FSF occurred at a mean volume of 378 mL supine and 354 mL sitting, with intra-subject variability over two years as quantified by the standard deviation (sd) of 76 and 100 mL (sd) respectively. MCC was 512 mL supine and 502 mL seated, with intra-subject sd of approximately 75 mL in both cases. Inter-subject sd's were a little larger: 76-144 mL. No significant differences in volumes or compliance over two years could be demonstrated.

Post hoc analysis of urodynamic (pressure flow) tests of male treated for LUTS with enlarged (unspecified) prostate and BOO (for a not specified proportion) showed test retest reproducibility to be good on the basis of parameter correlations, but without kappa or Bland and Altmann analysis [Kraus 2010].

A total of 48 children ±10 years were enrolled in a study to evaluate the influence of position during UDS in this patient group, with 60% neurologically affected. No difference was noted for maximum cystometric capacity, DLPP or pressure specific volumes at 20 and 30 cmH_2O between the supine and sitting positions. Statistically significant lower values were found for the volume of FSF and volume at which DO was first detected, with lesser difference for abdominal or Valsalva leak point pressure in the sitting position. Significant differences were also noted with position changes in regard to detection of DO and UI episodes, being more prevalent in the sitting position [Lorenzo 2007].

Summary

In patients and in healthy volunteers, if cystometry is repeated either during the same session or within about 4 weeks, the bladder volumes at which the various sensations are felt and the bladder capacity tends to increase by 30-50 mL, while the proportion of traces showing DO tends to fall. These systematic changes are fairly small in comparison with the random within-subject variability, which has an average range of about 50-60 mL.

Conclusions (level 2)

- A number of studies have reported test retest variation of ±10-15% for various parameters (volume, pressure or flow) and observations; this can be regarded as the physiological variation of urodynamic testing.
- Various studies have demonstrated clinically relevant practice variation and inter-rater/observer variation.

Recommendations (grade B)

- The committee recommends that investigators and clinicians take into account the inherent physiological variability of urodynamic testing.
- The committee recommends investigators and clinicians evaluate the 'representativity' of the tests (which is an evaluation based on the patient's perception as to how well the tests have reproduced their usual lower urinary tract symptoms and function, helped e.g. by the voiding diary.) and the committee recommends that examiners strive towards maximal representativity.
- The committee recommends sitting position during cystometry, because that can increase sensitivity of the diagnosis of filling phase abnormalities.
- The committee recommends persistent attention to the standardisation of techniques, to education, and to practice quality evaluation, and consistency of interpretation of results, especially to reduce intra and inter-practice variation and inter–observer variability.

Topics for research

- The committee suggests further consideration of standardisation of urodynamic tests, procedures and evaluation, especially to reduce inter-practice variation.
- The committee suggests intensive dissemination of up-to-date standards and careful training of urodynamic investigators and suggests evaluation of the effect of these standards and training on health care quality.

5. REPRODUCIBILITY OF AMBULATORY URODYNAMICS

There is no published data on the reproducibility or test retest differences of ambulatory urodynamic studies. There is no report that evaluates the investigator dependency on the -post test- analysis of the recorded data.

II. CYSTOMETRY: NORMAL VALUES

1. NORMAL VALUES: FILLING CYSTOMETRY AND AMBULATORY URODYNAMICS

Normal values for cystometric variables are reported by a number of authors. A striking observation is that there is great inter-centre variability, even for tests in nominally similar persons or patients. There is no evidence from these studies that these variations are strongly associated with differences in filling rate, infusate temperature, or patient position. In addition to and referring to the previous consultations we report only the relatively recent studies on volumes, pressures, compliance, capacity and sensations.

Wyndaele et al [Wyndaele 2002] examined 50 volunteers; The bladder was filled at 30 mL/min with body temperature saline. For males (n=18; mean age 22 ± 3 years), FSF occurred at 222 mL ± 151 mL; FDV occurred at 325 mL ± 140 mL; and strong desire to void (SDV) occurred at 453 mL ± 94 mL, which was taken as maximum capacity. For females (n=32; mean age 21 ± 2 years) FSF occurred at 176 ± 96 mL; FDV at 272 mL ± 106 mL; and SDV at 429 mL ± 153 mL. DO was observed in 7/50 (14%) of these normal volunteers. The group also published a study with symptom free 'middle-aged' female volunteers. Of their volunteers, a substantial number were excluded because of asymptomatic abnormalities. The remaining had an average capacity during cystometry of 586 mL (sd 193 m) with 258 mL and 1092 mL as extremes [Pauwels 2004].

Twenty-four women without a history of frequent urgency and without DO (mean age 50.2 years, range 22-80 years), including 7 pre- (29.2 years), 7 peri- (48.8 years), and 10 postmenopausal (66.0 years) women were studied with uroflowmetry and video urodynamics to determine normative data for LUT function in asymptomatic continent women without DO across the age span. For all subjects, median maximum single VV in bladder diary was 500 mL and median MCC was 580 mL. SDV was reported at 287, 366, and 425 mL for pre-, peri-, and postmenopausal groups, respectively. The maximum flow rate was 25, 32, and 23 mL/sec in uroflowmetry and 23, 24, and 18 mL/sec during the pressure-flow study, respectively. Median PVR was below 20 mL in all groups. At maximum flow rate subjects voided with detrusor pressures of 29, 26, and 24 cm H_2O, respectively and MUCP was 94, 74, and 42 cm H_2O, respectively [Pfisterer 2007].

Thirty healthy males aged 21-32 years volunteered for an ambulatory urodynamic 24 h investigation, with a suprapubic catheter, to study natural fill urodynamics during normal and increased fluid intake. The recorded micturition data were: frequency (f), VV, voiding time, maximum flow rate (Q_{max}) and time to Q_{max}. The number of sensed and not-sensed detrusor contractions, and their duration and time in relation to voiding were also recorded. During the recording day, subjects were randomized to normal (30 mL/kg body weight per day) or larger (60 mL/kg body weight per day) fluid intake. There was a larger urine production and an increased voiding frequency in the fluid-loaded group ($p<0.0001$). The detrusor pressure ($pdetQ_{max}$) was significantly higher in the fluid-loaded group (73 cm H_2O, range 57-94) than in the normal fluid intake group (60 cm H_2O, range 45-86) ($p=0.003$). No other urodynamic data differed significantly between the two groups. Ambulatory urodynamics in normal young men showed a large inter -individual variation, detrusor contractions during filling were frequently recorded, and premicturition contractions were consistently found. The data found in this study were similar to

previous home flow recordings in the same group [Schmidt 2004].

In a retrospective study of 186 selected investigations the influence of urine production during filling cystometry on total bladder volume was observed. Mean filled volume (external infusion plus urine production) was 346 ± 152 mL, but mean real bladder capacity (VV + residual urine) was 391 ± 170 mL. In all patients, 14% extra urine was produced due to urine production (mean rate, 6.1 mL/min). In 42% of the investigations, the real bladder capacity was more than 110% of the infused volume. In 18% of the patients, the contribution of natural bladder filling was more than 25% of the infused volume [Heesakkers 2003].

Urodynamic tests were, in another study, conducted on 39 asymptomatic male volunteers with a mean age of 25.8 years (range 21 to 31) and mean weight of 75.5 kg (range 63 to 95) to examine the pressure-flow relationship and obtain evidence to support the hypothesis that fluid consumption has a role in detrusor voiding function. Volunteers were divided into 2 groups according to water consumption regimen of 30 mL/kg daily (17 patients, group 1) and 60 mL/kg daily (12, group 2). Bladder pressure was monitored via a suprapubic catheter and abdominal pressure was measured via a rectal balloon using an ambulatory system with an average duration of 20.5 hours. Doubling of water consumption increased urethral opening pressure from 51.2 ± 3.2 to 61.5 ± 5.1 cm. H_2O ($p<0.05$), maximum detrusor pressure from 58.9 ± 4.5 to 70.0 ± 6.2 cm. H_2O ($p<0.01$) and contractility from 15.4 ± 1.4 to 17.7 ± 1.4 W/m2. There were no significant differences due to water consumption in maximum flow rate (24.4 ± 1.4 to 25.2 ± 1.8 mL/s) or bladder capacity (286 ± 20 to 329 ± 15 mL) but a significant increase in the number of micturitions from 5.8 ± 0.5 to 9.8 ± 0.5 per day ($p<0.001$) proportional to water consumption [Schmidt 2002; Nager 2007].

2. COMPLIANCE

Compliance is the ratio of a change in volume measured relative to the corresponding change in pressure. Usually compliance is calculated over the change in volume from an empty bladder to that at MCC.

In 17 healthy subjects, using a filling rate of 35 mL/min,[Waalwijk 1992] the range of compliance values was very wide (range = 11-150 mL/cm H_2O; mean ± sd = 46 ± 40 mL/cm H_2O). Such a mean value implies only a small rise in pressure on filling (a few cm H_2O), consistent with having high compliance. Even higher values of compliance were reported by Hosker (range = 31-800 mL/cm H_2O; mean ± sd = 124± 150 mL/cm H_2O) in 72 healthy females (age 25-75 years) and these reproduced the wide range of values already published [Hosker 2004].

The results were comparable in elderly, peri and post menopausal women [Pfisterer 2007]. In another selected group of healthy middle aged, volunteers compliance was 'high' on average, however with a large variation [Pauwels 2004]. Similarly, Robertson showed that in 17 healthy male and female volunteers, the median detrusor pressure rise on conventional filling cystometry was 5 or 6 cm H_2O at filling rates of 50 and 100 mL/min respectively [Robertson 1999]. On ambulatory monitoring the median pressure rise was 0 cm H_2O however, a significantly smaller value.

Compliance cannot only be quantified in the units of mL/cmH_2O but also as a dimensionless number measured from empty to MCC. Compliance increases with age (because bladder capacity increases with age). This dimensionless value of compliance is to present a value that is independent of age (BUT not into old age). This is presented to be especially relevant in children when intra- and inter- individual test (retest) comparisons are made [Wahl 2004]. Consistently, among 22 healthy female volunteers, conventional cystometry and ambulatory study, performed in random order, showed a larger detrusor pressure rise on conventional filling as compared with ambulatory studies [Harlington 1996].

3. NORMAL SENSATIONS AND BLADDER CAPACITY

Earlier consultations have indicated the striking variability from centre to centre: FSV for example occurs at about 100 mL in one centre but at about 350 mL in another, a value large enough to provoke a strong desire to void in the first.

The bladder capacity is somewhat less variable from centre to centre, its mean varying from 340 to 570 mL. Apart from this inter-centre variability, the inter-subject variability of all the parameters is also substantial, with an sd of about 100 mL. Some of this variation represents genuine differences between subjects, but it should be noted that the within-subject variability is also quite large, in order of magnitude 50 mL.

As a rule of thumb in healthy adult subjects, and omitting some of the more inconsistent values, FSF occurs at about 170-200 mL, FDV or NDV (the ICS makes no distinction [Abrams 1988] at 250 mL, and strong desire to void at about 400 mL; MCC is about 480 mL. It is interesting that the mean VV on ambulatory monitoring falls between FSV (on cystometry) and FDV/NDV. Thus, in daily life, the bladder is usually emptied long before a strong or even a 'normal' desire to void would be felt on cystometry, although much more can be held if voiding has to be postponed. Correspondingly, there is a discrepancy in bladder capacity between daily life and urodynamic study, also depending on the method of measurement (uroflowmetry, voiding diary or cystometry) [Hertzberg 2003]. There is no evidence after the last

consultation to show that this inter investigator variability has decreased.

4. DETRUSOR (OVER-) ACTIVITY IN NORMAL SUBJECTS

DO is observed during conventional cystometry in up to 17% of asymptomatic subjects with a mean percentage of about 8%. The percentage is much higher, up to 69%, with ambulatory studies, although lower in other observations. DO can be observed during urodynamic testing, in healthy subjects (without the symptoms that are usually associated with OAB) which might also indicate that the observation of 'detrusor overactivity' should not always be interpreted as 'synonymous with pathology that demands treatment'. Nevertheless the false positive percentage remains unknown in those uncontrolled studies.

Conclusions (level 2)

- Various studies have been helpful in giving normal values and test retest variation of urodynamic parameters in healthy volunteers.
- There is some evidence that evaluation of filling sensation may be different between laboratories, (thus: 'may be observer dependent'), making data exchange as well as generalization and interpretation of published data difficult.

Recommendations (grade B)

- The committee recommends that investigators and clinicians bear in mind the results of urodynamic testing in healthy persons and to recognize 'normal' test-retest variation as well as the differences and/or variations between 'usual lower urinary tract behaviour', ambulatory monitoring and office urodynamic testing.
- The committee suggests that clinicians should be sufficiently aware of the normal variation, and normal values of lower urinary tract function and urodynamic studies.
- The committee recommends further standardisation and a practical objective means of recognizing and recording the parameters relevant to sensation during bladder filling.

5. INFLUENCE OF CATHETER ON VOIDING

A urodynamic database of 600 consecutive women referred for the evaluation of voiding symptoms was reviewed to examine the effect of a 7F transurethral catheter on flowrate. Before urodynamics, all patients voided privately using a standard toilet and free flow was recorded. Only 100 patients who voided similar volumes, varying by less than 20%, on the free flow, and pressure flow studies were included. In each VV category and urodynamic diagnosis, pressure-flow parameters were significantly different from the equivalent free flow parameters in all but 4 cases. Specifically the maximum flow rate was significantly less and flow time was significantly longer on pressure versus free flow studies (each $p<0.01$). An intermittent flow pattern was more common on pressure-flow, than in free flow measurements (43% versus 9%) [Groutz 2000].

Women between the ages of 30 and 70 years, without LUT complaints and without a history of surgery for UI, were recruited to prospectively examine the effect of a 6F urethral catheter on the urinary flow rate in healthy women without LUT symptoms. After a free flow rate, cystometry and pressure-flow studies were performed twice using a 6F urethral catheter. With a 6F urethral catheter in place, the women had a mean maximum flow rate of 16 mL/s on the first study and 15 mL/s on the second. A significant difference was demonstrated between the free and intubated maximum flow rates for both the first ($p = 0.0006$) and the second ($p = 0.0001$) study. No significant difference was detected between the two intubated maximum flow rates ($p = 0.262$) [Baseman 2002].

The impact of three different sized (4.5-, 6- and 7F) catheters on pressure-flow studies was studied in 60 women undergoing urodynamic evaluation for LUT symptoms, divided into two groups (A and B) of 30 women each. The patients underwent non-invasive free-flow uroflowmetry with determination of PVR. In group A the two consecutive pressure-flow studies were performed using a 4.5F catheter once and a 6F catheter once; in group B the two consecutive pressure-flow studies were performed using a 4.5F catheter once and a 7F catheter once. Free-flow rates were better with lesser residual. There was no significant difference in maximum flow rate, average flow rate and flow time between 4.5- and 6F catheter pressure-flow studies (A). However, there was a statistically significant difference between 4.5- and 7F pressure-flow studies (B) in those uroflowmetry parameters. Detrusor pressure at maximum flow ($p_{det}Q_{max}$) and maximum detrusor pressure ($p_{det\ max}$) in group A did not show statistically significant differences between 4.5- and 6F pressure-flow studies whereas in group B, $p_{det}Q_{max}$ and $p_{det\ max}$ were significantly different between 4.5- and 7F pressure-flow studies [Scaldazza 2005]. This more or less resembles the results in male patients, when a higher percentage of BOO shows that a 'mechanical' catheter effect is probably clinically relevant with catheters of 7F and larger [Zhao 2006; Trumbeckas 2006].

Conclusion (level 3):

- There is evidence that, in general, flow is reduced when voiding with a urodynamic catheter in the urethra and that this reduction is partially caused by the size of the catheter.

Conclusion (level 4):

- It is also the opinion of the committee that single catheters 6-8F incorporating both a filling channel

and a pressure-sensing channel should be used for intravesical pressure measurement during cystometry (i.e. double lumen catheters in the case of using fluid filled pressure lines).

Recommendations (grade B)

- The committee recommends that investigators interpret pressure-flow voiding parameters and the subsequent post void residual together with the free flow (not catheterised, representative) voiding parameters.
- The committee recommends the 'standard' use of, as thin as possible, 'one-catheter-systems' (dual lumen if fluid filled) for filling and pressure recording during urodynamic testing.

III. REPRODUCIBILITY, RELIABILITY AND NORMAL VALUES OF URETHRAL PRESSURE MEASUREMENTS

1. NORMATIVE AND COMPARATIVE DATA FOR MAXIMUM URETHRAL CLOSURE PRESSURE

Tables in the previous consultations show that the between-centre variability in the values reported, with mean MUCP is large and that the between-subject differences, reported in most studies show a wide range. However in spite of this variability, the mean MUCP was consistently lower in patients with signs and symptoms of SUI than in non-SUI women. There is nevertheless so much overlap that MUCP cannot be regarded useful for diagnosis of SUI [Weber 2001].

Eighty primiparous women with self-reported new SUI, 9-12 months postpartum, were compared with 80 primiparous continent controls and 80 nulliparous continent controls to identify impairments specific to SUI. MUCP (± sd) in primiparous incontinent women (62.9 ± 25.2 cm H20) was lower than in primiparous continent women (83.9±21.0) who were similar to nulliparous women (90.3 ± 25.0). This lower MUCP followed by ultrasound assessment of bladder neck mobility on coughing was the measure most associated with de novo SUI after first vaginal birth [DeLancey 2007].

Studies providing normative data for men are scant, but there are some data on the UPP in normal males, however without any relevance for UI (neither for BOO or storage dysfunction) [Yalla; Abrams 1977].

2. RELIABILITY OF URETHRAL PRESSURE VARIABLES

In clinical practice, use of a fluid-perfusion technique to measure resting urethral pressure profile parameters such as MUCP yields an sd that ranges from 3.3 to 8.1 cm H_2O. On average, the sd is approximately 5 cm H_2O (95% confidence limits ± 10 cm H_2O) or ± 5%. With a micro tip transducer technique the sd varies between 3.3 and 16.5 cm of water, which means that the 95% confidence limits may be as large as ± 33 cm H_2O. The coefficient of variation when using the micro tip transducer technique has been reported to be 17% (95% confidence limits ± 34%). In one study using fluid perfusion the coefficient of variation of MUCP varied from 3% to 11% (95 % confidence limits 6% - 23%) [Toguri 1980].

Another, comparative study between fluid-filled and micro tip pressure transducers observed that MUCP obtained from the fluid-filled catheter was significantly higher than that obtained from the microtip catheter. However, the authors also concluded that the use of the double-lumen fluid-filled catheter for the measurement of MUCP can be considered a reliable technique since its reproducibility is as good as that of the micro tip catheter [Wang 2002].

A significant difference between MUCP values recorded by micro transducer versus fibre optic catheter systems has also been observed. Significantly lower mean MUCP's were recorded by the fibre optic system than by the micro transducer system. No significant difference was however observed between these two systems in the measurement of VLPP [Culligan 2001].

As mentioned above, the performance of air-charged catheters in measuring MUCP has been shown to be comparable to micro transducers in the measurement of maximum urethral closures pressure in a non-randomised study [Pollak 2004]. However, there was a difference in functional urethral length which was attributed to the different diameters of the two catheters.

In 2008, Zehnder et al carried out a randomised comparison of these air-charged catheters with micro tip catheters in 64 women and found that the air-charged catheter was as least as reliable as the micro tip for measuring both MUCP and functional urethral length. However, they found that the air-charged catheter gave a higher reading of both parameters compared to the micro tip device [Zehnder 2008].

3. AGING

It is well established that in women the UPP changes with age. A recent study of 255 women, ages 20-77 years, without DO, overt neuropathy or pelvic or UI surgery, confirmed that the MUCP is negatively associated with age ($r = -0.5$, $p < 0.0001$) [Schick 2003].

4. OTHER PARAMETERS AFFECTING THE MEASUREMENT OF URETHRAL CLOSURE PRESSURE

The 2002 ICS standardisation reports, relating to urethral closure pressures, discusses that the value of MUCP is not only dependent on the type of catheter

used but also its orientation within the urethra, the degree of bladder fullness and the position of the patient [Lose 2002]. There is no new evidence, nor evidence regarding newer techniques, that the intrinsic (urethral pressure) measuring quality has improved to a clinically relevant level with regard to sensitivity, specificity and reliability.

Conclusions (level 2)

- Various studies have shown considerable test-retest variation of all urethral pressure measurements or parameters.
- Various studies have shown that normal and pathological values of urethral pressure parameters are largely overlapping.
- Various studies have shown that urethral pressure(s) (parameters) are affected by age.
- Studies have shown that urethral pressures depend on patient position, volume of fluid in the bladder and position of the patient.
- Studies have shown that urethral pressures depend on the pressure recording catheter used and its orientation within the urethra.

Recommendations (grade B)

- The committee recommends that investigators and clinicians recognize the poor sensitivity and specificity of urethral pressure measurements and their 'normal' test retest variation.
- The committee does not recommend urethral pressure measurement as the only urodynamic test in patients with urinary incontinence either to confirm or to refute stress urinary incontinence.
- The committee recommends that the clinical relevance of urethral pressure measurements, if performed, is judged in relation to other urodynamic tests (such as cystometry) and to the clinical examination.

IV. LEAK POINT PRESSURE

1. INTRODUCTION

The detrusor pressure or the intravesical pressure (p_{det} or p_{ves}) at which involuntary expulsion of urine from the urethral meatus is observed is the LPP. The rise in bladder pressure causing leakage may originate either from the detrusor (caused for example by the filling of a low-compliance bladder) or from an increase in the abdominal pressure. Thus there are two different leak point pressures – the DLPP (DDLPP) and the abdominal LPP. The abdominal pressure increase during the latter is produced voluntarily by coughing (CLPP) or by Valsalva (VLPP).

LPP is not consistently defined throughout the reports in literature and we have not found any standardisation (report) of the technique. Any comparison of findings between studies is hindered by this.

The elements of CLPP or VLPP which could be standardised include: 1) the basic definition of LPP (baseline value of pressure; route of measurement – urethral, vaginal or rectal), 2) whether Valsalva or cough is used to produce leakage, 3) the technique to confirm urine loss, 4) location of catheter, and shift in location on cough or strain, 5) calibre of catheter (if transurethral) 6) type of pressure sensor 7) the volume in bladder, 8) the rate of prior bladder filling and 9) patient position [Weber 2001].

The same elements are relevant for DLPP except pressure measurement has to be from the bladder but could be through a suprapubic catheter.

2. RELIABILITY OF LEAK POINT PRESSURE MEASUREMENTS

a) Diagnosis

In a study that recruited 168 patients it was seen that women who demonstrate urodynamic SUI at lower bladder volumes do not report greater bother from the UI than women who leak at higher volumes. The authors concluded that leakage severity 'quantified' by this urodynamic method, is not an adequate reflection of UI related quality of life (QoI) and or subjective UI severity [Lowenstein 2007]. Another study confirms these observations [Albo 2007].

A total of 200 women with SUI were clinically evaluated and underwent urodynamic study to determine the correlation between VLPP and the UPP. A progressive correlation of VLPP with MUCP was found when UPP was performed at 50 mL ($r = 0.305$, $p<0.0001$), at 250 mL ($r = 0.483$, $p<0.0001$) and at maximum bladder filling ($r = 0.561$, $p<0.0001$). The authors concluded that there is a significant correlation between MUCP and VLPP [Almeida 2005]. Another prospective study in 109 patients assessed the relationship between CLPP and VLPP with SUI (n=61; 56%), DO (n=21; 19%) or a combination of these (n=27 25%). More women with SUI leaked during CLPP than during the VLPP; fewer women with DO leaked during CLPP and more during the VLPP [Sinha 2006]. LPP's are reported to be dependent on patient position; being lower in the standing position as compared to supine position [Nguyen 2002]. Another study with the goal of determining the effect of position on UPP seems to have been troubled by 'poor test retest reproducibility' in the standing position [Dorflinger 2002].

Two studies have been performed, one with 369 patients, including some without UI, and another study with 65 female patients with UI stratified into groups with various levels of LPP, various grades of urethral (hyper-)mobility, and various grades of UI severity. Both studies were unable to find strong 'urodynamic' discriminators for the type or the severity of UI

and concluded that all values overlapped. Patients with SUI can be characterised by LPP and change in the urethral angle and or mobility, although these variables have never resulted in define discrete classes [Fleischmann 2003; Schick 2004].

The results of these newer studies confirm the earlier conclusion in an expert review: 'It is not apparent that either LPP measurement or UPP can accurately predict which patients will achieve the best outcome of surgical treatment for SUI. Other parameters assessed during urodynamic evaluation might provide prognostic information regarding the risk of voiding dysfunction postoperatively and the possibility of persistent urgency-related leakage following surgery, though not directly predict cure' [Lemack 2004].

b) Treatment

Can any value of LPP (Valsalva or cough) and/or UPP help in the selection of treatment for patients with SUI? This question has been addressed by various investigators.

In a retrospective cohort analysis of 3-month outcomes in 145 subjects (TOT = 85; tension-free vaginal tape (TVT) = 60) it was observed that relative risk of postoperative urodynamic SUI, 3 months after surgery, in patients with a preoperative MUCP of ≤ 42 cmH_2O, was 5.89 (1.02 to 33.90, 95% confidence interval) when TOT was compared with TVT tape [Lemack 2004].

The value of urethral hypermobility, MUCP in the diagnosis of SUI was evaluated in 369 women with clinical symptoms suggestive of SUI without symptoms of detrusor overactivity. The cohort was divided into 2 groups according to continence or incontinence status. Continent and incontinent patients differed with regards to MUCP and hypermobility (each $p<0.0001$). Incontinent patients had a greater probability of a higher grade of each factor. MUCP was significantly lower in the incontinent group ($p<0.001$) [Schick 2004].

A prospective study assessed the difference in measured urethral function before and after TVT procedure. Twenty-three (65.7%) of 35 consecutive women had a preoperative diagnosis of intrinsic sphincter deficiency (ISD) as defined by MUCP < 20 cm H_2O and/or VLPP <60 cm H_2O. Subjective (Impact of Incontinence score and Urodynamic Distress Inventory) and objective success rates were 91% and 83%, respectively. The mean change in MUCP was -1.3 cm H_2O (95% CI -5.9, 3.3), whereas the pressure transmission ratio increased 15.7% (95% CI 5.0%, 26.3%). The mean decrease in straining urethral angle was 16.3 degrees (95% CI -23.9 degrees, -8.7 degrees). Cured subjects, demonstrating hypermobility preoperatively, continued to do so postoperatively. The effectiveness of the TVT did not appear to depend on a clinically significant change in the straining urethral angle. [Mutone 2001]

A total of 221 women 29 to 80 years old (mean age 55.2) were included in a later study to evaluate the outcome of the TVT procedure for SUI with low VLPP. Mean follow-up was 10.5 months (range 6 to 52). Patients were divided into 61 with low (<60 cm H_2O) and 160 with higher (>60 cm H_2O) VLPP. The overall cure rate was significantly lower in patients with low versus higher VLPP (82.0% versus 93.1%, $p = 0.013$). In women with low VLPP, multivariate analysis indicated that urgency symptoms and low MUCP were independent factors for treatment failure (OR 15.12, 95% CI 1.90 to 120.61, $p = 0.010$ and OR 0.92, 95% CI 0.86 to 0.99, $p = 0.018$, respectively). [Paick 2004]

174 consecutive patients who underwent a distal polypropylene sling procedure for the treatment of SUI were prospectively evaluated and reported in a slightly earlier study. The group was divided by VLPP into group 1: 60 patients who did not leak on urodynamics, group 2: 27 patients with VLPP > 80 cm H_2O, group 3: 71 patients with VLPP 30 to 80 cm H_2O and group 4: 16 patients with VLPP < 30 cm H_2O. Mean follow-up was 14.7 months (range 12 to 30) and mean patient age was 62 years (range 32 to 88). The groups were well matched before surgery with respect to age, number of previous surgeries, and severity of SUI symptoms and UUI. The percentage of patients who were cured or improved was similar among groups. After surgery there was no statistical difference among patient mean self-reported symptoms of or bother from SUI or UUI. The distal urethral polypropylene sling provides similar symptom improvement in all patients regardless of preoperative VLPP. LPP is helpful in the diagnosis of SUI but appears to be of minimal benefit in predicting the outcome of the distal urethral polypropylene sling procedure. [Rodriguez 2004]

A later study reported that neither MUCP nor LPP were good predictors of post-operative SUI but, because this was not the primary outcome measure of this study, there may not be adequate power to make this a definitive conclusion. [Paick 2007]

UDS which included CLPP and pressure flow studies that were performed twice at two visits 2 weeks apart were reported in a subsequent study to determine reproducibility in various diagnosis groups. Thirty-one women completed both visits, of those 14 had SUI in both sets of UDS, 11 had mixed UI result at UDS on both visits, six had SUI on one visit and mixed UI result in the other. The UDS variables of MCC and cough LPP have the most repeatability. Analysis in women with SUI alone compared to USI together with DO showed that the repeatability for pressure flow parameters and CLPP was better in women without DO, of which the CLPP was significantly different ($p = 0.036$). [Rahmanou 2008]

c) Within-patient variability

Sixty consecutive women with 'genuine' SUI underwent duplicate VLPP determinations by use of 8F

and 3F vesical and 8F vaginal catheters. Subjects also underwent a standard resting UPP, CLPP determinations, and pressure-flow micturition studies. Leakage was demonstrated on both Valsalva maneuvers in approximately 80% of subjects with both catheters and a high correlation between the test-retest VLPP within both catheters. The inter-catheter correlation between the 8F and 3F VLPP was significant but much weaker than the intra-catheter correlations; 8F VLPP's were significantly higher than 3F VLPP, although there were individual exceptions to this observation. The authors concluded in 1995 that VLPP technique must be precisely described, standardized, and validated before a technique can be advocated for clinical use. A later study to determine the quantitative and qualitative effects of patient position on coughing and VLPP in women with USI was done in 2002. Thirty-seven patients with genuine SUI and 4 with mixed incontinence underwent standardized UDS. LPP were performed using 8 Fr microtip catheters placed in the bladder and vagina at a bladder volume of 250 ml in the supine, semi recumbent and standing positions. UPP was performed in the semi recumbent position at similar bladder volume. The mean (+/- standard deviation) VLPP in the supine, semi recumbent and standing positions were 82 +/- 23, 73 +/- 24 and 63 +/- 22 cmH_2O, respectively ($p<0.001$). The mean (+/- standard deviation) CLPP also decreased as the patients were moved from the supine (98 +/- 29 cmH_2O) to the semi recumbent (88 +/- 24 cmH_2O) and standing positions (77 +/- 24 cmH_2O) ($p<0.001$). The correlation between LPP and MUCP was statistically significant and was dependent upon patient position and the provocative maneuver used. [Nguyen 2002]

The committee has found no reports on inter-observer variability.

Conclusions (level 2/3)

- Different definitions and techniques to determine (urine) leak point pressure exist.
- Various studies have demonstrated a weak association between abdominal leak point pressures and the patient experience of, or measured severity of bother, or amount of incontinence. It can be born in mind, in this regard, that one millilitre of fluid is already 20 drops and a 10cm diameter wet spot on a cotton cloth.
- Studies have shown that the 'isolated' parameters from abdominal leak point pressure measurements are not very helpful as predictors of success from surgery with either tension free vaginal tape or transobturator tape in patients with stress urinary incontinence.
- Studies have shown that different techniques and patient positions influence the results of leak point pressures determination.

Recommendations (grade B/C)

- The committee does not recommend abdominal leak point pressure measurement as a single urodynamic test in patients with urinary incontinence either to reject the diagnosis of stress urinary incontinence, or to select treatment.
- The committee recommends that the result of abdominal leak point pressure measurements, when performed on patients with urinary incontinence, should be judged in relation to other urodynamic tests such as cystometry and to the clinical examination.
- The committee considers detrusor leak point pressure in patients with neurogenic lower urinary tract dysfunction a relevant parameter. This is discussed in section III (neurogenic lower urinary tract dysfunction) and in section IV (patient evaluation: children).

V. DIAGNOSTIC PERFORMANCE OF FILLING CYSTOMETRY AND AMBULATORY MONITORING

1. SENSITIVITY AND SPECIFICITY OF FILLING CYSTROMETRY IN OVERACTIVE BLADDER SYNDROME

Earlier consultations [Homma 2002; Rosier 2010; Rosier 2010; Rosier 2010] have summarized scientific evidence for positive sensitivity, specificity and predictive value of symptoms for urodynamic SUI. Specificity, sensitivity and predictive value of symptoms were found to be less for DOI and also the association of 'mixed symptoms' of UI with UDS results was very low. We have found some additional studies and summarize the newest results.

a) Detrusor overactivity incontinence

The association of the results from UDS and symptoms assessment was summarized to be around 70% in the previous consultations; three more or less relevant studies are reported here predominantly reporting on patients with mixed symptoms of UI. It was noted in one study that some women with mixed symptoms of SUI and OAB reported worsening of their UI in a prospective trial, of duloxetine, used to improve urethral storage function. In this study, an assessment was made, as to whether pre-treatment pressure flow studies predicted which women with USI, in combination with DO(I) experienced increased leakage after treatment with duloxetine. All women included had mixed symptoms of UI with moderate or severe symptoms (bother) of SUI. Pressure flow studies of women who recorded a worsening of their UI were compared to those women who recorded no change or an improvement of their UI. The maximum or average flow rate, the bladder capacity, the detrusor pressure at maximum flow and volume voided showed no difference when the two

groups were compared. The pre-treatment voiding time was however longer in women who got worse following treatment with duloxetine. [Vella 2010]

The authors of another monocenter study in retrospection concluded that (semi-recumbent) UDS diagnoses of DO, and USI with DO are associated with significantly worse UI related bother and health related quality of life when compared to those with USI without OAB (or DO). [Haessler 2009]

The purpose of another study was to assess clinically relevant relationships between urinary diary and quality of life as well as to evaluate the reproducibility of validated questionnaires and urinary diaries in women with SUI as well as OAB symptoms of UI; a combination that is frequently, but imprecisely defined, named mixed UI. Forty-seven women with mixed symptoms of UI completed 7-day diaries, the Urinary Distress Inventory (UDI-6), Incontinence Impact Questionnaire, and the Medical, Epidemiological, and Social Aspects of Aging -questionnaire 2 weeks apart. The number of UU(I) episodes predicted UI severity on UDI-6 (R (2) = .38, p< .03). Except for the number of SUI episodes, diary variables and questionnaire responses were reproducible (range from Spearman's rho = .7 to rho = .96, p< .001). The 6 questions of the UDI-6 were concluded to adequately represent UI severity.

b) Detrusor overactivity alone

The sensitivity, specificity and predictive value of symptoms for the diagnosis of DO, was given in a review of papers quoted in the third ICI [Colli 2003] All authors of the various manuscripts and the reviewers have concluded, more or less strongly that the correlation between symptoms and DO is modest; underlining the necessity of urodynamic testing to obtain an objective diagnosis. Van Brummen et al [Brummen 2004] examined the sensitivity of DO, observed during conventional UDS, for UUI. They examined 95 women, with OAB, symptomatic SUI, and/or POP. Symptoms were assessed by a bladder diary and conventional filling cystometry was performed (sitting, fill rate 60 mL/min). Urinary frequency, urgency and UUI had similar associations with the cystometric observation of DO. Among patients with only one of these symptoms, DO was however not observed in 77-81%. In another study 171 women were recruited. The aim of this study was to develop a scoring system to discriminate between the symptoms of SUI and OAB. Physicians completed a specially developed questionnaire for all women complaining of LUTS. Women then underwent UDS. A scoring system based on the likelihood of each symptom for DO was developed using odds ratios and 95% confidence intervals (CI). This scoring system was subsequently used to discriminate those women with OAB from those with SUI. This scoring system had a sensitivity of 79%, a specificity of 78% and a positive predictive value of 73% to identify DO. Investigators suggested that the scoring system could be applicable in primary care to help discriminate between SUI (USI) and OAB (DO). [Vella 2008]

In a similar study, the accuracy of a UI questionnaire in the diagnosis of various types of UI was classified according to the results of multichannel UDS. Using a UI questionnaire consisting of 12 urinary symptoms questions, 129 women with symptoms of UI were interviewed. Of the 12 questions, only three questions (two SUI symptoms and one OAB symptom) were significantly associated with the diagnoses of (urodynamic) USI or DO. The sensitivity and specificity of the questions was relatively low leading to the author's conclusion that symptoms of UI were not sufficient to predict types of UI, and the suggestion that UDS is essential in the diagnosis and management of female UI. [Roongruangsilp 2005]

In a study to determine the prevalence and associations of 'sensory urgency' in comparison with DO 592 women, attending for an initial urogynaecological /urodynamic assessment, took part. The group was separated into those having 'sensory urgency'; OAB symptoms, without urodynamic DO, or those with DO. The only difference in the clinical profile between the groups was increased prevalence of the symptom of UUI. The authors concluded that sensory urgency and DO appear to be part of the same clinical spectrum of bladder dysfunction. [Haylen 2007]

To determine and compare the urodynamic characteristics in patients with OAB and patients with combined symptoms of OAB plus SUI (OAB+SUI), 120 patients (60 each in OAB and OAB+SUI groups) underwent detailed history, physical examination, complete UDS and 20-minute pad test. FDV, SDV, urgency, and the percentage of urodynamic SUI were greater in the OAB+SUI group; and functional urethral length, maximal urethral pressure and MUCP were significantly lower in the OAB-SUI group, than those in the OAB group (p<0.03). [Lin,L.Y. 2004]

c) Overactive bladder syndrome and detrusor overactivity

Many studies have been done to compare, more or less systematically retrieved, symptoms with the results of UDS. Apart from the fact that symptoms assessment varies between studies, (and UDS-techniques vary), the committee has stated in the introduction that it is highly unlikely that one subjective symptom (or a few symptoms) can be identical to the result of the UDS, which gives a broader view on the individual's LUT function. Nevertheless we report the recent studies in this regard.

Digesu et al [Digesu 2003] studied whether UDS is useful in the management **(Table1)** of women with symptoms of an overactive bladder (OAB). Women with LUTS and or UI were fully evaluated, with history,

urinary symptoms questionnaire, frequency-volume chart, vaginal examination, and UDS. Women with symptoms consistent with OAB (urinary frequency, urgency, and/or urge incontinence) were selected. Women with neurological disorders were excluded. A total of 4,500 women 22-73 years of age were studied. Only 843 women (18.7%) could be classified as having an OAB. Of these, 457 women (54.2%) had DO, whereas 386 women (45.8%) had no DO. Sixty-eight (8.1%) of the women studied had PVR greater than 100 mL. Of the 4,500 women studied, 1,641 (36.5%) had DO on UDS. Only 27.5% of these women (457 of 1,641) had OAB symptoms. False positive and false negative symptoms of 'OAB' were frequently noted and therefore the study concluded that OAB symptomatic diagnosis did not correlate with DO and that UDS remains mandatory for an exact diagnosis.

Table 1. Overactive bladder symptoms and detrusor overactivity, from [Digesu 2003]

	Detrusor overactivity	No detrusor overactivity	Totals
OAB symptoms	457	386	843
No OAB symptoms	1184	2473	3657
Totals	1641	2859	4500

Sekido et al [Sekido 2006] retrospectively reviewed the UDS of 50 adult patients (selected from a series of 137, referred with UI) with urinary urgency (12 males and 38 females) and looked into the correlation between bladder storage function (FSF, MCC, compliance and DO) versus OAB. 75% of male patients with OAB symptoms had DO in supine position and only 36.8% female patients.

Hyman et al [Hyman 2001] examined 160 men, mean age 61 + 15 years, without neuropathy but with symptoms 'suggestive of DO' . They observed DO in 68; a sensitivity of 43% for OAB symptoms. When there was UUI, then DO was seen more often than with symptoms of frequency, urgency, nocturia alone, suggesting a higher sensitivity for UUI.

In a retrospective study with 1,626 women with mixed (or 'combined') symptoms of UI were divided into stress predominant mixed urinary incontinence (MUI); urge predominant MUI; or equal severity of stress and urge MUI on the basis of the symptom scored most severe on the King's Health Questionnaire. [Digesu 2008] The frequency of different UDS diagnoses for the all women with MUI and in each of the above groups was calculated. Overall 3.338 women were studied. Of these 49% (1.626/3.338) reported MUI symptoms and were included. In this group 29% (464/1.626) had stress predominant MUI, 15% (248/1,626) had urge predominant MUI and 56% (912/1.626) had equal severity of urge and stress MUI. On UDI 42% (665/1,626) had pure USI, 25% (414/1.626) had pure DO, 18% (299/1.626) had both DO and USI and 15% (248/1.626) had UDS without abnormal filling phase. In those with stress predominant MUI, 82% had USI; in those with urge predominant MUI, 64% had DO. The UDS diagnoses were different for the different balance of symptoms (Chi2; $p< 0.05$). In women with equal severity of UUI and SUI, 46% had DO while 54% had UDS. The relative severity of MUI symptoms from the Questionnaire significantly distinguished between different UDS diagnoses in this evaluation that concluded that women with urge predominant MUI are more likely to have DO while those with stress predominant MUI are more likely to have USI.

In another study, 1457 adult males and females were retrospectively selected, based on OAB syndrome symptoms, to determine how well the symptoms of OAB syndrome correlated with urodynamic DO using ICS definitions. A better correlation in results between OAB symptoms and the urodynamic diagnosis of DO was observed in men than in women. Of men 69% and 44% of women with urgency (OAB dry) had DO, while 90% of men and 58% of women with urgency and UUI (or OAB wet) had DO. SUI seems to have accounted for the decreased rates in women since 87% of women with UUI also had the symptom of SUI. The ICS definition does not specify what constitutes abnormal voiding frequency. Analysis of results showed that increasing voiding frequency did not have any effect on increasing the accuracy of diagnosis of DO except in women with 10 or more daytime micturition episodes. The authors concluded that the bladder is a better and more reliable witness in men than in women. [Hashim 2006]

The association between urinary symptoms and the UDS diagnoses of DO and USI was calculated to describe the relationship between symptoms reported in a self-completed postal questionnaire, and urinary disorders based on UDS. The study population was selected from women aged 40 years or over living in the community, who responded to a postal questionnaire. Four hundred eighty-eight women completed UDS; 29.1% (142/488) were found to have DO (with and without leakage), 33.6% (164/488) USI, 20.7% (101/488) mixed diagnosis of incontinence, and 16.6% (81/488) no abnormality on filling cystometry. SUI and UUI were included in the risk model for USI. SUI reported monthly or more, was associated with more frequent diagnosis of USI, and UUI reported weekly or more, with less frequent diagnosis of USI (sensitivity: 76.9%; specificity: 56.3%; positive predictive value: 67.8%). Strong or overwhelming urgency, UI monthly or more, and nocturia once a night or more, were all significantly associated with an increased diagnosis of DO. Reporting of SUI monthly or more reduced the risk of DO (sensitivity 63.1%; specificity 65.1%; positive predictive value 63.1%). The conclusion was that a postal urinary symptoms questionnaire

was associated with UDS diagnosis with moderate accuracy and applicable. [Matharu 2005]

One hundred and fourteen women attending a tertiary urogynaecology clinic were included in a randomised crossover study to either an initial interview-assisted questionnaire in the clinic, with a follow up postal questionnaire, or an initial pre-outpatient questionnaire followed by an interview-assisted questionnaire at the clinic visit. Question responses were compared with urodynamic diagnoses. With the interview method, only severity of UI was significantly associated with DO ($p = 0.012$). With self-completion, severity of nocturia ($p< 0.05$), urgency ($p = 0.003$), UUI ($p = 0.003$), leakage without warning ($p = 0.035$) and incomplete voiding ($p = 0.01$) were significantly associated with DO. On interview, the symptom of SUI ($p = 0.002$) and use of pads ($p = 0.011$) were significantly associated with a diagnosis of USI. Severity of SUI ($p< 0.001$), frequency of leakage ($p = 0.004$), use of protection ($p< 0.018$), nocturnal incontinence ($p = 0.002$) and quantity of leakage ($p< 0.05$) on self-completion were strongly associated with diagnosed USI. There was no association between the symptoms of urgency or UUI, and USI. Concluded in this study was that no symptom had a high enough specificity and sensitivity to replace UDS in this postal questionnaire responses and had a better relationship with DO, for USI and for DO, than interview-assisted questionnaire responses. [Khan 2004]

The pattern of filling sensations was evaluated during standard UDS bladder filling in 75 patients who complained of UU(I) and showed DO, to evaluate whether a compelling desire to void is always perceived suddenly, or whether it can result from the gradual build-up of bladder-filling sensations. A compelling desire to void occurred suddenly, without a preceding sensation in 13% of the patients, at lower intravesical volumes, whereas 66% reported at least two normal preceding filling sensations before a compelling desire to void. The bladder volume at which the FSF was reported was not different regardless of whether it was described as a FSF , a FDV or a compelling desire to void ($p = 0.42$). The warning volumes were not different between patients with one or no filling sensation landmarks ($p = 0.7$), but they were significantly smaller than in patients with two or three filling sensations ($P = 0.85$). Compelling desire to void can occur suddenly if normal filling sensation is disturbed, but also gradually if the usual filling sensations are reported. In cases of disturbed filling sensation, the volume at compelling desire to void and the warning volume are significantly lower. [Wachter 2008]

To evaluate the reliability of spontaneously reported bladder sensations during real and faked cystometry in patients with non-neurogenic LUTD. In another study by the same researchers, fifty-nine patients with non-neurogenic LUTD were submitted to a real and a faked (no water infused) filling cystometry and were asked to describe all bladder-related sensations during the investigations. During the genuine cystometry, the expected pattern of filling sensations was reported by 88%. During the faked cystometry, not one of the patients reported the normal pattern of filling sensations. However, a minority of patients reported some sensation of bladder filling without actual bladder filling from the UDS equipment. The investigators concluded that patients with a non-neurogenic LUTD can reliably report bladder filling sensations during UDS. [Wachter 2008]

Five hundred and ninety-two women attending for an initial urogynaecological/urodynamic assessment were enrolled in a prospective study. Many signs symptoms and observations were reported but the reported prevalence of sensory urgency (defined as increased perceived bladder sensation during filling, a low FDV and low MCC in the absence of recorded urinary tract infection or DO) was 13%. The only differences in the clinical and UDS profiles of it and DO were reported as a significantly increased prevalence of the symptom of UUI and (by definition) the detrusor contractions during filling cystometry in women with DO. The authors concluded that ‘sensory urgency’ and DO appeared to be part one spectrum of LUT dysfunction. [Haylen 2007]

Fifty-eight patients with USI, 29 with DO, and 22 with both USI and DO were analysed in another monocenter cohort study. From 3-day hand-written and computer-analysed bladder diaries, average and maximum VV were calculated, and also voiding frequency and 24 hr urine production, as well as number, severity and type (whether accompanied by activity or urge) of UI -episodes, to compare frequency-volume and UI episode patterns in patients with USI and DO. Compared to the USI patients, the DO patients tended to have higher voiding frequency, lower VV, more urgency-related than activity-related leaks, smaller volume and equally frequent leaks and higher severity -scores for UI symptoms. The age- and volume-adjusted percentiles better separated the USI and DO groups’ frequency and volume measurements than did the raw measurements. Almost 60% of the USI patients had low VV measurements, high voiding frequency, and 40% had leaks with urgency sensations. A subgroup of 29 USI patients with ‘low’ (average volume <30th reference population percentile) VV measurements had high incidences of urgency and UUI. Reference population percentiles better separate the frequency /volume patterns of USI and DO than do the raw measurements. The investigators observed a substantial subgroup of patients with USI that had an OAB-like clinical picture, again suggesting that symptom assessment is important but not diagnostic with regard to the underlying LUTD. [Parsons 2007]

The UDS of women with DOI and USI, before

undergoing tension-free vaginal tape (TVT) surgery were retrospectively reviewed to determine if specific pre-operative urodynamic parameters could predict DO following TVT in patients with urodynamic mixed incontinence. Patients underwent clinical evaluation pre-operatively and those with persistent SUI after conservative treatments underwent TVT. Patients were re-assessed after at least 6 months post-operatively. Fifty-one women were reviewed. Forty-six of the 51 attended follow-up and 35/51 agreed to conventional urodynamic studies. Seventeen of the 35 reported OAB symptoms, and 18/35 were asymptomatic. Nineteen of the 35 women had DO and 16/35 had normal UDS. The median pre-operative opening detrusor pressure was higher in women with overactive bladder symptoms post-operatively. The median pre-operative opening detrusor pressure in women with DO post-operatively was 33.0 cmH_2O and the median pre-operative opening detrusor pressure in those with normal UDS post-operatively was 16 cmH_2O (15.0-23.0 cmH_2O $p< 0.05$ Mann-Whitney U-test). The investigators have concluded, in retrospect, that opening detrusor pressure before treatment is related to post-operative DO after TVT, in their series, but that higher numbers of patients are required to demonstrate the real predictive value of opening detrusor pressure. [Panayi 2009]

Conclusions (level 2)

- Many studies have shown the weak correlation between symptoms and the result of urodynamic investigation, especially filling cystometry, in patients with urinary incontinence.
- The committee concludes that the sensitivity and the specificity of the symptoms, when systematically assessed and voiding diary is included, is at best and in the 'most typical patients', around 60-70%, in comparison with the result of the objective results of urodynamic testing.
- The correlation of the symptom 'stress urinary incontinence' (expressed, or questioned) with the result of urodynamic investigation is somewhat better than the correlation of urgency or urgency urinary incontinence (expressed, or questioned) with urodynamic investigation.
- The committee concludes that especially when frequent voiding, urgency and/or urgency incontinence is part of the symptom complex of patients with incontinence, urodynamic investigation is of value to obtain an objective diagnosis, prior to invasive therapy.
- Taking into account the variation between various institutes and the test-retest variation, the committee considers it relevant that investigators and clinicians judge also how adequate the results of the performed tests represent the individual patients' symptoms.

Recommendations (grade B)

- The committee recommends urodynamic testing in patients with incontinence when an objective diagnosis is warranted. This is commonly the case when symptoms do not exclusively direct to stress incontinence, or when (for all types of incontinence) conservative measures have not been successful, or when relevant co morbidity exists or relevant previous surgery has been performed.
- The committee recommends interpretation of the results of the complete urodynamic testing in relation with the symptoms, signs, and the clinical (or other) examinations and with the voiding diary in all patients.

d) Distinguishing or defining characteristics of detrusor overactivity

Several groups have attempted to find characteristics of DO that may distinguish DO incontinence with different aetiologies, or DO incontinence of different severity.

One group [Flisser 2003; Romanzi 2001] examined 132 patients with OAB symptoms (with and without neurological disease) by videourodynamics. Based on the characteristics of their filling phase, patients were divided into 4 categories: type 1- no evidence of DO on videourodynamics; type 2 – DO present, and patient aware and able to abort them; type 3 – DO(I) present, patient aware and able to contract the sphincter (judged from the videourodynamics) but not to abort contractions; and type 4 – DO(I) present and patient unaware but unable to contract the sphincter or abort contractions. There was no significant relationship between the category and severity of symptoms as judged by voiding frequency, functional bladder capacity, or pad test. The authors concluded that the characteristics of the DO were not distinct enough to aid in differential diagnosis, but that the ability to abort DO and stop incontinent flow might have prognostic implications, especially for the response to behaviour modification, biofeedback training, and pelvic floor exercises.

Cucchi et al [Cucchi 2007] looked into detrusor contraction strength, detrusor contraction velocity and contraction sustainability. In this retrospective review, the authors separated male patients (without relevant neurological abnormalities) into three groups; Group 1 had DO, with urgency and UUI. Group 2 was similar to group 1 but did not have urgency before DO and Group 3 consists of 'normal' men. They found that detrusor contraction velocity was increased (or higher) in the group with urgency versus no urgency or normal, implying that this may be an underlying mechanism for urgency.

Defreitas and co-workers [Defreitas 2003] examined three groups of patients: group 1, men with LUTS and no known neurological condition for DO (n = 22); group 2, men with Parkinson's disease and

LUTS (n = 39); and group 3, women with Parkinson's disease and LUTS (n = 18). Patients with Parkinson's disease had a significantly lower median volume at first detrusor contraction than those with non-neurogenic DO. The percentage of group-1 patients with UUI was significantly lower than that found in the other two groups (9% versus 54% and 56%, p<0.001 and 0.002, respectively). No statistically significant correlation between the duration or severity of Parkinson's disease and urodynamic parameters was found. The distinction between Parkinson's disease proper and multiple system atrophy, which appears to be important with regard to bladder dysfunction,[Fowler 2001]was not made in this study.

In the study cited above,[Hyman 2001] 160 older men without neuropathy, but with symptoms 'suggestive of DO', were examined. DO was seen more often when there was UUI, than with symptoms of frequency, urgency and nocturia alone. The bladder volume at which DO was observed tended to be lower in those with UUI, frequency and urgency than in those without UUI (p = 0.07). The prevalence of DO was similar in men with and without BOO.

Ockrim at al [Ockrim 2005] compared the variability of DO in men with LUTS to that in men with SCI by sequentially repeating urodynamic studies three times. They observed a significant decrease in the number and amplitude of DO contractions in the 60 patients with non-neurogenic LUTS, whilst in the 35 SCI patients, the urodynamic variables remained the same over the subsequent studies.

The urodynamic characteristics of DO in women with multiple sclerosis (MS) (n = 54) were compared with the detrusor pressure 'pattern' found in women with LUTS and idiopathic DO (n = 42) in a retrospective study. Among other parameters, the amplitude of the first contraction, maximum detrusor contraction, and threshold volume for the first contraction were evaluated. The amplitude of the first contraction was statistically greater in the patients with MS and DO compared with patients with IDO (28.3 versus 20.5 cm H_2O, p = 0.003), as was the maximum detrusor contraction (46.4 versus 30.8 cm H_2O, p = 0.002). The threshold volume for DO was greater among patients with neurogenic DO (186.8 versus 150.5 mL, p = 0.037), which was likely to be secondary to the elevated PVR volume noted among patients with MS (p = 0.049). The authors concluded that additional investigation is required to determine whether these differences are due to neurogenic influences directly on the detrusor muscle through aberrant innervation or by other mechanisms. [Lemack 2006]

Miller et al [Miller 2002] suggested that functional bladder capacity was smaller in those with more severe incontinence as judged from the voiding diary in a study to evaluate quantification of DO.

Conclusions (level 2)

- Studies have not been able to show relevant differences in patterns or characteristics of detrusor overactivity whether the cause of overactivity is neurogenic or idiopathic.
- Various studies have not been unable to reliably quantify the severity of detrusor overactivity, in a clinically or scientifically applicable way.

Recommendation (grade C)

- The committee recommends that neither the cause (neurogenic or idiopathic) nor the severity of detrusor overactivity is diagnosed on the basis of parameters from urodynamic investigation (cystometry).

Topics for research

- The committee recommends further evaluation and development of objective parameters for assessing the treatment outcome of detrusor overactivity.

e) Provocative manoeuvres

Some studies have shown that 50% of DO occurs during supine cystometry without provocation and that the remaining 50% is revealed by posture change, standing cystometry, on provocation by cough, or on catheter removal. [Turner Warwick 1979; Arnold 1974]

Awad and McGinis [Awad 1983] observed DO in 30% of female patients in the supine position versus 61% in the standing position. A systematic review of the literature by Al-Hayek et al [Al-Hayek 2008] concluded that supine cystometry failed to detect a significant percentage of patients with DO.

Webster et al [Webster 1984] concluded that in 52% of women with DO, provocation by fast filling in the standing position, with exercises such as coughing, was required to reveal it. Investigative technique, in particular the inflation of a balloon in the proximal urethra [Colstrup 1982] or the instructions given to the patient [Blaivas 2001], is also said to affect the frequency of the observation of DO.

Choe et al [Choe 1999] systematically examined which manoeuvres were most provocative of DO. In 134 women with symptomatic UUI they performed gas (CO2) cystometry. Six provocative manoeuvres were performed consecutively to evoke DO, including lying supine, rising to a seated position, walking toward the bathroom, hand washing, coughing and sitting on the toilet with instructions not to void. By filling to maximum capacity and performing these manoeuvres in 2 different orders, they were able to demonstrate DO in 76/134 subjects (67%). Sitting on a toilet with a full bladder and with the instruction not to void was the most provocative manoeuvre, responsible for revealing DO in 52 of the 76 (68%). Hand washing was a distant second, revealing overactivity in 15 of the 76 (20%). Other manoeuvres revealed very little DO.

An extreme provocative manoeuvre is the bladder cooling (ice water) test advocated by Geirsson et al. [Geirsson 1993]; The empty bladder is filled with water at a temperature of less than 10°C. This stimulates C-fibres that normally carry afferents from receptors sensitive to temperature and pain. In infants, stimulation of these receptors can initiate a detrusor contraction, but this response is normally lost at ages over 5 years. The bladder cooling test stimulated detrusor contraction (neurogenic DO) in 91-97% of patients with traumatic upper motor neuron lesion, but in only 47% of those with presumed idiopathic DO. Detrusor contraction was not observed in any patient with a lower motor neuron lesion or 'pure' (urodynamic) SUI. Thus the conclusion was that the bladder cooling test is highly sensitive for neurogenic DO, and highly specific for DO in general.

The bladder cooling reflex, elicited by the ice water test (IWT) was performed in patients with painful bladder syndrome (PBS, n = 17), idiopathic DO (IDO, n = 22), neurogenic DO, n = 4) and SUI (as controls, n = 21). The IWT was performed by intravesical instillation of cold saline (0 - 4 degrees C). A positive IWT was observed in IDO (27.3%) and neurogenic DO (100%) patients, but was negative in all PBS and all control patients. Thirteen (76.5%) PBS patients reported pain during the IWT, with significantly higher pain scores during ice water instillation compared to the baseline (p = 0.0002), or equivalent amount of bladder filling (100 mL) with saline at room temperature (p = 0.015). [Mukerji 2006]

A total of 114 patients over50 years, with an International Prostate Symptom Score (IPSS) >8 and QoL >2, were evaluated by UDS and IWT to investigate whether DO and/or the response to the IWT were related to night time urinary frequency. The DO-positive IWT responders had a significantly higher BOO-index than did the DO-positive IWT non-responders and the DO-negative IWT non-responders. The DO-positive IWT responders had significantly more frequent nocturia and smaller night time maximal and lesser VV than did the DO-negative IWT non-responders without any difference in the nocturnal VV. The patients with nocturia, two or more times, had a significantly larger nocturnal VV and smaller night time minimal VV than the patients with nocturia less than two times. The incidence of DO-positive IWT responders was significantly greater among the patients with nocturia three or more times than that among those with nocturia less than three times. The authors concluded that high grade BOO leads to development of C-fibre reflex activity. [Hirayama 2005]

Conclusions (level 2)

- A systematic review concludes that more detrusor overactivity is seen when the patient is in the sitting position during cystometry, when compared to the supine position.
- There is some evidence that moving to a toilet, and also hand washing, is strongly provocative of detrusor overactivity.
- Evidence suggests that ice water cystometry can be applied to elicit detrusor overactivity in patients with NLUTD and that a detrusor contraction during filling with ice water can be interpreted as a sign of pathologic (existing only in patients with relevant neurology) C-fibre reflex activity. It has however also been shown in this regard that false-negative tests do occur.

Recommendations (grade B)

- The committee recommends that the results of provocative cystometry are interpreted in the light of the patients' symptoms and to bear in mind whether the results obtained are representative.
- The committee recommends the performance of urodynamic investigation in the sitting position whenever possible, because of the better sensitivity for filling phase abnormalities, but also because of the better possibility of representative voiding and better patient comfort.
- The committee recommends that the position of the patient during filling cystometry is always taken into account because it can influence the demonstration of detrusor overactivity. Repeating the cystometry in a different position can be helpful when it is deemed clinically necessary.

2. AMBULATORY URODYNAMICS: SENSITIVITY AND SPECIFICITY

Ambulatory urodynamics is performed in an effort to capture more realistic or more physiological observations, especially of UI episodes. Thus, similar to provocative manoeuvres, it is an attempt to increase sensitivity by providing a longer time for DO to manifest itself. Strict protocols for the test (e.g. duration) and standards for systematic analysis are lacking. The authors of a review article [Cassidenti 1999] concluded that ambulatory monitoring detects UI better than conventional cystometry.

Radley et al. [Radley 2001] found that ambulatory monitoring revealed DO in 70/106 women with symptoms suggestive of DO (twice as many as conventional cystometry with provocation by hand washing), and that it detected DOI in 40 of the 70. The observation of DOI was correlated with symptom severity, but it was not clear how many women complaining of UUI showed DOI. Therefore the sensitivity observed in this study has remained unknown. The specificity of this method is at present not evaluated, and it is not very likely that therapy can be improved on the basis of (additional) ambulatory testing.

Conclusions (level 3)

- Studies have shown that ambulatory monitoring

is more sensitive to detrusor overactivity however the predictive value towards the selection (and outcome) of optimal treatment is still unknown.

Recommendation (grade A)

- The committee does not recommend ambulatory monitoring in the routine diagnosis of patients with urinary incontinence.

3. THE ADJUNCT USE OF IMAGING AND ELECTROMYOGRAPHY

Videourodynamics is an investigation where cystometry is carried out simultaneously with imaging (usually x-rays) of the lower urinary tract. This can be useful in the management of some patients; particularly children and patients with NLUTD and is briefly discussed in the relevant chapters. There is a fuller discussion of videourodynamics in the chapter on Imaging, Neurophysiology and other tests.

Another adjunct to cystometry is the simultaneous measurement of striated muscle activity using EMG. Most frequently this is used in the investigation of patients with NLUTD and often surface electrodes are placed on the perineum to detect (all - unspecific) striated muscle activity from pelvic floor muscles. Amongst other uses, failure of the urethra/pelvic floor to relax and pelvic floor voiding dysfunctions can theoretically be detected during voiding using this technique. Unfortunately, it is technically difficult to ensure a good quality EMG signal from the precise and relevant muscle(s) during this procedure and there have been no publications in at least the last 20 years investigating the benefits of combining EMG with cystometry.

VI. THERAPEUTIC PERFORMANCE OF FILLING CYTOMETRY AND AMBULATORY MONITORING

1. PREDICTION OF TREATMENT RESPONSE

a) Filling cystometry

The authors of a review of papers from 1980-2000 [Colli 2003] concluded that it is not possible to correlate the results of urodynamic tests with the effects of non-invasive therapy. Consistent with the table, Malone-Lee et al [Malone 2003] reported on 356 female patients with OAB symptoms. On urodynamics, 266 showed DO. There was no significant difference (between those with and without DO) in treatment outcome after 6-8 weeks of oxybutynin and bladder retraining.

On the other hand, previous reviews have concluded that women with UI and DO respond less well to surgery for SUI than those without DO. [Homma] Friis et al [Friis 1982] conducted a blinded prospective study to evaluate the usefulness of urodynamic examination compared to clinical diagnosis. The study showed that when urodynamic examination was added to the preoperative planning of treatment for female UI a more beneficial cure rate was found if the patient was treated in accordance with the urodynamic findings. However, the patient material is small and the power of the study is weak.

A retrospective study has shown that a careful minimal evaluation may be adequate to identify ISD, predict postoperative voiding difficulties and maximize surgical outcomes. [Thompson 2000] A Cochrane review concluded that current evidence is insufficient to demonstrate a clear improvement in clinical outcomes as a result of performing urodynamic studies. [Glazener 2002]

In men, fewer studies have been done. Golomb et al [Golomb 1999] examined whether preoperative urodynamic examination allows us to predict the risk of UI after radical prostatectomy. A small group of 20 patients underwent radical retropubic prostatectomy for prostate cancer. Urodynamics showed DO in 12/20 pre-operatively. 5 of these 12 suffered from UUI post-operatively. The positive predictive value of preoperative DO for post-operative UI was thus only 42%.

In a literature overview of the diagnostic and therapeutic value of urodynamic investigations in patients undergoing POP surgery, the reviewers found a large heterogeneity of results. 'Occult' SUI showed large variation between studies and de novo DO after TVT as adjunct to POP surgery was observed in inconsistent and unpredictable percentages. It was impossible to estimate the predictive value of urodynamic testing on the basis of this review and prospective studies were demanded. [Roovers 2007] A later clinical study confirmed this view. [Roovers 2007]

A study presented a decision-analytic model that evaluated the cost-effectiveness of basic office evaluation before surgery in women with POP and SUI symptoms and contrasted it with that of urodynamic testing. Costs were obtained from the Federal Register; effectiveness of treatment for UI was based on the published literature. The strategies of basic office evaluation and urodynamic testing had the same cure rate of UI (96%) after initial and secondary treatment. Under baseline assumptions incremental cost-effectiveness (cost for single extra cure of UI) of urodynamic testing was $328,601. According to sensitivity analyses, basic office evaluation was more cost-effective than urodynamic testing when the prevalence of pure DO was <8% or when the cost of urodynamic testing was >$103. The analysis concluded that urodynamic testing before surgery in women with POP and SUI symptoms is not cost-effective relative to basic office evaluation. [Weber 2000]

b) Ambulatory monitoring

Brown and Hilton [Brown 1999] used conventional

and ambulatory urodynamic monitoring to study the incidence of DO before and after colposuspension. They showed that preoperative ambulatory monitoring was unable significantly to predict which patients would suffer from urgency postoperatively, or even which women would demonstrate DO post-surgery. Another paper addressed specifically the effect on clinical management of doing ambulatory urodynamics. [Gorton 2000] In this retrospective chart review of 71 women, there were technical difficulties in 30/71 ambulatory studies although only 2 were not interpretable. 32/71 women showed DO and nearly all were treated with medication. Among the remainder without DO fewer received medication. However, fewer than half of those who received medication improved. The authors concluded that ambulatory urodynamics was not very helpful in deciding on management.

Conclusions (level 2/3)

- Various studies have shown that the result of urodynamic investigation does not perfectly predict the outcome of relevant treatment in all patients; either in patients with urodynamic detrusor overactivity or in patients with urodynamic stress incontinence and also not in patients with a 'double' urodynamic diagnosis.
- A retrospective study with subsequent health economic modelling has shown that in patients with 'pure symptoms of stress incontinence' urodynamic testing might not be cost effective.

Recommendations (grade B/C)

- The committee recommends that the result of urodynamic investigation is applied to 'optimize' treatment strategy without attributing perfect specificity to the result of treatment, in an individual patient.
- The committee recommends that the cost effectivity of urodynamic testing is taken into account when discussing the necessity of urodynamic investigation with the patient.

Topics for research

- The committee suggests that large multicentre ('national') prospective studies might be of help to better understand the cost-effectiveness of high quality urodynamic testing in health care quality for patients with incontinence.

C. CLINICAL APPLICATIONS OF URODYNAMIC STUDIES

I. PATIENT EVALUATION: WOMEN

1. INTRODUCTION

The clinical evaluation of an incontinent woman is based on the combination of the medical history, physical examination and, when appropriate, selected urodynamic tests.

The patient's symptom SUI is clearly defined and the sign often can be objectively demonstrated as 'the observation of urine leakage from the urethra synchronous with exertion/effort, or sneezing or coughing'. Traditionally, cystometry with cough tests at representative volumes has been the core test for the urodynamic diagnosis of USI. Dynamic urethral closure pressure profilometry, leak point pressure testing and ambulatory urodynamics have been used to sub classify patients with USI.

In the previous report two expert reviews were cited which summarize the likelihood of correctly predicting the result of the UDS from symptoms and signs. [Harvey,M.A. 2001; Homma,Y. 2002] There have been further studies [Agur,W. 2009; Digesu, 2003], reporting that confirmation of USI in the group of patients with the sole symptom of SUI is observed in ±70-80% of the patients. However, patients with that 'sole symptom' were only a relatively small proportion of all reported and analysed cohorts. There have been 2 other studies highlighting the unpredictability and large variation of urodynamic diagnosis on the basis of symptoms in women [Mc Nanley, et al; Hameed, et al] An earlier study [van Waalwijk van Doorn,E.S. 1992] showed that, in a group of 154 females with both complaints and urodynamic demonstration of incontinence, the clinical observation of pure USI had a sensitivity and specificity of 90% and 65% respectively for the isolated symptom of SUI which would be challenged by these 2 further (retrospective) studies, both of which use a much larger data bases, one of over 6000 patients.

The objective information about LUT function adds to the diagnosis that is made on the basis of signs and symptoms. This addition can be of value for the professional when selecting a treatment to offer to the patient. However, it should be noted that besides their diagnostic potential, UDS can contribute qualitative and quantitative information about the underlying or coexisting pathophysiology that is valuable for the patient as well. One study did use a patient preference model to assess the utility of UDS in assessment. This study did highlight that whilst on QoL evaluation, UDS, by itself, did not lead to a better outcome, patient compliance with treatment was better in the group having UDS. Secondly far more women opted for UDS than was predicted. [Majumdar,A. 2010]

Malone Lee however, demonstrated that the presence or absence of DO in patients with symptoms OAB did not relate to outcome of anticholinergic treatment in a prospective randomised trial. [Malone-Lee,J.G. 2009] Likewise 2 studies have shown that symptoms reported during UDS vary between groups, and comparison of the results between groups may be difficult. [van Mastrigt,R. 2004; van Mastrigt,R. 2006]

The committee discusses in the following paragraphs the clinical application of UDS in patients with signs or symptoms of UI. Firstly women with SUI, followed by women with OAB with UUI.

2. STRESS URINARY INCONTINENCE

a) Urethral pressures and severity of stress urinary incontinence

There is no consensus on how to measure the severity of SUI clinically or urodynamically. Severity can be expressed on the basis of simple clinical measures such as questionnaires, or on a bladder diary or on pad weighing tests. A review concludes that static UPP parameters such as MUCP or cough profile parameters such as pressure transmission ratio cannot be used to characterize the severity of incontinence and suggested that abdominal LPP measurement might be a useful tool to quantify urethral dysfunction associated with SUI. [Weber,A.M. 2001]

However, other studies have found no correlation between leak point pressures and the severity of UI as measured by bladder diaries and QoL instruments. [Albo,M. 2007; Chen,C.C. 2008; Theofrastous,J.P. 1995; Nager,C.W. 2001] Leak point pressures are also limited as a diagnostic tool by the lack of standardisation of the technique. [Rodrigues,P. 2006]

A total of 221 women, 29 to 80 years old (mean age 55.2), were included in a prospective TVT treatment study, performed mostly using local anaesthesia with a mean follow-up of 10.5 months. Patients were divided into 61 with low (less than 60 cm H_2O) and 160 with higher (60 cm H_2O or greater) VLPP. The overall (subjective and stress test) cure rate was 10% lower in patients with low versus the patients with higher VLPP and, in women with low VLPP, but multivariate analysis indicated that symptoms of OAB, independent from low MUCP, were independent factors for treatment failure The authors concluded that women with urgency symptoms and or with low MUCP should be considered to be at higher risk for failure after the TVT procedure. [Paick,J.S. 2004] In another report the role of preoperative VLPP in predicting the outcome of the suburethral sling procedure for the treatment of SUI was prospectively evaluated in 174 consecutive patients with diverse grades of VLPP. The TVT provided similar symptom improvement in all the patients regardless of preoperative VLPP [Rodriguez,L.V. 2004] which was confirmed in a more recent study. [Costantini,E. 2008]

An expert review of the use of LPP testing and urethral pressure profilometry prior to surgical treatment for SUI, concluded that there remains no consistency as to whether this testing enhances surgical outcome of SUI treatments by improving case selection or altering the surgical approach based on study findings. The reviewer found little evidence to suggest that patients with more severe forms of USI on urodynamic testing fare more poorly after the most commonly offered surgical treatment than those with less severe forms. [Lemack,G.E. 2004] Subsequent studies and reviews have tried, without positive results, to identify ways in which UDS may predict voiding difficulties after suburethral tapes. [Mostafa, et al.; Murray,S. 2010]. However, the lack of (multicenter standardised) prospective evaluations has been implicated in the lack of progress on this topic. There is also a lack of knowledge with regard to subclasses of SUI and (types of) pelvic floor muscle exercises. [Herderschee,R. 2011]

Most retrospective monocenter studies show higher failure rates after surgery in women with low MUCP (≤ 20 cm H_2O) at MCC. [Weber,A.M. 2001; Miller,J.J. 2006; Guerette,N.L. 2008] However, other investigators have shown that a low MUCP is not an efficient predictor of surgical failure. [Homma,Y. 2002; Weber,A.M. 2001] In a recent prospective, randomised trial of women undergoing either Burch retropubic suspension or bladder neck slings, LPP's were not found to be predictive of surgical outcome for SUI. [Nager,C.W. 2008]

The value of urethral hypermobility, MUCP and urethral incompetence was analysed in a study with 369 women with symptoms suggestive of SUI, without symptoms of DO. Continent and incontinent patients differed with regards to urethral incompetence and hypermobility. Incontinent patients had a greater probability of a higher grade of each factor. Even after adjusting for the older age of incontinent patients by ANCOVA, MUCP was significantly lower in the incontinent group. The best univariate optimized cut-off point for discriminating continence from incontinence was obtained with urethral incompetence greater than grade I. [Schick,E. 2004]

In an attempt to define the urodynamic contraindications to Burch colposuspension, 79 patient's, eligible for continuous postoperative follow-up were enrolled in a prospective study. On post-hoc analysis, a VLPP level <60 cm H_2O was not found to represent an absolute contraindication to Burch colposuspension, provided that other parameters, such as MUCP and functional urethral length, are within acceptable ranges. [Bai,S.W. 2005]

From a total of 168 women, the 31% that demonstrated SUI at lower bladder volumes (100 mL) did not report greater bother from UI than the 35% women who leak at higher volumes (>400 mL). The Urogenital Distress Inventory, Incontinence Impact Questionnaire, and also the MUCP and VLPP were similar in the groups. Among the 116 patients who had a sling procedure, USI persistence did not differ according to the volume at which USI occurred preoperatively (p=0.72). The authors concluded that 'bladder volume when leaking' during a urodynamic study is not an adequate reflection of UI related QoL. [Lowenstein,L. 2007]

A review was done to highlight controversies, concerning the use of UDI prior to surgical treatment for SUI. The review focused on LPP testing and UPP. On the basis of the literature available at that time it was concluded that there remains no clear consensus as to whether UPP or V(A)LPP testing enhances surgical outcome of SUI treatments by improving case selection or altering the surgical approach based on study findings. Furthermore the author concluded that there was little evidence to suggest that patients with more severe symptoms of SUI by UPP or V(A)LPP testing fare more poorly after the most commonly offered surgical treatment than those with less severe forms. The third observation done in this review was that there are certain sub-populations of women who appear to be at higher risk of 'persistent urgency' and or of voiding dysfunction following incontinence surgery, and that UDI may aid in identifying this group. Overall was concluded that it is not apparent that either ALPP measurement or UPP can accurately predict which patients will achieve the best outcome of surgical treatment for SUI. The author suggested that other parameters assessed during UDI might provide prognostic information regarding the risk of voiding dysfunction postoperatively and the possibility of persistent urge-related leakage following surgery, though not directly predict cure. [Lemack,G.E. 2004]

Conclusions (level 2/3)

- Various studies have shown a weak association of incontinence severity with urethral function tests (leak point pressures and urethral closure pressures).
- Cohort studies have shown that incontinence volume and intravesical volume at leakages are poorly associated with symptoms severity and or with patients' quality of life.
- Studies have shown that urethral function tests (leak point pressures and urethral closure pressures) are of very little value in predicting the outcome of treatment with suburethral tapes.
- No studies have shown the relevance of urethral function tests (leak point pressures and urethral closure pressures) in predicting the outcome of non surgical or other treatments for stress urinary incontinence.

Recommendations (grade B/C)

- The committee recommends that urethral function measurements of leak point pressures and urethral closure pressures are not used as a single factor to grade the severity of incontinence.
- The committee does not recommend the use of contemporary urethral function tests to prediction the outcome of any surgical treatment for stress urinary incontinence.

Topics for research

- The committee suggests further studies with the aim of better understanding urethral closure function and dysfunction, in relation to the diverse treatments (especially conservative) of stress urinary incontinence.

b) Aspects of urodynamic studies relevant to therapy for stress urinary incontinence

In a systematic meta analysis (only) 129 (out of 6009) studies were relevant for inclusion using the Quality Assessment of Diagnostic Studies (QUADAS) tool to identify and synthesize studies of diagnostic processes of UI and to construct an economic model to examine the cost-effectiveness of simple, commonly used primary care tests. The diary appears to be the most cost-effective in the diagnosis of USI of the three primary care tests (diary, pad test and validated scales) used in addition to clinical history and clinical stress test. However, the meta-analysis also conceded that if a patient is to undergo an invasive urodynamic procedure, multichannel urodynamics is likely to give the most accurate result in a secondary care setting. [Martin,J.L. 2006] Two attempts to use artificial intelligence in UDS interpretation have been reported [Serati,M. 2011; Witjes,W l998], one reported neural networking and the second an automated analysis process of uroflow: neither was felt to be robust enough to improve diagnostic accuracy.

In 2006 in the UK, the National Institute of Health and Clinical Excellence (NICE) issued guidelines, on the basis of expert opinion collated by a modified Delphi process, that urodynamics was recommended before surgery for UI only if there is a clinical suspicion of DO or, if there has been previous surgery for SUI, or is anterior compartment POP or, if there are symptoms suggestive of voiding dysfunction [National Institute for Health and Clinical Excellence] and urodynamics was not routinely recommended for women before surgery for a 'clearly defined clinical diagnosis of SUI'. The evidence base for this recommendation has been disputed and is controversial and challenged and is now subject to several studies [Nager,C.W. 2008; Nager,C.W. 2001] and the reports of these are awaited. A study in 2008 by Agur et al casts doubt on the wisdom of the UK-NICE recommendation. [Agur,W. 2009] In their tertiary centre, patients are referred with lower urinary tract symptoms. A database of systematic analysis before UDS was used retrospectively to identify women aged 18-80 years who had UDS for UI over a 17-year period (1 January 1990 to 31 December 2006). The reliability of the patients' history in predicting 'pure' USI in patients with 'pure' SUI on the basis of the NICE criteria, was investigated. Only 324/6276 (5.2%) women had pure SUI; moreover, a quarter of those with pure SUI symptoms ultimately had urodynamic diagnoses other than USI, that could affect the outcome of continence surgery.

They concluded that only a small group of women fulfil the NICE criteria of pure SUI and it seems inevitable that even with these strict criteria, a woman could go forward to a surgical procedure with potentially important urodynamic findings unaddressed.

Conclusion (level 1)

- It is concluded in a model study, based on a selected retrospective cohort, that urodynamic testing is not cost effective in the primary health care setting for women with predominant stress incontinence symptoms.
- It shown that in the referred population, urodynamic investigation is the most accurate way to obtain an objective diagnosis in an individual patient with urinary incontinence symptoms.

Conclusion (level 3)

- It has been shown in retrospective and prospective cohort studies that symptoms of 'pure stress urinary incontinence' do not exclude other abnormalities of lower urinary tract function.

Recommendation (grade A)

- The committee recommends that the cost effectiveness of urodynamic testing is kept in mind when discussing 'cost and gain' of the various methods of diagnosis for urinary incontinence, in relation to the method of treatment.

Recommendation (grade B)

- The committee recommends urodynamic studies are carried out in all women prior to surgical intervention for stress urinary incontinence.

Topic for research

- The committee suggests that multicentre studies should address the question as to whether women with symptoms of 'pure' stress urinary incontinence are more at risk of failure from surgical treatment of their incontinence without pre-operative urodynamics, or have more adverse events following surgery without pre-operative urodynamics than women who have pre-operative urodynamic studies.
- The committee suggests that the balance of (over-) diagnosis (when urodynamic testing is used) versus (over–)treatment (with surgical interventions and risk of harm) carefully analysed in a prospective series of consecutive (otherwise unselected) referred women with incontinence.

c) Prediction of failure of surgery

Based on review of the available evidence it has been concluded that urethral pressure profilometry is not standardised, reproducible, or able to contribute to the differential diagnosis in women with SUI symptoms. [Weber,A.M. 2001] This review was done on studies of treatments done before suburethral tapes were widely used, but has been confirmed in the era of tapes. [Lemack,G.E. 2004]

Urethral retro-resistance pressure has also been studied as a potential predictor of surgical success. However, it has failed to show any predictive value for surgical success with colposuspension, retropubic suburethral slings and transobturator suburethral slings. [Tunn,R. 2007] This was underscored in a later manuscript. [Roderick,T. 2009]

Ward and colleagues carefully examined the impact of urodynamic testing on decision-making and treatment recommendations in incontinent women. They found that the probability that urodynamics would alter recommendations for medical treatments was 27% and 46% for surgical treatment. [Ward. 2002]. Johan [Johan, et al.] looked for similar effects with POP in 72 randomly selected cases. A total of 60% of the patients underwent preoperative UDS and 53% of the 43 women undergoing UDS had an abnormal result with POP reduction; 19% of these had pure SUI, and 30% had DO, either in isolation or in combination with SUI. The surgical management was altered in 7%, who had an additional continence procedure performed as a consequence of the UDS. UDS changed management in 33% patients and in 7% of patients, the surgical procedure was changed.

Conclusion (level 2)

- Leak point pressures are reported not to correlate with failure (or success) rates of colposuspensions, transobturator and retropubic suburethral, bone-anchored suburethral slings.

Conclusion (level 3)

- There is conflicting evidence that low urethral closure pressures are associated with poorer success rates of sub-urethral slings.
- It is the opinion of the committee that most evidence suggests now that urethral pressures (profile or leakpoint) are not relevant to predict the outcome of treatment in women with uncomplicated stress incontinence.

Recommendation (grade B/C)

- The committee recommends that measurements of urethral function (leak point pressures and urethral closure pressures) are not used to predict the likelihood of success after surgical treatment for women with uncomplicated primary stress incontinence.

d) Voiding difficulties after surgery

Surgery for SUI may lead to voiding difficulties. [Botros,S.M. 2007; Jarvis,G.J. 1994; Wang,A.C. 2003] One major problem is that many published studies do not use an unambiguous (urodynamic)

definition of voiding difficulties, BOO or underactive detrusor in women. Despite the 2002 ICS nomenclature this remains an area of contention because of the lack of specific numeric definitions or precise research on female pressure flow analysis. Various studies have presented a variety of parameters and cut-off values to define BOO [Bhatia,N.N. 1984; Iglesia,C.B. 1998; Lose,G. 1987; Gravina,G.L. 2007] or detrusor contraction or contractility. [Coolseat, et al.; Tan,T.L. 2003]

Furthermore, the ability of urodynamic analysis of voiding to predict difficulties after suburethral tapes is low. Shukla and colleagues found no urodynamic factors that were predictive of postoperative voiding difficulty following tension-free vaginal tape procedures in a multivariate regression analysis of 411 patients. [Shukla,A. 2007] This was confirmed in another large study. However patients considered 'at risk' (with 'abnormal UDS') were not enrolled for treatment in this study. [Lemack,G.E. 2008] However some investigators showed a significant relationship between flow rate values and the risk of voiding dysfunction and/or the need for clean intermittent (self-)catheterisation (CIC). [Dawson,T. 2007; Wheeler,T.L.,2nd 2008; Duckett,J.R. 2008]

Conclusion (level 3)

- Female voiding dysfunction is defined in many ways throughout the many publications and consistency in urodynamic analysis is lacking.
- Current test methods have not been unable to reliably predict which patients will develop voiding difficulties after surgery for stress urinary incontinence. In particular, normal urodynamic studies do not predict voiding difficulties after sub-urethral sling.
- However, flow rates, if abnormal, may be useful in predicting post-operative voiding dysfunction and retention following retropubic and transobturator suburethral slings.

Recommendation (grade C)

- The committee recommends that patients are informed that it is difficult to predict who will develop voiding difficulty following surgery for stress urinary incontinence.
- The committee recommends that patients with poor flow rates before (intended) surgery are informed that they have a higher likelihood of having voiding problems following suburethral sling placement for (urodynamic) stress urinary incontinence.

e) Postoperative urgency

The preoperative symptoms of UUI and urgency, and the UDS observation of DO, have each consistently been shown to be associated with poorer surgical outcome in patients with mixed UI. [Kulseng-Hanssen,S. 2008] Several studies where the amplitude of DO was graded have shown that the risk of persistent urgency was more closely associated with high-pressure DO (pdet ≥ 25 cm H_2O) than low-pressure DO. [Lose, G.1988; Pow-Sang,J.M. 1986; Lockhart, J.L.1984] Consequently it was suggested at that time that cystometry may allow a more precise selection of patients who respond to surgery despite DO with or without urgency symptoms. The success rate after anti-incontinence surgery in patients with low-pressure contractions are reported to be similar to the success rate in those without DO in a number of studies, [Lose, G. 224; Pow-Sang,J.M. 1986; Lockhart, J.L. 1984; Schrepferman,C.G. 2000] but the success rate in women with high-pressure DO is however reproted to be less than 50%. [561 Lose, G. 1988; Pow-Sang,J.M. 1986; Lockhart, J.L.1984; Schrepferman,C.G. 2000] On the other hand are reports that preoperative urgency symptoms resolve in a proportion of patients. [Nilsson,C.G. 2001; McGuire,E.J. 1980; Ward,K. 2002] Hypothetically, and suggested by some, surgical correction of the bladder outlet prevents ingress of urine into the proximal urethra which if it occurs, has been said to induce urgency or DO in some patients. [Jung,S.Y. 1999; Karlson,S.1953; McGuire,E.J. 1976]

De novo UUI has however also been reported to occur in 10-20% of patients after surgery. [Jarvis,G.J. 1994; Holmgren,C. 2007]

There is scant information on clinical or urodynamic risk factors; possibly the type of surgery plays a role. A recent retrospective trial suggested that the incidence of de novo UUI is higher in bladder neck slings than in retropubic suburethral slings which were also associated with more de novo UUI than transobturator suburethral slings. [Alperin,M. 2008; Botros,S.M. 2007] Another study showed that women with preoperative mixed symptoms of incontinence and DO, as well as women that used anticholinergics, had significantly worse outcome at 6 weeks. [Kenton,K. 2009] This observation was confirmed in a large longer term prospective follow-up study. [Lee,J.K. 2011]

Conclusions (level 2)

- Prospective studies have indicated that overactive bladder syndrome, mixed symptoms of incontinence and or detrusor overactivity during urodynamics at presentation have a negative effect on the outcome of (all available) surgical interventions for stress incontinence.
- Current test methods have been unable to reliably predict which patients will develop de-novo urinary urgency (overactive bladder syndrome) after surgery for stress urinary incontinence.
- Post hoc evidence suggests that procedures for the treatment of stress urinary incontinence which are more 'obstructing' produce a higher chance of de novo urinary urgency (OAB-syndrome).

Recommendation (grade B)

- The committee recommends that patients with stress urinary incontinence are informed that the chance of developing urinary urgency (overactive bladder -syndrome) following surgery is unpredictable.
- The committee recommends that patients are counselled before surgical intervention with regard to the possibility of a lesser success rate when OAB symptoms and or (urodynamic) signs of detrusor overactivity (or reduced compliance and or capacity) exist.

Topics for research

- The committee suggests further work to evaluate predictors of voiding difficulties or urinary urgency after contemporary (moderately invasive) treatments of stress urinary incontinence (e.g. transobturator or trans-vaginal tapes).
- The committee suggest that the hypothesis that suburethral tapes cure urgency, overactive bladder syndrome and or detrusor overactivity be challenged, in a properly designed prospective study.

f) The role of urodynamic studies in predicting occult stress urinary incontinence in women due to be treated for pelvic organ prolapse

Because 11 to 22% of continent women undergoing vaginal repair for a large cystocoele develop SUI following surgical repair [Beck,R.P. 1991; Borstad,E. 1989], it would be helpful to devise methods to evaluate patients who are at risk for this complication. [Ghoniem,G.M. 1994] Women with severe POP may develop urinary incontinence symptoms when the POP is reduced; this is frequently named 'occult' SUI. Voiding difficulty and BOO may coexist with occult SUI; all may be associated with POP, and all may be altered if the POP is reduced during UDS. The overall incidence of occult SUI was 25% when UDS was performed with and without pessary support of the bladder base during 'stress manoeuvres'. [Versi,E. 1998]. A special technique for reducing POP during multichannel urodynamics, revealed a 56% incidence of low-pressure urethra and an overall incidence of occult SUI of 83% in women with massive POP but without clinical UI. [Veronikis,D.K. 1997] More recently in 2008, the CARE trial in the United States examined 322 stress-continent women with stages II-IV POP who underwent standardised urodynamics. Five POP reduction methods were tested: two at each site and both were performed in each subject. Clinicians were masked to urodynamic results. At sacrocolpopexy, participants were randomised to Burch colposuspension or no Burch colposuspension (control). Preoperatively, only 12 of 313 (3.7%) subjects demonstrated USI without POP reduction. Women who demonstrated preoperative USI during POP reduction were more likely to report postoperative SUI, regardless of concomitant colposuspension. [Visco,A.G. 2008] Conventional urodynamic testing, including pessary testing, has been applied to initiate a plausible management strategy for patients with POP. [Smith,P.P. 2005; Ballert,K.N. 2009] Many studies emphasize the importance of urodynamic assessment with POP reduction to assess potential occult SUI and possibly DO. [Romanzi,L.J. 1999; Ghoniem,G.M. 1994; Versi,E. 1998; Weber,A.M. 2000; Marinkovic,S.P. 2004] However, although occult SUI is revealed in a high proportion of cases with severe POP, studies that assess reproducibility are lacking, inconclusive and or conflicting. [Bump,R.C. 1996; Colombo,M. 1997; Gordon,D. 1999; Heesakkers,J.P. 2005] Another study [Gravina 2007]concluded, on the basis of a mathematical model, that included DO, that urodynamic testing before a POP operation was not cost-effective if performed in all patients.

Conclusions (Evidence level 1)

- Various studies have shown that symptoms of stress urinary incontinence can appear after surgery for pelvic organ prolapse.
- There are a variety of methods to uncover 'occult stress urinary incontinence' in women with pelvic organ prolapse. In prospective studies. it is demonstrated that all have different sensitivities and specificities. Standardisation of these tests is necessary.

Recommendation (grade B)

- The committee recommends that patients with pelvic organ prolapse are informed about the relatively unpredictable chance of developing stress incontinence after surgery for pelvic organ prolapse.

3. URGENCY URINARY CONTINENCE

a) Pathophysiology and severity of urgency urinary incontinence

Urgency urinary incontinence (UUI) is the symptom, complaint, or sign of involuntary urine loss of urine associated with urgency. DO is the occurrence of involuntary detrusor contractions occurring during filling cystometry. Precise individual relationships between symptom severity and the various variables observed during urodynamic testing have not been established. Individual symptom severity is dependent on other factors besides lower urinary tract function, furthermore, urodynamic testing measures lower urinary tract function, in isolation from those factors. Studies have shown that symptoms and treatment result relate to Qol. [Kubota,Y. 2011; Payne,C.K. 2007]

As already indicated above, treatment and treatment response seem to depend relatively little on urodynamic measures, and also patients with OAB symptoms but without DO improve on antimuscarinergic treatment. [Malone-Lee,J.G. 2009]

Although urodynamic classification of UI type is related to adverse effects on QoL, no studies have

been successful in relating the quantified urodynamic abnormalities, when DO exists, to the symptom severity. [Duggan,P. 2011], although high scores on the urgency severity scale predict the finding of DO. [Chung,S.D. 2011] Urodynamic capacity, volume at first contraction, and or amplitude of the first, or highest contraction, are used as endpoints in treatment studies, and are, in those studies, observed to be altered in the direction of symptom improvement. (We refer to the treatment section for these observations.) A precise association between symptoms, symptom change and urodynamic findings can however not be deduced from this.

b) Prediction of treatment response

The positive predictive value of OAB (urgency usually accompanied by frequency and nocturia with or without UUI) for urodynamically determined DO is reported to be around 50%. [Digesu,G.A. 2003] On the other hand DO is reported in 10-69% of asymptomatic female volunteers, depending on the definition and type of cystometry. [van Waalwijk van Doorn,E.S. 1992; Heslington,K. 1996; Robertson,A.S. 1999; Homma,Y. 2002; Morgan, K; Turner-Warwick, et al 1979]

There are studies that show that, in patients with OAB, treatment response is not per se dependant on the observation of DO, however this does not make clear whether the urodynamics simply 'missed' the DO. It does also not exclude the necessity of urodynamics in the patients that has failed medical treatment which are the most common patients in referral clinics. [Saleem,A. 2010; Malone-Lee,J.G. 2009] Studies on voiding difficulties or de novo SUI or mixed incontinence (as a consequence of increased capacity because of treatment for UUI) have not been published.

Conclusions (level 2/3)

- Studies have not been able to show a strong association between overactive bladder symptoms and detrusor overactivity during urodynamic investigation.
- Various studies have directly or indirectly concluded that the individual prediction of the response to treatment for overactive bladder symptoms, on the basis of the characterization or quantification of detrusor overactivity during urodynamic investigation, is impossible.

Recommendation (grade B/C)

- The committee recommends that investigators and clinicians discuss with patients, with detrusor overactivity, that neither the quantity nor specific characteristics of detrusor overactivity predicts the response to any of the therapeutic approaches.

Topics for research

- The committee suggests further studies to find predictors of response on treatment for patients with overactive bladder syndrome.
- The committee suggests further studies to find urodynamic predictors of response for patients with overactive bladder without detrusor overactivity.

4. RECOMMENDATIONS FOR URODYNAMIC STUDIES IN WOMEN WITH URINARY INCONTINENCE

Recommendations for clinical practice:

1) The committee recommends non-invasive urodynamics (voiding and incontinence diary, PVR, and possibly uroflowmetry) for all patients with urinary incontinence.

2) The committee suggests that treatment, without invasive urodynamic testing, is offered in situations where the type of UI is clear, if the patient accepts the uncertainty margins of the diagnosis and there are no complicating factors. Furthermore the planned treatment should be not invasive and be simply reversible. The committee provides the following examples:

- Uncomplicated symptoms of stress urinary incontinence with normal bladder diary, normal flowmetry and without relevant post-void residual urine. (Symptomatic pure stress urinary incontinence with no symptoms or signs of voiding difficulties), for treatment with pelvic floor muscle training.
- Uncomplicated symptoms of urgency urinary incontinence, with a bladder diary in accordance with these symptoms, with normal flowmetry and without relevant post-void residual urine. (Symptomatic pure urge urinary incontinence with no symptoms or signs of voiding difficulties), for treatment by bladder training with or without combined pharmacotherapy.

3) The committee recommends that, whenever surgical intervention is planned, whenever there is doubt about the pathophysiology, or about whether the UI is uncomplicated or not, that invasive urodynamics should be performed in order to provide the knowledge on which rational treatment decisions and prognosis can be based. The committee also recommends urodynamics for patients that have had failed first therapies. The investigation should be tailored to the individual patient; typically this means that it will be a comprehensive examination of multiple aspects of storage and voiding function, and not just of the incontinence itself.

Recommendations for research:

1) The committee recommends research programs:

- to more clearly establish the technical and physiological basis of the urodynamic observations that are made in women with urinary incontinence

- to design and conduct randomised studies that may provide objective documentation of the utility of soundly based tests
- to conduct studies that may provide objective evidence of the utility of performing urodynamics in near-normal subjects and in defined patient groups

o note that the more complex and morbid the pathophysiological situation, the greater the differences between patients, and thus the more important it is to do urodynamics in order to obtain knowledge of what is to be treated

- to develop new tests, for example tests of urethral properties, which have a sound technical and physiological basis and lead to clinically relevant sub-classes of urinary incontinence

2) The committee recommends that no new therapy for urinary incontinence should be introduced without extensive urodynamic testing of all accessible aspects of its effect on lower urinary tract function and dysfunction.

II. PATIENT EVALUATION: MEN

1. INTRODUCTION

The incidence of UI in men is generally regarded as much lower than in women. The incidence of LUTS, in general, including OAB and symptoms suggestive of BOO in men however increase with age, as in women. [Kondo, et al.2002], although the QoL of women is more likely to be affected by OAB than men. Both men and women with bothersome OAB were significantly more likely to seek treatment, and to report the lowest levels of health related Qol. [Coyne,K.S. 2011]

In this section, the characteristic pathologies that lead to UI in men, rather than women, are discussed from the point of view of urodynamic testing. Although UI associated with, BOO (including BPO) or to prostatic surgery is most frequently encountered, other pathological conditions such as nocturnal enuresis and post-micturition dribbling are also clinically relevant (but not specific for) in men. [Kondo, et al.2002; Coyne,K.S. 2011] This section is organized according to the suspected origin or cause of UI or related LUTS, reflecting the diverse aetiologies responsible for incontinence in men.

2. URODYNAMIC TESTING OF DETRUSOR OVERACTIVITY AND OVERACTIVE BLADDER IN MEN

It has been estimated that 29.8 million adults aged >=40 years in the United States have bothersome OAB symptoms. The prevalence of OAB symptoms at least 'sometimes' was 27.2% in men and the prevalence of moderate/severe UI was 4.5%. [Coyne,K.S. 2011] The prevalence increased with age from 0.7% in 20 to 34 years old, to 16.0% in men 75 years old or older. [Markland,A.D. 2010] Storage LUTS was more prevalent than voiding or post-micturition LUTS in men (44.6%, 28.5%, 15.9%, respectively). The most prevalent LUTS was nocturia (36.6%). [Lee,Y.S. 2011] Significant negative correlation exists, between pre-treatment mean ICIQ-SF score and first sensation, and positive correlation between pre-treatment mean ICIQ-SF score and maximum detrusor pressure, were noted in a group of (male and female) patients taking pharmacotherapy for OAB. [Seckiner,I. 2007; Irwin,D.E. 2009] LUTS, OAB, UI, and LUTS/BOO are highly prevalent conditions, in men. [Irwin,D.E. 2009; Irwin,D.E. 2011] Treatment options for UI are rapidly expanding. Initial managements of LUTS including UI, include basic diagnostic tests to exclude an underlying disease or conditions such as UTI. In the EAU guideline the advised initial treatment is conservative (lifestyle interventions, physiotherapy, physical therapy, pharmacotherapy) and of empirical nature. [Thuroff,J.W. 2011]

In a systematic review on several longitudinal studies it was shown that OAB and UI symptom severity progresses dynamically over time, and may persist over long time periods for many individuals. [Irwin,D.E. 2010] The overall incidence of DO was 76.1% in male OAB patients, 63% of men with urgency (OAB dry) had DO, while 93% of men with urgency and urgency urinary incontinence (OAB wet) had DO. A better correlation in results between OAB symptoms and the urodynamic diagnosis of DO in men, than in women, was reported, more so in OAB wet than in OAB dry. [Al-Ghazo,M.A. 2011]. A high urgency severity score (USS) recorded in conjunction with a voiding diary, and OAB wet, were strongly associated with urodynamic DO. [Chung,S.D. 2011]

Detrusor contraction velocity is observed to be related to urgency, and urgency may have a role in enhancing and sustaining detrusor contractions in patients with DO. [Cucchi,A. 2007] First sensation ratio and bladder urgency velocity were statistically significantly correlated with the Urgency Perception Score. Urodynamic variables correlated with bladder sensation questionnaire scores and may be an objective method to assess sensory dysfunction. [Rapp,D.E. 2009] However among the 84 'BPH-DO' patients, 52 reported the symptom of urgency while 32 did not. Hypothetically, BPO patients with DO may neglect the symptom of urgency due to abnormal bladder sensation, or negate the symptom by subconscious sphincter contraction to abort the overactivity. [Tong,Y.C. 2007]

Reduced bladder sensation is defined as a bladder volume at first sensation >300 mL. Increased bladder sensation is defined as bladder volume at the first sensation <100 mL. Chronic post void residual and neuropathies are the most common cause of reduced (late) bladder sensation. In contrast, my-

elopathies are the most commonly reported cause of increased (early) bladder sensation and reduced capacity without DO. [Tsunoyama,K. 2011]

Idiopathic detrusor underactivity (DUA) is reported to result from two-stage development. [Cucchi,A. 2007] Patients with idiopathic DUA could be divided into group 1: low maximum possible detrusor contraction velocity, low isovolumic detrusor pressure and bladder emptying efficiency <67%; group 2: low maximum possible detrusor contraction velocity, low isovolumic detrusor pressure and bladder emptying efficiency >67%; and group 3: low maximum possible detrusor contraction velocity, normal isovolumic detrusor pressure and bladder emptying efficiency >67%. [Cucchi,A. 2009]

During filling cystometry, rectal contractions (RC) are frequently detected, the clinical significance of which has not been investigated, however reduced bladder compliance and bladder trabeculations were more common in patients with RC. The occurrence of RC correlated with the incidence of cerebrovascular accidents in males in a large monocenter retrospective cohort. [Cho,S.Y. 2010] Ambulatory urodynamics are complex but sensitive for the detection of DO, are prone to artefacts and time consuming. Therefore, the method is considered of best value when all other diagnostic means have failed. [Pannek,J. 2008]

Conclusions:

- Epidemiologic studies show that lower urinary tract symptoms in men >50 years of age are highly prevalent and that storage lower urinary tract symptoms are relatively more reported than voiding or postmicturition symptoms.
- Case series indicate, in male patients, that overactive bladder wet is associated with urodynamic DO. Overactive bladder dry symptoms might involve other lower urinary tract dysfunction or be the result of obstructed and or ineffective voiding.
- Guidelines suggest that the initial treatment for male lower urinary tract symptoms can be based on the predominant symptoms, without urodynamic testing.
- Guidelines recommend, on the basis of expert opinion, urodynamic testing when the initial management fails to resolve the storage lower urinary tract symptoms.

3. LOWER URINARY TRACT SYMPTOMS RELATED TO MALE LOWER URINARY TRACT DYSFUNCTION: DETRUSOR OVERACTIVITY AND BLADDER OUTLET OBSTRUCTION

Lower urinary tract dysfunction is as prevalent in elderly men as in women however urinary incontinence is less prevalent in elderly male, (without a history of relevant surgery) However if UI is present in men, urodynamics can be helpful. Coexistence of UI in men with BOO and DO increases with age and with the degree of BOO. [Oelke,M. 2008; Vesely,S. 2003] The prevalence of UI ranges from 11% to 34% among community-dwelling men aged ≥65 years. BPO-related incontinence may be related to progression of BPH, through BPE, or as a post surgical complication. [Han,E. 2007] Significantly more cases (14%) reported reduced sexual activity and decreased enjoyment of sexual activity because of LUTS in a large case control series of elderly men, and significantly fewer cases were satisfied with their sex lives compared with controls. [Irwin,D.E. 2008]

Among 1418 men investigated urodynamically (median age: 63 yr) 864 (60.9%), had DO. In univariate analysis, men with DO were significantly older, had larger prostates, and higher grades of BOO, higher storage IPSS sub scores, a lower VV at free uroflowmetry, and a lower bladder capacity at cystometry. In patients with 'clinical BPH', DO was independently associated with age and BOO. [Oelke,M. 2008]

LUTS in elderly men does not equate to BOO due to BPE, and, in particular, young men presenting with LUTS have a different prevalence of underlying aetiologies. Urodynamic studies are useful in the evaluation of this group of patients Abnormal UDS were noted in 36 (72%), including DO in 9 (18%), underactive detrusor / acontractility in 5 (10%) and BOO in 21 (42%). Fourteen (28%) had primary bladder neck dysfunction and five (10%) had BPO in a retrospective monocenter report of 50 men < 50 years. [Toh,K.L. 2006]

LUTS can result from a complex interplay of pathophysiological features that can include bladder dysfunction and BPO or poor relaxation of the urethral sphincter. About one third of men with LUTS who were older than 55 years of age had BPO. Patients younger than 55 years old with LUTS were more likely to have poor relaxation of the urethral sphincter. [Kuo,H.C. 2007] In a group of men with LUTS and small prostates (mean prostate volume was 29.2 +/- 7.2 mL and mean IPSS was 13.5 +/- 4.6) BOO was diagnosed in 42 (50.0%) patients, and underactive detrusor in 41 (48.8%) and DO in 28 (33.3%) were the other diagnoses. The results emphasize the value of urodynamics in this population, especially when invasive treatments are being considered. [Gomes,C.M. 2008]

Non-invasive investigations such as uroflowmetry and measurement of PVR are easy to perform, but, even in simple situations, can only give clues to the underlying pathology. Low Q_{max} on uroflowmetry cannot distinguish BOO from the poor detrusor contraction. [Chancellor,M.B. 1991] furthermore there is also a significant variation in Q_{max} in repeated tests. [Feneley,M.R. 1996] A recent study showed that the time to flow, while performing uroflowmetry, associates with the reported symptom of urinary hesitancy on IPSS. [Park,K.K. 2011] Relatively strong relationships were found between average flow rate and

flow time with scores of intermittency, weak stream and IPSS scores in elderly men with LUTS and a reduced flow rate. [Itoh,H. 2006]

Seki at al reported that DO, at initial evaluation, negatively affected outcome in a retrospective study of 384 patients who had undergone TURP for symptomatic benign prostatic enlargement. [Seki,N. 2006] In another study with patients with prostate carcinoma and symptoms, it was demonstrated that 95% of men who proceeded to TURP on the basis of urodynamic diagnosis, had improved flow rates at 12 months after palliative TURP. [Gnanapragasam,V.J. 2011] Monoski at al found, in 40 men who underwent photoselective laser vaporisation prostatectomy for 'BPH' and retention, that the presence of DO in patients on pre-surgery Urodynamics, is associated with significantly more storage symptoms, and are twice as likely to require anticholinergic treatment than the patient without DO. [Monoski,M.A. 2006]

After HoLEP, 29 patients (16.2%) had de novo UI, most of which resolved within 1-6 months; low MUCP at baseline urodynamics was found to be the independent urodynamic predictor of de novo UI after surgery, amongst others in a multivariate analysis. [Cho,M.C. 2011] UDS was used to assess the functional outcome following KTP -laser prostatectomy. All selected patients in this uncontrolled monocenter series (n=45) showed significant improvement in the IPSS in urodynamic pressure and flow. Detrusor contractility was not affected. [Hamann,M.F. 2008]

In an experts group discussion, it was concluded that UDS is indicated for the evaluation of effectiveness of new treatment modalities for elderly male patients. As in the existing guidelines, this expert group supports, on the basis of their expert opinion that UDS are not necessary before pelvic floor muscle training or medical treatment of LUTS/BPO or OAB. [Bosch,J.L. 2011]

Silodosin is evaluated to improve DO and BOO grade in patients with BPH and urodynamic testing showed objective improvement of voiding in a proportion of patients in a small monocenter study. [Yamanishi,T. 2010] In elderly male with OAB symptoms anticholinergics do not seem to influence effectivity of (urodynamic) voiding. [Ronchi,P. 2009]

The role of urodynamics and the finding of DO, in predicting continence outcome, after radical prostatectomy, still remains controversial. Aboseif et al compared 92 men with and without DO on pre-operative urodynamics before radical prostatectomy. They found, after one year, a significantly higher incidence of UI (39% v/s 3%) in patients with pre-operative DO compared to those without pre-operative DO. [Aboseif,S.R. 1994] On the other hand, Kleinhans et al concluded (44 patients) that preoperative DO did not correlate with post surgical UI eight months after radical prostatectomy. [Kleinhans 1999]

Conclusions:

- Various studies indicate that male lower urinary tract symptoms including incontinence may be due to detrusor dysfunction and or bladder outlet obstruction.
- Monocenter cohort observations demonstrate that detrusor overactivity and urethral sphincter dysfunction should also be considered in young men with lower urinary tract symptoms or men with a small prostate.
- Mono and multicenter cohorts show that although urodynamic studies do not unequivocally predict outcomes of pharmacological or surgical treatment, treatment results are however shown to be better predicted in patients who have had objective urodynamic tests.

Recommendations (grade C)

- Evidence that urodynamics improves outcome is limited, but nevertheless the committee recommends that all elderly male patients with incontinence should receive a complete urodynamic evaluation in order to understand the problem
- The committee recommends that clinical parameters are investigated which correlate with urodynamic results such as BOO or DO, in order to achieve better treatment outcome for LUTS in men, without invasive urodynamics.

4. POST-PROSTATECTOMY INCONTINENCE

a) General

After prostatectomy, a noticeable number of patients suffer from UI. The reported incidence following surgery varies widely and is believed to be related to patient age, pre-surgery lower urinary tract function, benign or malignant prostatic disease and the type of surgery and furthermore depends on the definition of incontinence that is applied. Approximately 10-14% of patients, suffer incontinence 2-5 years after radical prostatectomy. [Penson,D.F. 2005] A prospective survey study on 1201 patients and 625 partners, of outcome after treatment for prostate cancer, showed that UI was at its worst 2 months after surgery and then improved in most patients. Factors that were associated with worse UI were, older age, black race, and a high PSA score at diagnosis. Patients in the brachytherapy group reported significant deterioration in 'urinary irritation', symptoms suggestive of BOO and UI, compared with baseline. UI after brachytherapy was reported by 4 to 6% of patients at 1 to 2 years after treatment. [Sanda,M.G. 2008] Comparative studies indicate that UI is the most incident adverse effect of radical prostatectomy. [Wilt,T.J. 2008] Understanding of prostato-vesical anatomy and the pelvic floor, and meticulous surgical technique, are of importance in preventing UI.

Using accumulated data from 573 patients, reported in 8 articles from 1978 to 1997, which collated urodynamic evidence for UI following surgery for 'BPH' or prostatic cancer, it was suggested that the most common aetiology was isolated sphincter weakness, followed by sphincter weakness plus DO, and also DOI and or reduced compliance alone. Thus, a blanket assumption that there is a single cause of the UI would be wrong in two-thirds of men after radical prostatectomy. Furthermore also obstructed voiding is reported in these series. [Kondo, et al 2002; Porena,M. 2007; Ficazzola,M.A. 1998; Huckabay,C. 2005]

UI was more prevalent in men who were obese and physically inactive (59% UI) after prostatectomy. The best outcomes were in men without obesity and physically active (16% UI). Pre-prostatectomy physical activity and weight (BMI) may be important factors in UI after radical prostatectomy and the return of continence. [Wolin,K.Y. 2010]

Preoperative DO was not associated with worse post radical prostatectomy UI outcomes, or increased incidence of UI. Monocenter observations suggest that even if DO is present in men with USI after radical prostatectomy they may be considered for a male sling procedure. [Ballert,K.N. 2010]

Conclusions:

- Many case series show that sphincter weakness is the most common aetiology of male urinary incontinence after prostatectomy. However case series and reviews show that other lower urinary tract dysfunction besides sphincter incompetence plays an incident role in post prostatectomy urinary incontinence.
- Case cohorts indicate that detrusor overactivity before radical prostatectomy is not an important indicator for the postoperative incidence of urinary incontinence, or for the outcome from surgical interventions to treat the urinary incontinence.

b) Transurethral resection of the prostate and Open Prostatectomy for benign disease.

Approximately 1% of patients who have undergone TURP suffer from post-prostatectomy incontinence. [Mebust, et al 1989] Das and his co-investigators [Das,A. 2001] showed that the role of urodynamic investigation in preventing post-operative incontinence before laser resection of the prostate may be marginal. Another large monocenter study showed that the incidence of post laser-prostatectomy incontinence is less than 1%. [Krambeck,A.E. 2010] A systematic review and health technology assessment did not show differences in the incidence of incontinence following various more or less invasive (non medical) interventions for 'symptomatic BPH'. [Lourenco,T. 2008]

Kuo [Kuo,H.C. 2002] urodynamically evaluated 185 men aged from 55 to 91 with a mean of 75 years who had had variable LUTS after TURP which had been refractory to conventional treatments. He found that UI was present in 74 patients (40%) and that BOO and DO with impaired contractility (DHIC) were the most common findings associated with post-prostatectomy incontinence, followed by DO. Post-transurethral- prostatectomy incontinence is usually due to sphincter damage as a complication of prostatectomy, but may result from other causes, such as DO. Urodynamics showed no significant change in filling or voiding parameters when suburethral 'male'-slings were implanted. [Wadie,B.S. 2010]

After HoLEP, 29 patients (16.2%) had de novo UI, most of which resolved within 1-6 months; 11 had SUI, 12 had UUI, and the remaining 6 had mixed UI. A lower MUCP, on baseline urodynamics, was found to be the independent predictor of de novo UI after surgery. [Cho,M.C. 2011]

Conclusions:

- Case series have concluded that urinary incontinence after prostatectomy may be attributed to bladder storage dysfunction and can exist in association with (neo-bladder neck) bladder outlet obstruction although the most prevalent cause is a lesion of sphincteric function.
- Retrospective studies have shown that urodynamic tests cannot predict which patient will develop SUI or detrusor overactivity (with or without urgency incontinence) after surgical treatment for benign prostatic obstruction.
- Studies have shown that urodynamic tests can identify the aetiology(ies) of urinary incontinence (or other lower urinary tract dysfunction) after surgical treatment for benign prostatic obstruction, however the predictive value for the outcome of subsequent treatment is unknown.

Recommendation (grade C)

- The committee recommends urodynamic testing when elderly male patients have urinary incontinence after surgical treatment for benign prostatic obstruction if further surgical or invasive treatment is planned.

c) Radical Prostatectomy and Radiotherapy

Is (invasive) urodynamic investigation of incontinence after radical prostatectomy necessary?

Sphincter weakness, neo bladderneck outlet obstruction, DO and mixed incontinence are contributing to post-prostatectomy incontinence. [Kuo,H.C. 2002; McCallum,T.J. 2001] These parameters can be only identified by urodynamics, which is considered by most [Sakamoto,K. 2001; Gomha,M.A. 2002; Yurkanin,J.P. 2001], but not all [Hindley,R.G. 2001], to be one of the main tools for investigating

UI after radical prostatectomy. In brachytherapy for prostate cancer, urodynamics may have some value for predicting which men might develop acute urinary retention or might require CIC after treatment when the prostatic oedema has caused temporary retention. [Henderson,A. 2002] Castille et al prospectively assessed 229 men who were scheduled to undergo radical retropubic prostatectomy with preoperative urodynamics in an attempt to help physiotherapists predict postoperative incontinence. [Castille,Y. 2003] They observed that all men diagnosed as having DO or neo bladderneck outlet obstruction were incontinent 6 weeks after operation but had improved 4 months later. DO and neo bladderneck outlet obstruction were considered risk factors for postoperative incontinence.

Groutz et al [Groutz,A. 2000] found that USI was the most common urodynamic abnormality after radical prostatectomy (73 patients, 88%), followed by DO in 6, neo bladderneck outlet obstruction in 1 impaired detrusor contractility in 1, and normal findings in 2. Of 73 men diagnosed as having USI, 27 suffered from pure urodynamic USI, and the remaining 46 had concomitant bladder disorders such as impaired detrusor contractility (22 men), neo bladderneck outlet obstruction (14 men) or DO (10 men). Huckabay et al evaluated 60 men and found that twenty-four (40%) men had DO with 8 (13%) also having DOI. Only one patient had impaired bladder compliance. All men had USI, but 21 (35%) men demonstrated it only after removal of the (7F) urethral catheter. For men leaking with and without the urethral catheter, the respective abdominal LPP was significantly different, 86.3 and 67 cmH_2O, respectively. The men who leaked only in the absence of the urethral catheter had significantly higher abdominal LPP measurements. [Huckabay,C. 2005] Although SUI was one of the predominant symptoms of incontinence following radical prostatectomy, half of patients had USI together with UUI or decreased bladder compliance. Co-existing detrusor dysfunction had to be taken into consideration, as well as ISD, in order to properly treat persistent post-prostatectomy incontinence. [McCallum,T.J. 2001; 130 Lai,H.H. 2009] Male SUI is mainly caused by sphincter lesions after retropubic radical prostatectomy (RRP). After RRP, two-thirds were continent after 6 months, whereas one-third still suffered from incontinence. MUCP and FPL in the SUI was significantly lower in comparison with the continent group, accompanied by a characteristic UPP configuration. Postoperative urodynamics after 6 months may be predictive for persistent incontinence at the bladder, sphincter, and both. [Bentzon,D.N. 2009] Based on a study of 29 men with incontinence after radical prostatectomy, it was concluded that abdominal LPP is relatively poorly associated with incontinence severity and, therefore, has limited clinical value in the urodynamic evaluation of post-prostatectomy incontinence. [Twiss,C. 2005] Another study also investigated if abdominal LPP correlates with objective incontinence severity in patients suffering from post-prostatectomy SUI. There was only a weak inverse correlation between abdominal LPP and 24-hr pad weight which was not statistically significant. Age and time from prostatectomy did not significantly correlate with abdominal LPP. The abdominal LPP was considered a relatively poor predictor of incontinence severity and, therefore, has limited clinical value in the urodynamic evaluation of post-prostatectomy incontinence. [Twiss,C. 2005] Several robot-assisted radical prostatectomy (RARP) series have reviewed the impact of the initial learning curve on perioperative outcomes. Outcomes between groups (cases 1-300, 301-500, and 501-700) were compared. Continence rates improved from 75% to 93% for cases 501-700 (p<or= 0.05). Furthermore, significant improvement in continence rates between consecutive case groups was observed at all postoperative time points. [Frank,S.J. 2007]

Is (invasive) urodynamic investigation of incontinence after radiotherapy necessary?

There are few manuscripts reporting the effects of radiotherapy in those with prostatic cancer, and even fewer discussing the place of urodynamics. [Choo,R. 2002; Do,V. 2002] Henderson et al. [Henderson,A. 2002] assessed 100 patients with prostate cancer patients for brachytherapy with a minimum dose of 145 Gy. Prior to the treatment an unselected group of 57 of the 100 patients had been evaluated urodynamically. Patients with larger prostatic volumes (> 35 mL) and or with (UDS confirmed) BOO were more prone to problems after brachytherapy. The authors concluded that urodynamics might have a role in the selection of treatment for men with prostate cancer. Beekman et al found in 204 patients that high PVR (> 100 mL) is associated with slower resolution of voiding symptoms, prolonged (more than 3 days) catheter dependency, and increased post-brachytherapy surgical intervention for BOO. [Beekman,M. 2005] Also Wehle et al suggested that the combination of urinary flow rate, prostate volume, postvoid residual urinary volume, combined with the American Urological Association symptom score helped to identify patients with underlying voiding dysfunction. Urinary flow rate was a statistically significant predictor of genitourinary tract morbidity after brachytherapy for localised prostate adenocarcinoma. [Wehle,M.J. 2004]

Men after brachytherapy were, in a monocenter retrospective cohort, reported to have a relatively high incidence of DO, prostatic and urethral strictures and prostatic urethral stones. [Blaivas,J.G. 2006] A survey amongst 625 (responding) patients that assed the Qol following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer showed that a better rate of urinary continence was maintained in those who underwent radiation based therapies. Better bowel function, lesser sexual function and

less urinary irritation was reported in those who underwent surgery. [Frank,S.J. 2007]

Conclusions:

- Case series and reviews show that the main cause of urinary incontinence after RRP is sphincter weakness and that detrusor overactivity contributes in only a small proportion of those patients.
- Case cohorts show that higher maximal urethral closure pressures or abdominal leak point pressures, indicating greater urethral sphincter resistance is not of utmost clinical relevance
- UI after RRP will improve with time. A study concluded that postoperative urethral pressure profile after 6 months may be predictive for persistent incontinence.

d) Artificial urinary sphincter and male sling

Gomha and Boone [Gomha,M.A. 2002] treated 86 patients who were incontinent following prostatectomy with implantation of an artificial urinary sphincter (AUS)and assessed whether or not prior radiation affected surgical outcomes in those who had or had not had radiotherapy. Urodynamic study prior to artificial sphincter implantation revealed that DO was much more prevalent in group with radiation (26%) than in group without radiation (5%). In spite of this, post-operative urgency with or without urgency incontinence was found in similar proportions of the 2 groups, and similar proportions wore 0 to 1 pad a day to protect against their incontinence. They concluded that the pre-operative urodynamic finding of DO did not predict outcome in this group. Similarly, Thiel and co-workers retrospectively reviewed 86 patients and concluded that patients with post radical prostatectomy USI, plus DO, low compliance, or decreased MCC and FSF have identical outcomes after AUS implantation to those just with USI. [Thiel,D.D. 2007]

The presence of adverse preoperative UDS features as: poor bladder compliance <10 mL/cm, the presence of DO, early sensation of bladder filling at <75 mL, an early FDV at <125 mL, reduced MCC of <200 mL, low abdominal LPP of <30 cm H(2)O, low peak flow of <10 mL/s, low detrusor pressure at peak flow of <10 cm, or a bladder contractility index of <100, did not negatively affect either the post-AUS daily pad use or the continence rate after AUS implantation in patients with post (radical) prostatectomy UI. [Lai,H.H. 2009]

Recent publications on the male suburethral sling show good continence cure rates in post prostatecomy cohorts. A monocenter retrospective study reported that, when post-hoc criteria are applied, cure rates were lower in men that used more pads before sling implant. [Bochove-Overgaauw,D.M. 2011] Also, Ullrich & Comiter evaluated 22 patients urodynamically, at a mean of 25 months after a male sling procedure, and found that patients with postoperative retrograde leak point pressure < 50 cm H_2O and DO were seen to be associated with failure. [Ullrich,N.F. 2004] The trans obturator -tape (TOT) for treatment of post-radical prostatectomy UI, was shown to be effective and well accepted by patients. The mean MUCP improved, which associated with cure, and a majority of patients in a small (n=20) uncontrolled single centre cohort was satisfied. [Rehder,P. 2007] At 12-month follow-up of this treatment, with a larger group of patients (n=118), 73.7% of the men were cured and using significantly less pads, 16.9% were improved, and 9.3% were still incontinent. The detrusor voiding pressure, postvoid residual urine volume and maximal flow rates remained unchanged, while the VLPP improved significantly). [Rehder,P. 2010]

A concern of any procedure in treating men with UI after radical prostatectomy is whether the treatment induces obstruction and causes retention. A study to evaluate this with regard to the 'male sling' questioned whether this treatment eliminates UI without affecting the voiding .The VLPP improved significantly and the detrusor voiding pressure, PVR volume, and maximal and average flow rates remained relatively unchanged. At 3 and 6 months postoperatively, the Incontinence Quality of Life scores had improved significantly compared with the preoperative scores with a reduction in pad-use (from 5 to 1) and urine loss (780g before and 70g after). [Davies,T.O. 2009]

These studies confirm the earlier observations, that the fixed urethral resistance of the perineal male sling for the treatment of (post RRP) SUI in male patients, did not cause BOO or cause de novo voiding dysfunction. Average maximum flow rate did not change significantly nor was there a significant change in detrusor pressure at maximum flow rate, but the pad use, LPP and UI scores were significantly improved after sling surgery. [Ullrich,N.F. 2004]

Conclusions:

- Studies have not consistently concluded that urodynamic variables provide predictive value for treatment in male post prostatectomy incontinence.
- There is weak evidence to support urodynamic evaluation (for patients with a large prostate) before radiotherapy for cancer of the prostate.
- Studies have shown that urodynamic tests are needed to identify the aetiology of urinary tract dysfunction after surgical or radiotherapy treatment of prostatic carcinoma. However the predictive value of urodynamics for the effect of subsequent treatment is unknown.
- Leak point pressures and urethral pressures, measured in their various ways, are consistently reported to be improved after anti -incontinence treatment using different surgical techniques, and

their improvement is associated with cure or reduction of incontinence volume and or pads use.

- Most single centre reports conclude that urodynamic variables, used to evaluate voiding, do not show clinically significant change after suburethral sling procedures or artificial urinary sphincter implantation.

Recommendations (grade B)

- The committee recognised that urodynamic testing for incontinence after radical prostatectomy is not particularly important for the diagnosis of sphincter dysfunction (stress urinary incontinence) in patients with post prostatectomy incontinence. However, the committee recommends that urodynamic testing is considered in patients where other dysfunctions of the lower urinary tract (obstructed voiding, significantly reduced bladder compliance and or detrusor overactivity) cannot be excluded on the basis of signs and symptoms.

Topics for research

- The committee suggests research to find predictors for lower urinary tract dysfunction after treatment for benign prostatic obstruction or for prostatic carcinoma.
- The committee suggests research to improve the prediction of success (whether or not on the basis of urodynamic testing) of treatment for lower urinary tract problems that may follow treatment of benign prostatic obstruction or prostatic carcinoma.

5. NEUROLOGICAL LESIONS RELATED TO MALE INCONTINENCE

Several ailments or pathological conditions have been reported to be closely associated with incontinence, e.g., neurological diseases, prior radiotherapy, neurogenic DO, diminished bladder compliance, nocturnal enuresis, post-micturition dribble and terminal dribbling. [Kondo, et al.] A history of prostatectomy as well as the existence of BPE in combination with one of the here before mentioned conditions may be a diagnostic challenge. Nocturia has a variety of potential causes and was shown to have high impact on bother score, strong associations with poor health and other LUTS. Nocturnal polyuria (NP) is a predominant cause of nocturia. Principal causes for nocturia were global polyuria in 17%, NP in 33% and small functional capacity <250 mL in 16.2%; 21.2% had mixed forms of NP and reduced bladder capacity and 12.6% suffered from other causes. [Klingler,H.C. 2009]

a) Nocturnal enuresis

Nocturnal enuresis in adult males is rather rare. Sakamoto and Blaivas reported, in a tertiary care practice, important interesting observations based on data of over 3000 patients referred for the evaluation of LUTS. [Sakamoto,K. 2001] They found that 8 of 3277 patients (0.02%) had adult onset nocturnal enuresis without daytime enuresis. All these patients were male, with a mean age of 63 years (48 to 80 years) and all suffered from BOO with mean maximum urinary flow rate 8.5 mL/s, mean IPSS 12.6, and mean PVR urine 350 mL (50 to 489 mL). The authors identified hydronephrosis in 5 of the 8 patients, a bladder diverticulum in 3/8, vesico-ureteric reflux in 4/8 and low bladder compliance in 4/8. Five of the 8 underwent TURP resulting in improved symptoms. Thus BOO is one of the distinct pathologies that can provoke nocturnal enuresis with variable LUTS, but it is not the only pathological factor. For example, Hunsballe [Hunsballe,J.M. 2000] found more delta activity in electroencephalography among adult primary enuretics compared to normal controls. Therefore, invasive urodynamics may be justified in such patients, because it is the only way of reliably identifying BOO.

Nocturnal enuresis plagues nearly 28% of patients with a neobladder. Indeed, 25 of 30 patients (83%) who underwent the Stanford pouch ileal bladder had nocturnal enuresis 1 year later. [Uygur,M.C. 2000] Patients older than 65 years are at greater risk because of the physiological increase in LUTD nocturnal diuresis associated with aging. An orthotopic neobladder produces variable LUTD including both failure to empty the bladder and failure to store urine. The urodynamic behaviour depends on the type, length, and configuration of the bowel segment used. [Steers,W.D. 2000] There may be overdistension, elevated PVR, lack of sensation, reduced MUCP, or more frequent and higher-pressure DO. [El Bahnasawy,M.S. 2000] The intestinal overactivity in a neobladder resembles bowel peristalsis. [Sakakibara,R. 2007]

El-Bahnasawy et al studied urodynamically 50 enuretic men at least 1 year after a radical cystoprostatectomy and ileal neobladder and compared them to 17 men with only occasional enuresis and 50 men without enuresis after similar surgery. Both enuretic groups had significantly higher residual urine volumes, higher pressures at mid-capacity and at maximum enterocystometric capacity, higher amplitude of contractions and lower compliance than continent men. Men with occasional enuresis also had a significantly higher frequency and duration of DO contractions and lower maximum urinary flow rates than continent men. [el-Bahnasawy,M.S. 2005]

Urodynamic investigation is important to establish the diagnosis and select treatment, although one group suggested that nocturnal enuresis or nocturia could be simply alleviated by waking up at least twice per night to void. [Uygur,M.C. 2000]

Conclusions

- Epidemiology shows that non- urologic causes for nocturia are prevalent and nocturnal polyuria can

be diagnosed with a 24 h frequency-volume chart.

- Urodynamic studies in elderly men indicate however that detrusor overactivity and/or bladder outlet obstruction with ineffective voiding may play a role in a proportion of patients with nocturnal enuresis.
- New onset, night time incontinence, in an elderly male, warrants urgent urodynamic pressure-flow analysis.

b) Stroke

Stroke is a common and well-known cause of enuresis and LUTD in the older population. The predominant symptoms are urinary frequency, urgency and UUI (including night-time incontinence) while DO is the most common finding on urodynamics. [Marinkovic,S.P. 2001] In patients after a stroke, incontinence (or LUTD in general) is a serious threat for Qol. [Edwards,D.F. 2006] Post-stroke UI is a predictor of greater mortality at 1 week, 6 months and 12 months after stroke. However, patients who regain normal bladder control in the first week have a comparable prognosis as the patients who do not have micturition disturbances following stroke. [Rotar,M. 2011]

Because DO in male stroke patients with LUTD is prevalent, conservative or pharmacologic treatment is often instituted without prior urodynamic investigation. An expert summary of the literature suggested that the size and the site of the stroke does have an influence on urological findings. [Badlani,G.et al] Experts agree that simple tests such as uroflowmetry and, especially, PVR urine assessment (by ultrasound) are however useful, since elevated residual urine is to be expected in a significant proportion of these patients, and its evaluation can improve caregiving and Qol. [Chan,H. 1997; Teng,C.H. 2005] Cystometry has limited value: the prevalence of DO in older people is quite high even in the absence of stroke (perhaps 10% in women and 25 to 35% in men). Therefore the observation of DO alone may not be helpful although the finding of other LUTD, such as obstructed voiding, is.

The prevalence for isolated UI, on admission, was 12.4%, for isolated faecal incontinence 7.6% and for double incontinence 33%. At discharge, the prevalence had decreased, to 8.1% for isolated UI, 4.9 % for isolated faecal incontinence and 15.1% for double incontinence. Double incontinence was more prevalent than isolated incontinence in patients after stroke during post-acute rehabilitation. [Kovindha,A. 2009]

Evaluation of the stroke type may be helpful in the determination of the type of urinary dysfunction and in deciding the appropriate bladder management: the ischemic group was reported to have DO (70.7%), underactive detrusor (29.3%), and hemorrhagic group has DO in 34.6%, and underactive detrusor in 65.4%. (P = 0.003). [Han,E. 2007]

In patients with stroke and voiding dysfunctions, UDI can be performed to identify the presence of BOO or dysfunctional voiding. Voiding dysfunction is also a significant problem in patients with head injury. NDO is seen in patients with injuries above the pontine micturition centre. The voiding abnormality has good prognosis and resolves spontaneously. [Singhania,P. 2010] Among the 36 patients with stroke and DO, 25 patients (62.5%) had DO without sphincter dyssynergy and 11 (27.5%) had DO with sphincter dyssynergy. UDS is a useful tool to assess and manage the bladder following stroke with UI. No significant correlation was found between UDS findings and site of (stroke) lesion in a retrospective single institute study with 18 women and 22 men. [Gupta,A. 2009] In a urodynamic study of bladder dysfunction in idiopathic normal pressure hydrocephalus (iNPH), LUTS were seen in 93% of the patients, with storage symptoms (93%) being more common than voiding symptoms (71%); and urinary urgency (overactive bladder) (64%) frequency (64%) being more common than UI (57%). Although the majority of patients had normal bladder volume at the first sensation (mean 134 mL), bladder capacity was small (mean 200 mL) and DO was seen in 95% of patients. [Sakakibara,R. 2001]

Conclusion:

- Detrusor overactivity and or underactive detrusor can be present in patients with stroke or other neurological lesion.
- In ambulatory male patients, after stroke, with voiding dysfunctions, careful urodynamic study can be offered to identify the presence of detrusor overactivity, or static (BPO) or dynamic (dyssynergic) bladder outlet obstruction.

c) Parkinson's disease

Parkinsonian diseases are known to significantly influence bladder function (see section D.V.6). LUTS may be the first sign, especially nocturia in male patients. Large capacity bladder (when discovered during urodynamic testing for LUTS) may also be a sign of Parkinsonism. [Purohit,R.S. 2008; Williams,D.R. 2009; Blackett,H. 2009; Cheon,S.M. 2008] DOI is common in male patients with Parkinsonism [Defreitas,G.A. 2003], but urodynamic findings differ in different diseases of this group. [Sakakibara,R. 2001] Defreitas et al carried out a retrospective review of the urodynamic results in men with DO due to BOO (22 patients) and compared them to men (39 patients) and women (18 patients) with Parkinson's disease. Patients with Parkinson's disease had a significantly lower median volume at first detrusor contraction than those with non-neurogenic DO. The percentage of urgency incontinence was significantly lower in patients without Parkinson's disease than in men and women with it (9.1% versus 53.8% and 55.6%). No statistically significant correlation between the duration or the severity

of Parkinson's disease and UDS parameters was found. [Defreitas,G.A. 2003] The most prevailing urinary symptom in Idiopathic Parkinson's Disease was nocturia (77.5%) followed by urgency (36.7%) and frequency (32.6%). Urodynamic tests revealed neurogenic DO in 33 patients (67.3%), underactive detrusor in 6 patients (12.2%), and 10 (20.4%) patients with normal detrusor function. However, no significant correlations between any of the urodynamic parameters and disease severity was found. The urinary (storage) symptoms manifested urodynamically as neurogenic DO are more common in IPD patients than voiding symptoms. [Ragab,M.M. 2011]

Urinary dysfunction, manifested primarily as storage disorders with subclinical voiding disorders and normal anal-sphincter electromyography, occurs in early and untreated PD patients. Urodynamic studies showed abnormal findings in the storage phase in 84%, with DO and increased bladder sensation without DO in 58.0% and 12.0% of patients, respectively. In the voiding phase, underactive detrusor, impaired urethral relaxation such as detrusor sphincter dyssynergia, and BOO were present in 50.0%, 8.0% and 16% of patients, respectively. In patients with both storage and voiding phase abnormalities, DO plus underactive detrusor was the most common finding. [Uchiyama,T. 2011]

One study investigated the LUTS and urodynamic and cystometric findings in PD, dementia with Lewy bodies (DLB), and Alzheimer disease (AD). Urgency and urgency incontinence suggest DO, which was more prevalent in dementia with Lewy bodies than in PD and Alzheimer disease, whereas mean VV, free flow, MCC, and detrusor pressure were similar in the groups; DO was seen in 92% of the patients with DLB, 46% of the patients with PD, and 40% of the patients with AD. [Ransmayr,G.N. 2008]

Conclusions:

- Detrusor overactivity and detrusor underactivity, with or without urethral sphincter dyssynergia, are commonly found in male patients with Parkinson's disease.
- Bladder outlet obstruction is not related to Parkinson's disease. For male patients with Parkinson's disease and voiding dysfunction, urodynamic testing is recommended to select appropriate treatment strategy.

d) Diabetes Mellitus (DM)

Men with DM and LUTS can present with varied urodynamic findings, apart from the classic sensory or motor cystopathy. Urodynamic studies showed delayed first sensation (>250 mL), increased capacity (>600 mL) underactive detrusor, DO, high postvoid residual urine volume (more than one third of capacity), and BOO (Abrams-Griffiths number >40) in 23.1%, 25.0%, 78.8%, 38.5%, 65.4%, and 28.8% of the men, respectively. [Bansal,R. 2011] Kebapci re-evaluated the urodynamic findings of LUTD in type 2 diabetic patients describing patient characteristics and concomitant chronic complications: LUTDD was present in 74.07% of men. The group defined 'diabetic cystopathy' as diminished sensation of filling and significant postvoid residual and observed that in 50% of their patients, also BOO, (25%) and DO (in 25%) were observed. 'Diabetic cystopathy' (in this specific definition was the most frequent finding. Ageing, duration of diabetes, worse metabolic control, PVR >100 mL, cardiac, oesophageal and gastric parasympathetic autonomic neuropathies, retinopathy, and microalbuminuria provided a means to predict LUTD, and select patients for urodynamics. [Kebapci,N. 2007]

It was observed in a monocenter retrospective case control study that patients with DM who undergo radical cystoprostatectomy take longer to regain daytime and, even more so, night time continence than non diabetic patients. [Kessler,T.M. 2008]

There is a relatively low prevalence of BOO in diabetic patients with prostate enlargement and LUTS. Of the 50 patients in the study, 23 (46%) had BOO. There was no correlation between the IPSS, uroflowmetry, post-voiding residual urine or prostate volume and the presence of BOO ($p > 0.05$). Non-invasive tests did not allow the identification of LUTD and only urodynamic evaluation is able to determine symptom aetiology. [Dib,P.T. 2008]

Conclusions:

- Clinical cohort studies show that men with diabetes and lower urinary tract symptoms can present with a variety of urodynamic findings, including detrusor overactivity, underactive detrusor and bladder outlet obstruction.
- Uncontrolled cohort studies indicate that non-invasive tests are less sensitive to relevant abnormalities in comparison with urodynamic evaluation and investigators have concluded that urodynamic investigation is necessary when lower urinary tract symptoms arise in patients with diabetes mellitus.

e) Recommendations for urodynamic investigation for men suffering from nocturnal enuresis, stroke, Parkinson's disease or DM

Conclusions (level of evidence 2/3)

- Nocturnal enuresis in adult males is rare but problematic, and it is associated with many possible aetiologies.
- Nocturia, nocturnal enuresis or lower urinary tract symptoms may be the first, or an early sign, of Parkinsonism in elderly male patients.
- Lower urinary tract dysfunction in patients with Parkinsonism can be the result of detrusor overactivity, (benign prostatic) bladder outlet obstruction,

dyssynergic voiding or post void residual urine or any combination thereof.

Recommendations (grade B/C)

- The committee recommends that urodynamic evaluation should be conducted in all cases of nocturnal enuresis in adult males
- The committee recommends that urodynamic evaluation should be performed in patients with Parkinsonism. There should be flowmetry and postvoid residual assessment in all cases and invasive testing when abnormalities are observed in flowmetry and postvoid residual assessment.
- The committee suggests that investigators should be alert for large capacity bladder and/or underactive detrusor (or large residual without significant bladder outlet obstruction) as an early sign of Parkinson's disease.

III. NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

1. INTRODUCTION

Neurogenic LUTD is not precisely defined. The International Continence Society has defined 'neurogenic detrusor overactivity' (NDO): 'when there is a relevant neurological condition'. [Abrams,P. 2002] The specificity and sensitivity of signs and symptoms to confirm a relevant neurological condition are unknown, which is more or less acknowledged in the ICS standard above. However, for some of the urodynamic outcomes, also mentioned in this standard, a confirmation of 'clinically normal neurology' is required. In a recent EAU guideline the term 'neurogenic LUTD' is referred to as 'secondary to confirmed pathology of the nervous supply' and a precise description of the advised neurourological examination is provided. [Stohrer,M. 2009] Neurogenic incontinence may be described by terms such as, 'Reflex' or 'overflow incontinence'. These terms are not currently recommended by the International Continence Society nor used in the EAU guideline but they will also be discussed below, together with other relevant topics for this group of patients which are not covered elsewhere in this chapter.

2. WHAT IS USUALLY EVALUATED?

Because not all patients with neurogenic conditions develop LUTS or have abnormal urodynamic findings, a specific understanding of the dysfunction in each individual is a prerequisite for the correct choice of therapy. The aim of the diagnostic tests is to describe the (dys)function of the bladder, the urethra and the pelvic floor, their coordination during filling and voiding, and their influence on other conditions (e.g. autonomic dysreflexia) or organ systems (e.g. renal function).

Except in a few diseases where empirical, conservative therapy can safely be instituted, or where LUT dysfunction is predictable (e.g. post-stroke), urodynamic investigation is usually deemed to be required on the basis of clinical practice guidelines and expert reviews. Urodynamics is advised to provide the understanding of the situation on which rational treatment must be based. Even when empirical therapy is instituted without urodynamics, experts' opinion usually agrees on the basis of good clinical practice which is that the patient must be carefully monitored to determine whether and when urodynamics is needed. [Stohrer,M. 2009; McGuire,E.J. 2010]

A large proportion of patients with neurological conditions show anatomical abnormalities that involve the LUT, especially those born with abnormal neurology (MMC-see in children section of this chapter), and do have congenital relevant 'end organ (LUT)-sequelae' that can be demonstrated by imaging. Videourodynamics is the test of choice usually advised on the basis of expert opinion when relevant anatomical information is needed and relevant to establish treatment. [Stohrer,M. 2009]

3. SPECIAL TESTS

In patients with spinal cord injury (as a result of a trauma in later life) the detrusor and its innervation can be assumed to have developed normally (unless there was a positive history of urologic or other relevant abnormalities), before the injury. [Yoo,P.B. 2011; Kennelly, M.J. 2010]. Also, it has e.g. been shown that urethral sphincter relaxation in persons with dyssynergic activity can be improved or normalized. [Huang,Y.H. 2008]

Ice water (bladder cooling) test is sometimes used in an attempt to identify neurogenic DO (see section C.V.1.e: provocative manoeuvres) or to demonstrate the integrity of the detrusor muscle function and or its innervation. The clinical relevance of the ice water test is however undetermined and in patients with high level spinal cord injury the test can cause autonomic dysreflexia. [Chancellor,M.B. 1998; Huwyler,M. 2007]

One channel cystometry is reported to be feasible and reliable because patients with complete spinal cord injury usually do not generate much (abdominal or other) muscle activity below the lesion level and intravesical pressure adequately represents detrusor (relaxation or) activity. [Wyndaele,J.J. 2009]

4. NEUROGENIC DETRUSOR OVERACTIVITY INCONTINENCE

DO in association with neurological disease, may lead to UI. Observed during urodynamics, this type of incontinence is termed neurogenic DOI. The corresponding clinical sign or symptom is however variable: if the DO is accompanied by sensation (desire to void) it might be termed UUI; frequently however any sensation is absent, and so the term urgency in-

continence is an incorrect description of the situation. For this reason the term 'reflex incontinence' was introduced [Abrams 1988], implying uncontrolled emptying of the bladder without sensation. This term is no longer recommended. [Abrams 2002]

When a selection of symptomatic patients with NDO was analysed retrospectively, it was observed that patients with incomplete lesions had similar amplitudes of detrusor contraction and that also leakpoint pressures did not differ from patients with complete lesions. The authors consider it therefore relevant to perform UDS in patients with incontinence who have incomplete SCI. [Moslavac,S. 2008]

5. DETRUSOR-SPHINCTER DYSSYNERGIA

Neurogenic DO is often accompanied by detrusor-sphincter dyssynergia: a neurogenically determined failure of pontine coordination of detrusor and bladder outlet. In DSD the failure of the urethral sphincter and or the pelvic floor to relax completely and sustained, when the detrusor contracts, causes a dynamic type of BOO which may not only prevent complete bladder emptying, but can also lead to chronic and or intermittent high detrusor pressures, during bladder filling and or attempted voiding or incontinence. If high intra -detrusor pressures are present for prolonged periods in daily life, renal function is endangered (see the following subsection on 'overflow incontinence').

6. LEAKAGE ASSOCIATED WITH CHRONICRESIDUAL/ RETENTION OF URINE ('OVERFLOW INCONTINENCE')

'Overflow incontinence' is another term that is no longer recommended. [Abrams 1988] It meant continuous or intermittent (-stress 'like') leakage from a constantly overdistended bladder. [Abrams 1988] However neither what constitutes 'overdistended' nor the cause of the leakage are defined by the term 'overflow incontinence'. The presenting symptom is usually characterised by small amounts of incontinence, exacerbated by increased abdominal pressure, together with an inability to empty the bladder by voiding. Whilst incontinence appears as a problem of lower urinary tract storage function, 'overflow incontinence' originates from a dysfunction of voiding. Overflow incontinence can exist in combination with BPE and BOO but also exists in conditions with relevant neurologic pathology. Incontinence due to neurogenic underactive detrusor (or acontractility) or DSD, with incomplete emptying, and neurogenic incomplete voiding with incontinence, are clinical (urodynamic) descriptions and have not been officially defined.

During urodynamics a frequent observation is of a bladder with low compliance and little or no detrusor activity; as the bladder is filled, the detrusor pressure rises because of the poor compliance, until it reaches a value sufficient to overcome urethral resistance and open the urethral sphincter; dribbling leakage then ensues. Clinically, the most important variable is usually reported to be the detrusor pressure at which leakage occurs, the detrusor leak point pressure (DLPP). If this pressure is elevated, and if similar pressures are attained during continual leakage in daily life, then renal function is endangered because the constantly high detrusor pressure hinders outflow of urine from the ureters into the bladder. Conventionally, DLPP's of 40 cm H_2O or more are believed to be unacceptable. There is evidence (mostly from paediatric studies with children with meningomyelocele) that upper urinary-tract deterioration is more probable when DLPP is elevated above that 40cmH_2O. [McGuire,E.J. 1996; Tanaka,H. 1999; Kurzrock,E.A. 1998] However, the evidence for a cut-off at 40 cm H_2O seems less clear and an expert opinion appears to introduce 'as low as reasonably achievable' and a 'safe' detrusor pressure of below 20 cmH_2O, over the entire 'daily' volume range, when CIC is part of the treatment, is advised. [McGuire,E.J. 2010]

7. REPRODUCIBILITY AND RELIABILITY OF TESTS

Since many patients with NLUTD have severe subpontine neuropathy, the influence of the emotional (limbic) nervous system on lower-tract function is reduced or eliminated; thus, urodynamic observations may be less influenced by the test circumstances than those made in individuals with an intact nervous system. Nevertheless, the test conditions (e.g. the rate of filling the bladder) do influence the results, and should be chosen carefully. [Homma et al 2002] Some advocate ambulatory monitoring to reduce the variability of filling cystometry. [Pannek,J. 2009] However, tests of longer duration with natural filling, did not relevantly assist in the diagnosis and selection of treatment in patients with SCI in a monocenter prospective comparison. [Martens,F.M. 2010]

8. DOES URODYNAMIC TESTING HELP TO SELECT (OPTIMAL) TREATMENT?

The aims of therapy for NLUTD are to achieve the most physiological filling and voiding conditions possible, as well as a management situation acceptable to the patient in daily life. Long periods of elevated detrusor pressure during bladder filling or (abnormally prolonged) voiding put the upper urinary tract at risk. [McGuire,E.J. 1996; Tanaka,H. 1999; Kurzrock,E.A. 1998]. The primary aim of therapy in patients with such problems is conversion to a low pressure bladder during filling, [Stohrer, 1994; Rivas, D.A. 1995; McGuire,E.J. 2010] achieve continence, and to manage incomplete emptying due to (medically induced) underactive detrusor or detrusor acontractility, with CIC. [Stohrer,M. 2009]

Adequate management depends on whether the detrusor is overactive or has reduced compliance, and only urodynamic testing can answer those questions unequivocally. Timely and adequate diag-

nosis is of paramount importance for the patient's Quol, as well as for safety. [Bomalaski,M.D. 1995; Cardenas,D.D. 1995] There is expert agreement that urodynamic investigation is essential to monitor the effects of any treatment and in the follow up of any sequelae of the disease and its management. Urodynamics is certainly needed to document the effects of new treatments or management strategies for patients with NLUTD. But changes in urodynamics do not always relate to clinically relevant improvements in these patients. [Huwyler,M. 2007; Pannek,J. 2009; Kabay,S.C. 2008] A retrospective study shows with 80 SCI patients and a minimum follow-up of 5 years, that it is possible to manage continence and preserve (100% of) upper tracts with ultrasound monitoring of the kidneys and repeated UDS. [Nosseir,M. 2007] Another retrospective observation indicates, in a series of 200 children with various types of NLUTD, that the intensity (frequency) of urodynamic follow up can be adapted according to the estimation of the risk for upper tact deterioration on the basis of urodynamic parameters achieved at a baseline. [Wang,Q.W. 2006]

Conclusions (level 3)

- There is expert agreement on the basis of a large number of case series that urodynamic testing is of great relevance to establish the management and to achieve the best long term clinical outcome in patients with neurogenic lower urinary tract dysfunction.
- On the basis of expert opinion, videourodynamics is necessary when anatomical information is deemed clinically relevant.
- Case series indicate that it is possible to monitor patients without anatomic abnormalities of the lower urinary tract (especially adult age spinal cord injury) with cystometry and ultrasound of the upper tract.
- No specific reports about the optimal frequency and techniques of follow –up urodynamics in patients with neurogenic lower urinary tract dysfunction exist
- No conclusive evidence exists about the predictive value towards (the outcome of) treatment with regard to ice water testing, or of ambulatory monitoring of patients with neurogenic lower urinary tract dysfunction.
- Some evidence from centres of excellence indicates that 'simple, one channel, cystometry' is feasible and reliable in the monitoring (follow-up) of a selected group of patients with complete spinal cord injury.

Recommendations (grade B/C)

- The committee recommends that patients with signs and symptoms of dysfunction of the lower urinary tract and relevant neurological abnormalities should receive urodynamic evaluation (including filling and voiding cystometry), if initial treatment will be affected as a consequence of the urodynamic diagnosis, or if 'simple' first line diagnosis and management have been unsuccessful.
- The committee recommends that at least at a baseline, to establish the state and function of the lower tract in patients with neurogenic lower urinary tract dysfunction, videourodynamic evaluation is indicated if relevant anatomical abnormalities are to be expected.
- The committee recommends that the frequency of testing and the techniques applied in the follow – up of patients with neurogenic lower urinary tract dysfunction be critically analysed and optimised, and to develop guideline recommendations on the basis of those analyses.
- The committee recommends that urodynamic testing in patients with neurogenic lower urinary tract dysfunction is done with special attention to the specific needs of the patients. It is highly preferable that all professionals involved are specifically trained for that purpose.

Recommendations for research:

- Comprehensive urodynamic testing should remain an integral part of the evaluation of new therapies and management strategies for neurogenic lower urinary tract dysfunction whether conservative, medical or surgical. The first goal of this should be to monitor the safety of the (developed) approach for the patient and the secondary goals of this urodynamic testing should be the efficacy outcomes (preferably on predefined urodynamic criteria).
- Specific urodynamic diagnosis categories and diagnostic techniques need to be developed to quantify detrusor sphincter dyssynergia and neurogenic underactive detrusor.

IV. PATIENT EVALUATION: CHILDREN

1. INTRODUCTION

The indications for urodynamic evaluation in children are usually neurological, anatomical and or functional abnormalities, with the types of studies to be performed being based on the presumed underlying pathological conditions rather than on the presenting symptoms.

Many of the conditions for which urodynamics is employed in children involve anatomical and or neurological abnormalities, in which LUT dysfunction is variable, and may be multifaceted and unpredictable on the basis of clinical signs and symptoms. UI in children is relatively more frequently seen (compared

to adults), and in combination with other lower urinary tract (or lower bowel or pelvic floor) dysfunctions. On the other hand, urinary continence (and lower urinary tract function) are the result of a normal maturation process that can be delayed in some, and 'cure' (or 'resolve') without requiring medical intervention. Urodynamic testing is used to establish as clearly as possible the baseline situation where needed, so that changes as a result of treatment and/or growth can be assessed, and some guidance is obtained in the choice of treatment. The result of urodynamic testing will, however, not necessarily be the only deciding factor in this regard. Perhaps more clearly than in any other patient group, the aim of urodynamic studies in children is to provide objective knowledge about LUT function and dysfunction as well as to provide understanding to the care-giver and to the patient (and her or his parents). More extensively than in other ages, non-invasive urodynamic techniques are initially explored, not only because they are easier accepted and better applicable for children, but also to have comparable parameters during follow-up, and to exactly identify those children and clinical conditions that will benefit from further invasive exams. Essential are a meticulous and complete history, physical examination including clinical neurological testing and assessment by voiding diaries. Furthermore, initial ultrasonographic measures of bladder volume and wall thickness have been reported more and more as a useful tool in selecting who will need invasive testing. [Bower,W.F. 2010; Drzewiecki,B.A. 2011]

2. NEUROGENIC BLADDER DYSFUNCTION

a) Myelodysplasia

For the last 20 years, initial urodynamic studies, very early in the neonatal period, have been recommended for children with myelodysplasia, the basis being that they help identify children at risk for subsequent urinary tract deterioration or a changing neurological picture. [Sidi,A.A. 1986] DO on cystometry, underactive detrusor during voiding, detrusor-sphincter dyssynergia (usually established on the basis of surface EMG), DLPP, and PVR are the key elements of a detailed urodynamic study that need to be considered. [McGuire,E.J. 1981; Bauer,S.B. 1984]

In an exhaustive review of the efficacy and reliability of urodynamic studies in newborns with myelodysplasia [McLellan 2003], of 24 studies analysed, 13 focused on EMG activity of the striated urethral sphincter or pelvic floor, 7 on bladder compliance and 2 on cystometric technique. Twenty-one studies had level of evidence 4, 2 had level 3 and one level 1 study was found. Nine of the 24 studies were performed at international sites and the remainder within the United States. The urodynamic patterns of normal detrusor function (66%), acontractile detrusor (33%), DO (57%), and detrusor compliance, as well as detrusor-sphincter dyssynergia (21%), DSD (37%) and sphincter denervation (60%) were similar, with little variability across comparable studies.

Van Meel et al have shown that repeating the IWT will increase its positivity. Combining the IWT and electrical perception threshold (EPT) will reinforce the results of both tests and can indicate more clearly the possibility of an unsuspected neurological cause of the dysfunction in children with idiopathic DO. In those with negative IWT's, the EPT's were significantly different between the neurological and not neurological patients, independent of the number of IWT's done. [Meel 2007]

Bladder capacity was studied in a group of 506 myelodysplastic children [Palmer 1997] and found to conform to the formula: capacity in mL = 24.5 x (age in years) + 62. This formula for the increase in bladder size with age is 20% less steep than published age-related bladder capacities in neurologically unaffected children (e.g. 30 x age + 30). [Starfield 1967; Koff 1983] However, those children who did not have DO had a bladder capacity similar to normals. Because neurological impairment affects detrusor compliance, cystometric filling rate also influenced the measured capacity and compliance as noted in 3 studies that addressed this issue. [Palmer 1997; Kaefer 1997; Landau 1994] The lower the filling rate the greater the compliance and the larger the capacity.

Bladder augmentation alone without simultaneous anti-reflux repair is usually considered sufficient for the resolution of pre-existing vesico-ureteral reflux in children with NLUTD. Cystometry can be used to evaluate the effect of this treatment. A retrospective study by Juhasz et al in 2008 suggested that diverse GI segments used for augmentation had identical effects on the urodynamic results and the resolution of vesico-ureteric reflux. [Juhas 2008]

Several studies that evaluated the urodynamic result of bladder augmentation have been published. Significant increase in bladder capacity and compliance were achieved and maintained in the long term. [Lima 2008] A recent small mono-centre study, showed that preoperative urodynamics has some predictive value on the outcome of augmentation towards the relief of vesico-ureteric reflux in those children. [Soygur 2010] Follow up of affected children after early childhood is relevant, and urodynamic testing forms the basis for (surgical) management. [Almodhen 2007] A 20 years follow-up of 52 children demonstrates also that the early urodynamic diagnosis has been an adequate basis for the management of children with meningomyelocele in a single centre of excellence. [Thoru 2011]

Rendeli et al retrospectively assessed the usefulness of urodynamic testing to determine the optimal timing of neurosurgery and to evaluate the evolution of bladder function in children with lipomeningocele. All patients underwent urodynamic testing

preoperatively and during extended follow up (mean 6.5 years, range 3 to 12). At the latest follow up, 65% of patients in the youngest group had improved urodynamic parameters compared to 33% of those 12 to 36 months old and 28% of those older than 36 months. Urodynamic evaluation and the presence of neurological impairment were considered to have had crucial roles in determining the optimal timing of surgery in patients with lipomeningocele, and in diagnosing the onset of tethered cord. [Rendeli 2007] A recent retrospective mono-centre study confirmed that urodynamic testing is relevant towards the outcome of neurosurgical interventions. [Maher 2009]

Six studies evaluated the relationship between level of the neurological lesion (on clinical examination) and LUT function, but none could predict a specific urodynamic pattern based on the level of the lesion. Sacral level lesions can be associated with an upper motor neuron urinary tract 'urodynamic pattern' just as readily as the expected lower motor neuron findings. [Dator 1992] Similar findings have been noted for children with thoracic or high lumbar level lesions where the incidence of sacral reflex sparing is 54%. [Pontari 1995]

Approximately 90% of children born with meningomyelocele will have a normal upper urinary tract at birth. Over time, many children who have not received proactive urological care develop upper and/or LUT deterioration. The deterioration is an acquired phenomenon secondary to the development or progression of various LUT hostility factors such as DO, reduced bladder compliance, detrusor-sphincter dyssynergia and/or high LPP. [Sidi 1986; Bauer 1984; Wang 2006] Despite the fact that only one study was at level 1, all urodynamic studies corroborated their reliability by reporting that the prediction of upper urinary tract deterioration on the basis of urodynamic testing is possible with 90% accuracy.

In 2006, Wang et al calculated a urodynamic risk score including a DLPP of >40 cmH_2O, a bladder compliance of <9 mL/cmH_2O and evidence of acontractile detrusor. They postulated that the selective use of urodynamic variables might be valuable for predicting the risk of upper urinary tract dilatation in children with neurogenic bladder-sphincter (or LUT) dysfunction. They found that decreased bladder compliance, increased DLPP and acontractile detrusor are the main urodynamic risk factors, and they reciprocally increase the occurrence and grades of upper urinary tract dilatation. The grades of renal dilatation are compatible with increases in relative unsafe cystometric capacity and the calculated urodynamic risk score. [Wang 2006] Severe bladder trabeculation in incontinent children with NLUTD is reported to be associated with BOO. [Khoury 2008]

Monocenter studies suggest that prevention of high bladder filling pressure (before upper tract dilatation is observed) is necessary and feasible even before any urodynamic diagnosis. [Dik 2006; Hopps 2003; Obara 2003; Jong 2008] However not all authors consider that prophylactic (high pressure prevention) treatment is beneficial, but all recommend periodic cystometry when new onset hydronephrosis, vesico-ureteric reflux or UI develops, the latter in children on a continence program already (i.e. CIC and/or drug therapy). [Bauer 1985; Geranio 1988] When new onset UI, not related to urinary infection, nor easily treated by increasing current treatment regimens occurs, one study has shown that repetition of cystometry, urethral pressure profilometry, and EMG measurements, is helpful in management. [Teichman 1994]

When incontinence develops in spite of strict adherence to bladder and bowel continence programs, or when changes occur in leg function or sensation, or when the child experiences back pain or increasing scoliosis, a change in neurological impairment might be expected. 4 studies, noted that a considerable number of myelodysplastic children (40% to 61%) regardless of their neurological level have progressive neurological deficits as they grow up and reach puberty. [Dator 1992; Spindel 1987; Lais 1993; Tarcan 2001] Two of these studies noted changes particularly early in infancy, while a third study noted changes throughout childhood. Most clinicians agree that myelodysplasia is a dynamic disease process which changes as the child grows and that warrants constant vigilance of both the neurological picture and lower urinary tract function.

In 2006, Schulte-Baukloh et al evaluated prospectively the efficacy and tolerability of propiverine for treating neurogenic DO in children and showed that urodynamic testing has been relevant to evaluate the treatment. [Schulte 2006] This was recently confirmed in a longer follow up with urodynamic evaluation as an outcome. [Schulte 2011]

Renal transplantation in patients with myelodysplasia is a challenging issue. Persistent LUT dysfunction carries increased risks for the grafted kidney. Recent publications suggested that renal transplantation is a safe and effective treatment modality in patient with myelodysplasia when objective analysis of LUT function is done and the results are taken into account properly. Some series show cohorts where videourodynamic tests were performed on all patients preoperatively as well as postoperatively. Augmentation cystoplasty has been reported to be required in a proportion of children to achieve a low-pressure reservoir with adequate capacity [Ali-El-Dein 2004; Bilg 2008; Luke 2003] to optimize the LUT for transplantation.

b) Occult spinal dysraphism

Several series characterising the preoperative urodynamic evaluation of children with occult spinal dysraphisms have documented abnormalities in striated urethral sphincter function (denervation and/or detrusor-sphincter dyssynergia) in 20 - 35%

of babies under 2 years of age with normal neurological examinations; thus emphasising the need for urodynamic testing in these children. [Keating 1988; Yip 1985; Satar 1997; Torre 2002; Hsie 2006; Kumar 2008] Six reports in older children revealed a greater correlation (70 – 90%) between an abnormal neurological examination and the likelihood of finding an abnormality on urodynamics. [Keating 1988; Hsie 2006; Kumar 2008; Satar 1995; Kondo 1986] A few studies demonstrated that between 10% and 20% of patients experience a loss in function immediately postoperatively (most of whom had abnormal LUT function preoperatively), and a variable number, usually inversely related to age, have improved sacral cord function on postoperative assessment 3 or more months after surgery. [Keating 1988; Satar 1997; Satar 1995; Kondo 1986; Fone 1997] Two studies, both retrospective, revealed an efficacious response in EMG activity, with stabilisation or improvement in up to 60%, on postoperative urodynamic assessment when the dysraphic state was corrected before 2 years of age. [Keating 1988; Satar 1995] When children were first operated on after 2 years of age, 2 urodynamic reports documented an additional 25 to 35% with progressive changes in urethral sphincter function with axial growth, very few of whom had a detectable change on physical examination. [Yip 1985; Satar 1995]

In a small prospective study in 2008, it was observed that children with meningomyelocele, as compared to closed dysraphism, tended to have more bladder dysfunction as exemplified on clinical history and urodynamic assessment. The authors concluded that a urodynamic study before neurosurgical intervention helped to identify the severity of bladder dysfunction in clinically overt cases and also identified LUTD in clinically silent cases. Evaluation after operation tended to show better outcome in children with closed dysraphism. The study also identifies deterioration in some patients with seeming clinical improvement. [Kumar 2008]

In 2007, Abrahamson et al studied the urodynamic findings in a consecutively treated population of children with meningomyelocele after untethering of the spinal cord. Severe bladder dysfunction, moderate dysfunction and mild dysfunction were defined preoperatively. After untethering, 35% of the patients experienced improved bladder function and 5% deteriorated. All of the patients who deteriorated before untethering improved afterward, and 90% of those who were stable preoperatively continued to be stable postoperatively. [Abrahamsson 2007; Snodgrass 2010]

Conclusions (level 2/3)

- Retrospective and prospective studies have shown that the urodynamic diagnosis of (neurogenic) detrusor overactivity and/or reduced detrusor compliance in patients with myelodysplasia or (occult) spinal dysraphism is not predictable on the basis of clinical signs or symptoms.
- Many retrospective and prospective studies have shown that regularly repeated urodynamic testing in patients (children) with meningomyelocele or (occult) spinal dysraphism reveals clinical relevant results with regard to management and surgical or medical treatment.
- On the basis of expert opinion, videourodynamic testing is preferable above urodynamic testing without video, however the exact advantage (e.g. in repeated investigation) is not substantiated.
- Various studies have shown that lower urinary tract function in children with myelodysplasia or (occult) spinal dysraphism may change over time (and physical growth)
- No studies have been published that are a help to determine the optimum of timing and frequency of urodynamic follow-up.

Recommendations (grade B/C)

- Comprehensive urodynamic testing is advised in all patients with myelodysplasia or (occult) spinal dysraphism throughout the entire life on a regular basis from earliest childhood.
- On indication, unscheduled urodynamic testing should be considered when relevant (lower body half and or urinary tract) clinical (or neurologic) signs or symptoms arise or when significant (surgical or medical) treatment changes have been instigated.

Recommendations (grade C)

- The advantages and disadvantages of the addition of video (x-ray) to urodynamic testing should be considered in children with myelodysplasia or (occult) spinal dysraphism on an individual basis.
- Timing and technique of urodynamic testing in patients with myelodysplasia or (occult) spinal dysraphism must be selected on an individual basis.
- To help identify children at risk for subsequent urinary tract deterioration or a changing neurological picture, initial urodynamic studies, very early in the neonatal period, are recommended for children with myelodysplasia or (occult) spinal dysraphism.
- The committee recommends on the basis of expert opinion that anorectal function or dysfunction is simultaneously evaluated with urinary tract function in children with myelodysplasia or (occult) spinal dysraphism (see also the chapter on faecal incontinence).

c) Sacral agenesis

Sacral agenesis, absence of the lowermost vertebral bony segments, is a lesion that can be missed in infancy because of its sometimes subtle clinical

manifestations, with generally no loss of lower extremity motor and sensory function, and the non-progressive nature of its pathophysiology. [Guzman 1983; Borrelli 1985] Urinary and/or faecal incontinence usually manifests at an older age when the child fails to toilet train on time. A careful physical examination noting flattened buttocks and a short gluteal crease is pathognomonic for the diagnosis. In 8 reports that provided enough data, urodynamic studies had been 90% accurate in delineating the neurological deficit, which cannot be predicted by the level of absent vertebrae. [Jabokson 1985; Gotoh 1991; Saito 1991; Boemers 1996; Boemers 1994; Boemers 1994; Wilmshurst 1999; Mosiello 2003; Taskinen 2002] These studies reveal that between 30 and 40% of these patients have an upper motor neuron type lesion with DO and an intact but dyssynergic sphincter, while 25 to 50% have signs of a lower motor neuron deficit with acontractile detrusor and denervation in the sphincter, and 15 to 20% have normal LUT function. [Guzman 1983; Jabokson 1985] Tethered cord occurs in children without sacral anomalies as well as in those with low anorectal malformation (ARM).

Mosiello et al [Mosiello 2003] recommend evaluation of all patients that have sacral agenesis with MRI, and this necessity has been confirmed by others, who found the extension of the sacral defect as a prognostic factor for retethering. [Kim 2010] When MRI shows sacral or spinal cord anomalies, UDS should be considered, preceded by neurological exam and considering neurophysiological testing (evoked potential testing) The authors of this and subsequent studies recommend a non-invasive evaluation for all other children, and urodynamics when NLUTD is suspected. [Borg 2009] It is presumed that the neurological deficit associated with this entity is fixed because no study showed any progression of the neurological disorder with increasing age.

Conclusions (level 3)

- Case series have shown that urodynamic evaluation of lower urinary tract function in children with (partial) sacral agenesis reveals a substantial incidence of clinically hidden dysfunction.
- It is shown that approximately one third of children with anorectal anomalies have spinal dysraphism and/or tethered spinal cord associated with urodynamically demonstrable neurogenic lower urinary tract dysfunction .

Recommendations (grade C)

- Clinicians should consider urodynamic testing in children with sacral agenesis and also after (surgery for) sacrococcygeal teratoma
- Clinicians must consider that in children with lower urinary tract dysfunction, otherwise clinically silent sacral agenesis can exist.

d) Spinal cord injury

The scarcity and variability of spinal cord injuries in children makes it difficult to propose any one treatment program unless the specific type of LUT function is known on the basis of urodynamic testing. [Chou 2006; Generao 2004; Silveri 2006] Even if the individual regains the ability to void spontaneously and empty his/her bladder, it is imperative to know the detrusor filling and emptying (detrusor) pressures. Even if the child is continent on CIC, it is important to measure detrusor compliance in order to determine the potential risk for vesico-ureteric reflux and hydroureteronephrosis. [Pannek 1997] Four studies extol the need for urodynamic studies once spinal shock from the initial injury wears off, to determine the presence of low filling and voiding pressures and the ability for complete emptying, for the reasons cited above. [Decter 1993; Kim 1998; Fanciullacci 1988; Iwatsubo 1985] All studies are monocenter, retrospective and use historical controls for comparison.

In the presence of elevated urodynamic filling and voiding pressures, a 30% incidence of upper urinary tract deterioration can be expected. [Kurzrock 1998] Effective voiding with pressures below 40 cm H_2O in the absence of detrusor-sphincter dyssynergia ensures a stable upper urinary tract. [Fanciullacci 1988] Urodynamic monitoring has been demonstrated to be relevant in the follow up and prevention of upper tract deterioration in a retrospective cohort study. [Generao 2004] In another study on 17 children aged 6 months-18 years with cervical (4), thoracic (8) and lumbar (5) SCI, all but one showed DO on first evaluation, which was changed to an acontractile and or compliant detrusor pattern by medical treatment; 7 had increased bladder capacity and 8 decreased DLPP at follow-up; only 2/17 developed minor UUT impairment. [Silveri 2006] A cauda equina injury usually leads to a lower motor neuron type of deficit of the striated sphincter that may not require any treatment to prevent upper tract damage because the bladder empties readily at low pressure, but it probably necessitates medical and/or surgical therapy to achieve continence. Urodynamic studies are invaluable to efficaciously manage any spinal cord lesion related LUT dysfunction, in order to maintain a healthy upper urinary tract and long-term survival with minimal morbidity. [Kim 1998; Watanabe 1996]

Urodynamic studies, undertaken no earlier than 6 weeks after injury, allow for the manifestation of the extent of the neurologic injury. [Iwatsubo 1985] Periodic urodynamic reassessment is appropriate up to 2 years after injury, due to the potential for changes during that time. Further urodynamic follow up is ‘standard’ as in adult patients. [Nosseir 2007]

Conclusion (level 2/3)

- Retrospective studies have shown that urody-

namic testing of all children with spinal cord injury is relevant.

- Retrospective studies have shown that urodynamic testing of children with spinal cord injury results in diagnoses and treatment similar to adults with spinal cord injury.

Recommendations (grade C)

- The committee recommends that urodynamic testing in children with spinal cord injury is planned on an individual basis, but no earlier than 6 weeks after injury.

e) Cerebral palsy

Only a few published studies describe the urodynamic findings in children with cerebral palsy. [Decter 1987; Mayo 1992; Reid 1993; Yokoyama 1989] The vast majority of the children with cerebral palsy tend to gain normal lower urinary tract function, but often at an age that is later than expected for normal individuals. [Decter 1987] Any incontinence is usually secondary to urinary urgency from DO. [Reid 1993] A meta-analysis of urodynamic studies performed in children with either persistent incontinence despite frequent toileting, or urinary tract infection, revealed either normal function (15%) or DO (73%; 85 of 117 patients);[Decter 1987; Mayo 1992; Reid 1993] detrusor sphincter dyssynergia is very rarely observed during voiding (5%; 12 of 249 patients). [Dator 1992; Mayo 1992; Yokoyama 1989] In some recent studies, detrusor-sphincter dyssynergia was present in higher prevalence then earlier reports (11% / 5%). [Karaman 2005; Bross 2007] Normal function was less prevalent (only 15%) in the more recent case series. [Bross 2007; Silva 2009]

Therefore, it has been suggested on the basis of expert opinion that cystometry and sphincter EMG are to be considered, but only when frequent toileting or anticholinergic therapy fails to control incontinent episodes, the child develops urinary infection from ineffective voiding, or when ultrasonography reveals hydronephrosis.

However, videourodynamic assessment can be considered in all patients with infantile cerebral palsy. The decision should not be based on clinical symptoms because at least half of the children with spastic cerebral palsy have clinically silent bladder dysfunction. 100% of children had clinical improvement postoperatively (selective dorsal rhizotomy), 71% who were incontinent preoperatively became continent and none had deterioration on urodynamics. [Bross 2007; Houle 1998; Farmer 2007] There is a spectrum of clinical and urodynamic LUT function in children with cerebral palsy: 77% void spontaneously but do have UI. Incontinent children have a lower age-related bladder capacity, as shown both in slow fill water cystometry study [Richardson 2009] and in a noninvasive evaluation (flowmetry plus PVR), showing a significant difference between observed and expected bladder capacity. [Ersoz 2009]

Conclusion (level 3)

- Some studies (with historical/ literature -control groups) have shown that clinically unexpected lower urinary tract dysfunction – predominantly dysfunctional voiding and lower bladder capacity - can occur in children with cerebral palsy.

Recommendations (grade C)

- Clinicians should carefully evaluate voiding in children with cerebral palsy and should consider complete urodynamic testing when dysfunction is suspected
- Urodynamic testing is to be considered in all patients with spastic cerebral palsy. Undiagnosed and untreated patient's bladder dysfunction remains pathological and potentially dangerous, and may damage the upper urinary tract.

f) Tumours

LUTD exists after sacrococcygeal teratoma resection and recently again it was, on the basis of a monocenter cohort, proposed that urodynamic testing is necessary for those children. [Mosiello 2003; Ozkan 2006; Berger 2011]

A recent study showed that children with central nervous tumours can have urodynamic abnormalities, whether the tumour is in the spinal cord or not. On the basis of this, a monocenter and selected cohort study concluded that a child with a CNS tumour regardless of location needed urological and urodynamic testing. [Nguyen 2010]

Conclusion (level 3)

- It was shown in monocenter cohorts that urodynamic testing is relevant after resection of a sacrococcygeal teratoma.
- A study showed that all children with central nervous system tumours can have lower urinary tract dysfunction regardless of the location of the tumour.

3. ANORECTAL MALFORMATION OR IMPERFORATE ANUS

Imperforate anus is classified as high, intermediate or low depending on whether or not the rectum ends above, at, or below the levator ani muscle. In the past, imperforate anus repair for high lesions frequently resulted in urinary (stress-) incontinence due to a pudendal nerve injury that often occurs from a perineal approach to bringing the rectum down to the anal verge. [Pena 1986] With the advent of the posterior sagittal anoplasty this complication has been eliminated as a cause for subsequent UI, although bladder neck incompetence may be a consequence of extensive mobilisation of the sigmoid colon which helps transfer the rectum to its final location. However,

reports of spinal MRI's reveal a 35% incidence of distal spinal cord abnormalities in children with an imperforate anus. [Barnes 1986; Greenfield 1991; Kakizaki 1994]

Wetting after definitive repair is reported to be the possible result of stress incontinence through ineffective emptying ('overflow incontinence') and underactive or acontractile detrusor rather than sphincter injury. In 2005, Shimada et al reported on the reconstruction of cloacal anomalies in a consecutive series of 11 girls. The main clinical characteristic of bladder dysfunction was a failure to empty. [Shimada 2005] They could not define the precise aetiology, but iatrogenic injury from extensive dissection can lead to the higher risks of peripheral nerve damage.

In 2004, Warne et al prospectively studied the effect of surgical reconstruction by posterior sagittal approach and total urogenital mobilisation in either causing or worsening bladder dysfunction in new patients with cloacal anomalies. A comparable group of patients with ARM were studied as comparative controls to assess the effect of posterior sagittal approach without urogenital surgery. Natural filling urodynamics via a suprapubic catheter showed that bladder dysfunction was present in 9 of 10 patients with cloacal anomalies and in 12 of 20 patients with ARM. After surgery there was significant deterioration (frequently a change to underactive detrusor) in bladder function in half of the cloacal group and in 1 of 20 patients with ARM. Patients with cloacal malformation have a high incidence of innate LUTD and surgical reconstruction can cause further deterioration particularly in the group that needs extensive intrapelvic mobilization. Urodynamic assessment is required to evaluate LUTD in these patients. [Warne 2004] In 2006, a prospective study reported on children with ARM, prior to and following definitive procedure, using urodynamic evaluation. Among these 19 children, 13 underwent re-evaluation after definitive surgery for ARM. Only 9 of the 19 patients had normal urodynamics pre-operatively and post-operatively, and the LUT function of 3 patients was found to be worsened postoperatively. [Kumar 2006]

Mosiello et al recommends evaluation of all patients with ARM using MRI. When MRI shows sacral or spinal cord anomalies, urodynamics should be performed. They recommend a non-invasive evaluation for all other children and urodynamics when NLUTD is suspected. [Mosiello 2003]

NLUTD occurs in 50% of those with ARM. [Kumar 2006; Boemers 1996] The prevalence of spinal dysraphism and/or tethered cord in patients with ARM is 32-34%, independently from the severity of ARM and a variable proportion (40-60%) of those patients who have tethered cord needed untethering. [Kim 2010; Suppiej 2009]

The reliability and reproducibility of these findings among the various studies analysed confers an important role for videourodynamic studies as an integral part of the evaluation and management of these children: it has diagnostic accuracy; it provides arguments to consider treatment of any intraspinal (neural) abnormality to improve the child's chances of achieving urinary and faecal continence. Urodynamic testing is also considered useful as a basis for future comparison, if LUTD should subsequently become a problem in children not undergoing early spinal cord exploration.

The VATER or VACTERL association is a group of diverse abnormalities that include Vertebral bony, Anal atresia, Cardiac, Tracheo-Esophageal fistula, Renal and Limb anomalies. [Cardenas 1995] Imperforate anus may occur as an isolated lesion or in conjunction with this association. Spinal cord pathology occurs in 38% of cases producing a picture of upper and/or lower motor neuron deficits to the LUT. [Boemers 1996; Greenfield 1991; Emir 1998; Capitanucci 1996; De Gennaro, M. 1994] By combining the incidences in 3 studies it was found that the presence of an abnormal sacrum increases the likelihood of LUTD to as high as 76% (38 of 50 children). [Boemers 1996; Emir 1998; Capitanucci 1996] When the rectum ends above the levator ani muscle there is a much greater chance of LUTD than when it ends below the pelvic floor [Mosiello 2003; Emir 1998] and the older the child is at the time of urodynamic assessment the more likely he/she is to have abnormal LUT function. [De Gennaro,M. 1994; Capitanucci,M.L. 1996]

Conclusions (level 3)

- Various studies have shown that a significant proportion of children with an anorectal malformation has primary or secondary dysfunction of the lower urinary tract, lower urinary tract innervation abnormalities or pelvic floor dysfunction.

Recommendations (grade C)

- Clinicians should consider urodynamic testing in children with imperforate anus when clinical signs of lower urinary tract dysfunction exist.
- Clinicians should consider urodynamic testing in children where, on the basis of an MRI, or on the basis of clinical examination, relevant neurological abnormalities exist, before and or after reconstructive surgery independent of (the existence of) lower urinary tract symptoms.

4. ANATOMIC ABNORMALITIES

The use of urodynamics for evaluating anatomic lesions that affect the lower and, consequently, the upper urinary tract in children is still somewhat controversial. Essentially, the evidence consists of uncontrolled case series and expert opinions although many clinicians now feel its usefulness is beyond question.

a) Posterior urethral valves

Nowhere is the above controversy more obvious

than in boys with posterior urethral valves. [Bauer 1979; Mitchell 1982; Glassberg 2001] Prior to the ready availability of urodynamics, persistent upper urinary tract dilation was managed with bladder neck resection and/or striated urethral sphincter resection. By demonstrating the presence of DO or secondary underactive detrusor, urodynamic studies have helped explain the findings of hydroureteronephrosis that many of the children exhibited over time despite adequate valve ablation. These studies changed the focus from increased bladder outlet resistance to altered bladder function as the aetiology of the longer term sequelae.

There are only a few urodynamic reports prior to valve ablation. In one, DO was seen in 60%, poor compliance in 10% and normal function in 30%. [Kim 1997] In the other, all 46 patients had 'bladder hypercontracility' (obsolete term, used in the manuscript) and comparable high maximum voiding detrusor pressures. At the end of follow -up (mean 4.5 years) in this second study, no patient in group 1 (22 patients who underwent simultaneous valve ablation and bladder neck incision at the 6 o'clock position) had 'bladder hypercontractility' or DO, and the mean maximum voiding detrusor pressure was 53 ± 15 cm H_2O. In comparison, 9 patients in group 2 (24 patients who underwent simple valve ablation) had 'bladder hypercontractility', 6 had DO and the mean maximum voiding detrusor pressure was 87 ± 45 cm H_2O ($p<0.01$). [Kajbafzadeh 2007] Another study compared urodynamic patterns before and after valve ablation, and within 15 days following ablation and at one year of life. At presentation, median cystometric bladder capacity was 22 mL (5 to 125) and maximum voiding pressure was 112 cm H_2O (40 to 331. No significant differences were found before and after ablation. Voiding pressures had significantly decreased ($p=0.01$) and bladder capacity had increased ($p<0.001$) at 1-year follow-up. [Taskinen 2009] Comparing the patterns found in other series of infants, voiding pressures in infants with posterior urethral valves are as high but not higher.

In a series of urodynamic studies after valve ablation, the type of bladder function observed, correlates with the time elapsed from surgery; DO is the predominant pattern initially [Bauer 1979] but changes are noted in both DO and compliance over time. [Holmdahl 1995; Holmdahl 1996; De Gennaro,M. 1996; De Gennaro,M. 2000; Donohoe 2004] In 2005, a series of 30 patients showed DO with single or multiple detrusor contractions in 60 %, and small capacity, reduced bladder compliance in 40%. [Puri 2005]

Myogenic failure, in conjunction with increasing capacity and poor emptying, are primarily a later phenomenon, and are most likely to be secondary to increased urine production and decreased frequency of voiding with advancing age. [Holmdahl 1996] Despite early valve ablation, a large proportion of boys treated for PUV have gradual detrusor 'decompensation' and/or secondary bladder neck outlet obstruction leading to obstructive voiding and finally underactive detrusor or acontractility. [Androulakakis 2005] Vesico-ureteric reflux was initially, in a small and selected series, most commonly noted in boys with DO, whereas hydronephrosis is most frequently seen with a poorly compliant bladder, [Peters 1990; Ghanem 2004] while in a recent study patient with and without reflux had similar voiding pressures. The persistence of upper urinary tract changes is related to the bladder's unresponsiveness to medical therapy for the DO and/or for detrusor underactivity (usually clean intermittent (self-) catheterisation). However, it is possible that this condition is secondary to sufficiently infrequent voiding in the face of increased urine production. BOO from a secondary hypertrophied bladder neck can also occur, requiring further intervention. [Kajbafzadeh 2007] Several studies have shown the predictability of the development of renal failure based on specific detrusor patterns seen on urodynamic evaluation; persistent poor compliance, high detrusor pressures, BOO and or chronic failure of the detrusor to adequately contract during voiding with increased PVR are the most likely causes of deterioration. [Bauer 1979; Mitchell 1982; Holmdahl 1995; Holmdahl 1996; Peters 1990; Lopez 2002; Ansari 2010] Most probably, the extended use of antenatal diagnosis could select a 'new generation' of valve patients, who undergo proper early ablation of the obstructing valves allowing normal cycling, which helps 'bladder healing'. Youssinf, comparing a group of 16 children who underwent valve ablation as newborns and a group of 16 boys observed after age 1 year, showed that post-void residual urine and vesicoureteral reflux improved in a higher percentage in those early treated. [Youssif 2009]

b) Bladder exstrophy and persistent Cloacal anomalies

Once the exstrophied bladder is closed it may be difficult to manage persistent UI, upper urinary tract dilation or vesico-ureteric reflux. Whether to further improve continence function and whether to perform augmentation cystoplasty for a small capacity, poorly compliant bladder are challenging questions. In addition, as more children undergo complete primary repair of the exstrophic bladder in the neonatal period, the most accurate assessment of bladder function is by urodynamics. Only a few studies report the change in LUT function following bladder neck reconstruction in patients with persistent incontinence; 20% show DO preoperatively versus 37% postoperatively, and compliance worsens in up to 50% after surgery. [Hollowell 1993; Diamond 1999; Burki 2006; Caione 2005] No studies are extant that have correlated incontinence with bladder capacity, compliance, DO and/or LPP. [Gargollo,P.C. 2008; Kajbafzadeh 2008; Camanni 2009]

c) Ectopic ureterocele

Urodynamic studies in babies with an ectopic ureterocele have shown that LUT function may be altered in as many as half the affected patients; 2 reports revealed that between 55 and 70% had a larger than normal capacity bladder for age with high compliance, and poor bladder emptying due to underactive detrusor. [Abrahamsson 1998; Sherman 2003] In another multicentre analysis of 616 children with a variety of ureterocele types, investigators found only a 6% incidence of bladder dysfunction (all in children with an ectopic ureterocele) consisting of primarily DO; less than 1% had poor bladder emptying whereas the remainder had normal bladder storage function and complete emptying. [Holmes 2002] In a recent study in 2007, voiding dysfunction was suspected in 23% of patients. [Shimada 2007] UI and/or infection following surgical incision or excision of a ureterocele is likely to be secondary to the obstructive effects of the ureterocele directly on the bladder outlet and not to any surgical complication. [Holmes 2002; Sherman 2003; Abrahamsson 1998] Patients undergoing bilateral ectopic ureterocele repair are at increased risk for postoperative voiding dysfunction. Whether this risk is present preoperatively or is a result of a trigonal lesion is unclear. Recently, there is an increasing agreement in favour of conservative management of paediatric duplex system ureteroceles, by mean of simple endoscopic puncture followed by close surveillance: reflux can resolve spontaneously in a significant number of patients, and bladder function should be conserved. [Matsui,F. 2009; Jesus 2011]

d) Vesicoureteral reflux

It had been shown that vesico-ureteric reflux may be a secondary phenomenon resulting from DO and not a primary anatomic abnormality at the ureterovesical junction in a significant proportion of children. [Koff 1979; Griffiths 1987; Sillen 1996; Greenfield 2000; Capitanucci 2000; Podesta 2004] There is growing evidence that DO may lead to vesico-ureteric reflux in a marginally competent ureterovesical junction mechanism. [Khoury 2008; Chandra 1996; Chandra 2000] This DO may be a natural phenomenon in the infant bladder, especially in boys, due to the presence of higher voiding pressures [Podesta 2004; Webster 1984; Sillen 1992; Sillen 1996; Yeung 1997; Bachelard 1999] and/or a learned dysfunction in older children who try to withhold voiding throughout the day. [Greenfield 2000] Several investigators have shown that DO tends to resolve with increasing age [Chandra 1996; Sillen 1996; Nielsen 1989; Sjostrom 2009], also showing, in a longitudinal study, that changes occur between the first and second year of life in children with dilating reflux, going from an immature pattern, with high pressure levels, to a high capacity bladder with incomplete voiding. [Sjostrom 2009]

The bladder pressure at the onset of vesico-ureteric reflux, as determined by nuclear cystometrography, is a significant independent predictor of vesico-ureteric reflux resolution in children. The pressure at the onset of vesico-ureteric reflux was also highly predictive of spontaneous resolution ($p = 0.0005$). Vesico-ureteric reflux occurring at greater pressures was more likely to resolve spontaneously, independent of the vesico-ureteric reflux grade or bladder volume at the onset of vesico-ureteric reflux. [Arendonk 2007] The degree of renal scarring ($p=0.018$) and the degree of reflux ($p=0.038$) were found associated with the detrusor pressure with highest detrusor pressure in the group with 'urge syndrome'. [Acar 2009] In addition to grade of reflux, bladder volume relative to predicted bladder capacity, at the onset of vesico-ureteric reflux, appears to provide additional prognostic information regarding the likelihood of spontaneous resolution of primary vesico-ureteric reflux. [McMillan,Z.M. 2006] Large bladder capacity and high compliance correlated with 'passive' reflux, while reflux during micturition correlated with low bladder capacity: the first pattern showed a lower resolution rate within the third year of life, in a longitudinal study by videocystometry. [Wahll,L. 2009]

Despite this finding, there is ample evidence in 4 studies to show that treating the DO and/or voiding dysfunction with anticholinergic agents leads to a faster rate of resolution of vesico-ureteric reflux (63 - 92% within 1 year) [Homsy 1985; Scholtmeijer 1994; Batista 1997] than it might when the child is treated only with antibiotics to prevent recurrent infection (resolution rate 25 - 54%). [Seruca 1989; Ural 2008]

In this setting, history-taking about voiding habits [Gool 1992], and urodynamics with cystometry and uroflowmetry to confirm the abnormal bladder and possibly sphincter function, become paramount, rather than just treating the child with antibiotics and getting yearly voiding or nuclear cystograms. Urodynamic studies have confirmed the presence of DO and/or high voiding pressures in at least half the babies studied with high grades of vesico-ureteric reflux, whereas only 38% had totally normal function. [Webster 1984; Bachelard 1999; Yeung 1998; Bachelard 1998; Sillen 1999; Ural 2008] Upper urinary tract damage is more apt to occur in children with abnormal bladder function as reported in 4 retrospective reviews. [Nielsen 1989; Scholtmeijer 1994; Sillen 1999; Leonardo 2007]

In 2006, videourodynamic studies were performed in 40 patients. LUTD was present in 76% of the children, with DO in 73% of the children with vesico-ureteric reflux, in 63% of the children with UI, in 77% of the children with episodic urinary tract infection, and in all of the children with diurnal enuresis. Compared to children without LUTD, the voiding pressure was significantly higher in children with dysfunctional voiding (with vesico-ureteric reflux, 61 ± 30 vs. 25 ± 16 cm H_2O, $p = 0.004$; without VUR, 53 ± 24 vs. 25 ± 16 cm H_2O, $p = 0.010$). [Kuo 2006] In the 5 patients

who had post-treatment urodynamic studies, biofeedback pelvic floor muscle training and treatment with antimuscarinics effectively decreased detrusor pressure, increased bladder capacity and maximum flow rate, and reduced the grade of VUR. In children with recurrent or persistent urinary tract infection, meticulous assessment of signs and symptoms is reported to have a ± 70-80% association with the result of invasive UDS. [Ramamurthy 2010]

Special attention should be given to secondary causes of vesicoureteral reflux such as primary bladderneck dysfunction (reported to be an underdiagnosed entity in those children), since conventional treatment will most likely fail if these conditions are not addressed which was shown to be relevant in a randomized trial. [Kajbafzadeh 2010; Glassberg 2010]

Many clinicians treating patients with vesico-ureteric reflux, advocate urodynamics to assess the LUT in children with high grade vesico-ureteric reflux, especially for those patients that have incontinence, renal damage, or who are about to undergo surgery for vesico-ureteric reflux. [Scholtmeijer 1994; Moran 2004; Musquera 2004; Fotter 2005; Kajbafzadeh 2010] Precise urodynamic (pressure flow) criteria for outlet conditions in children are however still undefined.

e) Urethral stricture

Urethral stricture disease in boys is rare, usually arising from a previously unsuspected straddle injury. Uroflowmetry can accurately predict the presence of a urethral stricture in 88% of affected males. [Martin 1995] The significantly decreased quotient of Q_{max} at greater and at smaller VV's was suggested to be useful to demonstrate a mild BOO. [Szabó 1996] An occult urethral obstruction develops in some asymptomatic children after hypospadias repair and uroflowmetry can be helpful [Orkiszewski 2004; Kaya 2007], as showed by significantly different pre- and post-meatotomy findings of Q_{max} (p=0.001), voiding times (p=0.03) and curve morphology. [VanderBrink 2008]

Periodic urinary flow rates, analysing the maximum flow rate in relation to volume voided, may alert the clinician to early signs of renarrowing but efficacy of periodic flow rates has not been corroborated. [Bukurov 1992] Uroflowmetry should be integral in the management of urethral stricture and complete urodynamic investigation is repeatedly required after treating traumatic rupture of the posterior urethra. [Otgun 2006]

Conclusions (level 3)

- Many case series have demonstrated frequent urodynamic abnormalities, predominantly detrusor overactivity and reduced bladder compliance or large capacity bladder with impaired filling sensation, in children with posterior urethral valves, urethral stricture, ectopic ureterocele, vesico-ureteric reflux or bladder exstrophy.
- Proper urodynamic assessment has shown to be of help to determine when further medical or surgical management is indicated in children with these abnormalities.
- The use of urodynamic studies has aided in an objective measurement of success or failure of treatments for these abnormalities.

Recommendations (grade C)

- Clinicians should consider complete urodynamic testing of the filling and voiding function, at least once, in children with posterior urethral valves, urethral stricture, ectopic ureterocele, vesico-ureteric reflux or bladder extrophy.
- Clinicians should consider regular uroflowmetry and postvoid residual urine assessment in the follow-up and further management of children with posterior urethral valves, urethral stricture ectopic ureterocele, vesico-ureteric reflux or bladder exstrophy.

5. FUNCTIONAL DISORDERS OF THE LOWER URINARY TRACT

When assessing functional disorders involving the LUT in children, one must take into account the dynamics of the maturing nervous system, learned habits of elimination for bladder and bowel function and social influences that might modulate the child's behaviour in a negative or in a positive manner. [Yeats 1976; MacKeith 1973]

a) Diurnal incontinence

Urodynamics has a limited place in diurnal (day and night) incontinence. This condition is not considered worrisome before age 5 or 6. When older, most children without an (until then unsuspected) anatomic or neurological lesion should be dry. [Bellman 1966; Neveus 2006] UI in children can have many causes and history and clinical investigation are very important in this regard. UI can also coincide with dysfunctional voiding and or bowel elimination problems. [O'Regan 1985; Koff 1998] Treating these elimination dysfunctions with behavioural modification, biofeedback training, drug therapy or CIC [Pohl 2002] and/or antibiotics to prevent further urinary infection is necessary before considering urodynamics. [McKenna 1999] Uroflowmetry with a PVR urine determination and cystometry are however indicated; especially if the incontinence persists despite medical therapy. A monocenter study reports that children with chronic constipation as the predominant symptom can also have unrecognized LUT problems. [Kasirga 2006]

In one study of girls with recurrent infection without vesico-ureteric reflux two distinct patterns of dysfunction emerged in 80% of those studied, either DO with a normal urinary flow pattern and complete emptying, or a normal detrusor with an intermittent flow pattern and incomplete emptying. [Borer 1999] In boys

with persistent day and night time incontinence, UDS is warranted to determine the presence of different forms of LUTD that may be contributing to the symptoms. [Ramakrishnan 2008; Yeung 2004]

Faecal incontinence in the absence of any anatomical or neurological deficit often affects LUT function and contributes to UI in a number of ways. Constipation and faecal impaction have been shown to cause DO and a reduced functional bladder capacity. [Kasirga 2006] Understanding and eliminating this possible aetiology can normalise LUT function. There is no need for urodynamic testing, before starting treatment for faecal impaction, in these cases. [O'Regan 1985]

Persistent daytime and night-time incontinence in the absence of urinary infection and a normal bladder and bowel emptying regimen warrants cystometry, pressure-flow studies and a urinary flow rate. A meta-analysis, over 20 years, of 460 children with daytime incontinence evaluated with urodynamic studies reveals DO in 57% (261 of 460), dysfunctional voiding (failure to relax the sphincter mechanism) in 22% (34 of 152) and normal findings in only 14% (64 of 460). [Webster 1984; Hanna 1981; Borzyskowski 1987; Rodriguez 1989] Many of those studies use terms that are outdated now and those should be replaced ('transformed' where possible) with the new. [Neveus 2006] In recent studies, dysfunctional voiding was present in 76% of 40 children with DO. [Kuo 2006; Zajaczkowska 2004] These findings are not gender-specific but are age-dependent, with most children outgrowing the abnormal findings by puberty. [Borzyskowski 1987] It is presumed that normal children, without day or night-time wetting, do not have a pronounced degree of DO or dyssynergia but the evidence for this is lacking due to the paucity of studies in normal children.

Urodynamic testing has clearly improved our understanding of the aetiology of diurnal incontinence but no study has shown that urodynamic characterisation of any abnormality has improved the efficiency of treatment for these children.

b) Enuresis (nocturnal)

Night-time wetting (enuresis) is a condition that is common in children aged 5 years but which improves with time, so that less than 15% of pubertal boys and 5% of pubertal girls continue to be affected. [Fergusson 1986] Multiple causes for the persistent wetting, ranging from genetic factors, to maturational delays, to sleep disturbances, to social causes, to attention deficit disorders, to bladder and urethral dysfunction, to excess fluid intake, to abnormal vasopressin secretion and/or to constipation, have been implicated. [O'Regan 1985; Hoebeke 1995; Hjalmas 1997; Chandra 1998; Neveus 2006] Although in various cultures there may be social and familial pressures to resolve the condition before puberty, in western societies it is generally not necessary to conduct urodynamics until adolescence, to determine why the wetting has not abated. Urodynamic testing in 615 enuretic children, with and without daytime symptoms, has identified DO in 61%. [Mayo 1990; Medel 1998; Hellerstein 2003] In a prospective study, bladder volume and wall thickness index was calculated based on ultrasound studies. The index was measured by dividing maximum bladder volume by mean bladder thickness. Bladder volume was expressed (normalized) as percentage by dividing the patients measured bladder capacity by expected bladder capacity and subsequently the detrusor was classified as thick (index:< 70), normal (70 to 130) or thin (>130). Of the patients with an index of less than 70: 96% exhibited DO on cystometry. [Yeung 2004; Sreedhar 2008] In another prospective study, 116 children with primary enuresis were evaluated and urodynamic abnormalities were seen in 80/116 (69%) patients namely DO 50/116 (43%), small bladder capacity 20/116 (17%), large bladder capacity 4/116 (3%), decreased bladder compliance 3/116 (3%) and detrusor sphincter dyssynergia 3/116 (3%). The combination of abnormal micturition history with daytime urinary urgency or frequency, or dysfunctional voiding symptoms like squatting and/or abnormal voiding charts, predicted abnormal results of urodynamics correctly, with a sensitivity of 81% and specificity of 86%. [Sehgal 2007] However, other studies state that urodynamic diagnoses are more distinctive than symptom complexes for LUTD in children. [Glassberg 2010]

When the children are divided into those with day and night-time incontinence (non monosymptomatic) versus those with just nocturnal wetting (monosymptomatic), the incidence of DO decreases from 64% to 35% in the latter group. [Medel 1998] In another prospective study comparing enuretics to age-matched non-enuretic controls, bladder capacity at night (enuretic capacity) was significantly less in those who wet versus those who did not. [Kawauchi 2003] Although the authors did not speculate on aetiology they felt that enuretics were less able to hold their urination than non-enuretics. Management should be directed at improving the child's ability to withhold urination. Treating the non monosymptomatic child using antimuscarinic agents can be very effective (as high as 77% cure) with low recidivism rates when based on the findings of urodynamic testing. [Porter 1995; Kosar 1999; Neveus 2010; Hoebeke 2010; Abidari 2002]

Conclusions (level 2/3)

- Various studies show that treatment for children with functional incontinence (and of the, frequently associated, bowel elimination problems) can be initiated on the basis of history, clinical exam, bladder diaries, bladder ultrasound and uroflowmetry with postvoid urine assessment.
- Various studies, reviews and guidelines agree on the relevance of urodynamic testing in children

with incontinence and nocturnal enuresis resistant to initial (conservative) treatment.

Recommendations (grade B/C)

- The committee recommends uroflowmetry and postvoid residual urine assessment (until -for the individual child- representative values are obtained) as 'urodynamic'-screening and evaluation in all children with lower urinary tract symptoms, urinary incontinence and or with nocturnal enuresis resistant to first line therapy.
- The committee suggests urologic signs and symptoms assessment in children with chronic constipation.
- The committee recommends complete urodynamic testing in children with urinary incontinence and or with nocturnal enuresis resistant to conservative treatment, if invasive or clinical (dry-bed training) treatments are contemplated.

Suggestion for research

- The committee suggests that further integrated approaches to the diagnosis (and management) of children with anorectal (elimination) dysfunction, in combination with lower urinary tract dysfunction are undertaken.

6. TECHNICAL CONCERNS: RELIABILITY AND REPRODUCIBILITY OF TESTS

Often, differences in urodynamic parameters exist from one study to another, or one year to the next. Chou et al provided reference ranges for 'normal' variability in urodynamic parameters that can be considered as 'no real change' from one study to the next. It was a retrospective chart review. Fifty consecutive individuals with spinal cord injury had 2 trials of urodynamic studies done 5 minutes apart. They established percentile ranges. Knowing these ranges of variability can be helpful in determining whether differences between filling trial 1 and filling trial 2 in a single study, or year-to-year changes in urodynamic studies, are significant or simply the normal variability of the urodynamic study. [Chou 2006]

'Functional' bladder capacity (as derived from the voiding diary, without the first voiding in the morning) is presented as a relevant parameter for the clinician in the International Childrens' Continence Society definitions. [Neveus 2010] To assess the voiding phase, pressure flow studies are performed immediately after filling cystometry. Available reports on detrusor pressure during voiding in symptom free children is reported to give a wide range; between ± 50-60 cmH_2O in one study [Wen 2007] and ±100cmH_2O in another [Yeung 1995]

A rate of filling resulting in 10% increment of the expected bladder volume per minute, has been recommended in children to determine detrusor compliance and functional bladder volume accurately and standardised. [Hoebeke 1998] Some investigators advocate that infants should be assessed with much lower rates of filling or with natural filling cystometry. [Yeung 1998; Sillen 1999] Several studies do show lower detrusor pressure increases under natural filling versus even slow filling rates during cystometry. [Norgaard 1995; Landau 1994; Kaefer 1997] Even though the practicality of time management plays a role in a busy urodynamic laboratory, it is essential to perform urodynamic testing in a way that reveals what one considers clinically important information. One study in particular [Kaefer 1997; Landau 1994] demonstrated that the intravesical pressure was lower when it was measured initially by catheterisation (before emptying the bladder) and then compared to the pressure at the same volume during the subsequent cystometogram. Except for determining bladder volumes at specific pressures, [Landau 1994] no study has shown that these differences are crucial in the management of children with LUTD. One study looked at the effect of the temperature of the instillate (25° versus 37.5°C) on measured detrusor pressures and found no significant differences in compliance. [Chin 2003] Van Meel et al have shown that repeating the IWT will increase its positivity. [Meel 2007]

The smallest dual-channel urethral catheter available should be used in children for the same reasons as specified for adults, although the measuring lumen must be large enough to measure pressures in a technically adequate manner. Although urethral catheters of moderate size (8F) do not always obstruct the urethra in girls [Griffiths 1982] or produce higher than the normal voiding pressures, as measured with suprapubic tubes, it is prudent to employ the smallest calibre catheters that are practical when doing a cystometogram that measures filling as well as voiding pressures. For very young infants it may be better to insert a suprapubic catheter placed under anaesthesia the day before the test to make the subsequent investigations more accurate [Yeung 1999; Yeung 1999] but this has not been assessed with any precision. Furthermore, precise standards for pressure-flow analysis in boys or girls, or for grading of BOO 'resistance', have not been published. The precise association and or prevalence of obstructed voiding with incontinence is therefore also unknown.

Most children can undergo urodynamic studies without pre-medication; only the most agitated may require some degree of sedation [Bozkurt 1996] and it does not appear to have a significant effect on the outcome of the testing. Even then, children should not be so heavily sedated that they cannot void around the catheter. However, there are no studies that show a difference in bladder filling pressure (whether related to compliance or to DO) in awake versus anaesthetised children.

In the previous consultation the recommendation was made that children should receive comprehensive urodynamic testing in a laboratory that is specialised in paediatric urodynamic testing with appropriately trained personnel. [Ramamurthy 2010; Bael 2009; Uluocak 2009]

Conclusions (level 3/4)

- The committee concludes (on the basis of various studies to determine normal and test retest values for urodynamic testing in children) that within the limits also provided for adults, urodynamic testing in children is reliable and reproducible.
- Although it is plausible and considered useful to reduce filling speed and catheter size in relation to patient size, the exact values cannot be given and the influence of the transurethral catheter size on voiding is unknown.
- The committee concludes that standards for pressure flow analysis in children are lacking.

Recommendations (grade C)

- The committee recommends that the specific demands of children, physically as well as psychologically are taken into account, before urodynamic testing is carried out as well as during the testing. The committee advises specialised workers, units and equipment to ensure this.
- The committee recommends that invasive diagnostic tests should be done if indicated by the results of non-invasive procedures and should be done only when the outcome will or can alter management.
- The committee recommends that clinicians take into account the variability and test retest differences of urodynamic testing in children and also take into account the effect of the (apparent psychologically stressing) laboratory-situation on the child's behaviour, and the implications for the results of the tests.

Suggestion for research

- The committee suggests to elaborate on standardisation of evaluations to judge how the 'laboratory' circumstances have influenced the child's behaviour, with the aim to better include how well the urodynamic tests have represented the actual dysfunction, in the evaluation of the test.

V. PATIENT EVALUATION: FRAIL ELDERLY

1. INTRODUCTION

Frail older patients are poorly represented in all studies, but especially in those involving invasive interventions or medications, By definition, they suffer from multiple impairments (e.g. poor mobility, cognitive impairment, renal failure) or disease conditions (heart failure, multiple medications). [Fairhall,N. 2011; Fried,L.P. 2001; Inouye,S.K. 2007] Such individuals are at risk of admission to hospital or a care home. [Hrisanfow,E. 2011] Older people age at different rates, with some developing a clinically recognised pattern of frailty characterised by impairments in a number of functions including a greater risk of developing incontinence. [Ferrucci,L. 2004; Baltes,P.B. 2003; Hirayama,F. 2008] However usually the multimorbidity excludes them from research trials, which limits appropriate continence care. [Narayanan,S. 2007; Ferrucci,L. 2004] Elderly patients should however not be considered differently from younger subjects simply because of their chronological age. LUTS, especially storage ones, showed age-related alterations in the two sexes in the absence of any overt underlying disease, and bladder function in both sexes may be subject to a gender-independent aging process. [Araki,I. 2003] UDI findings in the (frail) elderly tend to demonstrate DO [Jones,K.W. 1985; Resnick,N.M. 1989], even in individuals that do not spontaneously report symptoms or bother. There may also be a reduction in bladder capacity, urinary flow rate and detrusor contractility. [Homma,Y. 1994] Because of these age dependent changes, the utility of UDI has to be judged against this specific background in the elderly where diagnosis and treatment of specific conditions is strongly dependent on and related to frailty by itself. [Homma,Y. 1994] These features need to be born in mind when considering the contributors to, and investigation of, incontinence. Limitations to care may also be appropriate in a frail older person who is nearing the end of their life. [Gillick,M. 2001] The invasive nature of conventional UDI becomes a relatively more important factor in the old or frail elderly, who may be more vulnerable to any intervention than younger people. For example, one study [Okorocha,I. 2002] showed that there was a significant association between age and the presence of asymptomatic bacteriuria before cystometry and between the bacteriuria and urgency (without DO) on cystometry. Asymptomatic bacteriuria did not influence the UDI outcome except in patients with urgency (without DO); and the authors recommended that screening and treatment be considered individually in older women who are being investigated for storage symptoms.

Given the multifactorial nature of incontinence in the elderly [Miller,K.L. 2002] and the fact that there may exist easily reversible causes or contributory factors relatively more frequently in these patients, it is suggested repeatedly that screening for contributing factors in the 'vulnerable elderly' is very relevant. [Resnick, 1984; Bing,M.H. 2007; Gibbs,C.F. 2007; Fonda, 522]

UDI is reserved for patients in whom conservative management and medical management, direct or

indirectly aimed at lower urinary tract improvement, has failed or has proved inadequate, and in whom more intensive or invasive therapy is being considered. Also in the elderly, there is a given group of patients who desire further attempts to correct or manage the incontinence, and who therefore need a detailed and objective diagnosis. [Sims,J. 2011] Improvements in the structure and process of 'continence care' for the elderly has resulted in improved patient reported (Quol) outcomes, and the structure presented by a geriatrics (ambulatory) clinic may serve as an example of care quality improvement. [Min,L.C. 2011] Certainly assessment of persistent LUTD and UI is of relevance in the elderly after urological interventions, however UDI diagnosis is rarely mentioned in the follow-up of persons with 'failed' interventions. [Shikanov,S. 2010; Namiki,S. 2009; Poulakis,V. 2007]

The place of UDI in the frail elderly with incontinence is not precisely established, given that the number of studies seeking to establish its clinical utility is even smaller than in younger adults: there is very little objective evidence for or against clinical UDI in this population group. However, the same principles apply as those in younger age groups, namely that UDI should only be done if it is going to affect the management of the patient and that conservative and medical therapy has failed with the patient desiring further treatment. [Abrams,P. 2009] A recent review, on the basis of a RAND procedure, to search for health care quality indicators underpins that UDI 'should be performed' in the workup of vulnerably elders when surgical intervention is considered. [Fung,C.H. 2007]

The changes in function that occur with age, not only in the LUT, but also in the neural system that controls it (or fails to control it), may all have impact on urological problems. UDI research studies, to establish what these changes are, how they are related to other aging associated changes, and how the changes might be reversed, are needed. [Inouye,S.K. 2007]

Overactive bladder syndrome is frequently diagnosed in the elderly and in the frail elderly and medical (pharmacological) treatment seems plausible for elderly, with extrapolated evidence from younger patients. In non-systematic reviews on pharmacotherapy UDS do not play an important role to initiate treatment for overactive bladder syndrome in the frail elderly. [Kraus,S.R. 2010; Staskin,D.R. 2005; Wagg,A.S. 2007]

2. ROUTINE EVALUATION

Among the frail elderly, incontinence is the paramount troublesome symptom, in both men and women, with a steeply rising incidence after age 80. [Hunskaar, S 2002] The type of incontinence appears to be predominantly urgency. [Hunskaar,S. 2002] Mixed symptoms of incontinence are the commonest in women [Valentini,F.A. 2010] SUI is relatively uncommon in men of any age (except post radical prostatectomy) and it seems to become gradually less common in women after the age of about 50, [604 Hunskaar 2002] or is reported with a range of incidences, [Wennberg,A.L. 2009] for reasons that are incompletely understood.

a) Urinary urgency incontinence

The symptoms of UUI are frequently the result of DO. Thus one possible reason to perform UDI might be to identify DO. The relevant test is filling cystometry. There are reasons to question whether this is the best approach because in straightforward symptoms of urinary urgency incontinence in the elderly, DO is highly probable, and it is considered possible to initiate pharmacological or behavioural therapy without a very significant possibility of harm. [Kraus,S.R. 2010; Staskin,D.R. 2005] On the other hand: DO is only one of the contributors to the symptoms of urinary urgency incontinence [Miller 2002; Griffiths 1996], and non voiding detrusor overactivity is believed to exist in (older) people who are apparently free of (bothersome) bladder symptoms. However, if making the diagnosis of DOI is essential, it is necessary to demonstrate leakage caused by an involuntary detrusor contraction.

Reduced bladder sensation or 'awareness' may lead to very little warning of impending leakage, and it is believed to have a neurological (cerebral) in the elderly with LUT symptoms. [Griffiths,D. 1998; Griffiths,D.J. 2002]

In symptomatic elderly people, UUI frequently coexists with incomplete bladder emptying. Among men who have not had prostate surgery, BPO is a frequent contributor to incomplete emptying. However, if there is no BOO, particularly in women, in whom the incidence of BOO is very low, incomplete emptying is usually a sign of impaired bladder contractility, termed by the ICS as underactive detrusor. The UDI abnormality underlying UUI with incomplete emptying (assuming no BOO) has also been named 'DHIC'. [Resnick,N.M. 1987] Its significance is that the standard pharmacological treatment of UUI – with antimuscarinics – may worsen bladder emptying and possibly lead to urinary tract infection, or even make the incontinence worse. However, on the other hand, if the patient has large residuals, then treatment with CIC may be considered indicated and therefore combining that with antimuscarinic therapy is an option, although such a combination can be problematic in frail elderly patients.

In frail elderly women, DO is reported to be the commonest UDI diagnosis in a large retrospective series of referred elderly women. Intrinsic sphincter deficiency, underactive detrusor and reduced bladder compliance [Valentini,F.A. 2010] were also prevalent in this series. Population surveys with symptoms questionnaires (without UDI's) confirm this pattern in various countries and care-

settings. [Burti,J.S. 2012; Malmsten,U.G. 2010; Kwong,P.W. 2010; Chen,Y.M. 2009; Verdejo,C. 2007; Sexton,C.C. 2011]

Simple cystometry:

Some report that UDI's in the elderly can be done by 'simple cystometry', if cystometry is indicated and no equipment or referral is available. [Wall,L.L. 1994] The procedure applies a large open syringe attached to a single-lumen catheter, steri1e water or saline and a tape measure. Fluid is infused by gravity and LUT function can be semi quantified at the bedside and may be applicable for disabled patients. [Sutherst,J.R. 1984; Sand,P.K. 1991; Ouslander,J. 1988; Dennis,P.J. 1991; Fonda,D. 1993; Galarneau,L. 2003] Simple cystometry, as compared with multichannel cystometry, has a specificity of 75-79% and a sensitivity of 75-88% for the observation of DO in those studies [Fonda,D 1993; Ouslander,J. 1988], and is improved by combining it with simpler tests [Sutherst,J.R. 1984; Ouslander,J. 1988] such as a clinical stress test. [Resnick,N.M. 1996] However, the clinical significance of these findings is limited because DO is found in up to 50% of symptom-free elderly while DOI is the most likely finding in incontinent frail elderly in any case. [Resnick,N.M. 1987; Resnick,N.M. 1989; Griffiths,D.J. 1992] Furthermore 'detrusor hyperactivity (2010: 'DO') with impaired contractility' (DHIC) [Resnick,N.M. 1989] is reported to be a common abnormality observed in the frail elderly population with incontinence and cannot be diagnosed with simple cystometry. [Resnick,N.M. 1987; Resnick,N.M. 1989] A total of 185 patients who had persistent LUTS after TURP were enrolled in one study, and the results revealed that a normal videourodynamic tracing was found in 9%, pure DO in 10%, 'low detrusor contractility' in 19%, DHIC in 14%, poor relaxation of the urethral sphincter in 19%, and recurrent or remaining BOO in 28%. [Kuo 2002] Single-channel cystometry is less sensitive for detecting low-pressure detrusor contractions than multichannel recording [Resnick,N.M. 1996] and if a detrusor contraction coincides with a cough, the leakage might be wrongly regarded as the sign of a positive stress test.

b) Stress urinary incontinence

Among older men, SUI is almost entirely confined to post radical prostatectomy patients (see section D.II, Patient evaluation: Men). Among elderly women, pure SUI seems to be rare. UDI testing usually follows the methods used in younger women. Frequently, it is difficult to perform a 'typical' examination because the patient is not able to produce a strong cough or valsalva in the upright position. On the other hand, it may be just such factors that make SUI less common in this population or of lesser relevance in this group.

3. EVIDENCE FOR REPRODUCIBILITY AND RELIABILITY OF URODYNAMIC TEST IN THE GERIATRIC OR FRAIL ELDERLY POPULATION

There is little published evidence about reproducibility and reliability in this patient population. Two groups have recently examined specific aspects of geriatric urodynamics which have some bearing on this topic. There is a little earlier evidence on the reproducibility of some parameters.

a) Filling cystometry

One group[Goode,P.S. 2002] sought UDI changes associated with behavioural and drug treatment of UUI in 105 ambulatory, non-demented, community-dwelling women, of mean age 67 years (range 55-91). Although oxybutynin and behavioural treatment were both effective, the authors were unable to demonstrate that the improvement in incontinence was related to the UDI changes observed, probably because of diverse UDI diagnoses at inclusion, as well as the variability of the UDI outcome. (See sections C.I and C.II).

b) Post-void residual urine

Residual urine is believed to depend on the presence of BOO (in men) as well as underactive detrusor. [Abrams, P 2001] Thus, in a man, the presence of substantial residual urine (> 100 mL), in the absence of a large prostate, and or severe BOO, suggests that the increased residual urine is mainly due to a reduction in detrusor contractility. [Rosier,P.F. 1996] There may be a clinically relevant age-dependent decrease in contractility in both sexes. [Abarbanel,J. 2007; Abdul-Rahman,A. 2010]

Post void residual urine varies in a given individual and can wax and wane over time. Significant daily variations have been observed in elderly patients of both sexes, with larger residuals (up to 40% greater) being measured in the early morning. Similar changes have been described in patients with BOO or underactive detrusor. [Bristow,S.E. 1996; Thind,P. 1995] Residual urine is an unspecific sign of dysfunction and also no clear predictor of deterioration of residual urine volume or of complete urinary retention has been identified in general, however prostatic obstruction is an undisputed prevalent cause of urinary retention in elderly male.

c) Pressure-flow studies

Another group retrospectively analysed UDI data on 84 females 53 years old or older, with UUI, who received either a titrated dose of antimuscarinic medication or placebo in a controlled trial. [Tan,T.L. 2003] The detrusor muscle is believed to deteriorate in function as a result of aging, by diverse investigators and since antimuscarinic treatment might affect detrusor voiding function urodynamics is applied to

monitor this. Driving a contraction to its maximum load (and zero contraction velocity) is a manner to evaluate muscle force, and stop-flow test is the practical way to do this. Three different variations of the stop test were therefore compared to analyse detrusor voiding contraction before and on treatment in this study. The voluntary stop test yielded isovolumetric detrusor pressure values inconsistent with the other 2 tests. The mechanical and continuous occlusion tests gave very similar results that were highly correlated with one another. Treatment with oxybutynin decreased isovolumetric contraction pressure only statistically significant for the continuous occlusion test. The authors concluded that voluntary stop test should not be used to evaluate detrusor contraction power, but that occlusion stop test can be of relevance to evaluate the effect of treatments that affect detrusor voiding contraction in the elderly.

4. EVIDENCE THAT PERFORMING URODYNAMIC TESTING IMPROVES CLINICAL OUTCOMES IN THE GERIATRIC POPULATION

Few relevant studies have been published in this population. One publication assessed the results of TVT for the treatment of SUI in 76 consecutive women more than 70 years old (median age 76 years). 31% (24/76) of the patients had OAB symptoms and 4 (3%) had proven DO. [Sevestre 2003]. All patients had preoperative multichannel UDI evaluation however the technique applied was very imprecisely described. At a mean follow up of 25 months, 67% of the patients were cured. Preoperative urgency symptoms were cured in 46% of the group. Among the failures, 14 (18%) had UUI, while 'de novo' urgency without incontinence was noted in 21%. Pre-operative UDI was not able to predict the outcome of a popular SUI procedure in older women in this monocenter uncontrolled cohort. It does show that post-operative difficulties may be due to urgency and UUI, however, symptoms are not a good 'predictor' of UDI diagnosis, and therefore pre-operative urodynamics in women undergoing SUI surgery is valuable in helping to counsel patients especially if they have signs or symptoms of OAB.

5. THE PRACTICAL INDICATIONS FOR URODYNAMIC STUDIES AND WHICH TESTS ARE NEEDED

a) Post-void residual urine

Based on the above, there is general agreement that, certainly in the elderly, PVR urine measurement is indicated before treatment of incontinence either with anticholinergic medication or by SUI surgery. A consistently large residual urine certainly is a reason for caution, and careful monitoring of bladder emptying, and may be a relative contra¬indication to such treatment. [Thuroff,J.W. 2011]

b) Uroflowmetry

Uroflowmetry is a simple and non-invasive test. A normal uroflow without much residual urine probably rules out significant BOO or underactive detrusor, but this finding is unusual in the elderly. Conversely, a poor uroflow is common in the elderly irrespective of sex, and although it cannot distinguish between BOO and underactive detrusor, in either case there is a relative contraindication to anticholinergic therapy. Consequently, uroflowmetry (with residual urine measurement) may be a useful screening tool prior to instituting therapy. However, interestingly, in a retrospective study of hundred women tested, the first free flow was not interpretable in 44% but interpretable in 91% on the second free flow. [Valentini,F.A. 2010] This confirms the usefulness of performing at least two free flows on patients. [Reynard 1996]

c) Pressure-flow studies

In male patients with cognitive impairments or Parkinson's disease or multiple system atrophy (MSA), is sometimes unclear whether the incontinence is due to BPO or to the cerebral changes. There is weak evidence to suggest that prostatectomy may improve the continence if UDS shows 'severe' BOO. [Gormley,E.A. 1993] If BOO is equivocal or absent, then there is little point in performing surgery in an attempt to alleviate the signs and symptoms. After screening with uroflowmetry and residual urine measurement, pressure-flow studies may be indicated in older men in whom BOO cannot be ruled out and surgery is at least contemplated.

6. THE URODYNAMIC PARAMETERS IMPORTANT IN VARIOUS GERIATRIC CONDITIONS

Various papers have examined the urodynamics of Parkinson's and related diseases. Parkinson's and related diseases as well as dementia's are prevalently associated with aging as are prostatic obstruction, detrusor and pelvic floor muscle degeneration and deterioration sensomotoric functions. UDS can be of relevance to determine the most important cause of the LUTS in the elderly, where central nervous system disease is a frequently occurring comorbidity and clinical signs and symptoms are regularly more difficult to obtain.

a) Parkinson's Disease

One group [Defreitas 2003] found that men with presumed BOO related LUTS were less likely to have DOI on UDI's than men or women with Parkinson's disease. DO associated with Parkinson's disease occurred at smaller bladder volumes than DO in BOO-related DO, although this finding was more pronounced in women than in men. The duration and severity of Parkinson's disease were reported not be related to the UDI abnormalities in this study.

Another group [Sakakibara 2001] found that the majority of patients with Parkinson's disease (72%) or MSA (100%) had symptoms of LUTD. DO was more common in Parkinson's disease. DSD was seen only in MSA. BOO (> 40) was more common in Parkinson's disease than in MSA. A detrusor underactivity was less common in Parkinson's disease than in MSA and PVR (> 100 mL) was only present in (47% of) patients with MSA.

Conclusions (Level 3-4)

- There is direct and indirect evidence that urinary incontinence in the (frail) elderly often has diverse and or multiple coexisting factors.
- Apart from general health, mobility, neurological diseases and medications, the lower urinary tract is directly affected by aging of the detrusor, and can be both overactive during storage as well as underactive during voiding,) and aging of the outlet; prostate, and pelvic floor muscle function.
- In common with all patients, but maybe even more relevant; symptoms are not synonymous to the abnormalities that can be measured with urodynamic studies
- Every test or procedure can cause harm in the (vulnerable) elderly but there is no published evidence that invasive urodynamic studies causes significantly more harm in the elderly.
- Simple bedside urodynamic testing has an inherent unreliability, and it is unclear whether the risk of misdiagnosis outweighs the 'simplicity' over conventional urodynamic studies.
- Especially, but not exclusively, male patients, with central neurological disease, can have urologic disease (e.g. prostatic obstruction) as a cause for incontinence or other lower urinary tract dysfunction.

Recommendations (grade C)

- As urinary incontinence in frail elderly people may be the result of a number of contributory factors, many of which are reversible by simple measures, such patients should be first evaluated by a clinician skilled in the care of older people before any invasive investigations or more potentially harmful medications are given.
- Post-void residual urine measurement by a non-invasive method is recommended before institution of pharmacological or surgical treatment of incontinence. It should be repeated to monitor the effect of such treatment
- Uroflowmetry should used to screen for voiding abnormalities prior to invasive treatment in the elderly.
- Filling cystometry, as a single investigation, has limited value in this patient population. 'Simple cystometry' is not recommended
- Simple cystometry can be used as a 'screening test' for non- invasive, or other low risk treatments, when a urethral or suprapubic catheter is already present for management. However, the low specificity and sensitivity towards complete urodynamic studies diagnosis must be taken into account.
- The committee recommends offering comprehensive urodynamic testing to all elderly, with due consideration of any co morbidity, that have not responded to management of relevant contributing factors, and or behavioural or pharmacological therapy, and in whom further invasive therapy is considered.
- The committee recommends that comprehensive urodynamic testing be performed in centres with a special interest in incontinence in the frail elderly, by trained and certified staff who frequently perform urodynamic testing of patients referred with suspected lower urinary tract dysfunction
- To maintain adequate urodynamic expertise in this difficult-to-examine patient population, and to provide a background of 'regular' patients against whom specific patients can be judged, it is essential that such centres examine substantial numbers of frail elderly patients

Topics for research

- Study of biological mechanisms of continence and incontinence in the frail elderly, especially those related to supraspinal control or lack thereof.
- Development and testing of treatments specific to the frail elderly with incontinence.
- Establishment of the reproducibility and reliability of urodynamic measurements in the frail elderly.
- Investigation of the associations of defecation and faecal loading or impaction of the bowel on detrusor contraction, incontinence and other lower urinary tract problems (e.g. UTI), as well as investigation of the management of combined faecal and urinary incontinence.
- Further investigation of the (cause of, and optimal management of) clinically observed association of DO and underactive detrusor during voiding (and post void residuals) in the (frail) elderly.

REFERENCES

Abarbanel J, Marcus EL. Impaired detrusor contractility in community-dwelling elderly presenting with lower urinary tract symptoms. Urology 2007 Mar;69(3):436-440.

Abdul-Rahman A, Al-Hayek S, Belal M. Urodynamic studies in the evaluation of the older man with lower urinary tract symptoms: when, which ones, and what to do with the results. Ther Adv Urol 2010 Oct;2(5-06):187-194.

Abidari JM, Shortliffe LM. Urinary incontinence in girls. Urol Clin North Am 2002 Aug;29(3):661-75, x.

Aboseif SR, Konety B, Schmidt RA, Goldfien SH, Tanagho EA, Narayan PA. Preoperative urodynamic evaluation: does it predict the degree of urinary continence after radical retropubic prostatectomy? Urol Int 1994;53(2):68-73.

Abrahamsson K, Hansson E, Sillen U, Hermansson G, Hjalmas K. Bladder dysfunction: an integral part of the ectopic ureterocele complex. J Urol 1998 Oct;160(4):1468-1470.

Abrahamsson K, Olsson I, Sillen U. Urodynamic findings in children with myelomeningocele after untethering of the spinal cord. J Urol 2007 Jan;177(1):331-4; discussion 334.

Abrams, P., Griffiths, D., Hofner, K., et al., The urodynamics of LUTS, in Benign Prostatic Hyperplasia, C. Chatelain, Denis, L., Foo, KT., et al., Editor. 2001, Plymbridge Distributors Ltd: Plymouth (UK). p. 227.

Abrams P, Blaivas JG, Stanton SL, Andersen JT. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. Scand J Urol Nephrol Suppl 1988;114:5-19.

Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21(2):167-178.

Abrams P, Chapple C, Khoury S, Roehrborn C, de la Rosette J, International Scientific Committee. Evaluation and treatment of lower urinary tract symptoms in older men. J Urol 2009 Apr;181(4):1779-1787.

Abrams PH, Torrens MJ. Urethral closure pressure profiles in the male: an analysis of 280 patients. Urol Int 1977;32(2-3):137-145.

Acar B, Arikan FI, Germiyanoglu C, Dallar Y. Influence of high bladder pressure on vesicoureteral reflux and its resolution. Urol Int 2009;82(1):77-80.

Addla SK, Marri RR, Daayana SL, Irwin P. Avoid cruising on the uroflowmeter: evaluation of cruising artifact on spinning disc flowmeters in an experimental setup. Neurourol Urodyn 2010 Sep;29(7):1301-1305.

Adekanmi OA, Edwards GJ, Barrington JW. The variation in urodynamic practice in the United Kingdom. J Obstet Gynaecol 2002 Jan;22(1):48-50.

Agur W, Housami F, Drake M, Abrams P. Could the National Institute for Health and Clinical Excellence guidelines on urodynamics in urinary incontinence put some women at risk of a bad outcome from stress incontinence surgery? BJU Int 2009 Mar;103(5):635-639.

Albo M, Wruck L, Baker J, Brubaker L, Chai T, Dandreo KJ, et al. The relationships among measures of incontinence severity in women undergoing surgery for stress urinary incontinence. J Urol 2007 May;177(5):1810-1814.

Al-Ghazo MA, Ghalayini IF, Al-Azab R, Hani OB, Matani YS, Haddad Y. Urodynamic detrusor overactivity in patients with overactive bladder symptoms. Int Neurourol J 2011 Mar;15(1):48-54.

Al-Hayek S, Belal M, Abrams P. Does the patient's position influence the detection of detrusor overactivity? Neurourol Urodyn 2008;27(4):279-286.

Ali-El-Dein B, Abol-Enein H, El-Husseini A, Osman Y, Shehab El-Din AB, Ghoneim MA. Renal transplantation in children with abnormal lower urinary tract. Transplant Proc 2004 Dec;36(10):2968-2973.

Almeida FG, Bruschini H, Srougi M. Correlation between urethral sphincter activity and Valsalva leak point pressure at different bladder distentions: revisiting the urethral pressure profile. J Urol 2005 Oct;174(4 Pt 1):1312-5; discussion 1315-6.

Almeida FG, Freitas DG, Bruschini H. Is the ultrasound-estimated bladder weight a reliable method for evaluating bladder outlet obstruction? BJU Int 2011 Sep;108(6):864-867.

Almodhen F, Capolicchio JP, Jednak R, El Sherbiny M. Postpubertal urodynamic and upper urinary tract changes in children with conservatively treated myelomeningocele. J Urol 2007 Oct;178(4 Pt 1):1479-1482.

Alperin M, Abrahams-Gessel S, Wakamatsu MM. Development of de novo urge incontinence in women post sling: the role of preoperative urodynamics in assessing the risk. Neurourol Urodyn 2008;27(5):407-411.

Androulakakis PA, Karamanolakis DK, Tsahouridis G, Stefanidis AA, Palaeodimos I. Myogenic bladder decompensation in boys with a history of posterior urethral valves is caused by secondary bladder neck obstruction? BJU Int 2005 Jul;96(1):140-143.

Ansari MS, Gulia A, Srivastava A, Kapoor R. Risk factors for progression to end-stage renal disease in children with posterior urethral valves. J Pediatr Urol 2010 Jun;6(3):261-264.

Araki I, Zakoji H, Komuro M, Furuya Y, Fukasawa M, Takihana Y, et al. Lower urinary tract symptoms in men and women without underlying disease causing micturition disorder: a cross-sectional study assessing the natural history of bladder function. J Urol 2003 Nov;170(5):1901-1904.

Arlandis Guzman S, Bonillo Garcia MA, Broseta Rico E. Voiding dysfunction after brachytherapy in patients with prostate cancer. Arch Esp Urol 2009 Dec;62(10):826-7837.

Arnold EP. Proceedings: Cystometry--postural effects in incontinent women. Urol Int 1974;29(3):185-186.

Awad SA, Bryniak SR, Lowe PJ, Bruce AW, Twiddy DA. Urethral pressure profile in female stress incontinence. J Urol 1978 Oct;120(4):475-479.

Awad SA, McGinnis RH. Factors that influence the incidence of detrusor instability in women. J Urol 1983 Jul;130(1):114-115.

Bachelard M, Sillen U, Hansson S, Hermansson G, Jodal U, Jacobsson B. Urodynamic pattern in asymptomatic infants: siblings of children with vesicoureteral reflux. J Urol 1999 Nov;162(5):1733-7; discussion 1737-8.

Bachelard M, Sillen U, Hansson S, Hermansson G, Jodal U, Jacobsson B. Urodynamic pattern in infants with urinary tract infection. J Urol 1998 Aug;160(2):522-526.

Badlani, G., Vohara, S., Mutola, JA., Detrusor behavior in patients with dominant hemispheric strokes Neurourology and Urodynamics, 1991. 10: p. 119

Bael A, Verhulst J, Lax H, Hirche H, van Gool JD, European Bladder Dysfunction Study EU BMH1-CT94-1006. Investigator bias in urodynamic studies for functional urinary incontinence. J Urol 2009 Oct;182(4 Suppl):1949-1952.

Bai SW, Park JH, Kim SK, Park KH. Analysis of the success rates of Burch colposuspension in relation to Valsalva leak-point pressure. J Reprod Med 2005 Mar;50(3):189-192.

Ballert KN, Biggs GY, Isenalumhe A,Jr, Rosenblum N, Nitti VW. Managing the urethra at transvaginal pelvic organ prolapse repair: a urodynamic approach. J Urol 2009 Feb;181(2):679-684.

Ballert KN, Nitti VW. Association between detrusor overactivity and postoperative outcomes in patients undergoing male bone anchored perineal sling. J Urol 2010 Feb;183(2):641-645.

Baltes PB, Smith J. New frontiers in the future of aging: from successful aging of the young old to the dilemmas of the fourth age. Gerontology 2003 Mar-Apr;49(2):123-135.

Bansal R, Agarwal MM, Modi M, Mandal AK, Singh SK. Urodynamic profile of diabetic patients with lower urinary tract symptoms: association of diabetic cystopathy with autonomic and peripheral neuropathy. Urology 2011 Mar;77(3):699-705.

Barnes PD, Lester PD, Yamanashi WS, Prince JR. MRI in infants and children with spinal dysraphism. AJR Am J Roentgenol 1986 Aug;147(2):339-346.

Baseman AG, Baseman JG, Zimmern PE, Lemack GE. Effect of 6F urethral catheterization on urinary flow rates during repeated pressure-flow studies in healthy female volunteers. Urology 2002 Jun;59(6):843-846.

Batista Miranda JE, Arano Bertran P, Caffaratti J, Regalado Pareja R, Garat Barredo JM, Errando Smet C, et al. Efficacy of oxybutynin chloride in children with vesico-ureteral reflux and detrusor instability. An Esp Pediatr 1997 Sep;47(3):251-257.

Bauer, S., The management of spina bifida from birth onwards, in Pediatric urology, R. Whitaker, Woodard, JR, Editor. 1985, Butterworths: London.

Bauer SB, Dieppa RA, Labib KK, Retik AB. The bladder in boys with posterior urethral valves: a urodynamic assessment. J Urol 1979 Jun;121(6):769-773.

Bauer SB, Hallett M, Khoshbin S, Lebowitz RL, Winston KR, Gibson S, et al. Predictive value of urodynamic evaluation in newborns with myelodysplasia. JAMA 1984 Aug 3;252(5):650-652.

Beck RP, McCormick S, Nordstrom L. A 25-year experience with 519 anterior colporrhaphy procedures. Obstet Gynecol 1991 Dec;78(6):1011-1018.

Beekman M, Merrick GS, Butler WM, Wallner KE, Allen ZA, Galbreath RW. Selecting patients with pretreatment postvoid residual urine volume less than 100 mL may favorably influence brachytherapy-related urinary morbidity. Urology 2005 Dec;66(6):1266-1270.

Bellman M. Studies on encopresis. Acta Paediatr Scand 1966:Suppl 170:1+.

Bent AE, Richardson DA, Ostergard DR. Diagnosis of lower urinary tract disorders in postmenopausal patients. Am J Obstet Gynecol 1983 Jan 15;145(2):218-222.

Bentzon DN, Graugaard-Jensen C, Borre M. Urethral pressure profile 6 months after radical prostatectomy may be diagnostic of sphincteric incontinence: preliminary data after 12 months' follow-up. Scand J Urol Nephrol 2009;43(2):114-118.

Berger M, Heinrich M, Lacher M, Hubertus J, Stehr M, von Schweinitz D. Postoperative bladder and rectal function in children with sacrococcygeal teratoma. Pediatr Blood Cancer 2011 Mar;56(3):397-402.

Bhatia NN, Bergman A. Urodynamic predictability of voiding following incontinence surgery. Obstet Gynecol 1984 Jan;63(1):85-91.

Bilginer Y, Aki FT, Topaloglu R, Tekgul S, Demirkaya E, Duzova A, et al. Renal transplantation in children with lower urinary tract dysfunction of different origin: a single-center experience. Transplant Proc 2008 Jan-Feb;40(1):85-86.

Bing MH, Moller LA, Jennum P, Mortensen S, Lose G. Pathophysiological aspects of nocturia in a danish population of men and women age 60 to 80 years. J Urol 2007 Aug;178(2):552-557.

Blackett H, Walker R, Wood B. Urinary dysfunction in Parkinson's disease: a review. Parkinsonism Relat Disord 2009 Feb;15(2):81-87.

Blaivas JG, Groutz A, Verhaaren M. Does the method of cystometry affect the incidence of involuntary detrusor contractions? A prospective randomized urodynamic study. Neurourol Urodyn 2001;20(2):141-145.

Blaivas JG, Olsson CA. Stress incontinence: classification and surgical approach. J Urol 1988 Apr;139(4):727-731.

Blaivas JG, Weiss JP, Jones M. The pathophysiology of lower urinary tract symptoms after brachytherapy for prostate cancer. BJU Int 2006 Dec;98(6):1233-7; discussion 1237.

Bochove-Overgaauw DM, Schrier BP. An adjustable sling for the treatment of all degrees of male stress urinary incontinence: retrospective evaluation of efficacy and complications after a minimal followup of 14 months. J Urol 2011 Apr;185(4):1363-1368.

Boemers TM, Beek FJ, van Gool JD, de Jong TP, Bax KM. Urologic problems in anorectal malformations. Part 1: Urodynamic findings and significance of sacral anomalies. J Pediatr Surg 1996 Mar;31(3):407-410.

Boemers TM, van Gool JD, de Jong TP, Bax KM. Urodynamic evaluation of children with the caudal regression syndrome (caudal dysplasia sequence). J Urol 1994 Apr;151(4):1038-1040.

Bomalaski MD, Teague JL, Brooks B. The long-term impact of urological management on the quality of life of children with spina bifida. J Urol 1995 Aug;154(2 Pt 2):778-781.

Bonney, V., On diurnal incontinence of urine in women. J Obstet Gynaecol Br Empire, 1923. 30: p. 358-365.

Borer, J. Predominant urodynamic parameters in girls with recurrent UTI Journal of Urology, 1999. 161: p. 162

Borg H, Holmdahl G, Olsson I, Wiklund LM, Sillen U. Impact of spinal cord malformation on bladder function in children with anorectal malformations. J Pediatr Surg 2009 Sep;44(9):1778-1785.

Borrelli M, Bruschini H, Nahas WC, Figueiredo JA, Prado MJ, Spinola R, et al. Sacral agenesis: why is it so frequently misdiagnosed? Urology 1985 Oct;26(4):351-355.

Borstad E, Rud T. The risk of developing urinary stress-incontinence after vaginal repair in continent women. A clinical and urodynamic follow-up study. Acta Obstet Gynecol Scand 1989;68(6):545-549.

Borzyskowski M, Mundy AR. Videourodynamic assessment of diurnal urinary incontinence. Arch Dis Child 1987 Feb;62(2):128-131.

Bosch JL, Cardozo L, Hashim H, Hilton P, Oelke M, Robinson D. Constructing trials to show whether urodynamic studies are necessary in lower urinary tract dysfunction. Neurourol Urodyn 2011 Jun;30(5):735-740.

Botros SM, Miller JJ, Goldberg RP, Gandhi S, Akl M, Beaumont JL, et al. Detrusor overactivity and urge urinary incontinence following trans obturator versus midurethral slings. Neurourol Urodyn 2007;26(1):42-45.

Bower WF, Swithinbank L, de Jong T, de Kort LM, Marschall-Kehrel D. Assessment of non-neurogenic incontinence and lower urinary tract symptoms in adolescents and young adults. Neurourol Urodyn 2010 Jun;29(5):702-707.

Bozkurt P, Kilic N, Kaya G, Yeker Y, Elicevik M, Söylet Y. The effects of intranasal midazolam on urodynamic studies in children. Br J Urol. 1996 Aug;78(2):282-6.

Bristow SE, Neal DE. Ambulatory urodynamics. Br J Urol 1996 Mar;77(3):333-338.

Broekhuis SR, Kluivers KB, Hendriks JC, Massolt ET, Groen J, Vierhout ME. Reproducibility of same session repeated cystometry and pressure-flow studies in women with symptoms of urinary incontinence. Neurourol Urodyn 2010 Mar;29(3):428-431.

Bross, S., et al., The role of the carbachol test and concomitant diseases in patients with nonobstructive urinary retention undergoing sacral neuromodulation. World J Urol, 2003. 20(6): p. 346-9.

Bross S, Honeck P, Kwon ST, Badawi JK, Trojan L, Alken P. Correlation between motor function and lower urinary tract dysfunction in patients with infantile cerebral palsy. Neurourol Urodyn 2007;26(2):222-227.

Brostrom S, Jennum P, Lose G. Short-term reproducibility of cystometry and pressure-flow micturition studies in healthy women. Neurourol Urodyn 2002;21(5):457-460.

Brown K, Hilton P. The incidence of detrusor instability before and after colposuspension: a study using conventional and ambulatory urodynamic monitoring. BJU Int 1999 Dec;84(9):961-965.

Bukurov NS, Stefanovic KB, Marinkovic JM. Uroflow via stenotic urethra. Int Urol Nephrol 1992;24(1):55-63.

Bump RC, Hurt WG, Theofrastous JP, Addison WA, Fantl JA, Wyman JF, et al. Randomized prospective comparison of needle colposuspension versus endopelvic fascia plication for

potential stress incontinence prophylaxis in women undergoing vaginal reconstruction for stage III or IV pelvic organ prolapse. The Continence Program for Women Research Group. Am J Obstet Gynecol 1996 Aug;175(2):326-33; discussion 333-5.

(80) Bunne G, Obrink A. Urethral closure pressure with stress--a comparison between stress-incontinent and continent women. Urol Res 1978;6(3):127-134.

Burki T, Hamid R, Duffy P, Ransley P, Wilcox D, Mushtaq I. Long-term followup of patients after redo bladder neck reconstruction for bladder exstrophy complex. J Urol 2006 Sep;176(3):1138-41; discussion 1141-2.

Burti JS, Santos AM, Pereira RM, Zambon JP, Marques AP. Prevalence and clinical characteristics of urinary incontinence in elderly individuals of a low income. Arch Gerontol Geriatr 2012 Mar;54(2):e42-6.

Cadogan, M., Awad, SA., Field, C, A comparison of the cough and standing urthral pressure profile in the diagnosis of stress incontinence. Neurourology and Urodynamics, 1988. 7: p. 327.

Caione P, Capozza N, Zavaglia D, De Dominicis M. Anterior perineal reconstruction in exstrophy-epispadias complex. Eur Urol 2005 Jun;47(6):872-7; discussion 877-8.

Camanni D, Zaccara A, Capitanucci ML, Mosiello G, Iacobelli BD, De Gennaro M. Bladder after total urogenital mobilization for congenital adrenal hyperplasia and cloaca--does it behave the same? J Urol 2009 Oct;182(4 Suppl):1892-1897.

Cantor TJ, Bates CP. A comparative study of symptoms and objective urodynamic findings in 214 incontinent women. Br J Obstet Gynaecol 1980 Oct;87(10):889-892.

Capitanucci ML, Iacobelli BD, Silveri M, Mosiello G, De Gennaro M. Long-term urological follow-up of occult spinal dysraphism in children. Eur J Pediatr Surg 1996 Dec;6 Suppl 1:25-26.

Capitanucci ML, Rivosecchi M, Silveri M, Lucchetti MC, Mosiello G, De Gennaro M. Neurovesical dysfunction due to spinal dysraphism in anorectal anomalies. Eur J Pediatr Surg 1996 Jun;6(3):159-162.

Capitanucci ML, Silveri M, Mosiello G, Zaccara A, Capozza N, de Gennaro M. Prevalence of hypercontractility in male and female infants with vesico-ureteral reflux. Eur J Pediatr Surg 2000 Jun;10(3):172-176.

Cardenas DD, Mayo ME, Turner LR. Lower urinary changes over time in suprasacral spinal cord injury. Paraplegia 1995 Jun;33(6):326-329.

Cassidenti AP, Ostergard DR. Multichannel urodynamics: ambulatory versus standard urodynamics. Curr Opin Obstet Gynecol 1999 Oct;11(5):485-487.

Castille Y, Opsomer RJ, Tombal B, Van Cangh PJ. Contribution of the preoperative urodynamic findings in the determination of risks factors of urinary incontinence after radical retropubic prostatectomy. Ann Readapt Med Phys 2003 Mar;46(2):79-83.

Chan H. Bladder management in acute care of stroke patients: a quality improvement project. J Neurosci Nurs 1997 Jun;29(3):187-190.

Chancellor MB, Blaivas JG, Kaplan SA, Axelrod S. Bladder outlet obstruction versus impaired detrusor contractility: the role of outflow. J Urol 1991 Apr;145(4):810-812.

Chancellor MB, Lavelle J, Ozawa H, Jung SY, Watanabe T, Kumon H. Ice-water test in the urodynamic evaluation of spinal cord injured patients. Tech Urol 1998 Jun;4(2):87-91.

Chandra M. Nocturnal enuresis in children. Curr Opin Pediatr 1998 Apr;10(2):167-173.

Chandra M, Maddix H. Urodynamic dysfunction in infants with vesicoureteral reflux. J Pediatr 2000 Jun;136(6):754-759.

Chandra M, Maddix H, McVicar M. Transient urodynamic dysfunction of infancy: relationship to urinary tract infections and vesicoureteral reflux. J Urol 1996 Feb;155(2):673-677.

Chen CC, Rooney CM, Paraiso MF, Kleeman SD, Walters MD, Karram MM, et al. Leak point pressure does not correlate with incontinence severity or bother in women undergoing surgery for urodynamic stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008 Sep;19(9):1193-1198.

Chen YM, Hwang SJ, Chen LK, Chen DY, Lan CF. Urinary incontinence among institutionalized oldest old Chinese men in Taiwan. Neurourol Urodyn 2009;28(4):335-338.

Cheon SM, Ha MS, Park MJ, Kim JW. Nonmotor symptoms of Parkinson's disease: prevalence and awareness of patients and families. Parkinsonism Relat Disord 2008;14(4):286-290.

Chin-Peuckert L, Komlos M, Rennick JE, Jednak R, Capolicchio JP, Salle JL. What is the variability between 2 consecutive cystometries in the same child? J Urol 2003 Oct;170(4 Pt 2):1614-1617.

Cho MC, Park JH, Jeong MS, Yi JS, Ku JH, Oh SJ, et al. Predictor of de novo urinary incontinence following holmium laser enucleation of the prostate. Neurourol Urodyn 2011 Sep;30(7):1343-1349.

Cho SY, Oh SJ. The clinical significance of rectal contractions that occur during urodynamic studies. Neurourol Urodyn 2010 Mar;29(3):418-423.

Choe JM, Gallo ML, Staskin DR. A provocative maneuver to elicit cystometric instability: measuring instability at maximum infusion. J Urol 1999 May;161(5):1541-1544.

Choo R, Do V, Herschorn S, DeBoer G, Danjoux C, Morton G, et al. Urodynamic changes at 18 months post-therapy in patients treated with external beam radiotherapy for prostate carcinoma. Int J Radiat Oncol Biol Phys 2002 Jun 1;53(2):290-296.

Chou FH, Ho CH, Chir MB, Linsenmeyer TA. Normal ranges of variability for urodynamic studies of neurogenic bladders in spinal cord injury. J Spinal Cord Med 2006;29(1):26-31.

Chung SD, Chiu B, Kuo HC, Chuang YC, Wang CC, Guan Z, et al. Transabdominal ultrasonography of detrusor wall thickness in women with overactive bladder. BJU Int 2010 Mar;105(5):668-672.

Chung SD, Liao CH, Chen YC, Kuo HC. Urgency severity scale could predict urodynamic detrusor overactivity in patients with overactive bladder syndrome. Neurourol Urodyn 2011 Sep;30(7):1300-1304.

Clarkson B, Griffiths C, McArdle F, Pickard R, Drinnan M. Continuous non-invasive measurement of bladder voiding pressure using an experimental constant low-flow test. Neurourol Urodyn 2011 Dec 20.

Clarkson B, Robson W, Griffiths C, McArdle F, Drinnan M, Pickard R. Multisite evaluation of noninvasive bladder pressure flow recording using the penile cuff device: assessment of test-retest agreement. J Urol 2008 Dec;180(6):2515-2521.

Clemens JQ, Bogart LM, Liu K, Pham C, Suttorp M, Berry SH. Perceptions of "urgency" in women with interstitial cystitis/bladder pain syndrome or overactive bladder. Neurourol Urodyn 2011 Mar;30(3):402-405.

Colli E, Artibani W, Goka J, Parazzini F, Wein AJ. Are urodynamic tests useful tools for the initial conservative management of non-neurogenic urinary incontinence? A review of the literature. Eur Urol 2003 Jan;43(1):63-69.

Colombo M, Maggioni A, Scalambrino S, Vitobello D, Milani R. Surgery for genitourinary prolapse and stress incontinence: a randomized trial of posterior pubourethral ligament plication and Pereyra suspension. Am J Obstet Gynecol 1997 Feb;176(2):337-343.

Colstrup, H., Andersen, JT., Walter, S. 12th Annual Meeting of the International Continence Society (Leiden, Holland), 1982: p. 201.

Coolsaet, B. in ICS Annual Meeting. 1979.

Cooper MA, Fletter PC, Zaszczurynski PJ, Damaser MS. Comparison of air-charged and water-filled urodynamic pressure measurement catheters. Neurourol Urodyn 2011 Mar;30(3):329-334.

Costantini E, Lazzeri M, Giannantoni A, Bini V, Vianello A, Kocjancic E, et al. Preoperative Valsalva leak point pressure may not predict outcome of mid-urethral slings. Analysis from a randomized controlled trial of retropubic versus transobturator mid-urethral slings. Int Braz J Urol 2008 Jan-Feb;34(1):73-81; discussion 81-3.

Coyne KS, Margolis MK, Hsieh R, Vats V, Chapple CR. Valida-

tion of the urinary sensation scale (USS). Neurourol Urodyn 2011 Mar;30(3):360-365.

Coyne KS, Sexton CC, Kopp ZS, Ebel-Bitoun C, Milsom I, Chapple C. The impact of overactive bladder on mental health, work productivity and health-related quality of life in the UK and Sweden: results from EpiLUTS. BJU Int 2011 Nov;108(9):1459-1471.

Coyne KS, Sexton CC, Vats V, Thompson C, Kopp ZS, Milsom I. National community prevalence of overactive bladder in the United States stratified by sex and age. Urology 2011 May;77(5):1081-1087.

Craggs MD. Objective measurement of bladder sensation: use of a new patient-activated device and response to neuromodulation. BJU Int 2005 Sep;96 Suppl 1:29-36.

Cucchi A, Quaglini S, Guarnaschelli C, Rovereto B. Urodynamic findings suggesting two-stage development of idiopathic detrusor underactivity in adult men. Urology 2007 Jul;70(1):75-79.

Cucchi A, Quaglini S, Rovereto B. Proposal for a urodynamic redefinition of detrusor underactivity. J Urol 2009 Jan;181(1):225-229.

Cucchi A, Quaglini S, Rovereto B. Relationships between micturition urgency and involuntary voiding dynamics in men with urinary incontinence from idiopathic detrusor overactivity. J Urol 2007 Aug;178(2):563-7; discussion 567.

Culligan PJ, Goldberg RP, Blackhurst DW, Sasso K, Koduri S, Sand PK. Comparison of microtransducer and fiberoptic catheters for urodynamic studies. Obstet Gynecol 2001 Aug;98(2):253-257.

Cundiff GW, Harris RL, Coates KW, Bump RC. Clinical predictors of urinary incontinence in women. Am J Obstet Gynecol 1997 Aug;177(2):262-6; discussion 266-7.

Das A, Kennett K, Fraundorfer M, Gilling P. Holmium laser resection of the prostate (HoLRP): 2-year follow-up data. Tech Urol 2001 Dec;7(4):252-255.

Dator DP, Hatchett L, Dyro FM, Shefner JM, Bauer SB. Urodynamic dysfunction in walking myelodysplastic children. J Urol 1992 Aug;148(2 Pt 1):362-365.

Davies TO, Bepple JL, McCammon KA. Urodynamic changes and initial results of the AdVance male sling. Urology 2009 Aug;74(2):354-357.

Dawson T, Lawton V, Adams E, Richmond D. Factors predictive of post-TVT voiding dysfunction. Int Urogynecol J Pelvic Floor Dysfunct 2007 Nov;18(11):1297-1302.

De Gennaro M, Capitanucci ML, Mosiello G, Caione P, Silveri M. The changing urodynamic pattern from infancy to adolescence in boys with posterior urethral valves. BJU Int 2000 Jun;85(9):1104-1108.

De Gennaro M, Mosiello G, Capitanucci ML, Silveri M, Capozza N, Caione P. Early detection of bladder dysfunction following posterior urethral valves ablation. Eur J Pediatr Surg 1996 Jun;6(3):163-165.

De Gennaro M, Rivosecchi M, Lucchetti MC, Silveri M, Fariello G, Schingo P. The incidence of occult spinal dysraphism and the onset of neurovesical dysfunction in children with anorectal anomalies. Eur J Pediatr Surg 1994 Dec;4 Suppl 1:12-14.

de Jong TP, Chrzan R, Klijn AJ, Dik P. Treatment of the neurogenic bladder in spina bifida. Pediatr Nephrol 2008 Jun;23(6):889-896.

de Jonge MC, Kornelis JA, van den Berg J. The static urethral closure pressure profile in female incontinence. A comparison between sphincter and detrusor incontinence. Prog Clin Biol Res 1981;78:231-238.

De Muylder X, Claes H, Neven P, De Jaegher K. Usefulness of urodynamic investigations in female incontinence. Eur J Obstet Gynecol Reprod Biol 1992 May 13;44(3):205-208.

De Wachter S, Van Meel TD, Wyndaele JJ. Can a faked cystometry deceive patients in their perception of filling sensations? A study on the reliability of spontaneously reported cystometric filling sensations in patients with non-neurogenic lower urinary tract dysfunction. Neurourol Urodyn 2008;27(5):395-398.

De Wachter S, Wyndaele JJ. How sudden is a compelling desire to void? An observational cystometric study on the suddenness of this sensation. BJU Int 2008 Apr;101(8):1000-1003.

De Wachter SG, Heeringa R, van Koeveringe GA, Gillespie JI. On the nature of bladder sensation: the concept of sensory modulation. Neurourol Urodyn 2011 Sep;30(7):1220-1226.

Decter RM, Bauer SB. Urologic management of spinal cord injury in children. Urol Clin North Am 1993 Aug;20(3):475-483.

Decter RM, Bauer SB, Khoshbin S, Dyro FM, Krarup C, Colodny AH, et al. Urodynamic assessment of children with cerebral palsy. J Urol 1987 Oct;138(4 Pt 2):1110-1112.

Deffontaines Rufin S, Jousse M, Verollet D, Guinet A, Ismael SS, Amarenco G. Cold perception of the bladder during ice water test. Study on 120 patients. Ann Phys Rehabil Med 2010 Nov;53(9):559-567.

Defreitas GA, Lemack GE, Zimmern PE, Dewey RB, Roehrborn CG, O'Suilleabhain PE. Distinguishing neurogenic from non-neurogenic detrusor overactivity: a urodynamic assessment of lower urinary tract symptoms in patients with and without Parkinson's disease. Urology 2003 Oct;62(4):651-655.

DeLancey JO, Miller JM, Kearney R, Howard D, Reddy P, Umek W, et al. Vaginal birth and de novo stress incontinence: relative contributions of urethral dysfunction and mobility. Obstet Gynecol 2007 Aug;110(2 Pt 1):354-362.

Dennis PJ, Rohner TJ,Jr, Hu TW, Igou JF, Yu LC, Kaltreider DL. Simple urodynamic evaluation of incontinent elderly female nursing home patients. A descriptive analysis. Urology 1991 Feb;37(2):173-179.

Diamond DA, Bauer SB, Dinlenc C, Hendren WH, Peters CA, Atala A, et al. Normal urodynamics in patients with bladder exstrophy: are they achievable? J Urol 1999 Sep;162(3 Pt 1):841-4; discussion 844-5.

Dib PT, Trigo-Rocha F, Gomes CM, Srougi M. Urodynamic evaluation in diabetic patients with prostate enlargement and lower urinary tract symptoms. Urol Int 2008;80(4):378-382.

Digesu GA, Athanasiou S, Chaliha C, Michalas S, Salvatore S, Selvaggi L, et al. Urethral retro-resistance pressure and urodynamic diagnoses in women with lower urinary tract symptoms. BJOG 2006 Jan;113(1):34-38.

Digesu GA, Basra R, Khullar V, Hendricken C, Camarata M, Kelleher C. Bladder sensations during filling cystometry are different according to urodynamic diagnosis. Neurourol Urodyn 2009;28(3):191-196.

Digesu GA, Hutchings A, Salvatore S, Selvaggi L, Khullar V. Reproducibility and reliability of pressure flow parameters in women. BJOG 2003 Aug;110(8):774-776.

Digesu GA, Khullar V, Cardozo L, Salvatore S. Overactive bladder symptoms: do we need urodynamics? Neurourol Urodyn 2003;22(2):105-108.

Digesu GA, Salvatore S, Fernando R, Khullar V. Mixed urinary symptoms: what are the urodynamic findings? Neurourol Urodyn 2008;27(5):372-375.

Dik P, Klijn AJ, van Gool JD, de Jong-de Vos van Steenwijk,C.C., de Jong TP. Early start to therapy preserves kidney function in spina bifida patients. Eur Urol 2006 May;49(5):908-913.

Diokno AC, Dimaculangan RR, Lim EU, Steinert BW. Office based criteria for predicting type II stress incontinence without further evaluation studies. J Urol 1999 Apr;161(4):1263-1267.

Do V, Choo R, Deboer G, Herschorn S, Danjoux C, Chen CH, et al. Urodynamic findings 3 months after radiotherapy in patients treated with conformal external beam radiotherapy for prostate carcinoma. BJU Int 2002 Jul;90(1):62-67.

Donohoe JM, Weinstein RP, Combs AJ, Misseri R, Horowitz M, Schulsinger D, et al. When can persistent hydroureteronephrosis in posterior urethral valve disease be considered residual stretching? J Urol 2004 Aug;172(2):706-11; discussion 711.

Dorflinger A, Gorton E, Stanton S, Dreher E. Urethral pressure profile: is it affected by position? Neurourol Urodyn 2002;21(6):553-557.

Drinnan MJ, McIntosh SL, Robson WA, Pickard RS, Ramsden PD, Griffiths CJ. Inter-observer agreement in the estima-

tion of bladder pressure using a penile cuff. Neurourol Urodyn 2003;22(4):296-300.

Drinnan MJ, Robson W, Reddy M, Pickard RS, Ramsden PD, Griffiths CJ. Transmission of penile cuff pressure to the penile urethra. J Urol 2001 Dec;166(6):2545-2549.

Drzewiecki BA, Bauer SB. Urodynamic testing in children: indications, technique, interpretation and significance. J Urol 2011 Oct;186(4):1190-1197.

Duckett JR, Patil A, Papanikolaou NS. Predicting early voiding dysfunction after tension-free vaginal tape. J Obstet Gynaecol 2008 Jan;28(1):89-92.

Duggan P. Urodynamic diagnoses and quality of life in women presenting for evaluation of urinary incontinence. Aust N Z J Obstet Gynaecol 2011 Oct;51(5):416-420.

Edwards DF, Hahn M, Dromerick A. Post stroke urinary loss, incontinence and life satisfaction: when does post-stroke urinary loss become incontinence? Neurourol Urodyn 2006;25(1):39-45.

El Bahnasawy MS, Osman Y, Gomha MA, Shaaban AA, Ashamallah A, Ghoneim MA. Nocturnal enuresis in men with an orthotopic ileal reservoir: urodynamic evaluation. J Urol 2000 Jul;164(1):10-13.

el-Bahnasawy MS, Gomha MA, Shaaban AA. Urethral pressure profile following orthotopic neobladder: differences between nerve sparing and standard radical cystectomy techniques. J Urol 2006 May;175(5):1759-63; discussion 1763.

el-Bahnasawy MS, Osman Y, Gomha MA, Shaaban AA. Persistent and occasional nocturnal enuresis in orthotopic urinary diversion: is there a urodynamic difference? BJU Int 2005 Dec;96(9):1373-1377.

Ellis-Jones J, Swithinbank L, Abrams P. The impact of formal education and training on urodynamic practice in the United Kingdom: a survey. Neurourol Urodyn 2006;25(5):406-410.

Emir H, Soylet Y. Neurovesical dysfunction in patients with anorectal malformations. Eur J Pediatr Surg 1998 Apr;8(2):95-97.

Ersoz M, Kaya K, Erol SK, Kulakli F, Akyuz M, Ozel S. Noninvasive evaluation of lower urinary tract function in children with cerebral palsy. Am J Phys Med Rehabil 2009 Sep;88(9):735-741.

Ertberg P, Moller LA, Lose G. A comparison of three methods to evaluate maximum bladder capacity: cystometry, uroflowmetry and a 24-h voiding diary in women with urinary incontinence. Acta Obstet Gynecol Scand 2003 Apr;82(4):374-377.

Fairhall N, Langron C, Sherrington C, Lord SR, Kurrle SE, Lockwood K, et al. Treating frailty--a practical guide. BMC Med 2011 Jul 6;9:83.

Fanciullacci F, Zanollo A, Sandri S, Catanzaro F. The neuropathic bladder in children with spinal cord injury. Paraplegia 1988 Apr;26(2):83-86.

Fantl JA, Wyman JF, McClish DK, Bump RC. Urinary incontinence in community-dwelling women: clinical, urodynamic, and severity characteristics. Am J Obstet Gynecol 1990 Apr;162(4):946-51; discussion 951-2.

Farag FF, Martens FM, D'Hauwers KW, Feitz WF, Heesakkers JP. Near-infrared spectroscopy: a novel, noninvasive, diagnostic method for detrusor overactivity in patients with overactive bladder symptoms--a preliminary and experimental study. Eur Urol 2011 May;59(5):757-762.

Farmer JP, Sabbagh AJ. Selective dorsal rhizotomies in the treatment of spasticity related to cerebral palsy. Childs Nerv Syst 2007 Sep;23(9):991-1002.

Feneley MR, Dunsmuir WD, Pearce J, Kirby RS. Reproducibility of uroflow measurement: experience during a double-blind, placebo-controlled study of doxazosin in benign prostatic hyperplasia. Urology 1996 May;47(5):658-663.

Fergusson DM, Horwood LJ, Shannon FT. Factors related to the age of attainment of nocturnal bladder control: an 8-year longitudinal study. Pediatrics 1986 Nov;78(5):884-890.

Ferrucci L, Guralnik JM, Studenski S, Fried LP, Cutler GB,Jr, Walston JD, et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. J Am Geriatr Soc 2004 Apr;52(4):625-634.

Ficazzola MA, Nitti VW. The etiology of post-radical prostatectomy incontinence and correlation of symptoms with urodynamic findings. J Urol 1998 Oct;160(4):1317-1320.

Fleischmann N, Flisser AJ, Blaivas JG, Panagopoulos G. Sphincteric urinary incontinence: relationship of vesical leak point pressure, urethral mobility and severity of incontinence. J Urol 2003 Mar;169(3):999-1002.

Flisser AJ, Walmsley K, Blaivas JG. Urodynamic classification of patients with symptoms of overactive bladder. J Urol 2003 Feb;169(2):529-33; discussion 533-4.

Fonda D, Brimage PJ, D'Astoli M. Simple screening for urinary incontinence in the elderly: comparison of simple and multichannel cystometry. Urology 1993 Nov;42(5):536-540.

Fone PD, Vapnek JM, Litwiller SE, Couillard DR, McDonald CM, Boggan JE, et al. Urodynamic findings in the tethered spinal cord syndrome: does surgical release improve bladder function? J Urol 1997 Feb;157(2):604-609.

Fotter R, Riccabona M. Functional disorders of the lower urinary tract in children. Radiologe 2005 Dec;45(12):1085-1091.

Fowler CJ. Urinary disorders in Parkinson's disease and multiple system atrophy. Funct Neurol 2001 Jul-Sep;16(3):277-282.

Frank SJ, Pisters LL, Davis J, Lee AK, Bassett R, Kuban DA. An assessment of quality of life following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer. J Urol 2007 Jun;177(6):2151-6; discussion 2156.

Frenkl TL, Railkar R, Palcza J, Scott BB, Alon A, Green S, et al. Variability of urodynamic parameters in patients with overactive bladder. Neurourol Urodyn 2011 Nov;30(8):1565-1569.

Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001 Mar;56(3):M146-56.

Friis E, Hjortrup A, Nielsen JE, Sanders S, Walter S. Urinary incontinence and genital prolapse: a prospective blind study of the value of urodynamic evaluation. J Urol 1982 Oct;128(4):764-765.

Fung CH, Spencer B, Eslami M, Crandall C. Quality indicators for the screening and care of urinary incontinence in vulnerable elders. J Am Geriatr Soc 2007 Oct;55 Suppl 2:S443-9.

Galarneau L. Bedside cystometry--a useful diagnostic tool for nurse continence advisors. Perspectives 2003 Spring;27(1):3-5.

Gargollo PC, Borer JG, Diamond DA, Hendren WH, Rosoklija I, Grant R, et al. Prospective followup in patients after complete primary repair of bladder exstrophy. J Urol 2008 Oct;180(4 Suppl):1665-70; discussion 1670.

Geirsson G, Fall M, Lindstrom S. The ice-water test--a simple and valuable supplement to routine cystometry. Br J Urol 1993 Jun;71(6):681-685.

Generao SE, Dall'era JP, Stone AR, Kurzrock EA. Spinal cord injury in children: long-term urodynamic and urological outcomes. J Urol 2004 Sep;172(3):1092-4, discussion 1094.

Geraniotis E, Koff SA, Enrile B. The prophylactic use of clean intermittent catheterization in the treatment of infants and young children with myelomeningocele and neurogenic bladder dysfunction. J Urol 1988 Jan;139(1):85-86.

Ghanem MA, Wolffenbuttel KP, De Vylder A, Nijman RJ. Long-term bladder dysfunction and renal function in boys with posterior urethral valves based on urodynamic findings. J Urol 2004 Jun;171(6 Pt 1):2409-2412.

Ghoniem GM, Walters F, Lewis V. The value of the vaginal pack test in large cystoceles. J Urol 1994 Sep;152(3):931-934.

Gibbs CF, Johnson TM,2nd, Ouslander JG. Office management of geriatric urinary incontinence. Am J Med 2007 Mar;120(3):211-220.

Gillick M. Pinning down frailty. J Gerontol A Biol Sci Med Sci 2001 Mar;56(3):M134-5.

Glassberg KI. The valve bladder syndrome: 20 years later. J Urol 2001 Oct;166(4):1406-1414.

Glassberg KI, Combs AJ, Horowitz M. Nonneurogenic voiding disorders in children and adolescents: clinical and videourodynamic findings in 4 specific conditions. J Urol 2010 Nov;184(5):2123-2127.

Glazener CM, Lapitan MC. Urodynamic investigations for management of urinary incontinence in adults. Cochrane Database Syst Rev 2002;(3)(3):CD003195.

Glezerman M, Glasner M, Rikover M, Tauber E, Bar-Ziv J, Insler V. Evaluation of reliability of history in women complaining of urinary stress incontinence. Eur J Obstet Gynecol Reprod Biol 1986 Mar;21(3):159-164.

Gnanapragasam VJ, Leonard A. Does a pre-operative urodynamic diagnosis of bladder outflow obstruction improve outcomes from palliative transurethral prostatectomy? Urol Int 2011 Feb;86(1):85-89.

Godec CJ, Esho J, Cass AS. Correlation among cystometry, urethral pressure profilometry and pelvic floor electromyography in the evaluation of female patients with voiding dysfunction symptoms. J Urol 1980 Nov;124(5):678-682.

Golomb J, Dotan Z, Leibovitch I, Mor Y, Ramon J. Can preoperative urodynamic examination allow us to predict the risk of incontinence after radical prostatectomy? Prog Urol 1999 Apr;9(2):288-291.

Gomes CM, Arap S, Trigo-Rocha FE. Voiding dysfunction and urodynamic abnormalities in elderly patients. Rev Hosp Clin Fac Med Sao Paulo 2004 Aug;59(4):206-215.

Gomes CM, Nunes RV, Araujo RM, Sacomani CR, Trigo-Rocha FE, Bruschini H, et al. Urodynamic evaluation of patients with lower urinary tract symptoms and small prostate volume. Urol Int 2008;81(2):129-134.

Gomha MA, Boone TB. Artificial urinary sphincter for postprostatectomy incontinence in men who had prior radiotherapy: a risk and outcome analysis. J Urol 2002 Feb;167(2 Pt 1):591-596.

Goode PS, Burgio KL, Locher JL, Umlauf MG, Lloyd LK, Roth DL. Urodynamic changes associated with behavioral and drug treatment of urge incontinence in older women. J Am Geriatr Soc 2002 May;50(5):808-816.

Gordon D, Groutz A. Evaluation of female lower urinary tract symptoms: overview and update. Curr Opin Obstet Gynecol 2001 Oct;13(5):521-527.

Gordon D, Groutz A, Wolman I, Lessing JB, David MP. Development of postoperative urinary stress incontinence in clinically continent patients undergoing prophylactic Kelly plication during genitourinary prolapse repair. Neurourol Urodyn 1999;18(3):193-7; discussion 197-8.

Gormley EA, Griffiths DJ, McCracken PN, Harrison GM, McPhee MS. Effect of transurethral resection of the prostate on detrusor instability and urge incontinence in elderly males. Neurourol Urodyn 1993;12(5):445-453.

Gorton E, Stanton S. Ambulatory urodynamics: do they help clinical management? BJOG 2000 Mar;107(3):316-319.

Gotoh T, Shinno Y, Kobayashi S, Watarai Y, Koyanagi T. Diagnosis and management of sacral agenesis. Eur Urol 1991;20(4):287-292.

Gravina GL, Costa AM, Ronchi P, Galatioto GP, Luana G, Vicentini C. Bladder outlet obstruction index and maximal flow rate during urodynamic study as powerful predictors for the detection of urodynamic obstruction in women. Neurourol Urodyn 2007;26(2):247-253.

Greenfield SP, Fera M. Urodynamic evaluation of the patient with an imperforate anus: a prospective study. J Urol 1991 Aug;146(2 (Pt 2)):539-541.

Greenfield SP, Wan J. The relationship between dysfunctional voiding and congenital vesicoureteral reflux. Curr Opin Urol 2000 Nov;10(6):607-610.

Griffiths, D., Kondo, A., Bauer, S., Diamant, N., Liao, L., Lose, G., Schaefer, W., Yoshimura, Y., Palmtag H., Dynamic Testing, in Incontinence: 3rd International Consultation on Incontinence, P. Abrams, Cardozo, L., Khoury, S., Wein, A., Editor. 2005.

Griffiths, D., Scholtmeijer, R.J. Detrusor instability in children. Neurourol and Urodyn, 1982. 1: p. 187.

Griffiths, D., Scholtmeijer, RJ. Precise urodynamic assessment of meatal and distal urethral stenosis in girls. Neurourol and Urodyn, 1982. 1: p. 89.

Griffiths, D., Scholtmeijer, RJ. Precise urodynamic assessment of meatal and distal urethral stenosis in boys. Neurourol and Urodyn, 1982. 1: p. 97.

Griffiths CJ, Harding C, Blake C, McIntosh S, Drinnan MJ, Robson WA, et al. A nomogram to classify men with lower urinary tract symptoms using urine flow and noninvasive measurement of bladder pressure. J Urol 2005 Oct;174(4 Pt 1):1323-6; discussion 1326; author reply 1326.

Griffiths CJ, Rix D, MacDonald AM, Drinnan MJ, Pickard RS, Ramsden PD. Noninvasive measurement of bladder pressure by controlled inflation of a penile cuff. J Urol 2002 Mar;167(3):1344-1347.

Griffiths D. Clinical studies of cerebral and urinary tract function in elderly people with urinary incontinence. Behav Brain Res 1998 May;92(2):151-155.

Griffiths DJ, McCracken PN, Harrison GM, Gormley EA. Characteristics of urinary incontinence in elderly patients studied by 24-hour monitoring and urodynamic testing. Age Ageing 1992 May;21(3):195-201.

Griffiths DJ, McCracken PN, Harrison GM, Gormley EA, Moore KN. Urge incontinence and impaired detrusor contractility in the elderly. Neurourol Urodyn 2002;21(2):126-131.

Griffiths DJ, McCracken PN, Harrison GM, Moore KN. Urge incontinence in elderly people: factors predicting the severity of urine loss before and after pharmacological treatment. Neurourol Urodyn 1996;15(1):53-57.

Griffiths DJ, Scholtmeijer RJ. Vesicoureteral reflux and lower urinary tract dysfunction: evidence for 2 different reflux/dysfunction complexes. J Urol 1987 Feb;137(2):240-244.

Groutz A, Blaivas JG, Chaikin DC, Weiss JP, Verhaaren M. The pathophysiology of post-radical prostatectomy incontinence: a clinical and video urodynamic study. J Urol 2000 Jun;163(6):1767-1770.

Groutz A, Blaivas JG, Sassone AM. Detrusor pressure uroflowmetry studies in women: effect of a 7Fr transurethral catheter. J Urol 2000 Jul;164(1):109-114.

Guerette NL, Bena JF, Davila GW. Transobturator slings for stress incontinence: using urodynamic parameters to predict outcomes. Int Urogynecol J Pelvic Floor Dysfunct 2008 Jan;19(1):97-102.

Gupta A, Defreitas G, Lemack GE. The reproducibility of urodynamic findings in healthy female volunteers: results of repeated studies in the same setting and after short-term follow-up. Neurourol Urodyn 2004;23(4):311-316.

Gupta A, Taly AB, Srivastava A, Thyloth M. Urodynamic profile in myelopathies: A follow-up study. Ann Indian Acad Neurol 2009 Jan;12(1):35-39.

Guzman L, Bauer SB, Hallett M, Khoshbin S, Colodny AH, Retik AB. Evaluation and management of children with sacral agenesis. Urology 1983 Nov;22(5):506-510.

Haessler AL, Nguyen JN, Bhatia NN. Impact of urodynamic based incontinence diagnosis on quality of life in women. Neurourol Urodyn 2009;28(3):183-187.

Haeusler G, Hanzal E, Joura E, Sam C, Koelbl H. Differential diagnosis of detrusor instability and stress-incontinence by patient history: the Gaudenz-Incontinence-Questionnaire revisited. Acta Obstet Gynecol Scand 1995 Sep;74(8):635-637.

Hamann MF, Naumann CM, Seif C, van der Horst C, Junemann KP, Braun PM. Functional outcome following photoselective vaporisation of the prostate (PVP): urodynamic findings within 12 months follow-up. Eur Urol 2008 Oct;54(4):902-907.

Hameed N, Ali MA, Azim W. Urodynamic findings in female patients reporting with lower urinary tract symptoms. J Ayub Med Coll Abbottabad. 2009 Jan-Mar;21(1):8-10.

Han E, Black LK, Lavelle JP. Incontinence related to management of benign prostatic hypertrophy. Am J Geriatr Pharmacother 2007 Dec;5(4):324-334.

Handa, V., Jensen, JK., Ostergard, DR. , Federal guidelines for the management of urinary incontinence in the United States: Which patients should undergo urodynamic testing? . International Journal Gynaecology Obstetrics, 1994. 6: p. 198.

Hanna MK, Di Scipio W, Suh KK, Kogan SJ, Levitt SB, Donner K. Urodynamics in children. Part II. The pseudoneurogenic bladder. J Urol 1981 Apr;125(4):534-537.

Harding C, Robson W, Drinnan M, Sajeel M, Ramsden P, Griffiths C, et al. Predicting the outcome of prostatectomy using noninvasive bladder pressure and urine flow measurements. Eur Urol 2007 Jul;52(1):186-192.

Harvey MA, Versi E. Predictive value of clinical evaluation of stress urinary incontinence: a summary of the published literature. Int Urogynecol J Pelvic Floor Dysfunct 2001;12(1):31-37.

Hashim H, Abrams P. Is the bladder a reliable witness for predicting detrusor overactivity? J Urol 2006 Jan;175(1):191-4; discussion 194-5.

Hashimoto K, Ohnishi N, Esa A, Sugiyama T, Park Y, Kurita T. Clinical efficacy of oxybutynin on sensory urgency as compared with that on motor urgency. Urol Int 1999;62(1):12-16.

Haylen BT, Chetty N, Logan V, Schulz S, Verity L, Law M, et al. Is sensory urgency part of the same spectrum of bladder dysfunction as detrusor overactivity? Int Urogynecol J Pelvic Floor Dysfunct 2007 Feb;18(2):123-128.

Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J 2010 Jan;21(1):5-26.

Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29(1):4-20.

Haylen BT, Freeman RM, Swift SE, Cosson M, Davila GW, Deprest J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) and grafts in female pelvic floor surgery. Neurourol Urodyn 2011 Jan;30(1):2-12.

Heeringa R, de Wachter SG, van Kerrebroeck PE, van Koeveringe GA. Normal bladder sensations in healthy volunteers: a focus group investigation. Neurourol Urodyn 2011 Sep;30(7):1350-1355.

Heesakkers JP, Vandoninck V, van Balken MR, Bemelmans BL. Bladder filling by autologous urine production during cystometry: a urodynamic pitfall! Neurourol Urodyn 2003;22(3):243-245.

Heesakkers JP, Vriesema JL. The role of urodynamics in the treatment of lower urinary tract symptoms in women. Curr Opin Urol 2005 Jul;15(4):215-221.

Hellerstein S, Linebarger JS. Voiding dysfunction in pediatric patients. Clin Pediatr (Phila) 2003 Jan-Feb;42(1):43-49.

Henderson A, Cahill D, Laing RW, Langley SE. (125)Iodine prostate brachytherapy: outcome from the first 100 consecutive patients and selection strategies incorporating urodynamics. BJU Int 2002 Oct;90(6):567-572.

Hendriksson L, Andersson KE, Ulmsten U. The urethral pressure profiles in continent and stress-incontinent women. Scand J Urol Nephrol 1979;13(1):5-10.

Herderschee R, Hay-Smith EJ, Herbison GP, Roovers JP, Heineman MJ. Feedback or biofeedback to augment pelvic floor muscle training for urinary incontinence in women. Cochrane Database Syst Rev 2011 Jul 6;(7)(7):CD009252.

Heslington K, Hilton P. Ambulatory monitoring and conventional cystometry in asymptomatic female volunteers. Br J Obstet Gynaecol 1996 May;103(5):434-441.

Hess MJ, Lim L, Yalla SV. Reliability of cystometrically obtained intravesical pressures in patients with neurogenic bladders. J Spinal Cord Med 2002 Winter;25(4):293-296.

Hilton P, Stanton SL. Algorithmic method for assessing urinary incontinence in elderly women. Br Med J (Clin Res Ed) 1981 Mar 21;282(6268):940-942.

Hindley RG, Mostafid AH, Brierly RD, Harrison NW, Thomas PJ, Fletcher MS. The 2-year symptomatic and urodynamic results of a prospective randomized trial of interstitial radiofrequency therapy vs transurethral resection of the prostate. BJU Int 2001 Aug;88(3):217-220.

Hirayama A, Fujimoto K, Matsumoto Y, Hirao Y. Nocturia in men with lower urinary tract symptoms is associated with both nocturnal polyuria and detrusor overactivity with positive response to ice water test. Urology 2005 Jun;65(6):1064-1069.

Hirayama F, Lee AH, Binns CW, Taniguchi H, Nishimura K, Kato K. Urinary incontinence in men with chronic obstructive pulmonary disease. Int J Urol 2008 Aug;15(8):751-753.

Hjalmas K. Pathophysiology and impact of nocturnal enuresis. Acta Paediatr 1997 Sep;86(9):919-922.

Hoebeke P, Bower W, Combs A, De Jong T, Yang S. Diagnostic evaluation of children with daytime incontinence. J Urol 2010 Feb;183(2):699-703.

Hoebeke P, Raes A, Vande Walle J, Van Laecke E. Urodynamics in children: what and how to do it? Acta Urol Belg 1998 May;66(2):23-30.

Hoebeke P, Van Laecke E, Raes A, Renson C, Theunis M, Vande Walle J. Bladder function and non-neurogenic dysfunction in children: classification and terminology. Acta Urol Belg 1995 May;63(2):93-98.

Hollowell JG, Hill PD, Duffy PG, Ransley PG. Evaluation and treatment of incontinence after bladder neck reconstruction in exstrophy and epispadias. Br J Urol 1993 Jun;71(6):743-749.

Holmdahl G, Sillen U, Bachelard M, Hansson E, Hermansson G, Hjalmas K. The changing urodynamic pattern in valve bladders during infancy. J Urol 1995 Feb;153(2):463-467.

Holmdahl G, Sillen U, Hanson E, Hermansson G, Hjalmas K. Bladder dysfunction in boys with posterior urethral valves before and after puberty. J Urol 1996 Feb;155(2):694-698.

Holmes NM, Coplen DE, Strand W, Husmann D, Baskin LS. Is bladder dysfunction and incontinence associated with ureteroceles congenital or acquired? J Urol 2002 Aug;168(2):718-719.

Holmgren C, Nilsson S, Lanner L, Hellberg D. Frequency of de novo urgency in 463 women who had undergone the tension-free vaginal tape (TVT) procedure for genuine stress urinary incontinence--a long-term follow-up. Eur J Obstet Gynecol Reprod Biol 2007 May;132(1):121-125.

Holtedahl K, Verelst M, Schiefloe A, Hunskaar S. Usefulness of urodynamic examination in female urinary incontinence--lessons from a population-based, randomized, controlled study of conservative treatment. Scand J Urol Nephrol 2000 Jun;34(3):169-174.

Homma, Y., Batista, J., Bauer, S., Urodynamics, in Incontinence: 1st International Consultation on Incontinence, P. Abrams, Cardozo, L., Khoury, S., Wein, A., Editor. 1999: Plymouth (UK).

Homma, Y., Batista, J., Bauer, S. Griffiths, D., Hilton, P., Kramer, G., Lose, G., Rosier, P., Urodynamics, in Incontinence: 2nd International Consultation on Incontinence, P. Abrams, Cardozo, L., Khoury, S., Wein, A., Editor. 2002: Plymouth (UK).

Homma Y. The clinical significance of the urodynamic investigation in incontinence. BJU Int 2002 Sep;90(5):489-497.

Homma Y, Imajo C, Takahashi S, Kawabe K, Aso Y. Urinary symptoms and urodynamics in a normal elderly population. Scand J Urol Nephrol Suppl 1994;157:27-30.

Homma Y, Kondo Y, Takahashi S, Kitamura T, Kawabe K. Reproducibility of cystometry in overactive detrusor. Eur Urol 2000 Dec;38(6):681-685.

Homsy YL, Nsouli I, Hamburger B, Laberge I, Schick E. Effects of oxybutynin on vesicoureteral reflux in children. J Urol 1985 Dec;134(6):1168-1171.

Honjo H, Kawauchi A, Nakao M, Ukimura O, Kitakoji H, Miki T. Impact of convenience void in a bladder diary with urinary perception grade to assess overactive bladder symptoms: a community-based study. Neurourol Urodyn 2010 Sep;29(7):1286-1289.

Hopps CV, Kropp KA. Preservation of renal function in children with myelomeningocele managed with basic newborn evaluation and close followup. J Urol 2003 Jan;169(1):305-308.

Hosker, G. Urodynamics In: The Yearbook of Obstetrics and Gynaecology, T. Hillard, Purdie, D., Editor. 2004, RCOG Press: London. p. 233-254.

Houle AM, Vernet O, Jednak R, Pippi Salle JL, Farmer JP. Bladder function before and after selective dorsal rhizotomy in children with cerebral palsy. J Urol 1998 Sep;160(3 Pt 2):1088-1091.

Hrisanfow E, Hagglund D. The prevalence of urinary incontinence among women and men with chronic obstructive pulmonary disease in Sweden. J Clin Nurs 2011 Jul;20(13-14):1895-1905.

Hsieh MH, Perry V, Gupta N, Pearson C, Nguyen HT. The effects of detethering on the urodynamics profile in children with a tethered cord. J Neurosurg 2006 Nov;105(5 Suppl):391-395.

Huang Foen Chung JW, Bohnen AM, Pel JJ, Bosch JL, Niesing R, van Mastrigt R. Applicability and reproducibility of condom catheter method for measuring isovolumetric bladder pressure. Urology 2004 Jan;63(1):56-60.

Huang YH, Chen SL, Tsai SJ, Bih LI, Lew HL. Urodynamic responses to anal stretch in patients with detrusor sphincter dyssynergia. Arch Phys Med Rehabil 2008 Sep;89(9):1748-1752.

Huckabay C, Twiss C, Berger A, Nitti VW. A urodynamics protocol to optimally assess men with post-prostatectomy incontinence. Neurourol Urodyn 2005;24(7):622-626.

Hunsballe JM. Increased delta component in computerized sleep electroencephalographic analysis suggests abnormally deep sleep in primary monosymptomatic nocturnal enuresis. Scand J Urol Nephrol 2000 Oct;34(5):294-302.

Hunskaar, S., Burgio, K., Diokno, AC., et al., Epidemiology and natural history of urinary incontinence, in Incontinence: 2nd International Consultation on Incontinence, C.L. Abrams P, Khoury S, Wein A, Editor. 2002, Plymbridge Distributors Ltd. p. 203.

Huwyler M, Schurch B, Knapp PA, Reitz A. Can the ice-water test predict the outcome of intradetrusor injections of botulinum toxin in patients with neurogenic bladder dysfunction? World J Urol 2007 Dec;25(6):613-617.

Hyman MJ, Groutz A, Blaivas JG. Detrusor instability in men: correlation of lower urinary tract symptoms with urodynamic findings. J Urol 2001 Aug;166(2):550-2; discussion 553.

Idzenga T, Pel JJ, Baldewsing RA, van Mastrigt R. Perineal noise recording as a non-invasive diagnostic method of urinary bladder outlet obstruction: a study in polyvinyl alcohol and silicone model urethras. Neurourol Urodyn 2005;24(4):381-388.

Idzenga T, Pel JJ, van Mastrigt R. A biophysical model of the male urethra: comparing viscoelastic properties of polyvinyl alcohol urethras to male pig urethras. Neurourol Urodyn 2006;25(5):451-460.

Iglesia CB, Shott S, Fenner DE, Brubaker L. Effect of preoperative voiding mechanism on success rate of autologous rectus fascia suburethral sling procedure. Obstet Gynecol 1998 Apr;91(4):577-581.

Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 2007 May;55(5):780-791.

Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int 2011 Oct;108(7):1132-1138.

Irwin DE, Milsom I, Chancellor MB, Kopp Z, Guan Z. Dynamic progression of overactive bladder and urinary incontinence symptoms: a systematic review. Eur Urol 2010 Oct;58(4):532-543.

Irwin DE, Milsom I, Kopp Z, Abrams P, Artibani W, Herschorn S. Prevalence, severity, and symptom bother of lower urinary tract symptoms among men in the EPIC study: impact of overactive bladder. Eur Urol 2009 Jul;56(1):14-20.

Irwin DE, Milsom I, Reilly K, Hunskaar S, Kopp Z, Herschorn S, et al. Overactive bladder is associated with erectile dysfunction and reduced sexual quality of life in men. J Sex Med 2008 Dec;5(12):2904-2910.

Itoh H, Kojima M, Okihara K, Ukimura O, Ushijima S, Kawauchi A, et al. Significant relationship of time-dependent uroflowmetric parameters to lower urinary tract symptoms as measured by the International Prostate Symptom Score. Int J Urol 2006 Aug;13(8):1058-1065.

Iwatsubo E, Iwakawa A, Koga H, Imamura A, Yamashita H, Komine S. Functional recovery of the bladder in patients with spinal cord injury--prognosticating programs of an aseptic intermittent catheterization. Hinyokika Kiyo 1985 May;31(5):775-783.

Jabokson, H., Holm-Bentzen, M., Hald, T The evaluation and management of children with sacral agenesis and dysgenesis Neurourology and Urodynamics, 1985. 4: p. 99.

James M, Jackson S, Shepherd A, Abrams P. Pure stress leakage symptomatology: is it safe to discount detrusor instability? Br J Obstet Gynaecol 1999 Dec;106(12):1255-1258.

Jarvis GJ. Surgery for genuine stress incontinence. Br J Obstet Gynaecol 1994 May;101(5):371-374.

Jarvis GJ, Hall S, Stamp S, Millar DR, Johnson A. An assessment of urodynamic examination in incontinent women. Br J Obstet Gynaecol 1980 Oct;87(10):893-896.

Jensen JK, Nielsen FR,Jr, Ostergard DR. The role of patient history in the diagnosis of urinary incontinence. Obstet Gynecol 1994 May;83(5 Pt 2):904-910.

Jesus LE, Farhat WA, Amarante AC, Dini RB, Leslie B, Bagli DJ, et al. Clinical evolution of vesicoureteral reflux following endoscopic puncture in children with duplex system ureteroceles. J Urol 2011 Oct;186(4):1455-1458.

Jha S, Toozs-Hobson P, Parsons M, Gull F. Does preoperative urodynamics change the management of prolapse? J Obstet Gynaecol. 2008 Apr;28(3):320-2.

Jones KW, Schoenberg HW. Comparison of the incidence of bladder hyperreflexia in patients with benign prostatic hypertrophy and age-matched female controls. J Urol 1985 Mar;133(3):425-426.

Juhasz Z, Somogyi R, Vajda P, Oberritter Z, Fathi K, Pinter AB. Does the type of bladder augmentation influence the resolution of pre-existing vesicoureteral reflux? Urodynamic studies. Neurourol Urodyn 2008;27(5):412-416.

Jung SY, Fraser MO, Ozawa H, Yokoyama O, Yoshiyama M, De Groat WC, et al. Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. J Urol 1999 Jul;162(1):204-212.

Kabay SC, Yucel M, Kabay S. Acute effect of posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with multiple sclerosis: urodynamic study. Urology 2008 Apr;71(4):641-645.

Kach O, Aeberhard A. Urodynamic evaluation of urinary incontinence using a microtransducer. Arch Gynecol 1984;234(4):269-278.

Kaefer M, Rosen A, Darbey M, Kelly M, Bauer SB. Pressure at residual volume: a useful adjunct to standard fill cystometry. J Urol 1997 Sep;158(3 Pt 2):1268-1271.

Kajbafzadeh AM, Baradaran N, Sadeghi Z, Tourchi A, Saeedi P, Madani A, et al. Vesicoureteral reflux and primary bladder neck dysfunction in children: urodynamic evaluation and randomized, double-blind, clinical trial on effect of alpha-blocker therapy. J Urol 2010 Nov;184(5):2128-2133.

Kajbafzadeh AM, Elmi A, Payabvash S, Salmasi AH, Saeedi P, Mohamadkhani A, et al. Transurethral autologous myoblast injection for treatment of urinary incontinence in children with classic bladder exstrophy. J Urol 2008 Sep;180(3):1098-1105.

Kajbafzadeh AM, Payabvash S, Karimian G. The effects of bladder neck incision on urodynamic abnormalities of children with posterior urethral valves. J Urol 2007 Nov;178(5):2142-7; discussion 2147-9.

Kakizaki H, Nonomura K, Asano Y, Shinno Y, Ameda K, Koyanagi T. Preexisting neurogenic voiding dysfunction in children with imperforate anus: problems in management. J Urol 1994 Apr;151(4):1041-1044.

Karaman MI, Kaya C, Caskurlu T, Guney S, Ergenekon E. Urodynamic findings in children with cerebral palsy. Int J Urol 2005 Aug;12(8):717-720.

Karlson S. Experimental studies on the functioning of the female urinary bladder and urethra. Acta Obstet Gynecol Scand 1953;32(3):285-307.

Kasirga E, Akil I, Yilmaz O, Polat M, Gozmen S, Egemen A. Evaluation of voiding dysfunctions in children with chronic functional constipation. Turk J Pediatr 2006 Oct-Dec;48(4):340-343.

Kaufman JM. Urodynamics in stress urinary incontinence. J Urol 1979 Dec;122(6):778-782.

Kawauchi A, Tanaka Y, Naito Y, Yamao Y, Ukimura O, Yoneda K, et al. Bladder capacity at the time of enuresis. Urology 2003 May;61(5):1016-1018.

Kaya C, Kucuk E, Ilktac A, Ozturk M, Karaman MI. Value of urinary flow patterns in the follow-up of children who underwent Snodgrass operation. Urol Int 2007;78(3):245-248.

Keating MA, Rink RC, Bauer SB, Krarup C, Dyro FM, Winston KR, et al. Neurourological implications of the changing apt proach in management of occult spinal lesions. J Urol 1988 Nov;140(5 Pt 2):1299-1301.

Kebapci N, Yenilmez A, Efe B, Entok E, Demirustu C. Bladder dysfunction in type 2 diabetic patients. Neurourol Urodyn 2007;26(6):814-819.

Kennelly MJ, Arena KC, Shaffer N, Bennett ME, Grill WM, Grill JH, et al. Electrical stimulation of the urethra evokes bladder contractions in a woman with spinal cord injury. J Spinal Cord Med 2010;33(3):261-265.

Kenton K, Richter H, Litman H, Lukacz E, Leng W, Lemack G, et al. Risk factors associated with urge incontinence after continence surgery. J Urol 2009 Dec;182(6):2805-2809.

Kessler TM, Ochsner K, Studer UE, Thalmann GN. Diabetes mellitus: does it impair urinary continence after radical cystoprostatectomy and ileal orthotopic bladder substitution? Eur Urol 2008 May;53(5):1040-1046.

Khan MS, Chaliha C, Leskova L, Khullar V. The relationship between urinary symptom questionnaires and urodynamic diagnoses: an analysis of two methods of questionnaire administration. BJOG 2004 May;111(5):468-474.

Khoury AE, Dave S, Peralta-Del Valle MH, Braga LH, Lorenzo AJ, Bagli D. Severe bladder trabeculation obviates the need for bladder outlet procedures during augmentation cystoplasty in incontinent patients with neurogenic bladder. BJU Int 2008 Jan;101(2):223-226.

Kim SM, Chang HK, Lee MJ, Shim KW, Oh JT, Kim DS, et al. Spinal dysraphism with anorectal malformation: lumbosacral magnetic resonance imaging evaluation of 120 patients. J Pediatr Surg 2010 Apr;45(4):769-776.

Kim YH, Horowitz M, Combs AJ, Nitti VW, Borer J, Glassberg KI. Management of posterior urethral valves on the basis of urodynamic findings. J Urol 1997 Sep;158(3 Pt 2):1011-1016.

Kim YH, Kattan MW, Boone TB. Bladder leak point pressure: the measure for sphincterotomy success in spinal cord injured patients with external detrusor-sphincter dyssynergia. J Urol 1998 Feb;159(2):493-6; discussion 496-7.

Klarskov, N., S.B. Rasmussen, and G. Lose, Pressure reflectometry: in vitro recordings with a new technique for simultaneous measurement of cross-sectional area and pressure in a collapsible tube. Physiol Meas, 2005. 26(3): p. 269-80.

Klarskov N, Lose G. Urethral pressure reflectometry and pressure profilometry in healthy volunteers and stress urinary incontinent women. Neurourol Urodyn 2008;27(8):807-812.

Klarskov N, Lose G. Urethral pressure reflectometry; a novel technique for simultaneous recording of pressure and cross-sectional area in the female urethra. Neurourol Urodyn 2007;26(2):254-261.

Klarskov N, Lose G. Urethral pressure reflectometry vs urethral pressure profilometry in women: a comparative study of reproducibility and accuracy. BJU Int 2007 Aug;100(2):351-356.

Klarskov N, Rasmussen SB, Lose G. Pressure reflectometry: in vitro recordings with a new technique for simultaneous measurement of cross-sectional area and pressure in a collapsible tube. Physiol Meas 2005 Jun;26(3):269-280.

Kleinhans B, Gerharz E, Melekos M, Weingartner K, Kalble T, Riedmiller H. Changes of urodynamic findings after radical retropubic prostatectomy. Eur Urol 1999;35(3):217-21; discussion 221-2.

Klingler HC, Heidler H, Madersbacher H, Primus G. Nocturia: an Austrian study on the multifactorial etiology of this symptom. Neurourol Urodyn 2009;28(5):427-431.

Koff SA. Estimating bladder capacity in children. Urology 1983 Mar;21(3):248.

Koff SA, Lapides J, Piazza DH. Association of urinary tract infection and reflux with uninhibited bladder contractions and voluntary sphincteric obstruction. J Urol 1979 Sep;122(3):373-376.

Koff SA, Wagner TT, Jayanthi VR. The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol 1998 Sep;160(3 Pt 2):1019-1022.

Kondo, A., Saito, M., Yamada, Y., et al., Prevalence of handwashing urinary incontinence in healthy subjects in relation to stress and urge incontinence. Neurourology and Urodynamics, 1992. 11: p. 519.

Kondo, A., Lin, TL., Nordling, J. et al., Conservative treatment in men, in Incontinence: 2nd International Consultation on Incontinence, P. Abrams, Cardozo, L., Khoury, S., Wein, A., Editor. 2002: Plymouth (UK).

Kondo A, Kato K, Kanai S, Sakakibara T. Bladder dysfunction secondary to tethered cord syndrome in adults: is it curable? J Urol 1986 Feb;135(2):313-316.

Korda A, Krieger M, Hunter P, Parkin G. The value of clinical symptoms in the diagnosis of urinary incontinence in the female. Aust N Z J Obstet Gynaecol 1987 May;27(2):149-151.

Kortmann BB, Sonke GS, Wijkstra H, Nordling J, Kallestrup E, Holm NR, et al. Intra- and inter-investigator variation in the analysis of pressure-flow studies in men with lower urinary tract symptoms. Neurourol Urodyn 2000;19(3):221-232.

Kosar A, Arikan N, Dincel C. Effectiveness of oxybutynin hydrochloride in the treatment of enuresis nocturna--a clinical and urodynamic study. Scand J Urol Nephrol 1999 Apr;33(2):115-118.

Kovindha A, Wattanapan P, Dejpratham P, Permsirivanich W, Kuptniratsaikul V. Prevalence of incontinence in patients after stroke during rehabilitation: a multi-centre study. J Rehabil Med 2009 May;41(6):489-491.

Krambeck AE, Handa SE, Lingeman JE. Experience with more than 1,000 holmium laser prostate enucleations for benign prostatic hyperplasia. J Urol 2010 Mar;183(3):1105-1109.

Kraus SR, Bavendam T, Brake T, Griebling TL. Vulnerable ele derly patients and overactive bladder syndrome. Drugs Aging 2010 Sep 1;27(9):697-713.

Kraus SR, Dmochowski R, Albo ME, Xu L, Klise SR, Roehrborn CG. Urodynamic standardization in a large-scale, multicenter clinical trial examining the effects of daily tadalafil in men with lower urinary tract symptoms with or without benign prostatic obstruction. Neurourol Urodyn 2010 Jun;29(5):741-747.

Kubota Y, Kojima Y, Shibata Y, Imura M, Kohri K, Sasaki S. Correlation between improvements in Overactive Bladder Symptom Score and health-related quality of life questionnaires in overactive bladder patients treated with an antimuscarinic drug. Neurourol Urodyn 2011 Sep;30(7):1309-1314.

Kuhn A, Bank S, Robinson D, Klimek M, Kuhn P, Raio L. How should bladder wall thickness be measured? A comparison of vaginal, perineal and abdominal ultrasound. Neurourol Urodyn 2010 Nov;29(8):1393-1396.

Kujansuu E, Kauppila A. Urodynamics in female stress incontinence of urine. Diagnostic and pathophysiological aspects. Arch Gynecol 1981;231(1):23-32.

Kulseng-Hanssen S, Husby H, Schiotz HA. Follow-up of TVT operations in 1,113 women with mixed urinary incontinence at 7 and 38 months. Int Urogynecol J Pelvic Floor Dysfunct 2008 Mar;19(3):391-396.

Kumar A, Agarwala S, Mitra DK. Occult neurovesical dysfunction with anorectal malformations. Indian J Pediatr 2006 Nov;73(11):999-1003.

Kumar R, Singhal N, Gupta M, Kapoor R, Mahapatra AK. Evaluation of clinico-urodynamic outcome of bladder dysfunction after surgery in children with spinal dysraphism - a prospective study. Acta Neurochir (Wien) 2008 Feb;150(2):129-137.

Kumar V, Toussi H, Marr C, Hough C, Javle P. The benefits of radical prostatectomy beyond cancer control in symptomatic men with prostate cancer. BJU Int 2004 Mar;93(4):507-509.

Kuo HC. Measurement of detrusor wall thickness in women with overactive bladder by transvaginal and transabdominal sonography. Int Urogynecol J Pelvic Floor Dysfunct 2009 Nov;20(11):1293-1299.

Kuo HC. Videourodynamic analysis of pathophysiology of men with both storage and voiding lower urinary tract symptoms. Urology 2007 Aug;70(2):272-276.

Kuo HC. Analysis of the pathophysiology of lower urinary tract symptoms in patients after prostatectomy. Urol Int 2002;68(2):99-104.

Kuo HC, Liu HT. Investigation of dysfunctional voiding in children with urgency frequency syndrome and urinary incontinence. Urol Int 2006;76(1):72-76.

Kurzrock EA, Polse S. Renal deterioration in myelodysplastic children: urodynamic evaluation and clinical correlates. J Urol 1998 May;159(5):1657-1661.

Kwong PW, Cumming RG, Chan L, Seibel MJ, Naganathan V, Creasey H, et al. Urinary incontinence and quality of life among older community-dwelling Australian men: the CHAMP study. Age Ageing 2010 May;39(3):349-354.

Lagro-Janssen AL, Debruyne FM, van Weel C. Value of the patient's case history in diagnosing urinary incontinence in general practice. Br J Urol 1991 Jun;67(6):569-572.

Lai HH, Hsu EI, Boone TB. Urodynamic testing in evaluation of postradical prostatectomy incontinence before artificial urinary sphincter implantation. Urology 2009 Jun;73(6):1264-1269.

Lais A, Kasabian NG, Dyro FM, Scott RM, Kelly MD, Bauer SB. The neurosurgical implications of continuous neurourological surveillance of children with myelodysplasia. J Urol 1993 Dec;150(6):1879-1883.

Landau EH, Churchill BM, Jayanthi VR, Gilmour RF, Steckler RE, McLorie GA, et al. The sensitivity of pressure specific bladder volume versus total bladder capacity as a measure of bladder storage dysfunction. J Urol 1994 Nov;152(5 Pt 1):1578-1581.

Lee JK, Dwyer PL, Rosamilia A, Lim YN, Polyakov A, Stav K. Persistence of urgency and urge urinary incontinence in women with mixed urinary symptoms after midurethral slings: a multivariate analysis. BJOG 2011 Jun;118(7):798-805.

Lee YS, Lee KS, Jung JH, Han DH, Oh SJ, Seo JT, et al. Prevalence of overactive bladder, urinary incontinence, and lower urinary tract symptoms: results of Korean EPIC study. World J Urol 2011 Apr;29(2):185-190.

Lekskulchai O, Dietz HP. Detrusor wall thickness as a test for detrusor overactivity in women. Ultrasound Obstet Gynecol 2008 Sep;32(4):535-539.

Lemack GE. Urodynamic assessment of patients with stress incontinence: how effective are urethral pressure profilometry and abdominal leak point pressures at case selection and predicting outcome? Curr Opin Urol 2004 Nov;14(6):307-311.

Lemack GE, Frohman EM, Zimmern PE, Hawker K, Ramnarayan P. Urodynamic distinctions between idiopathic detrusor overactivity and detrusor overactivity secondary to multiple sclerosis. Urology 2006 May;67(5):960-964.

Lemack GE, Krauss S, Litman H, FitzGerald MP, Chai T, Nager C, et al. Normal preoperative urodynamic testing does not predict voiding dysfunction after Burch colposuspension versus pubovaginal sling. J Urol 2008 Nov;180(5):2076-2080.

Lemack GE, Zimmern PE. Identifying patients who require urodynamic testing before surgery for stress incontinence based on questionnaire information and surgical history. Urology 2000 Apr;55(4):506-511.

Leonardo CR, Filgueiras MF, Vasconcelos MM, Vasconcelos R, Marino VP, Pires C, et al. Risk factors for renal scarring in children and adolescents with lower urinary tract dysfunction. Pediatr Nephrol 2007 Nov;22(11):1891-1896.

Lima SV, Araujo LA, Vilar Fde O, Lima RS, Lima RF. Nonsecretory intestinocystoplasty: a 15-year prospective study of 183 patients. J Urol 2008 Mar;179(3):1113-6; discussion 1116-7.

Lin LY, Yeh NH, Lin CY, Sheu BC, Lin HH. Comparisons of urodynamic characteristics between female patients with overactive bladder and overactive bladder plus stress urinary incontinence. Urology 2004 Nov;64(5):945-949.

Lockhart, J. Vorstman, B., Politano, VA. Anti-incontinence surgery in female with detrusor instability. Neurourology and Urodynamics, 1984. 3: p. 201.

Lopez Pereira P, Martinez Urrutia MJ, Espinosa L, Lobato R, Navarro M, Jaureguizar E. Bladder dysfunction as a prognostic factor in patients with posterior urethral valves. BJU Int 2002 Aug;90(3):308-311.

Lorenzo AJ, Wallis MC, Cook A, Buffett-Fairen A, Bozic D, Bagli DJ, et al. What is the variability in urodynamic parameters with position change in children? Analysis of a prospectively enrolled cohort. J Urol 2007 Dec;178(6):2567-2570.

Lose G, Jørgensen L, Mortensen SO, Mølsted-Pedersen L, Kristensen JK. Voiding difficulties after colposuspension. Obstet Gynecol. 1987 Jan;69(1):33-8.

Lose G, Griffiths D, Hosker G, Kulseng-Hanssen S, Perucchini D, Schafer W, et al. Standardisation of urethral pressure measurement: report from the Standardisation Sub-Committee of the International Continence Society. Neurourol Urodyn 2002;21(3):258-260.

Lose G, Jorgensen L, Mortensen SO, Molsted-Pedersen L, Kristensen JK. Voiding difficulties after colposuspension. Obstet Gynecol 1987 Jan;69(1):33-38.

Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, et al. Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement. Health Technol Assess 2008 Nov;12(35):iii, ix-x, 1-146, 169-515.

Lowenstein L, Dooley Y, Kenton K, Rickey L, FitzGerald MP, Mueller E, et al. The volume at which women leak first on urodynamic testing is not associated with quality of life, measures of urethral integrity or surgical failure. J Urol 2007 Jul;178(1):193-196.

Lowenstein L, Kenton K, FitzGerald MP, Brubaker L. Clinically useful measures in women with mixed urinary incontinence. Am J Obstet Gynecol 2008 Jun;198(6):664.e1-3; discussion 664.e3-4.

Luke PP, Herz DB, Bellinger MF, Chakrabarti P, Vivas CA, Scantlebury VP, et al. Long-term results of pediatric renal transplantation into a dysfunctional lower urinary tract. Transplantation 2003 Dec 15;76(11):1578-1582.

MacKeith, R., Meadow, SR., Turner, RK., How children become dry, in Bladder control and enuresis, I. Kolvin, MacKeith RL., Meadow, SR, Editor. 1973, Lippincott: Philadelphia. p. 3.

Maher CO, Bauer SB, Goumnerova L, Proctor MR, Madsen JR, Scott RM. Urological outcome following multiple repeat spinal cord untethering operations. Clinical article. J Neurosurg Pediatr 2009 Sep;4(3):275-279.

Majumdar A, Latthe P, Toozs-Hobson P. Urodynamics prior to

treatment as an intervention: a pilot study. Neurourol Urodyn 2010 Apr;29(4):522-526.

Malmsten UG, Molander U, Peeker R, Irwin DE, Milsom I. Urinary incontinence, overactive bladder, and other lower urinary tract symptoms: a longitudinal population-based survey in men aged 45-103 years. Eur Urol 2010 Jul;58(1):149-156.

Malone-Lee J, Henshaw DJ, Cummings K. Urodynamic verification of an overactive bladder is not a prerequisite for antimuscarinic treatment response. BJU Int 2003 Sep;92(4):415-417.

Malone-Lee JG, Al-Buheissi S. Does urodynamic verification of overactive bladder determine treatment success? Results from a randomized placebo-controlled study. BJU Int 2009 Apr;103(7):931-937.

Marinkovic SP, Badlani G. Voiding and sexual dysfunction after cerebrovascular accidents. J Urol 2001 Feb;165(2):359-370.

Marinkovic SP, Stanton SL. Incontinence and voiding difficulties associated with prolapse. J Urol 2004 Mar;171(3):1021-1028.

Markland AD, Goode PS, Redden DT, Borrud LG, Burgio KL. Prevalence of urinary incontinence in men: results from the national health and nutrition examination survey. J Urol 2010 Sep;184(3):1022-1027.

Martens FM, van Kuppevelt HJ, Beekman JA, Heijnen IC, D'Hauwers KW, Heesakkers JP. No primary role of ambulatory urodynamics for the management of spinal cord injury patients compared to conventional urodynamics. Neurourol Urodyn 2010 Nov;29(8):1380-1386.

Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, et al. Systematic review and evaluation of methods of assessing urinary incontinence. Health Technol Assess 2006 Feb;10(6):1-132, iii-iv.

Martin-Crespo Izquierdo R, Luque Mialdea R, Cerda Berrocal J, Arrojo Vila F. Indications for urodynamic studies in childhood: our experience with 214 surgical patients. Cir Pediatr 1995 Jan;8(1):31-36.

Mastrigt R, Huang Foen Chung JW. Comparison of repeatability of non-invasive and invasive urodynamics. Neurourol Urodyn 2004;23(4):317-321.

Matharu G, Donaldson MM, McGrother CW, Matthews RJ. Relationship between urinary symptoms reported in a postal questionnaire and urodynamic diagnosis. Neurourol Urodyn 2005;24(2):100-105.

Matsui F, Shimada K, Matsumoto F, Obara T, Kubota A. Bladder function after total urogenital mobilization for persistent cloaca. J Urol 2009 Nov;182(5):2455-2459.

Mayo ME. Lower urinary tract dysfunction in cerebral palsy. J Urol 1992 Feb;147(2):419-420.

Mayo ME, Burns MW. Urodynamic studies in children who wet. Br J Urol 1990 Jun;65(6):641-645.

McLennan, M.T., C.F. Melick, and A.E. Bent, Clinical and urodynamic predictors of delayed voiding after fascia lata suburethral sling. Obstet Gynecol, 1998. 92(4 Pt 1): p. 608-12.

McNanley AR, Duecy EE, Buchsbaum GM. Symptom-based, clinical, and urodynamic diagnoses of urinary incontinence: how well do they correlate in postmenopausal women? Female Pelvic Med Reconstr Surg. 2010 Mar;16(2):97-101.

McCallum TJ, Moore KN, Griffiths D. Urinary incontinence after radical prostatectomy: implications and urodynamics. Urol Nurs 2001 Apr;21(2):113-9, 124.

McGuire EJ. Urodynamics of the neurogenic bladder. Urol Clin North Am 2010 Nov;37(4):507-516.

McGuire EJ, Cespedes RD, O'Connell HE. Leak-point pressures. Urol Clin North Am 1996 May;23(2):253-262.

McGuire EJ, Fitzpatrick CC, Wan J, Bloom D, Sanvordenker J, Ritchey M, et al. Clinical assessment of urethral sphincter function. J Urol 1993 Nov;150(5 Pt 1):1452-1454.

McGuire EJ, Lytton B, Kohorn EI, Pepe V. The value of urodynamic testing in stress urinary incontinence. J Urol 1980 Aug;124(2):256-258.

McGuire EJ, Lytton B, Pepe V, Kohorn EI. Stress Urinary Incontinence. Obstet Gynecol 1976 Mar;47(3):255-264.

McGuire EJ, Woodside JR, Borden TA, Weiss RM. Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 1981 Aug;126(2):205-209.

McKenna PH, Herndon CD, Connery S, Ferrer FA. Pelvic floor muscle retraining for pediatric voiding dysfunction using interactive computer games. J Urol 1999 Sep;162(3 Pt 2):1056-62; discussion 1062-3.

McKinney TB, Hessami S (2000) Comparison of fiberoptic, microtip, water and air-charged pressure transducer catheters for the evaluation of urethral pressure profiles (UPP). Int Urogynecol J 11[Suppl 1]: S53

McLellan D, Bauer SB In: Section on Urology. American Academy of Pediatrics. 2003. New Orleans.

McMillan ZM, Austin JC, Knudson MJ, Hawtrey CE, Cooper CS. Bladder volume at onset of reflux on initial cystogram predicts spontaneous resolution. J Urol 2006 Oct;176(4 Pt 2):1838-1841.

Mebust, W., Holtgrewe, HL., Current status of transurethral prostatectomy: a review of the AUA National Cooperative Study. World Journal of Urology, 1989. 6: p. 194.

Medel R, Ruarte AC, Castera R, Podesta ML. Primary enuresis: a urodynamic evaluation. Br J Urol 1998 May;81 Suppl 3:50-52.

Mehnert U, Knapp PA, Mueller N, Reitz A, Schurch B. Heart rate variability: an objective measure of autonomic activity and bladder sensations during urodynamics. Neurourol Urodyn 2009;28(4):313-319.

Miller JJ, Botros SM, Akl MN, Aschkenazi SO, Beaumont JL, Goldberg RP, et al. Is transobturator tape as effective as tension-free vaginal tape in patients with borderline maximum urethral closure pressure? Am J Obstet Gynecol 2006 Dec;195(6):1799-1804.

Miller KL, DuBeau CE, Bergmann M, Griffiths DJ, Resnick NM. Quest for a detrusor overactivity index. J Urol 2002 Feb;167(2 Pt 1):578-84; discussion 584-5.

Min LC, Reuben DB, Adams J, Shekelle PG, Ganz DA, Roth CP, et al. Does better quality of care for falls and urinary incontinence result in better participant-reported outcomes? J Am Geriatr Soc 2011 Aug;59(8):1435-1443.

Mitchell, M., Persistent ureteral dilation following valve resection, in Dialogues in Pediatric Urology. 1982.

Moiyadi AV, Devi BI, Nair KP. Urinary disturbances following traumatic brain injury: clinical and urodynamic evaluation. Neuu roRehabilitation 2007;22(2):93-98.

Monoski MA, Gonzalez RR, Sandhu JS, Reddy B, Te AE. Urodynamic predictors of outcomes with photoselective laser vaporization prostatectomy in patients with benign prostatic hyperplasia and preoperative retention. Urology 2006 Aug;68(2):312-317.

Moore KC, Emery SJ, Lucas MG. Quality and quantity: an audit of urodynamics practice in relation to newly published National Standards. Neurourol Urodyn 2011 Jan;30(1):38-42.

Moran Penco JM, Gomez Fraile A, Rodriguez Alarcon J, Garcia Merino F, Vela D, Sanjuan Rodriguez S, et al. Evolution of the treatment of vesicoureteral reflux in Spain. J Urol 2004 Feb;171(2 Pt 1):834-837.

Morgan, K., Bergmann, M., Kiely, D., et al., The voiding pattern of normal elders. Neurourology and Urodynamics, 2000. 19: p. 536.

Mortensen S, Lose G, Thyssen H. Repeatability of cystometry and pressure-flow parameters in female patients. Int Urogynecol J Pelvic Floor Dysfunct 2002;13(2):72-75.

Mosiello G, Capitanucci ML, Gatti C, Adorisio O, Lucchetti MC, Silveri M, et al. How to investigate neurovesical dysfunction in children with anorectal malformations. J Urol 2003 Oct;170(4 Pt 2):1610-1613.

Mosiello G, Gatti C, De Gennaro M, Capitanucci ML, Silveri M, Inserra A, et al. Neurovesical dysfunction in children after treating pelvic neoplasms. BJU Int 2003 Aug;92(3):289-292.

Moslavac S, Dzidic I, Kejla Z. Neurogenic detrusor overactivity: comparison between complete and incomplete spinal cord injury patients. Neurourol Urodyn 2008;27(6):504-506.

Mostafa A, Madhuvrata P, Abdel-Fattah M. Preoperative urodynamic predictors of short-term voiding dysfunction following a transobturator tension-free vaginal tape procedure. Int J Gynaecol Obstet. 2011 Oct;115(1):49-52.

Mukerji G, Waters J, Chessell IP, Bountra C, Agarwal SK, Anand P. Pain during ice water test distinguishes clinical bladder hypersensitivity from overactivity disorders. BMC Urol 2006 Dec 27;6:31.

Murray S, Lemack GE. Defining the role of urodynamics in predicting voiding dysfunction after anti-incontinence surgery: a work in progress. Curr Opin Urol 2010 Jul;20(4):285-290.

Musquera Felip M, Errando Smet C, Prados Saavedra M, Arano Bertran P, Villavicencio Mavrich H. False postvoid residual volume diagnosed by videourodynamics. Actas Urol Esp 2004 Nov-Dec;28(10):792-795.

Mutone N, Mastropietro M, Brizendine E, Hale D. Effect of tension-free vaginal tape procedure on urodynamic continence indices. Obstet Gynecol 2001 Oct;98(4):638-645.

Nager CW, Albo ME, Fitzgerald MP, McDermott S, Wruck L, Kraus S, et al. Reference urodynamic values for stress incontinent women. Neurourol Urodyn 2007;26(3):333-340.

Nager CW, Brubaker L, Daneshgari F, Litman HJ, Dandreo KJ, Sirls L, et al. Design of the Value of Urodynamic Evaluation (ValUE) trial: A non-inferiority randomized trial of preoperative urodynamic investigations. Contemp Clin Trials 2009 Nov;30(6):531-539.

Nager CW, FitzGerald M, Kraus SR, Chai TC, Zyczynski H, Sirls L, et al. Urodynamic measures do not predict stress continence outcomes after surgery for stress urinary incontinence in selected women. J Urol 2008 Apr;179(4):1470-1474.

Nager CW, Schulz JA, Stanton SL, Monga A. Correlation of urethral closure pressure, leak-point pressure and incontinence severity measures. Int Urogynecol J Pelvic Floor Dysfunct 2001;12(6):395-400.

Nakamura N, Shikama N, Takahashi O, Ito M, Hashimoto M, Uematsu M, et al. Variability in bladder volumes of full bladders in definitive radiotherapy for cases of localized prostate cancer. Strahlenther Onkol 2010 Nov;186(11):637-642.

Namiki S, Ishidoya S, Tochigi T, Ito A, Arai Y. Quality of life after radical prostatectomy in elderly men. Int J Urol 2009 Oct;16(10):813-819.

Naoemova I, Van Meel T, De Wachter S, Wyndaele JJ. Does sensory bladder function during cystometry differ from that in daily life? A study in incontinent women. Neurourol Urodyn 2009;28(4):309-312.

Narayanan S, Cerulli A, Kahler KH, Ouslander JG. Is drug therapy for urinary incontinence used optimally in long-term care facilities? J Am Med Dir Assoc 2007 Feb;8(2):98-104.

National Institute for Health and Clinical Excellence. Urinary Incontinence - The management of urinary incontinence in women. 2006: London

Neveus T. The evaluation and treatment of therapy-resistant enuresis: a review. Ups J Med Sci 2006;111(1):61-71.

Neveus T, Eggert P, Evans J, Macedo A, Rittig S, Tekgul S, et al. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol 2010 Feb;183(2):441-447.

Neveus T, von Gontard A, Hoebeke P, Hjalmas K, Bauer S, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol 2006 Jul;176(1):314-324.

Nguyen HT, Sencan A, Silva A, Carvas FA, Bauer SB. Urodynamic studies are recommended in children with central nervous system tumors regardless of location. J Urol 2010 Dec;184(6):2516-2520.

Nguyen JK, Gunn GC, Bhatia NN. The effect of patient position on leak-point pressure measurements in women with genuine stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2002;13(1):9-14.

Nielsen JB. Lower urinary tract function in vesicoureteral reflux. Scand J Urol Nephrol Suppl 1989;125:15-21.

Nilsson CG, Kuuva N, Falconer C, Rezapour M, Ulmsten U. Long-term results of the tension-free vaginal tape (TVT) procedure for surgical treatment of female stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2001;12 Suppl 2:S5-8.

Norgaard JP. Technical aspects of assessing bladder function in children. Scand J Urol Nephrol Suppl 1995;173:43-6; discussion 46-7.

Nosseir M, Hinkel A, Pannek J. Clinical usefulness of urodynamic assessment for maintenance of bladder function in patients with spinal cord injury. Neurourol Urodyn 2007;26(2):228-233.

Obara K, Komeyama T, Mizusawa T, Tsutsui T, Wakatsuki H, Arai K, et al. The consequence after introduction of clean intermittent catheterization (CIC) in children with neurogenic bladder dysfunction secondary to spina bifida--the comparison of patients with and without upper urinary tract dilation at the time CIC was introduced. Nihon Hinyokika Gakkai Zasshi 2003 Nov;94(7):664-670.

Ockrim J, Laniado ME, Khoubehi B, Renzetti R, Finazzi Agro E, Carter SS, et al. Variability of detrusor overactivity on repeated filling cystometry in men with urge symptoms: comparison with spinal cord injury patients. BJU Int 2005 Mar;95(4):587-590.

Oelke M, Baard J, Wijkstra H, de la Rosette JJ, Jonas U, Hofner K. Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. Eur Urol 2008 Aug;54(2):419-426.

Oelke M, Mamoulakis C, Ubbink DT, de la Rosette JJ, Wijkstra H. Manual versus automatic bladder wall thickness measurements: a method comparison study. World J Urol 2009 Dec;27(6):747-753.

Okorocha I, Cumming G, Gould I. Female urodynamics and lower urinary tract infection. BJU Int 2002 Jun;89(9):863-867.

O'Regan S, Yazbeck S, Schick E. Constipation, bladder instability, urinary tract infection syndrome. Clin Nephrol 1985 Mar;23(3):152-154.

Orkiszewski M, Leszniewski J. Morphology and urodynamics after longitudinal urethral plate incision in proximal hypospadias repairs: long-term results. Eur J Pediatr Surg 2004 Feb;14(1):35-38.

Otgun I, Karnak I, Senocak ME, Tanyel FC, Ciftci AO, Buyukpamukcu N. Late urodynamic findings after treating traumatic rupture of the posterior urethra in boys. BJU Int 2006 Feb;97(2):367-370.

Ouslander J, Leach G, Abelson S, Staskin D, Blaustein J, Raz S. Simple versus multichannel cystometry in the evaluation of bladder function in an incontinent geriatric population. J Urol 1988 Dec;140(6):1482-1486.

Ouslander J, Staskin D, Raz S, Su HL, Hepps K. Clinical versus urodynamic diagnosis in an incontinent geriatric female population. J Urol 1987 Jan;137(1):68-71.

Ozawa H, Igarashi T, Uematsu K, Watanabe T, Kumon H. The future of urodynamics: non-invasive ultrasound videourodynamics. Int J Urol 2010 Mar;17(3):241-249.

Ozkan B, Demirkesen O, Durak H, Uygun N, Ismailoglu V, Cetinel B. Which factors predict upper urinary tract deterioration in overactive neurogenic bladder dysfunction? Urology 2005 Jul;66(1):99-104.

Ozkan KU, Bauer SB, Khoshbin S, Borer JG. Neurogenic bladder dysfunction after sacrococcygeal teratoma resection. J Urol 2006 Jan;175(1):292-6; discussion 296.

Paick JS, Cho MC, Oh SJ, Kim SW, Ku JH. Factors influencing the outcome of mid urethral sling procedures for female urinary incontinence. J Urol 2007 Sep;178(3 Pt 1):985-9; discussion 989.

Paick JS, Ku JH, Shin JW, Son H, Oh SJ, Kim SW. Tension-free vaginal tape procedure for urinary incontinence with low Valsalva leak point pressure. J Urol 2004 Oct;172(4 Pt 1):1370-1373.

Palmer LS, Richards I, Kaplan WE. Age related bladder capacity and bladder capacity growth in children with myelomeningocele. J Urol 1997 Sep;158(3 Pt 2):1261-1264.

Panayi DC, Duckett J, Digesu GA, Camarata M, Basu M, Khullar V. Pre-operative opening detrusor pressure is predictive of detrusor overactivity following TVT in patients with pre-operative mixed urinary incontinence. Neurourol Urodyn 2009;28(1):82-85.

Panayi DC, Khullar V, Digesu GA, Hendricken C, Fernando R, Tekkis P. Is ultrasound estimation of bladder weight a useful tool in the assessment of patients with lower urinary tract symptoms? Int Urogynecol J Pelvic Floor Dysfunct 2009 Dec;20(12):1445-1449.

Panayi DC, Khullar V, Fernando R, Tekkis P. Transvaginal ultrasound measurement of bladder wall thickness: a more reliable approach than transperineal and transabdominal approaches. BJU Int 2010 Nov;106(10):1519-1522.

Pannek J, Diederichs W, Botel U. Urodynamically controlled management of spinal cord injury in children. Neurourol Urodyn 1997;16(4):285-292.

Pannek J, Hilfiker R, Goecking K, Bersch U. Preoperative urodynamic assessment in patients with spinal cord lesions undergoing sphincterotomy: is success predictable? Urol Int 2009;83(4):386-391.

Pannek J, Pieper P. Clinical usefulness of ambulatory urodynamics in the diagnosis and treatment of lower urinary tract dysfunction. Scand J Urol Nephrol 2008;42(5):428-432.

Pardo Y, Guedea F, Aguilo F, Fernandez P, Macias V, Marino A, et al. Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. J Clin Oncol 2010 Nov 1;28(31):4687-4696.

Parekh DJ, Pope JC,4th, Adams MC, Brock JW,3rd. The use of radiography, urodynamic studies and cystoscopy in the evaluation of voiding dysfunction. J Urol 2001 Jan;165(1):215-218.

Park KK, Lee SH, Kim YJ, Choi YD, Mah SY. Association between urinary hesitancy symptoms and uroflowmetry measured urinary hesitancy time in men with lower urinary tract symptoms. Neurourol Urodyn 2011 Apr;30(4):578-582.

Parsons M, Amundsen CL, Cardozo L, Vella M, Webster GD, Coats AC, et al. Bladder diary patterns in detrusor overactivity and urodynamic stress incontinence. Neurourol Urodyn 2007;26(6):800-806.

Pauwels E, De Wachter S, Wyndaele JJ. Normality of bladder filling studied in symptom-free middle-aged women. J Urol 2004 Apr;171(4):1567-1570.

Payne CK, Kelleher C. Redefining response in overactive bladder syndrome. BJU Int 2007 Jan;99(1):101-106.

Pel JJ, Bosch JL, Blom JH, Lycklama a Nijeholt AA, van Mastrigt R. Development of a non-invasive strategy to classify bladder outlet obstruction in male patients with LUTS. Neurourol Urodyn 2002;21(2):117-125.

Pel JJ, van Mastrigt R. A flow rate cut-off value as a criterion for the accurate non-invasive measurement of bladder pressure using a condom-type catheter. Urol Res 2003 Jul;31(3):177-182.

Pena A. Posterior sagittal approach for the correction of anorectal malformations. Adv Surg 1986;19:69-100.

Penson DF, McLerran D, Feng Z, Li L, Albertsen PC, Gilliland FD, et al. 5-Year Urinary and Sexual Outcomes After Radical Prostatectomy: Results from the Prostate Cancer Outcomes Study. J Urol 2005 May;173(5):1701-1705.

Peters CA, Bolkier M, Bauer SB, Hendren WH, Colodny AH, Mandell J, et al. The urodynamic consequences of posterior urethral valves. J Urol 1990 Jul;144(1):122-126.

Pfisterer MH, Griffiths DJ, Rosenberg L, Schaefer W, Resnick NM. Parameters of bladder function in pre-, peri-, and postmenopausal continent women without detrusor overactivity. Neurourol Urodyn 2007;26(3):356-361.

Phua SM, Low JJ, Chew SY. The role of urodynamics in evaluating incontinent females. Singapore Med J 1992 Apr;33(2):139-142.

Podesta ML, Castera R, Ruarte AC. Videourodynamic findings in young infants with severe primary reflux. J Urol 2004 Feb;171(2 Pt 1):829-33; discussion 833.

Pohl HG, Bauer SB, Borer JG, Diamond DA, Kelly MD, Grant R, et al. The outcome of voiding dysfunction managed with clean intermittent catheterization in neurologically and anatomically normal children. BJU Int 2002 Jun;89(9):923-927.

Pollak JT, Neimark M, Connor JT, Davila GW. Air-charged and microtransducer urodynamic catheters in the evaluation of urethral function. Int Urogynecol J Pelvic Floor Dysfunct 2004 Mar-Apr;15(2):124-8; discussion 128.

Pontari MA, Keating M, Kelly M, Dyro F, Bauer SB. Retained sacral function in children with high level myelodysplasia. J Urol 1995 Aug;154(2 Pt 2):775-777.

Porena M, Mearini E, Mearini L, Vianello A, Giannantoni A. Voiding dysfunction after radical retropubic prostatectomy: more than external urethral sphincter deficiency. Eur Urol 2007 Jul;52(1):38-45.

Porter T, Weerasinghe N, Malone PS. Modification of therapy based on videourodynamics in neurologically normal children: Southampton 1988-1993. Br J Urol 1995 Dec;76(6):779-81; discussion 781-2.

Poulakis V, Witzsch U, de Vries R, Dillenburg W, Becht E. Laparoscopic radical prostatectomy in men older than 70 years of age with localized prostate cancer: comparison of morbidity, reconvalescence, and short-term clinical outcomes between younger and older men. Eur Urol 2007 May;51(5):1341-8; discussion 1349.

Pow-Sang JM, Lockhart JL, Suarez A, Lansman H, Politano VA. Female urinary incontinence: preoperative selection, surgical complications and results. J Urol 1986 Oct;136(4):831-833.

Puri A, Bhatnagar V, Grover VP, Agarwala S, Mitra DK. Urodynamics-based evidence for the beneficial effect of imipramine on valve bladders in children. Eur J Pediatr Surg 2005 Oct;15(5):347-353.

Purohit RS, Blaivas JG, Saleem KL, Sandhu J, Weiss JP, Reddy B, et al. The pathophysiology of large capacity bladder. J Urol 2008 Mar;179(3):1006-1011.

Radley SC, Rosario DJ, Chapple CR, Farkas AG. Conventional and ambulatory urodynamic findings in women with symptoms suggestive of bladder overactivity. J Urol 2001 Dec;166(6):2253-2258.

Ragab MM, Mohammed ES. Idiopathic Parkinson's disease patients at the urologic clinic. Neurourol Urodyn 2011 Sep;30(7):1258-1261.

Rahmanou P, Chaliha C, Kulinskaya E, Khullar V. Reliability testing of urodynamics, pressure flow studies and cough leak point pressure in women with urodynamic stress incontinence with and without detrusor overactivity. Int Urogynecol J Pelvic Floor Dysfunct 2008 Jul;19(7):933-938.

Ramakrishnan K. Evaluation and treatment of enuresis. Am Fam Physician 2008 Aug 15;78(4):489-496.

Ramamurthy HR, Kanitkar M. Non invasive urodynamic assessment in children--are they reliable? Validation of non-invasive urodynamics in children with functional voiding disorders. Indian J Pediatr 2010 Dec;77(12):1400-1404.

Ransmayr GN, Holliger S, Schletterer K, Heidler H, Deibl M, Poewe W, et al. Lower urinary tract symptoms in dementia with Lewy bodies, Parkinson disease, and Alzheimer disease. Neurology 2008 Jan 22;70(4):299-303.

Rapp DE, Neil NJ, Govier FE, Kobashi KC. Bladder sensation measures and overactive bladder. J Urol 2009 Sep;182(3):1050-1054.

Rehder P, Gozzi C. Transobturator sling suspension for male urinary incontinence including post-radical prostatectomy. Eur Urol 2007 Sep;52(3):860-866.

Rehder P, Mitterberger MJ, Pichler R, Kerschbaumer A, Glodny B. The 1 year outcome of the transobturator retroluminal repositioning sling in the treatment of male stress urinary incontinence. BJU Int 2010 Dec;106(11):1668-1672.

Reid CJ, Borzyskowski M. Lower urinary tract dysfunction in cerebral palsy. Arch Dis Child 1993 Jun;68(6):739-742.

Rendeli C, Ausili E, Tabacco F, Focarelli B, Massimi L, Caldarelli M, et al. Urodynamic evaluation in children with lipomeningocele: timing for neurosurgery, spinal cord tethering and followup. J Urol 2007 Jun;177(6):2319-2324.

Resnick N.M, Brandeis GH, Baumann MM, Morris JN. Evaluating a national assessment strategy for urinary incontinence in nursing home residents: reliability of the minimum data set and validity of the resident assessment protocol. Neurourol Urodyn, 1996. 15(6): p. 583-98.

Resnick NM, Brandeis GH, Baumann MM, DuBeau CE, Yalla SV. Misdiagnosis of urinary incontinence in nursing home women: prevalence and a proposed solution. Neurourol Urodyn 1996;15(6):599-613; discussion 613-8.

Resnick NM, Yalla SV. Detrusor hyperactivity with impaired contractile function. An unrecognized but common cause of incontinence in elderly patients. JAMA 1987 Jun 12;257(22):3076-3081.

Resnick NM, Yalla SV, Laurino E. The pathophysiology of urinary incontinence among institutionalized elderly persons. N Engl J Med 1989 Jan 5;320(1):1-7.

Reynard JM, Lim C, Peters TJ, Abrams P. The significance of terminal dribbling in men with lower urinary tract symptoms. Br J Urol 1996 May;77(5):705-710.

Richardson DA. Value of the cough pressure profile in the evaluation of patients with stress incontinence. Am J Obstet Gynecol 1986 Oct;155(4):808-811.

Richardson I, Palmer LS. Clinical and urodynamic spectrum of bladder function in cerebral palsy. J Urol 2009 Oct;182(4 Suppl):1945-1948.

Rivas DA, Chancellor MB. Neurogenic vesical dysfunction. Urol Clin North Am 1995 Aug;22(3):579-591.

Robertson AS. Behaviour of the human bladder during natural filling: the Newcastle experience of ambulatory monitoring and conventional artificial filling cystometry. Scand J Urol Nephrol Suppl 1999;201:19-24.

Roderick T, Paul M, Christopher M, Douglas T. Urethral retroresistance pressure: association with established measures of incontinence severity and change after midurethral tape insertion. Neurourol Urodyn 2009;28(1):86-89.

Rodrigues P, Afonso Y, Hering FO, Campagnari JC, Azoubel A. Valsalva leak point pressure to determine internal sphincter deficiency in stress urinary incontinence. Urol Int 2006;76(2):154-158.

Rodriguez E, Delucchi A, Holzer J, Valdes B, Valenzuela C. Urodynamics in children with recurrent urinary infection, enuresis and bladder incontinence. Rev Chil Pediatr 1989 Sep-Oct;60(5):283-286.

Rodriguez LV, de Almeida F, Dorey F, Raz S. Does Valsalva leak point pressure predict outcome after the distal urethral polypropylene sling? Role of urodynamics in the sling era. J Urol 2004 Jul;172(1):210-214.

Romanzi LJ, Chaikin DC, Blaivas JG. The effect of genital prolapse on voiding. J Urol 1999 Feb;161(2):581-586.

Romanzi LJ, Groutz A, Heritz DM, Blaivas JG. Involuntary detrusor contractions: correlation of urodynamic data to clinical categories. Neurourol Urodyn 2001;20(3):249-257.

Ronchi P, Gravina GL, Galatioto GP, Costa AM, Martella O, Vicentini C. Urodynamic parameters after solifenacin treatment in men with overactive bladder symptoms and detrusor underactivity. Neurourol Urodyn 2009;28(1):52-57.

Roongruangsilp U, Lertsithichai P, Kochakarn W, Ratana-Olarn K. Correlation between symptoms and urodynamic findings in Thai female patients with urinary incontinence. J Med Assoc Thai 2005 Mar;88(3):364-370.

Roovers JP, Oelke M. Clinical relevance of urodynamic investigation tests prior to surgical correction of genital prolapse: a literature review. Int Urogynecol J Pelvic Floor Dysfunct 2007 Apr;18(4):455-460.

Roovers JP, van Laar JO, Loffeld C, Bremer GL, Mol BW, Bongers MY. Does urodynamic investigation improve outcome in patients undergoing prolapse surgery? Neurourol Urodyn 2007;26(2):170-175.

Rosier PF, de Wildt MJ, Wijkstra H, Debruyne FF, de la Rosette JJ. Clinical diagnosis of bladder outlet obstruction in patients with benign prostatic enlargement and lower urinary tract symptoms: development and urodynamic validation of a clinical prostate score for the objective diagnosis of bladder outlet obstruction. J Urol 1996 May;155(5):1649-1654.

Rosier PF, Gajewski JB, Sand PK, Szabo L, Capewell A, Hosker GL, et al. Executive summary: The International Consultation on Incontinence 2008--Committee on: «Dynamic Testing»; for urinary incontinence and for fecal incontinence. Part 1: Innovations in urodynamic techniques and urodynamic testing for signs and symptoms of urinary incontinence in female patients. Neurourol Urodyn 2010;29(1):140-145.

Rosier PF, Hosker GL, Szabo L, Capewell A, Gajewski JB, Sand PK, et al. Executive Summary: The International Consultation on Incontinence 2008--Committee on: «Dynamic Testing»; for urinary or fecal incontinence. Part 3: Anorectal physiology studies. Neurourol Urodyn 2010;29(1):153-158.

Rosier PF, Szabo L, Capewell A, Gajewski JB, Sand PK, Hosker GL, et al. Executive summary: The International Consultation on Incontinence 2008--Committee on: «Dynamic Testing»; for urinary or fecal incontinence. Part 2: Urodynamic testing in male patients with symptoms of urinary incontinence, in patients with relevant neurological abnormalities, and in children and in frail elderly with symptoms of urinary incontinence. Neurourol Urodyn 2010;29(1):146-152.

Rotar M, Blagus R, Jeromel M, Skrbec M, Trsinar B, Vodusek DB. Stroke patients who regain urinary continence in the first week after acute first-ever stroke have better prognosis than patients with persistent lower urinary tract dysfunction. Neurourol Urodyn 2011 Sep;30(7):1315-1318.

Rud T. The effects of estrogens and gestagens on the urethral pressure profile in urinary continent and stress incontinent women. Acta Obstet Gynecol Scand 1980;59(3):265-270.

Saito M, Kondo A, Kato K. Diagnosis and treatment of neurogenic bladder due to partial sacral agenesis. Br J Urol 1991 May;67(5):472-476.

Sajeel M, Harding C, Robson W, Drinnan M, Griffiths C, Pickard R. Categorization of obstruction using noninvasive pressure flow measurements: sensitivity to change following prostatectomy. J Urol 2007 Sep;178(3 Pt 1):996-1000; discussion 1000-1.

Sakakibara R, Awa Y, Naya Y, Tobe T, Uchiyama T, Hattori T. Neobladder overactivity; an equivalent to spontaneous rectal contraction. Int J Urol 2007 Nov;14(11):1054-1056.

Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry 2001 Nov;71(5):600-606.

Sakamoto K, Blaivas JG. Adult onset nocturnal enuresis. J Urol 2001 Jun;165(6 Pt 1):1914-1917.

(551) Saleem A. In women with urinary incontinence how necessary is cystometry? J Pak Med Assoc 2010 May;60(5):356-359.

Salvatore S, Khullar V, Cardozo L, Anders K, Zocchi G, Soligo M. Evaluating ambulatory urodynamics: a prospective study in asymptomatic women. BJOG 2001 Jan;108(1):107-111.

Sand PK, Brubaker LT, Novak T. Simple standing incremental cystometry as a screening method for detrusor instability. Obstet Gynecol 1991 Mar;77(3):453-457.

Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008 Mar 20;358(12):1250-1261.

Sandvik H, Hunskaar S, Vanvik A, Bratt H, Seim A, Hermstad R. Diagnostic classification of female urinary incontinence: an epidemiological survey corrected for validity. J Clin Epidemiol 1995 Mar;48(3):339-343.

Satar N, Bauer SB, Scott RM, Shefner J, Kelly M, Darbey M. Late effects of early surgery on lipoma and lipomeningocele in children less than 1 year old. J Urol 1997 Apr;157(4):1434-1437.

Satar N, Bauer SB, Shefner J, Kelly MD, Darbey MM. The effects of delayed diagnosis and treatment in patients with an occult spinal dysraphism. J Urol 1995 Aug;154(2 Pt 2):754-758.

Scaldazza CV, Morosetti C. Effect of different sized transurethral catheters on pressure-flow studies in women with lower urinary tract symptoms. Urol Int 2005;75(1):21-25.

Schafer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn 2002;21(3):261-274.

Schick E, Dupont C, Bertrand PE, Jolivet-Tremblay M, Tessier J. Predictive value of maximum urethral closure pressure, urethral hypermobility and urethral incompetence in the diagnosis of clinically significant female genuine stress incontinence. J Urol 2004 May;171(5):1871-1875.

Schick E, Tessier J, Bertrand PE, Dupont C, Jolivet-Tremblay M. Observations on the function of the female urethra: I: relation between maximum urethral closure pressure at rest and urethral hypermobility. Neurourol Urodyn 2003;22(7):643-647.

Schmidt F, Jorgensen TM, Djurhuus JC. Twenty-four-hour ambulatory urodynamics in healthy young men. Scand J Urol Nephrol Suppl 2004;(215)(215):75-83.

Schmidt F, Shin P, Jorgensen TM, Djurhuus JC, Constantinou CE. Urodynamic patterns of normal male micturition: influence of water consumption on urine production and detrusor function. J Urol 2002 Oct;168(4 Pt 1):1458-1463.

Scholtmeijer RJ, Nijman RJ. Vesicoureteric reflux and videourodynamic studies: results of a prospective study after three years of follow-up. Urology 1994 May;43(5):714-718.

Schrepferman CG, Griebling TL, Nygaard IE, Kreder KJ. Resolution of urge symptoms following sling cystourethropexy. J Urol 2000 Nov;164(5):1628-1631.

Schulte-Baukloh H, Murtz G, Heine G, Austin P, Miller K, Michael T, et al. Urodynamic effects of propiverine in children and adolescents with neurogenic bladder: Results of a prospective long-term study. J Pediatr Urol 2011 Sep 8.

Schulte-Baukloh H, Murtz G, Henne T, Michael T, Miller K, Knispel HH. Urodynamic effects of propiverine hydrochloride in children with neurogenic detrusor overactivity: a prospective analysis. BJU Int 2006 Feb;97(2):355-358.

Seckiner I, Yesilli C, Mungan NA, Aykanat A, Akduman B. Correlations between the ICIQ-SF score and urodynamic findings. Neurourol Urodyn 2007;26(4):492-494.

Sehgal R, Paul P, Mohanty NK. Urodynamic evaluation in primary enuresis: an investigative and treatment outcome correlation. J Trop Pediatr 2007 Aug;53(4):259-263.

Seki N, Takei M, Yamaguchi A, Naito S. Analysis of prognostic factors regarding the outcome after a transurethral resection for symptomatic benign prostatic enlargement. Neurourol Urodyn 2006;25(5):428-432.

Sekido N, Hinotsu S, Kawai K, Shimazui T, Akaza H. How many uncomplicated male and female overactive bladder patients reveal detrusor overactivity during urodynamic study? Int J Urol 2006 Oct;13(10):1276-1279.

Serati M, Salvatore S, Cattoni E, Soligo M, Cromi A, Ghezzi F. Ultrasound measurement of bladder wall thickness in different forms of detrusor overactivity. Int Urogynecol J 2010 Nov;21(11):1405-1411.

Serati M, Salvatore S, Siesto G, Cattoni E, Braga A, Sorice P, et al. Urinary symptoms and urodynamic findings in women with pelvic organ prolapse: is there a correlation? Results of an artificial neural network analysis. Eur Urol 2011 Aug;60(2):253-260.

Seruca H. Vesicoureteral reflux and voiding dysfunction: a prospective study. J Urol 1989 Aug;142(2 Pt 2):494-8; discussion 501.

Sevestre S, Ciofu C, Deval B, Traxer O, Amarenco G, Haab F. Results of the tension-free vaginal tape technique in the elderly. Eur Urol 2003 Jul;44(1):128-131.

Sexton CC, Coyne KS, Thompson C, Bavendam T, Chen CI, Markland A. Prevalence and effect on health-related quality of life of overactive bladder in older americans: results from the epidemiology of lower urinary tract symptoms study. J Am Geriatr Soc 2011 Aug;59(8):1465-1470.

Sherman ND, Stock JA, Hanna MK. Bladder dysfunction after bilateral ectopic ureterocele repair. J Urol 2003 Nov;170(5):1975-1977.

Shikanov S, Desai V, Razmaria A, Zagaja GP, Shalhav AL. Robotic radical prostatectomy for elderly patients: probability of achieving continence and potency 1 year after surgery. J Urol 2010 May;183(5):1803-1807.

Shimada K, Matsumoto F, Matsui F. Surgical treatment for ureterocele with special reference to lower urinary tract reconstruction. Int J Urol 2007 Dec;14(12):1063-1067.

Shimada K, Matsumoto F, Tohda A, Ainoya K. Urinary control after the definitive reconstruction of cloacal anomaly. Int J Urol 2005 Jul;12(7):631-636.

Shukla A, Paul SK, Nishtar A, Bibby J. Factors predictive of voiding problems following insertion of tension-free vaginal tape. Int J Gynaecol Obstet 2007 Feb;96(2):122-126.

Sidi AA, Dykstra DD, Gonzalez R. The value of urodynamic testing in the management of neonates with myelodysplasia: a prospective study. J Urol 1986 Jan;135(1):90-93.

Sillen U. Bladder dysfunction in children with vesico-ureteric reflux. Acta Paediatr Suppl 1999 Nov;88(431):40-47.

Sillen U, Bachelard M, Hansson S, Hermansson G, Jacobson B, Hjalmas K. Video cystometric recording of dilating reflux in infancy. J Urol 1996 May;155(5):1711-1715.

Sillen U, Bachelard M, Hermanson G, Hjalmas K. Gross bilateral reflux in infants: gradual decrease of initial detrusor hypercontractility. J Urol 1996 Feb;155(2):668-672.

Sillen U, Hellstrom AL, Hermanson G, Abrahamson K. Comparison of urodynamic and free voiding pattern in infants with dilating reflux. J Urol 1999 Jun;161(6):1928-1933.

Sillen U, Hjalmas K, Aili M, Bjure J, Hanson E, Hansson S. Pronounced detrusor hypercontractility in infants with gross bilateral reflux. J Urol 1992 Aug;148(2 Pt 2):598-599.

Silva JA, Alvares RA, Barboza AL, Monteiro RT. Lower urinary tract dysfunction in children with cerebral palsy. Neurourol Urodyn 2009;28(8):959-963.

Silveri M, Salsano L, Pierro MM, Mosiello G, Capitanucci ML, De Gennaro M. Pediatric spinal cord injury: approach for urological rehabilitation and treatment. J Pediatr Urol 2006 Feb;2(1):10-15.

Sims J, Browning C, Lundgren-Lindquist B, Kendig H. Urinary incontinence in a community sample of older adults: prevalence and impact on quality of life. Disabil Rehabil 2011;33(15-16):1389-1398.

Singh G, Lucas M, Dolan L, Knight S, Ramage C, Hobson PT, et al. Minimum standards for urodynamic practice in the UK. Neurourol Urodyn 2010 Nov;29(8):1365-1372.

Singhania P, Andankar MG, Pathak HR. Urodynamic evaluation of urinary disturbances following traumatic brain injury. Urol Int 2010;84(1):89-93.

Sinha D, Nallaswamy V, Arunkalaivanan AS. Value of leak point pressure study in women with incontinence. J Urol 2006 Jul;176(1):186-8; discussion 188.

Sjostrom S, Bachelard M, Sixt R, Sillen U. Change of urodynamic patterns in infants with dilating vesicoureteral reflux: 3-year followup. J Urol 2009 Nov;182(5):2446-2453.

Slack M, Culligan P, Tracey M, Hunsicker K, Patel B, Sumeray M. Relationship of urethral retro-resistance pressure to urodynamic measurements and incontinence severity. Neurourol Urodyn 2004;23(2):109-114.

Slack M, Tracey M, Hunsicker K, Godwin A, Patel B, Sumeray M. Urethral retro-resistance pressure: a new clinical measure of urethral function. Neurourol Urodyn 2004;23(7):656-661.

Smith PP, Appell RA. Pelvic organ prolapse and the lower urinary tract: the relationship of vaginal prolapse to stress urinary incontinence. Curr Urol Rep 2005 Sep;6(5):340-347.

Snodgrass W, Barber T, Cost N. Detrusor compliance

changes after bladder neck sling without augmentation in children with neurogenic urinary incontinence. J Urol 2010 Jun;183(6):2361-2366.

Sorensen S. Urodynamic investigations and their reproducibility in healthy postmenopausal females. Scand J Urol Nephrol Suppl 1988;114:42-47.

Sorensen S, Gregersen H, Sorensen SM. Long term reproducibility of urodynamic investigations in healthy fertile females. Scand J Urol Nephrol Suppl 1988;114:35-41.

Soygur T, Burgu B, Zumrutbas A, Suer E. The need for ureteric re-implantation during augmentation cystoplasty: video-urodynamic evaluation. BJU Int 2010 Feb;105(4):530-532.

Spindel MR, Bauer SB, Dyro FM, Krarup C, Khoshbin S, Winston KR, et al. The changing neurourologic lesion in myelodysplasia. JAMA 1987 Sep 25;258(12):1630-1633.

Sreedhar B, Yeung CK, Leung VY, Chu CW. Ultrasound bladder measurements in children with severe primary nocturnal enuresis: pretreatment and posttreatment evaluation and its correlation with treatment outcome. J Urol 2008 Apr;179(4):1568-72; discussion 1572.

Starfield B. Functional bladder capacity in enuretic and nonenuretic children. J Pediatr 1967 May;70(5):777-781.

Staskin DR. Overactive bladder in the elderly: a guide to pharmacological management. Drugs Aging 2005;22(12):1013-1028.

Steers WD. Voiding dysfunction in the orthotopic neobladder. World J Urol 2000 Oct;18(5):330-337.

Stohrer, M., Kramer, G., Lochner-Ernst, D., et al., Diagnosis and treatment of bladder dysfunction in spinal cord injury patients. European Urology Update series, 1994.

Stohrer M, Blok B, Castro-Diaz D, Chartier-Kastler E, Del Popolo G, Kramer G, et al. EAU guidelines on neurogenic lower urinary tract dysfunction. Eur Urol 2009 Jul;56(1):81-88.

Summitt RL,Jr, Stovall TG, Bent AE, Ostergard DR. Urinary incontinence: correlation of history and brief office evaluation with multichannel urodynamic testing. Am J Obstet Gynecol 1992 Jun;166(6 Pt 1):1835-40; discussion 1840-4.

Suppiej A, Dal Zotto L, Cappellari A, Traverso A, Castagnetti M, Drigo P, et al. Tethered cord in patients with anorectal malformaə tion: preliminary results. Pediatr Surg Int 2009 Oct;25(10):851-855.

Sutherst JR, Brown MC. Comparison of single and multichannel cystometry in diagnosing bladder instability. Br Med J (Clin Res Ed) 1984 Jun 9;288(6432):1720-1722.

Szabó L, Kiss ÁL, Csizy I. Simple Methods to detect mild bladder outflow obstruction. Eur. Urol 1996; Supp. 30: 218. 24.

Tan TL, Bergmann MA, Griffiths D, Resnick NM. Which stop test is best? Measuring detrusor contractility in older females. J Urol 2003 Mar;169(3):1023-1027.

Tanaka H, Kakizaki H, Kobayashi S, Shibata T, Ameda K, Koyanagi T. The relevance of urethral resistance in children with myelodysplasia: its impact on upper urinary tract deterioration and the outcome of conservative management. J Urol 1999 Mar;161(3):929-932.

Tarcan T, Bauer S, Olmedo E, Khoshbin S, Kelly M, Darbey M. Long-term followup of newborns with myelodysplasia and normal urodynamic findings: Is followup necessary? J Urol 2001 Feb;165(2):564-567.

Taskinen S, Heikkila J, Rintala R. Posterior urethral valves: primary voiding pressures and kidney function in infants. J Urol 2009 Aug;182(2):699-702; discussion 702-3.

Taskinen S, Valanne L, Rintala R. Effect of spinal cord abnormalities on the function of the lower urinary tract in patients with anorectal abnormalities. J Urol 2002 Sep;168(3):1147-1149.

Teichman JM, Scherz HC, Kim KD, Cho DH, Packer MG, Kaplan GW. An alternative approach to myelodysplasia management: aggressive observation and prompt intervention. J Urol 1994 Aug;152(2 Pt 2):807-811.

Teng CH, Huang YH, Kuo BJ, Bih LI. Application of portable ultrasound scanners in the measurement of post-void residual urine. J Nurs Res 2005 Sep;13(3):216-224.

Theofrastous JP, Bump RC, Elser DM, Wyman JF, McClish DK. Correlation of urodynamic measures of urethral resistance with clinical measures of incontinence severity in women with pure genuine stress incontinence. The Continence Program for Women Research Group. Am J Obstet Gynecol 1995 Aug;173(2):407-12; discussion 412-4.

Thiede HA, Saini VD. Urogynecology: comments and caveats. Am J Obstet Gynecol 1987 Sep;157(3):563-568.

Thiel DD, Young PR, Broderick GA, Heckman MG, Wehle MJ, Igel TC, et al. Do clinical or urodynamic parameters predict artificial urinary sphincter outcome in post-radical prostatectomy incontinence? Urology 2007 Feb;69(2):315-319.

Thind P. The significance of smooth and striated muscles in the sphincter function of the urethra in healthy women. Neurourol Urodyn 1995;14(6):585-618.

Thind P, Lose G, Colstrup H. Initial urethral pressure increase during stress episodes in genuine stress incontinent women. Br J Urol 1992 Feb;69(2):137-140.

Thompson PK, Duff DS, Thayer PS. Stress incontinence in women under 50: does urodynamics improve surgical outcome? Int Urogynecol J Pelvic Floor Dysfunct 2000;11(5):285-289.

Thorup J, Biering-Sorensen F, Cortes D. Urological outcome after myelomeningocele: 20 years of follow-up. BJU Int 2011 Mar;107(6):994-999.

Thuroff JW, Abrams P, Andersson KE, Artibani W, Chapple CR, Drake MJ, et al. EAU guidelines on urinary incontinence. Eur Urol 2011 Mar;59(3):387-400.

Thuroff JW, Abrams P, Andersson KE, Artibani W, Chapple CR, Drake MJ, et al. EAU Guidelines on Urinary Incontinence. Actas Urol Esp 2011 Jul-Aug;35(7):373-388.

Toguri AG, Bee DE, Bunce H,3rd. Variability of water urethral closure pressure profiles. J Urol 1980 Sep;124(3):407-409.

Toh KL, Ng CK. Urodynamic studies in the evaluation of young men presenting with lower urinary tract symptoms. Int J Urol 2006 May;13(5):520-523.

Tong YC. Comparisons of urodynamic findings and voiding habits in patients with concomitant benign prostatic hyperplasia and detrusor overactivity presenting with or without the symptom of urgency. Urol Int 2007;78(3):219-225.

Torre M, Planche D, Louis-Borrione C, Sabiani F, Lena G, Guys JM. Value of electrophysiological assessment after surgiŧ cal treatment of spinal dysraphism. J Urol 2002 Oct;168(4 Pt 2):1759-62; discussion 1763.

Trumbeckas D, Milonas D, Jievaltas M, Danilevicius M, Matjosaitis AJ. Influence of catheter on urinary flow during urodynamic pressure-flow study in men with symptomatic benign prostatic hyperplasia. Medicina (Kaunas) 2006;42(1):15-21.

Tsunoyama K, Sakakibara R, Yamaguchi C, Uchiyama T, Yamamoto T, Yamanishi T, et al. Pathogenesis of reduced or increased bladder sensation. Neurourol Urodyn 2011 Mar;30(3):339-343.

Tunn R, Marschke J, Wildt B, Gauruder-Burmester A. Clinical experience with urethral retro-resistance pressure measurement: a prospective pre- and postoperative evaluation in women with stress urinary incontinence. Neurourol Urodyn 2007;26(2):262-266.

Turner-Warwick R, Whiteside CG, Milroy EJ, Pengelly AW, Thompson DT. The intravenous urodynamogram. Br J Urol. 1979 Feb;51(1):15-18.

Twiss C, Fleischmann N, Nitti VW. Correlation of abdominal leak point pressure with objective incontinence severity in men with post-radical prostatectomy stress incontinence. Neurourol Uropॐ dyn 2005;24(3):207-210.

Uchiyama T, Sakakibara R, Yamamoto T, Ito T, Yamaguchi C, Awa Y, et al. Urinary dysfunction in early and untreated Parkinson's disease. J Neurol Neurosurg Psychiatry 2011 Dec;82(12):1382-1386.

Ullrich NF, Comiter CV. The male sling for stress urinary incontinence: urodynamic and subjective assessment. J Urol 2004 Jul;172(1):204-206.

Uluocak N, Oktar T, Ander H, Ziylan O, Acar O, Rodoplu H, et al. Which method is the most reliable in determination of bladder capacity in children with idiopathic overactive bladder? A com-

parison of maximum voided volume, uroflowmetry and maximum cystometric capacity. J Pediatr Urol 2009 Dec;5(6):480-484.

Ural Z, Ulman I, Avanoglu A. Bladder dynamics and vesicoureteral reflux: factors associated with idiopathic lower urinary tract dysfunction in children. J Urol 2008 Apr;179(4):1564-1567.

Uygur MC, Tan MO, Altug U, Yilmaz C, Erol D. Clinical, urodynamic and endoscopic characteristics of the stanford pouch ileal neobladder constructed with absorbable staples. Int J Urol 2000 Dec;7(12):440-446.

Valente S. The usefulness of urodynamics in urogynaecological disorders. Clin Exp Obstet Gynecol 1988;15(3):102-107.

Valentini FA, Robain G, Marti BG, Nelson PP. Urodynamics in a community-dwelling population of females 80 years or older. Which motive? Which diagnosis? Int Braz J Urol 2010 Mar-Apr;36(2):218-224.

Van Arendonk KJ, Madsen MT, Austin JC, Hawtrey CE, Graham MM, Cooper CS. Nuclear cystometrogram-determined bladder pressure at onset of vesicoureteral reflux predicts spontaneous resolution. Urology 2007 Apr;69(4):767-770.

van Brummen HJ, Heintz AP, van der Vaart CH. The association between overactive bladder symptoms and objective parameters from bladder diary and filling cystometry. Neurourol Urodyn 2004;23(1):38-42.

van Gool JD, Hjalmas K, Tamminen-Mobius T, Olbing H. Historical clues to the complex of dysfunctional voiding, urinary tract infection and vesicoureteral reflux. The International Reflux Study in Children. J Urol 1992 Nov;148(5 Pt 2):1699-1702.

van Koeveringe GA, Rahnama'i MS, Berghmans BC. The additional value of ambulatory urodynamic measurements compared with conventional urodynamic measurements. BJU Int 2010 Feb;105(4):508-513.

van Mastrigt R, Huang Foen Chung JW. Bladder volume sensitivity of isovolumetric intravesical pressure. Neurourol Urodyn 2006;25(7):744-751.

van Meel TD, de Wachter S, Wyndaele JJ. Repeated ice water tests and electrical perception threshold determination to detect a neurologic cause of detrusor overactivity. Urology 2007 Oct;70(4):772-776.

van Meel TD, Wyndaele JJ. Reproducibility of urodynamic filling sensation at weekly interval in healthy volunteers and in women with detrusor overactivity. Neurourol Urodyn 2011 Nov;30(8):1586-1590.

van Waalwijk van Doorn,E.S. Doctoral Thesis, 122 1993.

(653) van Waalwijk van Doorn ES, Remmers A, Janknegt RA. Conventional and extramural ambulatory urodynamic testing of the lower urinary tract in female volunteers. J Urol 1992 May;147(5):1319-25; discussion 1326.

VanderBrink BA, Gitlin J, Palmer LS. Uroflowmetry parameters before and after meatoplasty for primary symptomatic meatal stenosis in children. J Urol 2008 Jun;179(6):2403-6; discussion 2406.

Vella M, Duckett J, Basu M. The predictive value of pre-treatment cystometry in the outcome of women with mixed incontinence treated with duloxetine. Eur J Obstet Gynecol Reprod Biol 2010 Aug;151(2):221-223.

Vella M, Robinson D, Cardozo L, Srikrishna S, Cartwright R. Predicting detrusor overactivity using a physician-based scoring system. Int Urogynecol J Pelvic Floor Dysfunct 2008 Sep;19(9):1223-1227.

Venhola M, Reunanen M, Taskinen S, Lahdes-Vasama T, Uhari M. Interobserver and intra-observer agreement in interpreting urodynamic measurements in children. J Urol 2003 Jun;169(6):2344-2346.

Verdejo C, Salinas J, Virseda M, Adot JM, Rexach L, Ribera JM. "Overactive bladder": Main urinary symptoms and urodynamic patterns in the elderly. Int Urol Nephrol 2007 Jan 31.

Veronikis DK, Nichols DH, Wakamatsu MM. The incidence of low-pressure urethra as a function of prolapse-reducing technique in patients with massive pelvic organ prolapse (maximum descent at all vaginal sites). Am J Obstet Gynecol 1997 Dec;177(6):1305-13; discussion 1313-4.

Versi, E., D.J. Lyell, and D.J. Griffiths, Videourodynamic diagnosis of occult genuine stress incontinence in patients with anterior vaginal wall relaxation. J Soc Gynecol Investig, 1998. 5(6): p. 327-30.

Versi E. Discriminant analysis of urethral pressure profilometry data for the diagnosis of genuine stress incontinence. Br J Obstet Gynaecol 1990 Mar;97(3):251-259.

Versi E, Lyell DJ, Griffiths DJ. Videourodynamic diagnosis of occult genuine stress incontinence in patients with anterior vaginal wall relaxation. J Soc Gynecol Investig 1998 Nov-Dec;5(6):327-330.

Vesely S, Knutson T, Fall M, Damber JE, Dahlstrand C. Clinical diagnosis of bladder outlet obstruction in men with lower urinary tract symptoms: reliability of commonly measured parameters and the role of idiopathic detrusor overactivity. Neurourol Urodyn 2003;22(4):301-305.

Videla FL, Wall LL. Stress incontinence diagnosed without multichannel urodynamic studies. Obstet Gynecol 1998 Jun;91(6):965-968.

Witjes WP, de la Rosette JJ, Zerbib M, Vignoli GC, Geffriaud C, Debruyne FM, Wijkstra H. Computerized artifact detection and correction of uroflow curves: towards a more consistent quantitative assessment of maximum flow. Eur Urol. 1998;33(1):54-63.

Visco AG, Brubaker L, Nygaard I, Richter HE, Cundiff G, Fine P, et al. The role of preoperative urodynamic testing in stress-continent women undergoing sacrocolpopexy: the Colpopexy and Urinary Reduction Efforts (CARE) randomized surgical trial. Int Urogynecol J Pelvic Floor Dysfunct 2008 May;19(5):607-614.

Wadie BS. Retropubic bulbourethral sling for post-prostatectomy male incontinence: 2-year followup. J Urol 2010 Dec;184(6):2446-2451.

Wagg A, Bayliss M, Ingham NJ, Arnold K, Malone-Lee J. Urodynamic variables cannot be used to classify the severity of detrusor instability. Br J Urol 1998 Oct;82(4):499-502.

Wagg AS, Cardozo L, Chapple C, De Ridder D, Kelleher C, Kirby M, et al. Overactive bladder syndrome in older people. BJU Int 2007 Mar;99(3):502-509.

Wahl EF, Lerman SE, Lahdes-Vasama TT, Churchill BM. Measurement of bladder compliance can be standardized by a dimensionless number: theoretical perspective. BJU Int 2004 Oct;94(6):895-897.

Wahll L, Bachelard M, Sjostrom S, Sillen U. Is the mode of occurrence of vesicoureteral reflux correlated to bladder function and spontaneous resolution? J Pediatr Urol 2009 Jun;5(3):170-177.

Wakavaiachi VM, Girao MJ, Sartori MG, Baracat EC, Rodrigues de Lima G, Novo NF. Changes in the lower urinary tract in continent women and in women with stress urinary incontinence, according to menopausal status. Int Urogynecol J Pelvic Floor Dysfunct 2001;12(3):156-160.

Wall LL, Wiskind AK, Taylor PA. Simple bladder filling with a cough stress test compared with subtracted cystometry for the diagnosis of urinary incontinence. Am J Obstet Gynecol 1994 Dec;171(6):1472-7; discussion 1477-9.

Walters MD, Shields LE. The diagnostic value of history, physical examination, and the Q-tip cotton swab test in women with urinary incontinence. Am J Obstet Gynecol 1988 Jul;159(1):145-149.

Wang AC, Chen MC. Comparison of tension-free vaginal taping versus modified Burch colposuspension on urethral obstruction: a randomized controlled trial. Neurourol Urodyn 2003;22(3):185-190.

Wang AC, Chen MC. A comparison of urethral pressure profilometry using microtip and double-lumen perfusion catheters in women with genuine stress incontinence. BJOG 2002 Mar;109(3):322-326.

Wang QW, Wen JG, Song DK, Su J, Che YY, Zhang P, et al. Is it possible to use urodynamic variables to predict upper urinary tract dilatation in children with neurogenic bladder-sphincter dysfunction? BJU Int 2006 Dec;98(6):1295-1300.

Ward K, Hilton P, United Kingdom and Ireland Tension-free Vaginal Tape Trial Group. Prospective multicentre randomised trial of

tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ 2002 Jul 13;325(7355):67.

Ward RM, Hampton BS, Blume JD, Sung VW, Rardin CR, Myers DL. The impact of multichannel urodynamics upon treatment recommendations for female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008 Sep;19(9):1235-1241.

Warne SA, Godley ML, Wilcox DT. Surgical reconstruction of cloacal malformation can alter bladder function: a comparative study with anorectal anomalies. J Urol 2004 Dec;172(6 Pt 1):2377-81; discussion 2381.

Warwick RT, Brown AD. A urodynamic evaluation of urinary incontinence in the female and its treatment. Urol Clin North Am 1979 Feb;6(1):203-216.

Watanabe T, Rivas DA, Chancellor MB. Urodynamics of spinal cord injury. Urol Clin North Am 1996 Aug;23(3):459-473.

Weber AM. Is urethral pressure profilometry a useful diagnostic test for stress urinary incontinence? Obstet Gynecol Surv 2001 Nov;56(11):720-735.

Weber AM. Leak point pressure measurement and stress urinary incontinence. Curr Womens Health Rep 2001 Aug;1(1):45-52.

Weber AM, Walters MD. Cost-effectiveness of urodynamic testing before surgery for women with pelvic organ prolapse and stress urinary incontinence. Am J Obstet Gynecol 2000 Dec;183(6):1338-46; discussion 1346-7.

Webster, G, Sihelnik, SA., Stone AR, Female urinary incontinence: the incidence, identification, and characteristics of detrusor instability. Neurourology and Urodynamics, 1984. 3: p. 235.

Webster GD, Koefoot RB, Jr, Sihelnik S. Urodynamic abnormalities in neurologically normal children with micturition dysfunction. J Urol 1984 Jul;132(1):74-77.

Wehle MJ, Lisson SW, Buskirk SJ, Broderick GA, Young PR, Igel TC. Prediction of genitourinary tract morbidity after brachytherapy for prostate adenocarcinoma. Mayo Clin Proc 2004 Mar;79(3):314-317.

Wennberg AL, Molander U, Fall M, Edlund C, Peeker R, Milsom I. A longitudinal population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in women. Eur Urol 2009 Apr;55(4):783-791.

Wheeler TL,2nd, Richter HE, Greer WJ, Bowling CB, Redden DT, Varner RE. Predictors of success with postoperative voiding trials after a mid urethral sling procedure. J Urol 2008 Feb;179(2):600-604.

White T, Kawasaki A, Ross RV, Adam RA, Duong TH. Correlation of maximum urethral closure pressure with Valsalva leak point pressure using air-charged urodynamic catheters. Int Urogynecol J Pelvic Floor Dysfunct 2009 Sep;20(9):1109-1112.

Wen JG, Tong EC. Cystometry in infants and children with no apparent voiding symptoms. Br J Urol. 1998 Mar;81(3):468-73.

Whiteside JL, Hijaz A, Imrey PB, Barber MD, Paraiso MF, Rackley RR, et al. Reliability and agreement of urodynamics interpretations in a female pelvic medicine center. Obstet Gynecol 2006 Aug;108(2):315-323.

Williams DR, Lees AJ. How do patients with parkinsonism present? A clinicopathological study. Intern Med J 2009 Jan;39(1):7-12.

Wilmshurst JM, Kelly R, Borzyskowski M. Presentation and outcome of sacral agenesis: 20 years' experience. Dev Med Child Neurol 1999 Dec;41(12):806-812.

Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. Ann Intern Med 2008 Mar 18;148(6):435-448.

Wolin KY, Luly J, Sutcliffe S, Andriole GL, Kibel AS. Risk of urinary incontinence following prostatectomy: the role of physical activity and obesity. J Urol 2010 Feb;183(2):629-633.

Wyndaele JJ, De Wachter S. Cystometrical sensory data from a normal population: comparison of two groups of young healthy volunteers examined with 5 years interval. Eur Urol 2002 Jul;42(1):34-38.

Wyndaele JJ, THi HV, Pham BC, Kovindha A, Huong VT, Weerts E. The use of one-channel water cystometry in patients with a spinal cord lesion: practicalities, clinical value and limitations for the diagnosis of neurogenic bladder dysfunction. Spinal Cord 2009 Jul;47(7):526-530.

Yalla, S., Fraser, A., Total and static pressure measurements for male lower urinary tract. Neurourology and Urodynamics, 1982. 1: p. 159

Yamanishi T, Mizuno T, Tatsumiya K, Watanabe M, Kamai T, Yoshida K. Urodynamic effects of silodosin, a new alpha 1A-adrenoceptor selective antagonist, for the treatment of benign prostatic hyperplasia. Neurourol Urodyn 2010 Apr;29(4):558-562.

Yeats, W., Bladder function in normal micturition, in Bladder control and enuresis, I. Kolvin, MacKeith RL., Meadow, SR, Editor. 1976, Lippincott: Philadelphia. p. 28.

Yeung CK, Godley ML, Ho CK, Ransley PG, Duffy PG, Chen CN, Li AK. Some new insights into bladder function in infancy. Br J Urol. 1995 Aug;76(2):235-40.

Yeung CK. Continuous real-time ambulatory urodynamic monitoring in infants and young children using infrared telemetry. Br J Urol 1998 May;81 Suppl 3:76-80.

Yeung CK, Chiu HN, Sit FK. Bladder dysfunction in children with refractory monosymptomatic primary nocturnal enuresis. J Urol 1999 Sep;162(3 Pt 2):1049-54; discussion 1054-5.

Yeung CK, Chiu HN, Sit FK. Sleep disturbance and bladder dysfunction in enuretic children with treatment failure: fact or fiction? Scand J Urol Nephrol Suppl 1999;202:20-23.

Yeung CK, Godley ML, Dhillon HK, Duffy PG, Ransley PG. Urodynamic patterns in infants with normal lower urinary tracts or primary vesico-ureteric reflux. Br J Urol 1998 Mar;81(3):461-467.

Yeung CK, Godley ML, Dhillon HK, Gordon I, Duffy PG, Ransley PG. The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. Br J Urol 1997 Aug;80(2):319-327.

Yeung CK, Sreedhar B, Leung VT, Metreweli C. Ultrasound bladder measurements in patients with primary nocturnal enuresis: a urodynamic and treatment outcome correlation. J Urol 2004 Jun;171(6 Pt 2):2589-2594.

Yip CM, Leach GE, Rosenfeld DS, Zimmern P, Raz S. Delayed diagnosis of voiding dysfunction: occult spinal dysraphism. J Urol 1985 Oct;134(4):694-697.

Yokoyama O, Nagano K, Hirata A, Hisazumi H, Izumida S. Clinical evaluation for voiding dysfunction in patients with cerebral-palsy. Nihon Hinyokika Gakkai Zasshi 1989 Apr;80(4):591-595.

Yoo PB, Horvath EE, Amundsen CL, Webster GD, Grill WM. Multiple pudendal sensory pathways reflexly modulate bladder and urethral activity in patients with spinal cord injury. J Urol 2011 Feb;185(2):737-743.

Youssif M, Dawood W, Shabaan S, Mokhless I, Hanno A. Early valve ablation can decrease the incidence of bladder dysfunction in boys with posterior urethral valves. J Urol 2009 Oct;182(4 Suppl):1765-1768.

Yurkanin JP, Dalkin BL, Cui H. Evaluation of cold knife urethrotomy for the treatment of anastomotic stricture after radical retropubic prostatectomy. J Urol 2001 May;165(5):1545-1548.

Zajaczkowska M, Moulhee NM, Piechuta L, Majewski M, Borzecka H. Dysfunctional voiding and urodynamic disorders in children with recurrent urinary tract infection. Ann Univ Mariae Curie Sklodowska Med 2004;59(2):385-391.

Zehnder P, Roth B, Burkhard FC, Kessler TM. Air charged and microtip catheters cannot be used interchangeably for urethral pressure measurement: a prospective, single-blind, randomized trial. J Urol 2008 Sep;180(3):1013-1017.

Zhao SC, Zheng SB, Tan WL, Zhang P, Qi H. Pressure-flow studies in patients with benign prostatic hyperplasia: a study comparing suprapubic and transurethral methods. Asian J Androl 2006 Nov;8(6):731-735.

Zimmern P, Nager CW, Albo M, Fitzgerald MP, McDermott S, Urinary Incontinence Treatment Network. Interrater reliability of filling cystometrogram interpretation in a multicenter study. J Urol 2006 Jun;175(6):2174-2177.

Committee 7

Imaging, Neurophysiological Testing and Other Tests

Chair

A. Tubaro (Italy)

Members

David B. Vodušek (Slovenia)

G. Amarenco (France)

Stergios K. Doumouchtsis (UK)

John O. L. DeLancey (USA)

Ruwan Fernando (UK)

Vik Khullar (UK)

Consultant

F. Puccini (Italy)

S. Podnar (Slovenia)

CONTENTS

A. INTRODUCTION

B. IMAGING IN URINARY INCONTINENCE AND PELVIC FLOOR DYSFUNCTION

I. IMAGING OF THE UPPER URINARY TRACT

II. IMAGING OF THE LOWER URINARY TRACT

III. SPECIAL ISSUES

C. Imaging in Anal Incontinence

I. INDICATIONS

II. IMAGING MODALITIES

III. SPHINCTERIC DISORDERS

IV. CONCLUSIONS

V. CONSENSUS STATEMENTS

VI. FUTURE RESEARCH AREAS

D. PAD TESTING

I. DEFINITION

II. INDICATION AND METHODOLOGY

III. OFFICE-BASED PAD TESTING

IV. HOME BASED PAD TESTING

V. CONCLUSIONS

VI. CONSENSUS STATEMENTS

VII. FUTURE RESEARCH AREAS

E. NEUROPHYSIOLOGY

I. INTRODUCTION

II. CLINICAL NEUROPHYSIOLOGICAL TESTS

III. EVIDENCE BASED USE OF CLINICAL NEUROPHYSIOLOGICAL TESTS

IV. CONSENSUS STATEMENT

F. OTHER INVESTIGATIONS

I. URINALYSIS

II. BLOOD TESTS

III. TISSUE ANALYSIS

G. CONCLUSIONS

REFERENCES

LIST OF ABBREVIATIONS

3D	- three dimensional
ACC	- anterior cyngulate cortex
ACG	- anterior cyngulate gyrus
ADH	- anti diuretic hormone
ARJ	- anorectal junction
ATT	- alpha-1 antitrypsin
BBI	- bladder base insufficiency
BCR	- bulbocavernosus reflex
BMI	- body mass index
BOO	- bladder outlet obstruction
BWT	- bladder wall thickness
CCC	- concordance correlation coefficient
CMAP	- compound muscle action potential
CMCT	- central motor conduction time
CNEMG	- concentric needle electromyography
CT	- computerised tomography
DO	- detrusor overcativity
EAS	- external anal sphincter
EAUS	- endoanal ultrasound ultrasound sonography
ED	- erectile dysfunction
EMG	- electromyography
FOV	- field of view
HASTE	- single-shot turbo spin echo
HOXA	- Homebox A
IAS	- internal anal sphincter
ICTP	- carboxy-terminal telopeptide of type I collagen
IIQ-7	- incontinence impact questionnaire
IP	- interference pattern
ISD	- intrinsic sphincter deficiency
IVU	- intra venous urography
LLM	- longitudinal layer muscle
LMR	- longitudinal muscle of the rectum
LUT	- lower urinary tract
LUTD	- lower urinary tract dysfunction
LUTS	- lower urinary tract symptoms
MCC	- maximum cystometric capacity
MEP	- motor evoked potential
MMPS	- matrix metalloproteinases
MRI	- magnetic resonance imaging
MSA	- multiple system atrophy
MU	- motor unit
MUP	- motor unit potential
PA	- puboanalis
PAG	- periacqueductal grey
PCL	- pubococcygeal line
PD	- Parkinson's disease
PET	- positron emission tomography
PFMT	- pelvic floor muscle training
PGPI	- patient global perception of improvement
PICP	- propeptide of type I procollagen
PIIINP	- amino-terminal propeptide of procollagen III
PIVS	- posterior intravaginal slingplasty
PMC	- pontine micturition centre
POP-Q	- pelvic organ prolapse quantification
PNTML	- pudendal nerve terminal motor latency
PUV	- posterior urethrovesical (angle)
PVR	- post-void residual
QST	- quantitative sensory testing
SCP	- sacrocolpopexy
SEP	- somatosensory evoked potential
SERMS	- selective estrogen-receptor modulators
SFEMG	- single fibre electromyography
SII	- symptom impact index
SMA	- supplementary motor area
SO	- symphysis orifice (distance)
SSF	- sacrospinous fixation
SSFSE	- single-shot fast spin echo
SSI	- symptom severity index
SSR	- sympathetic skin responses
STARD	- Standards for Reporting of Diagnostic Accuracy
SUI	- stress urinary incontinence
T/A	- turns/amplitude
TE	- echo time
TGF-β	- transforming growth factor-β
TIMP	- tissue inhibitor of metalloproteinases
TR	- repetition time
UAR	- urehral axis at rest
UAS	- urethral axis suring straining
UEBW	- ultrasound estimated bladder weight
UP	- urethropelvic (angle)
UPP	- urethral pressure profile
USI	- urodynamic stress incontinence
USS	- ultrasonography
UTI	- urinary tract infection
VCCU	- voiding colpo cystourethrography
VUCG	- voiding urethrocystogram
WA	- white American

Imaging, Neurophysiological Testing and Other Tests

A. Tubaro,

David B. Vodušek,G. Amarenco, Stergios K. Doumouchtsis, John O. L. DeLancey, Ruwan Fernando, Vik Khullar, F. Puccini, S. Podnar

A. INTRODUCTION

The Committee was given the task of updating the evidence on imaging, neurophysiological testing and other tests in the field of urinary and anal incontinence. The Medline, Embase and Cochrane databases were searched for the relative subjects from January 2008 and February 2012. All references obtained from the database search were screened for relevance, full text papers were obtained and reference list were used as additional source of evidence when appropriate.

The chapter covers different issues including: imaging, neurophysiological testing, and other investigations (laboratory tests, tissue analysis and Pad test) in the paediatric and adult population, male and female subjects, neurogenic and non-neurogenic patients.

The following keywords were used for the difference subjects:

- Imaging: the Medline database was searched using the following keywords: imaging, urinary incontinence, continence, anal incontinence and faecal incontinence; the search has been limited to period from 2004 to 2008.
- Neurophysiology: clinical neurophysiology, conventional urodynamics, neurourology, urinary dysfunction.
- Other investigations: keywords including urinary incontinence, continence, pad test, urinalysis, urine culture, tissue analysis were used.

Members of the committee were allocated the different topics of the chapter based on their specific expertise in the field. The first draft of the chapter was reviewed by all committee members, the final draft was then edited first by the Committee Chair and then by the book Editors.

Diagnostic techniques were evaulated with reference to the technique and its standardisation, intraobserver and interobserver variability, diagnostic accuracy, cost/benefit ratio and clinical benefit. The level of evidence was graded taking into consideration that imaging, neurophysiological testing and the other tests pertain to the area of "diagnosis" and the quality of the published papers is graded according to the criteria specific for this area. Areas of future research were identified.

Notwithstanding the large body of evidence research on imaging in anal and urinary incontinence, its clinical benefit remains questionable. Test-retest, intraobserver and interobserver accuracy are often provided for diagnostic tests although diagnostic accuracy is sometimes difficult to calculate. When ultrasound is used to measure bladder volume, catheterisation can be used as a reference standard and accuracy can be easily calculated but when sphincter volume is calculated with ultrasonography, there is no solid reference standard except another imaging technique (e.g.: MRI) and the validity of the measurement is tested against another weak test such as Valsalva Leak Point pressure of maximum urethral pressure profile. Imaging can either be performed to better understand the pathophysiology of incontinence and pelvic organ prolapse and it may be of importance although no immediate clinical benefit is evident (e.g.: calculation of sphincter volume with ultrasound). It can be performed as a diagnostic test in patients undergoing surgery so that quantification of the clinical benefit requires complex clinical trials (e.g.: MR imaging of pelvic organ prolapse in patient undergoing prolapse repair) in which different reference standards can be used (e.g.: physical examination or anatomic finding during surgery). Although imaging can sometimes offer a better understanding of the anatomy underlying the condition (e.g.: presence of an enterocele) the clinical benefit of this additional information may not be observed in all patients.

Although imaging is clearly a difficult area for research, the consensus regarding introduction of a

diagnostic test into our daily practise must rely on the evidence of clinical benefit in terms of safety, outcome or cost-benefit ratio.

Imaging studies belong to the area of diagnostic studies, they should follow the suggestions of the STARD initiative and they differ substantially from other types of clinical trials (Bossuyt 2003). The aim of clinical studies of diagnostic tests should be to provide information regarding the diagnostic accuracy of the proposed test although, this is not always possible.

A few considerations regarding the levels of evidence in imaging studies may be instrumental in reading this chapter and are summarised herewith.

Imaging of parameters with known prognostic value (e.g. PVR)

- The first issue is to prove that imaging studies image what they are supposed to image. Although the issue may be trivial in case of PVR imaging or anal sphincter imaging, the issue is relevant in other areas (eg: enterocele imaging) and should be solved using imaging in cadavers or other approaches such as intraoperative confirmation of the observed condition.
- When the imaging is quantitative, accuracy versus the gold standard technique should be provided. When the imaging is qualitative (e.g. presence or absence of vaginal vault prolapse) the diagnostic value should be provided (sensitivity, specificity, positive and negative predictive value, accuracy, inter-rater and intrarater variablity).
- Once validity has been proven, one can assume that the predictive value of the imaging study is equal to that observed for the parameter measured with the gold standard. The same applies to its value for patient management.

Imaging of parameters with unknown prognostic value (e.g. MRI of the pelvic floor)

- When the imaging is qualitative (eg: intact versus damaged levator ani), once validity is proven, the diagnostic value should be investigated providing sensitivity, specificity, positive and negative predictive value, accuracy, interrater and intrarater variability in cadavers or patients undergoing surgery.
- Once validity is proved, the prognostic value for patient management should be investigated.
- Confirmation of the proposed imaging study by independent groups is required ideally for both validity and prognostic value or at least for the latter parameter (we can assume that confirmation of the prognostic value is obtained, validity of the imaging technique can be inferred).

B. IMAGING IN URINARY INCONTINENCE AND PELVIC FLOOR DYSFUNCTION

This is a very wide area that often requires a multiprofessional and muldisciplinary approach. The patient population is quite heterogenous including children, female and male subjects suffering congenital malformation of the genital and urinary tract, neurogenic disorders, iatrogenic conditions and traumatic lesions. Clinical guidelines always refer to the so called “standard patient” but the majority of subjects referred to secondary and tertiary referral centres cannot be defined as such and their management sometimes requires deviation from guidelines recommendations. The large variability and the uniqueness of the observed cases may justify the adoption of a knowledge-based management in the absence of proven clinical benefit. Research on imaging of urinary incontinence and genital prolapse remains very active. Although all guidelines recommend not to use imaging in the evaluation of the standard patient, many clinicians believe this is an ideal adjunct to physical examination in evaluating the anatomical condition of the individual subject.

Urinary incontinence is defined as the complaint of any involuntary leakage of urine, it can be urethral or extraurethral [1]. This latter condition either results from congenital anomalies such as ectopic ureters (inserting in the female distal urethra or vagina), iatrogenic or traumatic conditions such as fistula. In some patients, LUTD causing UI, might compromise the transport of urine from the kidneys to the bladder resulting in hydronephrosis and renal failure. The relationship between high bladder storage pressure and renal deterioration was first identified in myelodysplatic children and then considered to apply in all neurogenic patients [2] and automatically transferred to male and female patients with or without neurogenic problems; the value of 40 cmH2O of bladder pressure as threshold value at which the UUT is at risk should therefore used with caution. In male patients, chronic retention of urine can be associated with UI and lead to chronic renal failure. In women, severe urogenital prolapse may cause angulation of the pelvic ureter by the uterine arteries leading to hydronephrosis [3] (**Figure B 1 a,b**).

I. IMAGING OF THE UPPER URINARY TRACT

1. INDICATIONS

Generally speaking, there is no need for upper tract imaging in patients with UI unless any of the

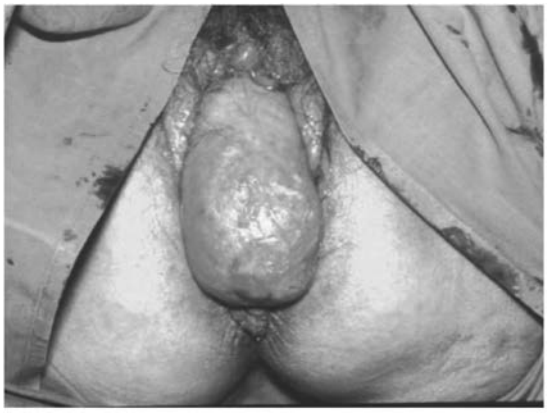


Figure B 1-a: Procidentia uteri

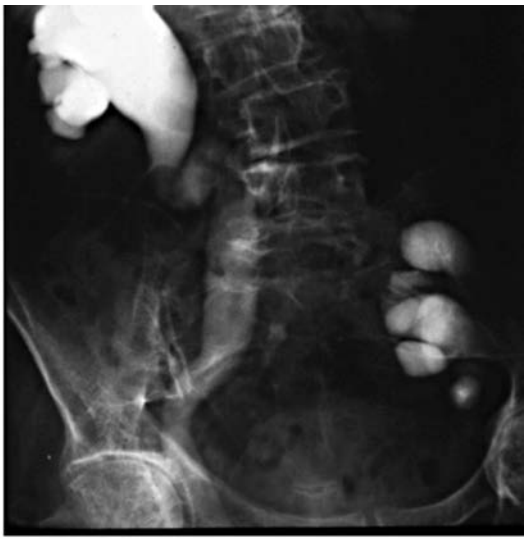


Figure B 1-b: IVU: bilateral hydronephrosis. Left kidney is in sacral ectopia.

previously described conditions is suspected or diagnosed. In children with extraurethral incontinence imaging of the UUT helps to identify the underlying cause.

The objectives of UUT in the incontinent patient are as follows:

1. Evaluation of the upper urinary tract when the presence of an ectopic ureter or ureterovaginal fistula are suspected.
2. Evaluation of the kidneys whenever UI is related to bladder dysfunction with high storage pressures (e.g. in neurogenic voiding dysfunction, chronic retention with overflow or low compliance bladders)
3. Exclusion of hydronephrosis in cases of UI associated with severe uterine prolapse (**Figure B 2 a,b,c,d**).

2. TECHNIQUES

Upper tract imaging modalities include intra-venous urogram (IVU), ultrasound sonography (USS), computerised tomography (CT scan), magnetic resonance imaging (MRI), and isotope scanning. No data regarding reproducibility, specificity, sensitivity, positive and negative predictive value in relation with the diagnosis and management of UI are available. The choice of the imaging modality also depends on availability, expertise, and local management policies. Generally speaking, low cost and low risk techniques such as USS are preferred. Unless otherwise described, the following considerations regarding the different imaging modalities are based on expert opinion.

a) Ultrasonography

USS is the gold standard technique for primary imaging of the upper urinary tract because of the relatively low cost of the equipment and the examination, its wide availability, the lack of any exposure to ionising radiation. Renal USS is independent on kidney function and provides a good evaluation of kidney morphology. Concomitant renal disorders such as urinary lithiasis and neoplasms can also be diagnosed. In patients with LUTD, the detection of hydronephrosis is of importance and it can be related to either vesico-ureteral reflux or obstruction. Although, no strict correlation exists between the degree of dilatation and the severity of obstruction, the grade of hydronephrosis is correlated with the extent of cortical damage [4]. In children, kidneys with a pelvic diameter >20 mm are considered to be at risk for deterioration and require intervention [5]. Measurement of the resistive index in the interlobar and arciform arteries of the kidney has been proposed for the diagnosis of urinary obstruction but this is rarely used in the evaluation of the incontinent patient [6]. Whenever hydronephrosis is diagnosed on USS, other imaging modalities are often used to evaluate renal function, the degree of obstruction or vesico-ureteral reflux. USS is an ideal technique to follow the degree of hydronephrosis over time or the response to treatment.

b) Intravenous Urography

IVU is the original radiographic examination of the upper urinary tract which allows evaluation of upper urinary tract anatomy and function. Successful examination is dependent upon adequate renal capacity to concentrate urine and the examination is currently contraindicate when creatinine levels exceed 2.0 mg/dL [7] because of the possible increased toxicity of the contrast medium and the lack of concentration of the contrast agent by the impaired kidneys. While the former can be taken care of by adequate hydration of the patient, the poor concentration

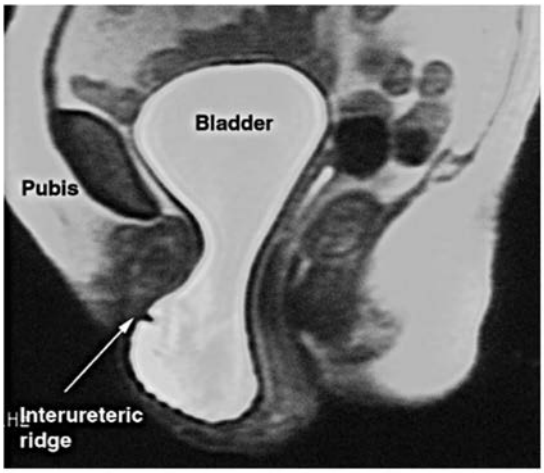


Figure B 2-a: MRI: complete urogenital prolapse

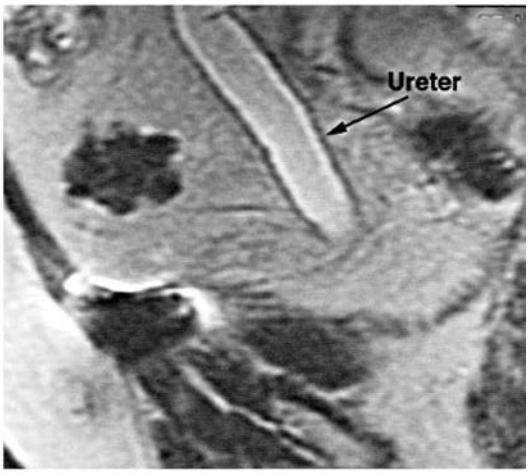


Figure B 2-b: MRI: ureteral dilation

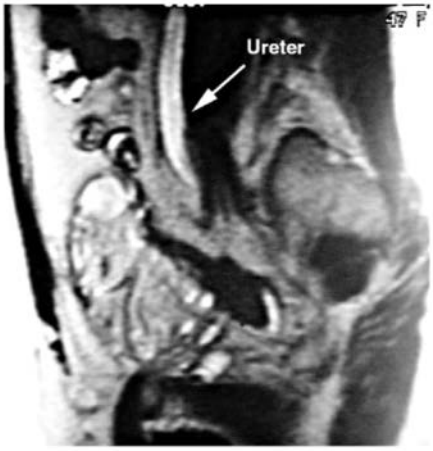


Figure B 2-c: MRI: ureteral dilation

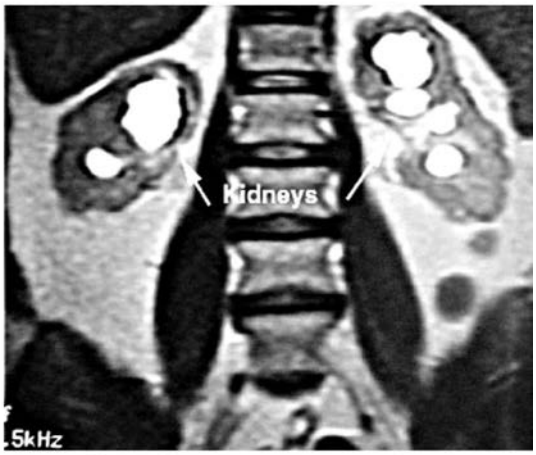


Figure B 2-d: MRI bilateral hydronephrosis

capacity of an impaired kidney limits the possibility to delineate the collecting system. A number of different conditions such as renal dysfunction, obstruction, congenital anomalies, fistula, stones and tumours may be detected. IVU is the appropriate first study in cases of extraurethral incontinence. When ectopic ureter is suspected (although this condition can also be responsible for urethral incontinence), delayed films and tomography are important because the renal unit or moiety associated with an ectopic ureter is often poorly functioning. In fact, IVU is sometimes unable to detect a small, malfunctioning moiety associated with a duplication and ectopic ureter or a poorly functioning or abnormally located kidney with a single ectopic system [8-10]. In such cases where the diagnosis of ectopia is still suspected after IVU, another imaging modality such as CT, MRI (**Figure B 3 a,b**) or isotope scanning should be considered [11-13]. IVU is the appropriate first imaging study when uretero-vaginal fistula is suspected, usually after pelvic surgery. Typically, one sees ureteropyelocaliectasis proximal to the level of the fistula. This finding has been reported in 84-92% of cases [14, 15]. Sometimes extravasation can be seen. Confirmation of the presence of the fistula, its size and exact location is often obtained with retrograde ureteropyelography.

c) Computerised tomography

High quality information of the upper urinary tract anatomy can be obtained using multidetector helical CT scans and 3D reconstruction software. Differently from IVU which only acquires images in the antero-posterior or oblique CT acquires images in the axial plane. Pictures can then be reconstructed in 2D along any plane or in 3D whenever required. CT scan can be used irrespective of renal function when no iodinated contrast medium is used. Whenever hydronephrosis is present, urine can be used to delineate the collecting system reducing the need for contrast agents. In general, intravenous contrast medium is required to highlight specific anatomic characteristics. CT scan is often used after a first line evaluation with USS and it has replaced IVU almost entirely. Sev-

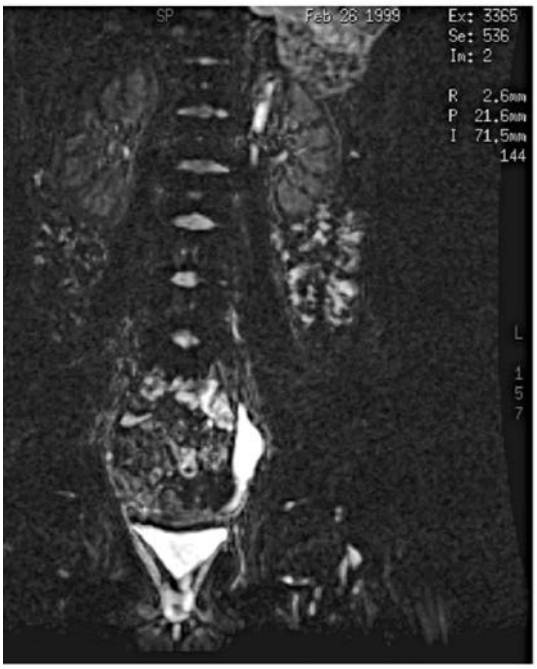


Figure B 3-a : MRI diagnosis of ureteral ectopia

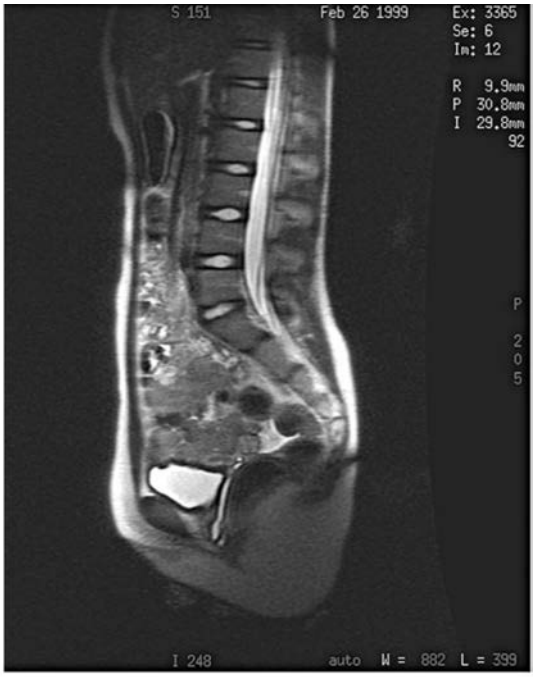


Figure B 3-b: MRI diagnosis of ureteral ectopia:

eral authors have reported the use of CT scan to detect ectopic ureter, in cases where the diagnosis is suspected, despite a normal IVU and ultrasound [16]. In these cases the small size and poor function of the ectopic moiety make diagnosis difficult by IVU.

d) Magnetic resonance imaging

MRI shares some of the advantages of CT over IVU in the evaluation of the upper urinary tracts. Furthermore acquisition can be performed along any plane and pictures can then be presented in a 2D or 3D fashion. The paramagnetic contrast medium is free of allergic reaction risk although its use in the upper urinary tract remains dependent upon renal function and concerns about its nephrotoxicity have been recently raised [17]. The development of the uro-MRI technique has gained an increasing role for the technology in the evaluation of hydronephrosis and urinary tract anomalies as an alternative to IVU. The use of MRI in the diagnosis of ectopic ureter has recently been described [18-20].

e) Isotopes

Isotopes are used primarily to examine morphological and functional characteristics of the upper urinary tract. Isotope scanning can be used to identify the location of a small kidney which is otherwise difficult to image with radiological techniques.

Renography is used to examine the differential function of the two kidneys, to identify disorders of urine transit and to quantify obstruction of the upper urinary tract. There are many physiological factors and technical pitfalls that can influence the outcome including the choice of radionucleotide, timing of diuretic injection, state of hydration and diuresis, fullness or back pressure from the bladder, variable renal function and compliance of the collecting system [21, 22]. Diuresis renography with bladder drainage is recommended when obstructive uropathy is suspected [23]. Renal scintigraphy may be useful in the evaluation of ectopic ureters associated with hypoplastic kidneys [24].

f) Conclusions

Imaging of the UUT is rarely required in LUTD unless the condition originates from a malformation, a traumatic or a iatrogenic problem of the UUT. More rarely a condition of the LUT may endanger renal function, the preservation of which is required to guarantee a normal life expectancy in patients with LUTD.

g) Consensus Statement

o Imaging of the UUT is NOT indicated in the evaluation of non-neurogenic stress, urgency or mixed UI. [**Level of Evidence 3, Grade of Recommendation C**]

o Imaging of the UUT is indicated in cases of:

a) neurogenic UI with high risk of renal damage (due to high detrusor pressure, e.g. myelodysplasia, spinal cord injury, and low compliance bladders) [**Level of Evidence 3, Grade of Recommendation C**]

b) chronic retention with UI [**Level of Evidence 3, Grade of Recommendation C**]

c) untreated severe POP [**Level of Evidence 3, Grade of Recommendation C**]

d) suspicion of extra-urethral UI by upper tract anomaly [**Level of Evidence 3, Grade of Recommendation C**]

o The choice of the imaging techniques and their sequence depend on the clinical question and their availability. The least invasive techniques should be preferred and should precede the more invasive, also taking into consideration cost effectiveness. [**Level of Evidence 3, Grade of Recommendation C**]

h) Suggested Research Areas

o Prevalence of upper tract deterioration in various UI populations

o Natural history of upper tract damage

o Relation between upper tract dilation, renal damage and bladder function

II. IMAGING OF THE LOWER URINARY TRACT

The use of imaging of the LUT in patients with UI dates back 40 years, particularly in female patients. The techniques have changed, over the decades from static to dynamic imaging, from qualitative to quantitative information. Although some of the techniques are now more than 50 years old their clinical value remains at best, unclear.

1. X-RAY IMAGING

Voiding cystourethrogram (VUCG) was the mainstay of x-ray imaging of the LUT but it has been replaced almost entirely by USS because of its ease of use, low cost and availability. While CT has not gained acceptance because of the exposure of ionising radiations, MRI took the lead as the most promising imaging modality because it offered a comprehensive view of the pelvis and enabled visualisation of the position of visceral organ in relation to bony reference points. 3- and 4D USS recently offered volume acquisition with limitations in terms of the volume that can be acquired. Continuous technical development in imaging technology and techniques made this research area particularly interesting.

In males the purpose of voiding cystourethrography has been mainly to locate infravesical obstruction separating the bladder neck from benign prostatic obstruction although it may play a role in the management of post-prostatectomy incontinence [1]. In children the diagnosis and classification of reflux and diagnosis of posterior urethral valves have been the primary goals [2]. The severity of the vesicoureteric reflux on one side determines the development of contralateral reflux and indicates a poorer resolution rate for reflux [3].

Positive-pressure urethrography has been used for the diagnosis of female urethral diverticula, it was shown to be more sensitive than voiding cystourethrography [4-6] although MRI is the gold standard for the diagnosis of diverticula and planning surgical repair [7, 8].

The rationale for imaging studies of the lower urinary tract in this field derives from the hypothesis that stress UI is caused by urethral hypermobility. This was the theoretical base of the classification of UI published by Green in 1968 and then modified by Blaivas and Olsson in 1998 [9, 10]. Investigation into cohorts of continent and incontinent patients failed to provide evidence to support the hypothesis and imaging techniques aiming at measuring bladder neck displacement during straining have been abandoned. The same applies to outcome research in urinary incontinence where surgery that limits bladder neck displacement does not necessarily lead to cure of the condition. A renewed interest derived from the availability of USS which took imaging out of the radiology suites and moved it into the urological and gynaecological outpatient clinics opening new opportunities for clinical research in this field. The possibility of imaging what was usually perceived during physical examination such as bladder neck mobility or POP increased the usefulness of USS. Research in the field of MRI first looked into the possibility of fast dynamic acquisition to image the displacement of visceral organs during effort to better qualify POP and then moved into morphological imaging of the pelvic organs muscular support to investigate the physiopathology of genital prolapse.

a) Female Cystourethrography

X-ray imaging of the urinary bladder and urethra has been used to assess the female urinary tract in women suffering UI to evaluate urethral/bladder neck hypermobility and to assess associated conditions such as urethral obstruction, vesico-urethral reflux, diverticula, fistula, stones and tumours. In males the purpose of voiding cystourethrography has been mainly to locate infravesical obstruction [1, 11].

The diagnosis and classification of reflux and diagnosis of posterior urethral valves in children have been the primary goals [2]. In a study comparing cystourethrography with direct radionuclide voiding cystography and voiding urosonography with contrast medium, voiding sonography and direct radionuclide voiding cystography were shown to be the most sensitive [12].

1. Background

History and methodology of cystourethrography in females had been reviewed by Olesen [6]. The technique is now over 70 years old. Voiding cys-

tourethrography with lateral projection was first done by Mikulicz-Radecki in 1931 [13]. The use of a metallic bead chain to identify the urethra was introduced by Stevens and Smith in 1937, and in 1956 Ardran, Simmons and Stewart reported on a cinematographic technique with contrast media also in the vagina and rectum [14, 15]. In an attempt to combine qualitative and quantitative information regarding the function of the lower urinary tract, the combined used of fluoroscopy and pressure-flow recordings was proposed during the nineteen sixties and seventies [16-20].

2. Methodology (projection, positioning and exposures)

Bladder neck displacement is best viewed and quantified in true lateral projection although image quality is sometimes poor because of the increased body mass and the overlap of bony structures with the bladder neck area. Consequently, oblique projections are sometimes used notwithstanding the lack of quantitative information. Achieving a quasi-physiological voiding in a radiology suite is difficult because of the inevitable impact of the environment. The use of a sitting position is recommended for micturition studies as voiding while standing or lying will increase the embarrassment and therefore many impair the quality of the examination [13]. Especially in patients with large body mass index, imaging of female urethra in a true lateral projection is difficult, it necessitates high radiation doses as the central x-ray beam must penetrate the trocanteric regions and further because the urethrovesical junction is sometimes overshadowed by the lateral parts of the bladder. A significant improvement in this area has been brought about by digital imaging which allows the subtraction of the bony structures [**Figure B 4**]. The position and mobility of the urethrovesical junction as well as urine leakage are supposed to be influenced by the filling volume as has been demonstrated on ultrasonography and leak point pressure measurements [21, 22]. However, in VCUG the bladder is filled to capacity. Addition of a urethral bead chain or catheter and vaginal contrast to improve the visualisation of the urethra, bladder neck and trigone has been abandoned. Contrast in the rectum is not necessary for urinary incontinence purposes. Exposures at rest should be supplemented with provocative manoeuvres to test bladder neck mobility by contracting and relaxing the pelvic floor (e.g.: coughing, straining, and squeezing). Whenever possible, pictures while the patient is voiding should be obtained. It is important to consider that coughing and straining result in a different effect on the pelvic floor. Straining might be associated with relaxation or contraction of the pelvic floor, and the imaging can change accordingly.

During coughing there is a reflex contraction of the pelvic floor, but coughs are of short duration and difficult to catch on spot films. Bladder suspension defects were diagnosed at rest in 49% of 420 examinations, while coughing and micturition disclosed a further number of 20% and 4% respectively [13]. Squeezing can demonstrate pelvic floor awareness and contraction [23].

3. Combined imaging and urodynamics

Videourodynamics has been by some regarded as the “gold standard” in the evaluation of LUTD [23]. Reproducibility of the combined examination has not been assessed and further the radiation dose has to be considered [15, 20, 24-26]. One study has attempted to compare videourodynamics with saline cystometry [23]. Independent observers carried out the two procedures with 75 women having the saline cystometry first and a further 75 women had videourodynamics first. The degree of bladder descent noted on screening was greater than on clinical ex-

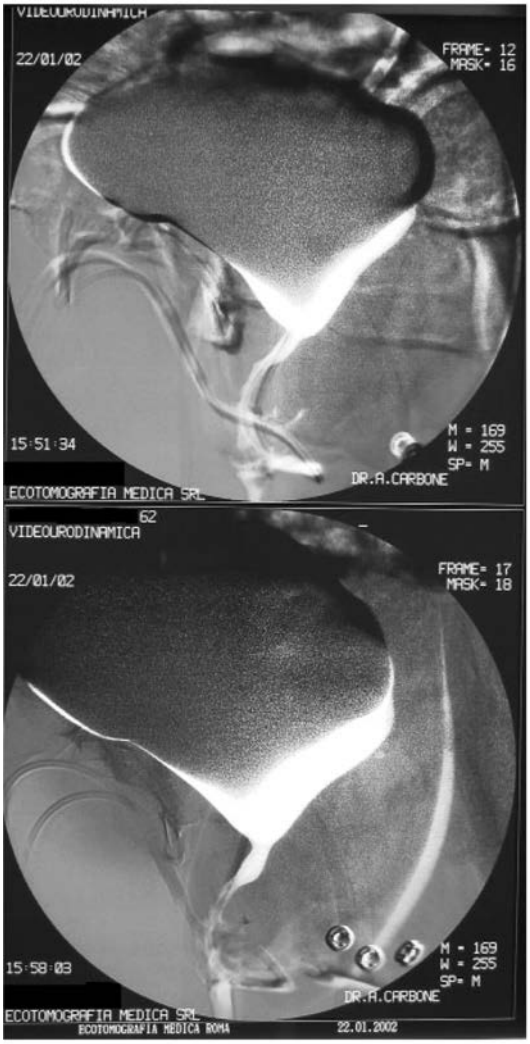


Figure B 4:VCUG with digital substraction (courtesy of Dr Carbone, Rome, Italy)

amination. Nineteen women had trabeculation and a further 11 women had bladder or urethral diverticula, urethral stenosis and vesicoureteric reflux [1, 11, 14]. Only seven of the eleven women could have been predicted by a selective imaging policy based on history alone which would image 43% of the 150 women. This suggests that a selective policy of screening will unnecessarily expose patients to radiation while not using the optimal technique for investigation for all patients who need the test. Nevertheless simultaneous videomonitoring along with tracings of pressure and urine flow rate are important to ensure that the exposures are made at appropriate moments so that the radiographs can be representative of the various functional states [13, 18, 27, 28].

Patients with Parkinson's disease and multiple system atrophy are best evaluated by videourodynamics and sphincter motor unit potential analyses to identify characteristic features of these conditions including: external sphincter denervation, neurogenic sphincter motor unit potentials, open bladder neck at rest and detrusor-external sphincter dyssinergia [29]. Neurogenic patients show severe bladder trabeculation with diverticula and pseudodiverticula, pelviureteric reflux, widening bladder neck and proximal urethra. Narrowing at the level of the membranous urethra can suggest, the presence of neurogenic dysfunction of the lower urinary tract (occult spinal dysraphism, non-neurogenic neurogenic bladder [also known as the Hinman syndrome]) even in the absence of neurogenic symptoms and signs [30-32]. Urodynamic parameters in children do not discriminate between those with or without vesicoureteral reflux thus videourodynamics have been considered essential. Additionally, children with non-neurogenic voiding dysfunction are found to have a number of abnormalities with videourodynamics [33, 34]. Indications for videourodynamics include previous continence and vaginal surgery, neurological disorders and suspicion of urethral diverticula.

4. Normal and defective bladder support

The whole issue about the clinical value of VCUG is about the role of defective bladder support in the pathophysiology of SUI in female patients and the relation between the surgical correction of such a defect and cure. The concept of urethral hypermobility was inherent to the classification of SUI and the concept that impaired transmission of abdominal pressure to female urethra could be responsible for the observed leakage. Little remains regarding the concept of urethral hypermobility in a modern view of female SUI and this contributed to the decreasing use of VCUG in the evaluation of a standard female patient.

The normal resting bladder has a smooth surface although bladder trabeculation is often seen in elderly women and not necessarily related to any pathological condition. The internal urethral orifice is located just above a horizontal line through the lowermost part of the symphysis in a coronal projection. The urethra is straight and runs anteriorly and caudally toward the external meatus.

On coughing and straining, relaxation of the pelvic floor results in downward movement of the bladder neck, which can be associated with a backward movement of the bladder neck resulting in a change in urethral axis. Squeezing (and sometimes also straining) results in contraction of the pelvic floor muscle with a cranial movement of the bladder neck **Figure B 5a**. During voiding (**Figure B 5b**) the bladder base is usually lowered about 1 cm, the angle between the urethra and the trigone is straightened, making a funnelled appearance of the proximal urethra and the bladder base, the bladder contour is rounded and a fine sawtooth irregularity of the mucosa becomes visible above the trigone. Angles and distances between the urethra, bladder base and symphysis pubis have been assessed radiologically. The following parameters have been assessed for reliability:

1. The posterior urethrovesical angle (PUV) is defined by lines along the posterior urethra and the trigone [35]. Cut off values were usually 115° or more [36, 37];
2. The urethral inclination is between the proximal urethral axis and the vertical plane, which is a plane outside the patient and, therefore, the angle

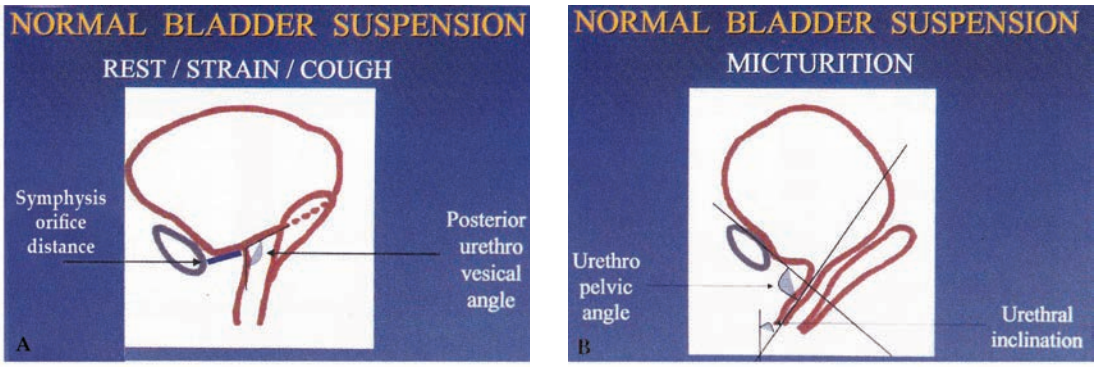


Figure B5: Female Cysto-urethrography 1a: normal appearance on couching, straining and squeezing b: normal appearance on voiding

also varies with pelvic inclination. In Green type I and type II descent the angle is less or more than 45° respectively [37];

3. The urethropelvic (UP) angle is measured during voiding as the anterior angle between a line through the middle of the internal urethral orifice and the urethral knee and a line through the posterior surface of the symphysis through the lowermost part of the obturator foramen closest to the film. In normal subjects the mean UP is about 95° and the cut off point for bladder descent are values below 70° [13];
4. Symphysis orifice (SO) distance is measured at rest as the distance on a horizontal line from the symphysis to the internal urethral orifice. Normal values are 31 ± 6 mm (mean ± SD) and values less than 20 mm are the cut off points for descent [13];
5. The urethral axis at rest (UAR) and during straining (UAS) (**Figure B 6**) Funnelling of the proximal urethra and flatness of the bladder base (both anterior and posterior to the internal urethral orifice) and the most dependent portion of the bladder base (the urethrovesical junction or a point posterior to that) are important qualitative parameters estimated on straining films [36].

Anterior bladder suspension defects or bladder base insufficiency (BBI) (**Figure B 7**) is defined as SO < 20 mm with a normally positioned vagina

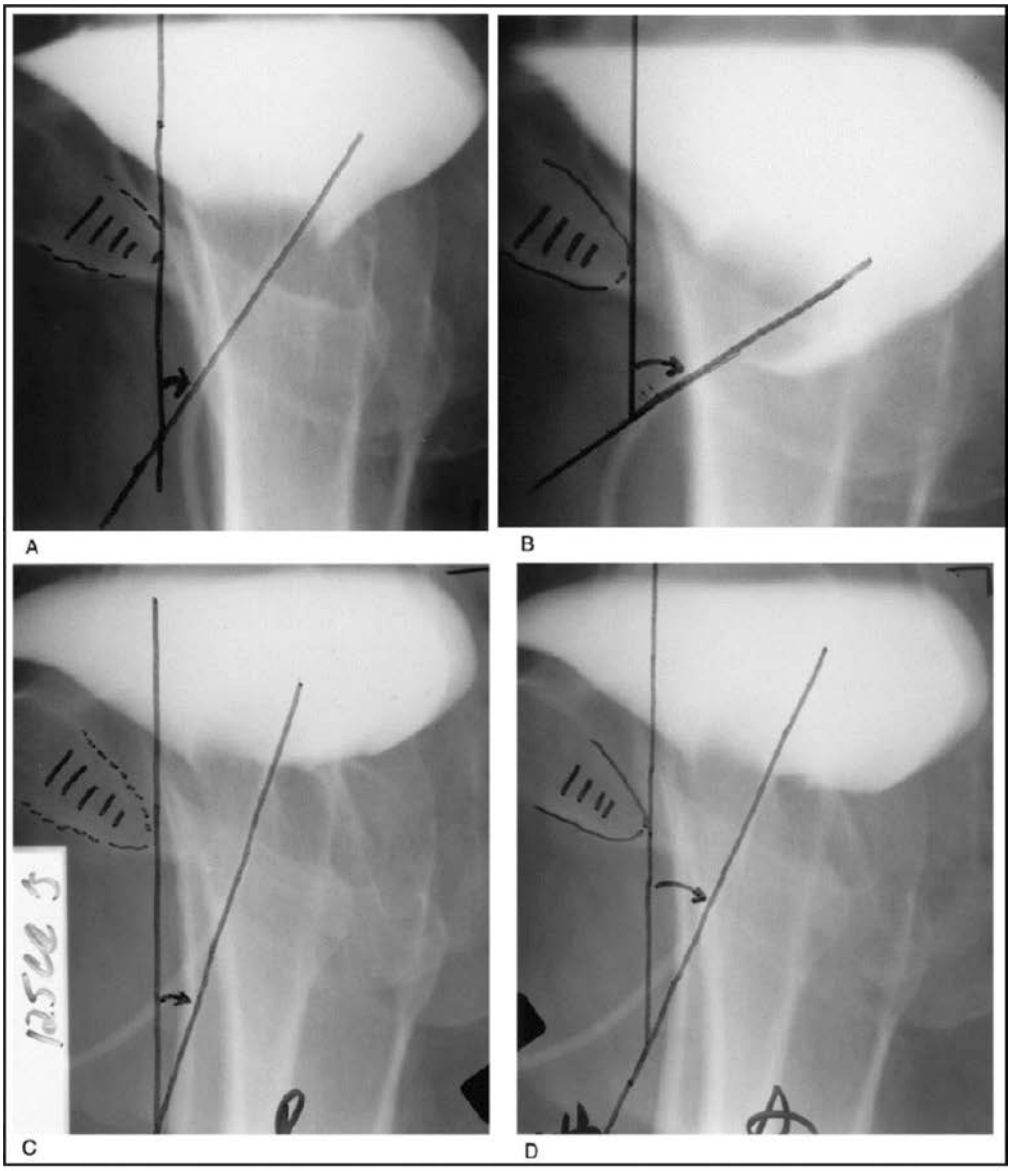


Figure B 6:Example of standing, lateral views on VCUG with 125 mL of contrast within the bladder. (A) Preoperative UAR. (B) Preoperative UAS. (C) Postoperative UAR. (D) Postoperative UAS. The urethral angle is calculated from a reference line drawn through the inferior portion of the pubic symphysis.

at rest, during coughing or micturition and/or funnelling of the bladder base at rest or with coughing. BBI can be graded 1-3, which corresponds to Green's type I descent [13, 38]. The supportive defect is supposed to be in the fascial and ligamentous system and their abnormal detachments (eg., paravaginal defects).

Posterior bladder suspension defects (**Figure B 8** are defined as a posterior-inferior bladder displacement and a UP of less than 70° [13]. It corresponds to Gruen's type II [39]. Sometimes (**Figure B 9**) only the trigone and posterior part of the bladder is involved. The supportive defect is supposed to be in the muscular pelvic floor, that is, the pubo-vesical part of the pubococcygeus muscle or in paravaginal detachment.

Interestingly, when UAR and UAS were examined in a group of 76 continent women and correlated with age, a perfect linear regression was noted between UAR and age (R2= 0.28). Patients with stress urinary incontinence were found to have an average UAR value of 25° with a mean UAS of 43° leading to a threshold value of hypermobility of about 20°. When standing cystourethrograms were repeated 3 to 6 months after surgery for SUI, UAR and UAS values were found to be close to normal suggesting a relation between the correction of the defective bladder support and cure [39]. A more structured definition of cystocele (ranked by height in centimetres) was also obtained, adding to the emerging data that the reliability of the pelvic organ prolapse quantification (POP-Q) system increases when measurements are performed in a more upright position [39].

5. Reproducibility

The observer variation has been evaluated in four university uro-gynecological units (**Table 1**) [23, 36, 40, 41]. The inter-observer agreement was 43-79% and the intra-observer agreement was 53-99%. These figures are in the same range as has been found for other diagnostic tests [42].

6. Accuracy for the diagnosis of SUI and post-operative results

Evaluation of accuracy is the mainstay in the evaluation of a diagnostic technique. One has to consider that sensitivity and specificity depend on intrinsic factors such as reproducibility (as measured by

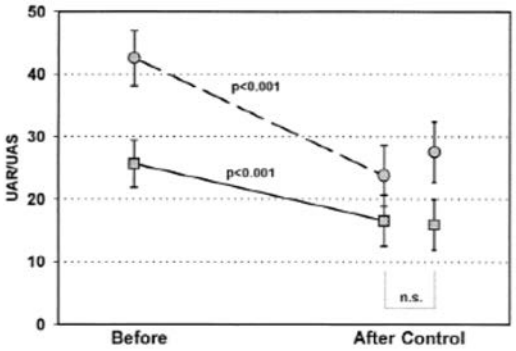


Figure B 9:Mean 6 95% confidence interval for UAR (squares) and UAS (circles) before and after surgical correction compared with age-matched controls. Difference from "before" to "after" was significant for both surgical groups; difference between "after" and "control" was not significant.

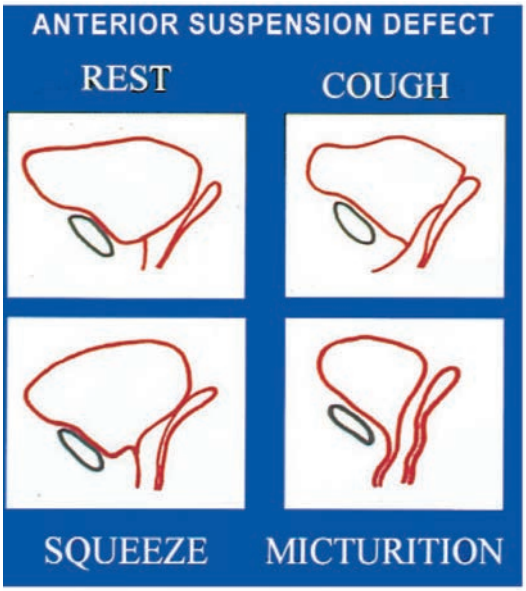


Figure B 7: Female Cysto-urethrography. Anterior bladder suspension defect

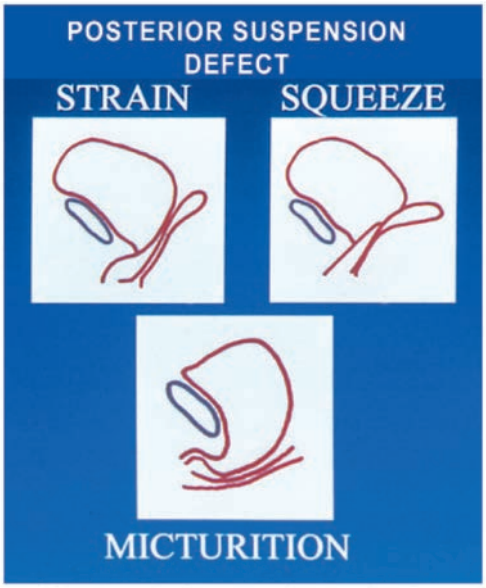


Figure B 8: Female Cysto-urethrography. Posterior bladder suspension defect

Table 1: Inter- and intra-observer variation (agreement) on cystourethrography in females with urinary incontinence.

Type of examination, patients and observers	Inter-observer variation	Intra-observer variation
Bead-chain [1] stress & urgency incontinence n°92 3 observers on 5 landmarks	45.8-80.7 %	
VCCU [2] stress incontinence n° 52 1 observer on type of descent	79% 95% c.l. 65-89	
VCCU [3] stress incontinence n° 29 2 observers on type of descent	70% 95% c.l. 75-89	53% 95% c.l. 27-78
VCCU [4] n° 93 stress & urgency incontinence 6 observers on type of descent	43-60% kappa 20-39%	72-99% kappa 57-98%
VCUG [5] Stress incontinence n° 11 2 observers on urethral angle shift from rest to straining	r = 0.83 (p=0.001) for UAR r = 0.82 (p=0.002) for UAS	

intraobserver and interobserver variation) and extrinsic ones such as the characteristic of the patient cohort used to assess accuracy.

The accuracy of the previously mentioned radiological criteria have been measured by comparing imaging data with the 'so called' index-test which in this case was a clinical diagnosis of urodynamic stress incontinence and expressed as specificity and sensitivity or as predictive values. Unfortunately the diagnosis of SUI is controversial and might be based on subjective criteria, urodynamic tests, or measurement of leakage. Even radiological criteria have been included in the diagnosis.

Reproducibility (e.g. test-re-test agreement) has not been measured, but intra- and inter-observer variation has been calculated and also adjusted for expected chance agreement (kappa coefficient). The predictive values and the kappa coefficient are supposed to depend on the prevalence, and therefore, comparison between different materials are difficult [42].

No consensus has been reached in the peer-review literature as to the lack of discriminant value of VCUG between SUI and continence, the majority of published papers are consistently negative although new promising data have been published [37, 39, 43-45]. The specificity of 5 radiological parameters on static bead chain VCUG was 44-76% and the sensitivity 53-100% [45, 46]. Neither was the degree of SUI correlated with the type or degree of suspension defects [23, 40, 47]. The positive and negative predictive values for a bladder suspension defect were 0.70 (95% C.I.: 0.62-0.78) and 0.52 (95% C.I. 0.41-0.63) respectively on voiding colpo-cystourethrography [38, 48]. In a later publication on 159 women, positive and negative predictive values of 0.56 and 0.74 were obtained [45]. Evaluation of the urethral angle at rest and during stress in controls and in patients with SUI and various grades of anterior vaginal prolapse show a significant relationship between UAR and aging (from 2.4° ± 14.9° in the third decade to 29° ± 9.2° in the 9th decade; r2= 0.28). In patients with SUI, UAR and UAS decreased from 25.7° ± 13.6 ° and 42.6° ± 15.9° to 16.6° ± 14.7° and 23.8° ± 17.5°, respectively; the observed changes were found to be statistically significant. A similarly significant difference was found in patients with moderate to grade 3 cystocele and urethral hypermobility (at least 5 cm descent of the bladder base below the inferior ramus of the pubic symphysis on the lateral view of a standing VUCG): UAR and UAS decreased from 48.1° ± 16.5 ° and 64.4° ± 16.8° to 22.3° ± 26.9° and 29.8° ± 22.8°, respectively.

Comparison of a randomly selected control cohort (aged-matched) with patients suffering SUI showed a significant difference of UAR and UAS at diagnosis

while similar values were found after surgery (**Figure B 10**). This was similar to patients with grade 3 cystocele in whom both UAR and UAS were significantly different from controls at baseline while showed similar values in the postoperative follow-up.

Measurement of the cystocele height (LATH), obtained as the distance between the inferior border of the pubic symphysis and the inferior edge of the cystocele in controls and patients with mild and severe cystocele showed a significant difference between the two cohorts (16.63 ± 10.9 versus 27.4 ± 12.3 mm versus 73.4 ± 15.6 mm, respectively). Following formal cystocele repair, a significant change of LATH values was found in patient with mild and severe cystocele (from 27.4 ± 12.3 mm to 13.9 ± 18.0 mm and from 73.4 ± 15.6 mm to 25.4 ± 24.6 mm, respectively [p<0.001]).

These are the first data supporting the used of standing VCUG as an outcome measured, previous peer-review papers suggested the inability of its technique to distinguish postoperative failures from success [13, 23, 42, 44, 46, 49-52].

7. Comparison of cystourethrography and ultrasonography

The development of USS techniques for the evaluation of the lower urinary tract raised the question of the relationship between X-ray and USS imaging. Static bead chain cystourethrography has been compared with transrectal and perineal USS and voiding colpo-cystourethrography has been compared with perineal USS [46, 47, 53, 54]. The findings correlated well regarding bladder neck position and mobility, PUV, urethral inclination, SO distance and rotation angle.

Specificity, sensitivity and interobserver agreement were also comparable for the two methods. All the authors seem to prefer the sonographic modality because imaging can be performed at the same time as the physical examination. This has also been the case in men with neuromuscular dysfunction [11]. Simple and extensive funnelling is more easily imaged in upright patients during cystourethrography than in the supine position frequently used for ultrasound studies [30].

8. Comparison of cystourethrography and MRI

The introduction of MRI in the assessment of the LUT required adequate comparison of this technique with standard X-ray imaging. The comparison of cystourethrography and colpocystourethrography with dynamic MRI showed comparable data on bladder neck position and cystocele extension [55, 56]. Although there is an obvious concern about the fact that dynamic MRI

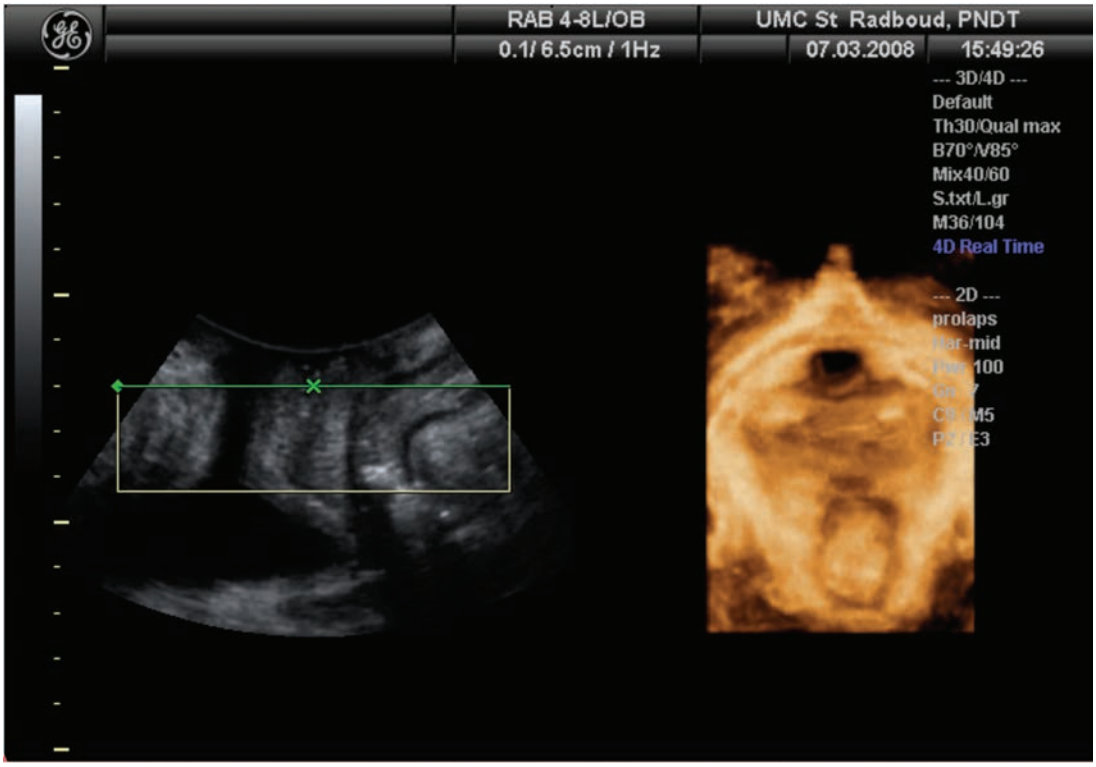


Figure B 10: Perineal midsagittal two-dimensional view and three-dimensional rendered image. Normal anatomy.

imaging is usually performed with the patient lying in a dorsal lithotomy position, comparison of standing and lying colpocystourethrography did not showed any significant difference [56].

9. Conclusions

VUCG does not have a major role in the evaluation of the standard female patient with UI confirmatory results on the clinical utility of measuring urethral angle and cystocele height in patients with UI and POP who are scheduled for surgery still missing. Defective bladder support can be diagnosed on VCUG with a reliability comparable with other diagnostic tests.

Dependent on local facilities the method might be considered if the choice of a surgical procedure is based on type and degree of supporting tissue deficiencies and possibly if new procedures are evaluated for the ability to restore this deficiency.

10. Consensus Statement

- o Cystourethrography is NOT indicated in primary uncomplicated stress, urge or mixed female urinary incontinence [Level of Evidence 3, Grade of Recommendation C].
- o Cystourethrography may be a reasonable option in the preoperative evaluation of complicated or recurrent female urinary incontinence [Level of Evidence 3, Grade of Recommendation C].

11. Suggested Research Areas

- o Variation of VCUG parameters in patients with SUI +/- ISD and prognostic value for surgical repair.
- o VCUG in re-do surgery for SUI

2. ULTRASONOGRAPHY

Ultrasonography has been used in the evaluation of urinary incontinence as early as 1980 [1]. Over the past three decades the quality of the ultrasound image and its processing has improved beyond what could have been imagined during the 70's. Various new developments, such as the use of contrast medium, colour Doppler, 360 degree transducers and three- and four dimensional imaging have been introduced and have led to more widespread use of ultrasonography in the evaluation of the lower urinary tract and pelvic floor disorders.

A number of studies have reported good correlations between ultrasonography and x-ray in the evaluation of urinary incontinence [2-9] Schenck et al 2011. In particular, the position of the bladder neck at rest and during Valsalva [10] manoeuvre has frequently been compared, and all authors agree on a good correlation. Some authors even found better accuracy for ultrasound [5], especially in obese women [2]. Ultrasonography is cheaper than X-ray imaging, it is often preferred by physicians because the imaging studies can be performed in their own office as part of the physical examination and it is also more acceptable to patients because of the lack of for radiation exposure. However ultrasound itself produces problems by needing to be in direct contact with the patient even during dynamic manoeuvres and the resolution is dependent on the frequency of the probe used. The higher the ultrasound frequency, the better the resolution but there is reduced penetration into the tissues.

a) Types Of Ultrasonography

Different imaging approaches have been used, such as abdominal, transvaginal, transrectal, perineal and transurethral. Synonyms for the perineal approach are transperineal, introital, labial or translabial access, all use a similar method and there does not appear to be a substantive difference between these terms, a common agreed term needs to be decided upon.

Abdominal ultrasonography is generally not considered to be helpful in pelvic floor and urethral imaging because of the acoustic shadow caused by the pubic bones particularly in the obese patient [1]. All approaches in ultrasound have a problem of distorting the tissue being imaged due to compression. With vaginal ultrasonography this risk is probably highest [11], although this has also been denied [12]. Most recent studies report on perineal ultrasonography that allows the visualisation of all three compartments in one image but again compression of the urethra may occur and imaging is impaired with vaginal prolapse or gas in the rectum. The development of three-dimensional ultrasonographic systems has brought increased accuracy to measuring volumes of irregular structures as well as reconstructed images from novel directions and allowing pelvic floor imaging. Three-dimensional ultrasonography was first described for the female urethra in 1999 [13]; the three-dimensional image can either be evaluated as a separate entity on the screen, or in combination with each of the two-dimensional planes from which it is derived (**Figure B 10**) (see figure in this document). These three two dimensional planes are at orthogonal to each other being the sagittal, coronal and axial planes. Three-dimensional images are built up as a rendered image of a self defined region of interest, major advantages over 2D imaging include the possibility of reviewing the acquired images from any investigator and the ability to analyse the acquired volume through any plane (similar to CT scans or MRI) (**Figure B11**). This means that the levator ani muscle can be easily visualised. However interest has focused on the absence of the pelvic floor being imaged and a defect being implied. Ultrasound produces images by being reflected by a tissue. These reflective surfaces produce images of great clarity and resolution which are independent

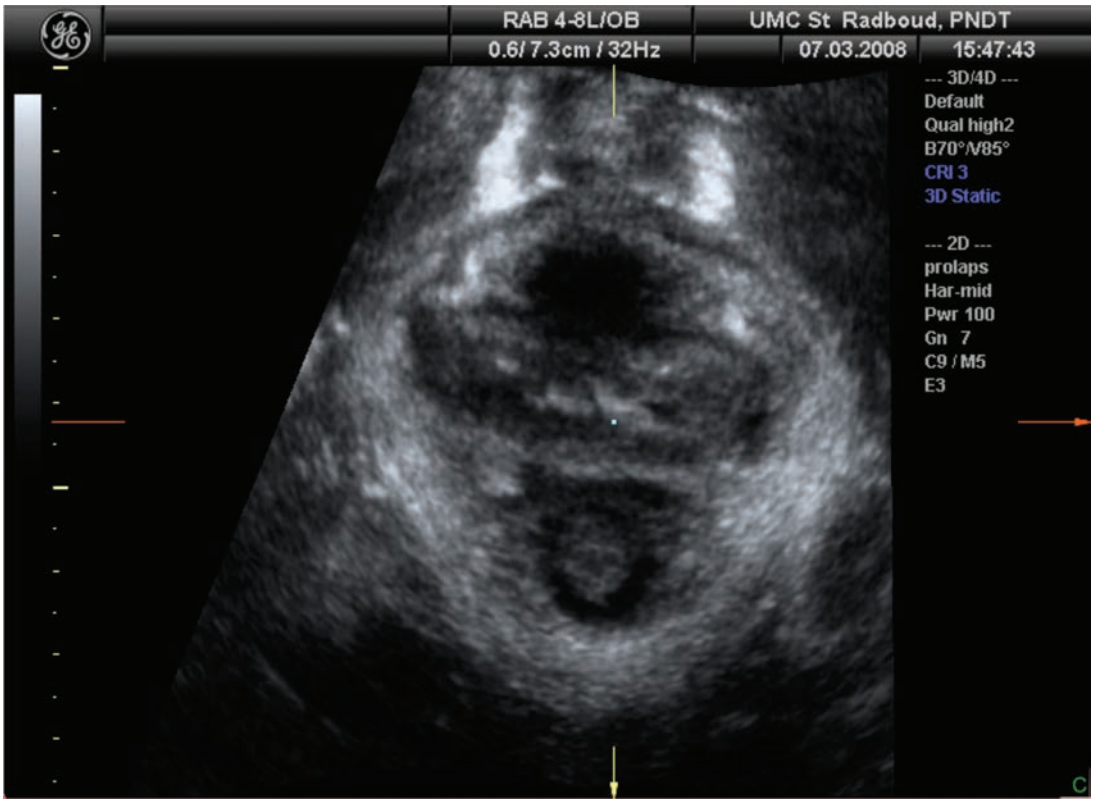


Figure B 11: Perineal midsagittal two-dimensional view. Normal anatomy of the levator ani muscle.

of the ultrasonic frequency. However once the tissue is perpendicular to the direction of travel of the ultrasound waves then axial resolution is effective, this limits the accuracy and the ability for tissues to be imaged. This highlights the importance of testing all ultrasound imaging modalities against a gold standard such as cadaveric dissection or comparing with another medium such as MRI or CT. Four-dimensional imaging involves a volume of tissue being continuously scanned, this inevitably involves a time delay and cannot be "real-time" but incorporates the enormous improvement in speed of three-dimensional systems over the last few years and it makes three-dimensional assessment of the dynamic relation of the pelvic organs on Valsalva manoeuvre and pelvic floor contraction possible.

b) Standardisation

No consensus has been reached as to the standardisation of image orientation. Some prefer orientation with cranial structures below **(Figure B 12a**) [14] whereas others prefer presentation of the cranial parts above (**Figure B 12b**) [15]. All authors agree that the symphysis pubis, and its inferior border in particular, is a well recognisable and fixed reference point. This point can be used in the evaluation of the various aspects of relevant structures at rest and during dynamic imaging. In general, ultrasonographic studies are performed in the supine position (**Figure B 13)**. Small differences between the supine and standing position of the patient have been documented, although these differences disappeared during a Valsalva manoeuvre [16]. Only a few studies have been performed in the standing position [17]. There is no clear consensus on the amount of bladder filling, some authors prefer significant bladder filling, others prefer a nearly empty bladder because an empty bladder seems to descend more on Valsalva manoeuvre compared with a full bladder [18, 19]. Attempts to standardise Valsalva manoeuvre, ideally with intra-abdominal pressure measurements, has not been widely accepted [12,20]. In one study [17], a peak flow meter has been used, where women were asked to "huff" maximally and to reach the same force during a number of "huffs". It has been shown that the mobility of the bladder neck differs between coughing and Valsalva manoeuvre [21]. Co-activation of the pelvic floor muscles during Valsalva manoeuvre has been documented and is one of the reasons for the lack of standardisation [21].

c) The Urethra And Bladder Neck

When collagen fibres and muscle fibres are located parallel to the ultrasound beam, the structure

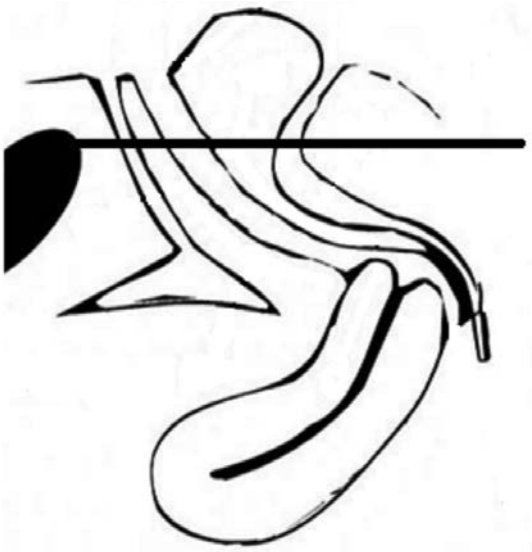


Figure B 12-a: Perineal midsagittal two-dimensional ultrasound view on three compartments and horizontal reference line according to Dietz.

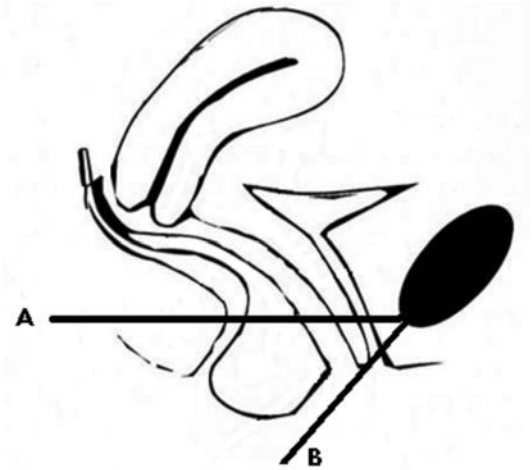


Figure B 12-b: Perineal midsagittal two-dimensional ultrasound view on three compartments and reference lines according to Tunn and Schaer.
A= horizontal reference line
B= central line of the symphysis as reference line for bladder neck descent

becomes hypoechoic. These same structures will become hyperechoic, however, when the fibres are located perpendicular to the beam. Ultrasonography may result in variable images of the urethra, since the echogeneity of the structures depends on the position of the transducer in relation to the urethra. This may produce confusing images, especially in the dynamic process of pelvic floor contraction and Valsalva manoeuvre. In the midsagittal plane on perineal ultrasonography, and with normal anatomical position of the urethra at rest, the internal sphincter and inner mucosal layer of the urethra will appear hypoechoic (**Figure B10**), these structures cannot be distinguished from each other on ultrasonography. In the midsagittal plane and with normal anatomical position of the urethra at rest, the striated external sphincter or rhabdosphincter will appear hyperechoic, and can hardly be distinguished from the surrounding structures. It will, however, be easily visible as a hyperechoic circular structure in the axial plane as seen on three-dimensional ultrasonography [22,23]. The rhabdosphincter has been found to be thinner dorsally [13], and both ventrally and dorsally [24] by various authors and more difficult to distinguish from the internal sphincter ventrally and dorsally compared with laterally [25]. These differences may be due to the approach used to image the structures as well as types of probes applied but this has not been addressed in any study to date.

With the use of ultrasonography, thickness and length of the urethral sphincter muscle can be measured and urethral volume calculated [15, 25, 26]. Intra-urethral ultrasonography has been used for this purpose although complete imaging of the lateral parts of the sphincter are difficult due to the higher frequencies emitted by these probes [27], others have used two- or three-dimensional ultrasonography of the urethra [13, 22, 24, 28,].

Comparison of transvaginal and transrectal approach showed a lower degree of urethral compression with the latter approach [24, 29]. Ultrasound measurement of the female urethra has been found to be reproducible [13, 22]. Sphincter volume may differ significantly when 2D or 3D imaging is used [22]. Urethral volumes, measured by 3D ultrasonography, were positively correlated with the actual volumes in cadavers [28]. A significant and positive correlation between rhabdosphincter volumes and symptoms and signs of urinary incontinence has been reported [13]; correlations with the urethral pressure profile

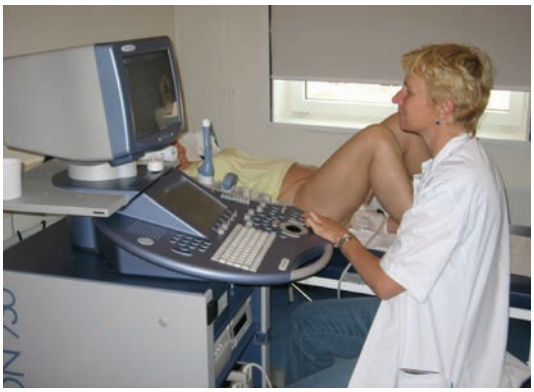


Figure B 13: Perineal ultrasound examination in the supine position.

(UPP) have been found [23, 25, 26, 28] but these data could not be reproduced [30]. Ultrasonography imaging during micturition has been explored with the aid of a remote control systems [31]. The use of intra-urethral ultrasonography with rotating probes (360°) has been proposed by various authors although no particular advantages over perineal US could be identified and incomplete imaging appears to be a problem due to the high ultrasound frequency emitted [27, 32-35].

The advantage of preoperative and intraoperative three-dimensional ultrasound scanning in women with urethral diverticula has been outlined by Yang et al. [36, 37].

d) Bladder Neck

The bladder neck and proximal urethra are easily visible on all types of ultrasonography without the need for catheterisation (**Figure B 10**). Measurements are usually taken at rest, during straining (Valsalva manoeuvre), and sometimes during a cough and squeeze. The position and movements are measured in relation to the lower margin of the symphysis pubis. The difference between rest and strain is referred to as the bladder neck descent (the distance between the bladder neck and a horizontal line through the lower end of the symphysis pubis) (**Figure B 14**). On Valsalva manoeuvre the bladder neck rotates in a posterior and inferior direction away from the symphysis pubis. The axis of the urethra in relation to a vertical or horizontal line can be measured in degrees and provide the degrees of urethral rotation or bladder neck mobility. Other parameters are the posterior urethrovesical angle and the anterior urethrovesical angle. A number of studies have validated the use of ultrasonography in the assessment of the position and mobility of the bladder neck and proximal urethra. Good results for this validity testing have been reported although the clinical value of such measurements is still elusive [4, 12, 38-40]. Normal values of bladder neck mobility have not been defined, since there is a great range in mobility even in young nulliparous women. In one study amongst nulliparous continent women of approximately 20 years of age, the bladder neck descent varied between 1mm and 40mm [41].

Others [38] found an average descent of 15 mm on Valsalva manoeuvre and 8 mm on a cough. Brandt et al. have found an average bladder neck descent of only 5 mm in 16 year old girls [42]. Racial differences have been demonstrated, with white women having greater bladder neck mobility compared with black women [43]. Genetic determination of bladder neck mobility has been suggested [44]. Numerous studies have found greater bladder neck mobility in parous compared with nulliparous women [12, 30, 45-47]. Bladder neck hypermobility, however defined, is considered to be related to stress urinary incontinence [15, 30]. A large number of studies have correlated ultrasonographic findings with urodynamic parameters [47-56]). Specificity and

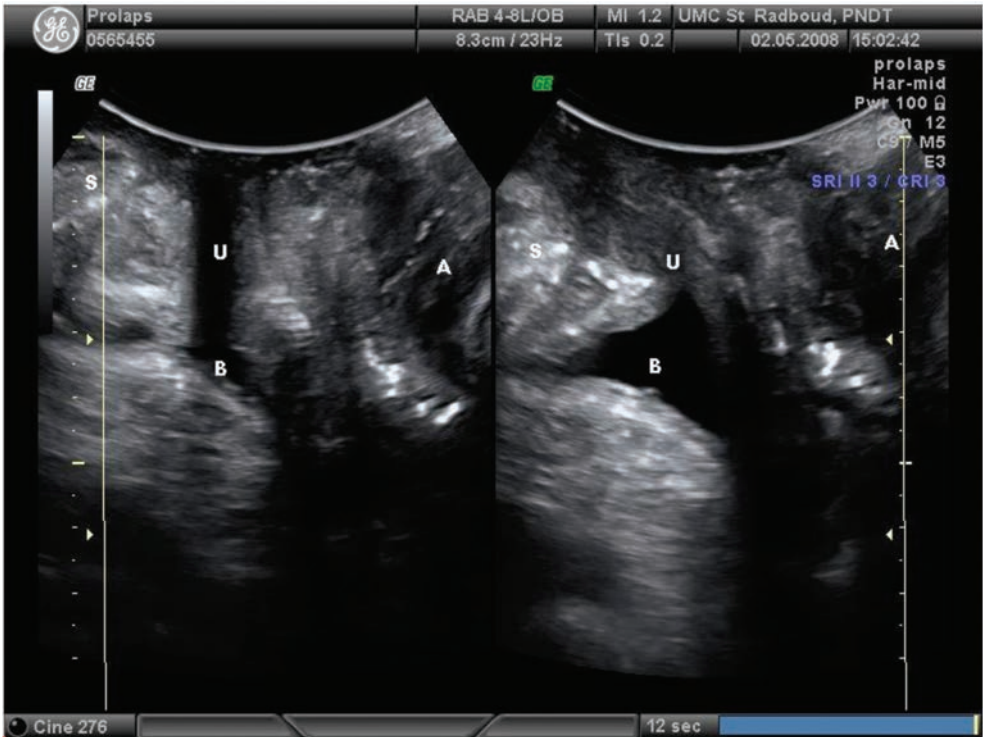


Figure B 14: Perineal midsagittal two-dimensional view at rest and on Valsalva manoeuvre. Bladder neck descent. (S= symphysis pubis; U= urethra; B= bladder; A= anal canal.)

sensitivity of ultrasonography for the diagnosis of stress incontinence were 83 and 68% in one study [50] and 92 and 96% in another study [57]. There is one study which has used ultrasound of the bladder neck movement on coughing and Valsalva as a marker with patients undergoing pelvic floor exercises. In this study the response to treatment was not associated with changes to the bladder neck mobility [58] underlining this is probably an associated phenomenon and not the cause for stress urinary incontinence.

One research group has specifically investigated simultaneous perineal ultrasonography and urethrometry. They were able to demonstrate that the variations in urethral pressure were caused by the activity of the urethral sphincter as well the pelvic floor muscles [59]. The contractions from the urethral sphincter during acute stress events such as coughing are thought to be due to fast contractions. Some studies have used ultrasonography in an attempt to optimise patient management, but despite the abundant literature on the use of ultrasonography in the investigation of women with urinary incontinence, disappointedly, a clinical advantage in terms of patient outcome has not been reported until now [60, 61].

Urethral funnelling can be observed on ultrasonography (**Figure B 15**) particularly with the use of contrast agents. It is a typical finding in women with stress urinary incontinence but can be seen in asymptomatic women as well [62-64]. In a study on stress incontinent women, funnelling was found to be present in nearly all women [63, 65]. Urinary incontinence can be demonstrated by the use of colour Doppler of the urethra [66, 67]. Colour Doppler has, furthermore, been used to visualise the periurethral vasculature in nulliparous women [68] and differences have been described between continent and incontinent women [69, 70] and before and after oestrogen supplementation in postmenopausal women. Doppler velocimetry has recently been used in a study on the vascularisation of the levator ani musculature and a correlation has been found between the absence of an end-diastolic flow and the presence of stress urinary incontinence [71]. The blood flow around the urethra and bladder has been studied with Doppler before and after insertion of tension free vaginal tape and the transobturator tape. The blood flow decreases only after insertion of the tensional free vaginal tape whereas the blood flow was unchanged after insertion of the transobturator tape which may relate to the direction of urethral compression [72].

e) Determination of the Post Void Residual Urine and Bladder Wall Thickness

Ultrasonography is the gold standard technique for measuring bladder volume and post-void residual urine [73-77]. Ultrasonographic data have been compared with residual volumes obtained by in and out catheterisation under ultrasound control and were found satisfactory. However, Khan et al. have

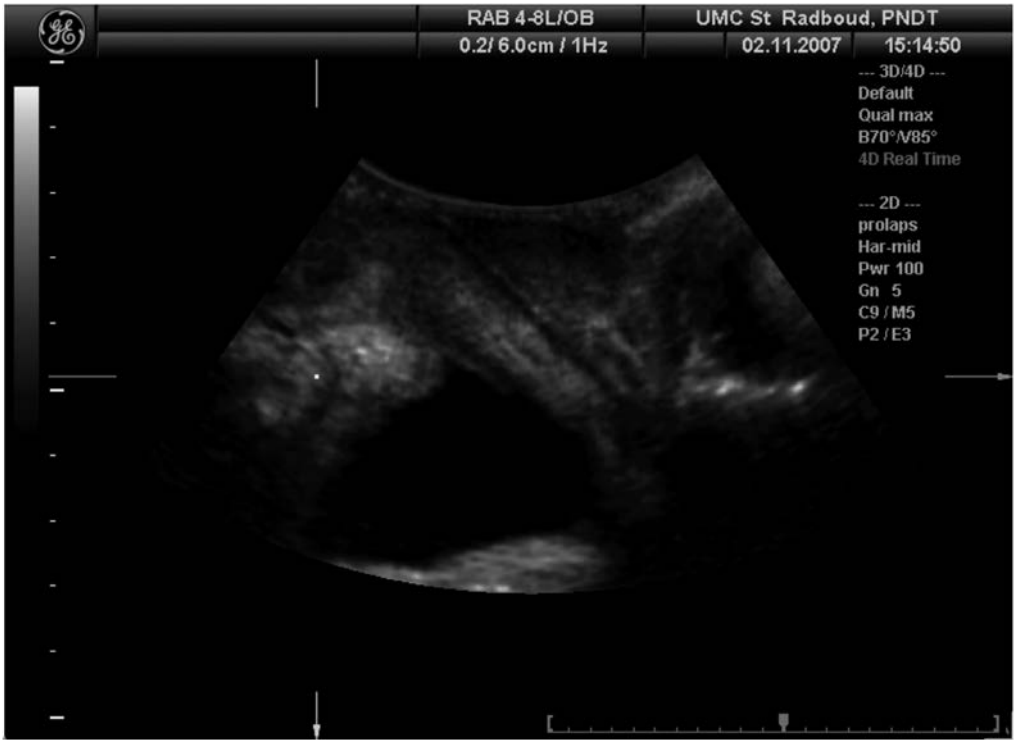


Figure B 15: Perineal midsagittal two-dimensional view. Urethral funnelling.

challenged the methodology of these studies and have found deficiencies in all reports on the topic [78]. A simple formula often used is [Height * Width* Depth](cm) * 0.7= Volume (ml) in which the factor 0.7 is the correction for the non circular shape of the bladder. Automated ultrasound systems for measuring bladder volume and post-void residual have been developed and have been found to be more accurate than standard ultrasound measurements, furthermore they can be used by health care providers with no training in ultrasound imaging[79]. These machines are widely used and are, in general, experienced as reliable enough for clinical use, however, in the case of ascites [80] or an ovarian cyst [81] for example, the estimated urinary volumes can be incorrect, and in post partum women.

Recently the normal values for the post void residual urinary volumes in asymptomatic women have been presented; in 60 year old women, the median residual volume was 19 ml, and 95% of women had a post void residual volume of less than 100 ml [74]. Ultrasound measurement of bladder wall thickness (BWT) and ultrasound estimated bladder weight (UEBW). Ultrasound measurement of BWT was first proposed as a non-invasive method for diagnosing infravesical obstruction in children [82]. More recently, BWT has been used to predict the outcome of children with primary nocturnal enuresis [82-84]. BWT has also been proposed as a risk factor for upper urinary tract deterioration in children with myelodysplasia [85]. Measurement of BWT was also proposed to diagnose bladder dysfunction (detrusor over activity and detrusor hypocontractility versus normal detrusor function) in children with urinary tract infection [86, 87]. Additional parameters such as the bladder wall thickness index (length x width x depth of the bladder at full bladder/average BWT) were proposed and a nomogram for the paediatric population provided [88].

In the adult population, higher BWT values have been measured in men than in women. Thickness may certainly differ depending the measurement technique; values of 3.3 +/- 1.1 mm and 3.0 +/- 1.0 mm, respectively were reported by Hackenberg and co-workers [89]. Oelke confirmed a significant difference between male and female detrusor thickness (1.4 versus 1.2 mm, respectively) [90]. A small increase of detrusor hypertrophy with age has been reported in both genders [89]. In men, measurement of bladder wall thickness proved to be the most sensitive parameter (outperforming uroflowmetry) to diagnose BOO in patients suffering LUTS [91, 92].

Transvaginal ultrasound was first proposed in 1994 for the measurement of BWT in women with bladder volume of less than 20 ml. A significant difference was shown in patients with DO and USI (6.7 +/- 0.6 versus 3.5 +/- 0.6 mm, respectively). Low intraobserver and interobserver variability were measured: 0.02 mm in both with a 95% confidence interval of -0.22 to 0.18 and -0.32 to 0.35 mm, respectively [93]. In 1996, Khullar and co-workers showed how ultrasound measurement of BWT is a sensitive method for diagnosing DO in symptomatic women without bladder outlet obstruction with 94% of women with BWT greater than 5 mm having involuntary detrusor contractions on videocystourethrography or ambulatory urodynamics [94]. In 2002, the same group showed no overlap in the 95% confidence intervals of BWT was shown in patients with DO and USI in women with storage symptoms, confirming the potential of this parameter for diagnosing DO [95]. In 2003, a study on ultrasound cystourethrography in women confirmed a significant association between age and intravesical pressure at maximum flow with BWT [96]. Methodological and technical issues in the ultrasound measurement of bladder wall thickness and weight remain open and constitute a major limitation for a more widespread use of these parameters. In 2005 Chalana and co-workers published an early report on automatic measurement of the ultrasound estimated bladder weight from three-dimensional ultrasound. An average value of 42 +/- 6 g was measured in healthy male subjects. A standard deviation of 4 g was seen among measurements performed in the same subject at different bladder volumes (200 to 400 ml) [97].

Further research in this area is certainly needed and further improvement in the accuracy of automated systems is eagerly awaited. Although data published in the peer review literature on this subject are quite consistent, two discordant papers were recently published from Australia. Blatt and co-worker showed uniform values of BWT measured using an abdominal approach among men and women with non-neurogenic voiding dysfunction suggesting this parameter cannot be used to diagnose storage or voiding dysfunction, this may reflect the thinning of the bladder wall with increasing bladder volume [98, 99, 100]. A retrospective study on women undergoing translabial ultrasonography suggests a significant association between BWT and DO although a low diagnostic accuracy was shown for the diagnosis of DO [101] which could be due to the fact that translabial ultrasound is unreliable [102].

The association between detrusor hypertrophy and bladder dysfunction (DO and BOO) is a well established fact in Urology. Ultrasound measurement of BWT and UEBW is an interesting alternative approach that may avoid invasive urodynamics in some patients. [103]. The reduction in bladder wall thickness has been found after the relief of bladder outlet obstruction [104]. The development of automated ultrasound systems for measuring UEBW is instrumental to foster further research in this area, particularly in the management of patients with LUTS [105] and in the evaluation of bladder response to pharmacological treatment [106].

f) Pelvic Floor Muscles

Ultrasonography can be used to assess pelvic floor muscles and their function. Contraction of the pelvic floor results in displacement of pelvic structures that can easily be imaged on ultrasound **(Figure B 16**) such as the cranial lift of the urethra in relation to the symphysis pubis during a maximal squeeze [16, 107] but also the dimensions of the genital hiatus or the posterior anorectal angle can serve this purpose [108]. Comparison with traditional measurements of pelvic floor muscle strength has been performed [107], and good correlations with palpation and perineometry have been found [109, 110]. Ultrasonography has been used to evaluate the effects of pelvic floor muscle training. A higher resting position of the bladder neck and a reduction in the rotational excursion of the urethra during Valsalva manoeuvre have been found with training [111]. Another research group has reported that the thickness of pelvic floor muscles increased after training [112]. A number of studies have assessed healthy female volunteers to establish normal values [41, 112], and one study has specifically compared elite athletes with normal volunteers [113]. Measurements of the levator ani muscle, with the use of two-dimensional imaging, has been recently described, and although direct comparisons to three dimensional ultrasonography are lacking, the acquired data were comparable [114]. However one study has compared three-dimensional ultrasound of the levator ani hiatus at rest and during contraction in a number of different groups of women with prolapse, urodynamic stress incontinence and asymptomatic women suggesting that these measurements are not sensitive enough to discriminate between different groups [115].

Almost half of women are unable to perform an optimal contraction of the pelvic floor muscles. Ultrasonography can be used in pelvic floor training to provide women with a visual feedback of their exercise [16, 116]. In one study, 57% of the women who were not able to perform a proper pelvic floor contraction, were able to do so with the help of visual biofeedback of ultrasonography to observe bladder neck movement [16]. This does not appear to produce better outcomes of changes with pelvic floor physiotherapy [117]. The contraction of the pelvic floor muscle just before and

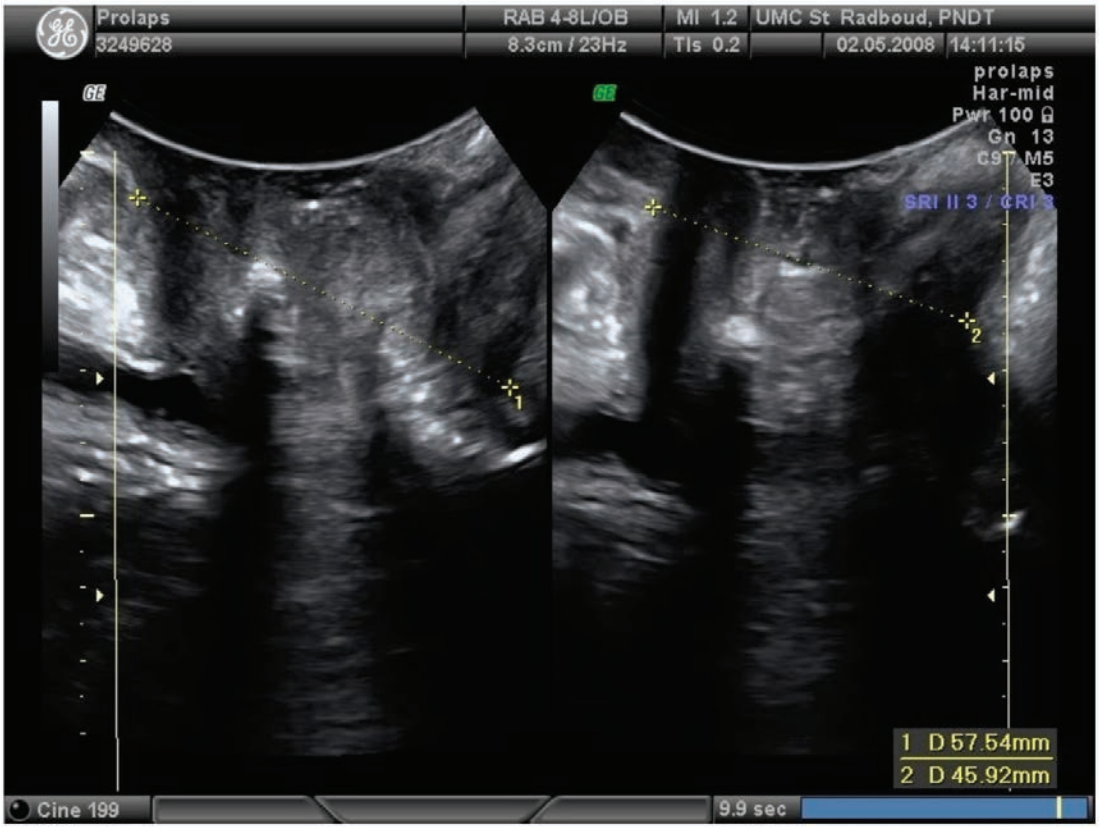


Figure B 16: Perineal midsagittal two-dimensional view at rest and on contraction. Levator contraction with ventro-cranial displacement of the urethra.
Measurement of minimal dimension of genital hiatus (from symphysis pubis to levator ani muscle)

during a cough, “the knack”, can also be visualized [118]. It has been demonstrated that the knack can significantly reduce urethral mobility during a cough.

Direct measurement of the pelvic floor muscles is possible with the use of two and three-dimensional perineal ultrasonography. An alternative technique makes use of a 360 degree rectal probe intravaginally (**Figure 17**) [114]. Most studies, however, have used three-dimensional perineal ultrasonography for this purpose [17, 108, 113, 119, 120]. The thickness of the muscles as well as the hiatal area can be measured. Hiatal dimensions and pelvic floor muscle thickness have been extensively validated and have good test retest and inter observer characteristics [17]. There is a learning curve to measurement of the levator ani hiatus needing over ten sets of scans to perform the measurement. However measurements of the pubic arch were not accurate suggesting that measurements of levator avulsion may require more training [121].

The pelvic floor muscles were found thinner in women with pelvic organ prolapse [15, 114, 122] and with urinary incontinence [123], whereas their genital hiatus was found larger [124] interestingly this finding does not produce a significantly reduced maximal voluntary contraction even with pubovisceral muscle defects [125]. Well trained women have thicker pelvic floor muscles compared with controls [113], and Chinese women had thinner muscles compared with Caucasian women [120]. In nulliparous Chinese women, the anterior/posterior hiatal diameter was significantly increased in women with a higher body mass index [120]. Pelvic floor biomechanics were investigated with ultrasound using the position of the bladder neck in combination with continuous vaginal pressure measurements [126, 127]. A novel biosensor was used to measure the force as well as the displacement of the pelvic floor during contraction [128]. Another research group has inserted a water filled plastic bag to study the shape of the vagina during contraction [129]). Others [130] have assessed elasticity by means of the correlation of the dynamic dimensions of the hiatal circumferences and direct palpation of the muscles.

1. Levator Trauma

Using three dimensional transperineal ultrasound avulsion of the levator ani muscle from the symphysis pubis has been described in up to 36% of parous women [131]. The integrity of the attachment of the pelvic floor muscle to the symphysis pubis can be visualised (**Figure B 11 and B 18a**).

A systematic review of diagnosing pubovisceral avulsions on ultrasound and MRI has been published which showed an association with pelvic organ prolapse and recurrence after surgery. However there was no association between pubovisceral avulsions and urinary symptoms or anorectal dysfunction [132]. This is similar to results from MRI studies, where it has been shown that the risk of pelvic organ prolapse further increases when the levator injury goes together with vaginal architectural distortion [133, 134].

Although these defects have recently been identified during labour, it is not known whether there is any reasonable (preventive) treatment for these women [135, 136]. There is an increase of the occurrence of levator muscle trauma with maternal age at first delivery [137]. There was a strong correlation between the presence of levator muscle avulsion and poorer muscle strength [138]. It has, however, been shown that the correlation between the clinical assessment (palpation of the muscle) and three-dimensional ultrasonographic assessment of muscular defects was only poor [139], as well as the inter-observer repeatability of the palpation of defects [140]. A quantification method for levator muscle defects on ultrasonography (tomographic ultrasound imaging) (**Figure B 18a and b**) has been described [119]. Another parameter, which has been found to be related to the severity of pelvic organ prolapse, was the size of the inner circumference at minimal hiatal

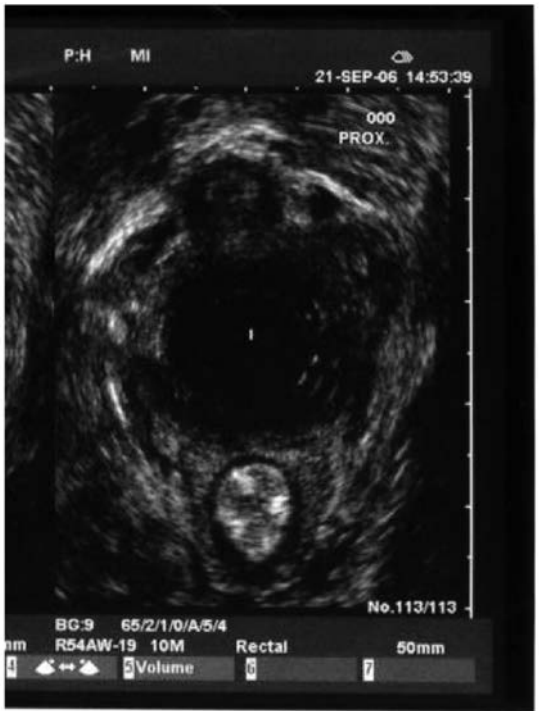


Figure B 17: Intravaginal 360 degree ultrasound imaging.
Levator ani muscle, urethra and anal sphincter complex.

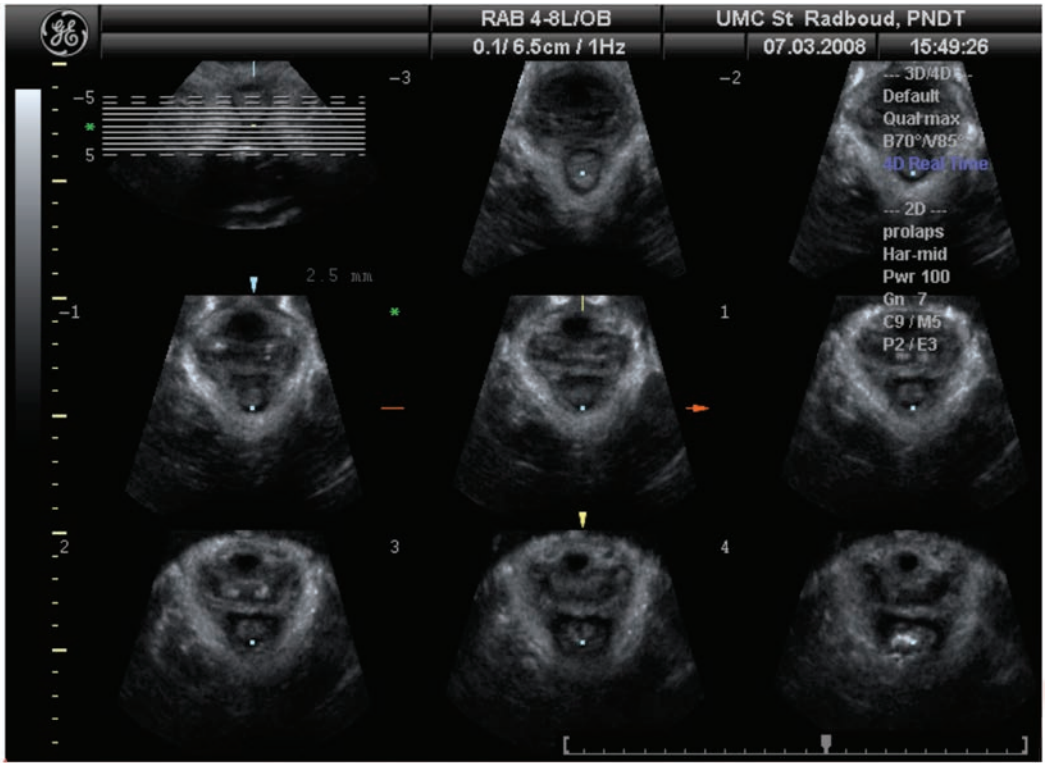


Figure B 18-a: Tomographic ultrasound imaging in oblique axial plane. Normal attachment of the levator ani muscle.

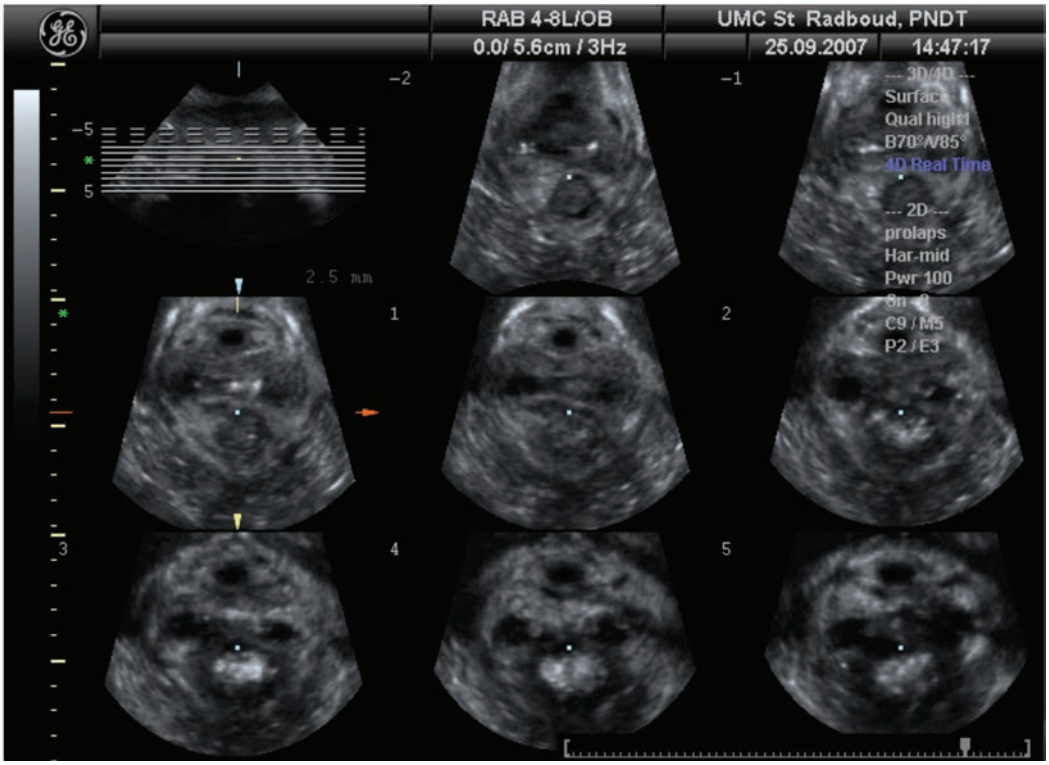


Figure B 18-b: Tomographic ultrasound imaging in oblique axial plane. Bilateral avulsion of the levator ani muscle from the symphysis pubis.

dimension of the levator ani muscle on Valsalva manoeuvre [114, 119, 135]. The area of the levator hiatus on Valsalva manoeuvre ranges from 6 to 36 cm2 in nulliparous women, with an outlier of almost 50 cm2 in a young nulliparous athlete [113, 124]. An area of more than 30 cm2, 35 cm2 and 40 cm2 on Valsalva manoeuvre has been described as mild, moderate and severe ballooning of the genital hiatus respectively (**Figure B 19**) [141]. The assessment of the levator hiatus has been shown to be a reproducible measurement [17, 131], whereas the reproducibility was less for muscle diameter measurements [17, 108, 124].

Comparisons of the hiatal diameters and hiatal area as measured by three-dimensional ultrasonography and MRI revealed good correlations, especially for the measurements at rest. The correlation for hiatal diameter at Valsalva manoeuvre was lower, which is most likely due to the difficulty to reach the correct plane of the levator ani muscle on MRI [142]. However at rest using MRI to alter the angle of acquisition plane has been shown to change the area of the levator hiatus by 10% [143]. This has been supported by subsequent papers showing a good inter and intra-observer relationship when measuring the levator hiatus with ultrasound and MRI [144] and even with interdisciplinary readers [145] though the later group did find only fair agreement when measuring the anorectal angle with ultrasound. The width of the levator ani hiatus on 3D transperineal ultrasound has been found to wider in black women than white women and the urethral sphincter volumes were significantly larger in black women than white women [146].

The presence and clinical relevance of paravaginal defects represent a controversial issue amongst urogynaecologists, and there is a lack of scientific proof for the concept. In a study by Reisinger et al., an echogenic layer in the lower anterior vagina, which was thought to be a part of the endopelvic fascia, could be identified reproducibly in nulliparous and parous women by transrectal three-dimensional ultrasonography [147]. According to more recent insights, however, previously described paravaginal defects with loss of the H-shape of the vagina in the axial plane on three-dimensional ultrasonography [138, 148, 149] are likely to represent the detachment of the levator ani muscle from the symphysis pubis [150]. However in a study comparing ultrasound and MRI to assess levator avulsion there was only a moderate correlation with ultrasound showing a higher

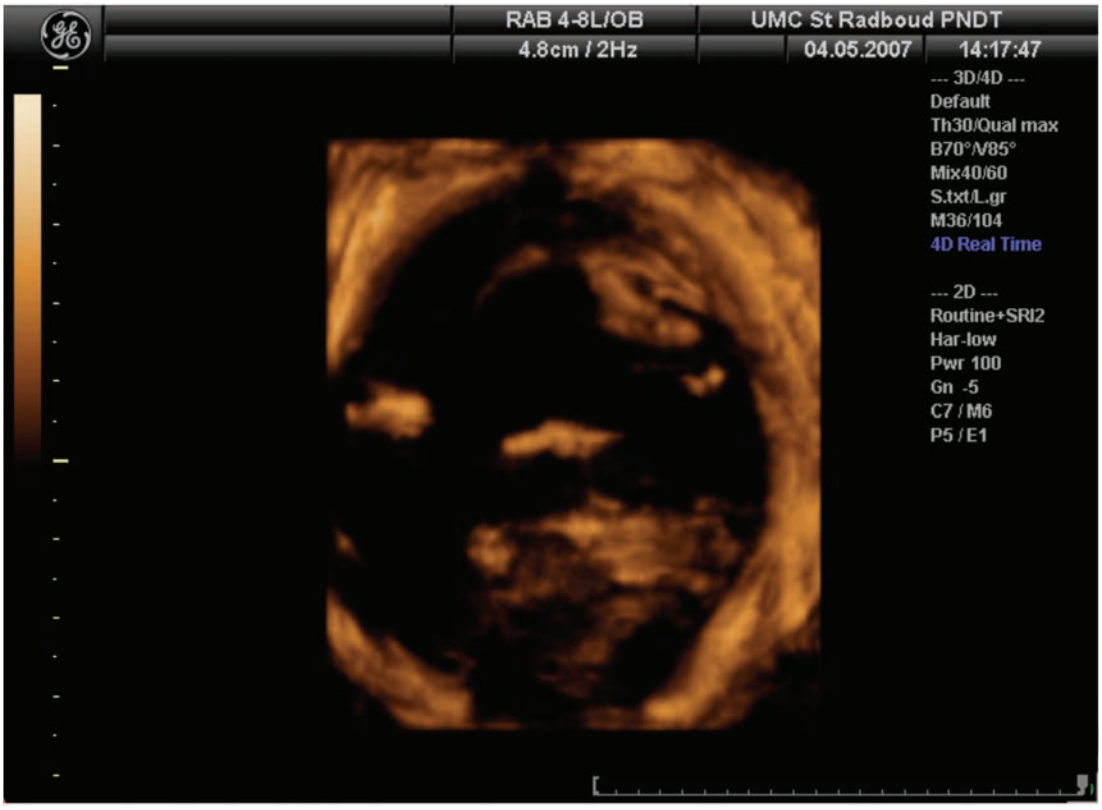


Figure B 19: Perineal three-dimensional rendered image. Ballooning of the genital hiatus

number of complete avulsions and MRI showing a higher number of partial avulsions [151]. In an attempt to increase validity of the levator avulsion diagnosis minimum criteria have been set [152], but even with these more stringent rules two out of three normal women were considered false positives where they were thought to have full avulsions. It is important to note that MRI studies tend to find thinning or aplasia rather than avulsion perhaps indicating that transperineal ultrasound may not have the resolution to visualise very thin levator ani muscles [153].

g) Pelvic Organ Prolapse

In cases of mild and moderate pelvic organ prolapse, perineal ultrasonography can be used, for the investigation of the prolapse. Ultrasonography should, however, only be used in addition to the patients history and clinical examination. In cases of severe pelvic organ prolapse, ultrasonographic assessment is not possible due to transducer dislocation by the prolapse. The ultrasonographic imaging of the anterior compartment (i.e. bladder, bladder neck and urethra) is the easiest to perform, and the majority of scientific studies deal with this compartment (**Figure B20**).

Correlations with clinical examination [154, 155] are also highest for this compartment. Reproducibility of ultrasonographic imaging of prolapse in the anterior compartment were shown to be good [155]. This reproducibility has not been studied for the other two compartments until now.

In studies amongst 83 and 117 women with the uterus in situ, the uterus could be visualized on perineal ultrasonography in 82% and 97% of cases, respectively (**Figure B 21**) [155, 156].

A number of studies have focused on the posterior compartment [157-165]). The distinction between enterocele (**Figure B 22**) and rectocele (**Figure B 23**) is known to be difficult on clinical assessment. In these cases, two-dimensional ultrasonographic imaging in the midsagittal plane can be helpful. The ultrasonographic visualisation of an enterocele has been confirmed with defaecography as well as intraoperative findings [157]. It has not been shown, until now, however, whether this extra ultrasonographic investigation indeed leads to superior clinical outcomes of prolapse surgery. Interestingly anterior compartment prolapse is related to levator ani area whereas posterior compartment prolapse is not as well as prolapse symptoms not being associated with levator ani hiatus area [166].

In a study on ultrasonography of the posterior compartment a differentiation between true rectocele, enterocele and perineal hypermobility has been made [160]. Intussusception can also be visual-

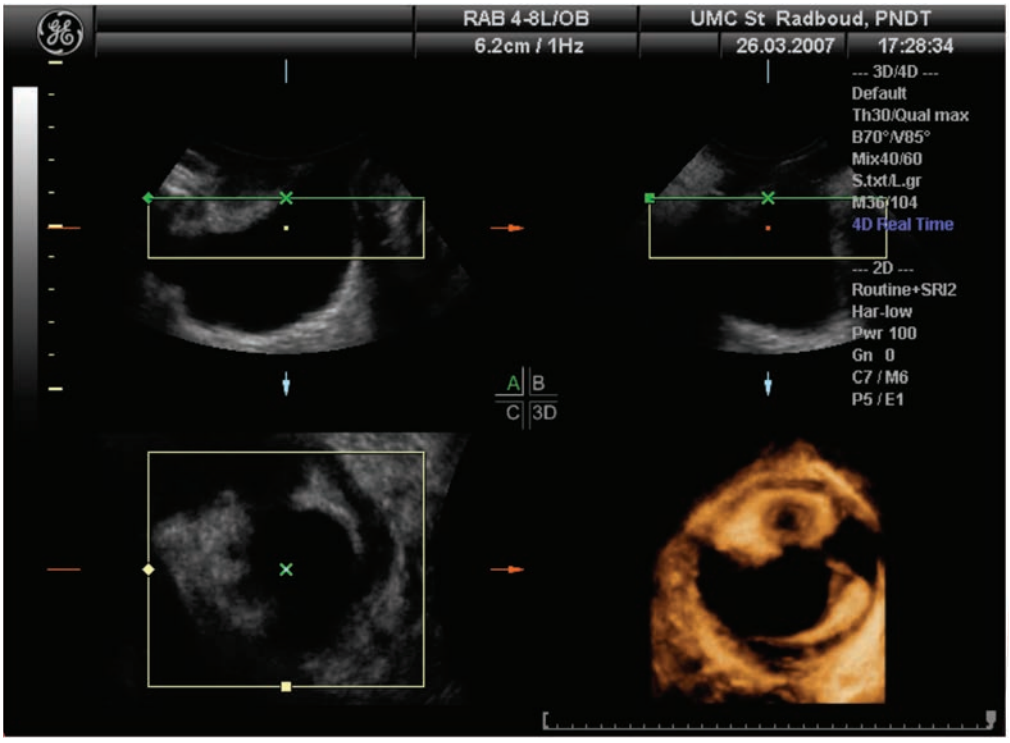


Figure B 20: Perineal midsagittal [left upper], coronal [right upper] and axial [left lower] two-dimensional view and three-dimensional rendered image [right lower].
Cystocele.

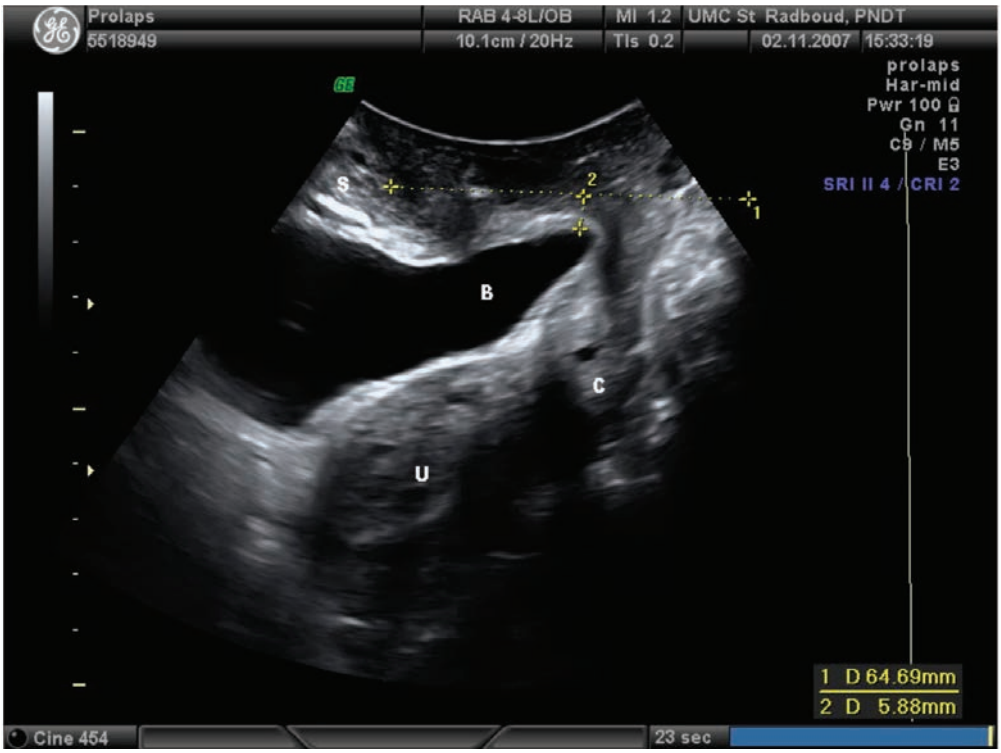


Figure B 21: Perineal midsagittal two-dimensional view. Cystocele and descending uterus. (S= symphysis pubis; B= bladder; U= Uterus; C= cervix.)

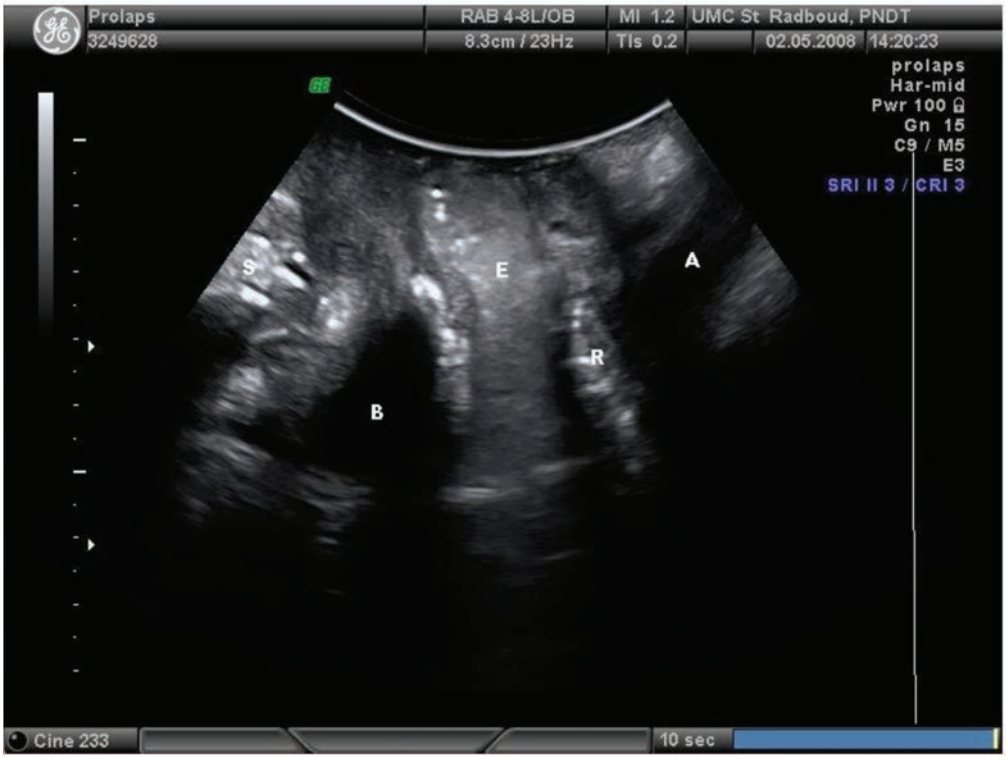


Figure B 22: Perineal midsagittal two-dimensional view and three-dimensional rendered image. Enterocele. (S= symphysis pubis; B= bladder; E= enterocele; R= rectum; A= anal canal.)

ised on ultrasonography [167]. Perineal hypermobility and an enterocele was seen as a descent of the rectovaginal septum or abdominal contents on Valsalva manoeuvre respectively, below a horizontal line through the inferior margin of the sympysis pubis (see below for more information on these measurements). Ultrasonographic staging was significantly correlated with clinical staging and the presence of symptoms of obstructed defaecation [15, 161]. In one third of the patients with clinically diagnosed rectocele, however, no ultrasonographic abnormality could be found. As far as interrater reliability was concerned, two expert ultrasonographists have reached moderate to good interrater reliability for the detection of a rectovaginal septum defect, descent of rectal ampulla, and the depth and width of a rectocele [160]. In one study, rectocele and perineal hypermobility were present in nulliparous women in 12 and 13% respectively the significance of these findings has not yet been determined [162]. The posterior anorectal angle, which is the angle between the anal canal and the posterior rectal wall, can be measured at rest and under dynamic circumstances such as straining and squeezing. A number of studies have compared these findings with defaecography and found in general a good correlation [164, 165, 168] but one study found poor inter-rater reliability [146].

1. Quantitative Assessment Of Pelvic Organ Prolapse

In the quantitative assessment of prolapse in the various compartments, a reference line, such as the hymen in POPQ, is needed. For ultrasonography, a horizontal line drawn from the inferior margin of the symphysis pubis is the most widely used reference line for this purpose. A disadvantage of this line is that there is only one fixed point through which the reference line can be drawn and the horizontal line may change with the rotation of a handheld transducer.

The effect of rotation is obviously increased with increasing distance from the fixed point, and consequently there is greatest error in the posterior compartment [155]. Although this problem has been overcome in research settings with the use of motion tracking systems, at the moment this is not a realistic option for routine use in clinical practice [169]. For quantitative assessment of rectoceles, the depths of the rectocele as measured in relation to a line through the anterior anal canal, may be more useful as compared with the descent in relation to the horizontal reference line [170].

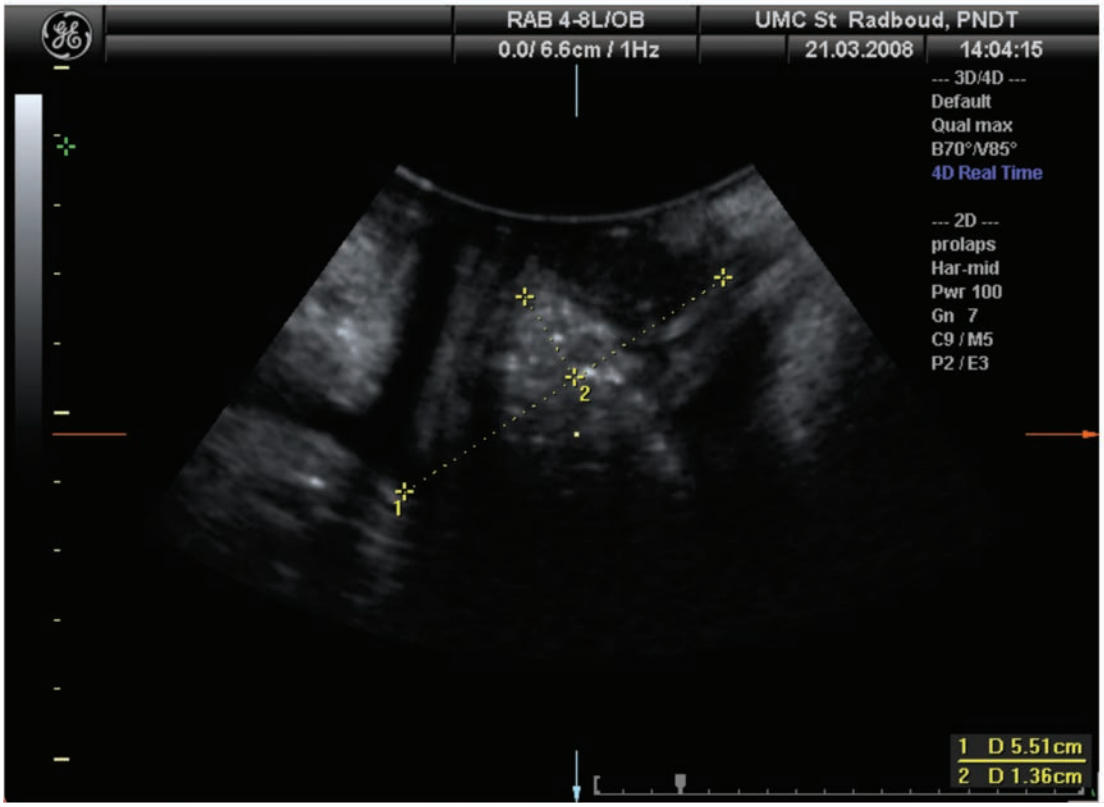


Figure B 23: Perineal midsagittal two-dimensional view.
Measurement of the depth of the rectocele, perpendicular to a straight line through the anterior border of the anal sphincter complex, i.e. 14 mm.

Since pelvic organ prolapse can be visualised well with the use of ultrasonography, it raises the question whether this assessment modality is superior to others, such as clinical examination. In a recent study on the relationship between prolapse symptoms and the most dependent point of the prolapse on POPQ and on ultrasonographic assessment, POPQ performed better in the prediction of prolapse symptoms with increasing stages of prolapse [170]. This finding has been replicated in all compartment underlining the superiority of clinical assessment over ultrasound [171]. In a previous study, where only women with a single compartment prolapse were studied, the area under the receiver operating curve was, however, as good as 0.86 and 0.82 for the anterior and posterior compartment respectively [172]. In both studies the cut-off value for symptomatic prolapse averaged 15 mm below the horizontal reference line through the symphysis pubis. Larger anterior vaginal wall prolapses do have larger levator ani hiatuses and are more likely to have avulsions (69% compared with 35%) [173].

As far as dynamic MRI and X-ray defecography are concerned, there are only a few studies available as yet, on comparisons with ultrasonography. For enterocele detection in women with obstructed defaecation, perineal ultrasonography has been compared with X-ray defaecography, but not with the clinical findings [164]. In the women in whom enterocele had been detected by either method, the enterocele was detected by both ultrasonography and X-ray in 71% of women. In this study, perineal ultrasonography showed more severe stages of enterocele compared with X-ray defaecography. In another recent study from a different research group, X-ray defaecography has been compared with perineal ultrasonography using a vaginal probe in women with impairment of the posterior pelvic floor. Good to excellent concordance has been found for the assessment of the anorectal angle, rectocele and intussusception. The authors claimed, however, that rectoceles with a depth less then 20 mm could not be detected on ultrasonography [159], which is discordant with most other publications on the topic and as well as the authors' experience.

h) Ultrasonography In Relation To Pregnancy And Delivery

Vaginal delivery is commonly accepted as the major risk factor for the development of pelvic organ prolapse later in life. In nulligravid women, there is a wide variation in pelvic organ descent for all three compartments [128, 156, 174-176]. In a study of 169 women who underwent ultrasonography during and after pregnancy, a significant increase in pelvic organ mobility (downwards displacement) was found in all three compartments [177]. The increase in mobility was significantly correlated with the length of second stage of labour and the mode of delivery. The greatest mobility was found in women who underwent an operative vaginal delivery, but no association was found with the gestation at delivery, length of the first stage of labour and birth weight, although birth weight reached borderline significance. In a similar study, focussing on the posterior compartment in 52 nulliparous pregnant women, 8 women developed de novo true rectoceles, and the descent of the rectovaginal septum increased with 22 mm for the entire group, which was statistically significant [178]. On the other hand, in a study amongst 207 women, of whom half of the women had a clinically diagnosed rectocele, no relation has been found with (vaginal) parity, and only a weak correlation has been found with age for a posterior vaginal wall prolapse as assessed with ultrasonography [160]. This suggests that the effect of vaginal parity on pelvic organ descent, is most evident in the anterior and central compartments, and may have another pathophysiology compared with the posterior compartment [177]).

Concerning bladder neck descent, it has been shown that the first delivery caused the most marked changes compared with the subsequent deliveries, with the most marked changes with forceps delivery [179].This is supported by two different research groups, who have reported that an increased antenatal ultrasonographic bladder neck descent was associated with normal vaginal delivery [180, 181]. Furthermore, vaginal delivery was strongly associated with a larger, and more distensible antenatal levator hiatus [180]. The underlying reason remains hypothetical, but more antenatal laxity of the structures may allow for a smoother delivery. Women with increased bladder neck mobility, however, also have an increased risk of de novo urinary incontinence post partum [20] but this outcome can be halved by antenatal pelvic floor exercises [182]. Avulsion of the levator ani muscle from the symphysis pubis, as outline above, is typically found in vaginally parous women only (**Figure B 18b**) [131, 183, 184]. It has, furthermore, been shown that a higher maternal age at first vaginal delivery is strongly related to an increased risk of these avulsions [131, 184]. Mode of delivery has a strong association with the incidence of levator ani injury such that vaginal delivery 15.4% are affected, 33.3% after ventouse delivery and 71.4% after a forceps delivery but there were no levator injuries detected in the Caesarean section group [185], similar findings have been reported by other groups [186-189]. The timing of the levator ani damage appears to be as the head crowns [190]. The levator ani hiatus has been reported as enlarging after vaginal delivery [191, 192] and this enlargement being maintained for up to three years later [193] but other groups have not found it enlarged nine months after delivery compared with antenatal measurements. However forceps delivery did lead to long term enlargement of the levator ani hiatus [194]. The risk of levator ani avulsions increased with enlarged head circumference and prolonged second stage in labour [195].

i) Pelvic Floor Surgery

Ultrasonography has been used during anti incontinence surgery with the aim of obtaining optimal results from surgery, for example during Burch colposuspension [196, 197]. On an individual basis, the bladder neck was lifted between 1 mm and 10 mm. The authors have obtained excellent results with a 94% continence rate after 1 year, but unfortunately no control group was incorporated in the study. Levator ani avulsions have been found to be associated with persistent vaginal prolapse even after attempted surgical repair [198].

1. Slings and Meshes

Monofilament meshes, for example polypropylene meshes, are easier to visualise on ultrasonography compared with multifilament meshes, such as IVS [199]. Ultrasonography has been widely used to localise the exact position of tension free midurethral tapes (**Figure B 24**) [180, 200-203]. The tape is generally easily visible as an hyperechogenic structure under the urethra and is easy to recognise, which contrasts with the poor images of polypropylene on MRI [204]. Exact midurethral position of the tape is not essential for proper function [205]. Despite the fact that the tape was located in the midurethra in only two-third of cases, this had no relation to postoperative continence status [206]. During Valsalva manoeuvre, the tape moves in a semicircle movement around the inferior margin of the symphysis pubis [207]. This results in a position closer to the symphysis, which consequently leads to a certain degree of mechanical compression during Valsalva manoeuvre. Another mechanism of action is kinking of the urethra around the tape [208]. A number of studies have looked at transobturator tape and compared these with retropubic tapes [199, 209-212]. Two studies could not detect any differences between the two types of tape [199, 212], whereas in the other two studies [209, 211], subtle differences with no apparent clinical consequences were found.

Imaging both tension-free and transobturator tape procedures during straining show a reduction in the diameter of the hypoechoic urethral core and the diameter became significantly smaller only in the successful procedures [213] and a reduction in the symphysis pubis to tape distance led to continence [214]. Other authors have suggested optimal positions of the tape being between the distal third and middle of the urethra with a tape-urethral distance of 2mm, greater than 3.9mm distance led to failure of the procedure. The tape to urethral distance can be reliably assessed using 4D ultrasound [215]. Midurethral tapes impinging on the urethra has been reported as being associated with voiding difficulty and the “V” shape of

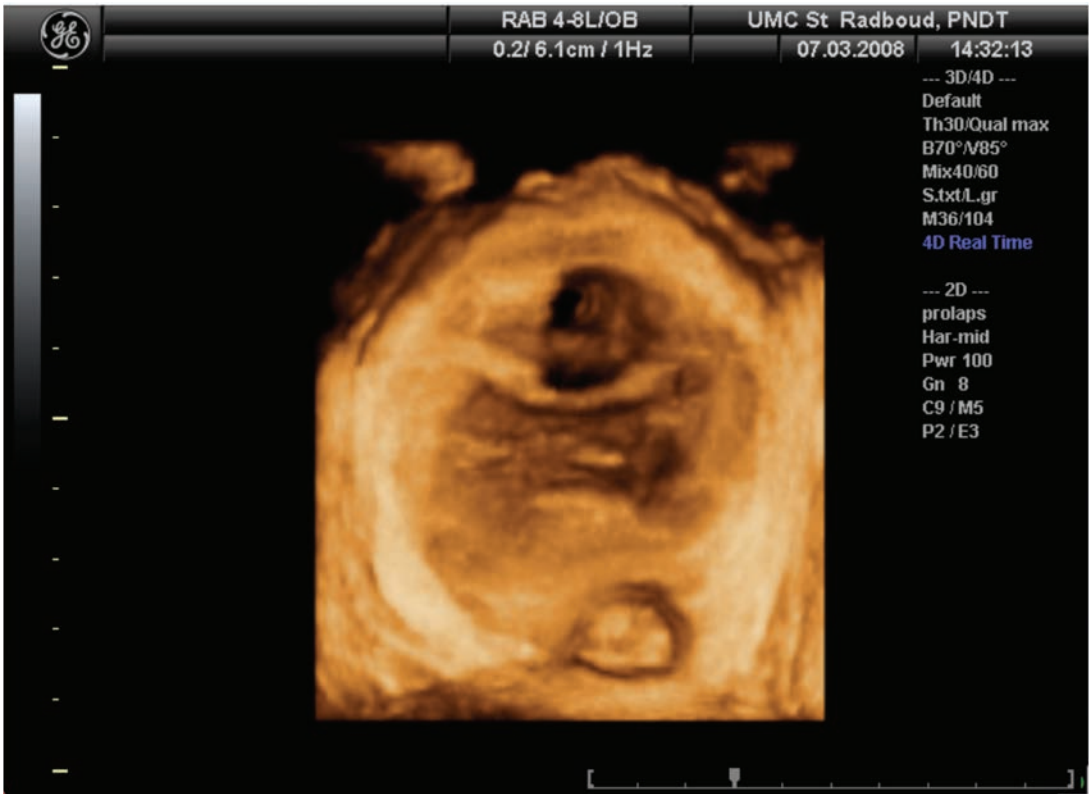


Figure B 24: Perineal three-dimensional rendered image. Polypropylene mesh (TVT-O) after one-sided incision of the tape.

the tape was the same regardless of the insertion method (ie TOT compared to TVT) [216]. Tapes sited around the midurethra resulted in a reduction in flow rate compared with a distal tape position under the urethra which did not change flow rates [217] and this positional information has been used to determine the management of de novo symptoms after surgery [218].

The bladder neck is displaced during insertion of a midurethral by using a rigid guide during insertion of a tension-free vaginal tape. Ultrasound has been used to determine that the bladder neck is moved by 1.4cm by this technique [219]. Recently, ultrasonographic localization of polypropylene mesh as used in prolapse surgery has been described (**Figures B 25 and B 26**) [220]. These meshes are usually easily visible on ultrasonography. It appears that the ultrasonographic appearance of the mesh is significantly shorter and narrower than the size at implantation within six weeks of the procedure [221]. It is unclear whether this is due to shrinkage of the mesh or represents difficulties in visualising the full extent of the implanted mesh. The failure of mesh to support vaginal prolapse was associated with mesh shrinkage [222, 223].

The differentiation between recurrent herniation and the detachment of the mesh arms from the pelvic sidewall for example, will aid in the better understanding of the mode of action of these meshes [224].

2. Bulking Agents / Injectables

Periuretral bulking agents/injectables, such as microparticulate silicone (Macroplastique), various gels (e.g. Durasphere), and collagen, can be visualised by imaging techniques. For MRI, an overview of appearances of periurethral bulking agents is already available [225]. On ultrasonography, the injectables appear hypoechoic after injection, and become more hyperechoic over time due to dehydrogenation. Good intra-observer variability of repeated measurements of periurethral collagen volumes have been found [226].

The location in relation to the bladder neck and a circumferential distribution of collagen injectables around the urethra, as well as the height and volumes of the injected periurethral collagen bumps, were associated with the treatment success of periurethral bulking agents [226-228]. Although the volume range was wide, a collagen volume of 2.8 cc on three dimensional ultrasonography has been assessed as optimum volume from a continence point of view. Poon et al. have published a decision tree, in which a combination of the patients´ symptoms after collagen injection and the configuration and volume of the periurethral collagen on three-

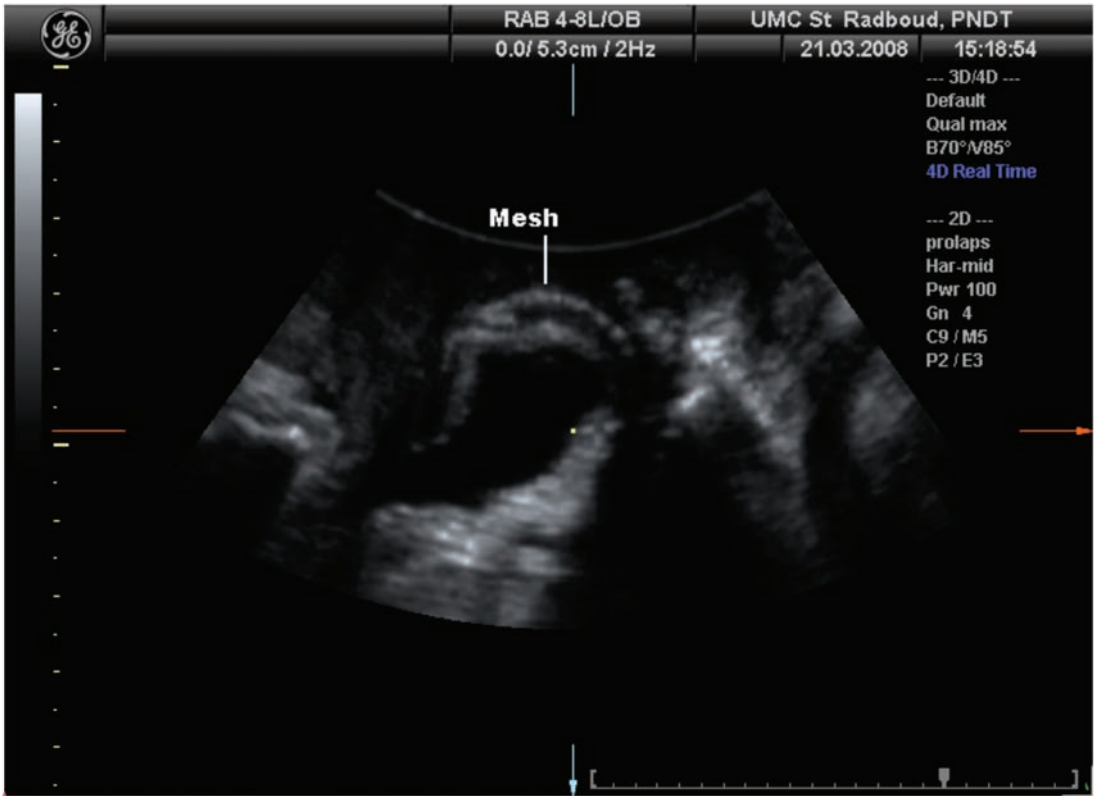


Figure B 25: Perineal midsagittal two-dimensional view. Polypropylene mesh of the anterior vaginal wall (Prolift anterior).

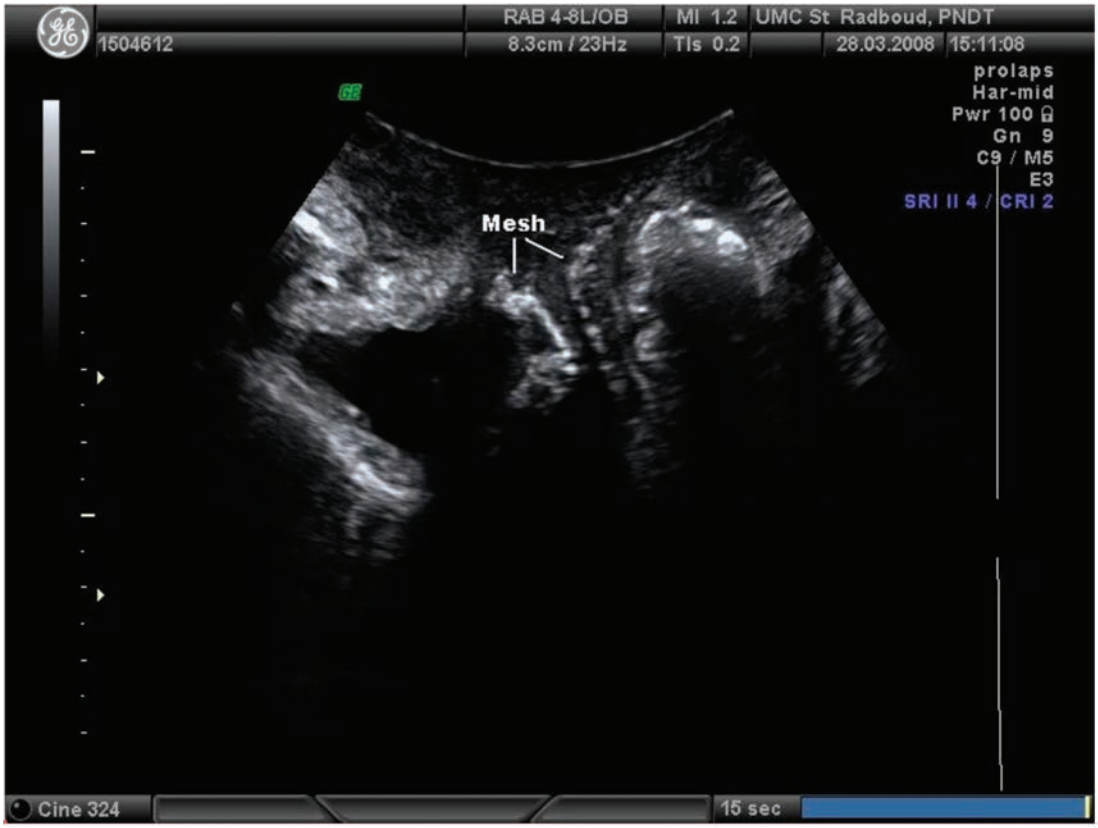


Figure B 26: Perineal midsagittal two-dimensional view. Polypropylene mesh of the anterior and posterior vaginal wall (Prolift).

dimensional ultrasonography, assist in the decision for further treatment of women with intrinsic sphincter deficiency [226]. In this algorithm, women with asymmetric deposition and/or low collagen volumes were offered further treatment with injectables as this is associated with failure [229].

Ultrasonography has not only been used for follow-up, but also during placement of periurethral injections. Transurethral ultrasonography-guided injection of autologous stem cells has been used in women and men with stress urinary incontinence. The technique allowed precise injection of the myoblasts directly into the rhabdosphincter, and was more effective in the resolution of incontinence compared with urethroscopic guided collagen injectables in the submucosa in a randomized controlled trial [230, 231]. The use of stem cells in the management of urinary incontinence is of great interest although the subject remains controversial and confirmatory studies are eagerly awaited.

j) Conclusions

Research in US imaging of the pelvic floor has flourished over the last decade although the clinical benefit of it remains uncertain. Standardisation of imaging techniques and terminology are eagerly awaited. Imaging of pelvic floor muscle in relation to POP is a promising area because of the possible insight into the pathophysiology of the condition and treatment outcome. Research suffers from a lack of coordination among different research groups and a more structured approach to research on imaging of UI and POP is advisable.

k) Consensus Statement

- Ultrasound is not recommended in the primary evaluation of patients with urinary incontinence and/or pelvic organ prolapse (rectal prolapse is dealt with in a different section). [**Level of evidence 3, Grade of recommendation C**]
- Ultasound is an optional test in the evaluation of patients with complex or recurrent urinary incontinence and/or pelvic organ prolapse. [**Level of evidence 3, Grade of recommendation C**]

l) Future Research Areas

- Standardisation of terminology of pelvic floor US imaging
- Internal and external validity of techniques of pelvic floor imaging
- Confirmatory studies to validate previously published evidence on imaging of UI and POP

o Accuracy of US diagnosis of levator ani injury

o Prognostic value of preoperative US imaging and outcome of POP surgery

o Health technology assessment of pelvic floor imaging in the management of UI and POP.

3. MRI (THE EVOLVING ROLE OF MRI IN THE ASSESSMENT OF THE FEMALE PELVIC FLOOR).

The role of magnetic resonance imaging (MRI) in evaluating pelvic floor disorders has been established in recent years and continues to evolve. This technique provides unparalleled images of pelvic floor muscles, connective tissue, and organs. In addition to the detailed static picture of the pelvic organ support system anatomy, MR can also reveal the downward movement of each pelvic compartment during increases in abdominal pressure. Advances in MR imaging, equipment and software have significantly improved image quality and now MRI provides ever more detailed pictures of anatomy and function. At present active investigation is ongoing to see how this imaging might result in a better understanding of these diseases and improve their diagnosis and management.

Although women might present with symptoms isolated to one of the pelvic compartments, they often have concomitant defects in other compartments or pelvic structures. In these women, imaging can provide information to extend what can be determined on physical examination [1]. Furthermore, surgical failures could result from lack of a thorough preoperative evaluation of the female pelvis and inadequate diagnosis and staging of pelvic floor deformation and dysfunction [2]. Accurate diagnosis of coexisting abnormalities is therefore essential in planning reconstructive and anti-incontinence procedures. Although most diagnoses of pelvic floor prolapse are made on detailed physical examination, the sensitivity and specificity of the pelvic examination in diagnosing various forms of pelvic floor prolapse is low [3] [4] [5]. Ultrasound and fluoroscopy have been used to improve diagnosis [6] [7] and the role of MRI in pelvic floor dysfunction is rapidly developing. A recent systematic review suggests that prolapse assessment on dynamic MR imaging may be useful in the posterior compartment, although clinical assessment and dynamic MR imaging seem interchangeable in the anterior and central compartment [8].

There is now a robust literature indicating that MRI provides detailed images of bladder neck and urethral mobility, rectocele, cystocele, enterocele and uterine prolapse, in a single non-invasive study without exposing the patient to ionizing radiation [9] [10] [11] [12] [13] [14] [15] [16] [17] [18]. MRI also provides a multiplanar thorough evaluation of pelvic organs including the uterus, ovaries, ureters, kidneys, and levator muscles, as well as the urethra, that is unavailable by any other imaging modality [11] [13] [14] [15] [16] [17] [19] [20]. MRI can identify ureteral obstruction, hydronephrosis, and uterine and ovarian pathology. In addition, MRI remains the study of choice for the evaluation of urethral diverticuli.

The following measurements using MRI in urogynecology and female urology have been highlighted in the recent IUGA/ICS Joint Report on the Terminology for Female Pelvic Floor Dysfunction [21]:

(a) Bladder neck and cervical descent/mobility:

- Position of bladder neck and cervix at rest and on Valsalva.
- Pubo-coccygeal line: A line extending from the inferior border of the pubic symphysis to the last joint of the coccyx. Bladder neck or cervical descent >2 cm below this line with straining indicates weakness of the pelvic floor. If alternative landmarks are used in scientific papers they should be clearly described.

(b) Intercurrent pelvic pathology: For example, fibroids, ovarian pathology.

(c) Uterine version: Anteverted or retroverted; flexion at the isthmus.

(d) Bladder abnormalities: For example, tumor; foreign body.

(e) Urethral abnormality: For example, diverticulum.

(f) Postoperative findings: For example, bladder neck mobility.

(g) Pelvic floor measurements/levator defects: Assessment of the configuration of pelvic floor muscles, in particular, the levator ani.

(h) Descent of pelvic organs.

This article is an update to the ICI article on the role of MRI in assessing the female pelvic floor [2009] and provides a current review of where we are in evaluating the role of MRI in understanding the causes and treatment of pelvic organ prolapse.

a) Technique

The evolution of MRI is partly due to new hardware implementation (3Tesla magnets, large magnet sections and opne magnets) but largely to software development in the sense on new sequences that open novel possibilities in the field of functional and dynamic imaging.

1. Conventional MRI

Standard MRI consists of two dimensional image acquisitions. Usually conventional T1 images and spin echo T2 weighted images are obtained. Proton density T2 weighted scans provide excellent soft-tissue definition [**Figure B 27**]. However, the long imaging time of conventional MRI hampers its ability to evaluate the movement of organs that are characteristic of POP.

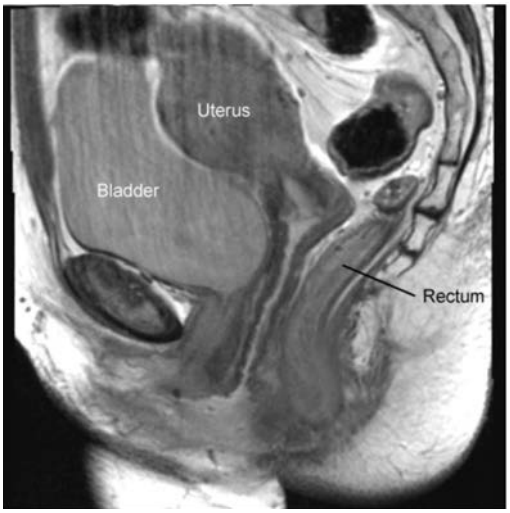


Figure B 27: Sagittal mid pelvic section showing anatomical detail visible in static images made with Proton Density sequence.

2. Ultra Fast Image Acquisition And Mr Sequences

Pelvic organ movement during Valsalva is identifiable using very fast single-shot MR sequences and the technical aspects have been summarised in our prior report [**Figure B 28**] (ICI 2009). [15] [16] [22] [23]. These sequential images are obtained approximately once per second, either as a series of images covering the entire pelvis (static imaging) or repetitively in one plane while the patient is straining (dynamic imaging). The patients are placed in the supine position with legs slightly spread apart, and knees bent and supported by a pillow. Most pelvic floor details can be seen without the need for bowel preparation, premedication, instrumentation or contrast medium but often, especially with MR defaecography, ultrasound gel or other suitable agents are used to enhance visibility of the rectum and vagina. The MRI torso coil is centered at the symphysis pubis. Images are acquired in the sagittal plane using single-shot fast spin echo (SSFSE) or half Fourier acquisition, single shot turbo spin echo (HASTE) sequences. Single, mid sagittal views are obtained during 3 seconds of apnoea with the patient relaxed and during various degrees of progressive abdominal straining.

Since the time of the last report, continued development of techniques have occurred to allow visualisation of the dynamics of pelvic organ during increases in abdominal pressure. Steady-state free precession gradient-echo imaging provides an alternative T2-like imaging contrast (T2- and T1-weighted imaging) with robust signal and a rapid acquisition time of less than 1 second, thereby permitting near real-time continuous imaging. This is an improvement on the HASTE approach that requires 1–2 seconds between acquisitions to allow T1 recovery; therefore, real-time imaging is not possible. Comparisons of the degree of POP shown on dynamic true fast imaging with steady-state precession (FISP) versus HASTE sequences in symptomatic patients reveal a greater degree of prolapse in all three compartments with a dynamic true FISP sequence. Near real-time continuous imaging with a dynamic true FISP sequence may therefore be useful to evaluate pelvic floor dysfunction in addition to dynamic multiplanar HASTE sequences [24).

During a typical study of pelvic organ movement two sets of images are obtained. The first set consists of static sagittal and para-sagittal images covering the pelvis from left to right sidewall. These images are used to select the mid-sagittal plane for the dynamic second set of images. This static sequence also allows for anatomic delineation of the pelvic sidewalls and muscular and fascial components of the pelvic floor [15] [16] [22] [23]. The perineal membrane and the levator ani musculature, as well as the anal sphincter anatomy, are also clearly demonstrated [25] [26]. The static set consists of 17-20 sequential images independently acquired in a total of about 18 seconds.

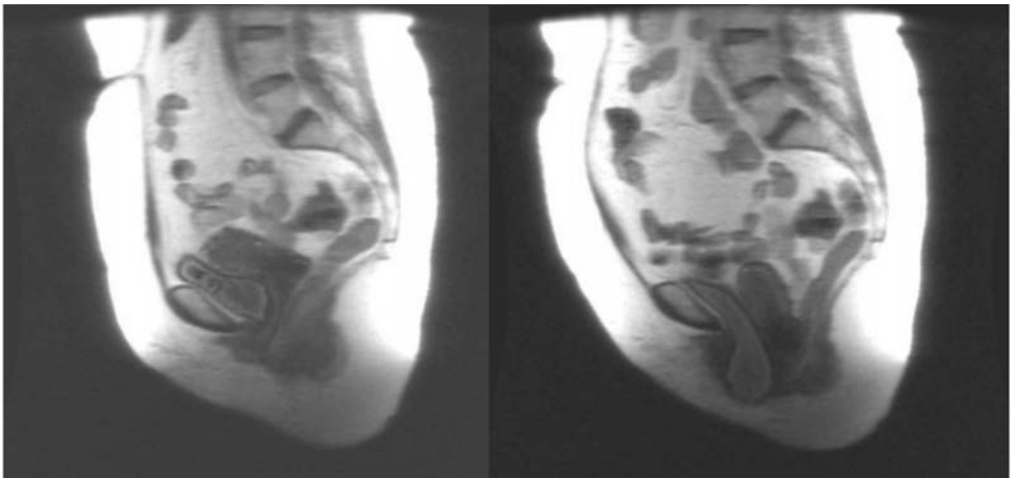


Figure B 28: The rest and strain image taken from a mid-sagittal dynamic MR sequence revealing cystocele and uterine descent using SSFSE sequence.

The second set of images consists of relaxed and straining mid-sagittal images used to assess the degree of pelvic floor relaxation and organ prolapse. Images can then be looped for viewing on a digital station as a cine stack.

Dynamic MRI allows detection of POP that may not be evident on conventional static sequences, as it permits both structural and functional evaluation. For example, in women with lower urinary tract symptoms evaluation of the urethra may be of added value. [27] There has been further clarification of how the conduct of the examination can affect what is seen. For example, the first time a woman performs a Valsalva maneuver, she may not get the prolapse to protrude to its maximal extent. Tumbarello et al [28] found that 40% of women have a greater than 2cm increase in prolapse size from their first to third Valsalva attempt and 95% of women extend their prolapse further with a third Valsalva. They concluded that, as with clinical examination, several attempts may be required to have maximal anterior compartment prolapse present during dynamic MRI of the pelvic floor. Delancey et al evaluated whether the use of a speculum blade modifies the evaluation of pelvic organ prolapse (POP) as assessed by dynamic MRI. Twenty-seven women with POP Quantification (POPQ) stage II or greater, scheduled for POP surgery, were evaluated using MRI. The procedure was repeated using the posterior blade of a standard plastic Grave's speculum to successively retract the anterior and posterior vaginal walls. Standard POPQ was 15% stage II (n =4), 59% stage III (n =16) and 26% stage IV (n =7). The use of a blade evidenced hidden pelvic prolapsed compartments in 59% (n =16) of cases. For 48% of patients (n =13), the variation of the leading edge of at least one additional prolapsed compartment was diagnosed as more than 20 mm. In this series, the use of a speculum blade during dynamic MRI modified the POP evaluation in a large proportion of patients with POP stage > or =II [29].

3. THREE DIMENSIONAL MRI

The nature of MRI technique where a series of parallel images are made allows them to represent a 3D block of tissue. Three dimensional (3-D) MRI provides precise detail of the bony and muscular pelvic structures (**Figure B 29**) so that 3D models can be constructed based on these detailed images. In this technique, static or dynamic images are reconstructed using consecutive planes in the axial, sagittal and coronal dimensions. Anatomic variations of the insertion and path of the pubococcygeus and iliococcygeus muscles can be seen. Fielding et al. made 3D models of the pelvic viscera and supporting muscles and bones with the marching-cubes algorithm and a surface-rendering method in nulliparous continent female volunteers and found that the muscle morphology, signal intensity and volume are relatively uniform [25]. They described an average volume of the levator ani of 46.6 cc, width of the levator hiatus of 41.7 mm and an average posterior urethrovesical angle of 143.5°. In addition, these 3D models made from multi-slice scans during a maximal Valsalva have allowed direct measurements of changes in the relationship between the vagina and pelvic walls.

3D MRI enables evaluation of paravaginal defects, apical descent and vaginal widening. Larson et al [30] studied the relative contributions of "midline defects" (widening of the vagina) and "paravaginal defects" (separation of the lateral vagina from the pelvic sidewall) in women with anterior prolapse using 3D MRI models of the anterior vaginal wall and found that changes in lateral anterior vaginal wall were considerably greater than changes in vaginal width in cases vs controls. These "paravaginal defects" were also highly correlated with apical descent.

The geometry of the arcus tendineus fascia pelvis (ATFP) and arcus tendineus levator ani (ATLA) in women with unilateral levator ani muscle defects and associated "architectural distortion" has been studied using 3D MRI. In those women, the ventral arcus anatomy is significantly altered in the presence of levator defects as well as architectural distortion, resulting in change of the supportive force direction along the lateral anterior vaginal wall, thus increasing the risk for anterior vaginal wall prolapse. [31]

a) Normal Pelvic Floor Functional Anatomy

Understanding how the pelvic floor works: one of the great challenge for every surgeon and physician involved in the management of disorders involving muscle, fascias and viscera on this complex area of the human body. Anatomical description of pelvic floor muscles at autopsy does not always reveal their function and the reasons of their dysfunction that not necessarily derive from anatomical changes but also from derangement of their networking. The variable weight of these two components may explain the variable outcome of conservative and invasive management in the individual subject. MRI offers a unique opportunity to investigate the pelvis

Figure B 29: Pelvic Organs as seen from caudal on a three-dimensional reconstruction from Magnetic resonance images. Copyright Mosby Inc.

a single functional unit and to investigate the relative contribute of its different parts and sections.

1. MR IMAGING OF NORMAL PELVIC SUPPORT STRUCTURES

MRI studies of normal subjects have improved our understanding of normal pelvic anatomy, its variations [25] [26] [32] as well as anatomic changes in pelvic floor dysfunction [20] [33] [34].

In the supine position the female pelvic floor is dome shaped at rest [34] [35]. During voluntary pelvic floor contractions the levator musculature straightens and becomes more horizontal. With bearing down the muscle descends, the pelvic floor becomes basin-shaped, and the width of the genital hiatus widens.

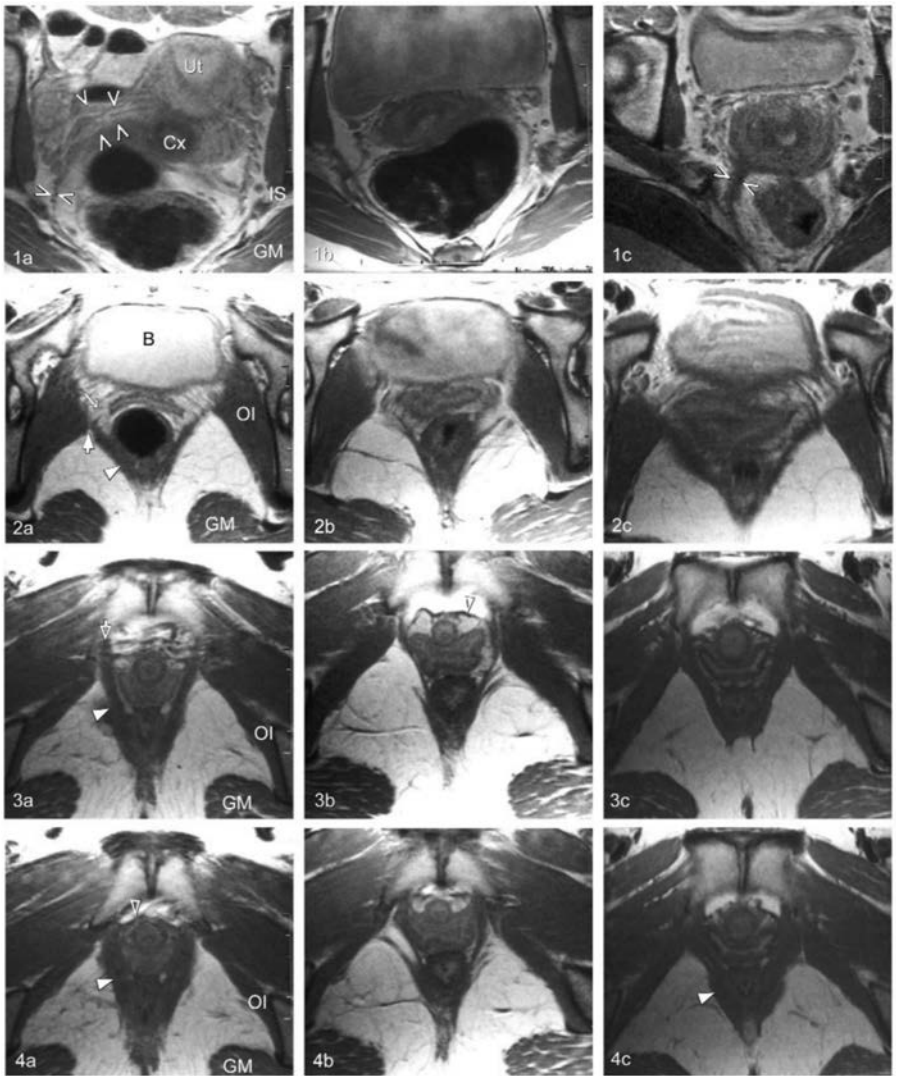


Figure B 30 : Axial images according , in 22-year-o ld (1a-4a), 24-year-old (1b-4b), and 34- year-old (1c-4c) nulliparous women without urogynecologic problems. 1a-c, Level of cervix (Cx) and ischial spine (IS); uterus (Ut) with bright endometrium is also seen. Paracolpium and parametrium suspend (open tips) vagina and cervix from lateral and posterior pelvic sidewall. Smooth muscle of uterosacral ligament (open tips) is best seen in 1c. GM, Gluteus maximus muscle. 2a-c, Level of bladder (B) base. Upper vagina between bladder and rectum (R) and its attachment to pelvic sidewall by vascular and connective tissue mesentery (small arrow) are seen. Levator ani muscle (iliococcygeal part, filled arrowhead) arises from arcus tendineus of levator ani muscle (filled arrow). OI, Obturator internus muscle. 3a-c, At level of proximal urethra, levator ani muscle (pubovisceralis part, filled arrowhead) arises from pubic bone (open arrow). Pubovesicalis muscle (open arrowhead) is clearly seen in 3b. Vessels (white gap) are visualized between smooth muscle layer of lateral vaginal wall and levator ani muscle at this level. 4a-c, At level of middle urethra, pubovesicalis muscle is seen as shown in 4a (open arrowhead). Vessel layer (white gap) between lateral vaginal wall and levator ani muscle (filled arrowhead) has disappeared; direct connection between vagina and levator ani muscle is seen at this level. Small white gap in levator ani suggests fascia between puborectalis and pubococcygeal muscles (especially in 4a and 4c). [123]

With MRI the specific structures are identified and their normal variations described **[Figure B 30**]. Tan [33] demonstrated the anatomy of the female pelvic floor with MRI. The pelvic and the urogenital diaphragm were well depicted as were urethral supporting structures—the peri-urethral and paraurethral ligaments, and the zonal anatomy of the urethra. The MRI findings in volunteers correlated with the endovaginal MR findings and gross anatomy in cadavers. Chou [36] studied the urethral support structures relative to the arcuate pubic ligament including the arcus tendineus fasciae pelvis, the perineal membrane, the pubococcygeal levator ani muscle and its vaginal and bony attachments, and the pubovesical muscle. Tunn et al [37] showed that 2- to 3-fold differences occur in distance, area, or volume measures of continence system morphologic features in continent nulliparous women with normal pelvic organ support and urodynamics. The uterosacral ligaments also exhibit greater anatomic variation than their name would imply [38].

More recently, characteristic anatomic features of the posterior compartment and perineal body have been studied with MR cross-sectional anatomy and can be further elucidated and integrated with 3-D anatomy. In nulliparous asymptomatic women the posterior compartment's upper, mid, and lower segments are best visualised in MRI in the axial plane. It is bounded inferiorly by the perineal body, ventrally by the posterior vaginal wall, and dorsally by the levator ani muscles and coccyx. In the upper portion, the compartment is bordered laterally by the uterosacral ligaments, whereas in the middle portion, there is more direct contact with the lateral levator ani muscles. In the lower portion, the contact becomes obliterated because the vagina and levator ani muscles become fused to each another and to the perineal body [39]. (**Figure B 31**). The perineal body anatomy has been possible to study using 2mm MR images. Visualisation of perineal body anatomy in living women and development of 3-D models enhanced our understanding of its 3 different regions: superficial, mid, and deep [40]. The three distinct perineal body regions are [1] a superficial region at the level of the vestibular bulb, [2] a midregion at the proximal end of the superficial transverse perineal muscle, and [3] a deep region at the level of the midurethra and puborectalis muscle. Structures are best visualised on axial scans, whereas craniocaudal relationships are appreciated on sagittal scans. In the superficial portion at the level of the vestibular bulb (VB), the bulbospongiosus (BS) inserts into the lateral margins of the perineal body, whereas the superficial transverse perineal muscle (STP) and external anal sphincter (EAS) traverse the region. In the perineal body's midregion at the proximal end of the superficial transverse perineal muscle, the puboperinealis muscle inserts into the lateral margins of the perineal body and in some individuals can be seen to cross the midline. This region also contains the distal internal anal sphincter. The puboanalis muscle is also visible as it inserts in the intersphincteric groove between internal and external anal sphincters. The puboanalis muscle and internal anal sphincter extend into the perineal body's most deep region at the level of the midurethra. Here the pubovaginalis muscle also becomes visible as it fuses with the vaginal side wall, sending fibers posteriorly to the perineal body. In this location, the longitudinal muscle of the rectum may be visible in the midline. The puborectalis muscle forms a loop behind the rectum at this level but

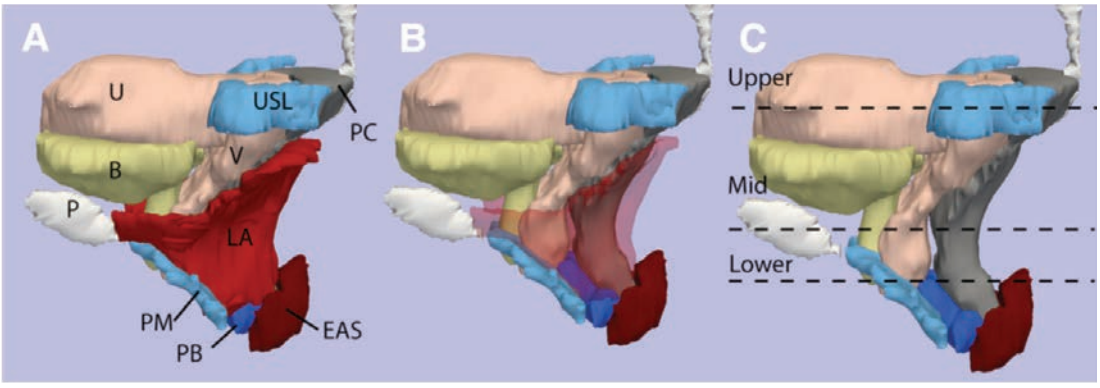


Figure B 31: The outline of the midsagittal pubic bone (P) is shown. The bladder (B) is yellow; the uterus (U) and vagina (V) are pink; the uterosacral ligament (USL) and perineal membrane (PM) are turquoise blue; the levator ani muscle (LA) is red; the perineal body (PB) is royal blue; the external anal sphincter (EAS) is dark red; and the posterior compartment (PC) is gray. Image A, All organs are shown. B, Levator ani muscles have been faded to show the underlying structures. C, Levator ani muscles have been removed. The locations of the upper, mid, and lower axial cross-sections are shown (39). Reprinted with permission from John O. L. DeLancey.

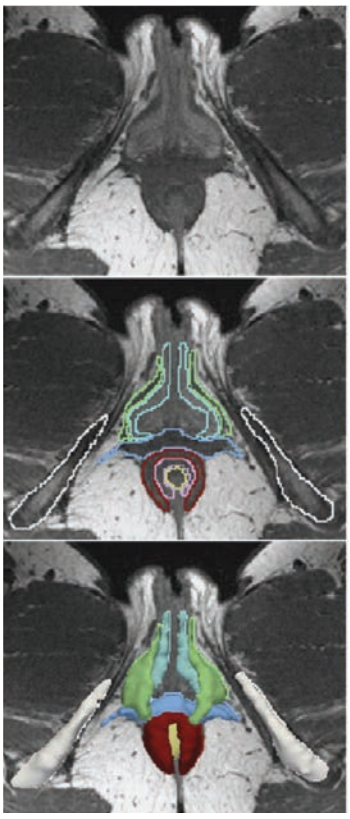


Figure B 32: 3D Model of the perineal body [40]

does not contribute fibres to the perineal body. (**Figures B 32-33**)

One of the key anatomical contributions MRI has made to the understanding of normal pelvic floor structure, regards the ability to make images of a wide variety of normal living women. The pelvic floor is greatly distorted in cadavers due to loss of muscle tone and pressures during embalming. Otcenasek et al have used MR images of a normal nulliparous woman to establish geometry and then added details from dissection to produce an anatomically based topographically normal 3-D model that displays the features of pelvic floor anatomy (**Figure B 34**) [41].

2) Levator ani muscle functional anatomy

Evidence from MR and CT images in volunteers and cadavers shows that the anterior transverse portion of the levator muscle is basin-shaped; the middle transverse portion funnel-shaped, while the posterior transverse portion dome-shaped. The puborectalis appears u-shaped outside the vertical portion [42]. On MR images of the five Terminologia Anatomica-listed levator ani components: pubovisceral (pubovaginal, puboperineal, and puboanal), puborectal and iliococcygeal portions of the levator ani muscle muscles in women with normal pelvic support, the puborectal muscle can be seen lateral to the pubovisceral muscle and decussating dorsal to the rectum in the axial plane. The course of the puboperineal muscle near the perineal body is also seen best in the axial plane. The coronal view is

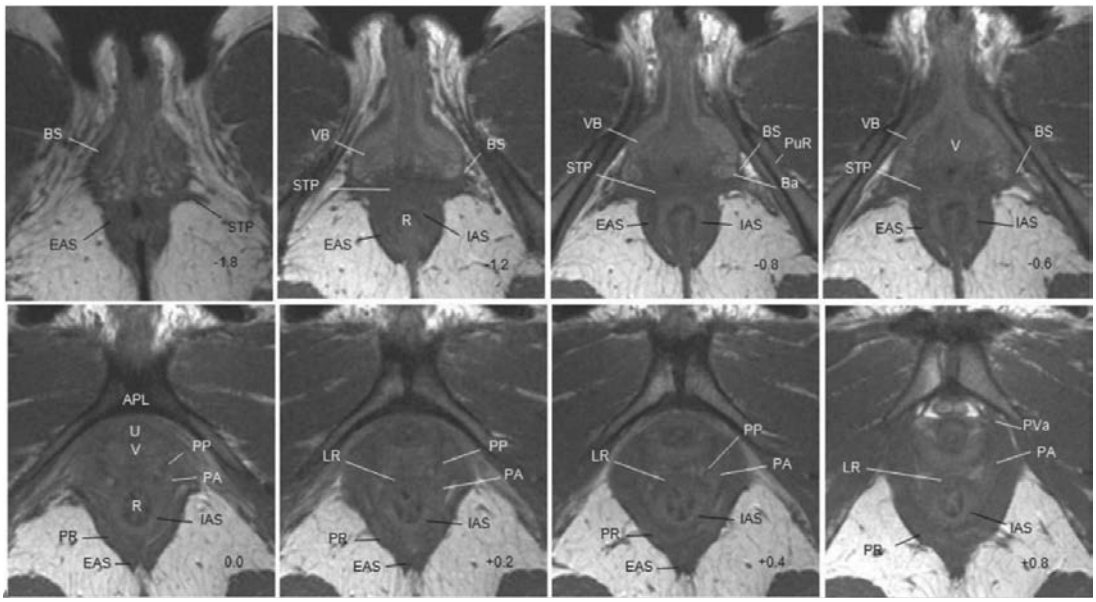


Figure B 33: Arcuate pubic ligament (APL) as reference slice. Negative numbers are caudal and positive numbers are cephalad to APL
B, bladder; Ba, Bartholins; IAS, internal anal sphincter; IC, iliococcygeus; PB, perineal body; PR, puborectalis; PS, pubic symphysis; PuR, pubic rami; R, rectum; U, urethra; V, vagina; VB, vestibular bulb [40].

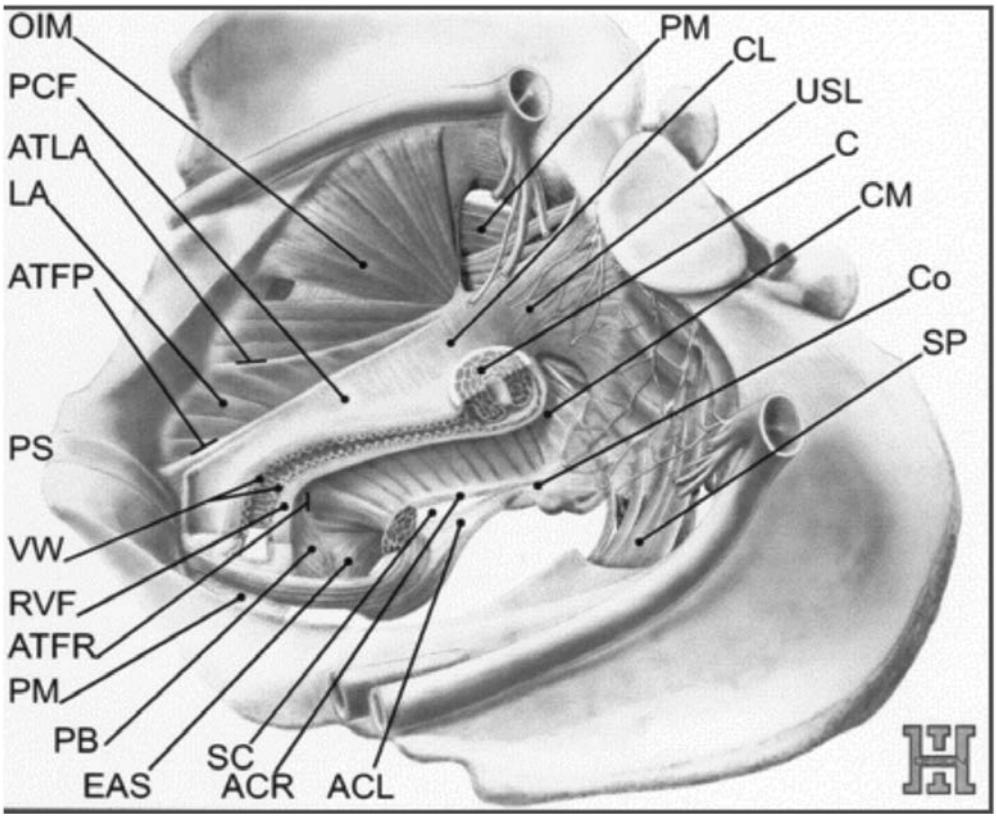


Figure B 34: Left lateral view from above the female pelvis. The vagina, endopelvic fascia, and levator ani muscle are cut in the sagittal plane. Urethra, urinary bladder, and rectum have been removed. OIM, obturator internus muscle; PCF, pubocervical fascia; ATLA, arcus tendineus levator ani; LA, levator ani muscle; ATFP, arcus tendineus fasciae pelvis; PS, pubic symphysis; VW, vaginal wall; RVF, rectovaginal fascia; ATFR, arcus tendineus fasciae rectovaginalis; PM, perineal membrane; PB, perineal body; EAS, external anal sphincter; SC, space of Courtney; ACR, anococcygeal raphe; ACL, anococcygeal ligament; PM, piriformis muscle; CL, cardinal ligament; USL, uterosacral ligament; C, cervix of the uterus; CM, coccygeus muscle; Co, coccyx; SP, sacral plexus. Illustration: Ivan Helekal [41].

perpendicular to the fiber direction of the puborectal and pubovisceral muscles and shows them as "clusters" of muscle on either side of the vagina. The sagittal plane consistently demonstrates the puborectal muscle passing dorsal to the rectum to form a sling that can be seen as a "bump". This plane is also parallel to the pubovisceral muscle fiber direction and shows the puboperineal muscle [43]. (**Figure B 35**).

b) Pathophysiology of pelvic floor disorders

1. Levator ani defects

One of the major contributions of MRI to understanding the cause of pelvic floor dysfunction came from its documentation. LA injury seen after vaginal birth is highly associated with POP. In [44] a case-control study with group matching for age, race, and hysterectomy status, women with prolapse (cases) were compared to those with normal support (controls). Major defects were those that lost more than 50% of the muscle bulk. Cases were more likely to have major levator ani defects than controls (55% compared with 16%), but equally likely to have minor defects (16% compared with 22%) (**Figure B 36-37**). Women with defects generated less vaginal closure force during a pelvic muscle contraction than women without defects (2.0 Newtons compared with 3.1 Newtons) and women with prolapse also generated less vaginal closure force during pelvic muscle contraction than controls (2.0 Newtons compared with 3.2 Newtons). This confirmed earlier uncontrolled observations with ultrasound [45].

It is important to distinguish between muscle thickness and muscle damage. A woman with a normally thin but intact muscle may have less muscle substance than a woman with naturally bulky muscles who has a defect that has involved 25% of her muscle bulk. The issue of muscle damage is relevant to seeing who is injured, while that of muscle bulk, with the capability of the muscle

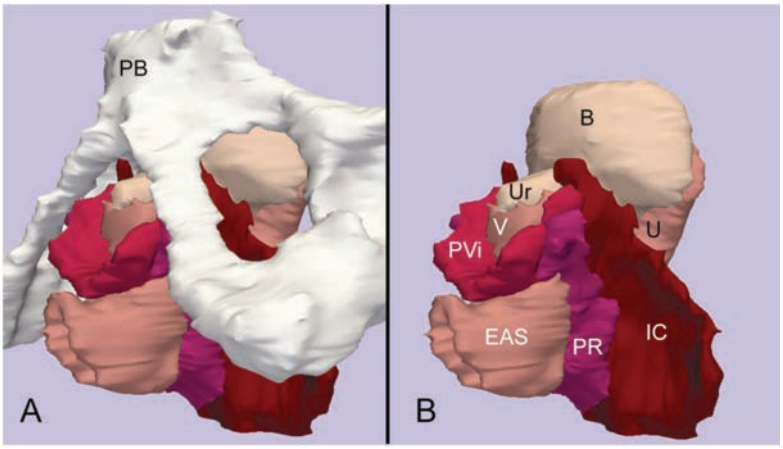


Figure B 35: Three-dimensional model of levator ani subdivisions including the pubic bone and pelvic viscera. This model was created by using the magnetic resonance images shown in Figures 2, 3, and 4. The pubovaginal, puboperineal, and puboanal muscles are all combined into a single structure, the pubovisceral muscle. Inferior, left 3-quarter view. B. The same model without the pubic bone. PB, pubic bone; V, vagina; U, uterus; Ur, urethra; B, bladder; IC, iliococcygeus muscle; PR, puborectal muscle; PVi, pubovisceral muscle; EAS, external anal sphincter. © DeLancey 2006. Margulies [43].

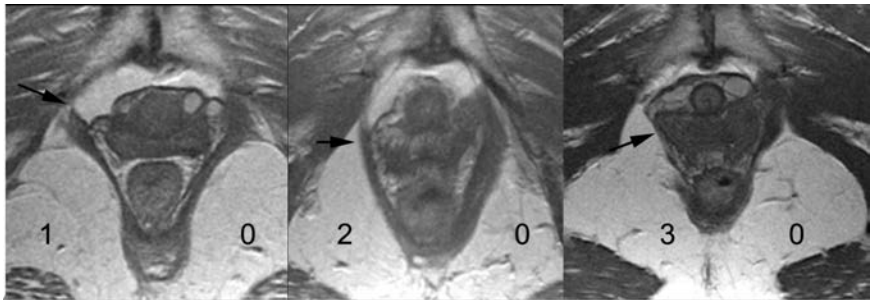


Figure B 36: Examples of grades of defects in the pubovisceral portion of the levator ani muscle in axial magnetic resonance images at the level of the mid urethra. These were selected to illustrate degrees of defects in individuals with a normal contralateral pubovisceral muscle. The score for each side is indicated on the figure, and the black arrows indicate the location of the missing muscle. A. A grade 1 defect; B. A grade 2 defect; and C. A grade 3 defect. © DeLancey 2006 [44].

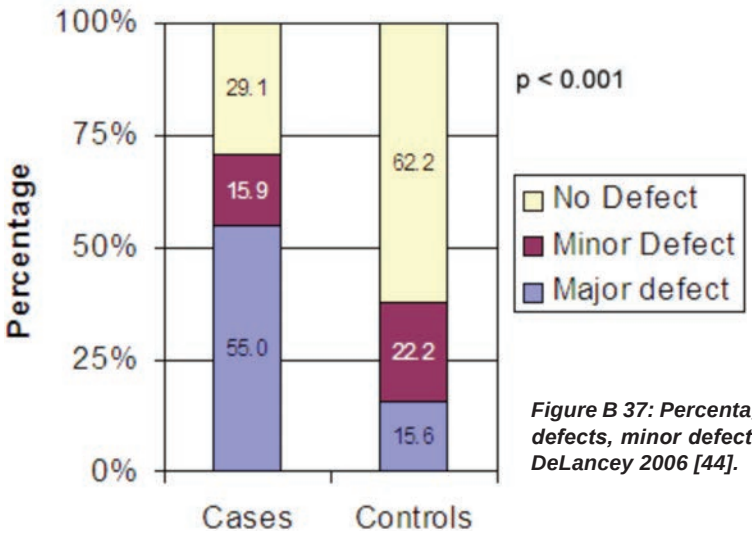


Figure B 37: Percentages of cases and controls with no defects, minor defects, and major defects; p≤ 0.001. © DeLancey 2006 [44].

to close the hiatus. Hoyte et al [46] examined 10 women with prolapse, 10 with urodynamic stress incontinence, and 10 asymptomatic volunteers. Mean 3-dimensional parameters in the 3 groups showed levator volumes of 32.2, 23.3, and 18.4 cm3 (P <0.005); hiatus widths of 25.7, 34.7, and 40.3 mm (P <0.005); left levator sling muscle gaps of 15.6, 20.3, and 23.8 mm (P =0.03), right levator sling muscle gaps of 15.6, 22.5, and 30.8 mm, (P =0.003), and levator shape (90%, 40%, and 20% dome shaped; P <0.005). Subsequently, using a novel thickness mapping [47], they found thicker, bulkier anterior portions of the levators in asymptomatic women, compared with women with prolapse or urodynamic stress incontinence while the more posterior portions of the muscle were not affected.

Hsu and colleagues quantified levator ani muscle cross-sectional area as a function of prolapse and muscle defect status [48]. Using muscle cross-sections from 3-D reconstructions they found that women with visible levator ani defects on MR have less muscle ventrally compared with women with intact muscles. Women with major levator ani defects had larger cross-sectional areas in the dorsal component than women with minor or no defects indicating a compensatory hypertrophy in this area. Furthermore, after controlling for prolapse, women with levator defects appear to have a more caudal location of their perineal structures and larger hiatuses at rest, maximum contraction, and maximum Valsalva manoeuvre [49].

Among women with POP, those with major LAD appear less likely to experience stress incontinence when “coughing, laughing, or sneezing” (odds ratio (OR) 0.27) and when “twisting, reaching, lifting, or bending over” (OR 0.26) than women with normal muscles. They are less likely to have obstructive symptoms characterized by assuming an “unusual toileting position” or “changing positions...to start or complete urination” (OR 0.27). Women with minor LAD appear more likely to experience stress incontinence with exercise (OR 3.1) and urge incontinence (OR 4.0) than those with normal muscles. Lower urinary tract symptoms are therefore less common among women with prolapse and major levator ani defects and more common among those with minor defects [50]. This may be explained by the fact that the women with major LA defects have larger prolapses than those who do not have major LA defects. It is a clinical observation that prolapse often reduces the occurrence of stress incontinence (urethral kinking?) and this hypothesis is consistent with the observations mentioned above.

2. Identifying the injury zone within the levator ani muscle most often involved by injury

MRI based 3D models show that in women with bilateral puborectal muscle avulsion after vaginal delivery, the damage affects the pubic origin of the muscle. This structural change alters the support to the whole endopelvic fascia and destabilizes both the anterior and the posterior vaginal walls [51]. In women with significant muscle on one side and damaged muscle in the same individual [52] the injury involves the muscle’s origin from the posterior pubic bone. (**Figure B 38**) Distortion of the surrounding connective tissue with lateral spilling of the vagina towards the obturator internus muscle is observed in 50% of women. The defect is right sided in 71% of patients. The average difference of the amount of muscle lost in these types of injury between the normal side and the defective side is up to 81% at locations nearest the pubic origin [53]. Almost all of the volume difference (13.7%, P=0.0004) is attributable to a reduction in the pubic portion (24.6%), not the iliococcygeal portion of the muscle.

3. Changes in the hiatus size and levator plate angle with prolapse

The levator ani muscle’s constant activity closes the genital hiatus. In addition to evaluating defect status and muscle bulk, MRI has revealed changes to the levator hiatus and angle of the levator plate (that midline portion of the muscle between the anus and the coccyx) which is presumed to be influenced by muscle action. Hsu and colleagues [54] studied 68 women with pelvic organ prolapse and 74 normal controls. During Valsalva, controls had a mean levator plate angle of 44.3 degrees. Cases had 9.1 degrees (21%) more caudally directed levator plate angle compared to controls (53.4 degrees vs. 44.3 degrees), 15% larger levator hiatus length (7.8 cm vs 6.8 cm), and 24% more caudal perineal body location (6.8 cm vs 5.5 cm). Increases in levator plate angle were correlated with increased levator hiatus length (r = 0.42) and perineal body location (r =0.51). The bladder neck descent at straining is also correlated with the levator plate angle at rest, hiatus length at rest and at straining [55]. Uterine cervix descent at straining is correlated with increased hiatus length and width at straining, and greater levator plate angle (p=0.007) at straining. Paradoxically anterior rectal bulging at straining is inversely correlated with the hiatus width at rest (p = 0.04).

Perineal descent and localised outward bulging of the levator ani during Valsalva was evaluated by Gearhart and colleagues [56]. In this study, dynamic MRI of symptomatic patients with pelvic floor prolapse demonstrated unsuspected levator ani hernia. Patients with POP, fecal and/or urinary incontinence, or chronic constipation were evaluated. Fifteen percent of patients (12/80) had unilateral (n = 8) or bilateral (n = 4) levator ani hernias on MRI. Perineal descent on physical examination was associated with a levator ani hernia in nine patients.

4. MRI and the bony pelvis

Studies of the bony pelvis dimensions and their associations with POP, levator ani defects and stress in-

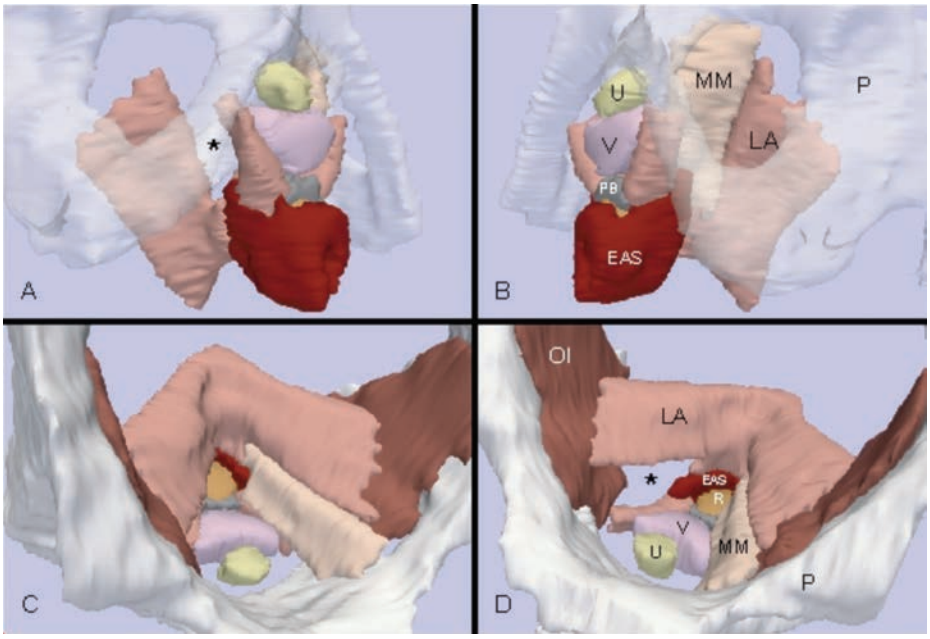


Figure B 38: Three-dimensional model generated from the axial MR scans shown in Figure A, and B, Oblique right and left inferolateral views, similar to the dorsal lithotomy position, are shown. In these panels the pubic bone is semitransparent and the obturator internus muscle is not shown. C, and D, Oblique right and left views peering over the pubic bone and down to the pelvic floor are shown. The urethra, vagina, and rectum have been truncated so as not to obscure the views of the levator muscles. EAS, external anal sphincter; LA, levator ani; MM, mirror image of the missing muscle; P, pubis; PB, perineal body; U, urethra; V, vagina. The missing muscle in A and D is denoted (asterisk). © DeLancey 2006 [52].

continence have recently been undertaken. Stein et al showed that bony pelvis dimensions are similar at the level of the muscular pelvic floor in white women with and without POP [57]. Further evaluation of the bony pelvis using MRI scans has also improved our understanding of the natural history of stress urinary incontinence as well as the associations of the bony pelvis dimensions with the prevalence of levator defects (Berger et al unpublished data). Other studies investigating the role that different pelvis shapes play for specific diseases will be described in subsequent sections of this review.

5. MRI OF PELVIC FLOOR AFTER VAGINAL DELIVERY

There are changes observed in the levator ani and pelvic floor musculature immediately after delivery, which change over time. Boreham [58] evaluated the normal visibility of the levator in post term nulliparas using 3-dimensional (3-D) MRI. LA insertion into the symphysis was visible in 93%, and the iliococcygeus muscle assumed a convex shape (arch) in 92% of 84 nulliparas. Mean LA volume was 13.5 (3.7) cm3. Interestingly there was a positive association between LA volume and higher fetal station with increasing BMI. The muscle signal intensity appears increased at 1 day postpartum on T2 weighted images, but normal by 6 months. The urogenital and levator hiatus decreases significantly by 2 weeks postpartum [59]. More recently, Lienemann [60] found thinning of the puborectal muscle in primiparous women after vaginal delivery (0.6 cm vs. 0.8 cm) and increased descent of the bladder, vaginal fornix, and anorectal junction during straining compared to healthy asymptomatic nulliparous volunteers.

The descent of the bladder and cervix on straining appears greater in women who delivered vaginally compared to those who had cesarean delivery and to nulliparous women. There is a positive correlation between the duration of labour and the area of the levator sling and also between birthweight and the descent of the cervix on straining [61].

The role of levator ani muscle damage and stress soon after birth has also been studied. An investigation of 80 nulliparous asymptomatic women and 160 vaginally primiparous women half of whom had new stress incontinence after their first birth was conducted 9 months after delivery. A visible defect in the levator ani muscle was identified in 32 primiparous. Twenty-nine of these 32 defects were in the pubovisceral portion of the levator and three were in the iliococcygeal portion. None of the nulliparous women showed these abnormalities [62]. In a further study of this cohort [63] evaluation of obstetric factors associated with levator ani injury after first vaginal birth showed increased odds ratios for levator defect: forceps use 14.7, anal sphincter rupture 8.1 and episiotomy 3.1 but not vacuum de-

livery (0.9) epidural use (0.9) or oxytocin use (0.8). Women with levator injury were 3.5 years older and had a 78-minute longer second stage of labour. Differences in gestational age, birth weight, and head circumference were not statistically significant.

Dannecker [64] compared women after spontaneous vaginal delivery to those delivered by vacuum extraction and a control group of healthy nulliparous volunteers. Significant differences for individual POPQ component measurements were noted for points Aa and Ba, TVL, and GH (spontaneous delivery versus control) and in addition for Ap, Bp, and D (vacuum extraction versus control). Significant differences were observed for the position of bladder base, bladder neck, posterior vaginal fornix, anorectal junction, hiatus perimeter and depth of rectocele. Looking into comparisons with the spontaneous vaginal delivery group, on clinical examination, there was more evidence of anterior vaginal wall descent after vaginal delivery, and TVL and GH. Differences between the groups with regard to points Ap and Bp reached only marginal significance. With MRI measurements primiparous women who underwent spontaneous vaginal delivery as compared to nulliparous women showed considerable and statistically significant descent of almost all assessed structures at rest and on straining. Bladder base, bladder neck and the anorectal junction descended even below the respective reference lines. The bladder neck showed considerably increased mobility, and the genital hiatus showed an increased change on straining. The depth of rectocele increased more than three times. One of 26 women (4%) had a rectocele >3 cm. POPQ measurements that differed significantly between primiparous women after vacuum extraction and nulliparous women of the control group indicated more evidence of anterior and posterior vaginal wall descent after vacuum extraction. In addition TVL and GH was increased and PB was decreased after vacuum extraction. MRI measurements after vacuum extraction, showed considerably increased descent and mobility of the bladder base and bladder neck on straining, and descent of the anorectal junction was prominent. The mean depth of rectocele was four times bigger than in the nulliparous group. Four of 49 women (9%) had a rectocele >3 cm.

Branham and colleagues [65] evaluated postpartum changes in the levator ani muscle in relation to obstetric events. In those subjects recovering to normal MR by 6 months an average of nearly 60% increase in right puborectalis muscle thickness compared with that seen at 6 weeks indicated the extent of the injury. Younger white primiparous women had a better recovery at 6 months than older white women. Subjects experiencing more global injury, in particular to the iliococcygeous, tended not to recover muscle bulk.

Heilbrun and colleagues investigated the correlation between the presence of major LAM injuries on MRI with faecal incontinence (FI), POP, and urinary incontinence (UI) in primiparous women 6-12 months postpartum using a scoring system to characterise LAM injuries on MRI. Major LAM injuries were observed in 19.1% women who delivered vaginally with external anal sphincter (EAS) injuries, 3.5% who delivered vaginally without EAS injury, and 0% who delivered by cesarean section before labor (p=0.0005). Among women with EAS injuries, those with major LAM injuries trended toward more FI, 35.3% vs. 16.7% (p=0.10) and POP, 35.3% vs 15.5% (p=0.09), but not UI (p=1.0). These data confirm that both EAS and LAM are important for fecal continence and that multiple injuries contribute to pelvic floor dysfunction [66] .

Handa and colleagues used MRI to measure bony and soft tissue pelvic dimensions in 246 primiparas, 6-12-months postpartum. A deeper sacral hollow was significantly associated with fecal incontinence (p = 0.005). Urinary incontinence was marginally associated with a wider intertuberous diameter (p = 0.017) and pelvic arch (p = 0.017). There were no significant differences in pelvimetry measures between women with and without prolapse in this study[67].

6. MRI and biomechanical investigation of the pelvic floor

MRI has allowed anatomically based biomechanical models to be constructed. Simulations have demonstrated important interactions between muscle and connective tissue in providing anterior vaginal wall support [68]. MRI has enabled construction of finite element analysis [69] [70]. It has also allowed for capture of 3D shape variation of the levator ani during straining where complete volumetric imaging is prohibited by the inherent temporal resolution of the scanning technique [71].

Chen developed and validated recently a 3D finite element computer model of the anterior vaginal wall and its supports based on spatial data from MR scans of normal women. They determined the combinations of muscle and connective tissue impairments that result in cystocele formation, as observed on dynamic MRI geometry from a healthy nulliparous woman. It included simplified representations of the anterior vaginal wall, levator muscle, cardinal and uterosacral ligaments, arcus tendineus fascia pelvis and levator ani, paravaginal attachments, and the posterior compartment. The authors found that development of a cystocele requires a levator muscle impairment, an increase in abdominal pressure, and weakening of apical and paravaginal support [72]. These simulations provide a way to see what specific changes in structural components do to pelvic organ support in ways that would be impossible to study in living women.

7. Racial differences in pelvic dimensions

There are differences that exist in the occurrence of

prolapse in women from different racial backgrounds. Several groups have evaluated racial differences in the bony pelvis and the levator ani muscles [73] [74] [75]. In a study by Handa et al [73], a wider transverse diameter (odds ratio 3.4) and a shorter obstetrical conjugate (odds ratio 0.2) were associated with pelvic floor dysfunction after controlling for age, race, and parity. Hoyte and colleagues found that levator ani volume was significantly greater in African-American (AA) asymptomatic nulliparous women without pelvic floor dysfunction compared to white American (WA) ones (mean = 26.8 vs. 19.8 cm3, P = .002). The levator-symphysis gap was smaller in the AA (left-18.2, right-18.8 mm) versus the WA group (22.4, 22.6 mm, p = 0.003, 0.048) on the left and right. Significant differences were also seen in bladder neck position, urethral angle, and the pubic arch angle [74]. In another study with 3D MRI levator thickness was significantly greater bilaterally in black nulliparas compared to white ones, yet obturator internus muscle thicknesses were similar [75].

Handa found that the pelvic inlet was wider among white women than African-American women (10.7+/-0.7 cm compared with 10.0.+0.7 cm, P<.001). The outlet was also wider (mean intertuberous diameter 12.3+/-1.0 cm compared with 11.8+/-0.9 cm, p<.001). There were no significant differences between racial groups in interspinous diameter, angle of the subpubic arch, anteroposterior conjugate, levator thickness, or levator hiatus. [76].

A broader group of races was studied by Rizk et al with MR in asymptomatic multiethnic nulliparous young volunteers from 5 ethnic groups (Emirati, other Arab, Filipino, Indian/Pakistani, and European/white volunteers), with the white volunteers as the reference group [77]. The white volunteers were taller (p< 0.0001) than the other women. Their levator hiatus was longer than the Emirati women (p= 0.03) and wider than the Filipino women (p= 0.04). The bladder neck descent on straining was also greater than the other groups (p< 0.00001). The white women also had the longest transverse diameter of the pelvic inlet (p= 0.002). Their sagittal outlet diameter was longer than the Emirati and Arab women (p= 0.02), and their interspinous diameter was longer than the Arab women (p= 0.002).

c) Pelvic Organ Prolapse

MRI has proven to be a key assessment for understanding pelvic organ prolapse; a problem that arises from damage to connective tissue, muscles, and nerves that are invisible on standard radiography. With the advent of 3D ultrasound and MRI, the actual structures involved in the cause of prolapse can be seen and examined. This is possible not only in static scans that reveal morphological details of the pelvic structure, but also in dynamic scans where the movements of the various organs can be studied.

Evaluation of the degree of anterior compartment (bladder) and apical compartment (cervix) prolapse at maximal Valsalva using dynamic MRI showed a strong correlation between how far the bladder base and uterine cervix were below normal with r2 = 0.53 indicating that slightly over half of the observed variation in anterior compartment support may be explained by apical support [78]. Further analysis in the same patients showed that vaginal length was the strongest secondary factor determining 30% of the variation after apical descent was taken into account. This finding that a longer vaginal wall was associated with increasing cystocele size was unexpected, but seems consistent with clinical observations [79].

Hsu et al found that vaginal thickness is similar in women with and those without pelvic organ prolapse. However, in prolapse patients the vaginal perimeter and cross-sectional areas are 11% and 20% larger respectively [80].

Broekhuis et al studied the relationship between patient symptoms using questionnaires' domain scores and the perineal position on dynamic MR imaging of 69 women. They found that POP symptoms were associated with the degree of descent of the perineum but perineal descent was not related to anorectal and/or urinary incontinence symptoms [81].

In another study examining correlations of patients' symptoms with findings on clinical examination and dynamic MR imaging of the pelvic floor, only the domain score genital prolapse was significantly correlated in the positive direction with the degree of POP as assessed by POP-Q and dynamic MR imaging (rs = 0.64 and 0.27, respectively), whereas the domain score urinary incontinence was inversely correlated (rs = -0.32 and -0.35, respectively). The sensation or visualization of a bulge in the vagina was the only symptom which correlated positively with the degree of POP, with clinical examination and dynamic MR imaging showing similar correlation in this respect [82].

Broekhuis et al concluded that correlations for the POP staging with the use of POP-Q, dynamic MR imaging, and perineal ultrasonography are only observed in the anterior compartment [83].

1. Enterocele

In the past, enteroceles were usually only appreciated on radiographic examination after repeated straining after evacuation and usually required opacification of the vagina in order to demonstrate the insinuation of small bowel loops between the rectum and vagina [84]. MRI has proven to be a much simpler and less invasive technique for the evaluation of enteroceles. In comparisons between physical examination, intraoperative findings and MR images in women with and without prolapse, MRI was significantly superior in detecting enterocele when compared to physical examinations with a sensitivity of 87%, specificity of

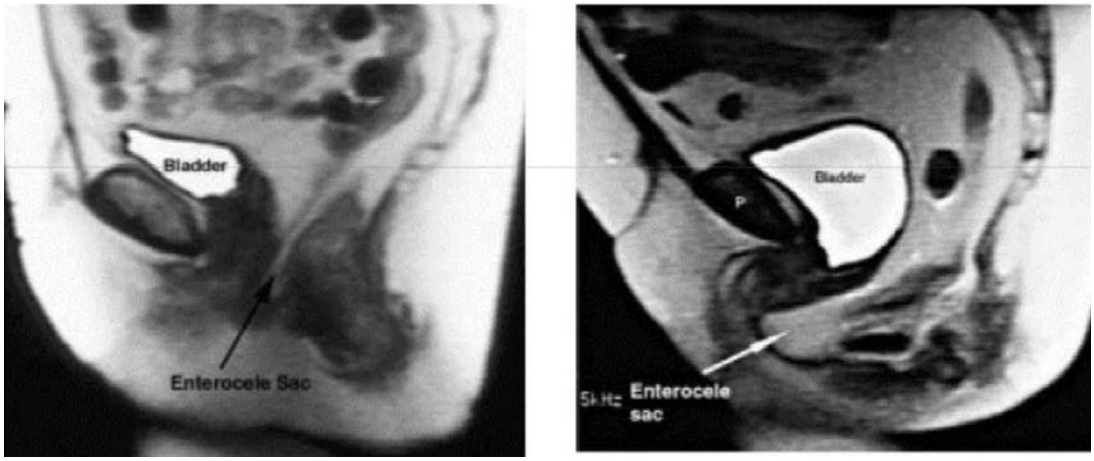


Figure B 39: Pelvic floor MRI: Enterocele at rest a) and during Valsalva b).

80%, and positive predictive value of 91% [16]. (**Figure B 39**). Similarly, MRI had a much higher sensitivity for detection of enteroceles when compared to physical exam and dynamic cystoproctography [85]. Whether or not this technique alters clinical outcome remains to be seen.

2. Cystocele

MRI has a sensitivity of 100%, specificity of 83%, and positive predictive value of 97% when evaluating for cystocele compared to intraoperative findings. In addition, urethral hypermobility and post-void urine residual can be documented, as well as evaluation of ureteral obstruction, hydroureteronephrosis and other pelvic abnormalities. **Figures B 40 a, b**

MRI can also be helpful in documenting the status of pelvic organ support as part of a program to assess operative efficacy [86] [87] and differentiating such problems as Müllerian remnant cysts from cystocele [88].

Larson et al showed that in women with anterior wall prolapse, Valsalva causes downward translation of the vagina along its length. A transition point separates a proximal region supported by levator muscles and a distal, unsupported region no longer in contact with the perineal body. In this latter region, sagittal and frontal plane "cupping" occurs. The distal vagina rotates inferiorly along an arc centered on the inferior pubis. Downward translation, cupping, and distal rotation are therefore novel characteristics of cystocele demonstrated by 3-D MR imaging [89]. (**figure B 41-42**)

3. Rectocele

The reported sensitivity of pelvic examination for diagnosis of rectocele ranges from 31% to 80% [3] [4] [6] [90] [91]. This is usually secondary to organ competition for space in the vagina with other significant prolapse [7]. In addition, it is often difficult to reliably distinguish an enterocele from a high rectocele. **Figure B 43** shows a rectocele diagnosed by dynamic MRI. A rectocele is easily seen when filled with gas, fluid, or gel. Although highly specific, when no rectal or vaginal opacification is used, MRI can miss up to 24% or rectoceles [16]. When rectal opacification is used, a correct diagnosis of rectocele can be made in 100% of patients studied when compared to intraoperative findings [19]. Rectal opacification by introducing sonographic transmission gel or gadolinium into

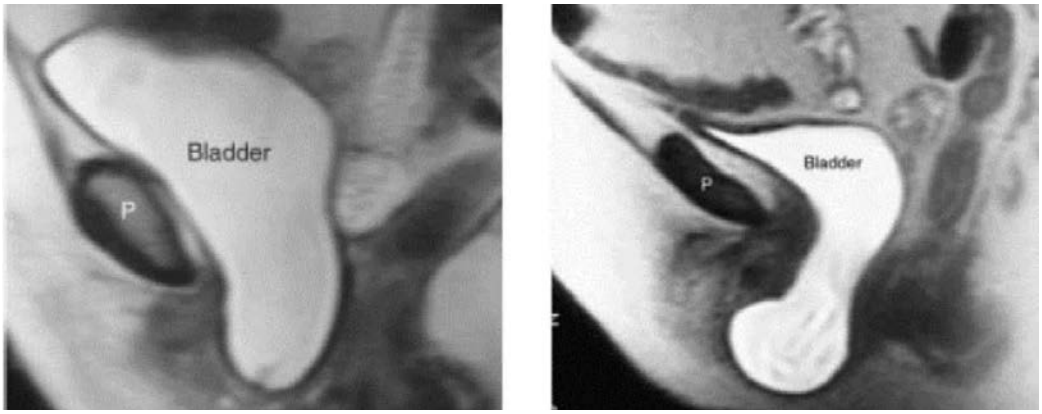


Figure B 40: Pelvic floor MRI: grade 2 (a) and grade 3 (b) cystocele

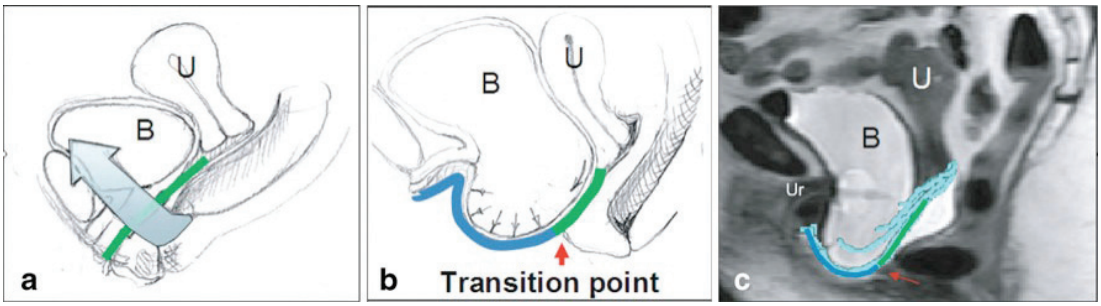


Figure B 41: Anterior vaginal wall models at rest and with Valsalva. A Midsagittal MR slice with subsequent outline of vaginal wall at rest (pink) and with Valsalva (turquoise, panel b). Uterovaginal junction shown with dark pink square. c Addition of midsagittal pelvic bones (white) and anterior vaginal wall model. d Powerpoint image of both resting and straining anterior vaginal wall models and their relationship to the normalized ATFP, shown here as green line extending from the pubic symphysis to the ischial spines (green square), or the P-IS line. © DeLancey 2009 [89].

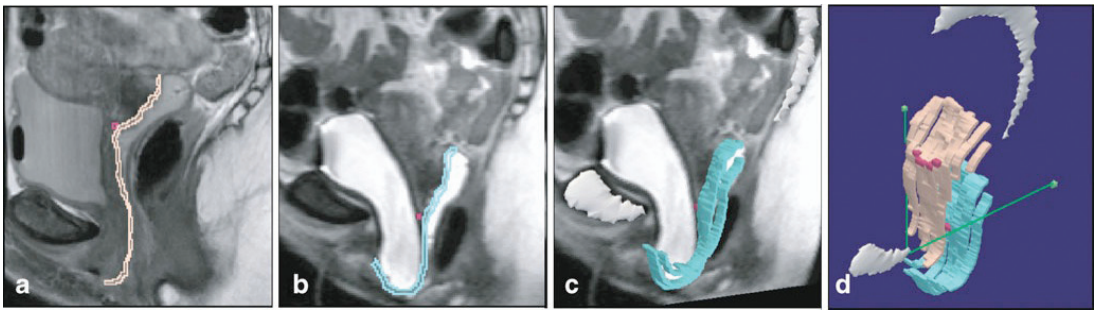


Figure B 42: Midsagittal view of pelvis with normal support (a) and with prolapse (b). Green represents area where levators (blue arrow) provide cranial reaction forces to counteract the action of intraabdominal pressure and caudal movement of the anterior wall. The red arrow delineates the transition to unsupported region lacking this opposing set of reaction forces (blue line), thereby creating a pressure differential acting caudally on that region. c Red arrow illustrates this point on midsagittal MRI with modeled anterior vaginal wall. U uterus, B bladder, Ur urethra. © DeLancey 2009 [89].

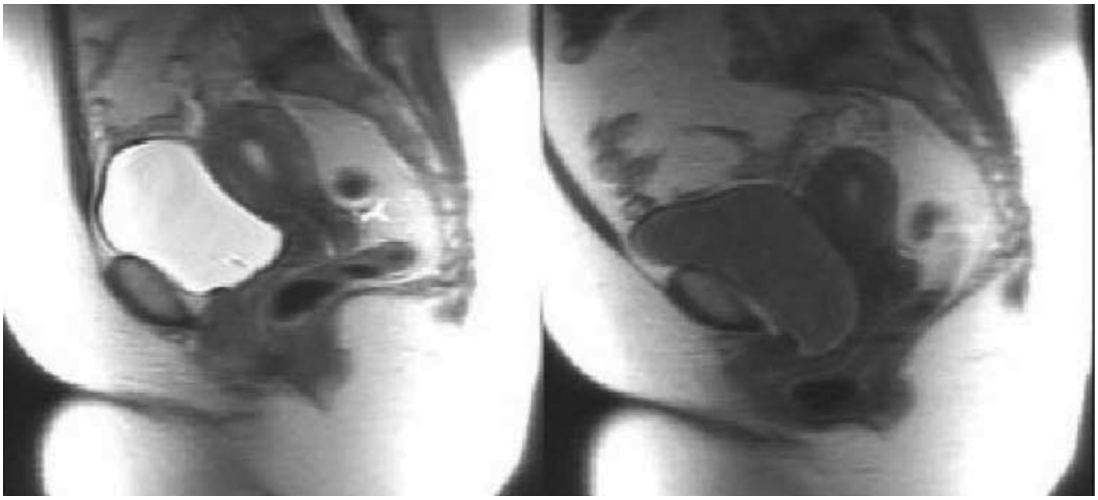


Figure B 43: Resting (a) and straining (b) midline sagittal section showing a rectocele that traps intestinal contents.

the rectum is therefore necessary to increase MRI's ability to diagnose rectocele. In complex situations such as rectal intussusception [92] MR can provide important information by distinguishing mucosal from full-thickness descent. MR defecography also shows movements of the whole pelvic floor. In this study, 30% of the patients studied were found to have associated abnormal anterior and/or middle pelvic organ descent that would not necessarily be seen in traditional evacuation proctography (unless opacification of vaginal, bladder and intestine are carried out).

At maximal Valsalva on MRI, structures are more caudal and the hiatus longer in women with posterior prolapse. The posterior vaginal wall is longer; this length and point Bp strongly correlate with MRI prolapse size ($r=0.5$; $p=0.002$; $r=0.7$; $p<0.001$, respectively). [93]

What remains unclear is the relationship between anatomical findings and functional problems. The diagnosis of an anatomical abnormality does not mandate surgery. Simply identifying a rectocele on an imaging study based on the location of the intestinal lumen to a reference line does not mean that correction of the rectocele will cure defecation problems. Rectocele surgery is not without complications and the risk of dyspareunia after posterior colporrhaphy is real. Attention should be paid to make sure that symptoms are truly depending on stool trapping and the condition must be shown on imaging.

4. Uterine Prolapse

Although uterine prolapse is easily diagnosed on physical examination MRI is an excellent modality to record the structural relationships with the bladder and rectum in patients with uterine prolapse (**Figure B 44**). In addition to depicting the position of the uterus and adjacent organs, it has the ancillary benefits of evaluating uterine size, position, orientation (retroversion) and pathology (fibroids, tumors, Nabothian cysts. etc.), but also ovarian pathology (cyst or mass) which may sometimes prove useful if these problems have not been picked up on physical examination. This is helpful information in determining the route of hysterectomy. Furthermore, MR imaging provides information on the presence or absence of cystocele, rectocele, urethral hypermobility and urethral diverticula, and evaluates for ureteral obstruction [10] [11] [14] [15] [16] [94]. Gousse et al. report a sensitivity of 83%, a specificity of 100% and a positive predictive value of 100% when comparing dynamic MR imaging to intraoperative findings. These numbers were similar when compared to physical examination alone [16]. More importantly, MRI was able to clearly define the other compartments of the pelvic floor and diagnose uterine and/or ovarian disorders in 30 of 100 patients evaluated [16].

5. Grading of pelvic floor relaxation

A number of studies have described reference values for grading POP [15] [16] [18]. In order to evaluate pelvic organ descent, certain anatomic landmarks are used. The pubococcygeal line (PCL) marks the distance from the pubis to the coccyx and serves as a fixed anatomical reference. In the nomenclature used by Comiter et al. [15], Gousse et

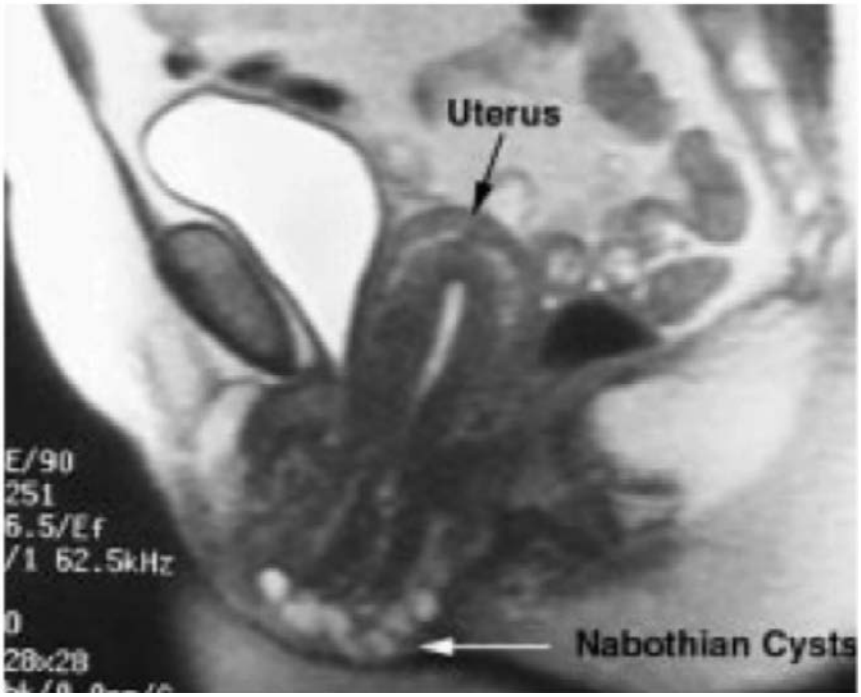


Figure B 44: Pelvic Floor MRI: Uterine Prolapse

al.[16],and Barbaric [23], the width of the levator hiatus is measured as the distance from the pubis to the pubococcygeus muscle (H-line). The hiatus is formed by the puborectalis muscle and encompasses urethra, vagina, and rectum. The M-line depicts the relaxation of the muscular pelvic floor by measuring the descent of the levator plate from the PCL. Using these three simple measurements, an MRI classification for degree of POP has been described [15] [23]. In the normal population, during straining, the hiatus (H-line) is less than 6 cm long and does not descend (M-line) more than 2 cm below the PCL. The upper urethra, urethrovesical junction, bladder, upper vagina, uterus, small bowel, sigmoid colon, mesenteric fat and rectum are all above the H-line. A combination of hiatal enlargement and pelvic floor descent constitutes relaxation. As the pelvic floor descends, so do the organs above it. The grading system for prolapse of any pelvic organ is based on 2 cm increments below the H-line. By determining the degree of visceral prolapse beyond the H-line, the degree of rectocele, enterocele, cystocele, and uterine descent can be graded in a 0 to 3 scale as follows: 0=none, 1=minimal, 2=moderate, and 3=severe (**Table 2**). Other similar systems have been described [18] highlighting the need for standardization of nomenclature and grading of organ prolapse using MRI. In a small study, Ginath et al showed that MRI measurements of pelvic landmark angles can differentiate between women with and without uterine prolapse and correlate best with POPQ point C [95].

Novellas and colleagues evaluated two classification systems (using the PCL and the midpubic line, MPL) in 30 patients with symptoms of POP. For prolapse detection, the correlation between clinical examination and MRI ranged between 74 and 89%. For prolapse staging, the correlation was poor to moderate. Inter-observer agreement was good to very good (kappa between 0.67 and 0.95). It was slightly better at the mid stage, with both systems (kappa between 0.83 and 0.97). Comparison of the inter-observer agreement between both MRI classification systems showed better results for the system using the pubococcygeal line ($p<0.005$). The classification system based on the pubococcygeal line appeared more reliable and simple for the evaluation of pelvic prolapse on MRI [96]. In another study, agreement between clinical and PCL staging was fair in the anterior (kappa = 0.29) and poor in the apical (kappa = 0.03) and posterior (kappa = 0.08) compartments. Agreement between clinical and MPL staging was fair in the anterior (kappa = 0.37), apical (kappa = 0.31), and posterior (kappa = 0.25) compartments. The MPL had higher agreement with clinical staging than the PCL in this study. However, neither reference line had good agreement with clinical staging [97]. The intra- and interobserver reliability of dynamic MR staging in POP patients has also been evaluated using various anatomical landmarks in relation to the PCL, H-line, and MPL. Clinical measurement points were assessed in relation to the mid-pubic line. Overall, the intra- and interobserver reliability of MR imaging measurements was excellent to good. The PCL showed superior reliability (intraclass correlation coefficients-ICC range 0.70-0.99). The reliability of clinical measurement points, however, was only moderate (ICC range 0.20-0.96). The intra- and interobserver reliability of quantitative prolapse staging on dynamic MR imaging were good to excellent. The PCL appeared the most reliable to use [98].

Singh et al [99] compared a new technique of grading POP by using dynamic MRI with the clinical staging proposed by the POP-Q system [100]. A new reference line, the mid-pubic line, was drawn on the MR image to correspond to the hymenal ring marker used in the clinical staging. The proposed staging by MRI showed good correlation with the clinical staging (kappa = 0.61). Torricelli [101] also used MRI to evaluate functional disorders of female pelvic floor. In symptomatic women MRI confirmed the pelvic examination findings in all cases; MRI also detected additional alterations (4 cases of uterine prolapse and 3 of enterocele) that had been missed at clinical evaluation. Deval [102] compared dynamic MR imaging with physical examination as an alternative to dynamic cystoproctography for the evaluation of POP. PCL and puborectalis muscle were the reference points. The grading system is based on degree of organ prolapse through the hiatus and the degree of puborectalis descent and hiatal enlargement. They also used, the mid pubic line, which was drawn on the MR image to correspond to the hymenal ring marker used in clinical staging. Intra-operative findings were considered the gold standard against which physical examination, dynamic colpocystodefaecography and MRI were compared. The sensitivity, specificity and positive predictive value of MRI were 70%, 100%,

Table 2. Grading of hiatal enlargement, pelvic organ prolapse and pelvic floor descent using MRI

Grade	Hiatal enlargement	Pelvic Organ Prolapse	Pelvic floor descent
0	Less than 6 cm	Organ above H line	0-2 cm
1	6-8 cm	0-2 cm below H line	2-4 cm
2	8-10 cm	2-4 cm below H line	4-6 cm
3	10 cm or more	4 cm or more below H line 6	cm or more

100% for cystocele; 42%, 81%, 60% for vaginal vault or uterine prolapse; 100%, 83%, 75% for enterocele; 87%, 72% and 66% for rectocele. More recently Etlik [103] found physical examination and MR findings to be very concordant in the diagnosis of pelvic prolapse. Statistical correlations in the stages of prolapse between both of the methods were significant for anterior and middle compartment ($p < 0.01$), as well as for posterior compartment ($p < 0.05$).

d) Assessing Treatment Outcome

1. Pelvic Organ Prolapse Operations:

Several studies have evaluated the anatomic changes seen after surgical procedures using MRI to better understand how surgical therapies affect pelvic support and structures. Lienemann et al. [104] evaluated women after abdominal sacrocolpopexy and found that functional MRI identified the exact sacral fixation points after the procedure and easily identified the axis of the vagina and the exact position of the synthetic material used for the repairs. Sze [105] used MRI to study vaginal configuration on MR after abdominal sacrocolpopexy and sacrospinous ligament suspension. This study demonstrated the differences in the geometry of these two operations and should prove helpful in establishing outcome variables for different surgical procedures. Similarly Rane [106] used MRI to compare the vaginal configuration following transvaginal sacrospinous fixation (SSF), posterior intravaginal slingplasty (PIVS) (infracoccygeal sacropexy) and sacrocolpopexy (SCP) and demonstrated improvements in the restoration of vaginal configuration and differences between the procedures in final anatomy. Boukerrou [107] compared outcomes of 1) abdominal sacral cervicopexy, 2) vaginal hysterectomy with paravaginal repair, sacrospinous suspension and posterior colporrhaphy and 3) sacrospinous suspension and posterior repair without paravaginal suspension with MRI. The correction provided by vaginal route was found to result in a return of the bladder and the vaginal apex to their normal positions. In addition, vaginal shortening and postoperative change in vaginal orientation were not present postoperatively.

Relationship between assessment of surgical correction studied with MR imaging and symptoms have been studied. Gufler [108] compared preoperative evaluations with those two to four months after surgery. Of the seven patients who had symptoms postoperatively, only two had abnormal findings on physical examination but MRI showed pathologic findings in five of the seven patients. Huebner et al assessed symptomatic changes after anterior levatorplasty with morphologic changes visualized by MR defaecography [109]. Anterior levatorplasty improved quality of life in patients with symptomatic rectocele and correction of rectocele is accurately documented by MR defecography, however only moderate correlation between morphologic and clinical improvements was observed.

MRI has also been used for the evaluation of the effectiveness of POP surgical mesh procedures.

Dynamic MRI may evaluate the support of anterior and posterior pelvic floor structures by anterior and posterior polypropylene implant respectively. But dynamic MRI evaluations in a small series by Siegmann and colleagues suggest that if one compartment of the pelvic floor is repaired another compartment frequently (73.3%) develops dysfunction. These results did not correspond to clinical symptoms on short-term follow-up (3 months) indicating the need for long-term follow-up studies to prove if dynamic MRI can reliably identify significant POP after surgery and before the onset of symptoms [110]. In another small series of ten women by Kasturi et al [111] undergoing intervention for POP with Prolift, postoperative MRIs supported the inert nature of polypropylene mesh.

Recently Larson et al examined structural relationships between anterior mesh kit suspension points and the upper vagina in women with normal support. Using MRI generated 3D models, they found that the anterior vagina extended above superior attachment points in 100% of women at rest and in 73% during Valsalva. It extended posterior to them in 82% and 100% (rest and Valsalva, respectively). The mean percentage of anterior vaginal length above superior anchoring sites was 40 ± 14% at rest and 29 ± 12% during Valsalva. The upper vagina was therefore found to lie above and posterior to superior suspension points in the majority of women with normal support [112].

2. Pelvic Muscle Exercises

Studies on the effects of pelvic muscle training on the pelvic floor [113] demonstrate reduced levator ani surface area and volume encircled by the levator ani muscle during contraction. When elite athletes are compared to normal women significant differences appear in the cross-sectional area and width of the pelvic floor muscles, [114]. These types of studies are being facilitated by improved techniques of aligning contracted and non-contracted muscle [115].

3. Comparison Of Mri With Other Examinations And Assessment Of Reliability

Dynamic contrast roentography and multiphasic fluoroscopic cystocolpoproctography (CCP) have previously been considered the best radiological studies for detecting POP. These studies rely on the opacification with contrast material of the bladder, vagina, small bowel, and rectum with all organs opacified together or in phases with each organ opacified individually prior to each straining phase [4] [106] [109][113]. These studies fail to detect up to 20 percent of all enteroceles [94] [116] [117] [118]. Therefore, MRI has proven to be a much simpler and less invasive technique for the evaluation of

enteroceles. In addition, MRI is able to differentiate the enteroceles according to their contents (small bowel, large bowel, rectosigmoidocele or mesenteric fat). MRI is also an excellent study to differentiate high rectoceles from enteroceles, thus allowing adequate surgical planning and safer planes of dissection [15] [16] [19] [85]. Although multiphasic MRI with opacification of organs and multiphasic fluoroscopic CCP have similar detection rates for enterocele [116], excellent images can be obtained from dynamic MRI without contrast for opacification of the small bowel or rectal contrast. Thus the minimal added information obtained by contrast administration does not seem to warrant the invasiveness of organ opacification at this time [16] [84] [117]. However, recent data suggest that MRI without rectal contrast shows statistically fewer pelvic floor abnormalities than CCP. Except for enteroceles, MRI with rectal contrast shows statistically similar frequency of POP as CCP [119].

Evacuation proctography has been used to diagnose enterocele, rectoceles, perineal descent and rectal intussusception. Dynamic contrast roentography or fluoroscopic CCP have also been used [4] [90] [91] [116] [120] to diagnose rectoceles. The disadvantages of these techniques are the inability to visualise the soft tissue planes comprising the pelvic floor, their invasiveness, and their use of significant levels of ionizing radiation. Without the use of rectal opacification, MRI appears to be a poor choice for the evaluation of rectoceles missing up to 25% of such defects. With rectal opacification a correct diagnosis of rectocele can be made in 100% of patients in comparison to intraoperative findings [19]. Triphasic dynamic MRI and triphasic fluoroscopic CCP have similar detection rates for rectocele [116]. Upright dynamic MR defaecating proctography has been reported [121]. Although these studies might prove to be more sensitive in detecting anorectal anomalies, their utility seems to be more pronounced in patients with disorders of defecation include anismus, intussusception, and others, and may be too invasive to justify their routine use in the evaluation of rectocele.

Kaufman [122] evaluated dynamic pelvic MRI and dynamic CCP in the surgical management of females with complex pelvic floor disorders. Physical examination, dynamic MRI, and dynamic CCP were concordant for rectocele, enterocele, cystocele, and perineal descent in only 41% of patients. Dynamic imaging lead to changes in the initial operative plan for 41% of patients. Dynamic MR was the only modality that identified levator ani hernias. Dynamic CCP identified sigmoidoceles and internal rectal prolapse more often than physical examination or dynamic MR. Whether this type of imaging creates measurably better outcomes remains to be seen. Singh et al [99] showed a reasonably good correlation between clinical staging and MRI staging (Kappa = 0.61) with the mid pubic line being used as a surrogate for the hymenal ring. In addition, specific features such as the levator-vaginal angle the area of the genital hiatus could be assessed quantitatively on MRI.

Torricelli [101] studied ten healthy volunteers and 30 patients with suspected pelvic floor deficiency with and without POP. They found good concordance between physical examination and MRI with four cases of uterine prolapse and three cases of enterocele seen on MRI that had not been suspected on pelvic examination. Whether these would have been detected at the time of surgery was not discussed. Deval [102] compared intraoperative findings as a gold standard for MRI based diagnosis. The sensitivity, specificity, and positive predictive value of MRI were 70%, 100%, 100% for cystoceles; 42%, 81%, 60% for vaginal vault or uterine prolapse; 100%, 83%, 75% for enteroceles; 87%, 72%, 66% for rectocele. Although all of these measurements are somewhat subjective, these figures show that it is possible to quantify the individual elements of pelvic floor dysfunction in reasonable parameters.

e) Conclusions

Proof that MR imaging has value will eventually need to come from increased operative success rates. Better documentation of preoperative and postoperative anatomy could allow us to seek reasons of operative failure. Because MR provides a detailed picture of a woman's pre-operative anatomy, once operative failures are discovered, it would be possible to look back at images from women with successful and unsuccessful operations to seek anatomical explanations for failure.

f) Consensus Statement

- MRI is not yet indicated in the routine evaluation of patients with [uncomplicated primary] pelvic organ prolapse; however data concerning the causes of prolapse are rapidly accumulating and this may change soon. It can provide useful information concerning complex prolapses and can be used in difficult cases. [Level of evidence 3, Grade of Recommendation C]

g) Future Research Areas

- Studies that identify specific defects in the connective tissue and the muscles of the pelvic floor that correlate these findings with the clinical presentation in prolapse are needed.
- Additional studies comparing MRI of healthy volunteers and patients with pelvic organ prolapse are needed to better evaluate the anatomic changes involved in pelvic floor prolapse.
- Standardization of measurement strategies and quality control in MRI, including issues related to consistency of measurement axes, maneuvers required to produce a maximal prolapse during MRI, bowel condition, bladder filling, pushing instructions, etc.)

III. SPECIAL ISSUES

1. POST-VOID RESIDUAL

Post-void residual urine (PVR) is defined as "the volume of urine left in the bladder at the end of micturition [1]. Evaluation of PVR prevalence in women with symptomatic pelvic floor dysfunction suggests that 81% have a post-void residual of 30 ml or less [2]. This is not significantly different from asymptomatic perimenopausal and postmenopausal women in whom 15% of subjects had a PVR greater than 50 ml [3]. If symptoms cannot predict elevated PVR, a urogenital prolapse beyond the hymen seems to be associated with incomplete bladder emptying [4]. Among patients older than 55 years with symptoms of overactive bladder, previous incontinence surgery, history of multiple sclerosis and vaginal prolapse stage 2 or greater, were found to be independent predictors of elevated PVR [5]. Similar data were obtained by Fitzgerald in patients with urgency incontinence, the presence of pelvic organ prolapse ≥stage 2, symptoms of voiding difficulty and absence of stress incontinence symptoms predicted 82% of patients with elevated PVR [6]. Higher prevalence of post-void residual was found in patients with stress urinary incontinence with 35.5% of women having a PVR >50 ml suggesting they have some degree of voiding dysfunction [7]. Although elevated PVR and bacteriuria are common among elderly residents in nursing homes, no association between the two was observed in a Swedish study [8]. Analysis of elderly patients with urinary incontinence failed to identify any significant association between PVR and any other clinical or urodynamic parameter [9]. Sanders and co-workers addressed the issue of the real need for measuring flow rates and post-void residual urine in women with urinary incontinence. Analysis of 408 women suggested a 4% incidence of PVR 200 ml or greater and a 6% rate of PVR 149 ml or greater. The authors calculated that only 1.5% of patients [6 of 408] had their management modified because of the results of free uroflowmetry and PVR measurement. In their opinion, these data do not justify the inclusion of these tests in the "minimal care" programme for assessing primary, uncomplicated, urinary incontinence in female patients [10].

PVR is often considered a safety parameter, which needs to be monitored in the follow-up of medical or surgical management of urinary incontinence. A number of studies have addressed the effect of antimuscarinic treatment in men with symptoms of overactive bladder to rule out the old dogma that banned the use of these drugs in elderly men. Actually, all published data suggest that antimuscarinic treatment is safe for men with benign prostatic enlargement and no significant change in PVR values was found in active treatment groups compared to placebo [11, 12]. In male patients with bladder outlet obstruction, antimuscarinic treatment may result in a significantly larger PVR (25 vs. 0 ml) that seems to be of no clinical relevance and with higher incidence of adverse events [13].

Measuring PVR is of importance in patients receiving intravesical injections of Botulinum toxin A for UUI. Significant increase of post void residual urine is observed following injection of onabolutinumtoxinA in patients with neurogenic urinary incontinence due to detrusor overcativity with 30 to 42% of patients needing to start clean intermittent catheterisation compared to 12 % in the placebo group [14]. In patients with idiopathic UUI, increase of PVR was observed in those receiving onabolutinumtoxinA compared to placebo although only 8 of 70 patients required CIC and only 3 patients had a PVR >200 ml at day 8 and only one at 6 months [15].

Although the prevalence of incomplete bladder emptying among male and female patients with urinary incontinence and pelvic floor dysfunction is low, there is a general consensus that PVR should be measured in incontinent patients [16] although the evidence suggests that only patients with UI and symptoms of voiding dysfunction are at risk [17].

a) Measuring PVR

The measurement of PVR can be performed by invasive and noninvasive means. Invasive methods include: in-and-out catheterisation and endoscopy. Noninvasive means are transabdominal ultrasonography with real-time ultrasound or fully automated systems, and radioisotope studies. In-and-out catheterisation has been considered for some time, the gold standard for the measurement of PVR. Nevertheless the method is subject to inaccuracies, if the person performing the catheterisation is not fully instructed as to the procedures and techniques to assure complete emptying (moving the catheter in and out slowly, twisting it, suctioning with syringe, suprapubic pressure), especially in cases of bladder diverticula and vesicoureteric reflux [18]. Stoller and Millard showed inaccuracies in 26% of 515 male patients evaluated by full-time urology nurses with a mean difference between the initial and the actual residual volume of 76 ml in those measurements that were found to be inaccurate [19]. After further education of the nurses, inaccurate assessments were reduced to 14% with a mean difference of 85 ml. PVR can be measured at the time of endoscopy, provided there is a blinded insertion of the instrument to avoid irrigation fluid inflow. Both invasive means are usually performed with some kind of local anaesthesia and carry a small risk of urethral damage and urinary infection.

Before the era of ultrasonography, PVR was measured non-invasively by the phenolsulfonphthaleine excretion test or with isotopes [20, 21].

In 1967, Holmes described the use of ultrasonography in the evaluation of bladder volume and this

technique rapidly gained widespread acceptance as a satisfactory level of accuracy was demonstrated [22, 23]. Using either three diameters (length, height, width) or the surface area in the transverse image and the length obtained in the longitudinal image, various volume formulae for a spherical or a ellipsoid body are utilised to estimate the bladder volume (**Table 3**). Twenty-one different formulae have been proposed over the years making assumptions about bladder shape which have often been questioned [24]. Comparison of values of bladder volumes obtained using different formulae did not result in any significant difference amongst the various calculations [25]. At present, no single formula can be regarded as the one best volume calculation formula. Several studies report sufficient accuracy with ultrasound estimation of PVR [23, 24, 26-29]. False negative results are rare with PVR less than 20 ml [30]. Recently portable scanners have been introduced, with automatic measurement of bladder volume. In a prospective comparison of one hundred measurements of PVR by portable ultrasound with measurements by catheterisation, the mean absolute error of the scanner was 52 ml [31]. For volumes below 200 ml and 100 ml, the error was 36 ml and 24 ml respectively. More recent studies suggest a good level of accuracy in both female and paediatric populations [32, 33]. Residual urine is usually referred to as an absolute value, but it can be measured as a percentage of bladder capacity.

The intra-individual variability of PVR is high from day to day and even within a 24 hours period. This was reported in men with BPH by Birch et al. and by Bruskevitz et al. [34, 35]. Griffiths et al. examined the variability of PVR among 14 geriatric patients (mean age 77 years), measured by ultrasound at three different times of day on each of two visits separated by 2-4 weeks [36]. Within-patient variability was large (SD 128 ml) because of a large systematic variation with time of day, with greatest volumes in the early morning. The inherent random variability of the measurement was much smaller (SD 44 ml). Several factors can influence PVR variability: voiding in unfamiliar surroundings, voiding on command with a partially filled or overfilled bladder, the interval between voiding and the estimation of residual (it should be as short as possible), the presence of vesicoureteric reflux or bladder diverticula. Several studies reported the questionable value of PVR as an important outcome prognosticator in male patients with benign prostatic enlargement and benign prostatic obstruction [37-42]. The cause of PVR is probably mutifactorial, and no consensus exists on the relation of PVR, bladder outlet obstruction and detrusor contractility.

b) Conclusions

Knowledge regarding pathophysiology of PVR remains unclear. In patients with urinary incontinence there is no consensus as to its value as a safety parameter and particularly its relationship with upper tract dilatation, bacteriuria and urinary infection. The intra-individual variability of PVR has been investigated mainly in male patients with bladder outlet obstruction but little information is available as to its variability in patients with urinary incontinence.

Ultrasound is the recommended method for assessing PVR because it is the least invasive and it is sufficiently accurate for clinical purposes yet it is the most expensive. In-and-out catheterisation is invasive and can be inaccurate even if carefully performed.

The general opinion is that PVR measurement forms an integral part of the study of urinary incontinence, as a safety parameter to exclude voiding dysfunction associated with incontinence.

Table 3. Comparison of different formulae to assess PVR by transabdominal ultrasound in 30 men with BPH scanned three times (35).

Author/reference	Method	Standard error	95% Confidence limits
Hakenberg et al (43)	625 x H x W x (D1+D2)/2	17.5	34.3
Poston et al (44)	7 x H x W x D1	20.0	39.2
Hartnell et al (45)	625 x H x W x D1	17.0	33.3
Rageth and Langer (46)	Nomogram based on areas	15.0	29.4

Modified from the Proceedings of the 4th International Consultation on Benign Prostatic Hyperplasia.

c) Consensus Statements

1. Residual urine measurement is recommended in the initial assessment of urinary incontinence as a safety parameter and in the evaluation of treatment outcome (**Level of Evidence 3- Grade of Recommendation C**)

2. Measurements should be performed using real-time sonography or a portable scanner or in and-out catheterisation (**Level of Evidence 3- Grade of Recommendation C**).

3. Due to intra-individual variability, in cases where significant PVR is detected by the first measurement, several measurements should be performed (**Level of Evidence 3- Grade of Recommendation C**)

4. The method of measurement should be recorded **(Level of Evidence 3- Grade of Recommendation C)**

d) Future Research Areas

1. Pathophysiology of PVR in male and female populations with UI;

2. Circadian variation of residual urine in patients with UI;

3. Determination of the cut off value of significant residual urine in different patient populations with UI

4. Residual urine as a prognostic indicator of outcome in the treatment of incontinence (**Level of Evidence 3- Grade of Recommendation C**)

c) References (see at the end of the chapter)

2. OPEN BLADDER NECK AND PROXIMAL URETHRA AT REST

The significance of open bladder neck and proximal urethra at rest observated during a voiding cystourethrogram or pelvic floor ultrasound scan remains doubtful [1] and the peer-reviewed literature is equally divided into papers associating such a condition with storage disorders and those suggesting this is a chance finding with no negative implications.

A 21% prevalence in nulliparous asymptomatic women has been reported [2]. In the non-neurogenic population there is no pathophysiological correlation between this and urinary incontinence, Digesu and co-workers reported a prevalence of 1:3 amongst females suffering LUTS. An open bladder neck at rest is not pathognomonic of sphincter incompetence although it is associated with USI [3]. In patients with stress incontinence, but also in asymptomatic women [4], funnelling of the internal urethral meatus may be observed on Valsalva and sometimes even at rest; funneling is often associated with leakage. However, funnelling may also be observed in urgency incontinence and cannot be used to prove SUI. Marked funnelling has been shown to be associated with poor urethral closure pressures [5, 6].

Reports in the peer reviewed literature suggest that an open bladder neck and proximal urethra at rest, during the storage phase, may be observed during cystography, videourodynamics or bladder ultrasound, both in patients with and without neurological disease and is interpreted as a sign of internal sphincter denervation as occurs in 53% of patients with Multiple System Atrophy [7]. Distal spinal cord injury has been associated with an open smooth sphincter area, but whether this is due to sympathetic or parasympathetic decentralisation or defunctionalisation remains uncertain [8]. Relative incompetence of the smooth sphincter area may also result from interruption of the peripheral reflex arc very similar to the dysfunction observed in the distal spinal cord injury. Twenty-one out of 54 patients with spinal stenosis were found to have an open bladder neck at rest [9]. In a review of 550 patients [10], 29 out of 33 patients with an open bladder neck had neurological disease. Although the association was more commonly seen in patients with thoracic, lumbar and sacral lesions, the difference when compared to cervical and supraspinal lesions was not significant. Damage to the sympathetic innervation to the bladder was also frequently observed in patients undergoing major pelvic surgery, such as, abdominal perineal resection of the rectum. Patients with myelodysplasia had an inordinately high incidence of open bladder neck (10 out of 18 patients versus 19 out of 290 having different neurological disorders).

Patients with sacral agenesis are included in the larger category of myelodysplastic patients and suffer from an open bladder neck with an underactive bladder. Shy-Drager syndrome is a Parkinson-like disorder with peripheral autonomic dysfunction. Neurogenic detrusor overactivity is usually found in association with an open bladder neck at rest and a denervated external sphincter [11]. Peripheral sympathetic injury results in an open bladder neck and proximal urethra from a compromised alpha-adrenergic innervation to the smooth muscle fibres of the bladder neck and proximal urethra [12). Although it can occur as an isolated injury it is usually associated with partial detrusor denervation and preservation of sphincter EMG activity. The loss of bladder neck closure suggests an autonomic neural deficit. The site and nature of the requisite deficit is unclear.

Most authors agree on the importance of the sympathetic system in maintaining the integrity of the bladder neck [13-16] although the possible role of parasympathetic innervation has been proposed by others [17, 18]. An open bladder neck at rest in children or in women without neurological disease can represent a different disorder, either related to a congenital anomaly or secondary to an anatomical pelvic floor defect. Stanton and Williams [19] described an abnormality in girls with both diurnal incontinence and bed-wetting, based primarily on

voiding cystourethrography, in which the bladder neck was wide open at rest. Murray et al [20] reported the "wide bladder neck anomaly" in 24.5% of the girls [35] and 9.3% of the boys [10] out of 251 children (143 girls and 108 boys) undergoing videourodynamics for the assessment of non-neurogenic bladder dysfunction (mainly diurnal incontinence). The authors considered the anomaly congenital and made the hypothesis that wide bladder neck anomaly in girls may provide a basis for the development of USI in later life.

The presence of an open bladder neck has been proposed to explain the pathophysiology of urinary incontinence but such hypothesis did not stand the test of time. An open bladder neck was a key point in defining type III stress incontinence according to the classification of Blaivas and Olsson [21]. This classification, no longer used in our daily practice, was based on history, imaging, and urodynamics, and distinguished five diagnostic categories of stress incontinence. Incontinence type III was diagnosed by the presence of an open bladder neck and proximal urethra at rest in the absence of any detrusor contraction suggesting an intrinsic sphincter deficiency.

In pelvic fracture with membranous urethral distraction defects, when cystography (and/or cystoscopy) reveals an open bladder neck before urethroplasty, the probability of postoperative urinary incontinence may be significant, although the necessity of a simultaneous (or sequential) bladder neck reconstruction is controversial [22-24]. Skala and co-workers suggest that an open bladder neck at rest is associated with an increased risk of postoperative complications and failure after open colposuspension [25].

a) Conclusions

In conclusion, the diagnosis of open bladder neck at rest does not seem to be helpful to diagnose the underlying cause of urinary incontinence.

b) Consensus Statements

When observing an open bladder neck and proximal urethra at rest in male patients, during the storage phase, whatever imaging technique is used, it may be worthwhile to evaluate the possibility of an underlying autonomic neural deficit. (**Level of Evidence 3, Grade of Recommendation C**)

c) Future Research Areas

1. The relation of open bladder neck and proximal urethra at rest to the different neurogenic disorder
2. Longitudinal study of wide bladder neck and proximal urethra at rest in asymptomatic women
3. Evaluate the prognostic value of the open bladder neck and proximal urethra at rest

d) References (see at the end of the chapter)

3. FEMALE URETHRAL DIVERTICULA

The prevalence of urethral diverticula ranges between 1 and 6% with rates up to 10% in among symptomatic women from tertiary referral centres [1, 2]. The suspicion of a urethral diverticulum stems from LUTS or urethral masses on physical examination. Urethral masses include leiomyoma, vaginal cysts, malignancy, ectopic ureter, granuloma and urethral diverticula. The first case of female urethral diverticulum was reported in 1805 [3]. Since the report from Davis and Cian in 1956 [4] using positive-pressure urethrography (PPU), the diagnosis has become much more common even though, despite increased clinical awareness, this pathology continues to be frequently overlooked. Urinary incontinence is often associated with a urethral diverticulum. Incontinence may be a sequel to urine loss from the diverticulum itself with stress manoeuvres, SUI or urgency incontinence [5]. Aldrige et al. [6] reported urethral diverticula in 1.4% of patients with stress urinary incontinence.

The presenting symptoms of a urethral diverticulum have classically been described as the three Ds (Dysuria, postvoid Dribbling, and Dyspareunia). Since most patients present with nonspecific lower urinary tract symptoms, and the pathognomonic presentation (postvoid dribbling, urethral pain, tender periurethral mass and expression of pus from the urethra) is very uncommon, these patients undergo extensive evaluation and treatment before a correct diagnosis is established [7, 8]. The diagnosis of a urethral diverticulum may be achieved by physical examination, voiding cystourethrography, positive-pressure (double-balloon) urethrography, urethroscopy, endocavitary (transurethral or transvaginal) or transperineal ultrasound sonography, urethral pressure profile or MRI. Positive pressure urethrography is usually accomplished using a double balloon catheter according to the method described by Davis and Cian [4]. Two different models exist: the Davis-TeLinde and the Tratner catheter. Positive-pressure urethrography (and voiding urethrography) may result in a false negative study when the inflammation of the diverticulum neck prevents contrast medium from flowing into the diverticulum cavity.

The accuracy of a diagnostic test may depend upon the characteristics of the study population and conflicting data are often reported in the peer-review literature. Blaivas et al reported a diagnostic accuracy of VCUG of 97% in a series of 66 patients and similar results (95%) were obtained by Ganabathi et al. [7, 9]. Less favourable results have been reported by others. Comparison of VCUG versus PPU in the diagnosis of urethral diverticula showed a clear superiority of the latter with good consistency among different studies [10, 11]. In some patients, VCUG only delineated the lower part of the diverticulum [12]. Ultrasound scanning and MRI should theoretically be free of such false negative imaging. Chancellor et al. [13] described the use of intraoperative intraluminal echographic evaluation which may be of help in dissecting the diverticulum and achieving

complete excision without damaging the bladder neck and urethra. A number of studies have shown that MRI is better than both voiding cystourethrography and positive-pressure urethrography and can be considered, if available, the imaging of choice when the diagnosis of urethral diverticulum is suspected [14-19] (**Figure B 28 a,b**). MRI is superior to VCUG or double-balloon urethrography, particularly in diagnosing diverticula with narrow, noncommunicating necks [15, 16]. MRI proved to be superior to radiological studies because diverticula can go undiagnosed on voiding cystourethrogram, furthermore size and complexity of the diverticulum is better defined on MRI [17]. Endoluminal MRI is considered to be of particular importance in the diagnosis of a circumferential urethral diverticulum, a condition that is relatively rare but the diagnosis may increase with the increased use of this imaging technique. Proper evaluation of the anatomy of the diverticulum is essential in planning reconstructive surgery [1, 20]. MRI also proved to be useful in diagnosing inflammation or tumour in the diverticulum [21, 22]. Endoluminal MRI with either a vaginal or rectal coil, may provide even better image quality than simple MRI [18]. A comparison of MRI versus urethrography and urethroscopy, in a group of 20 women with urethral diverticulum, reported a 69 and 77 per cent accuracy of the two latter imaging studies versus MRI [14]. When surgical findings were compared to MRI, urethrography and urethroscopy, the diagnostic ability of the three methods was 70, 55 and 55 per cent, respectively. Diverticula ostia could not be identified by MRI not withstanding the use of contrast material. Neitlich et al. [15] reported in a series of 19 patients that MRI (using a fast spin echo T2-weighted pulse sequence and a dedicated pelvic multicoil) had a higher sensitivity for detecting urethral diverticula and a higher negative predictive rate in comparison to double balloon urethrography. Blander et al.[17], compared MRI and VGUG in 27 patients with urethral diverticula and found that endoluminal (endorectal or endovaginal) MRI was extremely accurate in determining the size and extent of urethral diverticula compared to VCUG; the related information can be critical when planning surgical approach, dissection and reconstruction. In conclusion, review of the peer reviewed literature suggests that positive pressure urethrography is still a valuable tool to diagnose female urethra diverticula notwithstanding both ultrasound sonography and particularly MRI represent better alternatives with a significantly higher diagnostic accuracy.

In males, both VCUG and ultrasonography can be successfully used to diagnose syringocele (cystic dilatation of the Cowper's gland), congenital and acquired diverticula [23].

a) Conclusions

Proper imaging of female diverticula is essential to diagnose the condition and, in planning and conducting proper surgical repair. Ultrasonography may suffice to identify size and location of the diverticulum although MRI imaging in preferable whenever available.

b) Consensus Statements

o In cases of female urinary incontinence if a urethral diverticulum is suspected, appropriate imaging (positive pressure urethrography, voiding cystourethrography, urethroscopy, ultrasound, MRI) is recommended. (The choice of the type of imaging depends on their availability. Data show a higher accuracy of MRI.) (**Level of Evidence 3 – Grade of Recommendation C**)

c) Future Research Areas

o Properly conducted prospective studies are needed to compare the accuracy of ultrasonography and MRI in the diagnosis and staging of female and male diverticula

d) References (see at the end of the chapter)

4. IMAGING OF THE NERVOUS SYSTEM

Lower urinary tract dysfunction often depends upon derangements of its neural control mechanism. Imaging of the spinal chord and central nervous system may help identifying occult neurological conditions or the site and extent of known neural damage. Functional imaging of the nervous system is a formidable research tool to better understand mechanisms of signal integration at the central level and its possible malfunctioning.

a) Lumbosacral Spine x-rays

In children with lower urinary tract dysfunction and urinary incontinence, the presence of a spinal dysraphism must be ruled out. Although in most of the cases abnormalities of the gluteosacral region and/or legs and foot are clearly visible, antero-posterior and lateral films of the lumbosacral spine have to be evaluated in order to identify vertebral anomalies. Sacral agenesis involves the congenital absence of part or all of two or more sacral vertebrae. In the absence of two or more sacral vertebrae a neurogenic bladder is usually found. Spina bifida occulta has a variable significance. Simple failure to fuse the laminae of the fourth and fifth lumbar vertebrae is unlikely to be important, but if the spinal canal is noticeably widened, there may be cord involvement (diastematomyelia, tethered cord syndrome).

b) CT, MRI, SPECT and PET

Numerous papers refer to rare neurological conditions presenting with different symptoms including urinary incontinence in which CT scan, MRI, SPECT, and PET imaging were carried out to identifying the underlying CNS disease. These references have little impact on daily practice although they can he helpful in occasional difficult cases.

With regards to the clinical diagnostic use of CT or MRI, a few papers evaluated the role of fetal MRI imaging. Fetal MRI has higher contrast resolution than prenatal sonography and allows better identification of normal and abnormal tissue. Moreover, MRI can

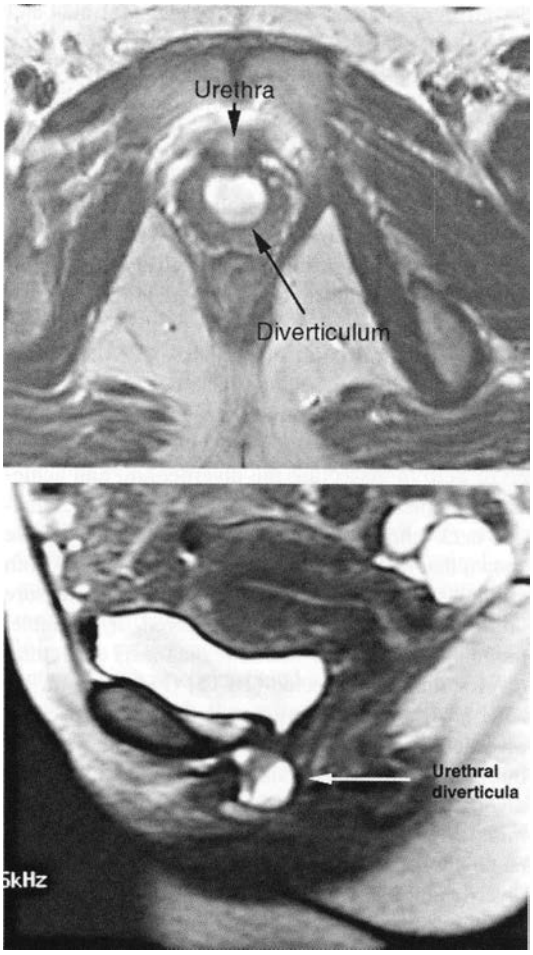


Figure B 28 ab: (a) MRI: urethral diverticulum (coronal view)
b: MRI: urethral diverticulum (sagittal view)

diagnose some abnormalities such as cerebral malformations and destructive lesions which can be occult on prenatal sonography, where the more anterior cerebral hemisphere cannot be properly evaluated due to reverberations by the overlying structures [2]. Common indications for fetal MRI include the evaluation of all the sonographically diagnosed abnormalities of ventriculi, corpus callosum, or posterior fossa, as well as all those fetuses at increased risk for brain abnormalities, such as in families with a history of a prior child or fetus with anomalies, genetic disorders, complications of monochorionic twinning, and maternal illness (such as maternal infection or major cardiac event). Moreover, with recent advances in fetal surgical techniques, fetal MRI is being increasingly used before surgical intervention [3]. The results of fetal MRI, whether verifying absence of abnormality, confirming sonographically detected abnormalities, or discovering additional abnormalities that were not apparent by sonography, have been shown to affect clinical decision-making during pregnancy, both by physicians and parents, resulting in changes in pregnancy management in nearly half of cases [2]. With regard to myelomeningocele, prenatal ultrasound can easily identify the absence of posterior elements of the vertebral bodies at affected levels and extension of the subarachnoid space posteriorly through the bony spina bifida, as well as the frequently associated presence of small posterior fossa alteration and herniation of cerebellar tissue into the cervical subarachnoid, which define the Chiari II malformation. However, fetal MRI can be a helpful adjunct when sonography analysis is limited, such as in cases of large maternal body habitus, oligohydramnios, low position of the fetal head, or when the fetal spine is positioned posteriorly with respect to the mother. Moreover, fetal MRI can be very useful to detect additional associated anomalies, such as callosal agenesis or hypogenesis, periventricular nodular heterotopia, cerebellar dysplasia, syringohydromyelia, and diastematomyelia [3]. If fetal surgery will be shown to improve long-term outcome, fetal MRI will surely become a routine examination for affected fetuses.

MRI is also recommended in children with anorectal abnormalities as abnormalities of the spine and of the spinal cord are diagnosed in 42 to 46% of cases and in about 50% of cases the spinal cord is involved [1]. Wraige et Borzyskowski suggested that spinal cord imaging should be considered in children in whom day-time wetting is associated with impaired bladder sensation or poor bladder emptying even in the absence of clinical or radiological suspicion of lumbosacral spine abnormalities. Four out of 10 children with these symptoms had a spinal cord defect diagnosed on MRI [4].

MRI of the lumbar spine is now the gold standard for evaluating children with spina bifida and adults in which an occult form of spina bifida is suspected. A potential technical update might be the use of intrathecal contrast medium to perform cisternography and ventriculography contrast-enhanced MRI. Munoz et al., evaluated a series of 10 patients with complex cerebrospinal fluid diseases, where other imaging techniques had been unclear or inconclusive, performing MRI with intrathecal administration of gadopentate dimeglumine. In 8 out of the 10 patients, imaging findings influenced or changed the clinical decision-making program and the surgical planning [5].

Sharma et al. recently evaluated with MRI the surgical outcome in patients with spinal dysraphism. Specifically, MRI spectroscopy was used to evaluated the composition of cerebrospinal fluid before and after surgery. Before surgery, high levels of lactate, alanine, acetate, glycerophosphorylcholine, and choline were observed in the cerebrospinal fluid of patients with spinal dysraphism, while these levels normalised postoperatively to those observed in control subjects. However, in those patients where cord tethering occurred, increased concentrations of lactate and alanine were found, suggesting that MRI spectroscopy might be a promising tool in the assessment of surgical outcomes in patients with spinal dysraphism [6].

Several papers refer to the use of CNS imaging in clinical research of voiding dysfunction and pathophysiology. Positron emission tomography (PET) and functional MRI studies provided information on specific brain structures involved in micturition in humans. During micturition an increase in regional blood flow was shown in the dorsomedial part of the pons close to the fourth ventricle, in the pontine micturition centre (PMC), in the mesencephalic periacqueductal grey (PAG) area, as well as in the hypothalamus including the preoptical area [1]. A good review on CNS imaging and lower urinary tract function was recently published by Drake and co-workers [7].

A couple of significant original studies have been published recently on the role of functional MRI in stress and urgency urinary incontinence. Specifically, previous brain imaging studies showed that during pelvic floor muscle contraction there was activity in the superior medial precentral gyrus, anterior cingulate cortex (ACC), cerebellum, supplementary motor cortex (SMA) and the thalamus [8, 9]. Similarly, during anal spincter contractions multifocal cerebral activity was shown in the primary and secondary sensory/motor cortices, the insula as well as the cingulate gyrus, prefrontal cortex, and the parietooccipital region [10]. Di Gangi Herms et al. evaluated the neuroplastic changes of cortical representation of pelvic floor motor function induced with pelvic floor muscle training (PFMT) by biofeedback in patients with SUI [11]. Specifically, the authors used functional MRI to evaluate 10 patients with SUI before and after a 12-week PFMT with EMG-biofeedback program. In the MRI performed before the beginning of PFMT, the authors identified significant brain activation in superior lateral and medial precentral gyrus and the superior lateral postcentral gyrus, in the SMA, the left premotor area, and in the left and middle cerebellum, as well as in the insula and in the ACC. In the MRI film after PFMT, less brain areas were activated, mainly the superior lateral and medial precentral gyrus, superior lateral postcentral gyrus and the insula. In other words, after PFMT there was more focused activation in the primary motor (superior lateral and superior medial precentral gyrus) and somatosensory areas, which is consistent with automation of the relearned skillful behavior [11]. PFMT with biofeedback may improve muscular strength therefore enhancing support of the urethra and also optimise central muscular control of the pelvic floor, modulate bladder sensation, and reflect the emotional neutralisation related to symptom reduction.

With regards to urgency urinary incontinence, Tadic et al. reported a small study, which used functional MRI to investigate 11 patients with urge urinary incontinence and 10 healthy controls. Specifically, the connections of the right insula (RI) and anterior cingulate gyrus (ACG) to other cortical area were evaluated, based on the assumption that the two areas were among the most important regions of the supraspinal neuronal network controlling the bladder. In normal subjects, there were significant positive effective connections with many of the regions involved in supraspinal bladder control, including left insula and frontotemporal and parietal regions, thalamus, putamen and claustrum, posterior cortex, cerebellum, pontine micturition centre and mesencephalic periacqueductal grey. Vice versa, in the patients with urgency incontinence, significant negative connections to left parieto-temporal lobes, hippocampus, parahippocampal gyrus and cerebellum were found, with few positive connections [12]. In subjects with normal bladder function, RI and/or ACG have been reconfirmed to have effective connections with many of the brain regions involved in bladder control such as the frontotemporal and sensorimotor regions, thalamus, putamen, cerebellum and midbrain, as well as to the posterior cortex, a region which may have a role in the control of bladder function. Vice versa, in the patients with urgency incontinence, the connections were shifted to an alternative complex of brain regions, such as left parieto-temporal lobes, parahippocampal gyrus and parts of cerebellum, which might represent expression of the recruitment of accessory pathways in order to control urgency and the voiding reflex as well as the emotional charge due to the abnormal sensation of urgency [12]. On the whole the data from these recently published studies have improved our knowledge of nervous functional anatomy related to vesicourethral function and dysfunction but, to date, have no clear clinical relevance.

In conclusion, central nervous system imaging is rarely indicated in urinary incontinence. Spinal cord imaging is recommended in cases of children with anorectal malformation and whenever spina bifida occulta is suspected. In the case of clinical neurological signs and/or symptoms suggestive of central nervous lesions, imaging may be indicated along with more specific neurophysiological tests (e.g., signal latency, testing, evoked potential, etc.). Further improvements in the knowledge of the correlation between morphological and functional evaluation of the CNS is foreseeable using present CNS functional imaging technology.

c) Consensus Statements

- In patients with suspected congenital neurogenic incontinence, with or without abnormalities of neurourological physical examination, lumbosacral spine anteroposterior and lateral radiological evaluation (or MRI) is indicated. (**Level Evidence 3, Grade of Recommendation C**)
- Neuroimaging should be considered when a nervous system disorder is suspected on the basis of clinical and/or neurophysiologic test findings (**Level of Evidence 3 - Grade of Recommendation C**)

d) Future Research Areas

- To investigate the effect of antimuscarinics and neuromodulation on brain activity;
- To standardise bladder filling parameters to investigate brain activity during different types and levels of bladder sensations;

- To investigate the effect of environmental and behavioural factors on brain activity in patients with urgency incontinence;
- To define the sequence of brain activation during bladder filling.

e) References (see at the end of the chapter)

5. ENDOSCOPY OF THE LOWER URINARY TRACT

Since the introduction of the cystoscope by Bozinni in 1805, endoscopy has played a critical role in the evaluation of lower urinary tract disorders [1]. Many investigators have proposed the routine use of urethrocystoscopy in the evaluation of urinary incontinence. These recommendations have rarely been based on evidence. There are five specific areas pertaining to urinary incontinence in which urethrocystoscopy has been advocated.

1. Observation of the female urethral sphincter to assess its ability to close and coapt. Urethrocystoscopy has been advocated in the static state to assess intrinsic sphincter deficiency (ISD) as well as in the dynamic state, when the patient is straining, to evaluate hypermobility and urethral closure while the patient is straining. It has been reported that sluggish closure of the bladder neck during periods of a rise in intra-abdominal pressure is associated with anatomical stress urinary incontinence. Intrinsic sphincter deficiency has classically been described as a fibrotic or pipe-stem urethra. It has been suggested that endoscopy can even help to differentiate between the hypermobile urethra and the intrinsically damaged urethra.

2. Assessment of the bladder, to rule out concomitant bladder conditions which may be the cause of detrusor overactivity and urinary incontinence or may simply require treatment.

3. Search of extraurethral causes of urinary incontinence, such as vesico-vaginal fistula and ectopic ureter.

4. Intraoperative cystourethroscopy during correction of USI to assess for bladder damage and ureteral patency.

5. Evaluation of the membranous and prostatic urethra in male patients with post-prostatectomy stress incontinence to evaluate possible iatrogenic damage of the external sphincter region. Assessment of bladder outlet in males with urgency incontinence considered to be secondary to bladder outlet obstruction to appraise prostate morphology.

a) Evaluation of the Female Bladder Outlet

Robertson described the procedure of dynamic urethroscopy to evaluate the bladder neck [2]. In this procedure a gas urethroscope is used to observe the urethra, bladder neck, and portions of the bladder. During visualisation manometric recording can be performed. Robertson described the appearance of SUI as a sluggish closure of the bladder neck and the appearance of the overactive bladder as a bladder neck that closes and then opens like the shutter of a camera. This procedure was reported to be extremely useful in patients with urinary incontinence as the bladder neck can then be observed at rest, with straining, and Valsalva manoeuvres. Unfortunately, in Robertson's original description of this procedure, it was never compared to other standard methods of measuring outlet resistance. Others who advocate the technique of Robertson reported that only 43% of patients with SUI actually had loss of bladder neck support on urethroscopy [3]. Scotti, et al performed a retrospective review of 204 patients who underwent dynamic urethroscopy for the evaluation of SUI [4]. Of the 204 patients, 99 had USI. Urethroscopy was found to be an imprecise predictor of USI with a 62% sensitivity, a 74.6% positive predictive value and a specificity of 79.1%. Moreover, there were many equivocal studies. The authors concluded that urodynamic evaluation rather than urethroscopy was a more accurate predictor of stress incontinence. Sand, and associates compared supine urethroscopic cystometry (dynamic urethroscopy) to the gold standard of multichannel urethrocystometry [5]. They found a sensitivity of only 24.6% and a positive predictive value of only 65.2% in predicting detrusor overactivity.

Horbach and Ostergard tried to predict urethral sphincter insufficiency in women with SUI using urethroscopy [6]. They retrospectively reviewed the records of 263 women who had a diagnosis of SUI. They defined ISD as a maximal urethra closure pressure of 20 cm H2O or less with the patient upright with a symptomatically full bladder. They then divided patients into two groups, those with ISD and those with maximal urethral closure pressures of more than 20 cm H2O. Based on this classification, 132 women, or 50.2%, had evidence of ISD. However, when urethral function was assessed by endoscopy, only six of 132 patients with ISD were found to have an open or partially open proximal urethra and urethrovesical junction at rest during urethrocystoscopy. Clinically, these patients had very low urethral pressures and reported difficulty with continuous leakage of urine. Endoscopy appeared to have little predictive value for ISD as defined by urethral pressure profilometry. Govier et al compared cystoscopic appearance of the female urethral sphincter mechanism to videourodynamic studies in 100 consecutive women with complex types of urinary incontinence [7]. Sphincter dysfunction was classified as minimal, moderate, and severe based on the radiographic appearance of the bladder neck with straining. Urethrocystoscopy underestimated the degree of sphincter deficiency 74% of the time in patients with moderate sphincter dysfunction and 44% of the time in patients with severe sphincter dysfunction. The authors concluded that cystoscopy is inadequate to judge the functional integrity of the bladder outlet. Furthermore, cystoscopy

alone will underestimate intrinsic sphincter deficiency in a large number of patients.

b) Evaluation of the Bladder

Is cystoscopy necessary to rule out concomitant bladder pathology in patients with urinary incontinence? Langmade and Oliver reported on 253 patients who were operated on for SUI [8]. They used a simple evaluation that consisted of history, stress tests, and urinalysis alone. They did, however, recommend cystoscopic evaluation if the patient also complained of symptoms of urgency. Although this dogmatic approach was recommended, it was never clearly stated if it made a difference to the treatment or outcome in these patients. Fischer-Rasmussen, et al performed extensive evaluation of women with urinary incontinence [9]. This included cystoscopy in 190 patients. They found cystoscopy to be abnormal in only 12 patients, 8 who had stress incontinence and 4 who had other types of incontinence. Abnormal findings were trabeculated bladder in five patients, benign bladder papillomas in four, and metaplasia of the trigone in two. None of these was considered to be a significant finding. The authors concluded that cystoscopic examination did not contribute to the classification of incontinence in any case. Cardozo and Stanton evaluated 200 patients with SUI and detrusor overcativity [10]. Cystoscopy revealed no abnormalities amongst the 100 patients with USI. Fourteen of the 100 patients with detrusor overactivity had cystoscopic abnormalities, eg trabeculation-11, injected mucosa- 1, sacculation -1, a bladder capacity of less than 100 cc-1. However, in none of these patients was the treatment affected by the results of cystoscopy. In support of these findings, Mundy has stated that there is no direct diagnostic value of endoscopy in a patient with an overactive bladder. It may sometimes be helpful to look for and exclude a cause of hypersensitivity when this is in the differential diagnosis [11]. Duldulao and colleagues found this necessary only in patients with haematuria [12]. They performed urinalysis, urine cytology, and cystoscopy on 128 women who presented with urgency incontinence and/or storage voiding symptoms. Of these, 68 patients had urgency incontinence, 35 of whom also had microscopic haematuria. One patient with urgency incontinence and haematuria was found to have a transitional cell carcinoma of the bladder. None of the patients with urgency incontinence (or storage symptoms only) and no haematuria were found to have significant cystoscopic findings. This would support the routine use of cystoscopy for patients with urgency incontinence only if haematuria is present.

c) Extra-Urethral Urinary Incontinence

Endoscopy can be an invaluable tool in the diagnosis and treatment of extraurethral incontinence due to vesico-vaginal fistula and ectopic ureter. With respect to vesico-vaginal fistula, cystoscopy can precisely localise the fistula site in the bladder and help plan surgical correction. Occasionally, a small fistula that is not seen on physical examination or radiographic studies, can only be diagnosed by cystoscopy. Incontinence due to ectopic ureter in the female is usually diagnosed by radiographic studies. However, the exact location of the ureteral orifice in urethra or vagina can be identified by cystourethroscopy and/or vaginoscopy. This can be extremely helpful in the planning corrective surgery.

d) Intraoperative Lower Urinary Tract Evaluation

Several authors have studied the value of routine cystoscopy during operative procedures for incontinence and prolapse. The approach may be transurethral [13] or transvesical [14]. The American College of OB/GYN has published a Bulletin on Operative Lower Urinary Tract Injuries [15] in which is stated “at the conclusion of the procedure, when hemostasis has been ensured, both ureters and the bladder should be inspected to confirm their integrity.” Harris and co-workers [13] reported 9 unsuspected ureteral or bladder injuries during urogynaecological surgery, which included 6 ureteral ligations, with four of these occurring after Burch cystourethropexy. Burch sutures were also found in the bladder as well as fascial lata from a sling procedure.

e) Evaluation of the Male Bladder Outlet

Urgency incontinence is one of the lower urinary tract symptoms associated with benign prostatic hyperplasia, bladder outlet obstruction, and aging in the male population. Based on the available evidence and world literature, The World Health Organization Fourth International Consultation on BPH made the following recommendation: “Diagnostic endoscopy of the lower urinary tract is an optional test in the standard patient with LUTS (lower urinary tract symptoms) because: 1) the outcomes of intervention are unknown, 2) the benefits do not outweigh the harms of the invasive study, 3) the patients’ preferences are expected to be divided. However, endoscopy is recommended as a guideline at the time of surgical treatment to rule out other pathology and to assess the shape and size of the prostate, which may have an impact on the treatment modality chosen [16]. Several contemporary series have described the value of urodynamics in the diagnosis of post-prostatectomy urinary incontinence [17-21]. However, only one describes the routine use of urethrocystoscopy. In that series 67% of patents had urethral fibrosis confirmed by endoscopy [18]. However, how this finding affected treatment was not discussed. In the study by Leach and Yun treatment of incontinence was based solely on urodynamic findings and was successful in 87% of patients [22]. Anastomotic strictures may be suspected based on uroflow and urodynamic (pressure-flow) studies and can be confirmed by voiding cystourethrogram or videourodynamics as well as by endoscopy. However, if intervention for the stricture is deemed necessary, endoscopy would be a more critical part of the evaluation. Furthermore if surgical treatment of incontinence, such as, an artificial urinary sphincter, is planned it would seem to make good clinical sense to evaluate the urethro-vesical anastomosis with endoscopy prior to surgery.

f) Evaluation of Urethral Sphincter In Post-Prostatectomy Incontinence.

Iatrogenic UI in males usually occurs after prostate surgery for benign and malignant conditions. The pathophysiology of UI following transurethral surgery for BPH includes sphincter damage from extending the resection too distal, particularly in the dorsal aspect of the sphincter where muscle fibres are more abundant. Endoscopy in post-TURP incontinence reveals insufficient closure at rest with tissue loss in the ventral aspect of the sphincter area, voluntary muscle recruitment is often good. The pathophysiology of UI in post-radical prostatectomy patients is unclear. Numerous studies have investigated the relationship between parameters of urethral pressure profile, morphology of the prostate apex and length of the external sphincter area to post-prostatectomy incontinence. Although the results of these studies suggest a relationship between sphincter competence and UI, no consensus has been reached regarding the gold standard test to be performed prior to surgery to assess the individual patient risk of incontinence. Recently, Gozzi and Rehder suggested that post-radical prostatectomy incontinence may be related to prolapse of the sphincter complex and that repositioning of it by a transobturator sling may be successful. Pre-operative selection of surgical candidates for such intervention include endoscopy of membranous urethra testing whether manual push-up of the centrus tendineus perinei results in recruitment of the sphincter fibres comparable to a voluntary contraction. Contraction of the sphincter muscle upon repositioning in a more cranial position is used as an indication for a transobturator sling with the Gozzi and Rehder technique [23-25]. Further research is required to confirm such an interesting pathophysiological explanation of post-radical prostatectomy incontinence and to support the role of endoscopy in the evaluation of these patients.

g) Consensus Statements

o Routine urethro-cystoscopy is NOT indicated in primary female urinary incontinence, when other pathologies are not suspected **(Level of Evidence 3, Grade of Recommendation C)**

o Endoscopy can be considered **(Level of Evidence 3, Grade of Recommendation C)**:

a) in urgency incontinence to rule out other pathologies, especially in case of microscopic haematuria (e.g., bladder tumour, interstitial cystitis, etc)

b) in the evaluation of recurrent or iatrogenic cases when surgery is indicated and planned

o Endoscopy is indicated in the evaluation of vesico vaginal fistula and extra-urethral urinary incontinence **(Level of Evidence 3, Grade of Recommendation C)**.

o Endoscopy is indicated intraoperatively in incontinence surgery to look for ureteral or vesical injury **(Level of Evidence 3, Grade of Recommendation C)**.

h) Future Research Areas

- The relationship between of bladder endoscopy and idiopathic detrusor overactivity
- The relationship between of bladder endoscopy and aging
- The relationship between bladder endoscopy and symptoms of voiding dysfunction in female patients with UI

i) References (see at the end of the chapter)

C. Imaging in Anal Incontinence

Anal incontinence may result from anatomical and/or neurological disruption of the anal sphincter complex. Prior to the development of anorectal imagining techniques, anal sphincter disruption was detected by digital palpation supported by EMG needle mapping and ano-rectal manometry. Use of endoanal ultrasonograpghy (EAUS) for anal sphincter imaging was first described by Wild in 1956 [1] but remained neglected for many decades because of the limitation of technology then available [2]. In 1989 Law and Bartum defined the technique of EAUS and endosonographic anatomy of the anal sphincter complex [3]. Since then EAUS has become the gold standard of imaging the anal sphincter complex.

Development of 3-D rendering technique over the last decade has enabled better quality imaging of the anal sphincter complex using the EAUS. Recently other imaging modalities such as transvaginal, transperineal and translabial ultrasonography, MRI, Defaecography and Sonoelastography have been described to assess the anal sphincter complex in patients with anal incontinence.

I. INDICATIONS

Anal sphincter imaging has become an integral part of the assessment of anal incontinence. Following detailed history and examination, the patient should be offered anal sphincter imaging (either 2D or 3D EAUS) depending on the availability of imaging modalities and the expertise. Even though ano-rectal physiological studies indicate dysfunction of the anal sphincter complex, they do not identify the anatomical site and the degree of anal sphincter disruption. EAUS has been the gold standard for detecting anal sphincter disruption or atrophy. EAUS is also used in the follow up of women after obstetric anal sphincter injuries to assess the success of the primary repair and to advise on subsequent delivery [4]. EAUS has been used intra-operatively to identify the damaged EAS prior to secondary repair and also to identify the IAS defects prior to injecting bulking agents.

II. IMAGING MODALITIES

1. ULTRASONOGRAPHY

The increased availability of ultrasound scanners to urologists and urogynaecologists and its high resolution

in the near field makes this the perfect tool to investigate patients with anal incontinence as a part of their physical examination.

a) ENDOANAL ULTRASOUND (EAUS)

EAUS is performed using a 360° rotating rectal probe with a 7-10 MHz transducer (focal range 2-4.5cm) with minimum beam width of 1.1mm. Several systems are currently available, and recently integrated 3D systems are also available (B&K Medical, Sandoften 9, 2820 Gentofte, Denmark). Women should be examined prone with an endoanal system to minimise anatomical distortion. **Figure C1** shows a schematic diagram of the anal sphincter complex in relation to the endoanal probe [4].

The standard EAUS image of the anal canal is of 4 layers (**Figure C 2**):

1. The subepithelial layer is moderately reflective.
2. The internal sphincter is the most obvious landmark and is a well-defined low reflective ring. The internal sphincter varies in thickness with age, being <1mm in neonate, 1-2mm in young adults, 2-3 in middle age and >3mm in the elderly.
3. The longitudinal layer is a complex structure with a large fibroelastic and muscle component, the latter formed from the puboanalis as well as the longitudinal muscle of the rectum (**Figure C 2**).
4. The external sphincter is better defined in men than women, where it tends to be less hypoechoic. It is distinguished mainly by interface reflections between muscle/fat planes either side (**Figure C 2**). In women the external sphincter is shorter anteriorly than posteriorly, which must not be misinterpreted as a tear. The transverse perineii muscles fuse anterior with the sphincter, whereas in men they remain separate.

With experience the examination can be performed in about 5 minutes and provides an ideal method for a rapid assessment of sphincter integrity and thickness.

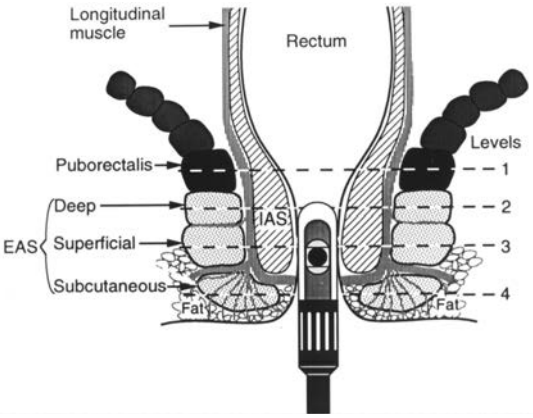


Figure C 1: A schematic diagram of the anal sphincter complex in relation to endoanal probe.

b) 3 Dimensional Endoanal Ultrasonography (3-D EAUS)

With 3D-EAUS, the anal canal is scanned in a conventional manner, and dedicated software provides a final 3D appearance (3D rendering). The data obtained from a series of closely spaced EAUS images (0.25 mm) are combined to create a 3D volume displayed as a cube. The image can then be freely rotated and it is possible to visualise defects at different angles and to obtain the most information from the data [5]. The advent of 3 D ultrasonographic multiplanar reconstruction of the anal canal has further improved the detection of anal sphincter injuries with nearly 95-100% sensitivity and specificity [6]. With 3D-EAUS, the aspect, localisation (circumference involved, height), size (in degrees or percentage of circumference) and number of sphincter defects can be described in detail, together with a calculation of the volume of such defects [7] (**Figures C3-C4-C5**). Defects of the puborectalis fibres of the levator ani are less common and these can be seen as heterogeneous remodelling or shortening of the two bands is visible after episiotomy or pelvic floor injury during vaginal delivery. Its role in the development of AI is probably underestimated and characterisation, particularly in terms of volume, would be of interest to assess the functional impact [6]. Two scoring systems has been introduced to objectively evaluate the anal sphincter defects detected in 3D EAUS [8, 9] and both these scoring system have shown acceptable intra observer and inter observer agreement [9].

Although EAUS has been accepted as the gold standard of imaging anal sphincter complex, the equipment and the expertise may not be readily available in some centres. Some patients may find EAUS

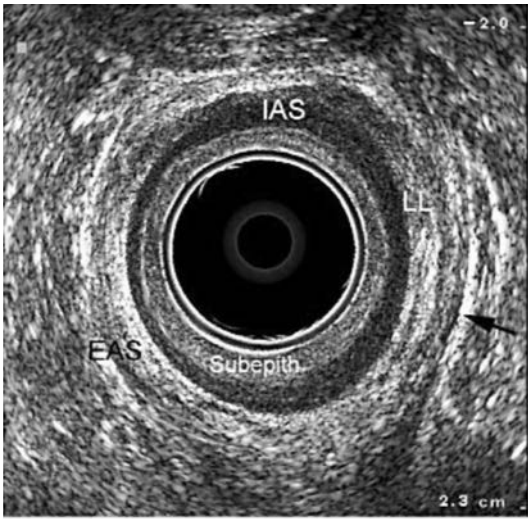


Figure C 2: Axial endosonography in the mid canal in a normal 38yr old female. Subepith: subepithial layer; IAS: internal anal sphincter; LL: longitudinal layer; EAS: external anal sphincter. The outer border of the external sphincter is defined by an interface reflection at the fat/muscle boundary (arrow).

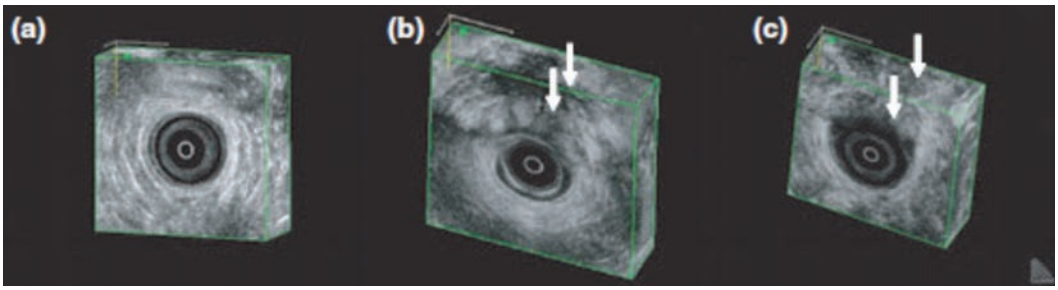


Figure C 3: Three-dimensional endoanal ultrasound showing no (a), partial (b) or complete EAS defect (c). Arrows indicate an EAS defect in the sagittal view (10).

technique embarrassing and unacceptable. Hard endoanal cone of EAUS may cause the disruption of normal anal canal anatomy. Because of these drawbacks, other imaging modalities such as Endovaginal, Transperineal and translabial ultrasonography have been evaluated to assess the anal sphincter complex.

c) Transvaginal Ultrasonography

Sultan et all first described the vaginal use of 360° rotating probe used for the EAUS and obtained clear images of anal sphincter complex [11]. Since then different types of probes including side-fire transrectal probe, a standard transvaginal probe and modified vaginal probe has been used to evaluate the anal sphincter complex with variable sensitivity and specificity for detecting anal sphincter injury [12].

d) Transperineal Ultrasonography

Transperineal ultrasonography (TPU) to image the anal sphincter complex was first described by Peschers et al. [13] and found to have a good inter observer reliability in detecting IAS and EAS defects compared with EAUS [14]. A recent study by Roos et al. [12] comparing endovaginal and transperineal ultrasonography to detect obstetric anal sphincter have concluded that neither of these modalities is sensitive enough to detect anal sphincter defects.

e) Translabial Ultrasonography

Translabial ultrasound (TLU) offers an alternative imaging modality of the anal sphincter complex and has proven to be well-tolerated by patients. It has been used to describe anal sphincter complex integrity [13, 15]. Hall et all evaluated 60 women with TLU and reported that mean sphincter measurements are given for symptomatic and asymptomatic intact women and are comparable to previously reported endoanal MRI and endoanal ultrasound measurements [16]. The advantages of TLU are that the equipment needed is readily available to all gynaecology and radiology imaging laboratories.

f) Integrated Multicompartmental Pelvic Floor Ultrasonography

Pelvic organ dysfunction includes multiple conditions such as pelvic organ prolapse, urinary incontinence, anal incontinence, defaecatory disorders and sexual dysfunction. Based on this concept integrated multicompartmental Pelvic Floor imaging including two-dimensional (2D), three-dimensional (3D) and 4D pelvic floor ultrasonography as well as transvaginal, endoanal and transperineal techniques, has been described from a global and multicompartmental perspective [17]. The value of this approach in routine assessment of pelvic floor dysfunction is yet to be evaluated.

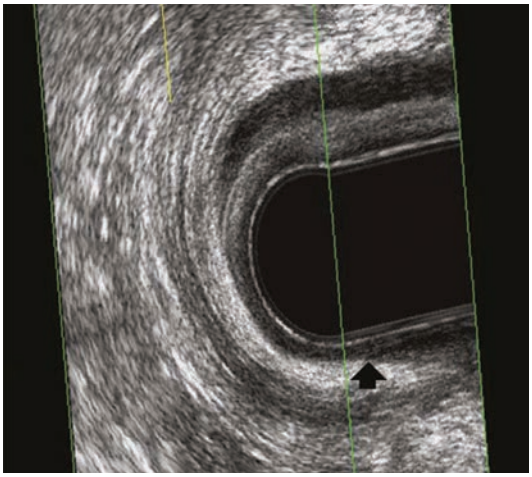


Figure C4: Complete defect of the internal anal sphincter

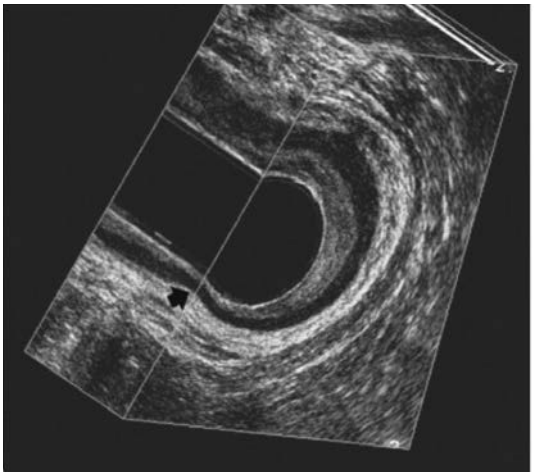


Figure C 5 : Partial defect of the internal anal sphincter (6).

g) Dynamic Anorectal Endosonography (DAE).

DAE uses a rigid biplane transrectal probe with a frequency of 7 MHz with the tip of the probe covered with a water-filled balloon to maintain the acoustic window for the ultrasound waves. By slowly and manually rotating the linear probe through 360°, various layers constituting the anal wall (mucosa, internal anal sphincter, and external anal sphincter), the layer forming the rectal wall, and the perirectal tissues (puborectalis muscle, bladder, and vagina, or prostate) has been demonstrated. After the initial examination, the patient simulates defaecation with the probe left in the same position [18]. In a study of 56 women using DAE and Dynamic MRI Defeaecography significantly more internal anal sphincter defects were found with DAE than with dynamic MRI defaecography. But there was no significant difference for the diagnosis of external anal sphincter defects [18].

h) Sonoelastography

Sonoelastography is a new imaging technique based on differences in radiofrequency signals following endogenous/exogenous compression due to different elastic properties of the targeted tissues or organs [19]. This technique has been evaluated in pathological conditions of breast, thyroid, pancreas and prostate. The elastographic pictures registered simultaneously with conventional grayscale B-mode images during sonography or endosonography are assumed to distinguish malignant from inflamed areas and thus facilitate diagnosis. Based on this concept it is assumed that Sonoelastograhy is able to diagnose different conditions causing anal incontinence. However there is only one published study comparing the conventional endoanal ultrasonography and elastography [20]. This prospective study included 50 patients with faecal incontinence following ano-rectal surgery and Crohn's disease. Elastogram colour distribution within the sphincter representing elastic properties was quantified using a visual analogue scale and an off-line computerised area calculation program. The IAS, a smooth muscle, and the EAS, a striated muscle, have different elastogram colour distributions, probably reflecting their different elastic properties. The absence of significant correlations with the major clinical and functional parameters suggests that in routine clinical practice ultrasound real-time elastography may not yield additional information in patients with faecal incontinence except in patients who have had radiation.

2. MRI

Anatomy of the anal sphincter complex has been redefined over the past 20 years by the use of body coil, endoanal coil and phased-array coil magnetic resonance imaging (MRI). However these different MRI techniques have led to conflicting anatomical descriptions of the anal sphincter complex [21]. Endoanal coil MRI studies by Rociu et al. [22, 23] have suggested that the levator ani muscle has only a transverse portion and that the EAS muscle is composed of only a subcutaneous and a superficial portion describing five image layers. **(Figure C6**)

However, body coil MRI studies by Guo and Li [24] suggested that the levator ani muscle also has a vertical portion (vertical levator), and separate body coil MRI studies by Hsu et al. [25] suggested that the EAS muscle has 3 separate components which has been identified in EAUS as well.

More recent study by Guo et al. [26] using multiplanar body-coil MRI studies demonstrated that the anal region actually has 7 image layers: the mucosa, submucosa, anal smooth muscle, inner space, vertical levator, outer space, and the EAS muscle (**Figure C7**). The authors reported that endoanal MRI does not reliably outline the superficial layers of the anal region because a blind zone is created in the anal canal near the coil. This blind zone led investigators to effectively ignore the mucosa, submucosa, anal smooth muscle, intersphincteric groove, and subcutaneous sphincter and this accounts for the early endoanal MRI description of the anal region as comprising only 5 image layers.

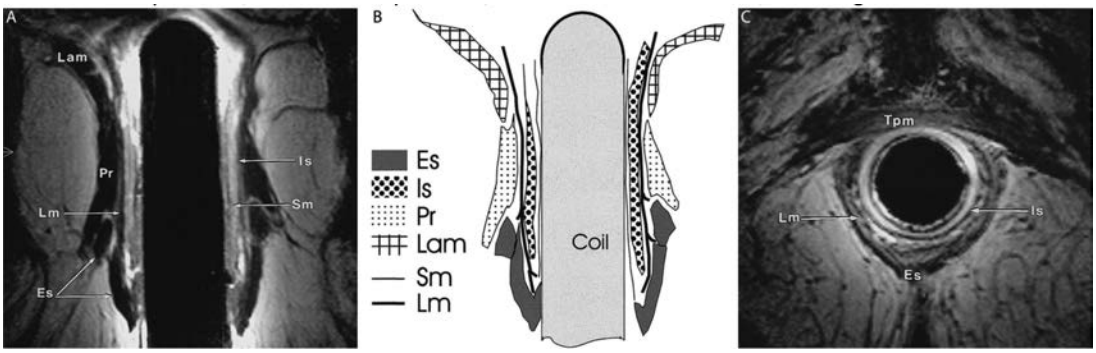


Figure C 6: Weighted turbo spin-echo endoanal coil MRI studies by Rociu et al.[22,23]
A: "5-layer" anal region and blind zone of the endoanal coil MRI.
B: Drawing of anal midcoronal section.
C: Inner intersphincteric space with high signal intensity is mislabeled as the internal sphincter.
Es - external sphincter; Is - internal sphincter; Lam - levator ani muscle; Lm -longitudinal rectal muscle; Pr -puborectalis; Sm -submucosa

Images of the anal sphincter complex obtained using endoanal MRI are thought to be superior to MRI performed with a body coil because of increased signal to noise ratio resulting in high spatial resolution images. Although the endoanal MRI allows comprehensive assessment of atrophy and focal defects of the external canal, the internal sphincter has been less well defined [27]. A meta analysis of nine studies, comparing endoanal MRI with endoanal ultrasound or surgical diagnosis in 157 patients by Tan et al. [28] has shown that Endoanal MRI was sensitive and specific for the detection of external sphincter injury and especially sphincter atrophy. It may be useful as an alternative to endoanal ultrasound in patients presenting with faecal incontinence. However, the limited availability of dedicated endoanal coils outside specialist units has resulted in less widespread familiarity with this technique and further clinical studies are needed to identify its best application in clinical practice.

In addition to the damage to the anal sphincter complex, levator ani muscle (LAM) injury has also been postulated as a cause for anal incontinence especially after childbirth. A recent MRI study by Helliburn et al. [29] reported major LAM injuries in 19% of women who delivered vaginally with external anal sphincter (EAS) injuries compared to 3% delivered vaginally without EAS injury, and 0% delivered by cesarean section before labour. Among women with EAS injuries, those with major LAM injuries tend to have more anal incontinence symptoms than those who did not have LAM injury. These data suggest that both EAS and LAM are important to maintain faecal continence.

3. EVACUATION DEFAECOGRAPHY (PROCTOGRAPHY)

Evacuation defaecography is indicated in patients with constipation, and in those with obstructive defaection associated with anal incontinence caused by overflow incontinence or post defaecation leakage. In these patients, defaecography is useful to visualise outlet obstruction due to an anatomical (e.g. enterocele, rectocele, intussusception) or a functional (e.g. anismus) cause. Evacuation defaecography is also useful to demonstrate bladder and uterovaginal prolapse as well as pelvic floor descent (**Figure C 8 a-b**) but gives limited information as to rectal function. Evacuation defaecography has shown good reproducibility in the diagnoses of enterocele, anterior rectocele and their grading in patients with faecal incontinence [30].

The rectum is opacified with 120 mls of a barium paste and the small bowel with a dilute barium suspension given orally about 30mins before defaecography starts. The patient is seated sideways within the fluoroscopic unit on a radiolucent commode. Evacuation of the barium paste is recorded either on video or on cut film at 1 frame/sec using a low dose protocol. At rest the anorectal junction is at the level of the ischial tuberosities and the anal canal closed. Evacuation is rapid (<30sec) and the rectum below the main fold should be emptied completely. During evacuation the anorectal angle widens as the anorectal junction descends and the anal canal opens. At the end of evacuation pelvic floor tone returns and the puborectalis pulls the anorectal junction upwards and forwards back to the resting position. Intra-anal intussusception creates a thick double fold of rectum, which impacts into the anal canal on straining at the end of rectal evacuation. Rectal prolapse represents an extension of this process, with passage of the intussusception through the anal canal and inversion of the rectum (**Figure C 9 a-c**)

Compared to conventional evacuation defaecography, dynamic MR defaecography at a vertical open magnet unit has become popular recently as it produces multiplanar images with increased soft tissue contrast and avoids radiation exposure. However the comparative results between conventional

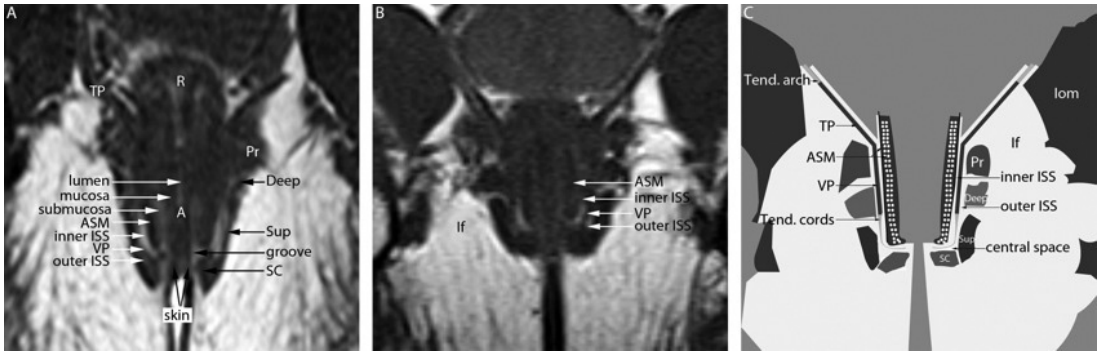


Figure C 7: Midcoronal T1-weighted turbo spin-echo body coil MRI images.
A, 7-layer anal region.
B, 3-layer intersphincteric space.
C, Drawing of anal midcoronal section.
A - imaging anal canal; ASM - anal smooth muscle; Deep -deep sphincter; If -ischioanal fossa; Iom -internal obturator muscle; ISS -intersphincteric space; Pr -puborectalis; R- rectum; SC -SC sphincter; Sup -superficial sphincter; TP- transverse levator; VP -vertical portion of the levator ani. [26]

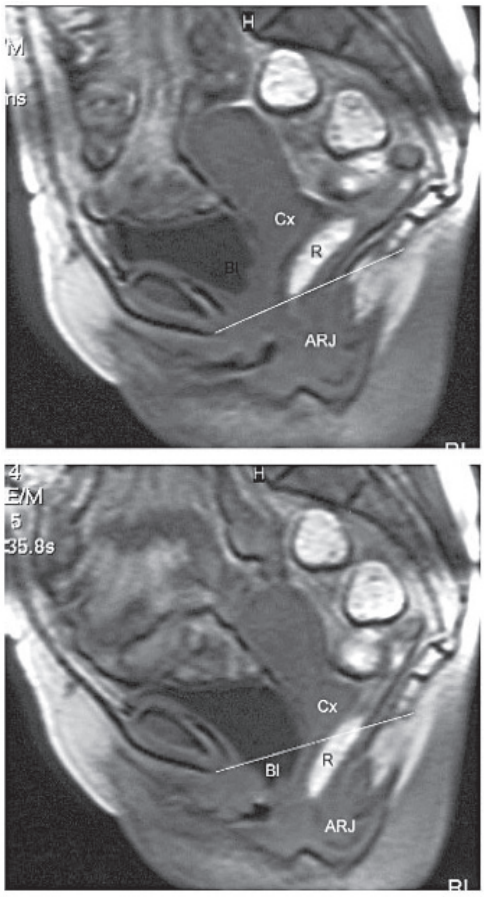


Figure C 8: Sagittal views from a dynamic MRI examination.
The dotted line indicates the position of the puborectal line. At rest (a) there is some descent as the anorectal junction (ARJ) is more than 1 cm below this. During pelvic stress (b) there is marked pelvic floor descent, with descent of the cervix (Cx) and bladder base (Bl).

defaecography and dynamic MR defaecography in patients with prolapse and anal incontinence are variable [31, 32]. Some of these variations have been attributed to the difference in technique. The main drawback of MR defaecography is the supine position required which causes sub optimal assessment of prolapse and evacation [31]. Since vertical open-magnet MR imaging units are not widely available, the role of MR defaecography in the diagnostic work-up of faecal incontinence is still limited.

III. SPHINCTERIC DISORDERS

1. THE INTERNAL ANAL SPHINCTER (IAS)

IAS is responsible for the maintenance of resting anal pressure and plays a vital role in maintaining anal continence. Isolated IAS defects are associated with surgery for ano-rectal malignancies, anal fissure and undetected obstetric anal sphincter injuries. These patients may present with passive faecal soiling and seepage rather than frank faecal incontinence.

Abnormalities of thickness are usually related to the patient's age. A sphincter less than 2mm thick in a patient more than 50 years of age is indicative of internal sphincter degeneration **(Figure C 10**) and is associated with passive faecal incontinence.

Obstetric trauma to the internal sphincter parallels that of the external sphincter in extent, but should always be in the anterior half, so that any defect between 3 and 9 is due to some other cause.

Sphincterotomy may be more extensive than was planned, particularly in women, and 3D studies are especially helpful to assess the longitudinal extent of the defect. The length of the sphincter divided relates directly to the risk of incontinence [33]. Dilatation procedures are hazardous and may completely fragment (**Figure C 11**) the internal sphincter.

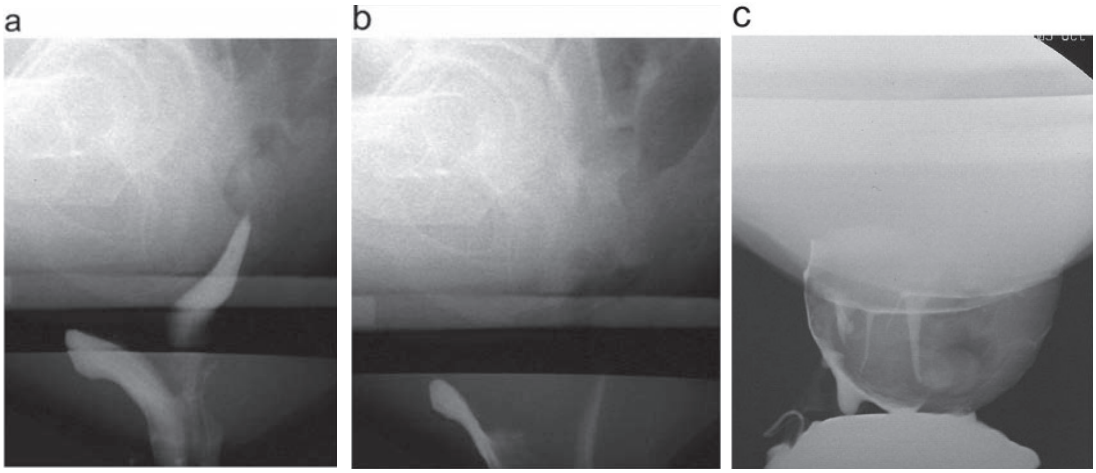


Figure C 9: Evacuation proctogram showing the development of rectal prolapse. Intussusception starts at the end of rectal emptying (a) and rapidly passes through the anal canal (b) to form the external prolapse(c).

2. THE EXTERNAL ANAL SPHINCTER

When striated muscle is stretched beyond the limits of its elasticity fibres rupture and heal with granulation tissue and eventually fibrosis. Most chronic tears are seen with scar formation, and present as a uniform area of low reflectivity distorting and obliterating normal anatomical planes (**Figure C 12**). A key to the diagnosis is lack of symmetry with the anterior part of the external sphincter not fusing at 12 o'clock as the probe is moved slowly down the canal. This may also be seen on 3D studies in the coronal plane (**Figure C 13**). Other perineal structures, such as the puboanalis and transverse perineii are frequently torn and distinguishing these tears from external sphincter trauma requires experience, and again may be helped by 3D multiplanar imaging. The distinction is important as tears of the puboanalis or transverse perineii are not associated with a significant fall in squeeze pressure [34], and it is only damage to the external sphincter that results in a significant change. Childbirth damage to the puborectalis part of the levator ani muscle with intact EAS and IAS has been reported as a distinct cause of anal incontinence. 3-D EAUS is reported to be superior in detecting this type of injury [35].

In healthy young adults a good correlation has been found between measurements of layers thicknesses on endosonography and endocoil MRI, with an Ri of 0.96 for the external sphincter [36]. The outer border of the external sphincter is easier to see on MRI, but fibrosis is not so markedly different in signal from normal muscle, so that the conspicuity of tears may not be as obvious as with endosonography.

Atrophy of EAS is a more difficult problem. Determining the thickness of the external sphincter on EAUS depends on visualising its borders from interface

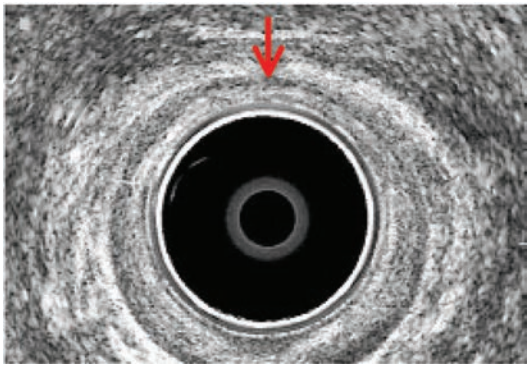


Figure C 10: Endosonography with an axial image in the mid canal of an elderly patient, aged 73yrs with passive faecal incontinence. The internal sphincter measures only 1.1mm (markers) indicative of internal sphincter degeneration

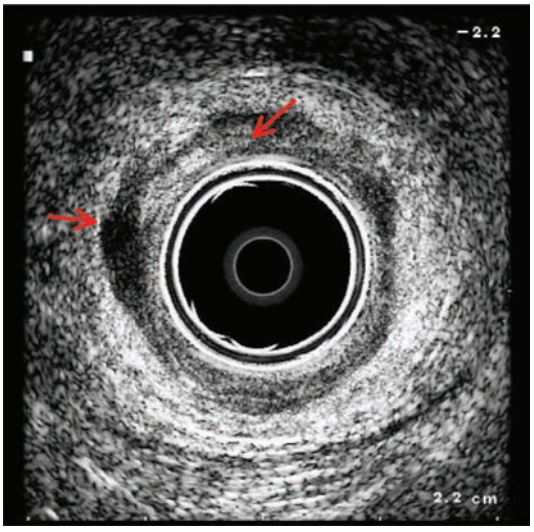


Figure C 11: Endosonography in the mid canalshowing gross internalsphincter irregularity, typicalof the "fragmented" appearance from trauma after an anal stretch procedure.

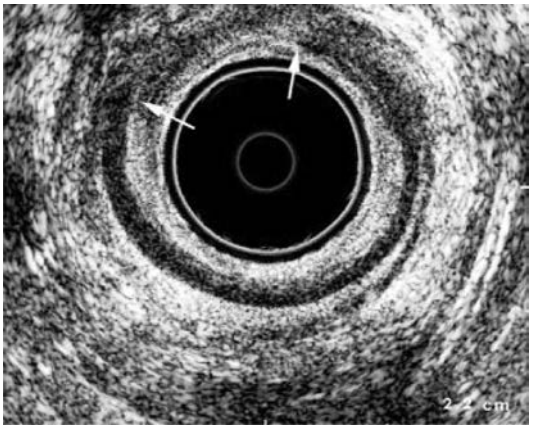


Figure C 12:Tears of internaland externalsphincters (arrows) between 10 and 1o'clock following a traumatic vaginal delivery

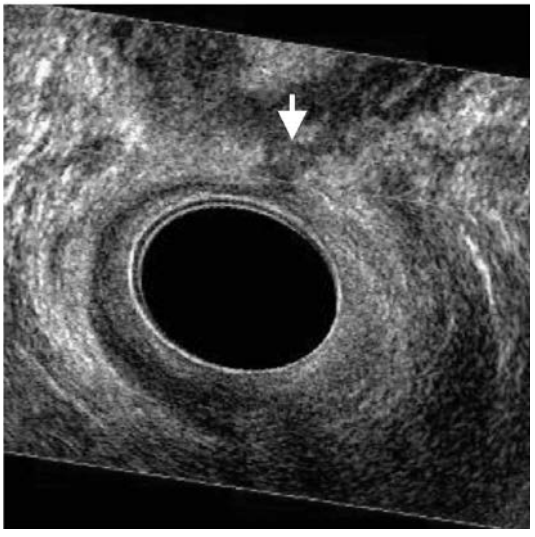


Figure C 13: 3D EAUS of a small tear to the external sphincter (arrow).

reflections between the longitudinal layer on the inside and subadventitial fat on the outer border. As atrophy involves a reduction of muscle fibres and an increase in fat, the outer interface reflection is lost and the thickness of the external sphincter cannot be measured **(Figure C 14**). Such loss of definition of the outer border of the external sphincter on endosonography has a positive predictive value of 71% for atrophy [37]. Using 3D EAUS and a grading system based on definition and echogenicity of the external sphincter showed a comparable accuracy to endocoil MRI in detecting atrophy [38].

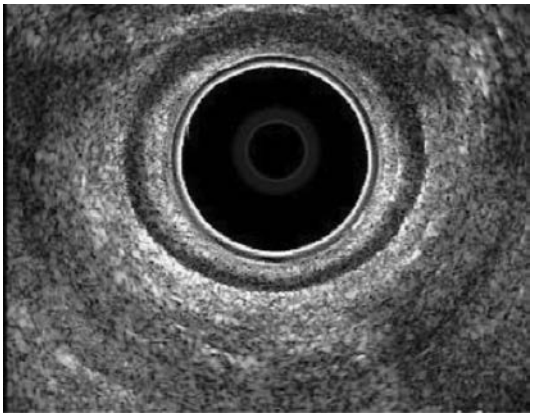


Figure C 14 : EAUS showing a normalinternal-sphincter, but the external sphincter is not visible as it is echogenic and the interface reflections due to advanced atrophy

IV. CONCLUSIONS

Claims for superiority of one or other modality for the detection of sphincter tears probably depend largely on individual experience, but the relative low cost and speed of EAUS makes this an ideal screening procedure to assess sphincter integrity. A leading issue is the significance of occult sphincter tears (diagnosed on endosonography but not apparent clinically) following vaginal delivery. Although these may be detected by careful examination immediately post partum [39], retrospective detection will still require EAUS. A meta-analysis of 717 vaginal deliveries revealed a 26.9% incidence of anal sphincter tears in primiparous, with 8.5% new tears in multiparous women. Overall 29.7% of women with tears were symptomatic, compared to only 3.4%without tears. The probability of faecal incontinence being due to a sphincter tear was 76.8-82.8% [40]. Recent studies confirm the strong relationship between obstetric sphincter damage and faecal incontinence [41], and its late onset [42,43]. Subsequent deliveries increase the risk of incontinence particularly if there has been a tear at the first delivery [44]. Tears that involve the internal sphincter increase the severity of incontinence [45]. A sphincter tear at EAUS is therefore an important finding, but how this is used to decide management is a little more controversial. Secondary anal sphincter repair has fallen out of fashion following the finding that results deteriorate over a few years46, although a more recent study [47] suggests a better response.

Fluoroscopic studies have little role in faecal incontinence, unless there is an underlying rectal abnormality such as obstructive defaectory symptoms and prolapse. Dynamic MRI studies have the added value of demonstrating prolapse in the rest of the pelvis, but apart from the lack of ionising radiation, has no real advantage for studying rectal function.

EAUS therefore remains the first line imaging investigation for anal incontinence, giving accurate information regarding the external and/or internal sphincter tears and the likelihood of atrophy. Dynamic studies of rectal evacuation are required only if there is some other problem suspected, such as prolapse. The advantages of using MRI are the lack of ionising radiation and a global view of the pelvic floor. Although imaging gives hard evidence of sphincter damage, this is really only part of a much more complex functional problem, and colorectal abnormalities may be just as important [48] with tears accounting for perhaps only 45% of incontinence [49].

V. CONSENSUS STATEMENTS

- EAUS is the first line imaging investigation for faecal incontinence providing accurate information regarding external and/or internal sphincter tears and the likelihood of atrophy. [**Level of Evidence 3, Grade of Recommendation C**].
- 3-D EAUS offer better quality images and diagnosis of the depth of anal sphincter injury. [**Level of Evidence 3, Grade of Recommendation C**]
- Routine use of 3-D EAUS is not recommended because of the cost. [**Level of Evidence 3, Grade of Recommendation C**]
- Routine use of transperineal, transvaginal and translabial ultrasonography to image the anal sphincter complex are not recommended. [**Level of Evidence 3, Grade of Recommendation C**].
- Dynamic imaging of rectal function is required when rectal abnormalities such as prolapse are suspected [**Level of Evidence 3, Grade of Recommendation C**].
- MRI offers no advantage over other imaging modalities except for the lack of ionising radiation and global view of the pelvis [**Level of Evidence 3, Grade of Recommendation C**]

VI. FUTURE RESEARCH AREAS

Better image quality with 3D EAUS and MRI have improved our understanding of pelvic floor anatomy, and this in turn has enabled sonographic anatomy to be re-evaluated, however, conflicting views of anal sphincter anatomy remain.

- Are clinical symptoms related to the size and the site of anal sphincter defect [50] or not [51]?
- Significance of imaging in detecting anal sphincter injury especially immediately after childbirth in preventing future anal incontinence [39, 52].
- The value of ano-rectal physiological studies combined with imaging in assessing the success of surgical repair of the anal sphincter complex [53].
- Identify (and modify) the risk factors leading to anal sphincter injury especially during childbirth and develop preventive strategies [54].

The most valuable aspect of 3-D ultrasonography and MRI imaging is that they give a global view of the pelvis, capable of investigating urological, gynaecological and coloproctological problems at the same time [17]. Many patients do not have faecal incontinence as an isolated symptom, but also have urinary, prolapse or defecatory problems. The overview provided by imaging sets the way for a combined approach to the pelvic floor and should be the prime area of future investigation [17].

D. PAD TESTING

The use of a perineal electronic nappy using electrical conductivity to estimate the amount of urine leakage was first proposed by James et al. [1, 2]. Accuracy of this technique was, however, questioned by others and the technique was improved [3-8]. Walsh & Mills and Sutherst et al. introduced a more simple approach by estimating leakage by perineal pad weight gain [9, 10]. These tests were not standardised until Bates et al. described a "structured" one hour pad test which was endorsed by the International Continence Society in 1988 [11]. This test, however, was shown to have poor interdepartmental correlation and to be highly dependent on bladder volume [12, 13]. In an attempt to make pad tests more reliable 24 hour and 48 hour pad tests were developed. A more precise estimation of urine loss was shown, but they were more cumbersome. The Pyridium pad test was also proposed for diagnosing urinary incontinence [14].

I. DEFINITION

The pad test is a diagnostic method to detect and quantify urine loss based on weight gain of absorbent pads during a test period under standardized conditions.

II. INDICATION AND METHODOLOGY

A pad test allows the detection and quantification of urine loss, but it is not diagnostic of the cause of the incontinence. Several different standards have been developed. Tests can be divided into four groups according to the length of the test: <1h, 1h, 24h and 48 h. (**Table 4**)

III. OFFICE-BASED PAD TESTING

Pad tests up to 2 hours were developed to be performed in outpatient clinics or hospital wards under supervised conditions. Bladder volume is predefined to reduce variability and a structured set of exercises is usually implemented to elicit the occurrence of urine loss.

1. SHORT PAD TEST

a) Quantification:

These tests are based on a fixed bladder volume and a standard set of activities to facilitate the occurrence of urine loss, if any, over a short period of time. Jakobseny et al. found that the 40 minute test with a bladder volume of 75% maximum cystometric capacity and similar activities as a 1-hour ward test produced consistently larger amounts of urine loss than a standard 1-hour ward test [17]. The difference was attributed to significantly larger bladder volumes during performance of physical activity in a 40 minute pad test.

Kinn & Larsson reported no correlation between a short 10 minute test with fixed bladder volume and the degree of incontinence as judged from the symptoms [18].

Hahn & Fall in a 20 minute test with half cystometric capacity showed no false negative results in 50 women with stress urinary incontinence although there was a discrepancy in 12% of patients between

Table 4: types of pad test

Author	Time	Bladder load	Exercise
Hahn & Fall (15)	20 min	50% of MCC*	stair climbing, 100 steps, coughing (10x), running (1 min), wash hands (1 min) jumping(1 min)
ICS (11)	1h	Drink 500 ml (15 min) before test	walking & stair climbing (30 min), standing up 10x, coughing (10x), running (1 min), bending (5x), wash hands (1 min)
Jorgensen et al. (16)	24h		Everyday activities
Jakobseny et al. (17)	48h		Everyday activities

*Maximum Cystometric Capacity

the perception of incontinence severity and pad test results [15].

These data suggest that short pad tests are more provocative than activities of daily living.

b) Reproducibility:

The correlation factor (Pitman's nonparametric permutation test) between two separate 20 minute tests was 0.94 ($p<0.001$) [15]. Kinn and Kinn & Larsson showed that the 10 minute test with a fixed pre-test bladder volume of 75% of maximal capacity was moderatey reproducible ($r=0.74$) [18]. Using a 1 hour pad test, a standardised bladder volume of 300ml and standardised physical activity mean differences of leakage was 8.5 ml and coefficient of repeatability was 33.6 ml [19].

2. ONE-HOUR PAD TEST

The use of a one-hour pad test has been investigated thoroughly for validity, reproducibility and sensitivity to change.

a) Quantification

Jakobseny et al. reported that a one hour test detected less leakage at 3 g compared to a 40 minute (7 g) and a 48 hour pad test (37 g) [17]. In the elderly, a one-hour ward test showed incontinence in 66% of those complaining of incontinence compared to 90% with a 24 in-patient monitoring of urine leakage [20]. A one hour pad test was found to reflect everyday incontinence in only 48% of patients in comparison to 81% with a 48 hour test and 77% with a 40 minute test. Jorgensen et al. noted that 90% completed the test and 69% had test results which correlated with daily leakage [16]. Lose et al. found a poor to moderate correlation of the modified one-hour test (200-300 ml in the bladder) with a history of stress urinary incontinence (n=31) [21]. Mouritsen et al. showed that a 1-hour ward pad test did not detect grade I stress incontinence in 46%, grade II in 27% and grade III in 66% [22]. Thind & Gerstenberg compared a 1-hour ward pad test to a 24-hour home pad test and found that a 1-hour pad test had a 36% false-negative rate as compared to a 24-hour home pad test [23].

b) Reproducibility

Klarskov & Hald demonstrated in 3 consecutive 1-hour pad tests, a correlation coefficient of 0.75 and 0.97 depending on the activity regimen [24]. The test, however, was quite demanding and a lot of patients did not complete the full testing. Christensen et al. compared a one-hour pad test in two different urological and one obstetrics & gynaecological departments (20 women) [13]. The test results in two urological departments did not differ with an average pad gain of 24g and 21 g ($p>0.1$). However, pad test results between the departments of urology and gynaecology differed significantly, with average pad weight gain 9 g and 24 g respectively ($p<0.05$).

Lose and co-workers showed a significant variation between 1-hour ward test and retest in 18 patients (correlation coefficient 0.68) [12]. In 50% of patients the leakage volume was variable due to differing bladder volume. When the results of the 1-hour pad test were corrected for urine volume, the correlation coefficient value increased to 0.96. Simons et al found the reproducibility of the standard 1 hour pad test to be poor [25].

c) Validity

Walsh & Mills in the elderly and Holm-Bentzen et al. in patients with an AMS artificial sphincter showed that the one hour pad test did not correlate with subjective patient satisfaction but this may due to other lower urinary tract symptoms [9, 26].

d) Bladder volume

Jorgensen et al showed test-retest correlation was improved when the bladder volume was taken into account and the correlation value (r) raised from 0.68 to 0.93 [16]. Fantl et al used a one hour test with the bladder filled to capacity and had a test-retest correlation of 0.97 which was improved if the fluid loss was expressed as a percentage of bladder volume [27]. Lose et al. using a 1-hour pad test with standardised bladder volume of 50% of maximal cystometric capacity (MCC) showed in 25 women a test retest correlation of 0.97 but the intertest variation was up to 24g [28]. Jakobsen et al. compared a 1-hour pad test with a bladder filled to 50% and 75% of maximal cystometric capacity and found that the final bladder volume was equal in both groups showing the importance of diuresis even with equal starting bladder capacities [29]. The amount of leakage in both groups was the same. Simons et al. found the volume in the bladder after a standard 1 hour pad test varies by –44 to +66g in a test-retest situation [25]. The fluid volume in the bladder appears to be critical in making the pad test reproducible and increasing the sensitivity of the test for detecting leakage.

Aslan et al compared a 1 hour pad test loss with the symptom impact index (SII) and the symptom severity index (SSI) [30]. Only the SSI showed a relationship between the severity of the score and the pad test loss. The 1 hour pad test has also been used in assessing the validity of the Incontinence Impact Questionnaire and the Urogenital Distress Inventory unfortunately both had poor correlations with the pad test [31]. This is to be expected as the questionnaires assess other urinary symptoms rather than just leakage.

e) Diagnosis

Fluid loss was significantly greater in patients with detrusor overactivity in comparison to urodynamic stress incontinence [27, 32]. The reverse finding was reported by Matharu and co-workers [33].

There is high variability in patients with detrusor overactivity making the test impractical as a diagnostic tool.

f) Sensitivity to change

The 1 hour pad test has been shown to be useful in detecting significant improvements after pelvic floor exercises for men suffering urinary incontinence after radical prostatectomy [34]. Ward et al. found the standard 1 hour pad test to show significant reductions in loss after tension free vaginal tape procedures from 18g (IQR 6-37) and Burch colposuspension from 16g (IQR 6-38) both decreasing to 0g (IQR 0) [35]. The 1 hour pad test has also been tested for the reduction in loss after conservative and surgical therapy [36]. The changes were significant but there was moderate correlation (r = 0.53) with the changes in the St. George Urinary Incontinence Score.

3. TWO-HOUR PAD TEST

A test period of 60-120 minutes after a 1 litre fluid load was proposed as the optimal duration for the pad test because of a consistently high bladder volume [37]. Han et al showed, however, that a 1-hour pad test is more practical [38]. In children a 2-hour ward pad test yielded 70% positive results for incontinence [39]. Richmond et al. compared two exercise regimens with a 2-hour pad test and showed no significant differences regarding which order the exercises were performed [40]. Walters et al. performed a 2-hour pad test with standard exercise in 40 women with SUI showing 78% positive tests (>1g pad gain) after 1 hour and 98% after the second hour [41]. Overall, the two-hour pad test was found to be superior to the one-hour one. There was no correlation between pad test results and the severity of a symptoms score.

IV. HOME BASED PAD TESTING

These tests were developed to diagnose and measure urine loss in a situation as close as possible to standard daily life of the patient. The longer observation period usually requires a less structured procedure.

1. 12-HOUR PAD TEST

a) Quantification:

Hellstrom et al. demonstrated in 30 children with incontinence a positive 12-hour home pad test in 68%. When a standard fluid load (13 ml/kg) was instituted in 20 children, the frequency of the positive test increased to 80% [39].

2. 24-HOUR PAD TEST

a) Quantification

Lose et al. found a 90% correlation of a 24-hour pad test with a history of stress incontinence in 31 women [21]. This was better than the results of a 1-hour test. Thirteen of 31 patients were found to be continent after a 1-hour ward test in comparison to only 3 with a 24-hour home pad test. Mouritsen et al. showed that the 24-h home test was well tolerated and as good at detecting incontinence as a 48-h test [22]. Griffiths et al. found only a 10% false negative rate of a 24-hour pad test in an elderly population [20]. Using non-parametric coefficient of correlation, they found a significant difference between the 1-hour test and the 24 hour test. Lose et al. found that a 24h home test performed during daily activities was more sensitive that a 1-hour ward test with standardised bladder volume of 200-300 ml [21]. High fluid intake did not change the results of a 24-h home test, but a low fluid intake reduced a positive test by 56% [42]. Ryhammer et al. showed that 24-h test is superior to subjective self-reported assessment of urinary incontinence [43].

b) Reproducibility

Lose et al showed poor correlation in a test-retest study with a variation of more than 100% [21] although Groutz et al. using Lin's concordance correlation coefficient (CCC), found the 24-h test to be very reliable instrument [44]. Increasing test duration to 48 and 72 hours slightly improved reliability but decreased patient compliance. (**Table 5**)

The values for the pad test increase in asymptomatic men and women were reported by Karantanis et al with the median value 0.3g (IQR 0.2 – 0.6; 95th centile 1.3g). It is surprising that the loss is so low and the same for men and women [45].

c) Diagnosis

Matharu et al found women with urodynamic stress incontinence leaked more than women with detrusor overactivity but the amounts were not diagnostic for the individual abnormalities [33]. Pad test loss is unaffected by the degree of hypermobility however there is increased loss associated with urethral sphincter incompetence diagnosed by a vesical leak point pressure less than 60 cmH2O [46].

d) Validity

Karantanis et al found the 24-hour pad test was poorly correlated in women with urodynamic stress incontinence with incontinence episodes on a 3 day urinary diary (Kendall's corr coeff b = 0.4) and the ICIQ-SF (r = 0.4) [47]. Singh et al. reported that fewer (52%) women after surgery were willing to complete a 24 hour pad test at follow up [48].

3. 48-HOUR PAD TEST

a) Quantification

Jakobseny et al. showed that 48-hour pad test reflects everyday incontinence in 81% of patients [17]. No statistical analysis data were given. Ekelund et al., found patients own weighing correlate well to control weighing at the clinic in 48-h pad test (r=0.99) [49].

Nygaard and Zmolek in 14 continent women showed a mean pad weight, attributed to sweat for all exer-

cise sessions of 3.19 + 3.16 g (the Kendall coefficient of concordance of the test-retest reliability was 0.96) but there was a lot of variation between patients [53] (**Table 6**). Pyridium staining was not helpful in increasing specificity. Similar results with Pyridium were reported by Wall et al. in a 1-hour ward test [14]. In his study (n=18) the Pyridium test was 100% positive in patients with SUI but had false positive results in normal women (52%).

Mean pad weight loss due to evaporation or leakage (was calculated to be 1.003 g, and ranged from -6.5 to +3.85 g (SD 1.85 g) [9]. Lose et al. showed no evidence of evaporation over 7 days if the pad was stored in a plastic bag [21]. Versi et al. showed pads wetted with saline showed no difference in weight after 1 week and less than 10% weight loss after 8 weeks [51]. Twelve pads were weighed by the patient and a healthcare worker with a coefficient of variance =1.55% with a mean deviation of 49%.

4. COMMENTS

Pad tests can either be used as a qualitative diagnostic tool to diagnose urinary incontinence and as a quantitative test to grade its severity. Pad test is unable to distinguish among different types of incontinence such as stress, urgency or mixed urinary incontinence. The ICS definition of urinary incontinence (the complaint of any involuntary leakage of urine) does not describe how the diagnosis is made but clearly refers to a patient's complaint that excludes urodynamics and rather points at the patient perception of the condition. Following this line of thought, research in this area has moved away from the evaluation of diagnostic accuracy of pad test versus a urodynamic diagnosis of UI and entered the more interesting field of the relationship between the patient perception of UI and pad test. Franco and co-workers in London, UK tested the correlation between different questionnaires for UI

Table 5. test-retest correlation

Author	Test	Correlation coefficient	Symptoms
Klarskov & Hald 1984 (24)	1-h	0.96	SUI&UUI
Lose et al 1986 (12)	1-h	0.68	SUI & MIX
Fantl et al. 1987 (27)	1-h (vol)	0.97	SUI
Fantl et al. 1987 (27)	1-h (vol)	0.84	SUI & UUI
Lose et al. 1988 (28)	45-m (vol)	0.97	SUI & MIX
Victor et al. 1987 (50)	24-h	0.66	SUI
Lose et al. 1989 (21)	24-h	0.82	LUTS
Mouritsen et al. 1989 (22)	24-h	0.87	MIX
Versi et al. (1996) (51)	24-h	0.9	LUTS
Groutz et al. (2000) (44)	24-h	0.89	LUTS
Victor et al. 1987 (50)	48-h	0.9	SUI
Versi et al. (1996) (51)	48-h	0.94	LUTS
Groutz et al. (2000) (44)	48-h	0.95	LUTS

Table 6. Pad-weight gain (g) in normal women

Author	Time	No	Mean (g)	Range (g)	SD	SEM	Note
Hahn & Fall 1991 (52)	20 min	10	0.0				
Nygaard & Zmolek, 1995 (53)	39.5 min	14	3.19	0.1-12.4	3.16		Exercise
Versi & Cardozo 1986 (54)	1h	90	0.39	0-1.15		0.04	
Sutherst et al. 1981 (55)	1h	50	0.26	0-2.1	0.36		
Walsh & Mills, 1981 (9)	2h	6	1.2	0.1-4.0	1.35		Daily activity
Lose et al. 1989 (21)	24h	46	4.0	0-10			
Jorgensen et al. 1987 (16)	24h	23	4.0	0-10			
Mouritsen et al. 1989 (22)	24h	25	2.6	0-7			
Karantanis et al. 2003 (45)	24h	120	0.3	0-1.3			
Versi et al. 1996 (51)	48h	15	7.13		4.32		

and 1-hour pad test showing that only the ICIQ-SF reached statistical significance with a Kendall's tb of 0.177 and a P value of 0.037 while no significant correlation was found for a 0 to 10 VAS score, a patient-based 3-point symptom severity scale, Stamey grade, Urogenital Distress Inventory and the Incontinence Impact Questionnaire (IIQ-7) [56]. In another study from Wijma and co-workers, the diagnostic accuracy of pad test for self-reported symptoms of UI was evaluated during pregnancy and after childbirth and the authors conclude that the diagnostic value of pad testing has no clinical relevance in this setting [57]. A similar analysis, performed in a male population undergoing sling surgery for post-radical prostatectomy incontinence suggested a good correlation between ICIQ-SF and the Patient Global Perception of Improvement (PGPI) with a 24-hour pad test [58].

Studies from the Urinary Incontinence Treatment Network in US investigated the relation between different measures of incontinence severity and showed how pad weight from a 24-hour test had a good correlation with the incontinence episode frequency derived from a 3-day bladder diary (Spearman correlation coefficient 0.61 but a much lower degree of correlation was found with questionnaires such as the Medical, Epidemiological, and Social Aspect of Aging (r=0.33), the Urogenital Distress Inventory (r=0.17) and the Incontinence Impact Questionnaire (r=0.34) [59]. In the same study, the use of pad testing as a prognostic parameter for treatment outcome was investigated but 24-hour pad testing showed no prognostic value for treatment failure in a study of Burch colposuspension versus autologous rectus fascia sling [60]. An interesting result was obtained in a predominantely female population of patients receiving neuromodulation for refractory urgency incontinence in which a 24-hour pad test performed after the initial test stimulation was able to predict long term satisfaction in this difficult patient population [61]. In this, as in other studies, the number of pads used per day proved to be an unreliable measure of urinary incontinence [62].

A couple of important methodological issues have been raised concerning the use of pad testing. Khan & Chien eloquently pointed out that test-retest comparison should include methods of blinding and use of an appropriate index of degree of agreement which is the intra-class correlation coefficient. In most of the literature this was not implemented [63]. Kromann-Andersen et al. argued that with considerable inter- and intra-individual variation of urine loss, the correlation of test/retest results may be overestimated and suggested different trials for small, modest and large leakage in large numbers of patients [64]. This trial has not been carried out.

A recent Health Technology Assessment of pad testing concluded that although high sensitivity and specificity for the diagnosis of UI was reported in some studies, it was difficult to draw any conclusions about the diagnostic accuracy for SUI because of the differences existing in pad test methodology. The number of studies comparing the same pad tests with adequate reporting is insufficient and no formal pooling of published data could be performed [65].

5. ROLE OF THE INVESTIGATION

The test has been standardised by ICS in 1988 for quantification of urine loss and suggested uses for assessment and comparison of treatment results for different types of urinary incontinence in different centres. Also, the AUA report on Surgical Management of Female Stress Urinary Incontinence includes a pad test (pretreatment evaluation) as a standard of efficiency for clinical trials [66]. The Urodynamic Society included a pad test in a Standards of Efficacy for Evaluation of Treatment Outcomes in Urinary Incontinence [67]. No suggestion was made in the last two reports of which test to use.

V. CONCLUSIONS

- o The 1-hour pad test is not very accurate unless a fixed bladder volume is applied.
- o Set exercises during the test improve test-retest reliability.
- o The sequence of exercises has little effect on test results.
- o A pad weight gain >1 g suggests a positive 1h test.
- o A 24 hour test correlates well with symptoms of incontinence.
- o A 24-hour test has good reproducibility but poorer compliance.
- o A pad weight gain >1.3g = positive 24 h test.
- o A test lasting longer than 24 h has little advantage.
- o A pad test cannot distinguish between urodynamic stress incontinence and detrusor overactivity.

VI. CONSENSUS STATEMENTS

- o The pad test is an optional investigative tool in the routine evaluation of urinary incontinence (**Level of Evidence 3, Grade of Recommendation C**)
- o Pad test is a useful outcome measure in clinical trials and research studies. (**Level of Evidence 3, Grade of Recommendation C**)

The following standards are suggested:

- o 20 min - 1 h ward/office test with fixed bladder volume (pad weight gain ≥ 1g = positive test) (**Level of Evidence 3, Grade of Recommendation C**)
- o 24 h home pad test during daily activity (pad weight gain ≥ 1.3g/24h = positive test) (**Level of Evidence 3, Grade of Recommendation C**)

VII. FUTURE RESEARCH AREAS

- o Proper validation analysis using the coefficient of variability
- o Evaluation of the ability to detect all the spectrum of urinary incontinence (from mild to severe)
- o Sensitivity to change in time of incontinence status for 24 hour pad tests
- o Validity of pad tests with other measures of incontinence such as urinary diaries and symptom questionnaires.

VIII. REFERENCES (SEE AT THE END OF THE CHAPTER)

E. NEUROPHYSIOLOGY

I. INTRODUCTION

Neurophysiological investigations of muscles and nerves in the perineum and pelvis originated over 60 years ago, and have evolved with developments in general clinical neurophysiology. The data from these investigations can assist clinicians in diagnosing neurological disease or injury, and are applicable in research. Compared to neurophysiological testing of the limbs and trunk, pelvic neurophysiological testing is relatively limited because of the restrictions imposed by pelvic neuroanatomy.

This text details the investigations, their applications and limitations, enabling investigator and clinicians to make a well informed decision regarding the use of these tests.

The present text is based on the previous chapter on clinical neurophysiology prepared for the International Consultations on Incontinence [1], which has been updated by a literature search in Medline using key words incontinence, clinical neurophysiology, electromyography, reflex, evoked potentials.

1. CLASSIFICATION OF CLINICAL NEUROPHYSIOLOGICAL TESTS

Although different types of tests may be included under the term “neurophysiological”, it is particularly the electrophysiological tests that shall be discussed in the present text.

Electrophysiological tests are an extension of the clinical examination, and a functional anatomical approach to classification makes most sense. For the purpose of this categorisation, the nervous system is divided into the somatic and the autonomic nervous systems. The somatic nervous system provides motor innervation to the skeletal muscles and joints, and sensory innervation from skin and muscle spindles. The autonomic nervous system provides motor innervation to the viscera and other end-organs not under voluntary control (e.g., sweat glands). Its sensory fibres are referred to as visceral afferents. Both systems have central pathways (neurons participating in spinal cord and supraspinal control) and peripheral nerves (those going to and from end-organs).

Thus, electrophysiological tests can be divided into: a) somatic motor system tests (EMG, terminal motor latency measurements/ motor nerve conduction studies, and motor evoked potentials (MEP)); b) somatosensory system tests (sensory neurography, somatosensory evoked potentials (SEP)); c) reflexes; and d) the autonomic nervous system tests (for sympathetic or parasympathetic fibres).

Electrophysiological tests may also be categorised “technically” into those which “just” record some bioelectrical activity (for instance: electromyography), and those which record some biological response to stimulation (these may be subsumed under the term “conduction tests”).

2. BIOLOGICAL CORRELATES OF ELECTROPHYSIOLOGICAL TESTS

a) Conduction Tests: Nerve Conduction, Evoked Potential and Reflex Studies

The electrophysiological responses obtained on stimulation are compound action potentials and relate to populations of biological units (neurons, axons, motor units, muscle fibres, etc.). Latency and amplitude are commonly measured parameters of responses during neurophysiological testing. If the onset of the potential is measured, the latency of a compound potential represents the fastest conduction through a particular neural channel. As a general rule, latency measurements are not markedly affected by technical factors, but provide little information about the loss of biological units (e.g., motor neurons or axons). The amplitude of the compound potential correlates with the number of activated biological units. In theory, the amplitudes are the more relevant physiological parameter, as they reflect the functional or structural loss of biological units. Unfortunately, amplitudes are also strongly influenced by many poorly controllable technical factors. Measurements of latencies and amplitudes of evoked potentials and reflex responses, including sympathetic skin responses, relate not only to conduction in peripheral and central neural pathways, but also to trans-synaptic transmission.

b) Electromyography (EMG)

Knowledge of the structure and function of the motor unit (**Figure E 1**) is fundamental to

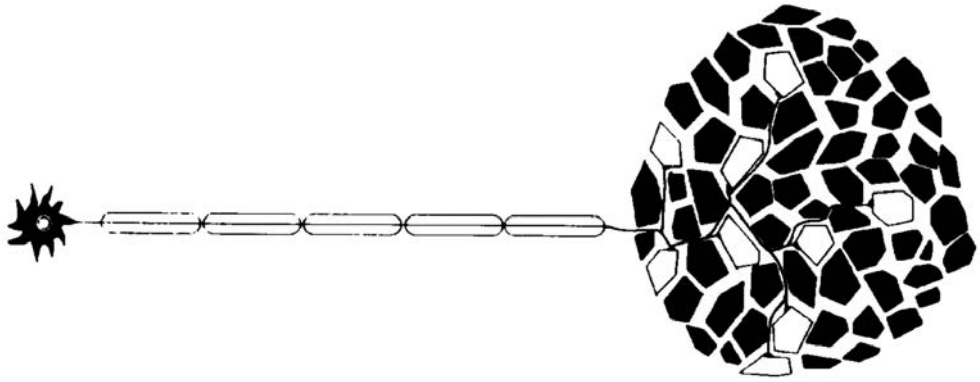


Figure E 1: Schematic representation of a motor unit. The alpha motor neuron with its cell body, its myelinated axon and the peripheral nerve endings is shown. The muscle fibres innervated by this alpha motor neuron are shown in white. (Note that the muscle fibres from one motor unit are intermingled with motor fibres from other motor units).

understanding the application of EMG. Motor neurons, which innervate striated muscle, lie in the anterior horn of the spinal cord and are called "lower motor neurons". (Neurons that innervate the sphincters lie in Onuf's nucleus in the sacral spinal cord; they are somewhat smaller than those innervating skeletal limb and trunk muscles). Within the muscle, the motor axon branches to innervate a certain number of muscle fibres, which are scattered throughout the muscle. All muscle fibres innervated by one lower motor neuron are activated simultaneously; all these constituents together are called "motor unit". The innervation of muscle fibres is such that it is unlikely that muscle fibres that are part of the same motor unit will be adjacent to one another.

It is difficult to estimate the number of muscle fibres innervated by a single axon (i.e., the "innervation ratio") or the number of motor units supplying a muscle, by clinically available neurophysiological techniques.

3. GENERAL METHODOLOGICAL CONSIDERATIONS

To date, there are no universally accepted standards for conducting individual uro-genital-anal neurophysiological tests, but the variations of testing in different laboratories are minor.

There are technical standards on equipment safety; standardisation of concentric needle EMG and penilo/clitoro-cavernosal testing has been proposed.

a) Equipment

Clinical neurophysiological tests are conducted with complex electronic instruments and various devices that come into contact with the patient. Alhough this equipment is mostly standard, some specially constructed electrodes or stimulating devices have been devised to conform to uro-genito-anal anatomy. As long as the standards of electrical safety are adhered to, the risk to patients is negligible.

The common form of neurophysiological testing is electrophysiological. Surface electrodes, which are applied to skin or mucosal surfaces, or needle electrodes are used for electrical stimulation and to record bioelectrical activity. The important neurophysiological difference between surface and needle electrodes is their selectivity, and the practical difference is their invasiveness. The choice and application of electrodes is guided by the need for selective recording or stimulation. Less commonly, special devices are used for magnetic and mechanical stimulation.

Stimulation Parameters. The electrical stimulus should be specified and characterised both in technical (e.g., rectangular pulse, 0.2 ms, 15 mA) and physiological terms (e.g., 3-times sensory threshold). A stimulus with defined technical parameters may have variable biological effects because of the variable influences of electrode condition, contact, tissue conductivity etc. Supramaximal stimulation is preferred to elicit a compound muscle action potential (CMAP) or sensory nerve action potential. Supramaximal stimuli yield responses with the largest amplitude and shortest latency, and are the least variable and most reproducible. The sites at which stimulation electrodes are applied should be described using anatomical terms.

b) Recording

1. Apparatus settings

For recording, the apparatus settings (gain, sweep speed) have to be adapted to the known range of amplitudes, latencies, and duration of the response and it has to be appropriately displayed for analysis. Particularly important is the frequency setting

of filters: for surface electrode recordings it is typically 2 Hz – 1 kHz; for concentric needle EMG recordings, it is 5 Hz – 10 kHz.

Placement of electrodes on the scalp for evoked potential recordings is defined according to the 10-20 International EEG System.

2. Reproducibility and Reliability

Any potential elicited by stimulation should be reproducible; therefore, as a rule, at least two consecutive recording procedures need to be performed. To improve the signal-to-noise ratio some small amplitude responses need to be averaged. Therefore, many repetitions of stimulation/recording need to be done (typically 100-200). Even such an averaged recording needs to be repeated at least twice. CMAPs (i.e., M-waves), MEP, sacral reflexes and sympathetic skin responses (SSR) are recognisable after single stimuli. However, as a rule, several responses are recorded to demonstrate reproducibility. In contrast, other responses (e.g., SSR) show marked fatigability with stimulus repetition.

3. Waveform Analysis

For a particular stimulation procedure, the shape, latency, and amplitude of the recorded potentials are analysed. Morphologically, a particular response (or part of it) needs to be recognised as present or absent. The shape of potentials is important to accurately determine the latency and amplitude of the response. The onset of the response (for M-waves, MEP and sacral reflex testing) or the individual peaks of the potentials (for SEP) are used to determine the latency. The amplitudes are analysed relative to the baseline or "peak to peak".

II. CLINICAL NEUROPHYSIOLOGICAL TESTS

1. SOMATIC MOTOR SYSTEM TESTS

a) Electromyography (EMG)

The term "EMG" is often used for several different procedures, the common denominator of which is the recording of bioelectrical activity from muscle. The term applies particularly to recordings from striated muscles.

EMG is used a) "just" to record muscle activity (as for instance in combined sphincter EMG and pressure-flow study) and b) to differentiate between normal, denervated, reinnervated, and myopathic muscle. For a) see below – "Kinesiological EMG".

Although EMG abnormalities are detected as a result of a host of different lesions and diseases, there are in principle only two standard manifestations which can occur: a) disease of the muscle fibres themselves ("myogenic" changes), and b) changes in their innervation ("neuropathic" changes). Myogenic changes may result from muscle disease, probably also from direct trauma (e.g., the anal sphincter tear during vaginal delivery). Neurogenic changes may be attributable to injury at any level along the lower motor neuron supplying the external anal sphincter, extending from the motor neuron body, sacral nerve roots to the small branches within the external sphincter. In the pelvic floor muscles, only neurogenic changes are well recognised and routinely evaluated.

The EMG signal may be further used to indicate that muscle has been activated through its motor nerve, either by stimulation applied to motor pathways (M-wave, MEP) or to sensory pathways (reflex response).

1. General Technique for Needle EMG in Pelvic Floor Striated Muscles

All tests requiring needle electrodes are invasive and some pain is inevitable, even with the use of local anaesthetics. Local anaesthesia is infrequently used for needle EMG examination. Intramuscular electrodes need to be appropriately placed in the target muscle.

The pelvic floor and perineal muscles can be examined, including the levator ani, the bulbocavernosus muscle and the striated anal and urethral sphincter muscle. Proper placement of needle examination requires some practice. As a rule, several sites from one or more skin penetrations are sampled, which is difficult in small muscles.

The audio output from the loudspeaker of the EMG apparatus helps in assessment of the quality of recording as well as in recognition of electrophysiological phenomena.

2. Concentric needle EMG (CNEMG)

The examination is conducted with a single use, disposable electrode. The commonly used amplifier filter settings for CNEMG are 5 Hz – 10 kHz, and need to be defined if MUP parameters are to be measured, as are filter settings employed during data acquisition.

The concentric needle electrode consists of a central insulated platinum wire inserted through a steel cannula and the tip ground to give an elliptical area which can record spike or near activity from about 20 muscle fibres [2]. The number of motor units recorded therefore depends both upon the local arrangement of motor units within the muscle fascicle and the level of contraction of the muscle.

CNEMG can provide information on a) insertion activity, b) abnormal spontaneous activity **(Figure E 2)**, c) MUPs, and d) interference pattern (IP).

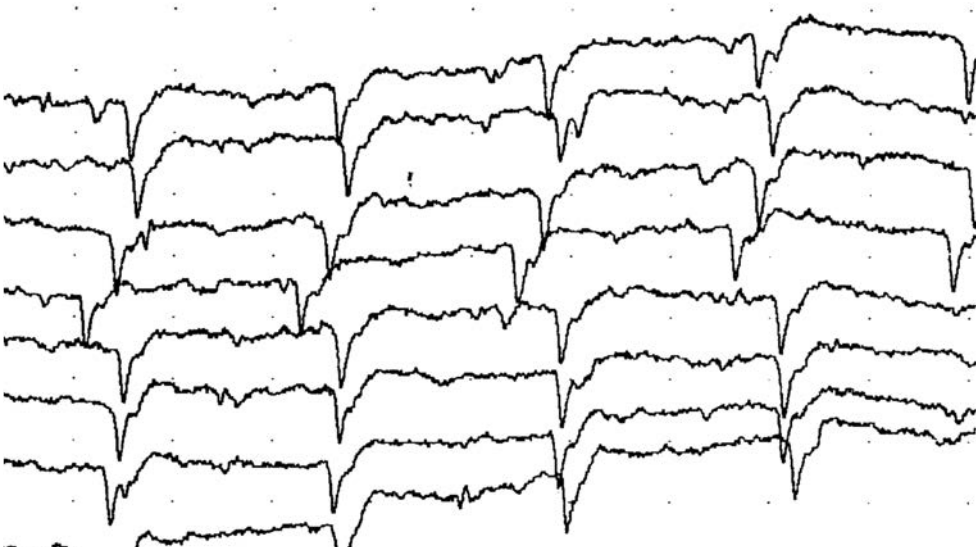


Figure E 2: Concentric needle EMG recording from right bulbocavernosus muscle of a 49-years old male with urinary incontinence diagnosed as possible Multiple system atrophy. Pathological spontaneous activity (a burst of positive sharp waves) is shown.

In normal muscle, needle movement elicits a short burst of "insertion activity," which is due to mechanical stimulation of excitable muscle cell membranes. This is recorded at a gain setting of 50 μV per division (sweep speed 5 – 10 ms/division), which is also used to record spontaneous activity. Absence of insertion activity with an appropriately placed needle electrode usually means a complete denervation atrophy of the examined muscle.

The amount of recruitable motor units during voluntary and reflex activation can also be estimated. Normally, MUPs should intermingle to produce an "interference" pattern on the oscilloscope during muscle contraction, and during a strong cough. In addition, the number of continuously active MUPs during relaxation [3], MUP variability as well as MUP recruitment on reflex and voluntary activation can be observed [4].

MUPs (and occasionally encountered end-plate activity) are recordable in normal resting sphincter muscles in a relaxed subject. This is in contrast to limb muscles where relaxation is associated with "electrical silence" by EMG. In addition to continuously firing motor units, new MUPs are recruited voluntarily and reflexly in the sphincters. It has been shown that the two MUP populations differ in their characteristics: reflexly or voluntarily activated "high-threshold MUPs" being larger than continuously active "low-threshold MUPs". As a consequence, standardised level of activity at which a template based multi-MUP analysis obtains 3-5 MUPs on a single muscle site was suggested [5]. In partially denervated sphincter muscle there is – by definition – a loss of motor units (MUs). This can be estimated during relaxation by counting the number of continuously firing low-threshold MUPs. In patients with cauda equina or conus medullaris lesions, fewer MUPs fire continuously during relaxation [6], probably due to partial axonal loss. The main obstacle to qualified assessment of reduced number of activated MUs and activation of MUs at increased firing rates (as occurs in limb muscles) is a lack of concomitant measurement of level of contraction of the examined muscle (this can be readily assessed when studying limb muscles).

There are two approaches to analysing the bioelectrical activity of motor units: either analysis of individual motor unit potentials (MUPs), or analysis of the overall activity of intermingled MUPs. (This is the so called "interference pattern" – IP. Exploring different sites of the activated muscle with a needle electrode provides "samples" of intermingled motor unit potentials (IP epochs), which can be analysed).

Generally three different techniques of MUP analysis (manual-MUP, single-MUP and multi-MUP) and 1 technique of IP analysis (turn/amplitude – T/A) are available on advanced EMG systems [6].

It is easy to grasp the "motor unit potential analysis", as it is simply a measurement (by different methods) of the "parameters" of single individual MUPs (ie. its amplitude, duration, number of phases…). The changes in MUP parameters furthermore are "direct" results of understandable physiological changes, and are thus "meaningful" to the interpreter.

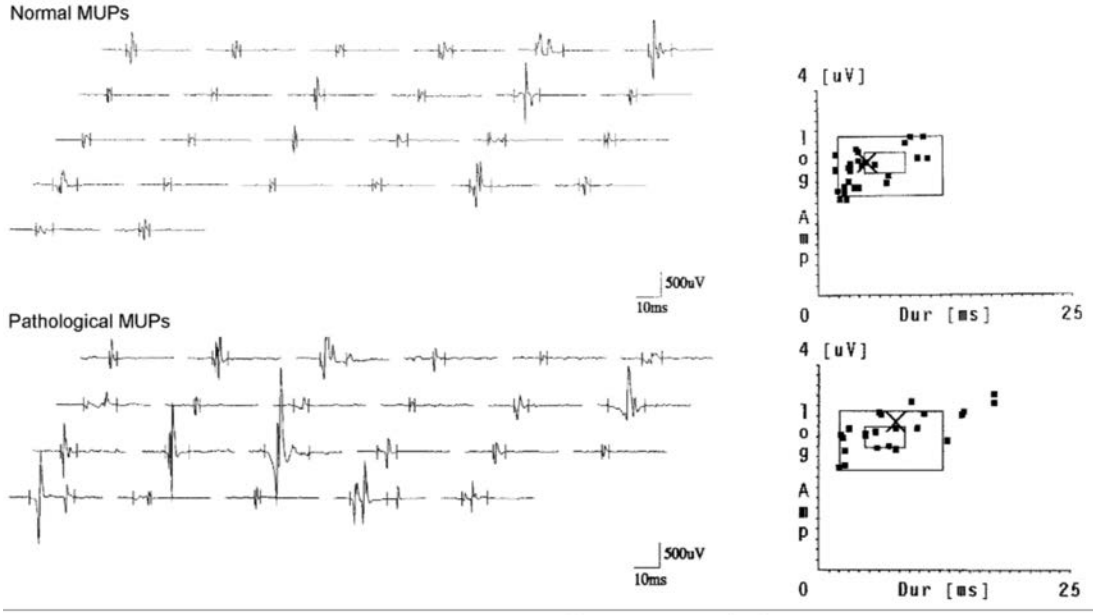
The changes in IP parameters are, however, less readily grasped. These are: numbers of turns per second (any peak or trough of the signal where the activity changes by more than 100 μV); amplitude/

turn (change in volts between two turns); number of short segments (parts of signal that has "sharp" activity) percent activity (percent of epoch with sharp activity); envelope (peak to trough amplitude exceeded by 1% of peaks/troughs). These parameters relate both to MUP parameters and to the activation level of the muscle. Recorded data are log transformed and linear regression lines are created. Amplitude/turn, and number of turns/second data from normal subjects can be used to create upper and lower boundaries (95 % confidence intervals) for assembly of future data from individual patients. Individual data create a scatter plot ("cloud") that compares to the normative boundaries. (**Figure E 3**). It has been asserted that this approach does not require a standardised muscle contraction, but the shape of the "cloud" is dependent on the strength of muscle contraction. Therefore it has been suggested to standardise the method by measuring pressure exerted by the contracting sphincter [7].

Both the template based multi-MUP analysis of MUP and T/A analysis of IP are fast (5-10 and 2-3 minutes per muscle, respectively), easy to apply, and, technically, represent clinically useful techniques.

• *CNEMG Findings Due to Denervation and Reinnervation*

After complete denervation, all motor unit activity ceases. In a denervated muscle, complete "electrical silence" is noted in the first days after such an event. The diagnosis of complete denervation



Anal sphincter muscle	#	Amp uV	Amp rel.SD	Amp <min	Amp >max	Dur ms	Dur rel.SD	Dur <min	Dur >max	Area uVms	Area rel.SD	Area <min	Area >max	Poly %
Normal	24	236	-1.6	1	0	5.0	-0.5	1	0	215	-1.0	2	0	8
Pathological	26	393	0.1	2	0	4.8	-1.8	2	0	317	-0.4	2	0	15

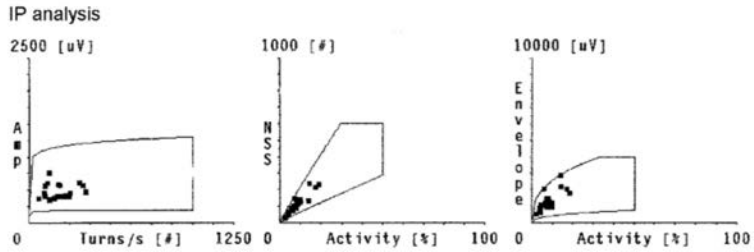


Figure E 3: Comparison of normal (above) and pathological (below) motor unit potentials (MUPs) sampled by multi-MUP analysis from the right halves of the subcutaneous parts of the external anal sphincter (EAS) muscles. To the right logarithm (amplitude) vs. duration plots of the MUPs are shown; the inner rectangle presents normative range for mean values, and the outer rectangle for "outliers". Below the MUP samples values are tabulated. Three plots on the bottom were obtained by turn/amplitude analysis in the cauda equina patient. Delineated areas ("clouds") present the normative range, and dots individual IP samples.

is confirmed by the absence of muscle response during electrical stimulation. Because motor axons take days to degenerate after injury, this proof is not available for up to 5-7 days after a denervation injury. However, it is rarely necessary to demonstrate complete denervation in the acute stage because the clinical condition is usually obvious. Denervated muscle fibres become hyperexcitable and start to fire spontaneously giving rise to abnormal spontaneous activity, but these may take up to three weeks to appear. The "insertion activity" becomes prolonged and short biphasic spikes (fibrillation potentials) and biphasic potentials with prominent positive deflections (positive sharp waves) appear (**Figure E 2**). Thus, concentric needle EMG (CNEMG) correlates of denervation are pathologically prolonged insertion activity and pathological spontaneous activity. Completely denervated muscle may be reinnervated by axonal regrowth from the proximal nerve stump with few muscle fibres constituting "nascent" motor units. These are short, bi- and triphasic, soon becoming polyphasic, serrated and with prolonged duration. In partially denervated muscle, collateral reinnervation takes place. Surviving motor axons will sprout and grow out to reinnervate those muscle fibres that have lost their nerve supply. This results in a change in the arrangement of muscle fibres within the unit. Whereas in healthy muscle, it is unusual for two adjacent muscle fibres to be part of the same motor unit, following reinnervation, several muscle fibres belonging to the same motor unit come to be adjacent to one another. CNEMG correlates are changes in MUPs (duration, amplitude, number of phases, turns, etc).

Early in the process of reinnervation, the newly outgrown motor sprouts are thin. Therefore, they conduct slowly such that the time taken for excitatory impulses to spread through the axonal tree is abnormally prolonged. Moreover, the neuromuscular transmission is unstable due to immaturity of the motor end-plates. The CNEMG correlate is instability of long-duration complex potentials.

In partially denervated muscle, some MUPs remain and mingle eventually with abnormal spontaneous activity. Changes due to collateral reinnervation are reflected by: prolongation of the waveform of the MUP (**Figure E 3**) which may have small, late components ("satellite potentials"). MUPs show "instability" due to insecure transmission in newly formed axon sprouts and end-plates. This "instability of potentials" (meaning both "jitter" and "blocking" of individual components in a complex potential) is not routinely assessed during sphincter EMG. Nonetheless, it can be a helpful parameter, and may be evaluated not only by SFEMG, as originally described (8), but also by CNEMG, if a low frequency cut-off filter of 0.5 (up to 2) kHz is used along with a trigger – delay unit. In skeletal muscle, the diameter of reinnervating axonal sprouts and conduction velocity increase with time, thereby improving synchrony of activation in the reinnervated motor unit. Thus MUP amplitude increases while MUP duration reverts towards normal. However, in degenerative neurological diseases (such as multiple system atrophy), long duration motor units are a prominent feature of anal sphincter reinnervation [9]. It is important to note that in patients with more severe neurogenic lesions, reinnervation may be inefficient resulting in MUP with parameters below confidence limits describing size (area, duration) [10].

The changes in MUP parameters (along with changed number of MUPs and changes in activation frequency of MUPs) will be reflected also in IP parameters.

Abnormalities of parameters evaluated by needle EMG are in principle non-specific, i.e. most abnormalities can occur both in neuropathic or myopathic conditions. It is the overall clinical picture that dictates interpretation of results. It has been suggested that the combination of MUP thickness and number of turns might be even more accurate [11] than previously suggested combination of MUP area, duration, and number of turns [12].

• *CNEMG of the External Anal Sphincter*

The external anal sphincter (EAS) is the most practical indicator muscle for sacral myotomes because it is easy to access, has enough muscle bulk for exact EMG analysis, and its examination is not too uncomfortable.

The needle electrode is inserted into the subcutaneous EAS muscle about 1 cm from the anal orifice, to a depth of a 3-6 mm under the non-keratinised epithelium. For the deeper part of the EAS muscle 1-3 cm deep insertions are made at the anal orifice, at an angle of about 30° to the anal canal axis [13]. In most patients only examination of the subcutaneous EAS muscle is necessary. Separate examinations of the left and right EAS muscles are recommended. The needle is inserted into the middle of the anterior and posterior halves of each side ("quadrants") of the EAS muscle. After insertion in two positions on each side the electrode is turned backwards and forwards in a systematic manner. At least 4 sites in each of the subcutaneous and/or the deeper EAS muscle are thus analysed [13, 14].

Use of quantitative MUP and IP analyses of the EAS is further facilitated by the availability of normative values [15] that can be introduced into the EMG systems' software. It has been shown that normative data are not significantly affected by age, gender [15], number of uncomplicated vaginal deliveries [16], mild chronic constipation [17] and the part of EAS muscle (i.e. subcutaneous or deeper) examined [16].

Intramuscular electrode insertion into other perineal muscles and pelvic floor muscles is not standardised and is described in textbooks and primary literature.

3. Single fibre EMG (SFEMG)

The SFEMG electrode has similar external proportions to a concentric needle electrode, but with a smaller recording surface. It will pick up activity from within a hemispherical muscle volume 300 µm in diameter, much smaller than the volume of 2-3 mm diameter from which a concentric needle electrode records [2]. Because of the arrangement of muscle fibres in a normal motor unit, a SFEMG needle will record only 1-3 single muscle fibres from the same motor unit.

The SFEMG parameter that reflects motor unit morphology is fibre density, which is defined as the mean number of muscle fibres belonging to an individual motor unit per detection site. To assemble these data, recordings from 20 different intramuscular detection sites are necessary [8].

SFEMG recording needles are very expensive, and disposable needles are not available.

4. Kinesiological EMG

Kinesiological EMG is used to assess patterns of individual muscle activity/inactivity during defined manoeuvres (**Figure E 4**), typically during urodynamics. As such, the specific interpretation of electrical activity within a muscle is based on its presence or absence, rather than the type of activity. Technical issues will be dealt here; the relevance for diagnostics will be discussed in the Chapter on dynamic testing.

Although either standard EMG equipment or EMG facilities contained within urodynamic systems can be used, the better visual and audio control provided by standard EMG equipment facilitate optimal electrode placement and improve recordings [18]. When using surface electrodes there are problems related to validity of signal (e.g., artefacts, contamination from other muscles). The quality of the EMG recorded from the external urethral sphincter (EUS) muscle is improved by a catheter-mounted surface electrode device that applies mild suction [19]. With intramuscular electrodes, the procedure is more invasive, and there are questions as to whether the whole muscle in large pelvic floor muscles is properly represented by the sampled muscle portions. Intramuscular electrodes should ideally be fine wire electrodes, as they do not dislodge, and no pain is induced with muscle contraction.

The kinesiological sphincter EMG recordings in health show continuous activity of MUPs at rest. It can be recorded in many but not all detection sites of the levator ani muscle. The urethral and anal sphincter as well as the other pelvic floor musculature (e.g. pubococcigei) can be voluntarily activated typically for less than 1 minute [20]. Timely activation of the levator ani muscle has been demonstrated to be an important aspect of stable bladder neck support; its activation precedes activity of other muscles in the cough reflex [21]. A consistent contraction sequence of the superficial and deep pelvic floor muscles is found in continent but not in incontinent women [22].

Sphincter activity during voiding is characterised by the cessation of all EMG activity prior to detrusor contraction. Needle electrodes are more useful than perineal patch electrodes to demonstrate MU quiescence during voiding [23]. A recent study using perineal surface patch electrodes confirmed that these electrodes are inappropriate [24].

Pathological incoordination of the detrusor and sphincter is called detrusor sphincter dyssynergia. In selected patients with neurogenic detrusor overactivity EMG of the EUS muscle can be also used to demonstrate the onset of detrusor contractions [20].

Apart from polygraph urodynamic recordings to assess detrusor-sphincter coordination, the diagnostic usefulness of kinesiologic EMG has not been established.

- *Surface Electromyography Using Noninvasive Electrode Arrays*

Recently, surface EMG recording using noninvasive electrode arrays and multichannel EMG amplifiers

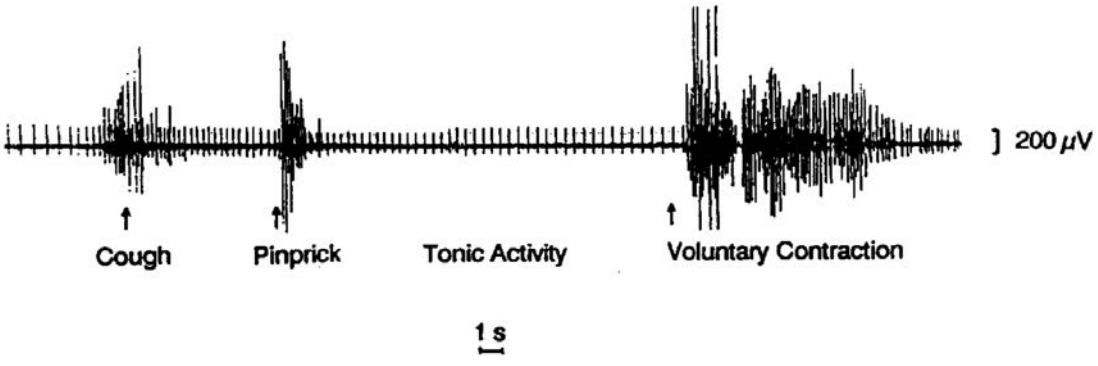


Figure E 4: Kinesiological EMG recording from the urethral sphincter muscle of a healthy 53 years old continent female. Recruitment of motor units on reflex manoeuvres and on a command to contract is shown; regular continuous activity of motor units represents "tonic activity". (Recorded with concentric needle electrode).

was introduced to the sphincter and pelvic floor muscles (eg, the EAS and puborectalis). Using this approach, investigators can localise muscle innervation zones and asymmetry in muscle innervation [25] and analyse discharge patterns of MUPs and propagation velocities along the muscle fibres [26]. Although observations in normal and pathological conditions have been published [27], the clinical value of these methods in diagnosing neurogenic sacral disorders has not yet been demonstrated.

5. Clinical application of EMG

• *Neurogenic Conditions*

Trauma, surgery, and neurological disease have all been implicated in denervation of pelvic floor and perineal muscles and pelvic organs. In a series of 194 consecutive patients referred for electrodiagnostic evaluation, quantitative needle EMG of the EAS muscles supported a diagnosis of a cauda equina or conus medullaris lesion in 36 patients, a lesion of the EAS muscle in 6, a pudendal nerve lesion in 2, and a sacral plexus lesion in 1 patient. Furthermore, neuropathic findings in the EAS were compatible with a diagnosis of multisystem atrophy in 11, and were most probably caused by severe polyneuropathy in 2 patients. In another 11 patients, the aetiology of the pathological findings could not be established at time of electrodiagnostic testing [28].

Lesions of the cauda equina or conus medullaris commonly cause pelvic floor dysfunction. These have mainly been a consequence of neural compression within the spinal canal caused by intervertebral disc herniation, spinal fractures, epidural haematomas, and, intraspinal tumours; or a result of spinal surgery, mainly on lumbar discs [29, 30]. Electrodiagnostic tests are also useful in the assessment of neurogenic lesions in children with spinal dysraphism [31]. After detailed clinical examination of the lumbosacral segments (with particular emphasis on perianal sensation), neurophysiological testing assesses the severity of the lesion and may clarify the diagnosis. In the authors' series, 10 percent of patients with cauda equina lesions reported normal perianal sensation [32]. Electrodiagnostic tests that need to be considered are bilateral needle EMG of the EAS muscle and the bulbocavernosus muscle in subacute situations; and electrophysiologic evaluation of the bulbocavernosus reflex [33] (when this is absent or equivocal clinically) [34]. Detection of spontaneous denervation activity by needle EMG is common from approximately 3 weeks to several months after injury, and the bulbocavernosus muscle is particularly helpful in this respect. Later, MUP analysis becomes more important for demonstrating reinnervation. The bulbocavernosus reflex is useful for assessing the integrity of the sacral reflex arc in subjects with cauda equina or conus medullaris lesions [34]. Most of these lesions cause partial denervation; a traumatic lesion to the lumbosacral spine or pelvis is probably the only acquired condition in which complete denervation of the perineal muscles can be observed [35, 36, 37].

Following a cauda equina or a conus medullaris lesion, the MUP of pelvic floor and perineal muscles are prolonged and polyphasic, of increased amplitude, area, number of turns [6]. Surgical dissections can also affect the innervation of the sphincter and lead to loss of motor units and reinnervation of those surviving [38]. After pelvic trauma, gross changes of denervation and reinnervation may be detected in pelvic floor muscles. The bulbocavernosus muscle is particularly useful in suspected recent minor partial denervation as it lacks on-going activity of low-threshold MU during relaxation. (In women the muscle is thin).

Neuropathic changes can also be recorded in sphincter muscles of patients with multiple system atrophy (MSA) [39]. MSA is a progressive neurodegenerative disease, which can be mistaken for Parkinson's disease (PD). Urinary incontinence and erectile dysfunction occur, often some years before the onset of obvious neurological features [40]. Sphincter EMG has been used in distinguishing MSA from Parkinson's disease. EMG is probably not helpful to distinguish MSA from the later stages of Parkinson's disease and from progressive supranuclear palsy. Sphincter EMG may not be sensitive in the early phase of the disease [41, 42], and is not specific after 5 years of parkinsonism [43]. Among 30 patients with a pathological diagnosis of multisystem atrophy, 24 had abnormal, 5 had a borderline, and only 1 had a normal sphincter EMG [44]. Some studies have failed to demonstrate the effectiveness of MUP analysis in sphincter muscles [45, 46], probably because of the exclusion of late components from MUP duration [9]. Extensive discussion on the subject can be found elsewhere [47]. The changes of chronic reinnervation may also be found in progressive supranuclear palsy [48, 49] and in Machado–Joseph disease [50] in which neuronal loss in Onuf's nucleus has also been demonstrated histologically [51].

In patients with acute idiopathic autonomic neuropathy and lower urinary tract (LUT) dysfunction the EMG of external sphincter muscles was reported as normal [52].

• *Changes in Primary Muscle Disease*

In skeletal muscle, the "typical" features of a myopathy are small, low amplitude polyphasic units recruited on mild effort. There are few reports of pelvic floor muscle EMG in generalised myopathy. In a nulliparous woman with limb-girdle muscular dystrophy, histology revealed involvement of pelvic floor muscles, but concentric needle EMG of the urethral sphincter was normal [53]. Myopathic EMG changes were observed in the puborectalis and the EAS in patients with myotonic dystrophy [54] but not in another group of patients with myopathy [55].

• *Stress Incontinence*

Pelvic floor muscle denervation has been implicated in the pathophysiology of urodynamic stress incontinence (USI) [56]. EMG techniques have been used to identify sphincter injury after childbirth and to evaluate women with USI. Stress incontinence and genitourinary prolapse were associated with partial denervation of the pelvic floor [57]. The changes were most marked in women who were incontinent after delivery, who had a prolonged second stage of labour, and had given birth to heavier babies. In a recent study, nearly all EMG parameters showed significant differences between continent and SUI women consistent with better motor unit recruitment in continent women. Continent women had larger-amplitude, longer-duration MUPs with increased turns and better MUP recruitment during bladder filling ($P < 0.05$) [58].

Myogenic histological changes in pelvic floor muscles after vaginal delivery were also reported [59], with some EMG support by another group [60]. Myopathic EMG changes (i.e. short, small MUPs) may, however, be a consequence of deficient reinnervation [35]. There were claims urethral sphincter EMG can assist in selecting the type of surgery for patients with intrinsic sphincter deficiency [59].

Although CNEMG of the urethral sphincter seems the logical choice in patients with urinary incontinence of possibly neurological origin, only a small amount of pathological muscle tissue remains in many incontinent parous women, which makes EMG of the muscle impractical [38]. CNEMG findings generally will not affect therapeutic considerations [61].

• *Idiopathic Faecal Incontinence*

"Idiopathic" faecal incontinence refers to patients in whom this symptom is not attributable to an underlying disorder, but it has been often implied that it is a neurogenic condition. Vaginal delivery has been shown to cause structural sphincter defects; it may cause outright sphincter denervation in rare cases, but its more widespread implication in causing "idiopathic" incontinence is controversial.

CNEMG may be helpful in selected patients with faecal incontinence if a specific neurogenic condition (e.g., trauma or disease affecting the conus, sacral roots, sacral plexus or pudendal nerves) is suspected on clinical grounds. Turns/amplitude, but not MUP analysis has been claimed to detect evidence of denervation and subsequent reinnervation in postpartum women with mild anal incontinence [62].

• *Idiopathic Urinary Retention in Women*

In the external urethral sphincter of young women with urinary retention (or obstructed voiding) complex repetitive discharges in profuse amounts (against a background of firing motor units) have been described, suggesting that these findings are of pathogenic and of diagnostic significance. The external urethral sphincter was reported to be hypertrophic. A percentage of these women were hirsute and had polycystic ovaries [63, 64]. The presence of such activity in the needle EMG of the EUS of young women with non-obstructive urinary retention (Fowler's syndrome) is the only predictor of the long-term success of therapeutic sacral neuromodulation [65]. The cause of this activity is unknown. In some women it may be the expression of an occult generalised dysautonomia [66].

Repetitive discharges are, however, prone to develop in chronically partially denervated sphincters, and are present even in a proportion of asymptomatic women [67]. The distinguishing feature of the spontaneous EMG activity defining the particular pathology in women with retention seems to be its abundance, but the issue remains disputed.

• *EMG in Urodynamic and Functional Anorectal Studies*

In health, voiding is characterised by cessation of motor unit firing in the urethral sphincter prior to detrusor contraction, as can be demonstrated by recording of "kinesiological EMG". Bladder-sphincter coordination is impaired with lesions between the lower sacral segments and the upper pons. Consequently, sphincter activity is not inhibited, and often increases before detrusor contraction (i.e., 'detrusor-sphincter dyssynergia'). On the basis of the temporal relationship between urethral sphincter and detrusor contractions, three types of dyssynergia have been described [68].

There are other clinical situations that mimic detrusor sphincter dyssynergia. Sphincter contraction or at least failure of relaxation during involuntary detrusor contractions can be seen in patients with Parkinson's disease. The pelvic floor muscle contractions of the so-called non-neurogenic voiding dyssynergia may be a learned abnormal behaviour [69], and are a feature of dysfunctional voiding [64].

The pubococcygeus in the healthy female reveals similar activity patterns to the urethral and anal sphincters at most detection sites: continuous activity at rest, often some increase of activity during bladder filling, and reflex increases in activity during any activation manoeuvre performed by the subject such as talking, deep breathing, coughing. The pubococcygeus relaxes during voiding; the muscles on either side act in unison [20]. In stress-incontinent patients, the patterns of activation and the co-ordination between the two sides can be lost [70]. A delay in muscle activation on coughing has also been demonstrated, as compared to continent women [21].

Little is known about the complex activity patterns of different pelvic floor muscles (the urethral sphincter, urethrovaginal sphincter, anal sphincter muscle, different parts of the levator ani) during different

manoeuvres. It is generally assumed that they all act in a co-ordinated fashion functionally as one muscle. However there are demonstrable differences between the intra- and peri-urethral sphincter in healthy females [71] and in activation of the levator ani and the urethral sphincter [72]. Co-ordinated behaviour is frequently lost in abnormal conditions.

Kinesiological needle EMG analysis of the urethra with the patient at rest and coughing may predict the outcome after certain types of incontinence surgery [73].

Current concepts suggest that defecation requires increased rectal pressure co-ordinated with relaxation of the anal sphincters and pelvic floor muscles. Pelvic floor relaxation allows opening of the anorectal angle and perineal descent, facilitating faecal expulsion. During defaecation puborectalis activity is as a rule inhibited, but was unchanged in 9 % and increased in 25 % of healthy subjects [74]. Thus, while "paradoxical" puborectalis contraction during defecation is used to diagnose pelvic floor dyssynergia in patients with typical symptoms, this finding may be a variation of the normal.

b) Pudendal Nerve Conduction Tests

Measurement of motor conduction velocity is routinely used to evaluate limb motor nerves, distinguishing between a demyelinating and axonal neuropathy. To make the measurement requires access to the nerve at two well-separated points and measurement of the distance between them, a requirement that cannot be met in the pelvis. Another way to evaluate peripheral motor nerve function is the measurement of the motor latency of a muscle response, requiring only a single stimulation site. The muscle response is the compound muscle action potential (CMAP) or M-wave. Because in limb nerves the site of stimulation to obtain only the motor latency (without measuring the actual conduction velocity) is as a rule placed distally on the nerve, it is also called the distal (or terminal) latency. For the pudendal nerve the site of stimulation may be more or less "distally", but the term distal or terminal has – in accordance to general clinical neurophysiology – become generally used. Distal motor latency can be measured by recording with a concentric needle electrode from the bulbocavernosus, the EAS and the urethral sphincter muscles in response to bipolar surface stimulation placed in the perianal/perineal region, or with selective needle stimulation of the pudendal nerve (branches) in the perineum.

The most widely employed technique to obtain pudendal nerve terminal motor latency (PNTML) relies on stimulation with a special surface electrode assembly fixed on a gloved index finger, known as the St Mark's stimulator [75]. It consists of a bipolar stimulating electrode on the tip of the gloved finger with the recording electrode pair placed proximally on the base of the finger. The finger is inserted into the rectum or vagina and stimulation is applied close to the ischial spine. It is assumed that, using this approach, the pudendal nerve is stimulated close to the ischial spine, and that the response recorded is of the EAS muscle. In women, intravaginal stimulation and recording from the bulbocavernosus muscles has also been undertaken, with similar distal latencies [76]. However, the latency of such a response is typically only around 2 msec, which seems unusually short compared with the perineal technique and with conduction in the much thicker motor fibers of peripheral nerves in the limbs. It seems unlikely that the PNTML using the St. Mark's electrode really evaluates conduction along the last 8 cm of the pudendal nerve. Stimulation of the terminal pudendal branches or pelvic floor muscles near their motor points seems more likely, and this is supported by the much longer PNTML (3.7 ± 0.9 msec) obtained with a monopolar intrarectal stimulation electrode [77].

If a catheter-mounted electrode is used for recording, EMG responses from the striated muscle of the urethral sphincter can be obtained. Experts differ in their estimation of validity of this test. A prospective evaluation of anorectal physiologic tests in 90 patients with faecal incontinence did not find that PNTML results changed treatment decisions [78]. Indeed, the American Gastroenterological Association statement indicated that "PNTML cannot be recommended for evaluation of patients with faecal incontinence" [79].

c) Anterior Sacral Root (Cauda Equina) Stimulation

Anterior root stimulation has been used to study conduction of the sacral nerve roots. Electrical stimulation with needle electrodes at vertebral laminae Th12-L1 elicit M-waves in the bulbocavernosus and EAS muscle [80].

Transcutaneous stimulation of deeply situated nervous tissue became possible with development of special electrical and magnetic stimulators. When applied over the spine, these stimulators activate the roots as they exit the vertebral canal. Needle EMG rather than non-selective surface electrodes should be used to record pelvic floor and particularly sphincter responses to electrical or magnetic stimulation of the cauda equina. These stimuli non-selectively depolarise underlying neural structures, thereby activating several muscles innervated by lumbosacral segments [81]. Lumbosacral stimulation often evokes a large stimulus artifact that can be decreased by positioning the ground electrode between the stimulating and recording electrodes [82]. Invasive percutaneous stimulation of individual roots in sacral foramina is used to identify patients with lower urinary and anorectal dysfunction who are likely to benefit from long-term stimulation, e.g. with the Interstim (Medtronic, Inc., Minneapolis, USA). Electrical stimulation of nerve roots at the level of the appropriate sacral foramina results in observable muscle contraction in the foot and perineum. These responses can be identified as MEP or reflex responses on the basis of their latency. Selective stimulation of

individual sacral roots is possible by appropriate positioning of surface stimulating electrodes [83].

In conclusion, demonstrating the presence of a perineal MEP on stimulation over lumbosacral spine may occasionally be helpful in patients without voluntarily activated muscles. It also identifies the particular nerve root before introducing therapeutic electrical stimulation. However, the clinical value of the test has yet to be established and there are no sensitivity and specificity data on test results in individual patients.

d) Motor Evoked Potentials

Using magnetic or electric stimulation, it is possible to depolarise the motor cortex and record a response from the pelvic floor. Magnetic cortical stimulation is better tolerated than electrical stimulation, which has been abandoned in awake subjects, but may be useful for intraoperative monitoring.

By performing the stimulation at two different sites (brain and spinal roots), it is possible to record three different conduction times: a total conduction time, a peripheral conduction time, and a central conduction time (**Figure E5**). The total conduction time corresponds to the transit time from brain to target muscle. The peripheral conduction time is the transit time from sacral roots to the muscle. The central conduction time is obtained by subtracting the peripheral conduction time from the total conduction time. The total conduction time can be measured both at rest and during a facilitation procedure. MEPs from the EAS, the urethral sphincter, the bulbocavernosus muscle, and the levator ani muscle have been reported, but normative values have only been obtained (for transcranial magnetic stimulation) for the urethral sphincter and the puborectal muscle in adult women [84]. A central conduction time of 15 to 16 msec without and 13 to 14 msec with facilitation is obtained for pelvic floor and sphincter muscles [85, 86, 87]. The necessity to use concentric needle EMG for recording has been reconfirmed [88].

Substantially longer central conduction times have been found in patients with multiple sclerosis and spinal cord lesions as compared to healthy controls [87, 88, 89]. However all patients in this study had clinically recognisable cord disease. Nevertheless, MEPs may be useful in patients with unclear localization of spinal lesions [87].

Conceptually, MEP may help to differentiate between involvement of motor and sensory pathways. However, the clinical utility of these measurements is not established. MEP have opened an avenue of research on excitability of motor cortex. It has been demonstrated that in comparison to the motor area for hand muscles the anal sphincter motor cortex has less intracortical inhibition [90].

2. SENSORY SYSTEM TESTS

There are several methods of sensory testing for the perineum, the genitourinary and anorectal tract. Clinical testing includes perineal and external genital skin sensation for light touch and pinprick, and sensation of bladder filling during cystometry. Anorectal sensory testing can be clinically assessed through rating of applied stimuli. More objective sensory testing can be performed with quantitative sensory testing (QST), which assesses sensory perception. For evaluation of the integrity of sensory pathways sensory neurography, and somatosensory evoked potentials (SEP) can be used.

a) Sensory Measurements During Cystometry

During routine cystometry bladder sensation is assessed by recording first sensation of bladder filling, first desire to void and strong desire to void.

Although not strictly a neurophysiologic test, measurement of electrical thresholds adds clinically non-obtainable information on sensory function of the lower urinary tract [91]. Bladder and urethral sensory thresholds have also been measured using electrical stimulation [91], and mechanical traction on the bladder trigone [92]. Electrical currents

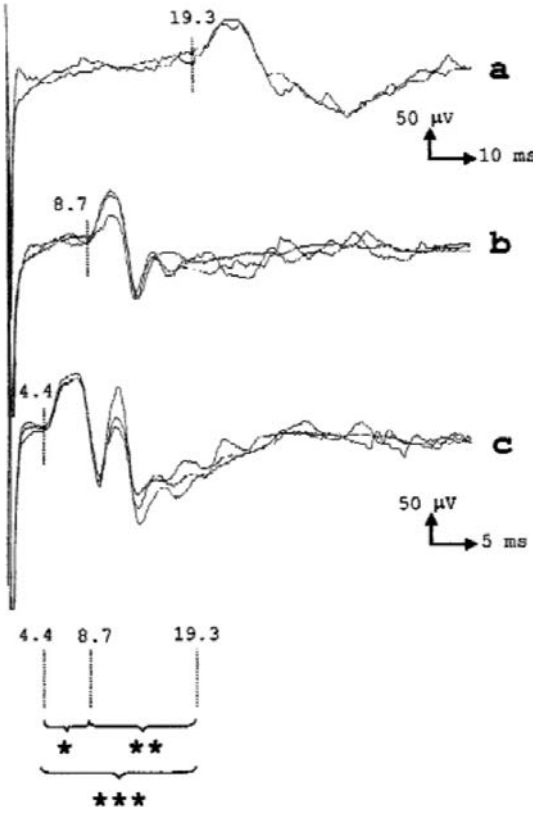


Figure E 5: MEPs recorded by concentric needle in the external urethral sphincter of a 51-year-old-woman. Cortical (a), thoracic (b), and sacral (c) stimulation. Central motor conduction time (CMCT) is calculated as cortical - lumbar latency (** = 10.6 ms). Cauda equina motor conduction time is calculated as lumbar - sacral latency (* = 4.3 ms). (From (Brostrom et al., 2003a), with permission).

are applied to the bladder, urethra or genital skin using catheter-mounted or surface electrodes. High-frequency stimulation (> 20 Hz), with a stimulus duration of 0.5 or 1 msec is used because it is more easily perceived in the lower urinary tract. Measurement of sensory thresholds with such stimulation is reproducible, and normative data have been published [91]. To date it has been used in only a few conditions (e.g., painful bladder syndrome) [93]. There is no established clinical use for any of these tests other than simple reporting of sensation during cystometry.

In addition, palmar SSR and perineal surface EMG recordings can be used for more objectively demonstrating sensations during cystometry. The activity of both appears and increases in parallel with the first sensation of bladder filling, and with the first desire to void, respectively [94]. Further studies using these methods are needed to establish their clinical utility.

b) Assessment of Anorectal Sensation

Rectal sensation is assessed by progressively distending a balloon manually or by a barostat while measuring thresholds for first perception, desire to defecate, and severe discomfort. The intensity of perception during rectal distension can be recorded by a visual analogue scale during phasic distensions of graded intensity [95]. The rate and pattern of distension affect rectal perception and internal sphincter relaxation [96].

Anal sensation can be assessed by determining the perception threshold to an electrical stimulus or temperature change in the anal canal. Electrical testing does not activate mucosal receptors. Temperature perception on the proximal anal canal has been found to be reduced in patients with passive anal incontinence compared to those with urgency incontinence [97].

c) Quantitative Sensory Testing

Quantitative sensory testing (QST) of the urogenitoanal system should provide more objective and reproducible data than routine clinical testing. QST sensory modalities applied to the evaluation of urogenital function include vibration [98], temperature [99], and electrical current [100]. There is no commonly accepted, detailed, standardised test, and the specificity and sensitivity of the tests are not known. The relationship of cutaneous quantitative sensory tests to bladder and urethral sensation and function is unknown. The physiological, psychophysiological and methodological issues and controversies will not be addressed in this chapter.

d) Sensory Neurography

Nerve conduction velocities of the dorsal nerve of the penis can be calculated by placing a pair of stimulating electrodes across the glans and a pair of recording electrodes across the base of penis. A nerve action potential can be recorded with amplitude of about 10 µV. It can also be recorded by stimulating trans-rectally or transperineally. There is no known association between penile sensory neuropathy and bladder/sphincter dysfunction.

A few studies have recorded activity in sacral roots during electrical stimulation. Intraoperatively, when the sacral roots are exposed, compound sensory action potentials on stimulation of dorsal penile and clitoral nerve may be recorded directly [101]. This helps to preserve roots mediating perineal sensation in spastic children undergoing dorsal rhizotomy, and reduce the incidence of postoperative voiding dysfunction [102]. These tests are limited to their very specific intraoperative indications.

e) Somatosensory Evoked Potentials (SEP)

Somatosensory evoked potentials are electric waveforms of biological origin elicited by stimulation of a sensory nerve (or a sensory innervated skin area – dermatome). The most commonly performed tests in the urogenitoanal region are pudendal somatosensory evoked potentials (SEP), which assesses conduction in large fibre pathways between the site of nerve stimulation and the parietal sensory cortex. Potentials can also be measured at the spinal level (spinal SEP). Visceral (thin) fibre pathways are assessed by recording SEPs while stimulating the proximal urethra and bladder, although this is technically not depolarisation of nerves, but a mesh of afferents.

1. Pudendal Somatosensory Evoked Potentials

• *Cerebral Pudendal SEP*

On electrical stimulation of the dorsal penile/clitoral or perineal nerve, a cerebral SEP can be recorded. (**Figure E 6**) This SEP is as a rule of highest amplitude at the central recording site (Cz - 2 cm : Fz of the International 10-20 EEG System) and is highly reproducible. The first positive peak at about 40 ms (called P40) is usually clearly defined in healthy subjects using a stimulus 2-4 times stronger than the sensory threshold [103]. The presence and amplitude of subsequent negative and positive waves are quite variable between subjects. Classically described pudendal SEP techniques stimulate both dorsal penile/clitoral nerves, thus reducing the sensitivity of the test.

However, techniques of pudendal SEP that isolate each dorsal penile/clitoral nerve may be more sensitive for identifying pathology [104].

Pudendal SEPs have been advocated in patients with neurogenic bladder dysfunction, e.g. in multiple sclerosis [105]. However, even in patients with multiple sclerosis and bladder symptoms, the tibial

cerebral SEP was more often abnormal than the pudendal SEP. The combination of an abnormal pudendal SEP with a normal tibial SEP suggests isolated conus involvement [106]. The pudendal SEP was less useful than neurological examination for identifying neurological disease in patients with uro-genital symptoms [107]. Following spinal cord injury, tibial and pudendal SEPs may be of some value for predicting recovery in bladder control [108]. Cerebral SEP during penile/clitoral stimulation may be useful for intraoperative monitoring. Pudendal SEP were used to study the mechanism of sacral neuromodulation [109].

• *Spinal Pudendal SEP*

Stimulating the dorsal penile nerve and recording with surface electrodes at the level of the Th12-L2 vertebrae (and the S1, Th6 or iliac spine as reference) reveals the postsynaptic segmental spinal cord activity (the spinal SEP). Unfortunately, this spinal SEP may be difficult to record even in normal (and particularly in obese) subjects.

3. SACRAL REFLEXES

Clinically, two reflexes are commonly elicited in the lower sacral segments: [1] the penilo- or clitoro-cavernosus (i.e. bulbocavernosus) reflex; and [2] the anal reflex [110]. To elicit sacral reflexes, electrical [111-118], mechanical [115, 116, 119] or magnetic [120] stimulation can be used. Whereas the latter two modalities have only been applied to the penis [117-119], clitoris, and the suprapubic area [115], electrical stimuli can be applied to various sites: to the dorsal penile or clitoral nerve; perianally; and, using a catheter-mounted ring electrode, to the bladder neck/proximal urethra [121].

a) Sacral Reflex on Electrical Stimulation

Electrical stimulation of the dorsal penile or clitoral nerve elicits (somato-somatic) sacral reflexes in perineal muscles with a typical latency approx. 33 ms (29.9 ± 5.7 msec in one study in men) [117], traditionally called the bulbocavernosus reflex (**Figure E 6**). In addition to single-pulse electrical stimulation, two identical electrical pulses separated by a 3-msec interval can be used (i.e., double-pulse electrical stimulation) [117, 118]. Double-pulse electrical stimulation is more efficient in eliciting sacral reflexes [117]. Stimulation of the perianal skin, bladder neck or proximal urethra elicits sacral reflexes with latencies above 50 ms. This latency is longer compared to responses conveyed by the pudendal nerve, suggesting that the afferent limb for these responses involves visceral afferent fibres accompanying the pelvic nerves, which are thinly myelinated and have a slower conduction velocity than the thicker pudendal afferents. With visceral denervation (e.g. following radical hysterectomy) the viscerosomatic reflexes (from both bladder and urethral stimulation) may be lost while the bulbocavernosus (penilo-/clitoro-cavernosus) reflex is preserved. Loss of bladder-urethral reflex with preservation of bladder-anal reflex has been described with urethral afferent injury after recurrent urethral surgeries [122].

The longer latency anal reflex (the contraction of the EAS on stimulation of the perianal region) is quite variable thus limiting its usefulness as a diagnostic tool.

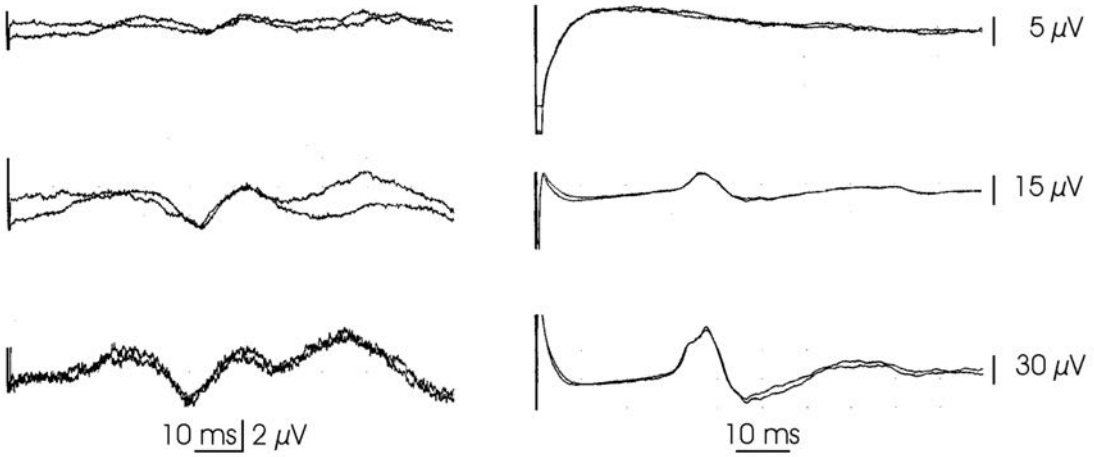


Figure E 6: SEPs (traces on the left) and sacral reflexes (traces on the right) in a healthy woman. Cerebral SEPs are recorded from Cz - 2 cm; sacral reflexes from the anal sphincter. The dorsal clitoral nerve is being stimulated with rectangular electrical pulses at 2 Hz. Stimulation and recording is performed with surface electrodes. The cerebral SEP and sacral reflex are recorded simultaneously. In the upper row the stimulation is just above sensory threshold, in the middle row the stimulation is 1.5, and in the lower row at 2-times sensory threshold (pulse duration 0.2 ms; two consecutive averages of 128 responses are superimposed).

On perianal stimulation, a short latency response can also be recorded, as a result of depolarisation of motor branches to the EAS, possibly involving antidromic travelling of the depolarisation, with "returning" of the depolarisation orthodromically to the sphincter at a branching point of the motor axon.

EMG recording of the sacral reflex has been shown to be more reliable than the clinically assessed response (e.g. observing and palpating the contraction) in males and particularly in females [123]. In men, value of 40, 36 and 36 msec have been suggested as the upper limit of normal for the shortest latency obtained on eliciting a series of reflex responses using single, double and mechanical stimulation, respectively [117].

In men with cauda equina lesions penilo-cavernosus reflex could not be elicited in 64%, 47% and 47% of patients on single electrical, double electrical, and mechanical stimulation, respectively. Measurement of the reflex latency increased the sensitivity to record abnormalities for 17%, 36%, and 34%, respectively. Furthermore, it has been shown that sacral reflex measurement increase sensitivity of quantitative EMG of the EAS muscles from 73% to 81-83% using the different stimulation techniques mentioned [118].

Sacral reflex testing has been studied extensively and is used in many laboratories in everyday practice to demonstrate objectively the integrity of the S2-S4 reflex arc. The sacral reflex evoked on dorsal penile or clitoral nerve stimulation (the bulbocavernosus or penilo-/clitoro-cavernosus reflex) was shown to be a complex response, often forming two components. The first component with a typical latency of about 33 ms, is the response that has been most often called the bulbocavernosus reflex. It is stable, does not habituate, and has other attributes of an oligosynaptic reflex response [112]. The second component has latency similar to the sacral reflexes evoked by stimulation perianally or from the proximal urethra, and is not always demonstrable as a discreet response. In those subjects in whom the first reflex component is difficult to elicit, stimulation strength should be increased, but preferably double electrical stimuli should be used. A complete reflex arc lesion should not be inferred by absence of a response if only single pulse is used for stimulation.

During voiding sacral reflexes are un-elicitable but in the presence of spinal cord lesions such as myelodysplasia this normal suppression is lost.

Sacral reflex responses recorded with needle or wire electrodes can be analysed separately for each side from the EAS or bulbocavernosus muscle. Using unilateral dorsal penile nerve blocks, the existence of two unilateral BCR arcs has been demonstrated. Thus by detection from the left and right bulbocavernosus (and also the EAS) muscles separate testing of right and left reflex arcs can be performed. Some authors reported that the sensitivity of the test can be increased by use of the interside latency difference (normative limits: < 3 ms), but finding could not be confirmed by others (normative limits: < 7.2 ms) [117]. In cases of unilateral (sacral plexopathy, pudendal neuropathy) or asymmetrical lesions (cauda equina), a healthy reflex arc may obscure a pathological one on clinical elicitation, but not on neurophysiological measurements of the sacral reflexes.

As described above, penilo-cavernosus reflexes were absent in 47-64%, and delayed in additional 17-19% of patients with conus/cauda lesions. Of these patients 47% were incontinent for urine and 47% of faeces. However, a reflex with a normal latency does not exclude the possibility of an axonal lesion in its reflex arc, as demonstrated by pathologic quantitative EMG of the EAS in 79-86% of patients with conus/cauda lesions [118]. Furthermore, much delayed sacral reflex responses are compatible with normal bladder and sexual function as found in patients with hereditary motor and sensory demyelinating neuropathy. In a proportion of women with non-neurogenic sacral dysfunction clitoro-cavernosus reflex latencies were found to be much longer compared to those obtained in women with intact sacral function [124].

Sacral reflex recording is suggested as a complementary test to CNEMG examination of pelvic floor muscles in patients with suspected peripheral nervous lesions [4].

In addition to latency, a number of other parameters can also be measured using electrical, but not mechanical stimulation. These are the sensory threshold (i.e., the stimulus strength (mA) at which subjects feels stimulation), and reflex threshold (i.e., the stimulus strength (mA) at which the reproducible penilo/clitoro-cavernosus reflex appears on the screen). They evaluate lower sacral sensory pathways, and excitation level of the sacral reflex pathway, respectively. Although for men normative data for these parameters are available [117], their utility in clinical situation remains unclear.

Continuous intraoperative recording of sacral reflex responses on penis/clitoris stimulation is feasible if double pulses or a train of stimuli are used [125].

b) Sacral Reflex on Mechanical Stimulation

Mechanical stimulation has been used to elicit BCR in both sexes and found to be a robust technique. Either a standard reflex hammer or a customised electromechanical hammer can be used. Using a reflex hammer, the stimulus is applied to a wooden spatula placed on the glans penis or clitoris [117, 118]. Such stimulation is painless and can be used in children [119]. The latency of the BCR elicited mechanically is comparable to the electrically elicited

reflex in the same patients, but depends on the electromechanical device used [117, 119].

4. AUTONOMICAL FUNCTION TESTS

Most uro-neurophysiological methods discussed so far assess myelinated fibres, but not the autonomic nervous system, especially the parasympathetic component, which is most relevant for pelvic organ functions. Methods for evaluating the autonomic nerves innervating the pelvic viscera are not available. Cystometry indirectly evaluates the parasympathetic innervation to the bladder. However, from a clinical neurophysiological point of view direct electrophysiological testing would be desirable.

a) Tests in Generalised Autonomic Neuropathy

Cardiovascular autonomic function tests are useful for identifying generalised autonomic dysfunction in patients with bladder or gastrointestinal motility disturbances.

In cases when a general involvement of thin fibres is expected, an indirect way to examine autonomic fibres is to assess thin sensory fibre function. Thin visceral sensory fibres are tested by stimulating the proximal urethra or bladder, and by recording sacral reflex responses or cerebral SEP.

b) Dartos reflex

In men, another approach to test lumbosacral sympathetic function is by neurophysiological measurement of the dartos reflex obtained by electrical cutaneous stimulation of the thigh. The dartos muscle is a sympathetically innervated dermal layer within the scrotum, distinct from the somatically innervated cremasteric muscle. A reliable and reproducible dartos reflex (i.e., scrotal skin contraction) with a latency of about 5 seconds has been demonstrated in healthy men [126].

c) Smooth Muscle Electromyography

Technical problems have so far limited smooth muscle electromyography of the detrusor muscle, and of genital smooth muscle. There is no evidence to prove the clinical utility of these tests in the evaluation of urinary tract function.

d) Sympathetic Skin Response (SSR)

The sympathetic nervous system mediates sweat gland activity in the skin. Changes in sweat gland activity lead to changes in skin resistance. On noxious stimulation (such as a sudden noise, electrical pulse, etc.) a potential shift can be recorded with surface electrodes from the skin of the palms and the soles, and has been reported to be a useful parameter in assessment of neuropathy involving non-myelinated nerve fibres. The response, known as the SSR, can also be recorded from perineal skin and the penis. Similarly, the SSR can be recorded from the genital region in women [127]. The SSR is a reflex, which consists of myelinated sensory fibres, a complex central integrative mechanism and a sympathetic efferent limb with postganglionic nonmyelinated C fibres. SSR is the only electrophysiological method directly testing sympathetic fibres. Limited literature exists regarding the relationship between SSR results and bladder dysfunction. A correlation has been shown between the absence of the SSR response in the foot and bladder neck dyssynergia following spinal cord injury [108]. Recording from the perineal region assesses sympathetic nerve function within the thoracolumbar cord [128].

III. EVIDENCE BASED USE OF CLINICAL NEUROPHYSIOLOGICAL TESTS

Only complete absence of response can be regarded as abnormal. Its utility in evaluating bladder and urethral dysfunction is not established.

Evidence-based medicine is founded on the assessment of evidence for and against the efficacy of particular types of therapeutic intervention. Clinical neurophysiology testing should thus demonstrate evidence that testing improves outcome (through treatment choice and patient selection), which would provide a strong basis for its use. However, testing and therapeutic intervention are different concepts, and neurophysiological testing has another important objective, which is not applicable to interventions and lies outside the scope of evidence-based medicine. It is to generate knowledge about the situation to be treated in a given patient, so that the practitioner can formulate rational treatment options based on evidence that is, he or she can practice “evidence-based medicine”.

To judge the importance of this second objective different criteria are needed. Particularly in the referral setting, the physician is confronted with complicated cases in which the underlying pathophysiology is quite uncertain, and what is required is to identify all the factors that may be contributing. Neurophysiology is helpful in assessment of neurogenic dysfunction because it contributes to “evidence-based medicine”, whether or not there is narrowly-defined “evidence” that it improves outcomes.

Of course, it remains true that we should seek evidence of the conventional kind for and against testing. Any test should be subjected to three questions:

1. Does the test have good technical performance?
2. Does the test have good diagnostic performance, ideally against a “gold standard” measure?
3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management, does the use of the test improve outcome?

Clinical diagnosis requires that measures obtained in individual patients be compared to population

norms with the intent of determining whether they are “normal” or “abnormal”. Data can be classified as “abnormal” only with the understanding that they are compared to a sample from the normal population. Predictive statements are made possible by the use of tolerance limits. For most clinical neurophysiological tests, one-tailed tolerance limits are recommended. For any given limit of normality, there is a certain probability of falsely interpreting values (obtaining false-positives or false-negatives). Further confounding these issues is the practice of applying multiple criteria of abnormality. But ultimately, the adequacy of any given normal limit in discriminating between normal and abnormal must be supported by appropriate clinical or clinico-pathological correlations; for uroneurophysiological techniques, such data are scarce.

1. USEFULNESS OF CLINICAL NEUROPHYSIOLOGICAL TESTS IN EVALUATION OF INDIVIDUAL PATIENTS

Whenever pathophysiology is uncertain or unpredictable, and especially if irreversible treatment is necessary or contemplated, it seems logical to gather quantitative knowledge of the dysfunction in order to make a rational treatment choice. In most patient groups with neurogenic incontinence, the pathophysiology is unpredictable and comprehensive urodynamic evaluation is essential in order to practice knowledge-based medicine. In selected patients from these groups, clinical neurophysiological testing will clarify issues related to the neural control of lower urinary tract, relevant for understanding pathophysiology. Most patients, however, will not require a precise definition of the neurological lesion.

As is generally true for electrophysiological tests, uroneurophysiological examinations are particularly useful for substantiating the clinical diagnosis of a peripheral nerve lesion. The potential usefulness of testing in an individual patient needs to be analysed in the overall clinical setting. The indications for testing are guided primarily by expert opinion, not on definitely established criteria derived from controlled studies.

In the incontinent patient without other signs or symptoms of a neurological condition, neurophysiological testing is generally unnecessary. In patients with stress/urge, or mixed urinary incontinence electrophysiological testing is as a rule non-contributory [61].

2. USEFULNESS OF CLINICAL NEUROPHYSIOLOGICAL TESTS IN RESEARCH

Uro-neurophysiological techniques have been most often applied in research, for instance to elucidate the innervation of pelvic floor muscles; to study the physiology of contraction of sphincter muscle, to describe activation patterns of pelvic floor muscles. Suggestions of increased efficacy of sacral neurostimulation with the use of neurophysiological tests have been made [129]. As understanding pathophysiology and neural control is essential in the application of more sophisticated therapeutic methods, such as electrical stimulation techniques, there seems to be a continuing place for clinical neurophysiology in research on neurogenic urinary and anorectal dysfunction and their therapy.

IV. CONSENSUS STATEMENT

1. CLINICAL NEUROPHYSIOLOGICAL TESTING

The information gained by clinical examination and urodynamic testing may be enhanced by uroneurophysiological tests in selected patient groups with suspected neurogenic urinary incontinence with lesions within the nervous reflex arcs of sacral segments 2 – 5. Concentric needle EMG to diagnose denervation and reinervation of pelvic floor and perineal muscles, and sacral reflex testing to assess the continuity of the sacral reflex arc, are the recommended tests. **(Level of Evidence: 2b; Grade of Recommendation: B**)

Clinical neurophysiological testing should be performed in accredited laboratories, by trained and certified staff, with formal control of the quality of the results. Ideally, the uroneurophysiologist should be in liaison with general clinical neurophysiologists.

It seems optimal to create interdisciplinary programs between urology, urogynaecology, proctology, and neurology departments. Organisation of such teams in tertiary medical centres should be encouraged.

2. TECHNICAL STANDARDS

Even in the more widely used “general” clinical neurophysiology there is no universal standardisation of tests. This is mainly due to different historical backgrounds of testing developed in different countries. The need to standardise methods is, however, recognised.

Proposals for standardisation for external anal sphincter CNEMG [4] and the bulbocavernosus (penilo/clitoro-cavernosus) reflex [117] have been made, and seem to be widely adopted. (**Level of Evidence: 2b, Grade of Recommendation: B**)

3. FUTURE RESEARCH AREAS

Clinical neurophysiological methods should be further used to better define the neural control in lower urinary tract function, demonstrating both the nervous system’s “hardware” (integrity of anatomy) as well as “software” (level of activity, excitation thresholds) for co-ordinated urinary storage and voiding, in physiological and in pathological conditions. In particular, there is the opportunity to better define neurophysiological changes induced by therapeutic electrostimulation.

There is the challenge to develop tests to assess directly the sacral parasympathetic system.

F. OTHER INVESTIGATIONS

I. URINALYSIS

"Urinalysis is a fundamental test that should be performed in all urological patients" [1]. In patients with urinary incontinence, urinalysis is not a diagnostic test for the condition, but it is rather used to screen for haematuria, glucosuria, pyuria and bacteriuria. Even in the absence of controlled studies, there is general expert consensus that the benefits of urinalysis clearly outweigh the costs involved [2]. A positive urinalysis will prompt infection treatment and/or the use of additional tests such as endoscopy and urinary tract imaging. In the evaluation of urinary incontinence in the female, urinalysis is recommended since 60% of women develop urgency symptoms at the time of urinary tract infection (UTI). Pyuria was found to be common among incontinent but otherwise asymptomatic, female patients. Pyuria was not necessarily associated with UTI, the significance of sterile pyuria in the elderly population is still unclear [3].

A Norwegian survey of general practitioners' management of female urinary incontinence suggested that urinalysis is the most frequently performed test (73%) and is far more frequent than gynaecological examination (54%) [4]. Another survey suggested that urinalysis is one of the three-part assessment of UI together with patient history and physical examination [5].The same apply, according to Stricker, for patient selection for collagen implant [6]. A minority of the reviewed papers suggested that urine culture should be carried out together with urinalysis [3, 7]. Urinalysis is also considered of importance in the evaluation of nursing home residents who are incontinent [8], in peri- and postmenopausal women [9], in older women reporting urinary incontinence [10]. Belmin et al, suggested than significant urine samples can even be obtained from disposable pads in elderly incontinent women [11, 12]. It is recommended that geriatric incontinent patients undergo history, physical examination, tests of lower urinary tract function and urinalysis. The latter test is proposed to rule out the presence of UTI [12]. The clinical relevance of asymptomatic bacteriuria in the elderly is controversial. Although DuBeau and Resnick suggest the use of urinalysis in the diagnostic algorithm to identify asymptomatic bacteriuria in incontinent residents of nursing homes [13], others consider that the condition does not require any treatment [11].

1. CONSENSUS STATEMENT

- It is considered standard practice to perform a urinalysis either by using a dipstick test or examining the spun sediment. (**Level of Evidence 3, Grade of Recommendation C**)
- If a dipstick test is used, it is recommended chosing of a "multiproperty" strip that includes testing for haematuria, proteinuria, glucose and ketones, leukocytes esterase (indicating the presence of leukocytes in the urine) and nitrite tests (suggesting bacteriuria). (**Level of Evidence 3, Grade of Recommendation C**)

2. FUTURE RESEARCH AREAS

- Needed to screen analysis of urinalysis in the diagnosis and treatment of UI, MUI and SUI

3. REFERENCES (SEE AT THE END OF THE CHAPTER)

II. BLOOD TESTS

The prevalence of renal damage or of biochemical abnormalities in the general population of patients with urinary incontinence is very low, but there are subgroups of patients where the prevalence can be higher (e.g., neurogenic incontinence, overflow incontinence). The routine use of a battery of common chemical and/or haematological tests in patients with urinary incontinence appears to be a prudent rule of good clinical practice in the following situations:

a) chronic retention with incontinence

b) neurogenic LUT dysfunction

c) when surgery is contemplated

d) when there is a clinical suspicion

e) sodium plasma concentration may be reduced in patients on desmopressin.

Special tests such as measurement of anti diuretic hormone (ADH) and atrial natriuretic polypeptide have proven useful in research of enuresis in childhood and nocturia in the elderly [1, 2]. Changes in the circadian rhythm of these, and probably also other hormones regulating the renal excretion of water, will in the future contribute to a better understanding of pathophysiology. Synthetic ADH analogues have already come into clinical use for the treatment of nocturnal enuresis. However, the clinical value of these specific tests remains to be established.

III. TISSUE ANALYSIS

Since the last report of the International Consultation on Incontinence in 2008, several papers have been published based on the analysis of sample of tissues coming from patients with stress urinary incontinence

(SUI) and/or pelvic organ prolapse aiming at evaluating the molecular bases of these conditions. The main targets of both preclinical and clinical research have been the pelvic floor-supporting tissues and the role of steroid hormones, with some intriguing linkages between the two lines of research.

Pelvic floor-supporting tissues are composed mainly of connective tissue in which fibrous elements such as collagen and elastic fibres and visco-elastic matrix based on proteoglycans are the predominant components of the so called extracellular matrix. Extracellular matrix is a complex network of numerous macromolecules that fulfill a large number of mechanical, chemical and biological functions [1]. While collagens and elastin fibres confer strength and elasticity to tissues, respectively, structural proteoglycans allow tissue cohesiveness. Specifically, collagen is the most prevalent component, with type I fibres usually well organised and associated with ligamentous tissue, while type III collagen is more common in the loose areolar tissue, which makes up the vaginal wall adventitia and surrounds the pelvic organs [2]. According to the molecular weight, indeed, proteoglycans are distinguished into large molecules (aggrecan, versican and perlecan) and small molecules, such as decorin, fibromodulin, biglycan, lumican and chondroadherin [3].

The organised structure of the matrix is due to a clear balance between the production of the different constituents and their breakdown. There are many proteolytic enzymes capable of degrading the elements of the extracellular matrix, falling into into three groups: the serine proteases, the cysteine proteases, and matrix metalloproteinases (MMPs) [4].

Several authors evaluated the expression of the different proteins as well as of their precursors and fragments of degradation. With regards to the metabolism of collagen, some studies seem to indicate that women with SUI have a reduced total collagen content in the skin and urogenital tissue [5-7], while other studies reported higher total collagen concentration and higher levels of mRNAs for type I and type III collagen in paraurethral connective tissue [8]. Chen et al., evaluating cultures of fibroblasts taken from endopelvic fascia and skin biopsies in 14 patients with stress urinary incontinence and 12 controls, showed that the overall collagen synthesis and the ratio of type III and type I fibres were not significantly different between fibroblasts obtained from women with or without SUI [4], indicating that alteration in the collagen synthesis might not be involved in SUI.

On the other hand, a few studies reported change in the relative percentages of the different fibres, with a decrease in type I and increase in type III ones [9, 10]. In women with SUI, Skorupski et al. evaluated the transcription factor Sp1-binding site in the gene encoding a-1 chain of type I collagen, and suggested that the observed G-T polymorphism is a risk factor for incontinence [11]. Again at molecular level, some studies evaluated the cycle regulatory proteins in patients with pelvic organ prolapse, showing controversial results. Some papers reported reduced expression of proteins such as p53 and p21 which normally cause cycle G1 arrest suggesting an increase in proliferation capacities for fibroblasts derived from human cardinal ligaments of patients with prolapse [2].

Other authors evaluated markers of collagen degradation. Specifically, Edwall et al. evaluated markers of collagen synthesis and breakdown such as the carboxy-terminal propeptide of type I procollagen (PICP), the carboxy-terminal telopeptide of type I collagen (ICTP), and the amino-terminal propeptide of procollagen III (PIIINP) in urogenital tissue homogenates and peripheral serum from 71 patients with SUI and 31 healthy control women [12]. After adjusting for age, BMI, parity, and hormonal status, the patients with SUI had significantly lower serum concentrations of PICP and significantly lower tissue concentrations of PIIINP and ICTP than the controls, suggesting reducing breakdown in the presence of unchanged synthesis of type I collagen and, regarding type III collagen, a potential reduction in either synthesis or breakdown, the second being considered more probable [12]. These data may lead to the hypothesis that SUI might be associated with impaired degradation of collagen, leading to reduced turnover and accumulation of aging collagen, negatively affecting the strength and elasticity of urogenital tissue. Further studies on transforming growth factor-β (TGF-β) identified the molecular basis of such mechanism, suggesting that overexpression of TGF-β might trigger the accumulation of aging collagen, inhibiting the expression of collagenases and increasing the production of the tissue inhibitor metalloproteinase [13-15]. Moreover, some genes, such as those of the Homebox A (HOXA) family, encoding transcription factors that regulate mammalian embryonic growth and development of the urogenital tract, have been shown to be underexpressed in patients with pelvic organ prolapse, suggesting a further molecular basis for the alterations in collagens [16].

Some other studies investigated the role of proteinases that may degrade elements of the extracellular matrix. Chen et al., evaluating full-thickness peri-urethral vaginal wall tissues from patients with SUI or prolapsed and matched control women, found significant decrease in mRNA and protein expressions of alpha-1 antitrypsin (ATT), a neutrophil elastase inhibitor in tissues from affected women, while no difference was found in neutrophil elastase and cathepsin K expressions [17]. Similarly, Gabriel et al. studied the expression of different MMPs in 17 women with prolapsed and

18 control, identifying higher expression of MMP2 in patients with prolapse [18]. These studies allowed to hypothesize that altered catabolism of some components of the extracellular matrix might contribute to the connective tissue alterations observed in pelvic floor dysfunction.

Other studies were focused on the expression of small proteoglycans. Wen et al. studied mRNA and protein levels of biglycan, decorin, and fibromodulin in vaginal wall tissue from women with SUI and menstrual-cycle matched continent women [1]. Specifically, the authors demonstrated that the mRNA expression of fibromodulin was significantly lower in patients in the proliferative phase compared to controls, while decorin mRNA expression was higher both in the proliferative and secretory phases in the patients with SUI, supporting the hypothesis that the expression of such small proteoglycans was hormonally modulated and may contribute to the altered pelvic floor connective tissues of women with SUI [1].

Oestrogens interact with specific receptors which, when activated by the ligand, have conformational change, dimerisation and recruitment of co-factors, once translocated into the nucleus, these promote the expression of region of oestrogen-responsive genes, called the oestrogen response elements, leading to the synthesis of proteins [19]. More recently, selective modulators of oestrogens receptors have been identified, that act modulating the activity of the receptors, working as agonists, partial agonists, or antagonists in a tissue-dependent manner [20]. Studies on these molecules supported a new role of oestrogens in SUI and pelvic organ prolapse. Specifically, in a randomized controlled trial testing one of these molecules (levormeloxifene) as osteoporosis treatment, a 3.4-fold increase in the reporting of pelvic organ prolapse and an almost 5-fold increase in the reporting of urinary incontinence have been observed [21]. To explain such effect, the expression of more than 500 proteins have been studied in the rat model, showing that oestradiol induced the expression of metalloproteinase 7 and 14, reduced the expression of their inhibitors such as TIMP-3, while selective modulators of oestrogens receptors such as raloxifene had minimal effects on metalloproteinase 7, and maintained or restored expression of the mRNA for tissue inhibitor of metalloproteinases-3 (TIMP-3) and other components of the extracellular matrix, such as glypican, and biglycan [19]. Although the role of selective oestrogen-receptor modulators (SERMs) in the expression of the component of extracellular matrix has to be further clarified, these findings support the hypothesis that the increased occurrence of urinary incontinence and pelvic organ prolapse observed with oestrogen therapy and SERMs such as levormeloxifene may be related to changes in expression of genes regulating collagen turnover that ultimately weaken the normal structural integrity and support for the genitourinary system [19].

1. CONSENSUS STATEMENT

- To date, all these tissue analyses are not part of the everyday clinical practice

2. FUTURE RESEARCH AREAS

- The relationship between tissue composition and risk of UI and POP
- The relationship between tissue composition and treatment outcome in patients with UI and POP

3. REFERENCES (SEE AT THE END OF THE CHAPTER)

G. CONCLUSIONS

Clinical research involving diagnostic accuracy and clinical benefit of imaging studies and other diagnostic tests is particularly difficult. Recommendation of a diagnostic test is based upon the evidence that the outcome of it provides valuable information for patient management and this often involves evaluating the outcome of surgery. Implementation of good clinical research in this area remains difficult and sometimes lacks adequate founding. We acknowledge that only a few of the imaging techniques and other investigations we reviewed in the current chapter have been properly evaluated with respect to reproducibility, specificity, sensitivity and predictive value in connection with the diagnosis and management of urinary incontinence. Nevertheless, we acknowledge the great amount of work performed in the last four years and the continuous advancement in this field. The use of imaging and other investigations, described in this chapter, remains mostly based on expert opinion, common sense, availability and local expertise, rather than on evidence based clinical research. The diagnostic tests we considered can be subdivided into safety tests, tests with specific and selected indications, investigational tests.

Safety tests - Intended to protect patients' health, they are indicated in all patients complaining of urinary incontinence. They include urinalysis and measurement of post-void residual urine. While a consensus is easily achieved for urinalysis, the clinical benefit and cost-effectiveness of PVR

measurement in the primary evaluation of urinary incontinence needs to be confirmed in prospective studies.

Tests with specific and selected indications. Upper urinary tract imaging (as well as renal function assessment) may be indicated in cases of neurogenic urinary incontinence with risk of renal damage, chronic retention with incontinence, incontinence associated with severe genitourinary prolapse and suspicion of extraurethral incontinence. No other imaging technique is recommended in the primary evaluation of uncomplicated urinary incontinence and/or pelvic organ prolapse. Cystourethrography remains a reasonable option only in the preoperative evaluation of complicated and/or recurrent cases. Video urodynamics, is the gold standard in the evaluation of neurogenic incontinence, particularly in the paediatric population, although the clinical benefit of it remains unclear. In female urinary incontinence videourodynamics is not recommended except under specific complex circumstances. MRI remains the gold standard for the diagnosis of urethral diverticula although ultrasonography is a good alternative option. Lumbosacral spine X-rays have specific indications in children with suspect neurogenic incontinence without gluteosacral stigmata. Imaging of the CNS should be considered when a neurological disorder is suspected on the basis of clinical, imaging and neurophysiological findings. Urethrocystoscopy is indicated in cases of incontinence with microscopic haematuria, in the evaluation of recurrent or iatrogenic cases, in the evaluation of vesico-vaginal fistula and extra-urethral urinary incontinence.

Endoanal ultrasound and endocoil MRI are the gold standard for the evaluation of anal sphincter disorders, dynamic X-ray imaging remains the standard for evaluating rectal prolapse.

Investigational tests

Pelvic floor ultrasound is widely used as an adjunct to physical examination in patients with urinary incontinence and/or pelvic organ prolapse. Although the technique is rapidly evolving and much progress has been made in clinical research in this field, ultrasonography remains optional as evidence of its clinical benefit is not there yet.

MRI of the pelvic floor is rapidly gaining popularity in the evaluation of enteroceles and in the morphological analysis of pelvic floor muscles although evidence of its clinical benefit is still lacking. Both ultrasonography and MRI are the most rapidly evolving techniques and hold promises for potential future clinical applications.

Research in this area is also performed to improve our understanding of the pathophysiology of continence disorders and pelvic organ prolapse. Functional neuroimaging continues to provide new insight regarding functional anatomy of CNS related to vesicourethral function and dysfunction. The content of the draft reflects the composition of the Committee is made up of clinicians with a particular interest in a specific area of imaging and neurophysiology. The chapter certainly reveals the enthusiasm the authors poured in clinical research into this area but we believe that the methodology implemented by the Consultation is the best guarantee of a balanced opinion and evidence based recommendations. We hope that this chapter will stimulate clinical research in this field and will inspire those involved in the management of continence disorders and pelvic organ prolapse.

Neurophysiological testing should be part of the armamentarium available in the management of neurogenic incontinence and the establishment of good collaboration with neurophysiologists is recommended.

REFERENCES

A. INTRODUCTION

1. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Clin Chem. 2003 Jan;49(1):7-18.

B. IMAGING IN URINARY INCONTINENCE AND PELVIC FLOOR DYSFUNCTION

B.I. Imaging of The Upper Urinary Tract

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, and Wein A. The standardisation of terminology of lower urinary tract function: Report from the Standardisation Subcommittee of the International Continence Society. Neurourology & Urodynamics 2002; 21:167-178
2. McGuire EJ, Woodside JR, Borden TA, Weiss RM. Prognostic value of urodynamic testing in myelodysplastic patients. J Urol. 1981 Aug;126(2):205-9.
3. Kontogeorgos L, Vassilopoulos P, Tentes A. Bilateral severe hydroureteronephrosis due to uterine prolapse. Br J Urol. 1985 Jun;57(3):360-1.
4. Konda R, Sakai K, Ota S, Abe Y, Hatakeyama T, Orikasa S. Ultrasound grade of hydronephrosis and severity of renal cortical damage on 99m technetium dimercaptosuccinic acid renal scan in infants with unilateral hydronephrosis during followup and after pyeloplasty. J Urol. 2002 May;167(5):2159-63.
5. Dhillon HK. Prenatally diagnosed hydro-nephrosis - the Great Ormond Street experi-ence. Br J Urol 1998; 81 (Suppl 2): 39-44.
6. Platt JF, Rubin JM, Ellis JH. Distinction between obstructive and nonobstructive pyelocaliectasis with duplex Doppler sonography. AJR Am J Roentgenol. 1989 Nov;153(5):997-1000.
7. Toprak O. Conflicting and new risk factors for contrast induced nephropathy. J Urol. 2007 Dec;178(6):2277-83.
8. Braverman RM, Lebowitz RL. Occult ectopic ureter in girls with urinary incontinence: diagnosis by using CT. AJR Am J Roentgenol. 1991 Feb;156(2):365-6.
9. Utsunomiya M, Itoh H, Yoshioka T, Okuyama A, Itatani H. Renal dysplasia with a single vaginal ectopic ureter: the role of computerized tomography. J Urol. 1984 Jul;132(1):98-100.
10. Prewitt LH, Jr., Lebowitz RL. The single ectopic ureter. AJR Am J Roentgenol. 1976 Dec;127(6):941-8.
11. Borer JG, Bauer SB, Peters CA, Diamond DA, Decter RM, Shapiro E. A single-system ectopic ureter draining an ectopic dysplastic kidney: delayed diagnosis in the young female with continuous urinary incontinence. Br J Urol. 1998 Mar;81(3):474-8.
12. Bozorgi F, Connolly LP, Bauer SB, Neish AS, Tan PE, Schofield D, et al. Hypoplastic dysplastic kidney with a vaginal ectopic ureter identified by technetium-99m-DMSA scintigraphy. J Nucl Med. 1998 Jan;39(1):113-5.
13. Carrico C, Lebowitz RL. Incontinence due to an infrasphincteric ectopic ureter: why the delay in diagnosis and what the radiologist can do about it. Pediatr Radiol. 1998 Dec;28(12):942-9.
14. Mandal AK, Sharma SK, Vaidyanathan S, Goswami AK. Ureterovaginal fistula: summary of 18 years' experience. Br J Urol. 1990 May;65(5):453-6.
15. Murphy DM, Grace PA, O'Flynn JD. Ureterovaginal fistula: a report of 12 cases and review of the literature. J Urol. 1982 Nov;128(5):924-5.
16. Pantuck AJ, Barone JG, Rosenfeld DL, Fleisher MH. Occult bilateral ectopic vaginal ureters causing urinary incontinence: diagnosis by computed tomography. Abdom Imaging. 1996 Jan-Feb;21(1):78-80.
17. Perazella MA. Gadolinium-contrast toxicity in patients with kidney disease: nephrotoxicity and nephrogenic systemic fibrosis. Curr Drug Saf. 2008 Jan;3(1):67-75.
18. Leyendecker JR, Barnes CE, Zagoria RJ. MR urograe phy: techniques and clinical applications. Radiographics. 2008 Jan-Feb;28(1):23-46; discussion -7.
19. Avni EF, Matos C, Rypens F, Schulman CC. Ectopic vaginal insertion of an upper pole ureter: demonstration by special sequences of magnetic resonance imaging. J Urol. 1997 Nov;158(5):1931-2.
20. Kaneko K, Ohtsuka Y, Suzuki Y, Yabuta K, Yamataka A, Miyano T. Masked ureteral duplication with ectopic ureter detected by magnetic resonance imaging. Acta Paediatr Jpn. 1996 Jun;38(3):291-3.
21. Conway JJ. "Well-tempered" diuresis renography: its historical development, physiological and technical pitfalls, and standardized technique protocol. Semin Nucl Med. 1992 Apr;22(2):74-84.
22. O'Reilly PH. Diuresis renography. Recent advances and recommended protocols. Br J Urol. 1992 Feb;69(2):113-20.
23. Ruikka I. Residual urine in aged women and its influence on the phenolsulfonphtalein excretion test. Gerontol Clin (Basel). 1963;5:65-71.
24. Pattaras JG, Rushton HG, Majd M. The role of 99mtechnetium dimercapto-succinic acid renal scans in the evaluation of occult ectopic ureters in girls with paradoxical incontinence. J Urol. 1999 Sep;162(3 Pt 1):821-5.

B.II.1 X-Ray Imaging of the Lower Urinary Tract

1. Andersen JT. Prostatism: Clinical, radiological, and urodynamic aspects. Neurourol Urodyn. 1982;1(3):241-93.
2. Bellinger MF. The management of vesicoureteric reflux. Urol Clin North Am. 1985 Feb;12(1):23-9.
3. Barroso U, Jr., Barroso VA, de Bessa J, Jr., Calado AA, Zerati Filho M. Predictive factors for contralateral reflux in patients with conservatively treated unilateral vesicoureteral reflux. J Urol. 2008 Jul;180(1):297-9; discussion 9.
4. Jacoby K, Rowbotham RK. Double balloon positive pressure urethrography is a more sensitive test than voiding cystourethrography for diagnosing urethral diverticulum in women. J Urol. 1999 Dec;162(6):2066-9.
5. Romanzi LJ, Groutz A, Blaivas JG. Urethral diverticulum in women: diverse presentations resulting in diagnostic delay and mismanagement. J Urol. 2000 Aug;164(2):428-33.
6. Olesen KP. Descent of the female urinary bladder. A radiological classification based on colpo-cysto-urethrography. Dan Med Bull. 1983 Mar;30(2):66-84.
7. Neitlich JD, Foster HE, Jr., Glickman MG, Smith RC. Detection of urethral diverticula in women: comparison of a high resolution fast spin echo technique with double balloon urethrography. J Urol. 1998 Feb;159(2):408-10.
8. Foster RT, Amundsen CL, Webster GD. The utility of magnetic resonance imaging for diagnosis and surgical planning before transvaginal periurethral diverticulectomy in women. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Mar;18(3):315-9.
9. Green TH, Jr. Classification of stress urinary incontinence in the female: an appraisal of its current status. Obstet Gynecol Survey. 1968(23):632-4.
10. Blaivas JG, Olsson CA. Stress incontinence: classification and surgical approach. J Urol. 1988;139:727-31.

11. Shapeero LG, Friedland GW, Perkash I. Transrectal sonographic voiding cystourethrography: studies in neuromuscular bladder dysfunction. AJR Am J Roentgenol. 1983 Jul;141(1):83-90.

12. Piscitelli A, Galiano R, Serrao F, Concolino D, Vitale R, D'Ambrosio G, et al. Which cystography in the die agnosis and grading of vesicoureteral reflux? Pediatr Nephrol. 2008 Jan;23(1):107-10.

13. v. Mikulicz-Radecki F. Röntgenologische studien zur ätiologie der urethralen inkontinenz. . Zbl Gynäk. 1931;55:795-810.

14. Stevens WE, Smith SP. Roentgenological examination of the female urethra. J Urol. 1937;37:194-2001.

15. Ardran GM, Simmons CA, Stewart JH. The closure of the female urethra. J Obstet Gynaecol Br Emp. 1956 Feb;63(1):26-35.

16. Enhoerning G, Miller ER, Hinman F, Jr. Urethral Closure Studied with Cineroentgenography and Simultaneous Bladder-Urethra Pressure Recording. Surg Gynecol Obstet. 1964 Mar;118:507-16.

17. Palm L. Bladder Function in women with diseases of the lower urinary tract. Thesis. Copenhagen1971.

18. Shopfner CE. Cystourethrography: methodology, normal anatomy and pathology. J Urol. 1970 Jan;103(1):92-103.

19. Bates CP, Whiteside CG, Turner-Warwick R. Synchronous cine-pressure-flow-cysto-urethrography with special reference to stress and urge incontinence. Br J Urol. 1970 Dec;42(6):714-23.

20. Olesen KP, Walter S. Colpo-cysto-urethrography: a radiological method combined with pressure-flow measurements. Dan Med Bull. 1977 Jun;24(3):96-101.

21. Theofrastous JP, Cundiff GW, Harris RL, Bump RC. The effect of vesical volume on Valsalva leak-point pressures in women with genuine stress urinary incontinence. Obstet Gynecol. 1996 May;87(5 Pt 1):711-4.

22. Klarskov P, Vedel Jepsen P, Dorph S. Reliability of voiding colpo-cysto-urethrography in female urinary stress incontinence before and after treatment. Acta Radiol. 1988 Nov-Dec;29(6):685-8.

23. Barnick CG, Cardozo LD, Benness C. Use of routine videocystourethrography in the evaluation of female lower urinary tract dysfunction. Neurourol Urodyn. 1989;8(5):447-9.

24. Pick EJ, Davis R, Stacey AJ. Radiation dose in cinecystourethrography of the female. Br J Radiol. 1960 Jul;33:451-4.

25. Westby M, Ulmsten U, Asmussen M. Dynamic urethrocystography in women. Urol Int. 1983;38(6):329-36.

26. Rud T, Ulmsten U, Westby M. Initiation of micturition: a study of combined urethrocystometry and urethrocystography in healthy and stress incontinent females. Scand J Urol Nephrol. 1979;13(3):259-64.

27. de Goeij WBKMV. Incontinence of urine in women. Thesis. Meppel1976.

28. Aldridge A, Jeffcoate TN, Roberts H. Stress incontinence of urine. J Obstet Gynaecol Br Emp. 1952 Oct;59(5):681-720.

29. Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry. 2001 Nov;71(5):600-6.

30. Hinman F. Urinary tract damage in children who wet. Pediatrics. 1974 Aug;54(2):143-50.

31. Allen TD. The non-neurogenic neurogenic bladder. J Urol. 1977 Feb;117(2):232-8.

32. Williams DI, Hirst G, Doyle D. The occult neuropathic bladder. J Pediatr Surg. 1974 Feb;9(1):35-41.

33. Podesta ML, Castera R, Ruarte AC. Videourodynamic findings in young infants with severe primary reflux. J Urol. 2004 Feb;171(2 Pt 1):829-33; discussion 33.

34. Soygur T, Arikan N, Tokatli Z, Karaboga R. The role of video-urodynamic studies in managing non-neurogenic voiding dysfunction in children. BJU Int. 2004 Apr;93(6):841-3.

35. Fantl JA, Hurt WG, Beachley MC, Bosch HA, Konerding KF, Smith PJ. Bead-chain cystourethrogram: an evaluation. Obstet Gynecol. 1981 Aug;58(2):237-40.

36. Drutz HP, Shapiro BJ, Mandel F. Do static cystourethrograms have a role in the investigation of female incontinence? Am J Obstet Gynecol. 1978 Mar 1;130(5):516-20.

37. Green TH, Jr. Development of a plan for the diagnosis and treatment of urinary stress incontinence. Am J Obstet Gynecol. 1962 Mar 1;83:632-48.

38. Gjorup T. Reliability of diagnostic tests. Acta Obstet Gynecol Scand Suppl. 1997;166:9-14.

39. Showalter PR, Zimmern PE, Roehrborn CG, Lemack GE. Standing cystourethrogram: an outcome measure after anti-incontinence procedures and cystocele repair in women. Urology. 2001 Jul;58(1):33-7.

40. Fischer-Rasmussen W, Hansen RI, Stage P. Predictive values of diagnostic tests in the evaluation of female urinary stress incontinence. Acta Obstet Gynecol Scand. 1986;65(4):291-4.

41. Gordon D, Pearce M, Norton P, Stanton SL. Comparison of ultrasound and lateral chain urethrocystography in the determination of bladder neck descent. Am J Obstet Gynecol. 1989 Jan;160(1):182-5.

42. Greenwald SW, Thornbury JR, Dunn LJ. Cystourethrography as a diagnostic aid in stress incontinence. An evaluation. Obstet Gynecol. 1967 Mar;29(3):324-7.

43. Kitzmiller JL, Manzer GA, Nebel WA, Lucas WE. Chain cystourethrogram and stress incontinence. Obstet Gynecol. 1972 Mar;39(3):333-40.

44. Pelsang RE, Bonney WW. Voiding cystourethrography in female stress incontinence. AJR Am J Roentgenol. 1996 Mar;166(3):561-5.

45. Bergman A, McKenzie C, Ballard CA, Richmond J. Role of cystourethrography in the preoperative evaluation of stress urinary incontinence in women. J Reprod Med. 1988 Apr;33(4):372-6.

46. v. Christ F, Meyer-Delpho W. Röntgendiagnostik bei der weiblichen harninkontinenz. Fortschr Röntgenstr. 1981;134:551-6.

47. Mouritsen L, Strandberg C, Jensen AR, Berget A, Frimodt-Moller C, Folke K. Inter- and intra-observer variation of colpo-cysto-urethrography diagnoses. Acta Obstet Gynecol Scand. 1993 Apr;72(3):200-4.

48. Stage P, Fischer-Rasmussen W, Hansen RI. The value of colpo-cysto-urethrography in female stress- and urge incontinence and following operation. Acta Obstet Gynecol Scand. 1986;65(5):401-4.

49. Ala-Ketola L, Kauppila A, Jouppila P, Ylikorkala O. Pre- and postoperative bead chain urethrocystography in female stress urinary incontinence. Acta Obstet Gynecol Scand. 1981;60(4):369-74.

50. Thunedborg P, Fischer-Rasmussen W, Jensen SB. Stress urinary incontinence and posterior bladder suspension defects. Results of vaginal repair versus Burch colposuspension. Acta Obstet Gynecol Scand. 1990;69(1):55-9.

51. Meyhoff HH, de Nully MB, Olesen KP, Lindahl F. The effects of vaginal repair on anterior bladder suspension defects. A radiological and clinical evaluation. Acta Obstet Gynecol Scand. 1985;64(5):433-5.

52. Thind PO, Lose G, Falkenlove P, Egeblad M. Assessment of micturition cystourethrography. Intra- and

inter-observer variation. Ugeskr Laeger. 1991 Jan 28;153(5):338-40.

53. Kolbl H, Bernaschek G, Wolf G. A comparative study of perineal ultrasound scanning and urethrocystography in patients with genuine stress incontinence. Arch Gynecol Obstet. 1988;244(1):39-45.

54. Dietz HP, Wilson PD. Anatomical assessment of the bladder outlet and proximal urethra using ultrasound and videocystourethrography. Int Urogynecol J Pelvic Floor Dysfunct. 1998;9(6):365-9.

55. Gufler H, DeGregorio G, Allmann KH, Kundt G, Dohnicht S. Comparison of cystourethrography and dynamic MRI in bladder neck descent. J Comput Assist Tomogr. 2000 May-Jun;24(3):382-8.

56. Gufler H, Ohde A, Grau G, Grossmann A. Colpocystoproctography in the upright and supine positions correlated with dynamic MRI of the pelvic floor. Eur J Radiol. 2004 Jul;51(1):41-7.

B.II.2. US imaging

1. White RD, McQuown D, McCarthy TA, Ostergard DR. Realtime ultrasonography in the evaluation of urinary stress incontinence. Am J Obstet Gynecol. 1980;138(2):235-7.

2. Shah W, Honeck P, Kwon ST, Badawi JK, Alken P, Bross S. The role of perineal ultrasound compared to lateral cysturethrogram in urogynecological evaluations. Aktuelle Urol. 2007;38(2):144-7.

3. Troeger C, Gugger M, Holzgreve W, Wight E. Correlation of perineal ultrasound and lateral chain urethrocystography in the anatomical evaluation of the bladder neck. Int Urogynecol J Pelvic Floor Dysfunct. 2003;14(6):380-4.

4. Schaer GN, Koechli OR, Schuessler B, Haller U. Perineal ultrasound for evaluating the bladder neck in urinary stress incontinence. Obstet Gynecol. 1995;85(2):220-4.

5. Mouritsen L, Strandberg C. Vaginal ultrasonography versus colpo-cysto-urethrography in the evaluation of female urinary incontinence. Acta Obstet Gynecol Scand. 1994;73(4):338-42.

6. Kohorn EI, Scioscia AL, Jeanty P, Hobbins JC. Ultrasound cystourethrography by perineal scanning for the assessment of female stress urinary incontinence. Obstet Gynecol. 1986;68(2):269-72.

7. Bergman A, Koonings P, Ballard CA, Platt LD. Ultrasonic prediction of stress urinary incontinence development in surgery for severe pelvic relaxation. Gynecol Obstet Invest. 1988;26(1):66-72.

8. Koelbl H, Bernaschek G. A new method for sonographic urethrocystography and simultaneous pressure-flow measurements. Obstet Gynecol. 1989;74(3 Pt 1):417-22.

9. Bernaschek G, Kratochwil A. Sonographic method for the measurement of the posterior urethrovesical angle. Gynakol Rundsch. 1980;20 Suppl 2:208-11.

10. SCHENCK et al. 2011 ? ref

11. Wise BG, Burton G, Cutner A, Cardozo LD. Effect of vaginal ultrasound probe on lower urinary tract function. Br J Urol. 1992 Jul;70(1):12-6.

12. Hol M, van Bolhuis C, Vierhout ME. Vaginal ultrasound studies of bladder neck mobility. Br J Obstet Gynaecol. 1995;102(1):47-53.

13. Athanasiou S, Khullar V, Boos K, Salvatore S, Cardozo L. Imaging the urethral sphincter with three-dimensional ultrasound. Obstet Gynecol. 1999;94(2):295-301.

14. Tunn R, Schaer G, Peschers U, Bader W, Gauruder A, Hanzal E, et al. Updated recommendations on ultrasonography in urogynecology. Int Urogynecol J Pelvic Floor Dysfunct. 2005;16(3):236-41.

15. Dietz HP. Ultrasound imaging of the pelvic floor. Part I: Two dimensional aspects. Ultrasound Obstet Gynecol. 2004;23(1):80-92.

16. Dietz HP, Wilson PD, Clarke B. The use of perineal ultrasound to quantify levator activity and teach pelvic floor muscle exercises. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12(3):166-8; discussion 8-9.

17. Braekken IH, Majida M, Ellstrom-Engh M, Dietz HP, Umek W, Bo K. Test-retest and intra-observer repeatability of two-three- and four-dimensional perineal ultrasound of pelvic floor muscle anatomy and function. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(2):227-35.

18. Dietz HP, Wilson PD. The influence of bladder volume on the position and mobility of the urethrovesical junction. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(1):3-6.

19. Martan A, Drbohlav P, Masata M, Halaska M, Voigt R. Changes in the position of the urethra and bladder neck during pregnancy and after delivery. Ceska Gynekol. 1996;61(1):35-9.

20. King JK, Freeman RM. Is antenatal bladder neck mobility a risk factor for postpartum stress incontinence? Br J Obstet Gynaecol. 1998;105(12):1300-7.

21. Howard D, Miller JM, Delancey JO, Ashton-Miller JA. Differential effects of cough, valsalva, and continence status on vesical neck movement. Obstet Gynecol. 2000;95(4):535-40.

22. Toozs-Hobson P, Khullar V, Cardozo L. Three-dimensional ultrasound: a novel technique for investigating the urethral sphincter in the third trimester of pregnancy. Ultrasound Obstet Gynecol. 2001 May;17(5):421-4.

23. Khullar V, Salvatore S, Cardozo L. Three dimensional ultrasound of the urethra and urethral pressure profiles. 1994;5:319.

24. Umek WH, Laml T, Stutterecker D, Obermair A, Leodolter S, Hanzal E. The urethra during pelvic floor contraction: observations on three-dimensional ultrasound. Obstet Gynecol. 2002;100(4):796-800.

25. Kondo Y, Homma Y, Takahashi S, Kitamura T, Kawabe K. Transvaginal ultrasound of urethral sphincter at the mid urethra in continent and incontinent women. J Urol. 2001;165(1):149-52.

26. Wiseman OJ, Swinn MJ, Brady CM, Fowler CJ. Maximum urethral closure pressure and sphincter volume in women with urinary retention. J Urol. 2002;167(3):1348-51; discussion 51-2.

27. Kirschner-Hermanns R, Klein HM, Muller U, Schafer W, Jakse G. Intra-urethral ultrasound in women with stress incontinence. Br J Urol. 1994;74(3):315-8.

28. Robinson D, Toozs-Hobson P, Cardozo L, Digesu A. Correlating structure and function: three-dimensional ultrasound of the urethral sphincter. Ultrasound Obstet Gynecol. 2004;23(3):272-6.

29. Umek WH, Obermair A, Stutterecker D, Hausler G, Leodolter S, Hanzal E. Three-dimensional ultrasound of the female urethra: comparing transvaginal and transrectal scanning. Ultrasound Obstet Gynecol. 2001;17(5):425-30.

30. Tunn R, Petri E. Introital and transvaginal ultrasound as the main tool in the assessment of urogenital and pelvic floor dysfunction: an imaging panel and practical approach. Ultrasound Obstet Gynecol. 2003;22(2):205-13.

31. Schaer GN, Siegwart R, Perucchini D, DeLancey JO. Examination of voiding in seated women using a remote controlled ultrasound probe. Obstet Gynecol. 1998;91(2):297-301.

32. Major H, Culligan P, Heit M. Urethral sphincter morphology in women with detrusor instability. Obstet Gynecol. 2002;99(1):63-8.

33. Heit M. Intraurethral ultrasonography: correlation of urethral anatomy with functional urodynamic parameters in stress incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2000;11(4):204-11.

34. Heit M. Intraurethral sonography and the test-retest reliability of urethral sphincter measurements in women. J Clin Ultrasound. 2002;30(6):349-55.

35. Frauscher F, Helweg G, Strasser H, Enna B, Klauser A, Knapp R, et al. Intraurethral ultrasound: diagnostic evaluation of the striated urethral sphincter in incontinent females. Eur Radiol. 1998;8(1):50-3.

36. Yang JM, Huang WC, Yang SH. Transvaginal sonography in the diagnosis, management and follow-up of complex paraurethral abnormalities. Ultrasound Obstet Gynecol. 2005;25(3):302-6.

37. Yang JM, Yang SH, Huang WC. Two- and three-dimensional sonographic findings in a case of distal urethral obstruction due to a paraurethral tumor. Ultrasound Obstet Gynecol. 2005;25(5):519-21.

38. Peschers UM, Fanger G, Schaer GN, Vodusek DB, DeLancey JO, Schuessler B. Bladder neck mobility in continent nulliparous women. BJOG. 2001;108(3):320-4.

39. Mouritsen L, Bach P. Ultrasonic evaluation of bladder neck position and mobility: the influence of urethral catheter, bladder volume, and body position. Neurourol Urodyn. 1994;13(6):637-46.

40. Mouritsen L, Rasmussen A. Bladder neck mobility evaluated by vaginal ultrasonography. Br J Urol. 1993;71(2):166-71.

41. Dietz HP, Steensma AB, Vancaillie TG. Levator function in nulliparous women. Int Urogynecol J Pelvic Floor Dysfunct. 2003 Feb;14(1):24-6; discussion 26.

42. Brandt FT, Albuquerque CD, Lorenzato FR, Amaral FJ. Perineal assessment of urethrovesical junction mobility in young continent females. Int Urogynecol J Pelvic Floor Dysfunct. 2000;11(1):18-22.

43. Howard D, Delancey JO, Tunn R, Ashton-Miller JA. Racial differences in the structure and function of the stress urinary continence mechanism. Obstet Gynecol. 2000;95(5):713-7.

44. Dietz HP, Hansell NK, Grace ME, Eldridge AM, Clarke B, Martin NG. Bladder neck mobility is a heritable trait. BJOG. 2005;112(3):334-9.

45. Quinn MJ, Beynon J, Mortensen NJ, Smith PJ. Transvaginal endosonography: a new method to study the anatomy of the lower urinary tract in urinary stress incontinence. Br J Urol. 1988;62(5):414-8.

46. Petri E, Koelbl H, Schaer G. What is the place of ultrasound in urogynecology? A written panel. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(4):262-73.

47. Dietz HP, Clarke B. The urethral pressure profile and ultrasound imaging of the lower urinary tract. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12(1):38-41.

48. Yalcin OT, Hassa H, Ozalp S. Effectiveness of ultrasonographic parameters for documenting the severity of anatomic stress incontinence. Acta Obstet Gynecol Scand. 2000;79(5):421-6.

49. Kiilholma PJ, Makinen JI, Pitkanen YA, Varpula MJ. Perineal ultrasound: an alternative for radiography for evaluating stress urinary incontinence in females. Ann Chir Gynaecol Suppl. 1994;208:43-5.

50. Chen GD, Su TH, Lin LY. Applicability of perineal sonography in anatomical evaluation of bladder neck in women with and without genuine stress incontinence. J Clin Ultrasound. 1997;25(4):189-94.

51. Chang HC, Chang SC, Kuo HC, Tsai TC. Transrectal sonographic cystourethrography: studies in stress urinary incontinence. Urology. 1990;36(6):488-92.

52. Bergman A, Vermesh M, Ballard CA, Platt LD. Role of ultrasound in urinary incontinence evaluation. Urology. 1989;33(5):443-4.

53. Bergman A, Ballard CA, Platt LD. Ultrasonic evaluation of urethrovesical junction in women with stress urinary incontinence. J Clin Ultrasound. 1988;16(5):295-300.

54. Bergman A, McKenzie CJ, Richmond J, Ballard CA, Platt LD. Transrectal ultrasound versus cystography in the evaluation of anatomical stress urinary incontinence. Br J Urol. 1988;62(3):228-34.

55. Bai SW, Kwon JY, Chung da J, Park JH, Kim SK. Differences in urodynamic study, perineal sonography and treatment outcome according to urethrovesical junction hypermobility in stress urinary incontinence. J Obstet Gynaecol Res. 2006;32(2):206-11.

56. Bai SW, Lee JW, Shin JS, Park JH, Kim SK, Park KH. The predictive values of various parameters in the diagnosis of stress urinary incontinence. Yonsei Med J. 2004;45(2):287-92.

57. Pregazzi R, Sartore A, Bortoli P, Grimaldi E, Troiano L, Guaschino S. Perineal ultrasound evaluation of urethral angle and bladder neck mobility in women with stress urinary incontinence. BJOG. 2002;109(7):821-7.

58. Hung HC, Chin SY, Tsauo JY. Exercise adherence to pelvic floor muscle stregthening is not a significant predictor of symptoms reduction for women with stress urinary incontinence. Arch Phys Med Rehabil. 2012 Mar 23. [Epub ahead of print]

59. Schaer GN, Koechli OR, Schuessler B, Haller U. Can simultaneous perineal sonography and urethrocystometry help explain urethral pressure variations? Neurourol Urodyn. 1997;16(1):31-8.

60. Enzelsberger H, Kurz C, Adler A, Schatten C. Effectiveness of Burch colposuspension in females with recurrent stress incontinence—a urodynamic and ultrasound study. Geburtshilfe Frauenheilkd. 1991;51(11):915-9.

61. Richmond DH, Sutherst JR. Burch colposuspension or sling for stress incontinence? A prospective study using transrectal ultrasound. Br J Urol. 1989;64(6):600-3.

62. Schaer GN, Perucchini D, Munz E, Peschers U, Koechli OR, Delancey JO. Sonographic evaluation of the bladder neck in continent and stress-incontinent women. Obstet Gynecol. 1999;93(3):412-6.

63. Schaer GN, Koechli OR, Schuessler B, Haller U. Usefulness of ultrasound contrast medium in perineal sonography for visualization of bladder neck funneling—first observations. Urology. 1996;47(3):452-3.

64. Huang WC, Yang JM. Bladder neck funneling on ultrasound cystourethrography in primary stress urinary incontinence: a sign associated with urethral hypermobility and intrinsic sphincter deficiency. Urology. 2003;61(5):936-41.

65. Schaer GN, Koechli OR, Schuessler B, Haller U. Improvement of perineal sonographic bladder neck imaging with ultrasound contrast medium. Obstet Gynecol. 1995;86(6):950-4.

66. Dietz HP, Clarke B. Translabial color Doppler urodynamics. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12(5):304-7.

67. Dietz HP, McKnoulty L, Clarke B. Translabial color Doppler for imaging in urogynecology: a preliminary report. Ultrasound Obstet Gynecol. 1999;14(2):144-7.

68. Wieczorek AP, Wozniak MM, Stankiewicz A, Santoro GA, Bogusiewicz T, Scholbach J. Quantitative assessment of urethral vascularity in nulliparous females using high-frequency endovaginal ultrasonography. World J Urol. 2011; 29 (5): 625-32.

69. Tsai E, Yang C, Chen H, Wu C, Lee J. Bladder neck circulation by Doppler ultrasonography in postmenopausal women with urinary stress incontinence. Obstet Gynecol. 2001;98(1):52-6.

70. Liang CC, Chang SD, Chang YL, Wei TY, Wu HM, Chao AS. Three-dimensional power Doppler measurement of perfusion of the periurethral tissue in incontinent women — a preliminary report. Acta Obstet Gynecol Scand. 2006;85(5):608-13.

71. Oliveira E, Castro RA, Takano CC, Bezerra LR, Sartori MG, Lima GR, et al. Ultrasonographic and Doppler velocimetric evaluation of the levator ani muscle in premenopausal women with and without urinary stress incontinence. Eur J Obstet Gynecol Reprod Biol. 2007;133(2):213-7.

72. Caruso S, Panella MM, Cianci S, Rampello L, Bandiera S, Giordano R, Matarazzo MG, Cianci A. TOT does not affect the urethral sphincter innervation: a pilot study. Int Urogynaecol J. 2011; 22 (6): 739-42.

73. Nwosu CR, Khan KS, Chien PF, Honest MRI. Is real-time ultrasonic bladder volume estimation reliable and valid? A systematic overview. Scand J Urol Nephrol. 1998;32(5):325-30.

74. Gehrich A, Stany MP, Fischer JR, Buller J, Zahn CM. Establishing a mean postvoid residual volume in asymptomatic perimenopausal and postmenopausal women. Obstet Gynecol. 2007;110(4):827-32.

75. Choe JH, Lee JY, Lee KS. Accuracy and precision of a new portable ultrasound scanner, the BME-150A, in residual urine volume measurement: a comparison with the BladderScan BVI 3000. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18(6):641-4.

76. Teng CH, Huang YH, Kuo BJ, Bih LI. Application of portable ultrasound scanners in the measurement of post-void residual urine. J Nurs Res. 2005;13(3):216-24.

77. Haylen BT, Frazer MI, MacDonald JH. Assessing the effectiveness of different urinary catheters in emptying the bladder: an application of transvaginal ultrasound. Br J Urol. 1989;64(4):353-6.

78. Khan KS, Chien PF, Honest MR, Norman GR. Evaluating measurement variability in clinical investigations: the case of ultrasonic estimation of urinary bladder volume. Br J Obstet Gynaecol. 1997;104(9):1036-42.

79. Resnick B. A bladder scan trial in geriatric rehabilitation. Rehabil Nurs. 1995;20(4):194-6, 203.

80. Yucel S, Kocak H, Sanli A, Tosun O, Tuncer M, Ersoy F, et al. How accurate is measuring postvoid residual volume by portable abdominal ultrasound equipment in peritoneal dialysis patient? Neurourol Urodyn. 2005;24(4):358-61.

81. Tan TL, Ding YY, Lieu PK. False positive findings in the ultrasound assessment of postvoid residual urine volume. Age Ageing. 2003;32(3):356.

82. Kaefer M, Barnewolt C, Retik AB, Peters CA. The sonographic diagnosis of infravesical obstruction in children: evaluation of bladder wall thickness indexed to bladder filling. J Urol. 1997;157(3):989-91.

83. Miyazato M, Sugaya K, Nishijima S, Owan T, Ogawa Y. Location of spina bifida occulta and ultrasonographic bladder abnormalities predict the outcome of treatment for primary nocturnal enuresis in children. Int J Urol. 2007;14(1):33- 8.

84. Yeung CK, Sreedhar B, Leung VT, Metreweli C. Ultrasound bladder measurements in patients with primary nocturnal enuresis: a urodynamic and treatment outcome correlation. J Urol. 2004;171(6 Pt 2):2589-94.

85. Tanaka H, Matsuda M, Moriya K, Mitsui T, Kitta T, Nonomura K. Ultrasonographic measurement of bladder wall thickness as a risk factor for upper urinary tract deterioration in children with myelodysplasia. J Urol. 2008;180(1):312-6; discussion 6.

86. Yeung CK, Sreedhar B, Leung YF, Sit KY. Correlation between ultrasonographic bladder measurements and urodynamic findings in children with recurrent urinary tract infection. BJU Int. 2007;99(3):651-5.

87. Liu JX, Leung VY, Chu WC, Sreedhar B, Metreweli C, Yeung CK. Characteristics of the bladder in infants with urinary tract infections: an ultrasound study. Pediatr Radiol. 2008;38(10):1084-8.

88. Leung VY, Chu WC, Yeung CK, Sreedhar B, Liu JX, Wong EM, et al. Nomograms of total renal volume, urinary bladder volume and bladder wall thickness index in 3,376 children with a normal urinary tract. Pediatr Radiol. 2007;37(2):181-8.

89. Hakenberg OW, Linne C, Manseck A, Wirth MP. Bladder wall thickness in normal adults and men with mild lower urinary tract symptoms and benign prostatic enlargement. Neurourol Urodyn. 2000;19(5):585-93.

90. Oelke M, Hofner K, Jonas U, Ubbink D, de la Rosette J, Wijkstra H. Ultrasound measurement of detrusor wall thickness in healthy adults. Neurourol Urodyn. 2006;25(4):308-17; discussion 318.

91. Oelke M, Hofner K, Jonas U, de la Rosette JJ, Ubbink DT, Wijkstra H. Diagnostic accuracy of noninvasive tests to evaluate bladder outlet obstruction in men: detrusor wall thickness, uroflowmetry, postvoid residual urine, and prostate volume. Eur Urol. 2007;52(3):827-34.

92. Manieri C, Carter SS, Romano G, Trucchi A, Valenti M, Tubaro A. The diagnosis of bladder outlet obstruction in men by ultrasound measurement of bladder wall thickness. J Urol. 1998;159(3):761-5.

93. Khullar V, Salvatore S, Cardozo L, Bourne TH, Abbott D, Kelleher C. A novel technique for measuring bladder wall thickness in women using transvaginal ultrasound. Ultrasound Obstet Gynecol. 1994;4(3):220-3.

94. Khullar V, Cardozo LD, Salvatore S, Hill S. Ultrasound: a noninvasive screening test for detrusor instability. Br J Obstet Gynaecol. 1996;103(9):904-8.

95. Dudley R, Kate A, Cardozo L, Bidmead J, Toozs-Hobson P, Khullar V. Can ultrasound replace ambulatory urodynamics when investigating women with irritative urinary symptoms? BJOG. 2002;109(2):145-8.

96. Yang JM, Huang WC. Bladder wall thickness on ultrasonographic cystourethrography: affecting factors and their implications. J Ultrasound Med. 2003;22(8):777- 82.

97. Chalana V, Dudycha S, Yuk JT, McMorrow G. Automatic Measurement of Ultrasound-Estimated Bladder Weight (UEBW) from Three-Dimensional Ultrasound. Rev Urol. 2005;7 Suppl 6:S22-8.

98. Blatt AH, Titus J, Chan L. Ultrasound measurement of bladder wall thickness in the assessment of voiding dysfunction. J Urol. 2008;179(6):2275-8; discussion 2278-9.

99. Oelke M, Hofner K, Jonas U, Ubbink D, de la Rosette J, Wiijkstra H. Ultrasound measurement of detrusor wall thickness in healthy adults. Neurourol Urodyn. 2006; 25 (4): 308-17.

100. Oelke M. international consultation on incontinence-research society (ICI-RS) report on non-invasive urodynamics: the need of standardization of ultrasound bladder and detrusor wall thickness measurements to quantify bladder wall hypertrophy. Neurourol Urodyn. 2010; 29 (4): 634-9.

101. Lekskulchai O, Dietz HP. Detrusor wall thickness as a test for detrusor overactivity in women. Ultrasound Obstet Gynecol. 2008;32(4):535-9.

102. Panayi DC, Khullar V, Fernando R, Tekkis P. transvaginal ultrasound measurements of bladder wall thickness: a more reliable approach than transperineal and transabdominal approaches. BJU Int. 2010; 106 (10): 1519-22

103. Oelke M, Hofner K, Jonas U, Ubbink D, de la Rosette J, Wiijkstra H. diagnostic accuracy of noninvasive test to evaluate bladder outlet obstruction in men: detrusor wall thickness, uroflowmetry, postvoid residual urine, and prostate volume. Eur Urol. 2007; 52 (3): 627-34.

104. Kuhn A, Brandner S, Kuhn P, Robinson D, Raio L. Does bladder wall thickness decrease when obstruction is resolved? Int Urogynecol J. 2012 Jan 17. [Epub ahead of print]

105. Panayi DC, Khullar V, Digesu GA, Hendricken C, Fernando R, Tekkis P. is ultrasound estimation of bladder weight a useful tool in the assessment of patients with lower urinary tract symptoms? Int Urogyanecol J Pelvic Floor Dysfunct. 2009; 20 (12): 1445-9.

106. Akino H, Maekawa M, Nakai M, ShioyamaR, Ishida H, Oyama N, Miwa Y, Yokoyama O. ultrasound-estimated bladder weight predicts risk of surgery for benign prostatic hyperplasia in men using alpha-adrenoreceptor blocker for LUTS. Urology. 2008; 72 (4): 817-20.

107. Dietz HP, Jarvis SK, Vancaillie TG. The assessment of levator muscle strength: a validation of three ultrasound techniques. Int Urogynecol J Pelvic Floor Dysfunct. 2002;13(3):156-9; discussion 159.

108. Weinstein MM, Jung SA, Pretorius DH, Nager CW, den Boer DJ, Mittal RK. The reliability of puborectalis muscle measurements with 3-dimensional ultrasound imaging. Am J Obstet Gynecol. 2007;197(1):68 e1-6.

109. Thompson JA, O'Sullivan PB, Briffa NK, Neumann P. Comparison of transperineal and transabdominal ultrasound in the assessment of voluntary pelvic floor muscle contractions and functional manoeuvres in continent and incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Jul;18(7):779-86.

110. Peschers UM, Gingelmaier A, Jundt K, Leib B, Dimpfl T. Evaluation of pelvic floor muscle strength using four different techniques. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12(1):27-30.

111. Balmforth JR, Mantle J, Bidmead J, Cardozo L. A prospective observational trial of pelvic floor muscle training for female stress urinary incontinence. BJU Int. 2006;98(4):811-7.

112. Bernstein IT. The pelvic floor muscles: muscle thickness in healthy and urinary-incontinent women measured by perineal ultrasonography with reference to the effect of pelvic floor training. Estrogen receptor studies. Neurourol Urodyn. 1997;16(4):237-75.

113. Kruger JA, Dietz HP, Murphy BA. Pelvic floor function in elite nulliparous athletes. Ultrasound Obstet Gynecol. 2007;30(1):81-5.

114. Athanasiou S, Chaliha C, Toozs-Hobson P, Salvatore S, Khullar V, Cardozo L. Direct imaging of the pelvic floor muscles using two-dimensional ultrasound: a comparison of women with urogenital prolapse versus controls. BJOG. 2007;114(7):882-8.

115. Chen R, Song Y, Jiang L, Hong X, Ye P. the assessment of voluntary pelvic floor muscle contraction by three-dimnsional transperineal ultrasonography. Arc Gynecol Obstet. 2011; 284 (4): 931-6.

116. Whittaker JL, Thompson JA, Teyhen DS, Hodges P. Rehabilitative ultrasound imaging of pelvic floor muscle function. J Orthop Sports Phys Ther. 2007;37(8):487- 98.

117. Hung HC, Hsiao SM, Chih SY, Lin HH, Tsauo JY. Effect of pelvic floor muscle streinghtening on bladder neck mobility: a clinical trial. Phys Ther. 2011; 91 (7): 1030-8.

118. Miller JM, Perucchini D, Carchidi LT, DeLancey JO, Ashton- Miller J. Pelvic floor muscle contraction during a cough and decreased vesical neck mobility. Obstet Gynecol. 2001;97(2):255-60.

119. Dietz HP. Quantification of major morphological abnormalities of the levator ani. Ultrasound Obstet Gynecol. 2007;29(3):329-34.

120. Yang JM, Yang SH, Huang WC. Biometry of the pubovisceral muscle and levator hiatus in nulliparous Chinese women. Ultrasound Obstet Gynecol. 2006;28(5):710-6.

121. Siafarikas F, Staer-Jensen J, Braekken I, Bo K, Ellström Engh M. Learning process for performing and analysing 3/4D transperineal ultrasound imaging and inter-rater reliability study. Ultrasound Obstet Gynecol. 2012 May 17 [Epub ahead of print].

122. Dietz HP. Ultrasound imaging of the pelvic floor. Part II: three-dimensional or volume imaging. Ultrasound Obstet Gynecol. 2004;23(6):615-25.

123. Morkved S, Salvesen KA, Bo K, Eik-Nes S. Pelvic floor muscle strength and thickness in continent and incontinent nulliparous pregnant women. Int Urogynecol J Pelvic Floor Dysfunct. 2004;15(6):384-9; discussion 390.

124. Dietz HP, Shek C, Clarke B. Biometry of the pubovisceral muscle and levator hiatus by three-dimensional pelvic floor ultrasound. Ultrasound Obstet Gynecol. 2005;25(6):580-5.

125. Majida M, Braekken IH, Bo K, Engh ME. Levator hiatus dimension and pelvic floor function in women with and without major defect of the pubovisceral muscle. Int Urogynecol J. 2012; 23 (6): 707-14.

126. Wijma J, Potters AE, de Wolf BT, Tinga DJ, Aarnoudse JG. Anatomical and functional changes in the lower urinary tract following spontaneous vaginal delivery. BJOG. 2003;110(7):658-63.

127. Wijma J, Weis Potters AE, van der Mark TW, Tinga DJ, Aarnoudse JG. Displacement and recovery of the vesical neck position during pregnancy and after childbirth. Neurourol Urodyn. 2007;26(3):372-6.

128. Constantinou CE, Omata S. Direction sensitive sensor probe for the evaluation of voluntary and reflex pelvic floor contractions. Neurourol Urodyn. 2007;26(3):386-91.

129. Jung SA, Pretorius DH, Padda BS, Weinstein MM, Nager CW, den Boer DJ, et al. Vaginal high-pressure zone assessed by dynamic 3-dimensional ultrasound images of the pelvic floor. Am J Obstet Gynecol. 2007;197(1):52 e1-7.

130. Thyer I, Shek C, Dietz HP. New imaging method for assessing pelvic floor biomechanics. Ultrasound Obstet Gynecol. 2008;31(2):201-5.

131. Dietz HP, Lanzarone V. Levator trauma after vaginal delivery. Obstet Gynecol. 2005;106(4):707-12.

132. Lammers K, Futterer JJ, Prokop M, Vierhout ME, Kluivers KB. Diagnosing pubovisceral avulsions: a systematic review of the clinical relevance of a prevalent anatomical defect. Int Urogynecol J. 2012 May 12. [Epub ahead of print]

133. Huebner M, Margulies RU, Delancey JO. Pelvic architectural distortion is associated with pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(6):863-7.

134. Margulies RU, Hsu Y, Kearney R, Stein T, Umek WH, DeLancey JO. Appearance of the levator ani muscle subdivisions in magnetic resonance images. Obstet Gynecol. 2006;107(5):1064-9.

135. Dietz HP. Why pelvic floor surgeons should utilize ultrasound imaging. Ultrasound Obstet Gynecol. 2006;28(5):629-34.

136. Dietz HP. Levator trauma in labor: a challenge for obstetricians, surgeons and sonologists. Ultrasound Obstet Gynecol. 2007;29(4):368-71.

137. Dietz HP, Simpson JM. Does delayed child-bearing increase the risk of levator injury in labour? Aust N Z J Obstet Gynaecol. 2007;47(6):491-5.

138. Dietz HP, Shek C. Levator avulsion and grading of pelvic floor muscle strength. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(5):633-6.

139. Dietz HP, Hyland G, Hay-Smith J. The assessment of levator trauma: a comparison between palpation and 4D pelvic floor ultrasound. Neurourol Urodyn. 2006;25(5):424-7.

140. Dietz HP, Shek C. Validity and reproducibility of the digital detection of levator trauma. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(8):1097-101.

141. Dietz HP, Hoyte LP, Steensma AB. Atlas of pelvic floor ultrasound. 1st ed. ed. London: Springer-Verlag; 2008.

142. Kruger JA, Heap SW, Murphy BA, Dietz HP. Pelvic floor function in nulliparous women using three-dimensional ultrasound and magnetic resonance imaging. Obstet Gynecol. 2008;111(3):631-8.

143. Gregory WT, Nardos R, Worstell T, Thurmond A. Measuring the levator hiatus wit axial MRI sequences: adjusting the angle of acquisition. Neurourol Urodyn. 2011; 30 (1): 113-6.

144 Majida M, Braekken IH, Umek W, Bo K, Saltyte Benth J, Ellström Engh M. Interobserver repeatability of three- and four-dimensional ultrasound assessment of pelvic floor muscle anatomy and function. Ultrasound Obstet Gynecol. 2009; 33 (5): 567-73.

145. Santoro GA, Wieczorek AP, Shobeiri SA, Mueller ER, Pilat J, Stankiewicz A, Battistella G. Interobserver and interdisciplinary reproducibility of 3D endovaginal ultrasound assessment of pelvic floor anatomy. Int Urogynecol J. 2011; 22 (1): 53-9.

146. Derpapas A, Ahmed S, Gopalan V, Digesu A, Regan L, Fernando R, Khullar V. racial differences in female urethral morphology and levator hiatal dimensions: an ultrasound study. Neurourol Urodyn. 2012; 31 (4). 502-7

147. Reisinger E, Stummvoll W. Visualization of the endopelvic fascia by transrectal three-dimensional ultrasound. Int Urogynecol J Pelvic Floor Dysfunct. 2006;17(2):165-9.

148. Wisser J, Schar G, Kurmanavicius J, Huch R, Huch A. Use of 3D ultrasound as a new approach to assess obstetrical trauma to the pelvic floor. Ultraschall Med. 1999;20(1):15-8.

149. Dietz HP, Steensma AB, Hastings R. Three-dimensional ultrasound imaging of the pelvic floor: the effect of parturition on paravaginal support structures. Ultrasound Obstet Gynecol. 2003;21(6):589-95.

150. Dietz HP, Pang S, Korda A, Benness C. Paravaginal defects: a comparison of clinical examination and 2D/3D ultrasound imaging. Aust N Z J Obstet Gynaecol. 2005;45(3):187-90.

151. Zhuang RR, Song YF, Chen ZQ, Ma M, Huang HU, Chen JH, Li YM. Levator avulsion using a tomographic ultrasound and magnetic resonance-based model. Am J Obstet Gynecol. 2011;205(3):232.e1-8.

152. Adisuroso T, Shek KL, Dietz HP. Tomographic ultrasound imaging of the pelvic floor in nulliparous pregnant women: limits of normality. Ultrasound Obstet Gynecol. 2012; 39 (6): 698-703.

153. Loubeyre P, Copercini M, Petignat P, Dubuisson JB. Levator ani muscle complex: anatomic findings in nulliparous patients at thin-section MR imaging with double opacification. Radiology. 2012; 262 (2): 538-43

154. Dietz HP, Eldridge A, Grace M, Clarke B. Does pregnancy affect pelvic organ mobility? Aust N Z J Obstet Gynaecol. 2004;44(6):517-20.

156. Dietz HP, Haylen BT, Broome J. Ultrasound in the quantification of female pelvic organ prolapse. Ultrasound Obstet Gynecol. 2001;18(5):511-4.

156. Dietz HP, Eldridge A, Grace M, Clarke B. Pelvic organ descent in young nulligravid women. Am J Obstet Gynecol. 2004;191(1):95-9.

157. Vierhout ME, van der Plas-de Koning YW. Diagnosis of posterior enterocele: comparison of rectal ultrasonography with intraoperative diagnosis. J Ultrasound Med. 2002;21(4):383-7; quiz 389.

158. Karaus M, Neuhaus P, Wiedenmann TB. Diagnosis of enteroceles by dynamic anorectal endosonography. Dis Colon Rectum. 2000;43(12):1683-8.

159. Grasso RF, Piciucchi S, Quattrocchi CC, Sammarra M, Ripetti V, Zobel BB. Posterior pelvic floor disorders: a prospective comparison using introital ultrasound and colpocystodefecography. Ultrasound Obstet Gynecol. 2007;30(1):86-94.

160. Dietz HP, Steensma AB. Posterior compartment prolapse on two-dimensional and three-dimensional pelvic floor ultrasound: the distinction between true rectocele, perineal hypermobility and enterocele. Ultrasound Obstet Gynecol. 2005;26(1):73-7.

161. Dietz HP, Korda A. Which bowel symptoms are most strongly associated with a true rectocele? Aust N Z J Obstet Gynaecol. 2005;45(6):505-8.

162. Dietz HP, Clarke B. Prevalence of rectocele in young nulliparous women. Aust N Z J Obstet Gynaecol. 2005;45(5):391-4.

163. Brusciano L, Limongelli P, Pescatori M, Napolitano V, Gagliardi G, Maffettone V, et al. Ultrasonographic patterns in patients with obstructed defaecation. Int J Colorectal Dis. 2007;22(8):969-77.

164. Beer-Gabel M, Assoulin Y, Amitai M, Bardan E. A comparison of dynamic transperineal ultrasound (DTP-US) with dynamic evacuation proctography (DEP) in the diagnosis of cul de sac hernia (enterocele) in patients with evacuatory dysfunction. Int J Colorectal Dis. 2008;23(5):513-9.

165. Beer-Gabel M, Teshler M, Schechtman E, Zbar AP. Dynamic transperineal ultrasound vs. defecography in patients with evacuatory difficulty: a pilot study. Int J Colorectal Dis. 2004;19(1):60-7.

166. Majida M, Braekken I, Bo K, Benth J, Engh M. Anterior but not posterior compartment prolapse is associated with levator hiatus area: a three- and four-dimensional transperineal ultrasound study. BJOG. 2011; 118 (3): 329-37.

167. Pracros JP, Tran-Minh VA, Wright C. Ultrasound in diagnosis of intussusception. Lancet. 1985;2(8457):733-4.

168. Barthet M, Portier F, Heyries L, Orsoni P, Bouvier M, Houtin D, et al. Dynamic anal endosonography may challenge defecography for assessing dynamic anorectal disorders: results of a prospective pilot study. Endoscopy. 2000;32(4):300-5.

169. Peng Q, Jones R, Shishido K, Constantinou CE. Ultrasound evaluation of dynamic responses of female pelvic floor muscles. Ultrasound Med Biol. 2007;33(3):342-52.

170. Kluivers KB, Hendriks JC, Shek C, Dietz HP. Pelvic organ prolapse symptoms in relation to POPQ, ordinal stages and ultrasound prolapse assessment. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(9):1299-302.

171. Lone FW, Thakar R, Sultan AH, Stankiewicz A. Accuracy of assessing pelvic organ prolapse quantification points using dynamic 2D transperineal ultrasound in women with pelvic organ prolapse. Int Urogynecol J. 2012 Apr 28. [Epub ahead of print]

172. Dietz HP, Lekskulchai O. Ultrasound assessment of pelvic organ prolapse: the relationship between prolapse severity and symptoms. Ultrasound Obstet Gynecol. 2007;29(6):688-91.

173. Eisenberg VH, Chantarasorn V, Shek KL, Dietz HP. Does levator ani injury affect cystocele type? Ultrasound Obstet Gynecol. 2010; 36 (5): 618-23.

174. Costantini S, Esposito F, Nadalini C, Lijoi D, Morano S, Lantieri P, Mistrangelo E. Ultrasound imaging of the female perineum: the effect of vaginal delivery on pelvic floor dynamics. Ultrasound Obstet Gynecol. 2006;27(2):183-7.

175. Reed H, Freeman RM, Waterfield A, Adekanmi O. Prevalence of bladder neck mobility in asymptomatic non-pregnant nulliparous volunteers. BJOG. 2004;111(2):172-5.

176. Peschers U, Schaer G, Anthuber C, Delancey

JO, Schuessler B. Changes in vesical neck mobility following vaginal delivery. Obstet Gynecol. 1996;88(6):1001-6.

177. Dietz HP, Bennett MJ. The effect of childbirth on pelvic organ mobility. Obstet Gynecol. 2003;102(2):223-8.

178. Dietz HP, Steensma AB. The role of childbirth in the aetiology of rectocele. BJOG. 2006;113(3):264-7.

179. Dietz HP, Wilson PD. Childbirth and pelvic floor trauma. Best Pract Res Clin Obstet Gynaecol. 2005;19(6):913-24.

180. Toozs-Hobson P, Balmforth J, Cardozo L, Khullar V, Athanasiou S. The effect of mode of delivery on pelvic floor functional anatomy. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(3):407-16.

181. Dietz HP, Lanzarone V, Simpson JM. Predicting operative delivery. Ultrasound Obstet Gynecol. 2006;27(4):409-15.

182. Reilly ET, Freeman RM, Waterfield AE, Steggies P, Pedlar F. prevention of postpartum stress incontinence in primigravidae with increased bladder neck mobility: a randomized controlled trial of antenatal pelvic floor exercises. BJOG. 2002; 109 (1): 68-75.

183. Dietz HP, Steensma AB. The prevalence of major abnormalities in the levator ani in urogynaecological patients. BJOG. 2006: 113 (2):225-30.

184. Otcenasek M, Halaska M, Krcmar M, Maresova D, Halaska MG. New approach to the urogynecological ultrasound examination. Eur J Obstet Gynecol Reprod Biol. 2002;103(1):72-4.

185. Chan SS, Cheung RY, Yiu AK, Lee LL, pang AW, Choy KW, Leung TY, Chung TK. Prevalence of levator ani muscle injury in Chinese women after first delivery. Ultrasound Obstet Gynecol. 2012; 39 (6): 704-9.

186. Shek KL, Dietz HP. The effect of childbirth on hiatal dimensions. Obstet Gynecol. 2009; 113 (6): 1272-8.

187. Krofta L, Otcenasek M, Kasikova E, Feyereisl J. Pubococcygeus-puborectalis trauma after forceps delivery: evaluation of the levator ani muscle with 3D/4D ultrasound. Int Urogynecol J Pelvic Floor Dysfunct. 2009; 20 (10): 1175-81.

188. Cassado Garriga J, Pessarrodona Isern A, Espuna Pons M, Duran Retamal M, Felgueroso Fabrega A, Rodriguez Carballeira M, Jordà Santamaria I. Four-dimensional sonographic evaluation of avulsion of the levator ani according to delivery mode. Ultrasound Obstet Gynecol. 2011; 38 (6): 701-6.

189. Albrich SB, laterza RM, Skala C, Salvatore S, Koelbl H, Naumann G. Impact of mode of delivery on levator morphology: a prospective observational study with three dimensional ultrasound early in the postpartum period. BJOG. 2012; 119 (1): 51-60.

190. Blasi J, Fuchs I, D'Amico R, Vinci V, la Sala GB, Mazza V, Henrich W. Intrapartum translabial three-dimensional ultrasound visualization of levator trauma. Ultrasound Obstet Gynecol. 2011;37(1):88-92.

191. Toozs-Hobson P, Balmforth J, Cardozo L, Khullar V, Athanasiou S. the effect of mode of delivery on pelvic floor functional anatomy. Int Urogynecol J Pelvic Floor Dysfunction. 2008; 19 (3): 407-16.

192. Falkert A, Endress E, Weigl M, Seelbach-Gobel B. three-dimensional ultrasound of the pelvic floor 2 days after first delivery: influence of constitutional and obstetric factors. Ultrasound Obstet Gynecol. 2010; 35 (5): 583-8.

193. Shek Kl, Chantarasorn V, Langer S, Dietz HP. Does levator trauma "heal"? Ultrasound Obstet Gynecol. 2012 May 30 [Epub ahead of print].

194. Cassado Garriga J, Pessarrodona Isern A, Espuna Pons M, Duran Retamal M, Felgueroso Fabregas A, Rodrigues-Carbaillera M. Tridimensional sonographic anatomical changes on pelvic floor muscle according to the type of delivery. Int Urogynecol J. 2011, 22 (8): 1011-8.

195. Valsky DV, lipschuetz M, Bord A, Eldar I, messing B, Hochner-Celnikier D, Lavy Y, Cohen Sm, Yagel S. Fetal head circumference and length of second stage of labor are risk factors for levator ani muscle injury, diagnosed by 3-diemnsional transperineal ultrasound in primiparous women. Am J Obstet Gynecol. 2009; 201 (1): 91.e1-7.

196. Viereck V, Bader W, Skala C, Gauruder-Burmester A, Emons G, Hilgers R, Krauss T.Determination of bladder neck position by intraoperative introital ultrasound in colposuspension: outcome at 6-month follow-up. Ultrasound Obstet Gynecol. 2004;24(2):186-91.

197. Viereck V, Bader W, Krauss T, Oppermann M, Gauruder-Burmester A, Hilgers R, Hackenberg R, Hatzmann W, Emons G. Intra-operative introital ultrasound in Burch colposuspension reduces post-operative complications. BJOG. 2005;112(6):791-6.

198. Model AN, Shek KL, Dietz HP. Levator defects are associated with prolapse after pelvic floor surgery. Eur J Obstet Gynecol Reprod Biol. 2010; 153 (2): 220-3.

199. Dietz HP, Barry C, Lim YN, Rane A. Two-dimensional and three-dimensional ultrasound imaging of suburethral slings. Ultrasound Obstet Gynecol. 2005;26(2):175-9.

200. Yalcin OT, Hassa H, Tanir M. A new ultrasonographic method for evaluation of the results of anti-incontinence operations. Acta Obstet Gynecol Scand. 2002;81(2):151-6.

201. Lo TS, Horng SG, Liang CC, Lee SJ, Soong YK. Ultrasound assessment of mid-urethra tape at three-year follow-up after tension-free vaginal tape procedure. Urology. 2004;63(4):671-5.

202. Lo TS, Wang AC, Horng SG, Liang CC, Soong YK. Ultrasonographic and urodynamic evaluation after tension free vagina tape procedure (TVT). Acta Obstet Gynecol Scand. 2001;80(1):65-70.

203. Virtanen HS, Kiilholma P. Urogynecologic ultrasound is a useful aid in the assessment of female stress urinary incontinence—a prospective study with TVT procedure. Int Urogynecol J Pelvic Floor Dysfunct. 2002;13(4):218-22; discussion 23.

204. Schuettoff S, Beyersdorff D, Gauruder-Burmester A, Tunn R. Visibility of the polypropylene tape after tension-free vaginal tape (TVT) procedure in women with stress urinary incontinence: comparison of introital ultrasound and magnetic resonance imaging in vitro and in vivo. Ultrasound Obstet Gynecol. 2006;27(6):687-92.

205. Dietz HP, Mouritsen L, Ellis G, Wilson PD. How important is TVT location? Acta Obstet Gynecol Scand. 2004;83(10):904-8.

206. Ng CC, Lee LC, Han WH. Use of three-dimensional ultrasound scan to assess the clinical importance of midurethral placement of the tension-free vaginal tape (TVT) for treatment of incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2005;16(3):220-5.

207. Dietz HP, Wilson PD. The 'iris effect': how two-dimensional and three-dimensional ultrasound can help us understand anti-incontinence procedures. Ultrasound Obstet Gynecol. 2004;23(3):267-71.

208. Sarlos D, Kuronen M, Schaer GN. How does tension-free vaginal tape correct stress incontinence? Investigation by perineal ultrasound. Int Urogynecol J Pelvic Floor Dysfunct. 2003;14(6):395-8.

209. Long CY, Hsu CS, Lo TS, Liu CM, Chen YH, Tsai EM. Ultrasonographic assessment of tape location following tension-free vaginal tape and transobturator tape procedure. Acta Obstet Gynecol Scand. 2008;87(1):116-21.

210. Foulot H, Uzan I, Chopin N, Borghese B, Chapron C. Monarc transobturator sling system for the treatment

of female urinary stress incontinence: results of a post-operative transvaginal ultrasonography. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18(8):857-61.

211. Cotte B, Dumousset E, Boda C, Mansoor A. Comparison of transobturator tape (TOT) and tension-free vaginal tape (TVT) using perineal ultrasound. Gynecol Obstet Fertil. 2006;34(4):298-303.

212. de Tayrac R, Deffieux X, Resten A, Doumerc S, Jouffroy C, Fernandez H. A transvaginal ultrasound study comparing transobturator tape and tension-free vaginal tape after surgical treatment of female stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2006;17(5):466- 71.

213. Lin KL, Juan YS, Lo TS, Liu CM, Tsai EM, Long CY. Three-dimensional ultrasonographic assessment of compression effect on urethra following tension-free vaginal tape and transobturator tape procedures. Ultrasound Obstet Gynecol. 2012; 39 (4): 452-7.

214. Chantarasorn V, Shek KL, Dietz HP. Sonographic appearance of transobturator slings: implications for function and dysfunction. Int Urogynecol J. 2011; 22 (4); 493-8

215. Yang JM, Yang SH, Huang WC. Dynamic interaction involved in the tension-free vaginal tape obturator procedure. J Urol. 2008, 180 (5): 2081-7

216. Chene G, Cotte B, Tardieu AS, Savary D, Mansoor A. clinical and ultrasonographic correlations following three surgical anti-incontinence procedures (TOT, TVT and TVT-O). Int Urogynecol J Pelvic Floor Dysfunc. 2008; 19 (8): 1125-31.

217. Duckett J, basu M, Papanikolau N. Transperineal ultrasound to assess the effect of tension-free vaginal tape position on flow rates. Ultrasound Obstet Gynecol. 2010; 36 (3): 379-83

218. Mouracade P, El Abiad S, Roy C, Lang H, Jacqmin D, Saussine C. correlation of introital ultrasound with LUTS after sling surgery. Int Urogynecol J. 2010; 21 (10): 1261-4

219. Abbasy SA, Kenton K, Brubaker L, Mueller ER. Measurements of transurethral bladder neck displacement during tension-free vaginal tape procedure. Int Urogynecol J. 2011; 22 (6): 721-4.

220. Tunn R, Picot A, Marschke J, Gauruder-Burmester A. Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. Ultrasound Obstet Gynecol. 2007;29(4):449- 52.

221. Tunn R, Picot A. Marschke J, Gaurunder-Burmester A. Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. Ultrasound Obste gynecol. 2007; 29 (4): 449-52.

222. Velemir L, Amblard J, Fatton B, Savary D, Jacquetin B. Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study. Ultrasound Obstet Gynecol. 2010; 35 (4): 474-80.

223. Svabik K, Martan A, Masata J, El-Haddad R, Hubka P, Pavlikova M. Ultrasound appearances after mesh implantation—evidence of mesh contraction or folding. Int urogynecol J. 2011; 22 (5): 529-33.

224. Shek C, Dietz HP. Transobturator mesh anchoring for the repair of large or recurrent cystocele. Neurourol Urodyn. 2006;25:554.

225. Bridges MD, Petrou SP, Lightner DJ. Urethral bulking agents: imaging review. AJR Am J Roentgenol. 2005;185(1):257- 64.

226. Poon CI, Zimmern PE. Role of three-dimensional ultrasound in assessment of women undergoing urethral bulking agent therapy. Curr Opin Obstet Gynecol. 2004;16(5):411-7. 227. 227. Defreitas GA, Wilson TS, Zimmern PE, Forte TB. Threedimensional ultrasonography: an objective outcome tool to assess collagen distribution in women with stress urinary incontinence. Urology. 2003;62(2):232-6.

228. Elia G, Bergman A. Periurethral collagen implant: ultrasound assessment and prediction of outcome. Int Urogynecol J Pelvic Floor Dysfunct. 1996;7(6):335-8.

229. Isom-batz G, Zimmern PE. Collagen injection for female urinary incontinence after urethral or periurethral surgery. J Urol. 2009; 181 (2): 701-4.

230. Strasser H, Marksteiner R, Margreiter E, Pinggera GM, Mitterberger M, Frauscher F, Ulmer H, Fussenegger M, Kofler K, Bartsch G.Autologous myoblasts and fibroblasts versus collagen for treatment of stress urinary incontinence in women: a randomised controlled trial. Lancet. 2007;369(9580):2179-86.

231. Strasser H, Marksteiner R, Margreiter E, Mitterberger M, Pinggera GM, Frauscher F, Fussenegger M, Kofler K, Bartsch G. Transurethral ultrasonography- guided injection of adult autologous stem cells versus transurethral endoscopic injection of collagen in treatment of urinary incontinence. World J Urol. 2007 Aug;25(4):385-92.

B.II.3. MRI

1. Maglinte, D. D., Kelvin, F. M., Fitzgerald, K., Hale, D. S., and Benson, J. T. 1999. Association of compartment defects in pelvic floor dysfunction. AJR Am J Roentgenol 172:439.

2. Safir, M. H., Gousse, A. E., Rovner, E. S., Ginsberg, D. A., and Raz, S. 1999. 4-Defect repair of grade 4 cystocele. J Urol 161:587.

3. Kelvin, F. M. and Maglinte, D. D. 1997. Dynamic cystoproctography of female pelvic floor defects and their interrelationships. AJR Am J Roentgenol 169:769.

4. Kelvin, F. M., Hale, D. S., Maglinte, D. D., Patten, B. J., and Benson, J. T. 1999. Female pelvic organ prolapse: diagnostic contribution of dynamic cystoproctography and comparison with physical examination. AJR Am J Roentgenol 173:31.

5. Stovall, D. W. 2000. Transvaginal ultrasound findings in women with chronic pelvic pain. Obstet Gynecol 95:S57.

6. Raz, S., Erickson, D., and Sussman, E. 1992. Operative repair of rectocele, enterocele and cystocele. Adv Urol 5:121.

7. Siproudhis, L., Ropert, A., Vilotte, J., Bretagne, J. F., Heresbach, D., Raoul, J. L., and Gosselin, M. 1993. How accurate is clinical examination in diagnosing and quantifying pelvirectal disorders? A prospective study in a group of 50 patients complaining of defecatory difficulties. Dis Colon Rectum 36:430.

8. Broekhuis, S. R., Futterer, J. J., Barentsz, J. O., Vierhout, M. E., and Kluivers, K. B. 2009. A systematic review of clinical studies on dynamic magnetic resonance imaging of pelvic organ prolapse: the use of reference lines and anatomical landmarks. Int Urogynecol J Pelvic Floor Dysfunct 20:721.

9. Klutke, C., Golomb, J., Barbaric, Z., and Raz, S. 1990. The anatomy of stress incontinence: magnetic resonance imaging of the female bladder neck and urethra. J Urol 143:563.

10. Yang, A., Mostwin, J. L., Rosenshein, N. B., and Zerhouni, E. A. 1991. Pelvic floor descent in women: dynamic evaluation with fast MR imaging and cinematic display. Radiology 179:25.

11. Goodrich, M. A., Webb, M. J., King, B. F., Bampton, A. E., Campeau, N. G., and Riederer, S. J. 1993. Magnetic resonance imaging of pelvic floor relaxation: dynamic analysis and evaluation of patients before and after surgical repair. Obstet Gynecol 82:883.

12. Strohbehn, K., Ellis, J. H., Strohbehn, J. A., and De-

Lancey, J. O. 1996. Magnetic resonance imaging of the levator ani with anatomic correlation. Obstet Gynecol 87:277.

13. Ozasa, H., Mori, T., and Togashi, K. 1992. Study of uterine prolapse by magnetic resonance imaging: topographical changes involving the levator ani muscle and the vagina. Gynecol Obstet Invest 34:43.

14. Lienemann, A., Anthuber, C., Baron, A., Kohz, P., and Reiser, M. 1997. Dynamic MR colpocystorectography assessing pelvic-floor descent. Eur Radiol 7:1309.

15. Comiter, C. V., Vasavada, S. P., Barbaric, Z. L., Gousse, A. E., and Raz, S. 1999. Grading pelvic prolapse and pelvic floor relaxation using dynamic magnetic resonance imaging. Urology 54:454.

16. Gousse, A. E., Barbaric, Z. L., Safir, M. H., Madjar, S., Marumoto, A. K., and Raz, S. 2000. Dynamic half Fourier acquisition, single shot turbo spin-echo magnetic resonance imaging for evaluating the female pelvis. J Urol 164:1606.

17. Rouanet, J. P., Mares, P., Courtieu, C., and Maubon, A. 2000. [Static and dynamic MRI of the normal and pathological female pelvic floor]. J Gynecol Obstet Biol Reprod (Paris) 29:237.

18. Lienemann, A., Sprenger, D., Janssen, U., Anthuber, C., and Reiser, M. 2000. [Functional MRI of the pelvic floor. The methods and reference values]. Radiologe 40:458.

19. Tunn, R., Paris, S., Taupitz, M., Hamm, B., and Fischer, W. 2000. MR imaging in posthysterectomy vaginal prolapse. Int Urogynecol J Pelvic Floor Dysfunct 11:87.

20. Healy, J. C., Halligan, S., Reznek, R. H., Watson, S., Phillips, R. K., and Armstrong, P. 1997. Patterns of prolapse in women with symptoms of pelvic floor weakness: assessment with MR imaging. Radiology 203:77.

21. Haylen, B. T., de Ridder, D., Freeman, R. M., Swift, S. E., Berghmans, B., Lee, J., Monga, A., Petri, E., Rizk, D. E., Sand, P. K., and Schaer, G. N. 2010. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 29:4.

22. Busse, R. F., Riederer, S. J., Fletcher, J. G., Bharucha, A. E., and Brandt, K. R. 2000. Interactive fast spin-echo imaging. Magn Reson Med 44:339.

23. Barbaric, Z. L., Marumoto, A. K., and Raz, S. 2001. Magnetic resonance imaging of the perineum and pelvic floor. Top Magn Reson Imaging 12:83.

24. Hecht, E. M., Lee, V. S., Tanpitukpongse, T. P., Babb, J. S., Taouli, B., Wong, S., Rosenblum, N., Kanofsky, J. A., and Bennett, G. L. 2008. MRI of pelvic floor dysfunction: dynamic true fast imaging with steady-state precession versus HASTE. AJR Am J Roentgenol 191:352.

25. Fielding, J. R., Dumanli, H., Schreyer, A. G., Okuda, S., Gering, D. T., Zou, K. H., Kikinis, R., and Jolesz, F. A. 2000. MR-based three-dimensional modeling of the normal pelvic floor in women: quantification of muscle mass. AJR Am J Roentgenol 174:657.

26. Goh, V., Halligan, S., Kaplan, G., Healy, J. C., and Bartram, C. I. 2000. Dynamic MR imaging of the pelvic floor in asymptomatic subjects. AJR Am J Roentgenol 174:661.

27. Bennett, G. L., Hecht, E. M., Tanpitukpongse, T. P., Babb, J. S., Taouli, B., Wong, S., Rosenblum, N., Kanofsky, J. A., and Lee, V. S. 2009. MRI of the urethra in women with lower urinary tract symptoms: spectrum of findings at static and dynamic imaging. AJR Am J Roentgenol 193:1708.

28. Tumbarello, J. A., Hsu, Y., Lewicky-Gaupp, C., Rohrer, S., and DeLancey, J. O. 2010. Do repetitive Valsalva maneuvers change maximum prolapse on dynamic MRI? Int Urogynecol J Pelvic Floor Dysfunct 21:1247.

29. Delaney, S., Fernandez, P., N'Guyen, A., Salomon, L., Carbonne, B., Laissy, J. P., and Ansquer, Y. 2009. Effect of a speculum blade on dynamic MRI evaluation of pelvic organ prolapse. Acta Obstet Gynecol Scand 88:831.

30. Larson, K. A., Luo, J., Guire, K. E., Chen, L., Ashton-Miller, J. A., and Delancey, J. O. 2011. 3D analysis of cystoceles using magnetic resonance imaging assessing midline, paravaginal, and apical defects. Int Urogynecol J.

31. Larson, K. A., Luo, J., Yousuf, A., Ashton-Miller, J. A., and Delancey, J. O. 2012. Measurement of the 3D geometry of the fascial arches in women with a unilateral levator defect and "architectural distortion". Int Urogynecol J 23:57.

32. Myers, R. P., Cahill, D. R., Kay, P. A., Camp, J. J., Devine, R. M., King, B. F., and Engen, D. E. 2000. Puboperineales: muscular boundaries of the male urogenital hiatus in 3D from magnetic resonance imaging. J Urol 164:1412.

33. Tan, I. L., Stoker, J., Zwamborn, A. W., Entius, K. A., Calame, J. J., and Lameris, J. S. 1998. Female pelvic floor: endovaginal MR imaging of normal anatomy. Radiology 206:777.

34. Hjartardottir, S., Nilsson, J., Petersen, C., and Lingman, G. 1997. The female pelvic floor: a dome--not a basin. Acta Obstet Gynecol Scand 76:567.

35. Hugosson, C., Jorulf, H., Lingman, G., and Jacobsson, B. 1991. Morphology of the pelvic floor. Lancet 337:367.

36. Chou, Q. and DeLancey, J. O. 2001. A structured system to evaluate urethral support anatomy in magnetic resonance images. Am J Obstet Gynecol 185:44.

37. Tunn, R., Delancey, J. O., Howard, D., Ashton-Miller, J. A., and Quint, L. E. 2003. Anatomic variations in the levator ani muscle, endopelvic fascia, and urethra in nulliparas evaluated by magnetic resonance imaging. Am J Obstet Gynecol 188:116.

38. Umek, W. H., Morgan, D. M., Ashton-Miller, J. A., and DeLancey, J. O. 2004. Quantitative analysis of uterosacral ligament origin and insertion points by magnetic resonance imaging. Obstet Gynecol 103:447.

39. Hsu, Y., Lewicky-Gaupp, C., and DeLancey, J. O. 2008. Posterior compartment anatomy as seen in magnetic resonance imaging and 3-dimensional reconstruction from asymptomatic nulliparas. Am J Obstet Gynecol 198:651 e1.

40. Larson, K. A., Yousuf, A., Lewicky-Gaupp, C., Fenner, D. E., and DeLancey, J. O. 2010. Perineal body anatomy in living women: 3-dimensional analysis using thin-slice magnetic resonance imaging. Am J Obstet Gynecol 203:494 e15.

41. Otcenasek, M., Baca, V., Krofta, L., and Feyereisl, J. 2008. Endopelvic fascia in women: shape and relation to parietal pelvic structures. Obstet Gynecol 111:622.

42. Guo, M. and Li, D. 2007. Pelvic floor images: anatomy of the levator ani muscle. Dis Colon Rectum 50:1647.

43. Margulies, R. U., Hsu, Y., Kearney, R., Stein, T., Umek, W. H., and DeLancey, J. O. 2006. Appearance of the levator ani muscle subdivisions in magnetic resonance images. Obstet Gynecol 107:1064.

44. DeLancey, J. O., Morgan, D. M., Fenner, D. E., Kearney, R., Guire, K., Miller, J. M., Hussain, H., Umek, W., Hsu, Y., and Ashton-Miller, J. A. 2007. Comparison of levator ani muscle defects and function in women with and without pelvic organ prolapse. Obstet Gynecol 109:295.

45. Dietz, H. P. and Steensma, A. B. 2006. The prevalence of major abnormalities of the levator ani in urogynaecological patients. BJOG 113:225.

46. Hoyte, L., Schierlitz, L., Zou, K., Flesh, G., and Field-

ing, J. R. 2001. Two- and 3-dimensional MRI comparison of levator ani structure, volume, and integrity in women with stress incontinence and prolapse. Am J Obstet Gynecol 185:11.

47. Hoyte, L., Jakab, M., Warfield, S. K., Shott, S., Flesh, G., and Fielding, J. R. 2004. Levator ani thickness variations in symptomatic and asymptomatic women using magnetic resonance-based 3-dimensional color mapping. Am J Obstet Gynecol 191:856.

48. Hsu, Y., Chen, L., Huebner, M., Ashton-Miller, J. A., and DeLancey, J. O. 2006. Quantification of levator ani cross-sectional area differences between women with and those without prolapse. Obstet Gynecol 108:879.

49. Clark, N. A., Brincat, C. A., Yousuf, A. A., and Delancey, J. O. 2010. Levator defects affect perineal position independently of prolapse status. Am J Obstet Gynecol 203:595 e17.

50. Morgan, D. M., Cardoza, P., Guire, K., Fenner, D. E., and DeLancey, J. O. 2010. Levator ani defect status and lower urinary tract symptoms in women with pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 21:47.

51. Otcenasek, M., Krofta, L., Baca, V., Grill, R., Kucera, E., Herman, H., Vasicka, I., Drahonovsky, J., and Feyereisl, J. 2007. Bilateral avulsion of the puborectal muscle: magnetic resonance imaging-based three-dimensional reconstruction and comparison with a model of a healthy nulliparous woman. Ultrasound Obstet Gynecol 29:692.

52. Margulies, R. U., Huebner, M., and DeLancey, J. O. 2007. Origin and insertion points involved in levator ani muscle defects. Am J Obstet Gynecol 196:251 e1.

53. Chen, L., Hsu, Y., Ashton-Miller, J. A., and DeLancey, J. O. 2006. Measurement of the pubic portion of the levator ani muscle in women with unilateral defects in 3-D models from MR images. Int J Gynaecol Obstet 92:234.

54. Hsu, Y., Summers, A., Hussain, H. K., Guire, K. E., and Delancey, J. O. 2006. Levator plate angle in women with pelvic organ prolapse compared to women with normal support using dynamic MR imaging. Am J Obstet Gynecol 194:1427.

55. Ansquer, Y., Fernandez, P., Chapron, C., Frey, C., Bennis, M., Roy, C., Salomon, L., Mandelbrot, L., and Carbonne, B. 2006. Static and dynamic MRI features of the levator ani and correlation with severity of genital prolapse. Acta Obstet Gynecol Scand 85:1468.

56. Gearhart, S. L., Pannu, H. K., Cundiff, G. W., Buller, J. L., Bluemke, D. A., and Kaufman, H. S. 2004. Perineal descent and levator ani hernia: a dynamic magnetic resonance imaging study. Dis Colon Rectum 47:1298.

57. Stein, T. A., Kaur, G., Summers, A., Larson, K. A., and DeLancey, J. O. 2009. Comparison of bony dimensions at the level of the pelvic floor in women with and without pelvic organ prolapse. Am J Obstet Gynecol 200:241 e1.

58. Boreham, M. K., Zaretsky, M. V., Corton, M. M., Alexander, J. M., McIntire, D. D., and Twickler, D. M. 2005. Appearance of the levator ani muscle in pregnancy as assessed by 3-D MRI. Am J Obstet Gynecol 193:2159.

59. Tunn, R., DeLancey, J. O., Howard, D., Thorp, J. M., Ashton-Miller, J. A., and Quint, L. E. 1999. MR imaging of levator ani muscle recovery following vaginal delivery. Int Urogynecol J Pelvic Floor Dysfunct 10:300.

60. Lienemann, A., Fischer, T., Anthuber, C., and Reiser, M. 2003. [Functional MRI of the pelvic floor: postpartum changes of primiparous women after spontaneous vaginal delivery]. Rofo 175:1100.

61. Baytur, Y. B., Serter, S., Tarhan, S., Uyar, Y., Inceboz, U., and Pabuscu, Y. 2007. Pelvic floor function and anatomy after childbirth. J Reprod Med 52:604.

62. DeLancey, J. O., Kearney, R., Chou, Q., Speights, S., and Binno, S. 2003. The appearance of levator ani muscle abnormalities in magnetic resonance images after vaginal delivery. Obstet Gynecol 101:46.

63. Kearney, R., Miller, J. M., Ashton-Miller, J. A., and DeLancey, J. O. 2006. Obstetric factors associated with levator ani muscle injury after vaginal birth. Obstet Gynecol 107:144.

64. Dannecker, C., Lienemann, A., Fischer, T., and Anthuber, C. 2004. Influence of spontaneous and instrumental vaginal delivery on objective measures of pelvic organ support: assessment with the pelvic organ prolapse quantification (POPQ) technique and functional cine magnetic resonance imaging. Eur J Obstet Gynecol Reprod Biol 115:32.

65. Branham, V., Thomas, J., Jaffe, T., Crockett, M., South, M., Jamison, M., and Weidner, A. 2007. Levator ani abnormality 6 weeks after delivery persists at 6 months. Am J Obstet Gynecol 197:65 e1.

66. Heilbrun, M. E., Nygaard, I. E., Lockhart, M. E., Richter, H. E., Brown, M. B., Kenton, K. S., Rahn, D. D., Thomas, J. V., Weidner, A. C., Nager, C. W., and Delancey, J. O. 2010. Correlation between levator ani muscle injuries on magnetic resonance imaging and fecal incontinence, pelvic organ prolapse, and urinary incontinence in primiparous women. Am J Obstet Gynecol 202:488 e1.

67. Handa, V. L., Lockhart, M. E., Kenton, K. S., Bradley, C. S., Fielding, J. R., Cundiff, G. W., Salomon, C. G., Hakim, C., Ye, W., and Richter, H. E. 2009. Magnetic resonance assessment of pelvic anatomy and pelvic floor disorders after childbirth. Int Urogynecol J Pelvic Floor Dysfunct 20:133.

68. Chen, L., Ashton-Miller, J. A., Hsu, Y., and DeLancey, J. O. 2006. Interaction among apical support, levator ani impairment, and anterior vaginal wall prolapse. Obstet Gynecol 108:324.

69. Lee, S. L., Darzi, A., and Yang, G. Z. 2005. Subject specific finite element modelling of the levator ani. Med Image Comput Comput Assist Interv 8:360.

70. Noakes, K. F., Bissett, I. P., Pullan, A. J., and Cheng, L. K. 2008. Anatomically realistic three-dimensional meshes of the pelvic floor & anal canal for finite element analysis. Ann Biomed Eng 36:1060.

71. Lee, S. L., Horkaew, P., Caspersz, W., Darzi, A., and Yang, G. Z. 2005. Assessment of shape variation of the levator ani with optimal scan planning and statistical shape modeling. J Comput Assist Tomogr 29:154.

72. Chen, L., Ashton-Miller, J. A., and DeLancey, J. O. 2009. A 3D finite element model of anterior vaginal wall support to evaluate mechanisms underlying cystocele formation. J Biomech 42:1371.

73. Handa, V. L., Pannu, H. K., Siddique, S., Gutman, R., VanRooyen, J., and Cundiff, G. 2003. Architectural differences in the bony pelvis of women with and without pelvic floor disorders. Obstet Gynecol 102:1283.

74. Hoyte, L., Thomas, J., Foster, R. T., Shott, S., Jakab, M., and Weidner, A. C. 2005. Racial differences in pelvic morphology among asymptomatic nulliparous women as seen on three-dimensional magnetic resonance images. Am J Obstet Gynecol 193:2035.

75. Downing, K. T., Hoyte, L. P., Warfield, S. K., and Weidner, A. C. 2007. Racial differences in pelvic floor muscle thickness in asymptomatic nulliparas as seen on magnetic resonance imaging-based three-dimensional color thickness mapping. Am J Obstet Gynecol 197:625 e1.

76. Handa, V. L., Lockhart, M. E., Fielding, J. R., Bradley, C. S., Brubaker, L., Cundiff, G. W., Ye, W., and Richter, H. E. 2008. Racial differences in pelvic anatomy by magnetic resonance imaging. Obstet Gynecol 111:914.

77. Rizk, D. E., Czechowski, J., and Ekelund, L. 2004. Dynamic assessment of pelvic floor and bony pelvis morphologic condition with the use of magnetic resonance imaging in a multiethnic, nulliparous, and healthy female population. Am J Obstet Gynecol 191:83.

78. Summers, A., Winkel, L. A., Hussain, H. K., and DeLancey, J. O. 2006. The relationship between anterior and apical compartment support. Am J Obstet Gynecol 194:1438.

79. Hsu, Y., Chen, L., Summers, A., Ashton-Miller, J. A., and DeLancey, J. O. 2008. Anterior vaginal wall length and degree of anterior compartment prolapse seen on dynamic MRI. Int Urogynecol J Pelvic Floor Dysfunct 19:137.

80. Hsu, Y., Chen, L., Delancey, J. O., and Ashton-Miller, J. A. 2005. Vaginal thickness, cross-sectional area, and perimeter in women with and those without prolapse. Obstet Gynecol 105:1012.

81. Broekhuis, S. R., Hendriks, J. C., Futterer, J. J., Vierhout, M. E., Barentsz, J. O., and Kluivers, K. B. 2010. Perineal descent and patients' symptoms of anorectal dysfunction, pelvic organ prolapse, and urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 21:721.

82. Broekhuis, S. R., Futterer, J. J., Hendriks, J. C., Barentsz, J. O., Vierhout, M. E., and Kluivers, K. B. 2009. Symptoms of pelvic floor dysfunction are poorly correlated with findings on clinical examination and dynamic MR imaging of the pelvic floor. Int Urogynecol J Pelvic Floor Dysfunct 20:1169.

83. Broekhuis, S. R., Kluivers, K. B., Hendriks, J. C., Futterer, J. J., Barentsz, J. O., and Vierhout, M. E. 2009. POP-Q, dynamic MR imaging, and perineal ultrasonography: do they agree in the quantification of female pelvic organ prolapse? Int Urogynecol J Pelvic Floor Dysfunct.

84. Weidner, A. C. and Low, V. H. 1998. Imaging studies of the pelvic floor. Obstet Gynecol Clin North Am 25:825.

85. Lienemann, A., Anthuber, C., Baron, A., and Reiser, M. 2000. Diagnosing enteroceles using dynamic magnetic resonance imaging. Dis Colon Rectum 43:205.

86. Rodriguez, L. V., Bukkapatnam, R., Shah, S. M., and Raz, S. 2005. Transvaginal paravaginal repair of high-grade cystocele central and lateral defects with concomitant suburethral sling: report of early results, outcomes, and patient satisfaction with a new technique. Urology 66:57.

87. Cortes, E., Reid, W. M., Singh, K., and Berger, L. 2004. Clinical examination and dynamic magnetic resonance imaging in vaginal vault prolapse. Obstet Gynecol 103:41.

88. Montella, J. M. 2005. Vaginal mullerian cyst presenting as a cystocele. Obstet Gynecol 105:1182.

89. Larson, K. A., Hsu, Y., Chen, L., Ashton-Miller, J. A., and DeLancey, J. O. 2010. Magnetic resonance imaging-based three-dimensional model of anterior vaginal wall position at rest and maximal strain in women with and without prolapse. Int Urogynecol J Pelvic Floor Dysfunct 21:1103.

90. Altringer, W. E., Saclarides, T. J., Dominguez, J. M., Brubaker, L. T., and Smith, C. S. 1995. Four-contrast defecography: pelvic "floor-oscopy". Dis Colon Rectum 38:695.

91. Cundiff, G. W., Nygaard, I., Bland, D. R., and Versi, E. 2000. Proceedings of the American Urogynecologic Society Multidisciplinary Symposium on Defecatory Disorders. Am J Obstet Gynecol 182:S1.

92. Dvorkin, L. S., Hetzer, F., Scott, S. M., Williams, N. S., Gedroyc, W., and Lunniss, P. J. 2004. Open-magnet MR defaecography compared with evacuation proctography in the diagnosis and management of patients with rectal intussusception. Colorectal Dis 6:45.

93. Lewicky-Gaupp, C., Yousuf, A., Larson, K. A., Fenner, D. E., and Delancey, J. O. 2010. Structural position of the posterior vagina and pelvic floor in women with and without posterior vaginal prolapse. Am J Obstet Gynecol 202:497 e1.

94. Gufler, H., DeGregorio, G., Allmann, K. H., Kundt, G., and Dohnicht, S. 2000. Comparison of cystourethrography and dynamic MRI in bladder neck descent. J Comput Assist Tomogr 24:382.

95. Ginath, S., Garely, A., Luchs, J. S., Shahryarinejad, A., Olivera, C., Zhou, S., Ascher-Walsh, C., Condrea, A., Brodman, M., and Vardy, M. 2010. MRI pelvic landmark angles in the assessment of apical pelvic organ prolapse. Arch Gynecol Obstet.

96. Novellas, S., Mondot, L., Bafghi, A., Fournol, M., Baudin, G., Coco, L., Bongain, A., and Chevallier, P. 2009. [Evaluation of two classifications systems for pelvic prolapse on dynamic MRI]. J Radiol 90:1717.

97. Woodfield, C. A., Hampton, B. S., Sung, V., and Brody, J. M. 2009. Magnetic resonance imaging of pelvic organ prolapse: comparing pubococcygeal and midpubic lines with clinical staging. Int Urogynecol J Pelvic Floor Dysfunct 20:695.

98. Broekhuis, S. R., Kluivers, K. B., Hendriks, J. C., Vierhout, M. E., Barentsz, J. O., and Futterer, J. J. 2009. Dynamic magnetic resonance imaging: reliability of anatomical landmarks and reference lines used to assess pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 20:141.

99. Singh, K., Reid, W. M., and Berger, L. A. 2001. Assessment and grading of pelvic organ prolapse by use of dynamic magnetic resonance imaging. Am J Obstet Gynecol 185:71.

100. Bump, R. C., Mattiasson, A., Bo, K., Brubaker, L. P., DeLancey, J. O., Klarskov, P., Shull, B. L., and Smith, A. R. 1996. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 175:10.

101. Torricelli, P., Pecchi, A., Caruso Lombardi, A., Vetruccio, E., Vetruccio, S., and Romagnoli, R. 2002. Magnetic resonance imaging in evaluating functional disorders of female pelvic floor. Radiol Med 103:488.

102. Deval, B., Vulierme, M. P., Poilpot, S., Menu, Y., and Levardon, M. 2003. [Imaging pelvic floor prolapse]. J Gynecol Obstet Biol Reprod (Paris) 32:22.

103. Etlik, O., Arslan, H., Odabasi, O., Odabasi, H., Harman, M., Celebi, H., and Sakarya, M. E. 2005. The role of the MR-fluoroscopy in the diagnosis and staging of the pelvic organ prolapse. Eur J Radiol 53:136.

104. Lienemann, A., Sprenger, D., Anthuber, C., Baron, A., and Reiser, M. 2001. Functional cine magnetic resonance imaging in women after abdominal sacrocolpopexy. Obstet Gynecol 97:81.

105. Sze, E. H., Meranus, J., Kohli, N., Miklos, J. R., and Karram, M. M. 2001. Vaginal configuration on MRI after abdominal sacrocolpopexy and sacrospinous ligament suspension. Int Urogynecol J Pelvic Floor Dysfunct 12:375.

106. Rane, A., Lim, Y. N., Withey, G., and Muller, R. 2004. Magnetic resonance imaging findings following three different vaginal vault prolapse repair procedures: a randomised study. Aust N Z J Obstet Gynaecol 44:135.

107. Boukerrou, A. M., Mesdagh, B. P., Ego, A. A., Lambaudie, A. E., Crepin, A. G., Robert, B. Y., and Cosson, A. M. 2005. An MRI comparison of anatomical changes related to surgical treatment of prolapse by vaginal or abdominal route. Eur J Obstet Gynecol Reprod Biol 121:220.

108. Gufler, H., DeGregorio, G., Dohnicht, S., Allmann, K. H., and Rohr-Reyes, A. 2002. Dynamic MRI after surgical repair for pelvic organ prolapse. J Comput Assist Tomogr 26:734.

109. Hubner, M., Hetzer, F., Weishaupt, D., Hahnloser, D., Clavien, P. A., and Demartines, N. 2006. A prospective comparison between clinical outcome and open-configuration magnetic resonance defecography findings before and after surgery for symptomatic rectocele. Colorectal Dis 8:605.

110. Siegmann, K. C., Reisenauer, C., Speck, S., Barth, S., Kraemer, B., and Claussen, C. D. 2010. Dynamic magnetic resonance imaging for assessment of minimally invasive pelvic floor reconstruction with polypropylene implant. Eur J Radiol.

111. Kasturi, S., Lowman, J., Kelvin, F. M., Akisik, F., Terry, C., and Hale, D. S. 2010. Pelvic magnetic resonance imaging for assessment of the efficacy of the Prolift system for pelvic organ prolapse. Am J Obstet Gynecol 203:504 e1.

112. Larson, K. A., Hsu, Y., and DeLancey, J. O. 2009. The relationship between superior attachment points for anterior wall mesh operations and the upper vagina using a 3-dimensional magnetic resonance model in women with normal support. Am J Obstet Gynecol 200:554 e1.

113. Dumoulin, C., Peng, Q., Stodkilde-Jorgensen, H., Shishido, K., and Constantinou, C. 2007. Changes in levator ani anatomical configuration following physiotherapy in women with stress urinary incontinence. J Urol 178:970.

114. Kruger, J. A., Murphy, B. A., and Heap, S. W. 2005. Alterations in levator ani morphology in elite nulliparous athletes: a pilot study. Aust N Z J Obstet Gynaecol 45:42.

115. Bendova, P., Ruzicka, P., Peterova, V., Fricova, M., and Springrova, I. 2007. MRI-based registration of pelvic alignment affected by altered pelvic floor muscle characteristics. Clin Biomech (Bristol, Avon) 22:980.

116. Kelvin, F. M., Maglinte, D. D., Hale, D. S., and Benson, J. T. 2000. Female pelvic organ prolapse: a comparison of triphasic dynamic MR imaging and triphasic fluoroscopic cystocolpoproctography. AJR Am J Roentgenol 174:81.

117. Brubaker, L., Retzky, S., Smith, C., and Saclarides, T. 1993. Pelvic floor evaluation with dynamic fluoroscopy. Obstet Gynecol 82:863.

118. Hock, D., Lombard, R., Jehaes, C., Markiewicz, S., Penders, L., Fontaine, F., Cusumano, G., and Nelissen, G. 1993. Colpocystodefecography. Dis Colon Rectum 36:1015.

119. Pannu, H. K., Scatarige, J. C., and Eng, J. 2009. Comparison of supine magnetic resonance imaging with and without rectal contrast to fluoroscopic cystocolpoproctography for the diagnosis of pelvic organ prolapse. J Comput Assist Tomogr 33:125.

120. Takano, M. and Hamada, A. 2000. Evaluation of pelvic descent disorders by dynamic contrast roentgenography. Dis Colon Rectum 43:S6.

121. Lamb, G. M., de Jode, M. G., Gould, S. W., Spouse, E., Birnie, K., Darzi, A., and Gedroyc, W. M. 2000. Upright dynamic MR defaecating proctography in an open configuration MR system. Br J Radiol 73:152.

122. Kaufman, H. S., Buller, J. L., Thompson, J. R., Pannu, H. K., DeMeester, S. L., Genadry, R. R., Bluemke, D. A., Jones, B., Rychcik, J. L., and Cundiff, G. W. 2001. Dynamic pelvic magnetic resonance imaging and cystocolpoproctography alter surgical management of pelvic floor disorders. Dis Colon Rectum 44:1575.

123. Tunn, R., DeLancey, J. O., and Quint, E. E. 2001. Visibility of pelvic organ support system structures in magnetic resonance images without an endovaginal coil. Am J Obstet Gynecol 184:1156.

B.III.1 Post-void residual

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21(2):167-78.

2. Haylen BT, Lee J, Logan V, Husselbee S, Zhou J, Law M. Immediate postvoid residual volumes in women with symptoms of pelvic floor dysfunction. Obstet Gynecol. 2008 Jun;111(6):1305-12.

3. Gehrich A, Stany MP, Fischer JR, Buller J, Zahn CM. Establishing a mean postvoid residual volume in asymptomatic perimenopausal and postmenopausal women. Obstet Gynecol. 2007 Oct;110(4):827-32.

4. Lukacz ES, DuHamel E, Menefee SA, Luber KM. Elevated postvoid residual in women with pelvic floor disorders: prevalence and associated risk factors. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Apr;18(4):397-400.

5. Milleman M, Langenstroer P, Guralnick ML. Post-void residual urine volume in women with overactive bladder symptoms. J Urol. 2004 Nov;172(5 Pt 1):1911-4.

6. Fitzgerald MP, Jaffar J, Brubaker L. Risk factors for an elevated postvoid residual urine volume in women with symptoms of urinary urgency, frequency and urge incontience. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12(4):237-9; discussion 9-40.

7. Tseng LH, Liang CC, Chang YL, Lee SJ, Lloyd LK, Chen CK. Postvoid residual urine in women with stress incontinence. Neurourol Urodyn. 2008;27(1):48-51.

8. Barabas G, Molstad S. No association between elevated post-void residual volume and bacteriuria in residents of nursing homes. Scand J Prim Health Care. 2005 Mar;23(1):52-6.

9. Griffiths DJ, McCracken PN, Harrison GM, Gormley EA, Moore KN. Urge incontinence and impaired detrusor contractility in the elderly. Neurourol Urodyn. 2002;21(2):126-31.

10. Sander P, Mouritsen L, Andersen JT, Fischer-Rasmussen W. Should measurement of maximum urinary flow rate and residual urine volume be a part of a “minimal care” assessment programme in female incontinence? Scand J Urol Nephrol. 2002;36(2):124-7.

11. Roehrborn CG, Kaplan SA, Jones JS, Wang JT, Bavendam T, Guan Z. Tolterodine Extended Release With or Without Tamsulosin in Men With Lower Urinary Tract Symptoms Including Overactive Bladder Symptoms: Effects of Prostate Size. Eur Urol. 2008 Jun 17.

12. Hofner K, Burkart M, Jacob G, Jonas U. Safety and efficacy of tolterodine extended release in men with overactive bladder symptoms and presumed non-obstructive benign prostatic hyperplasia. World J Urol. 2007 Dec;25(6):627-33.

13. Abrams P, Kaplan S, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. J Urol. 2006 Mar;175(3 Pt 1):999-1004; discussion

14. Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. European urology. 2011 Oct;60(4):742-50.

15. Denys P, Le Normand L, Ghout I, Costa P, Chartier-Kastler E, Grise P, et al. Efficacy and safety of low doses of onabotulinumtoxinA for the treatment of refractory idiopathic overactive bladder: a multicentre, double-blind, randomised, placebo-controlled dose-ranging study. European urology. 2012 Mar;61(3):520-9.

16. Gormley EA. Evaluation of the patient with incontinence. Can J Urol. 2007 Dec;14 Suppl 1:58-62.

17. Lucas MG, Bosch JLHR, Cruz FR, Madden TB, Nambiar A, Neisius A, et al. Guidelines on Urinary Incontinence. 2012 [cited 2012 1st May 2012]; Available from: http://www.uroweb.org/guidelines/online-guidelines/

18. Purkiss SF. Assessment of residual urine in men following catheterisation. Br J Urol. 1990 Sep;66(3):279-80.

19. Stoller ML, Millard RJ. The accuracy of a catheterized residual urine. J Urol. 1989 Jan;141(1):15-6.

20. Ruikka I. Residual urine in aged women and its influence on the phenolsulfonphtalein excretion test. Gerontol Clin (Basel). 1963;5:65-71.

21. Mulrow PJ, Huvos A, Buchanan DL. Measurement of residual urine with I-131-labeled Diodrast. J Lab Clin Med. 1961 Jan;57:109-13.

22. Holmes JH. Ultrasonic studies of the bladder. J Urol. 1967 Apr;97(4):654-63.

23. McLean GK, Edell SL. Determination of bladder volumes by gray scale ultrasonography. Radiology. 1978 Jul;128(1):181-2.

24. Pedersen JF, Bartrum RJ, Grytter C. Residual urine determination by ultrasonic scanning. Am J Roentgenol Radium Ther Nucl Med. 1975 Oct;125(2):474-8.

25. Simforoosh N, Dadkhah F, Hosseini SY, Asgari MA, Nasseri A, Safarinejad MR. Accuracy of residual urine measurement in men: comparison between real-time ultrasonography and catheterization. J Urol. 1997 Jul;158(1):59-61.

26. Beacock CJ, Roberts EE, Rees RW, Buck AC. Ultrasound assessment of residual urine. A quantitative method. Br J Urol. 1985 Aug;57(4):410-3.

27. Griffiths CJ, Murray A, Ramsden PD. Accuracy and repeatability of bladder volume measurement using ultrasonic imaging. J Urol. 1986 Oct;136(4):808-12.

28. Widder B, Kornhuber HH, Renner A. [Measurement of residual urine in outpatient clinics with a small ultrasound device]. Dtsch Med Wochenschr. 1983 Oct 14;108(41):1552-5.

29. Piters K, Lapin S, Bessman AN. Ultrasonography in the detection of residual urine. Diabetes. 1979 Apr;28(4):320-3.

30. Roehrborn CG, Chinn HK, Fulgham PF, Simpkins KL, Peters PC. The role of transabdominal ultrasound in the preoperative evaluation of patients with benign prostatic hypertrophy. J Urol. 1986 Jun;135(6):1190-3.

31. Ding YY, Sahadevan S, Pang WS, Choo PW. Clinical utility of a portable ultrasound scanner in the measurement of residual urine volume. Singapore Med J. 1996 Aug;37(4):365-8.

32. De Gennaro M, Capitanucci ML, Di Ciommo V, Adorisio O, Mosiello G, Orazi C, et al. Reliability of bladder volume measurement with BladderScan in paediatric patients. Scand J Urol Nephrol. 2006;40(5):370-5.

33. Bano F, Arunkalaivanan AS, Barrington JW. Comparison between bladderscan, real-time ultrasound and suprapubic catheterisation in the measurement of female residual bladder volume. J Obstet Gynaecol. 2004 Sep;24(6):694-5.

34. Bruskewitz RC, Iversen P, Madsen PO. Value of postvoid residual urine determination in evaluation of prostatism. Urology. 1982 Dec;20(6):602-4.

35. Birch NC, Hurst G, Doyle PT. Serial residual volumes in men with prostatic hypertrophy. Br J Urol. 1988 Dec;62(6):571-5.

36. Griffiths DJ, Harrison G, Moore K, McCracken P. Variability of post-void residual urine volume in the elderly. Urol Res. 1996;24(1):23-6.

37. Abrams PH, Griffiths DJ. The assessment of prostatic obstruction from urodynamic measurements and from residual urine. Br J Urol. 1979 Apr;51(2):129-34.

38. Andersen JT. Prostatism: Clinical, radiological, and urodynamic aspects. Neurourol Urodyn. 1982;1(3):241-93.

39. Barry MJ, Cockett AT, Holtgrewe HL, McConnell JD, Sihelnik SA, Winfield HN. Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. J Urol. 1993 Aug;150(2 Pt 1):351-8.

40. Dunsmuir WD, Feneley M, Corry DA, Bryan J, Kirby RS. The day-to-day variation (test-retest reliability) of residual urine measurement. Br J Urol. 1996 Feb;77(2):192-3.

41. el Din KE, Kiemeney LA, de Wildt MJ, Rosier PF, Debruyne FM, de la Rosette JJ. The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol. 1996 Sep;156(3):1020-5.

42. Leblanc G, Tessier J, Schick E. The importance and significance of post-micturitional bladder residue in the evaluation of prostatism. Prog Urol. 1995 Sep;5(4):511-4.

43. Hakenberg OW, Ryall RL, Langlois SL, Marshall VR. The estimation of bladder volume by sonocystography. J Urol. 1983 Aug;130(2):249-51.

44. Poston GJ, Joseph AE, Riddle PR. The accuracy of ultrasound in the measurement of changes in bladder volume. Br J Urol. 1983 Aug;55(4):361-3.

45. Hartnell GG, Kiely EA, Williams G, Gibson RN. Real-time ultrasound measurement of bladder volume: a comparative study of three methods. Br J Radiol. 1987 Nov;60(719):1063-5.

46. Rageth JC, Langer K. Ultrasonic assessment of residual urine volume. Urol Res. 1982;10(2):57-60.

B.III.2. Open Bladder Neck and Proximal Urethra at Rest

1. Versi E. The significance of an open bladder neck in women. Br J Urol. 1991 Jul;68(1):42-3.

2. Chapple CR, Helm CW, Blease S, Milroy EJ, Rickards D, Osborne JL. Asymptomatic bladder neck incompetence in nulliparous females. Br J Urol. 1989 Oct;64(4):357-9.

3. Digesu GA, Khullar V, Cardozo L, Salvatore S. The open bladder neck: a significant finding? Int Urogynecol J Pelvic Floor Dysfunct. 2004 Sep-Oct;15(5):336-9.

4. Schaer GN, Perucchini D, Munz E, Peschers U, Koechli OR, Delancey JO. Sonographic evaluation of the bladder neck in continent and stress-incontinent women. Obstet Gynecol. 1999 Mar;93(3):412-6.

5. Dietz HP, Clarke B. The urethral pressure profile and ultrasound imaging of the lower urinary tract. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12(1):38-41.

6. Huang WC, Yang JM. Bladder neck funneling on ultrasound cystourethrography in primary stress urinary incontinence: a sign associated with urethral hypermobility and intrinsic sphincter deficiency. Urology. 2003 May;61(5):936-41.

7. Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry. 2001 Nov;71(5):600-6.

8. Wein AJ, Levin RM, Barrett DM. Voiding Dysfunction: Relevant Anatomy, Physiology and Pharmacology. In: Gillenwater Y, Grayhack JT, Howard SS, Duckett JW, editors. Adult and Pediatric Urology. Chicago: Year Book Medical Publisher, Inc. ; 1992. p. 800-62.

9. Wein AJ. Neuromuscular Dysfunction of the Lower Urinary Tract. In: Walsh PC, Retik AB, Stamey TA, Vaughan ED, editors. Campbell's Urology. Philadelphia: Saunders Company; 1992. p. 573-642.

10. Barbalias GA, Blaivas JG. Neurologic implications of the pathologically open bladder neck. J Urol. 1983 Apr;129(4):780-2.

11. Salinas JM, Berger Y, De La Rocha RE, Blaivas JG.

Urological evaluation in the Shy Drager syndrome. J Urol. 1986 Apr;135(4):741-3.

12. Blaivas JG, Barbalias GA. Characteristics of neural injury after abdominoperineal resection. J Urol. 1983 Jan;129(1):84-7.
13. De Groat WC, Steers WD. Autonomic Regulation of the Urinary Bladder and Sexual organs. In: Loewry AD, Spyers KM, editors. Central regulation of the Autonomic Functions. 1st ed. Oxford: Oxford University Press; 1990. p. 313.
14. Nordling J. Influence of the Sympathetic Nervous System on Lower Urinary Tract in Men. Neurourol Urodyn. 1983;2:3.
15. McGuire EJ. Combined radiographic and manometric assessment of urethral sphincter function. J Urol. 1977 Oct;118(4):632-5.
16. McGuire EJ. The effects of sacral denervation on bladder and urethral function. Surg Gynecol Obstet. 1977 Mar;144(3):343-6.
17. Nordling J, Meyhoff HH, Olesen KP. Cysto-urethrographic appearance of the bladder and posterior urethra in neuromuscular disorders of the lower urinary tract. Scand J Urol Nephrol. 1982;16(2):115-24.
18. Gosling JA, Dixon JS, Lendon RG. The autonomic innervation of the human male and female bladder neck and proximal urethra. J Urol. 1977 Aug;118(2):302-5.
19. Stanton SL, Williams D. The wide bladder neck in children. Br J Urol. 1973;45:60.
20. Murray K, Nurse D, Borzyskowski M, Mundy AR. The “congenital” wide bladder neck anomaly: a common cause of incontinence in children. Br J Urol. 1987 Jun;59(6):533-5.
21. Blaivas JG, Olsson CA. Stress incontinence: classification and surgical approach. J Urol. 1988 Apr;139(4):727-31.
22. MacDiarmid S, Rosario D, Chapple CR. The importance of accurate assessment and conservative management of the open bladder neck in patients with post-pelvic fracture membranous urethral distraction defects. Br J Urol. 1995 Jan;75(1):65-7.
23. Iselin CE, Webster GD. The significance of the open bladder neck associated with pelvic fracture urethral distraction defects. J Urol. 1999 Aug;162(2):347-51.
24. Shivde SR. Re: The significance of the open bladder neck associated with pelvic fracture urethral distraction defects. J Urol. 2000 Feb;163(2):552.
25. Skala C, Emons G, Krauss T, Hilgers R, Gauruder-Burmester A, Lange R, et al. Postoperative funeneling after anti-incontinence surgery--a prognostic indicator?--Part 1: colposuspension. Neurourol Urodyn. 2004;23(7):636-42.

B.II.3. Female Urethral Diverticula

1. Rovner ES. Urethral diverticula: a review and an update. Neurourol Urodyn. 2007;26(7):972-7.
2. Lorenzo AJ, Zimmern P, Lemack GE, Nurenberg P. Endorectal coil magnetic resonance imaging for diagnosis of urethral and periurethral pathologic findings in women. Urology. 2003 Jun;61(6):1129-33; discussion 33-4.
3. Hey W. Practical Observations in Surgery. Philadelphia: Humphries, J.; 1805.
4. Davis HJ, Cian LG. Positive pressure urethrography: a new diagnostic method. J Urol. 1956;75:753.
5. Leach GE, Trockmann BA. Surgery for vesicovaginal and urethrovaginal fistula and urethral diverticulum. In: Walsh PC, Retik AB, Vaughan DE, Wein A, editors. Campbell’s Urology: WB Saunders Company; 1998. p. 1135-53.
6. Aldridge CW, Jr., Beaton JH, Nanzig RP. A review of office urethroscopy and cystometry. Am J Obstet Gynecol. 1978 Jun 15;131(4):432-7.
7. Ganabathi K, Leach GE, Zimmern PE, Dmochowski R. Experience with the management of urethral diverticulum in 63 women. J Urol. 1994 Nov;152(5 Pt 1):1445-52.
8. Romanzi LJ, Groutz A, Blaivas JG. Urethral diverticulum in women: diverse presentations resulting in diagnostic delay and mismanagement. J Urol. 2000 Aug;164(2):428-33.
9. Blaivas JG, Flisser AJ, Bleustein CB, Panagopoulos G. Periurethral masses: etiology and diagnosis in a large series of women. Obstet Gynecol. 2004 May;103(5 Pt 1):842-7.
10. Jacoby K, Rowbotham RK. Double balloon positive pressure urethrography is a more sensitive test than voiding cystourethrography for diagnosing urethral diverticulum in women. J Urol. 1999 Dec;162(6):2066-9.
11. Wang AC, Wang CR. Radiologic diagnosis and surgical treatment of urethral diverticulum in women. A reappraisal of voiding cystourethrography and positive pressure urethrography. J Reprod Med. 2000 May;45(5):377-82.
12. Golomb J, Leibovitch I, Mor Y, Morag B, Ramon J. Comparison of voiding cystourethrography and double-balloon urethrography in the diagnosis of complex female urethral diverticula. Eur Radiol. 2003 Mar;13(3):536-42.
13. Chancellor MB, Liu JB, Rivas DA, Karasick S, Bagley DH, Goldberg BB. Intraoperative endo-luminal ultrasound evaluation of urethral diverticula. J Urol. 1995 Jan;153(1):72-5.
14. Kim B, Hricak H, Tanagho EA. Diagnosis of urethral diverticula in women: value of MR imaging. AJR Am J Roentgenol. 1993 Oct;161(4):809-15.
15. Neitlich JD, Foster HE, Jr., Glickman MG, Smith RC. Detection of urethral diverticula in women: comparison of a high resolution fast spin echo technique with double balloon urethrography. J Urol. 1998 Feb;159(2):408-10.
16. Daneshgari F, Zimmern PE, Jacomides L. Magnetic resonance imaging detection of symptomatic noncommunicating intraurethral wall diverticula in women. J Urol. 1999 Apr;161(4):1259-61; discussion 61-2.
17. Blander DS, Broderick GA, Rovner ES. Images in clinical urology. Magnetic resonance imaging of a “saddle bag” urethral diverticulum. Urology. 1999 Apr;53(4):818-9.
18. Blander DS, Rovner ES, Schnall MD, Ramchandani P, Banner MP, Broderick GA, et al. Endoluminal magnetic resonance imaging in the evaluation of urethral diverticula in women. Urology. 2001 Apr;57(4):660-5.
19. Takano M, Hamada A. Evaluation of pelvic descent disorders by dynamic contrast roentgenography. Dis Colon Rectum. 2000 Oct;43(10 Suppl):S6-11.
20. Rovner ES, Wein AJ. Diagnosis and reconstruction of the dorsal or circumferential urethral diverticulum. J Urol. 2003 Jul;170(1):82-6; discussion 6.
21. Khati NJ, Javitt MC, Schwartz AM, Berger BM. MR imaging diagnosis of a urethral diverticulum. Radiographics. 1998 Mar-Apr;18(2):517-22.
22. Greenberg M, Stone D, Cochran ST, Bruskewitz R, Pagani JJ, Raz S, et al. Female urethral diverticula: double-balloon catheter study. AJR Am J Roentgenol. 1981 Feb;136(2):259-64.
23. Pavlica P, Barozzi L, Menchi I. Imaging of male urethra. Eur Radiol. 2003 Jul;13(7):1583-96.

B.III.4a. Imaging of the Nervous System: Lumbosacral spine X-rays

1. Tubaro A, Artibani W, Bartram C, Delancey JD, Dietz HP, Khullar V, Zimmern P. Imaging and other investigations. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence, 3rd International Consultation on Incontinence. Plymouth: Health Publication Ltd; 2005. pp. 707–797.
2. Glenn OA, Barkovich AJ. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis, part 1. AJNR Am J Neuroradiol. 27(8):1604-11, 2006.
3. Glenn OA, Barkovich J. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis: part 2. AJNR Am J Neuroradiol. 27(9):1807-14, , 2006
4. Wraige E, Borzyskowski M. Investigation of daytime wetting: when is spinal cord imaging indicated? Arch Dis Child. 87(2):151-5, 2002.
5. Muñoz A, Hinojosa J, Esparza J. Cisternography and ventriculography gadopentate dimeglumine-enhanced MR imaging in pediatric patients: preliminary report. AJNR Am J Neuroradiol. 28(5):889-94, 2007.
6. Sharma U, Pal K, Pratap A, Gupta DK, Jagannathan NR. Potential of proton magnetic resonance spectroscopy in the evaluation of patients with tethered cord syndrome following surgery. J Neurosurg. 105(5 Suppl):396-402, 2006.
7. Blok, B.F.M., Sturms, L.M., Holstege, G. A PET study on cortical and subcortical control of pelvic floor musculature in women. J. Comp. Neurol. 389, 535–544, 1997.
8. Blok, B.F.M., Sturms, L.M., Holstege, G.. Brain activation during micturition in women. Brain 121, 2033–2042, 1998.
9. Kern, M.K., Arndorfer, R.C., Hyde, J.S., Shaker, R. Cerebral cortical representation of external anal sphincter contraction: effect of effort. Am. J. Physiol.: Gastrointest Liver Physiol. 286, G304–G311, 2004.
10. Di Gangi Herms AM, Veit R, Reisenauer C, Herms A, Grodd W, Enck P, Stenzl A, Birbaumer N. Functional imaging of stress urinary incontinence. Neuroimage. 29(1):267-75, 2006.
11. Tadic SD, Griffiths D, Schaefer W, Resnick NM. Abnormal connections in the supraspinal bladder control network in women with urge urinary incontinence. Neuroimage 39(4):1647-53, 2008.

B.III.4b. Imaging of the Nervous System: CT, MRI, SPECT and PET

1. Tubaro A, Artibani W, Bartram C, Delancey JD, Dietz HP, Khullar V, Zimmern P. Imaging and other investigations. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence, 3rd International Consultation on Incontinence. Plymouth: Health Publication Ltd; 2005. pp. 707–797.
2. Glenn OA, Barkovich AJ. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis, part 1. AJNR Am J Neuroradiol. 2006; 27(8):1604-11.
3. Glenn OA, Barkovich J. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis: part 2. AJNR Am J Neuroradiol. 2006; 27(9):1807-14.
4. Wraige E, Borzyskowski M. Investigation of daytime wetting: when is spinal cord imaging indicated? Arch Dis Child. 2002: 87(2):151-5.
5. Muñoz A, Hinojosa J, Esparza J. Cisternography and ventriculography gadopentate dimeglumine-enhanced MR imaging in pediatric patients: preliminary report. AJNR Am J Neuroradiol. 2007. 28(5):889-94.
6. Sharma U, Pal K, Pratap A, Gupta DK, Jagannathan NR. Potential of proton magnetic resonance spectroscopy in the evaluation of patients with tethered cord syndrome following surgery. J Neurosurg. 2006; 105(5 Suppl):396-402.
7. Drake M.J., Tannenbaum C, and Kanai, AJ. Potential Insights Into Lower Urinary Function Derived From CNS Imaging. Neurourology and Urodynamics 2010; 29:629–633.
8. Blok, B.F.M., Sturms, L.M., Holstege, G. A PET study on cortical and subcortical control of pelvic floor musculature in women. J. Comp. Neurol. 389, 535–544, 1997.
9. Blok, B.F.M., Sturms, L.M., Holstege, G.. Brain activation during micturition in women. Brain 1998; 121:2033– 2042.
10. Kern, M.K., Arndorfer, R.C., Hyde, J.S., Shaker, R. Cerebral cortical representation of external anal sphincter contraction: effect of effort. Am. J. Physiol.: Gastrointest Liver Physiol. 2004; 286, G304–G311.
11. Di Gangi Herms AM, Veit R, Reisenauer C, Herms A, Grodd W, Enck P, Stenzl A, Birbaumer N. Functional imaging of stress urinary incontinence. Neuroimage. 2006; 29(1):267-75.
12. Tadic SD, Griffiths D, Schaefer W, Resnick NM. Abnormal connections in the supraspinal bladder control network in women with urge urinary incontinence. Neuroimage 2008, 39(4):1647-53.

B.III.5. Endoscopy of the lower urinary tract

1. Samplaski MK, Jones JS. Two centuries of cystoscopy: the development of imaging, instrumentation and synergistic technologies. BJU Int. 2009 Jan;103(2):154-8. Epub 2008 Dec 8.
2. Robertson JR. Urethroscopy - the neglected gynecologic procedure. Clin Obstet Gynecol. 1976 Jun;19(2):315-40.
3. Aldridge CW, Jr., Beaton JH, Nanzig RP. A review of office urethroscopy and cystometry. Am J Obstet Gynecol. 1978 Jun 15;131(4):432-7.
4. Scotti RJ, Ostergard DR, Guillaume AA, Kohatsu KE. Predictive value of urethroscopy as compared to urodynamics in the diagnosis of genuine stress incontinence. J Reprod Med. 1990 Aug;35(8):772-6.
5. Sand PK, Hill RC, Ostergard DR. Supine urethroscopic and standing cystometry as screening methods for the detection of detrusor instability. Obstet Gynecol. 1987 Jul;70(1):57-60.
6. Horbach NS, Ostergard DR. Predicting intrinsic urethral sphincter dysfunction in women with stress urinary incontinence. Obstet Gynecol. 1994 Aug;84(2):188-92.
7. Govier FE, Pritchett TR, Kornman JD. Correlation of the cystoscopic appearance and functional integrity of the female urethral sphincteric mechanism. Urology. 1994 Aug;44(2):250-3.
8. Langmade CF, Oliver JA, Jr. Simplifying the management of stress incontinence. Am J Obstet Gynecol. 1984 May 1;149(1):24-8.
9. Fischer-Rasmussen W, Hansen RI, Stage P. Predictive values of diagnostic tests in the evaluation of female urinary stress incontinence. Acta Obstet Gynecol Scand. 1986;65(4):291-4.
10. Cardozo LD, Stanton SL. Genuine stress incontinence and detrusor instability--a review of 200 patients. Br J Obstet Gynaecol. 1980 Mar;87(3):184-90.
11. Mundy AR. The unstable bladder. Urol Clin North Am. 1985 May;12(2):317-28.
12. Duldulao KE, Diokno AC, Mitchell B. Value of urinary cytology in women presenting with urge incontinence and/or irritative voiding symptoms. J Urol. 1997 Jan;157(1):113-6.

13. Harris RL, Cundiff GW, Theofrastous JP, Yoon H, Bump RC, Addison WA. The value of intraoperative cystoscopy in urogynecologic and reconstructive pelvic surgery. Am J Obstet Gynecol. 1997 Dec;177(6):1367-9; discussion 9-71.

14. Timmons MC, Addison WA. Suprapubic teloscopy: extraperitoneal intraoperative technique to demonstrate ureteral patency. Obstet Gynecol. 1990 Jan;75(1):137-9.

15. Lower urinary tract operative injuries. ACOG Technical Bulletin. 1997;238.

16. Roehrborn CG, Andersen JT, Correa RJ, Di Silverio F, Kaplan SA, K.H. K, et al. Initial diagnostic evaluation of men with lower urinary tract symptoms. In: Cockett ATK, Khoury S, Aso Y, Chatelain C, Denis L, Griffiths K, et al., editors. The 3rd International Consultation on benign Prostatic Hyperplasia (BPH) - Proceedings: Scientific Communication International Ltd.; 1995. p. 167-254.

17. Leach GE, Trockman B, Wong A, Hamilton J, Haab F, Zimmern PE. Post-prostatectomy incontinence: urodynamic findings and treatment outcomes. J Urol. 1996 Apr;155(4):1256-9.

18. Desautel MG, Kapoor R, Badlani GH. Sphincteric incontinence: the primary cause of post-prostatectomy incontinence in patients with prostate cancer. Neurourol Urodyn. 1997;16(3):153-60.

19. Gudziak MR, McGuire EJ, Gormley EA. Urodynamic assessment of urethral sphincter function in post-prostatectomy incontinence. J Urol. 1996 Sep;156(3):1131-4; discussion 4-5.

20. Chao R, Mayo ME. Incontinence after radical prostatectomy: detrusor or sphincter causes. J Urol. 1995 Jul;154(1):16-8.

21. Goluboff ET, Chang DT, Olsson CA, Kaplan SA. Urodynamics and the etiology of post-prostatectomy urinary incontinence: the initial Columbia experience. J Urol. 1995 Mar;153(3 Pt 2):1034-7.

22. Leach GE, Yun SK. Post-prostatectomy incontinence: Part II. The results of treatment based on urodynamic evaluation. . Neurourol Urodyn. 1992;11:99.

23. Gozzi C, Bauer RM, Becker AJ, Schorsch I, May F, Rehder P, et al. Functional retrourethral sling. A change of paradigm in the treatment of stress incontinence after radical prostatectomy. Urologe A. 2008 Sep;47(9):1224-8.

24. Rehder P, Gozzi C. Transobturator sling suspension for male urinary incontinence including post-radical prostatectomy. Eur Urol. 2007 Sep;52(3):860-6.

25. Rehder P, Gozzi C. Re: Surgical technique using AdVance sling placement in the treatment of post-prostatectomy urinary incontinence. Int Braz J Urol. 2007 Jul-Aug;33(4):560-1.

C. IMAGING IN ANAL INCONTINENCE

1. Wild JJ, Reid JM. Diagnostic use of ultrasound. Br J Phys Med.1956;19:248-57.

2. Papachrysostomou M, Pye SD, Wild SR, Smith AN. Anal endosonography in asymptomatic subjects. Scandinavian Journal of Gastroenterology 1993; 28:551-6

3. Law PJ, Bartram CI. Anal endosonography: Technique & normal anatomy. Gastrointestinal Radiology 1989; 14:349-353.

4. Sultan AH, Thakar R. Lower genital tract and anal sphincter trauma. Best Practice & Research in Clinical Obstetrics & Gynaecology 2002; 16:99-115.

5. Santoro GA, Di Falco G. Endoanal ultrasonography in the staging of anal carcinoma. In: Atlas of endoanal and endorectal ultrasonography. Milan: Springer-Verlag; 2004.

6. Etienney I & de Parades V. Three-dimensional endoanal ultrasonography in daily proctological practice. Clinics inHepatology & Gastroenterology 2011; 35:260-270.

7. West RL, Felt-Bersma RJ, Hansen BE, Schouten WR, Kuipers EJ. Volume measurements of the anal sphincter complex in healthy controls and fecal-incontinent patients with a three-dimensional reconstruction of endoanal ultrasonography images. Dis Colon Rectum. 2005; 48:540-8.

8. Stark M, Bohe M, Valentin L. Effect of vaginal delivery on endosonographic anal sphincter morphology. Eur J Obstet Gynecol Reprod Biol. 2007; 130:193-201.

9. Norderval S, Dehli T, Vonon B. Three-dimensional endoanalultrasonography: intraobserver and interobserver agreement using scoring systems for classification of anal sphincterdefects. Ultrasoud Obstet Gynecol. 2009, 33:337-43.

10. Wasserberg N, Mazaheri A, Petrone P, Tulchinsky H and Kaufman HS. Three-dimensional endoanal ultrasonography of external anal sphincter defects in patients with faecal incontinence correlation with symptoms and manometry Colorectal Diseases. 2011; 13:449-53.

11. Sultan AH, Loder PB, Bartram CI, et al. Vaginal endosonography: new approach to imagethe undisturbed anal sphincter. Dis Colon Rectum. 1994; 37:1296.

12. Roos AM, Abdool Z, Sultan AH, Thakar R. The diagnostic accuracy of endovaginal and transperineal ultrasound for detecting anal sphincter defects: The PREDICT study. Clinical Radiology. 2011; 66:597-604.

13. Peschers UM, DeLancey JO, Schaer GN, Schuessler B Exoanal ultrasound of the anal sphincter: normal anatomy and sphincter defects. Br J Obstet Gynaecol. 1997: 104(9):999-1003.

14. Roche B, Deleaval J, Fransioli A, et al. Comparison of transanal and external perineal ultrasonography. Eur Radiol. 2001; 11:1165.

15. Zetterström JP, Mellgren A, Madoff RD, Kim DG, Wong WD Perineal body measurement improves evaluation of anterior sphincter lesions during endoanal ultrasonography. Dis Colon Rectum 1998; 41(6):705–713.

16. R. J. Hall : R. G. Rogers : L. Saiz : C. Qualls. Translabial ultrasound assessment of the anal sphincter complex: normal measurements of the internal and external anal sphincters at the proximal, mid-, and distal levels. Int Urogynecol J. 2007; 18:881-888.

17. Santoro GA, Wieczorek AP, Dietz HP, Mellgren A, Sultan AH, Shobeiri SA, Stankiewicz A, Bartram C. State of the art: an integrated approach to pelvic floor ultrasonography. Ultrasound Obstet Gynecol. 2011; 37(4):381-96.

18. Vitton V, Vignally P, Barthet M, Cohen V, Durieux O, Bouvier M, Grimaud JC. Dynamic anal endosonography and MRI defecography in diagnosis of pelvic floor disorders: comparison with conventional defecography. Dis Colon Rectum. 2011; 54(11):1398-404.

19. Frey H, Dietrich CF. Sonoelastography: a new ultrasound modality for assessing tissue elasticity. In: Dietrich CF, editor. Endoscopic ultrasound. Stuttgart, Germany: Thieme Verlag; p. 56–69. 2008.

20. Allgayer H, Ignee A, Dietrich CF Endosonographic elastography of the anal sphincter in patients with fecal incontinence. Scand J Gastroenterol. 2010; 45(1):30-8.

21. Standring S, Ellis H, Healy J, Johnson D, Williams A, eds. Gray's Anatomy: The Anatomical Basis of Clinical Practice, 40th ed. New York: Elsevier Churchill Livingstone; 2008.

22. Rociu E, Stoker J, Eijkemans MJ, Lameris JS. Normal anal sphincter anatomy and age- and sex-related variations at highspatial resolution endoanal MR imaging. Radiology. 2000: 217:395–401.

23. Stoker J, Rociu E, Zwamborn AW, Schouten WR, Lameris JS. Endoluminal MR imaging of the rectum and anus: technique, applications, and pitfalls. Radiographics.1999; 19:383–398.

24. Guo M, Li D. Pelvic floor images: anatomy of the levator ani muscle. Dis Colon Rectum. 2007; 50:1647-1655.

25. Hsu Y, Fenner DE, Weadock WJ, DeLancey JO. Magnetic resonance imaging and 3-dimensional analysis of external anal sphincter anatomy. Obstet Gynecol. 2005; 106:1259-1265.

26. Guo M, Gao C, Li D, Guo W, Shafik AA, Zbar AP, Pescatori M. MRI anatomy of the anal region. Dis Colon Rectum. 2010; 53(11):1542-8.

27. Malouf AJ, Williams AB, Halligan S, Bartram CI, Dhillon S, Kamm MA. Prospective assessment of accuracy of endoanal MR imaging and endosonography in patients with fecal incontinence. AJR Am J Roentgenol. 2000: 175(3):741-745.

28. Tan E; Anstee A; Koh DM; Gedroyc W; Tekkis PP. Diagnostic precision of endoanal MRI in the detection of anal sphincter pathology: a meta-analysis. Int J Colorectal Dis. 2008: 23:641-65.

29. Heilbrun ME, Nygaard IE, Lockhart ME, Richter HE, Brown MB, Kenton KS, Rahn DD, Thomas JV, Weidner AC, Nager CW, Delancey JO. Correlation between levator ani muscle injuries on magnetic resonance imaging and fecal incontinence, pelvic organ prolapse, and urinary incontinence in primiparous women. Am J Obstet Gynecol. 2010; 202(5):488.

30. Dobben AC, Wiersma TG, Janssen LW et al. Prospective assessment of interobserver agreement for defecography in fecal incontinence. AJR Am J Roentgenol. 2005 185:1166-1172.

31. Terra MP, Beets-Tan RG, Vervoorn I, Deutekom M, Wasser MN, Witkamp TD, Dobben AC, Baeten CG, Bossuyt PM, Stoker J. Pelvic floor muscle lesions at endoanal MR imaging in female patients with faecal incontinence. Eur Radiol. 2008, 18(9):1892-901.

32. Schoenenberger AW, Debatin JF, Guldenschuh I, Hany TF, Steiner P,Krestin GP. Dynamic MR defecography with a superconducting, open-configuration MR system. Radiology 1998; 206:641-646.

33. Garcia-Aguilar, J., Belmonte, Montes C., Perez, J. J., Jensen, L., Madoff, R. D., Wong, and WD. Incontinence after lateral internal sphincterotomy: anatomic and functional evaluation. Diseases of the Colon & Rectum 1998; 41:423-427.

34. Williams, A. B., Bartram, C. I., Halligan, S., Spencer, J. A.,Nicholls, R. J., and Kmiot, W. A.. Anal sphincter damage after vaginal delivery using three-dimensional endosonography. Obstet.Gynecol. 2001; 97;770-775.

35. Williams, A. B., Bartram, C. I., Halligan, S., Marshall, M. M.,Nicholls, R. J., and Kmiot, W. A. Endosonographic anatomyof the normal anal canal compared with endocoil magnetic resonance imaging. Dis. Colon Rectum 2002; 45:176-183

36. Thomas C, Etienney I, Atienza P. Evaluation of the role of the puborectal part of the levator ani muscle in anal incontinence: a prospective study of 78 female patients with anal incontinence. Dis Colon Rectum. 2011; 54(9):1129-33.

37. Williams, A. B., Bartram, C. I., Modhwadia, D., Nicholls, T.,Halligan, S., Kamm, M. A., Nicholls, R. J., and Kmiot, W. A. Endocoil magnetic resonance imaging quantification of external anal sphincter atrophy. Br.J.Surg. 2001; 88:853-859.

38. Cazemier, M., Terra, M. P., Stoker, J., de Lange-de Klerk ES, Boeckxstaens, G. E., Mulder, C. J., and Felt-Bersma, R. J..Atrophy and defects detection of the external anal sphincter: comparison between three-dimensional anal endosonography and endoanal magnetic resonance imaging. Dis.Colon Rectum 2006; 49;20-27.

39. Andrews, V., Sultan, A. H., Thakar, R., and Jones, P. W. Occult anal sphincter injuries—myth or reality? BJOG. 2006; 113:195-200

40. Oberwalder, M., Connor, J., and Wexner, S. D.. Meta-analysis to determine the incidence of obstetric anal sphincter damage. Br.J.Surg. 2003; 90:1333-1337.

41. de Leeuw, J. W., Vierhout, M. E., Struijk, P. C., Hop, W. C., and Wallenburg, H. C.. Anal sphincter damage after vaginal delivery: functional outcome and risk factors for fecal incontinence. Acta Obstet.Gynecol.Scand. 2001; 80:830-834.

42. Oberwalder, M., Dinnewitzer, A., Baig, M. K., Thaler, K., Cotman, K., Nogueras, J. J., Weiss, E. G., Efron, J., Vernava, A. M., III, and Wexner, S. D.. The association between late onset fecal incontinence and obstetric anal sphincter defects. Arch.Surg.2004; 139:429-432.

43. Damon, H., Bretones, S., Henry, L., Mellier, G., and Mion, F.. Long-term consequences of first vaginal delivery-induced anal sphincter defect. Dis.Colon Rectum 2005; 48:1772-1776.

44. Faltin, D. L., Sangalli, M. R., Roche, B., Floris, L., Boulvain, M., and Weil, A. Does a second delivery increase the risk of anal incontinence? BJOG 2001; 108:684-688.

45. Mahony, R., Behan, M., Daly, L., Kirwan, C., O'Herlihy, C., and O'Connell, P. R. Internal anal sphincter defect influences continence outcome following obstetric anal sphincter injury. Am.J.Obstet. Gynecol. 2007; 196:217-5.

46. Malouf, A. J., Norton, C. S., Engel, A. F., Nicholls, R. J., and Kamm, M. A. Long-term results of overlapping anterior anal sphincter repair for obstetric trauma. Lancet 2000; 355:260-265.

47. Norderval, S., Oian, P., Revhaug, A., and Vonen, B. Anal incontinence after obstetric sphincter tears: outcome of anatomic primary repairs. Dis. Colon Rectum 2005; 48:1055-1061.

48. Bharucha, A. E., Fletcher, J. G., Harper, C. M., Hough, D.,Daube, J. R., Stevens, C., Seide, B., Riederer, S. J., and Zinsmeister, A. R.. Relationship between symptoms and disordered continence mechanisms in women with idiopathic faecal incontinence. Gut 2005; 54:546-555.

49. Abramowitz, L., Sobhani, I., Ganansia, R., Vuagnat, A., Benifla, J. L., Darai, E., Madelenat, P., and Mignon, M.. Are sphincter defects the cause of anal incontinence after vaginal delivery? Results of a prospective study. Dis.Colon Rectum 2000: 43:590-596.

50. Damon, H., Henry, L., Barth, X., and Mion, F.. Fecal incontinence in females with a past history of vaginal delivery: significance of anal sphincter defects detected by ultrasound. Dis. Colon Rectum 2002; 45:1445-1450.

51. Voyvodic, F., Rieger, N. A., Skinner, S., Schloithe, A. C., Saccone, G. T., Sage, M. R., and Wattchow, D. A. Endosonographic imaging of anal sphincter injury: does the size of the tear correlate with the degree of dysfunction? Dis. Colon Rectum 2003; 46:735-741.

52. Starck, M., Bohe, M., and Valentin, L. Results of endosonographic imaging of the anal sphincter 2-7 days after primary repair of third- or fourth-degree obstetric sphincter tears. Ultrasound Obstet.Gynecol. 2003; 22:609-615.

53. Nazir, M., Carlsen, E., Jacobsen, A. F., and Nesheim, B. I. Is there any correlation between objective anal testing, rupture grade, and bowel symptoms after primary repair of obstetric anal sphincter rupture?: an observational cohort study. Dis. Colon Rectum 2002; 45:1325-1331.

54. Rizk DE. Minimizing the risk of childbirth-induced pel-

vic floor dysfunctions in the developing world: "preventive" urogynecology. Int Urogynecol J Pelvic Floor Dysfunct 2009; 20(6):615-617.

D. PAD TESTING

1. James ED, Flack FC, Caldwell KP, Martin MR. Continuous measurement of urine loss and frequency in incontinent patients. Preliminary report. Br J Urol. 1971 Apr; 43(2):233-7.
2. Caldwell K. Proceedings: Clinical use of recording nappy. Urol Int. 1974; 29(3):172-3.
3. Eadie AS, Glen ES, Rowan D. The Urilos recording nappy system. Br J Urol. 1983 Jun; 55(3):301-3.
4. James ED, Flack FC. Proceedings: Assessment of recording nappy. Urol Int. 1974; 29(3):174-5.
5. Rowan D, Deehan C, Glen ES. Detection of urine loss using the Exeter recording nappy and other similar devices. Urol Int. 1976; 31(1-2):70-7.
6. Stanton SL. Urilos: the practical detection of urine loss. Am J Obstet Gynecol. 1977 Jun 15; 128(4):461-3.
7. Wilson PD, Al Samarrai MT, Brown AD. Quantifying female incontinence with particular reference to the Urilos System. Urol Int. 1980; 35(4):298-302.
8. Mayne CJ, Hilton P. The distal urethral electrical conductance test: Standardisation of method and clinical reliability. Neurourol Urodyn. 1988; 7(1):55-60.
9. Walsh JB, Mills GL. Measurement of urinary loss in elderly incontinent patients. A simple and accurate method. Lancet. 1981 May 23; 1(8230):1130-1.
10. Sutherst JR, Brown MC, Richmond D. Analysis of the pattern of urine loss in women with incontinence as measured by weighing perineal pads. Br J Urol. 1986 Jun; 58(3):273-8.
11. Abrams P, Blaivas JG, Stanton SL, Andersen JT. The standardization of terminology of lower urinary tract function. International Continenece Society Committee on Standardisation of Terminology. Neurourol Urodyn. 1988; 7:403-26.
12. Lose G, Gammelgaard J, Jørgensen TJ. The one-hour pad-weighing test: Reproducibility and the correlation between the test result, the start volume in the bladder, and the diuresi. 1986; 5(1):17-21.
13. Christensen SJ, Colstrup H, Hertz JB, Lenstrup C, Frimodt-Møller C. Inter- and intra-departmental variations of the perineal pad weighing test. Neurourol Urodyn. 1986; 5(1):23-8.
14. Wall LL, Wang K, Robson I, Stanton SL. The Pyridium pad test for diagnosing urinary incontinence. A comparative study of asymptomatic and incontinent women. J Reprod Med. 1990 Jul; 35(7):682-4.
15. Hahn I, Fall M. Objective Quantification of stress urinary incontinence: A short reproducible, provocative Pad-Test. Neurourol Urodyn. 1991; 10:475-81.
16. Jorgensen L, Lose G, Andersen JT. One-hour pad-weighing test for objective assessment of female urinary incontinence. Obstet Gynecol. 1987 Jan; 69(1):39-42.
17. Jakobseny H, Vedel P, Andersen JT. Objective assessment of urinary incontinence: An evaluation of three different pad-weighing tests. Neurourol Urodyn. 1987; 6(4):325-30.
18. Kinn AC, Larsson B. Pad test with fixed bladder volume in urinary stress incontinence. Acta Obstet Gynecol Scand. 1987; 66(4):369-71.
19. Persson J, Bergqvist CE, Wolner-Hanssen P. An ultrashort perineal pad-test for evaluation of female stress urinary incontinence treatment. Neurourol Urodyn. 2001; 20(3):277-85.
20. Griffiths DJ, McCracken PN, Harrison GM. Incontinence in the elderly: objective demonstration and quantitative assessment. Br J Urol. 1991 May; 67(5):467-71.
21. Lose G, Jorgensen L, Thunedborg P. 24-hour home pad weighing test versus 1-hour ward test in the assessment of mild stress incontinence. Acta Obstet Gynecol Scand. 1989; 68(3):211-5.
22. Mouritsen L, Berild G, Hertz J. Comparison of different methods for quantification of urinary leakage in incontinent women. Neurourol Urodyn. 1989; 8(6):579-86.
23. Thind P, Gerstenberg TC. One-hour ward test vs. 24-hour home pad weighing test in the diagnosis of urinary incontinence. Neurourol Urodyn. 1991; 10(3):241-5.
24. Klarskov P, Hald T. Reproducibility and reliability of urinary incontinence assessment with a 60 min test. Scand J Urol Nephrol. 1984; 18(4):293-8.
25. Simons AM, Yoong WC, Buckland S, Moore KH. Inadequate repeatability of the one-hour pad test: the need for a new incontinence outcome measure. BJOG. 2001 Mar; 108(3):315-9.
26. Holm-Bentzen MH, Klarskov P, Opsomer RJ, Maegaard EM, Hald T. Objective assessement of urinary incontinence after successful implantation of AMS artificial urethral sphincter. Neurourol Urodyn. 1985; 4:9-13.
27. Fantl JA, Harkins SW, Wyman JF, Choi SC, Taylor JR. Fluid loss quantitation test in women with urinary incontinence: a test-retest analysis. Obstet Gynecol. 1987 Nov; 70(5):739-43.
28. Lose G, Rosenkilde P, Gammelgaard J, Schroeder T. Pad-weighing test performed with standardized bladder volume. Urology. 1988 Jul; 32(1):78-80.
29. Jakobsen H, Kromann-Andersen B, Nielsen KK, Maegaard E. Pad weighing tests with 50% or 75% bladder filling. Does it matter? Acta Obstet Gynecol Scand. 1993 Jul; 72(5):377-81.
30. Aslan E, Beji NK, Coskun A, Yalcin O. An assessment of the importance of pad testing in stress urinary incontinence and the effects of incontinence on the life quality of women. Int Urogynecol J Pelvic Floor Dysfunct. 2003 Nov; 14(5):316-9; discussion 20.
31. Harvey MA, Kristjansson B, Griffith D, Versi E. The Incontinence Impact Questionnaire and the Urogenital Distress Inventory: a revisit of their validity in women without a urodynamic diagnosis. Am J Obstet Gynecol. 2001 Jul; 185(1):25-31.
32. Prajsner A, Radziszewski P. Ambulatory diagnosis of urinary incontinence among women: the role of a one-hour pad weigh test. Wiad Lek. 1998; 51(5-6):254-9.
33. Matharu GS, Assassa RP, Williams KS, Donaldson M, Matthews R, Tincello DG, et al. Objective assessment of urinary incontinence in women: comparison of the one-hour and 24-hour pad tests. Eur Urol. 2004 Feb; 45(2):208-12.
34. Floratos DL, Sonke GS, Rapidou CA, Alivizatos GJ, Deliveliotis C, Constantinides CA, et al. Biofeedback vs verbal feedback as learning tools for pelvic muscle exercises in the early management of urinary incontinence after radical prostatectomy. BJU Int. 2002 May; 89(7):714-9.
35. Ward KL, Hilton P. A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up. Am J Obstet Gynecol. 2004 Feb; 190(2):324-31.
36. Blackwell AL, Yoong W, Moore KH. Criterion validity, test-retest reliability and sensitivity to change of the St George Urinary Incontinence Score. BJU Int. 2004 Feb; 93(3):331-5.
37. Haylen BT, Frazer MI, Sutherst JR. Diuretic response to fluid load in women with urinary incontinence: optimum duration of pad test. Br J Urol. 1988 Oct; 62(4):331-3.

38. Han HC. One-hour or two-hour perineal pad test, which would you choose? Proceedings of the Annual Meeting of the International Continence Society - Athens. 1996; 382.

39. Hellstrom AL, Andersson K, Hjalmas K, Jodal U. Pad tests in children with incontinence. Scand J Urol Nephrol. 1986; 20(1):47-50.

40. Richmond DH, Sutherst JR, Brown MC. Quantification of urine loss by weighing perineal pads. Observation on the exercise regimen. Br J Urol. 1987 Mar; 59(3):224-7.

41. Walters MD, Dombroski RA, Prihoda TJ. Perineal pad testing in the quantitation of urinary incontinence. Int Urogynecol J. 1990; 1(1):3-6.

42. Rasmussen A, Mouritsen L, Dalgaard A, Frimodt-Moller C. Twenty-four hour pad weighing test: reproducibility and dependency of activity level and fluid intake. Neurourol Urodyn. 1994; 13(3):261-5.

43. Ryhammer AM, Laurberg S, Djurhuus JC, Hermann AP. No relationship between subjective assessment of urinary incontinence and pad test weight gain in a random population sample of menopausal women. J Urol. 1998 Mar; 159(3):800-3.

44. Groutz A, Blaivas JG, Chaikin DC, Resnick NM, Engleman K, Anzalone D, et al. Noninvasive outcome measures of urinary incontinence and lower urinary tract symptoms: a multicenter study of micturition diary and pad tests. J Urol. 2000 Sep; 164(3 Pt 1):698-701.

45. Karantanis E, O'Sullivan R, Moore KH. The 24-hour pad test in continent women and men: normal values and cyclical alterations. BJOG. 2003 Jun; 110(6):567-71.

46. Fleischmann N, Flisser AJ, Blaivas JG, Panagopoulos G. Sphincteric urinary incontinence: relationship of vesical leak point pressure, urethral mobility and severity of incontinence. J Urol. 2003 Mar; 169(3):999-1002.

47. Karantanis E, Fynes M, Moore KH, Stanton SL. Comparison of the ICIQ-SF and 24-hour pad test with other measures for evaluating the severity of urodynamic stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2004 Mar-Apr; 15(2):111-6; discussion 6.

48. Singh M, Bushman W, Clemens JQ. Do pad tests and voiding diaries affect patient willingness to participate in studies of incontinence treatment outcomes? J Urol. 2004 Jan; 171(1):316-8; discussion 8-9.

49. Ekelund P, Bergstrom H, Milsom I, Norlen L, Rignell S. Quantification of urinary incontinence in elderly women with the 48-hour pad test. Arch Gerontol Geriatr. 1988 Dec; 7(4):281-7.

50. Victor A, Larsson G, Asbrink AS. A simple patient-administered test for objective quantitation of the symptom of urinary incontinence. Scand J Urol Nephrol. 1987; 21(4):277-9.

51. Versi E, Orrego G, Hardy E, Seddon G, Smith P, Anand D. Evaluation of the home pad test in the investigation of female urinary incontinence. Br J Obstet Gynaecol. 1996 Feb; 103(2):162-7.

52. Hahn I, Fall M. Objective quantification of stress urinary incontinence: a short reproducible, provocative pad-test. Neurourol Urodyn. 1991; 10:475-81.

53. Nygaard I, Zmolek G. Exercise pad testing in continent exercisers: reproducibility and correlation with voided volume, pyridium staining, and type of exercise. Neurourol Urodyn. 1995; 14(2):125-9.

54. Versi E, Cardozo LD. Perineal pad weighing versus videographic analysis in genuine stress incontinence. Br J Obstet Gynaecol. 1986 Apr; 93(4):364-6.

55. Sutherst J, Brown M, Shawer M. Assessing the severity of urinary incontinence in women by weighing perineal pads. Lancet. 1981 May 23; 1(8230):1128-30.

56. Franco AV, Lee F, Fynes MM. Is there an alternative to pad tests? Correlation of subjective variables of severity of urinary loss to the 1-h pad test in women with stress urinary incontinence. BJU Int. 2008; 102(5):589-90.

57. Wijma J, Weis Potters AE, Tinga DJ, Aarnoudse JG. The diagnostic strength of the 24-h pad test for self-reported symptoms of urinary incontinence in pregnancy and after childbirth. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Apr; 19(4):525-30.

58. Twiss CO, Fischer MC, Nitti VW. Comparison between reduction in 24-hour pad weight, International Consultation on Incontinence-Short Form (ICIQ-SF) score, International Prostate Symptom Score (IPSS), and Post-Operative Patient Global Impression of Improvement (PGI-I) score in patient evaluation after male perineal sling. Neurourol Urodyn. 2007; 26(1):8-13.

59. Albo M, Wruck L, Baker J, Brubaker L, Chai T, Dandreo KJ, et al. The relationships among measures of incontinence severity in women undergoing surgery for stress urinary incontinence. J Urol. 2007 May; 177(5):1810-4.

60. Richter HE, Diokno A, Kenton K, Norton P, Albo M, Kraus S, et al. Predictors of treatment failure 24 months after surgery for stress urinary incontinence. J Urol. 2008 Mar; 179(3):1024-30.

61. Foster RT, Sr., Anoia EJ, Webster GD, Amundsen CL. In patients undergoing neuromodulation for intractable urge incontinence a reduction in 24-hr pad weight after the initial test stimulation best predicts long-term patient satisfaction. Neurourol Urodyn. 2007; 26(2):213-7.

62. Dylewski DA, Jamison MG, Borawski KM, Sherman ND, Amundsen CL, Webster GD. A statistical comparison of pad numbers versus pad weights in the quantification of urinary incontinence. Neurourol Urodyn. 2007; 26(1):3-7.

63. Khan KS, Chien PF. Evaluation of the home pad test in the investigation of female urinary incontinence. Br J Obstet Gynaecol. 1996 Jul; 103(7):720.

64. Kromann-Andersen B, Jakobsen H, Thorup Andersen J. Pad-weighing tests: A literature survey on test accuracy and reproducibility. 1989; 8(3):237-42.

65. Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, et al. Systematic review and evaluation of methods of assessing urinary incontinence. Health Technol Assess. 2006 Feb; 10(6):1-132.

66. Leach GE, Dmochowski RR, Appell RA, Blaivas JG, Hadley HR, Luber KM, et al. Female Stress Urinary Incontinence Clinical Guidelines Panel summary report on surgical management of female stress urinary incontinence. The American Urological Association. J Urol. 1997 Sep; 158(3 Pt 1):875-80.

67. Blaivas JG, Appell RA, Fantl JA, Leach G, McGuire EJ, Resnick NM, et al. Standards of efficacy for evaluation of treatment outcomes in urinary incontinence: recommendations of the Urodynamic Society. Neurourol Urodyn. 1997; 16(3):145-7.

E. **NEUROPHYSIOLOGY**

1. Vodušek DB, Amarenco G, Batra A, Benson T, Bharucha AE, Podnar S, Yang CC. Clinical neurophysiology. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. Plymouth (UK): Health Publication Ltd, 2005:675-706.

2. Nandedkar SD, Barkhaus PE, Sanders DB, Stålberg EV. Analysis of amplitude and area of concentric needle EMG motor unit action potentials. Electroencephalogr Clin Neurophysiol 1988a;69:561-7.

3. Podnar S, Mrkaic M, Vodušek DB. Standardization of anal sphincter electromyography: quantification of continuous activity during relaxation. Neurourol Urodyn 2002a;21:540-5.

4. Podnar S, Vodušek DB. Protocol for clinical neurophysiologic examination of the pelvic floor. Neurourol Urodyn 2001;20:669-82.

5. Podnar S, Vodušek DB. Standardisation of anal sphincter EMG: high and low threshold motor units. Clin Neurophysiol 1999;110:1488-91.

6. Podnar S, Vodušek DB, Stålberg E. Comparison of quantitative techniques in anal sphincter electromyography. Muscle Nerve 2002c;25:83-92.

7. Gregory WT, AL Clark, K Simmons, JS Lou. Determining the shape of the turns-amplitude cloud during anal sphincter quantitative EMG. Int Urogynecol J 2008;19:971-6.

8. Stålberg E, Trontelj JV. Single Fiber Electromyography: Studies in Healthy and Diseased Muscle (2nd edition). New York: Raven Press, 1994.

9. Podnar S, Fowler CJ. Sphincter electromyography in diagnosis of multiple system atrophy: technical issues. Muscle Nerve 2004;29:151-6.

10. Podnar S, Oblak C, Vodušek DB. Sexual function in men with cauda equina lesions: a clinical and electromyographic study. J Neurol Neurosurg Psychiatry 2002b;73:715-20.

11. Pino LJ, Stashuk DW, Podnar S. Bayesian characterization of external anal sphincter muscles using quantitative electromyography. Clin Neurophysiol 2008;119:2266-73.

12. Podnar S, Mrkaić M. Predictive power of motor unit potential parameters in anal sphincter electromyography. Muscle Nerve 2002;26:389-94.

13. Podnar S, Rodi Z, Lukanovič A, Tršinar B, Vodušek DB. Standardization of anal sphincter EMG: technique of needle examination. Muscle Nerve 1999;22:400-3.

14. Podnar S, Vodušek DB. Standardization of anal sphincter electromyography: uniformity of the muscle. Muscle Nerve 2000b;23:122-5.

15. Podnar S, Vodušek DB, Stålberg E. Standardization of anal sphincter electromyography: normative data. Clin Neurophysiol 2000b;111:2200-7.

16. Podnar S, Lukanovič A, Vodušek DB. Anal sphincter electromyography after vaginal delivery: neuropathic insufficiency or normal wear and tear? Neurourol Urodyn 2000a;19:249-57.

17. Podnar S, Vodušek DB. Standardization of anal sphincter electromyography: effect of chronic constipation. Muscle Nerve 2000a;23:1748-51.

18. De EJ, Patel CY, Tharian B, et al.: Diagnostic discordance of electromyography (EMG) versus voiding cystourethrogram (VCUG) for detrusor-external sphincter dyssynergy (DESD). Neurourol Urodyn 2005;24:616-21.

19. Stafford RE, Sapsford R, Ashton-Miller J, Hodges PW: A novel transurethral surface electrode to record male striated urethral sphincter electromyographic activity. J Urol 2010;183:378-85.

20. Deindl FM, Vodušek DB, Hesse U, Schussler B. Activity patterns of pubococcygeal muscles in nulliparous continent women. Br J Urol 1993;72:46-51.

21. Podnar S, Barbič M. Non-neurogenic urinary retention (Fowler's syndrome) in two sisters. Neurourol Urodyn 2006;25:739-41; discussion 42-3.

22. Devreese A, Staes F, Janssens L, et al.: Incontinent women have altered pelvic floor muscle contraction patterns. J Urol 2007;178:558-62.

23. Mahajan ST, Fitzgerald MP, Kenton K, Shott S, Brubaker L: Concentric needle electrodes are superior to perineal surface-patch electrodes for electromyographic documentation of urethral sphincter relaxation during voiding. BJU Int 2006;97:117-20.

24. Kirby AC, Nager CW, Litman HJ, Fitzgerald MP, Kraus S, Norton P, Sirls L, Rickey L, Wilson T, Dandreo KJ, Shepherd J, Zimmern P; Urinary Incontinence Treatment Network. Perineal surface electromyography does not typically demonstrate expected relaxation during normal voiding. Neurourol Urodyn 2011;30(8):1591-6.

25. Enck P, Franz H, Davico E, et al.: Repeatability of innervation zone identification in the external anal sphincter muscle. Neurourol Urodyn 2010;29:449-57.

26. Merletti R, Holobar A, Farina D: Analysis of motor units with high-density surface electromyography. J Electromyogr Kinesiol 2008;18:879-90.

27. Cescon C, Bottin A, Fernandez Fraga XL, Azpiroz F, Merletti R: Detection of individual motor units of the puborectalis muscle by non-invasive EMG electrode arrays. J Electromyogr Kinesiol 2008;18:382-9.

28. Podnar S: Which patients need referral for anal sphincter electromyography? Muscle Nerve 2006;33:278-82.

29. Podnar S: Cauda equina lesions as a complication of spinal surgery. Eur Spine J 2010;19:451-7.

30. Podnar S: Epidemiology of cauda equina and conus medullaris lesions. Muscle Nerve 2007;35:529-31.

31. Torre M, Planche D, Louis-Borrione C, et al.: Value of electrophysiological assessment after surgical treatment of spinal dysraphism. J Urol 2002;168:1759-62.

32. Podnar S: Saddle sensation is preserved in a few patients with cauda equina or conus medullaris lesions. Eur J Neurol 2007;14:48-53.

33. Podnar S: Sphincter electromyography and the penilo-cavernosus reflex: are both necessary? Neurourol Urodyn 2008;27:813-8.

34. Podnar S: Clinical and neurophysiologic testing of the penilo-cavernosus reflex. Neurourol Urodyn 2008;27:399-402.

35. Podnar S: Electromyography of the anal sphincter: which muscle to examine? Muscle Nerve 2003;28:377-9.

36. Podnar S, Oblak C, Vodusek DB: Sexual function in men with cauda equina lesions: a clinical and electromyographic study. J Neurol Neurosurg Psychiatry 2002;73:715-20.

37. Podnar S, Vodusek DB, Stalberg E: Comparison of quantitative techniques in anal sphincter electromyography. Muscle Nerve 2002;25:83-92.

38. Hale DS, Benson JT, Brubaker L, Heidkamp MC, Russell B. Histologic analysis of needle biopsy of urethral sphincter from women with normal and stress incontinence with comparison of electromyographic findings. Am J Obstet Gynecol 1999;180:342-8.

39. Eardley I, Quinn NP, Fowler CJ, Kirby RS, Parkhouse HF, Marsden CD, Bannister R. The value of urethral sphincter electromyography in the differential diagnosis of parkinsonism. Br J Urol 1989;64:360-2.

40. Beck RO, Betts CD, Fowler CJ. Genitourinary dysfunction in multiple system atrophy: clinical features and treatment in 62 cases. J Urol 1994;151:1336-41.

41. Stocchi F, Carbone A, Inghilleri M, et al.: Urodynamic and neurophysiological evaluation in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry 1997;62:507-11.

42. Yamamoto T, Sakakibara R, Uchiyama T, et al.: When is Onuf's nucleus involved in multiple system atrophy? A sphincter electromyography study. J Neurol Neurosurg Psychiatry 2005;76:1645-8.

43. Libelius R, Johansson F: Quantitative electromyography of the external anal sphincter in Parkinson's disease and multiple system atrophy. Muscle Nerve 2000;23:1250-6.

44. Paviour DC, Williams D, Fowler CJ, Quinn NP, Lees AJ: Is sphincter electromyography a helpful investigation in the diagnosis of multiple system atrophy? A

retrospective study with pathological diagnosis. Mov Disord 2005;20:1425-30.

45. Schwarz J, Kornhuber M, Bischoff C, Straube A: Electromyography of the external anal sphincter in patients with Parkinson's disease and multiple system atrophy: frequency of abnormal spontaneous activity and polyphasic motor unit potentials. Muscle Nerve 1997;20:1167-72.

46. Giladi N, Simon ES, Korczyn AD, et al.: Anal sphincter EMG does not distinguish between multiple system atrophy and Parkinson's disease. Muscle Nerve 2000;23:731-4.

47. Vodušek DB. Sphincter EMG and differential diagnosis of multiple system atrophy. Mov Disord 2001;16:600-7.

48. Valldeoriola F, Valls-Sole J, Tolosa ES, Marti MJ: Striated anal sphincter denervation in patients with progressive supranuclear palsy. Mov Disord 1995;10:550-5.

49. Winge K, Jennum P, Lokkegaard A, Werdelin L: Anal sphincter EMG in the diagnosis of parkinsonian syndromes. Acta Neurol Scand 2010;121:198-203.

50. Shimizu H, Yamada M, Toyoshima Y, et al.: Involvement of Onuf's nucleus in Machado-Joseph disease: a morphometric and immunohistochemical study. Acta Neuropathol 2010;120:439-48.

51. Scaravilli T, Pramstaller PP, Salerno A, et al.: Neuronal loss in Onuf's nucleus in three patients with progressive supranuclear palsy. Ann Neurol 2000;48:97-101.

52. Sakakibara R, Uchiyama T, Asahina M, Suzuki A, Yamanishi T, Hattori T. Micturition disturbance in acute idiopathic autonomic neuropathy. J Neurol Neurosurg Psychiatry 2004;75:287-91.

53. Dixon PJ, Christmas TJ, Chapple CR. Stress incontinence due to pelvic floor muscle involvement in limb-girdle muscular dystrophy. Br J Urol 1990;65:653-4.

54. Herbaut AG, Nogueira MC, Panzer JM, Zegers de Beyl D. Anorectal incontinence in myotonic dystrophy: a myopathic involvement of pelvic floor muscles. Muscle Nerve 1992;15:1210-1.

55. Caress JB, Kothari MJ, Bauer SB, Shefner JM. Urinary dysfunction in Duchenne muscular dystrophy. Muscle Nerve 1996;19:819-22.

56. Snooks SJ, Setchell M, Swash M, Henry MM. Injury to innervation of pelvic floor sphincter musculature in childbirth. Lancet 1984;2:546-50.

57. Smith AR, Hosker GL, Warrell DW. The role of partial denervation of the pelvic floor in the aetiology of genitourinary prolapse and stress incontinence of urine. A neurophysiological study. Br J Obstet Gynaecol 1989;96:24-8.

58. Kenton K, Mueller E, Brubaker L. Continent women have better urethral neuromuscular function than those with stress incontinence. Int Urogynecol J 2011;22:1479-84.

59. Jundt K, Kiening M, Fischer P, Bergauer F, Rauch E, Janni W, Peschers U, Dimpfl T. Is the histomorphological concept of the female pelvic floor and its changes due to age and vaginal delivery correct? Neurourol Urodyn 2005;24:44-50.

60. Takahashi S, Homma Y, Fujishiro T, Hosaka Y, Kitamura T, Kawabe K. Electromyographic study of the striated urethral sphincter in type 3 stress incontinence: evidence of myogenicdominant damages. Urology 2000;56:946-50.

61. Vodušek DB. The role of electrophysiology in the evaluation of incontinence and prolapse. Curr Opin Obstet Gynecol 2002;14:509-14.

62. Gregory WT, Lou JS, Simmons K, Clark AL: Quantitative anal sphincter electromyography in primiparous women with anal incontinence. Am J Obstet Gynecol 2008;198:550.e1-6.

63. Fowler CJ, Christmas TJ, Chapple CR, Parkhouse HF, Kirby RS, Jacobs HS. Abnormal electromyographic activity of the urethral sphincter, voiding dysfunction, and polycystic ovaries: a new syndrome? Br Med J 1988;297:1436-8.

64. Deindl FM, Bischoff C, Vodušek DB, Hartung C. Two different forms of dysfunctional voiding in women: predominance of the pelvic floor or the external urethral sphincter? Neurourol Urodynam 1996;15:358.

65. De Ridder D, Ost D, Bruyninckx F: The presence of Fowler's syndrome predicts successful long-term outcome of sacral nerve stimulation in women with urinary retention. Eur Urol 2007;51:229-33.

66. Amarenco G, Raibaut P, Ismael SS, Rene-Corail P, Haab F: Evidence of occult dysautonomia in Fowler's syndrome: alteration of cardiovascular autonomic function tests in female patients presenting with urinary retention. BJU Int 2006;97:288-91.

67. FitzGerald MP, Blazek B, Brubaker L. Complex repetitive discharges during urethral sphincter EMG: clinical correlates. Neurourol Urodyn 2000;19:577-83.

68. Blaivas JG, Zayed AA, Labib KB. The bulbocavernosus reflex in urology: a prospective study of 299 patients. J Urol 1981;126:197-9.

69. Rudy DC, Woodside JR. Non-neurogenic neurogenic bladder: The relationship between intravesical pressure and the external sphincter electromyogram. Neurourol Urodyn 1991;10:169.

70. Deindl FM, Vodušek DB, Hesse U, Schussler B. Pelvic floor activity patterns: comparison of nulliparous continent and parous urinary stress incontinent women. A kinesiological EMG study. Br J Urol 1994;73:413-7.

71. Chantraine A, de Leval J, Depireux P. Adult female intra- and periurethral sphinctreelectromyographic study. Neurourol Urodyn 1990;9:139-44.

72. Kenton K, Brubaker L. Relationship between levator ani contraction and motor unit activation in the urethral sphincter. Am J Obstet Gynecol 2002;187:403-6.

73. Kenton K, FitzGerald MP, Shott S, Brubaker L. Role of urethral electromyography in predicting outcome of Burch retropubic urethropexy. Am J Obstet Gynecol 2001;185:51-5.

74. Fucini C, Ronchi 0, Elbetti C. Electromyography of the pelvic floor musculature in the assessment of obstructed defecation symptoms. Dis Colon Rectum 2001;44:1168-75.

75. Kiff ES, Swash M. Normal proximal and delayed distal conduction in the pudendal nerves of patients with idiopathic (neurogenic) faecal incontinence. J Neurol Neurosurg Psychiatry 1984;47:820-3.

76. Cavalcanti GA, Manzano GM, Giuliano LM, et al.: Pudendal nerve latency time in normal women via intravaginal stimulation. Int Braz J Urol 2006;32:705-11.

77. Lefaucheur J, Yiou R, Thomas C: Pudendal nerve terminal motor latency: age effects and technical considerations. Clin Neurophysiol 2001;112:472-6.

78. Liberman H, Faria J, Tement CA, Blatchford GJ, Christensen MA, Thorson AG. A prospective evaluation of the value of anorectal physiology in the management of fecal incontinence. Dis Colon Rectum 2001;44:1567-74.

79. AGA. American Gastroenterological Association medical position statement on anorectal testing techniques. Gastroenterology 1999;116:732-60.

80. Ertekin C, Mungan B. Sacral spinal cord and root potentials evoked by the stimulation of the dorsal nerve of penis and cord conduction delay for the bulbocavernosus reflex. Neurourol Urodyn 1993;12:9-22.

81. Sato T, Nagai H. POudendal nerve "complete" motor latencies at four different levels in the anal sphincter system in young adults. Dis Colon Rectum 2002;45:923-7.

82. Lefaucheur JP: Intrarectal ground electrode improves the reliability of motor evoked potentials recorded in the anal sphincter. Muscle Nerve 2005;32:110-2.

83. Pelliccioni G, Scarpino O: External anal sphincter responses after S3 spinal root surface electrical stimulation. Neurourol Urodyn 2006;25:788-91.

84. Brostrom S, Jennum P, Lose G. Motor evoked potentials from the striated urethral sphincter and puborectal muscle: normative values. Neurourol Urodyn 2003a;22:306-13.

85. Opsomer RJ, Caramia MD, Zarola F, Pesce F, Rossini PM: Neurophysiological evaluation of central-peripheral sensory and motor pudendal fibres. Electroencephalogr Clin Neurophysiol 1989;74:260-70.

86. Brostrom S: Motor evoked potentials from the pelvic floor. Neurourol Urodyn 2003;22:620-37.

87. Schmid DM, Curt A, Hauri D, Schurch B: Motor evoked potentials (MEP) and evoked pressure curves (EPC) from the urethral compressive musculature (UCM) by functional magnetic stimulation in healthy volunteers and patients with neurogenic incontinence. Neurourol Urodyn 2005;24:117-27.

88. Brostrom S, Jennum P, Lose G. Motor evoked potentials from the striated urethral sphincter: a comparison of concentric needle and surface electrodes. Neurourol Urodyn 2003b;22:123-9.

89. Eardley I, Nagendran K, Lecky B, Chapple CR, Kirby RS, Fowler CJ. Neurophysiology of the striated urethral sphincter in multiple sclerosis. Br J Urol 1991;68:81-8.

90. Lefaucheur J-P. Excitability of the motor cortical representation of the external anal sphincter. Exp Brain Res 2005;160:268-72.

91. Wyndaele JJ, Van Eetvelde B, Callens D. Comparison in young healthy volunteers of 3 different parameters of constant current stimulation used to determine sensory thresholds in the lower urinary tract. J Urol 1996;156:1415-7.

92. Gillman GS, Schaitkin BM, May M, Klein SR. Bell's palsy in pregnancy: a study of recovery outcomes. Otolaryngol Head Neck Surg 2002;126:26-30.

93. Fitzgerald MP, Koch D, Senka J: Visceral and cutaneous sensory testing in patients with painful bladder syndrome. Neurourol Urodyn 2005;24:627-32.

94. Reitz A, Schmid DM, Curt A, et al.: Electrophysiological assessment of sensations arising from the bladder: are there objective criteria for subjective perceptions? J Urol 2003;169:190-4.

95. Law NM, Bharucha AE, Undale AS, Zinsmeister AR. Cholinergic stimulation enhances colonic motor activity, transit and sensation in humans. Am J Physiol Gastrointestinal and Liver Physiology 2001;281:G1228-37.

96. Sun WM, Read NW, Prior A, Daly JA, Cheah SK, Grundy D. Sensory and motor responses to rectal distention vary according to rate and pattern of balloon inflation. Gastroenterology 1990;99:1008-15.

97. Salvioli B, Bharucha AE, Rath-Harvey D, Pemberton JH, Phillips SF. Rectal compliance, capacity, and rectoanal sensation in fecal incontinence. Am J Gastroenterol 2001;96:2158-68.

98. Ganzer H, Madersbacher H, Rumpl E. Cortical evoked potentials by stimulation of the vesicourethral junction: clinical value and neurophysiological considerations. J Urol 1991;146:118-23.

99. Gerstenberg TC, Klarskov P, Hald T. Pudendal somatosensory, urethral and bladder wall evoked potentials in normals. Proceedings of ICS, 1982. pp 150-77.

100. Schmid DM, Reitz A, Curt A, Hauri D, Schurch B. Urethral evoked Sympathetic Skin Responses (SSR) and Viscerosensory Evoked Potentials (VSEP) as a diagnostic tool to evaluate urogenital autonomic afferent innervation in spinal cord injured patients. J Urol 2004;171:1156-60.

101. Vodušek DB, Deletis V, Abbott R, Epstein FJ, Turndorf HH. Intraoperative monitoring of pudendal nerve function. In: Rother M, Zwiener U, editors. Quantitative EEG Analysis – Clinical Utility and New Methods. Jena: Universitätsverlag Jena, 1993:309-12.

102. Huang JC, Deletis V, Vodušek DB, Abbott R. Preservation of pudendal afferents in sacral rhizotomies. Neurosurgery 1997; 41(2): 411-5.

103. Vodušek DB. Pudendal SEP and bulbocavernosus reflex in women. Electroencephalogr Clin Neurophysiol 1990a;77:134-6.

104. Yang CC, Bowen JR, Kraft GH. Cortical evoked potentials of the dorsal nerve of the clitoris and female sexual dysfunction in multiple sclerosis. J Uro1 2000;164:2010.

105. Sau G, Siracusano S, Aiello I, d'Aloia G, Liguori G, Stener S, Lissiani A, Belgrano E. The usefulness of the Somatosensory evoked potentials of the pudendal nerve in diagnosis of probable multiple sclerosis. Spinal Cord 1999;37:258-63.

106. Rodi Z, Vodušek DB, Denišlič M. Clinical uro-neurophysiological investigation in multiple sclerosis. Eur J Neurol 1996b;3:574-80.

107. Delodovici ML, Fowler CJ. Clinical value of the pudendal somatosensory evoked potential. Electroencephalogr Clin Neurophysiol 1995;96:509-15.

108. Curt A, Rodic B, Schurch B, Dietz V. Recovery of bladder function in patients with acute spinal cord injury: significance of ASIA scores and somatosensory evoked potentials. Spinal Cord 1997;35:368-73.

109. Malaguti S, Spinelli M, Giardiello G, Lazzeri M, Van Den Hombergh U. Neurophysiological evidence may predict the outcome of sacral neuromodulation. J Urol 2003;170:2323-6.

110. Podnar S: Nomenclature of the electrophysiologically tested sacral reflexes. Neurourol Urodyn 2006;25:95-7.

111. Vodusek DB, Janko M, Lokar J: Direct and reflex responses in perineal muscles on electrical stimulation. J Neurol Neurosurg Psychiatry 1983;46:67-71.

112. Vodušek DB, Janko M. The bulbocavernosus reflex – a single motor neuron study. Brain 1990;113(III):813-20.

113. Hanson P, Rigaux P, Gilliard C, Biset E: Sacral reflex latencies in tethered cord syndrome. Am J Phys Med Rehabil 1993;72:39-43.

114. Amarenco G, Kerdraon J: Clinical value of ipsi- and contralateral sacral reflex latency measurement: a normative data study in man. Neurourol Urodyn 2000;19:565-76.

115. Amarenco G, Bayle B, Ismael SS, Kerdraon J: Bulbocavernosus muscle responses after suprapubic stimulation: analysis and measurement of suprapubic bulbocavernosus reflex latency. Neurourol Urodyn 2002;21:210-3.

116. Amarenco G, Ismael SS, Bayle B, Kerdraon J: Dissociation between electrical and mechanical bulbocavernosus reflexes. Neurourol Urodyn 2003;22:676-80.

117. Podnar S: Neurophysiologic studies of the penilocavernosus reflex: Normative data. Neurourol Urodyn 2007a;26:864-9.

118. Podnar S: The penilo-cavernosus reflex: Comparison of different stimulation techniques. Neurourol Urodyn 2007b;27:244-8.

119. Podnar S, Vodušek DB, Tršinar B, Rodi Z. A method of uroneurophysiological investigation in children. Electroenceph Clin Neurophysiol 1997;104:389-92.

120. Loening-Baucke V, Read NW, Yamada T, Barker AT: Evaluation of the motor and sensory components of the pudendal nerve. Electroencephalogr Clin Neurophysiol 1994;93:35-41.

121. Hansen MV, Ertekin C, Larsson LE: Cerebral evoked potentials after stimulation of the posterior urethra in man. Electroencephalogr Clin Neurophysiol 1990;77:52-8.

122. Benson JT. Clinical neurophysiologic techniques in urinary and fecal incontinence. In: Bent AE, editor. Ostergaard's Urogynecology and Pelvic Floor Dysfunction. 5 ed. Philadelphia: Lippincott Williams & Wilkins, 2003:71.

123. Wester C, FitzGerald MP, Brubaker L, Welgoss J, Benson JT. Validation of the clinical bulbocavernosus reflex. Neurourol Urodynam 2003;22:589-92.

124. Podnar S. Neurophysiologic studies of the sacral reflex in women with "non-neurogenic" sacral dysfunction.Neurourol Urodyn 2011;30:1603-8.

125. Rodi Z, Vodušek DB. Intraoperative monitoring of the bulbocavernosus reflex: the method and its problems. Clin Neurophysiol 2001;112:879-83.

126. Yilmaz U, Yang CC, Berger RE: Dartos reflex: a sympathetically mediated scrotal reflex. Muscle Nerve 2006;33:363-8.

127. Secil Y, Ozdedeli K, Altay B, et al.: Sympathetic skin response recorded from the genital region in normal and diabetic women. Neurophysiol Clin 2005;35:11-7.

128. Rodic B, Curt A, Dietz V, Schurch B. Bladder neck incompetence in patients with spinal cord injury: significance of sympathetic skin response. J Urol 2000;163:1223-7.

129. McLennan MT. The role of electrodiagnostic techniques in the reprogramming of patients with a delayed suboptimal response to sacral nerve stimulation. Int Urogynecol J Pelvic Floor Dysfunct 2003;14:98-103.

F. OTHER INESTIGATIONS

F.I. Urinalysis

1. Nitti VW, Blaivas JGUie, pathophysiology, evaluation, and management overview. . Urinary incontinence: epidemiology, pathophysiology, evaluation, and management overview. . In: Wein JA, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh Urology. 9th ed: Elsevier; 2007.

2. Tubaro A, Artibani W, Bartram C, Delancey JD, Dietz HP, Khullar V, et al. Imaging and other investigations. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence - 3rd International Consultation on Incontinence. Plymouth: Health Publication Ltd; 2005. p. 707-97.

3. Ouslander JG, Schapira M, Schnelle JF, Fingold S. Pyuria among chronically incontinent but otherwise asymptomatic nursing home residents. J Am Geriatr Soc. 1996 Apr;44(4):420-3.

4. Sandvik H, Hunskaar S. General practitioners' management of female urinary incontinence. Medical records do not reflect patients' recall. Scand J Prim Health Care. 1995 Sep;13(3):168-74.

5. Kennedy KL, Steidle CP, Letizia TM. Urinary incontinence: the basics. Ostomy Wound Manage. 1995 Aug;41(7):16-8, 20, 2 passim; quiz 33-4.

6. Stricker PD. Proper patient selection for Contigen Bard Collagen implant. Int J Urol. 1995 Apr;2 Suppl 1:2-6; discussion 16-8.

7. Stein M, Discippio W, Davia M, Taub H. Biofeedback for the treatment of stress and urge incontinence. J Urol. 1995 Mar;153(3 Pt 1):641-3.

8. Ouslander JG, Schnelle JF. Incontinence in the nursing home. Ann Intern Med. 1995 Mar 15;122(6):438-49.

9. Young SB, Pingeton DM. A practical approach to perimenopausal and postmenopausal urinary incontinence. Obstet Gynecol Clin North Am. 1994 Jun;21(2):357-79.

10. McIntosh LJ, Richardson DA. 30-minute evaluation of incontinence in the older woman. Geriatrics. 1994 Feb;49(2):35-8, 43-4.

11. Midthun SJ, Paur RA, Lindseth G, Von Duvillard SP. Bacteriuria detection with a urine dipstick applied to incontinence pads of nursing home residents. Geriatr Nurs. 2003 Jul-Aug;24(4):206-9.

12. Ouslander JG. Geriatric urinary incontinence. Dis Mon. 1992 Feb;38(2):65-149.

13. DuBeau CE, Resnick NM. Evaluation of the causes and severity of geriatric incontinence. A critical appraisal. Urol Clin North Am. 1991 May;18(2):243-56.

F.II. Blood tests

1. Rittig S, Knudsen UB, Norgaard JP, Pedersen EB, Djurhuus JC. Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. Am J Physiol. 1989 Apr;256(4 Pt 2):F664-71.

2. Matthiesen TB, Rittig S, Norgaard JP, Pedersen EB, Djurhuus JC. Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. J Urol. 1996 Oct;156(4):1292-9.

F.III. Tissue analysis

1. Wen Y, Zhao YY, Li S, Polan ML, Chen BH. Differences in mRNA and protein expression of small proteoglycans in vaginal wall tissue from women with and without stress urinary incontinence. Hum Reprod. 2007 Jun;22(6):1718-24.

2. Chung da J, Bai SW. Roles of sex steroid receptors and cell cycle regulation in pathogenesis of pelvic organ prolapse. Curr Opin Obstet Gynecol. 2006 Oct;18(5):551-4.

3. Levens E, Luo X, Ding L, Williams RS, Chegini N. Fibromodulin is expressed in leiomyoma and myometrium and regulated by gonadotropin-releasing hormone analogue therapy and TGF-beta through Smad and MAPK-mediated signalling. Mol Hum Reprod. 2005 Jul;11(7):489-94.

4. Chen Y, DeSautel M, Anderson A, Badlani G, Kushner L. Collagen synthesis is not altered in women with stress urinary incontinence. Neurourol Urodyn. 2004;23(4):367-73.

5. Keane DP, Sims TJ, Abrams P, Bailey AJ. Analysis of collagen status in premenopausal nulliparous women with genuine stress incontinence. Br J Obstet Gynaecol. 1997 Sep;104(9):994-8.

6. Rechberger T, Postawski K, Jakowicki JA, Gunja-Smith Z, Woessner JF, Jr. Role of fascial collagen in stress urinary incontinence. Am J Obstet Gynecol. 1998 Dec;179(6 Pt 1):1511-4.

7. Liapis A, Bakas P, Pafiti A, Frangos-Plemenos M, Arnoyannaki N, Creatsas G. Changes of collagen type III in female patients with genuine stress incontinence and pelvic floor prolapse. Eur J Obstet Gynecol Reprod Biol. 2001 Jul;97(1):76-9.

8. Falconer C, Ekman-Ordeberg G, Blomgren B, Johansson O, Ulmsten U, Westergren-Thorsson G, et al. Paraurethral connective tissue in stress-incontinent women after menopause. Acta Obstet Gynecol Scand. 1998 Jan;77(1):95-100.

9. Bakas PG, Liapis AE, Zervolea I, Voutsinas G, Kletsas D, Creatsas G. mRNA assessment for procollagen production in women with genuine stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2004 Nov-Dec;15(6):429-31; discussion 31.

10. Gabriel B, Denschlag D, Gobel H, Fittkow C, Werner M, Gitsch G, et al. Uterosacral ligament in postmenopausal women with or without pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2005 Nov-Dec;16(6):475-9.

11. Skorupski P, Krol J, Starega J, Adamiak A, Jankiewicz

K, Rechberger T. An alpha-1 chain of type I collagen Sp1-binding site polymorphism in women suffering from stress urinary incontinence. Am J Obstet Gynecol. 2006 Feb;194(2):346-50.

12. Edwall L, Carlstrom K, Jonasson AF. Markers of collagen synthesis and degradation in urogenital tissue from women with and without stress urinary incontinence. Neurourol Urodyn. 2005;24(4):319-24.
13. Koslowski R, Seidel D, Kuhlisch E, Knoch KP. Evidence for the involvement of TGF-beta and PDGF in the regulation of prolyl 4-hydroxylase and lysyloxidase in cultured rat lung fibroblasts. Exp Toxicol Pathol. 2003 Nov;55(4):257-64.
14. Arendt E, Ueberham U, Bittner R, Gebhardt R, Ueberham E. Enhanced matrix degradation after withdrawal of TGF-beta1 triggers hepatocytes from apoptosis to proliferation and regeneration. Cell Prolif. 2005 Oct;38(5):287-99.
15. Suzme R, Yalcin O, Gurdol F, Gungor F, Bilir A. Connective tissue alterations in women with pelvic organ prolapse and urinary incontinence. Acta Obstet Gynecol Scand. 2007;86(7):882-8.
16. Connell KA, Guess MK, Chen H, Andikyan V, Bercik R, Taylor HS. HOXA11 is critical for development and maintenance of uterosacral ligaments and deficient in pelvic prolapse. J Clin Invest. 2008 Mar;118(3):1050-5.
17. Chen B, Wen Y, Polan ML. Elastolytic activity in women with stress urinary incontinence and pelvic organ prolapse. Neurourol Urodyn. 2004;23(2):119-26.
18. Gabriel B, Watermann D, Hancke K, Gitsch G, Werner M, Tempfer C, et al. Increased expression of matrix metalloproteinase 2 in uterosacral ligaments is associated with pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Sep;17(5):478-82.
19. Cox DA, Helvering LM. Extracellular matrix integrity: a possible mechanism for differential clinical effects among selective estrogen receptor modulators and estrogens? Mol Cell Endocrinol. 2006 Mar 9;247(1-2):53-9.
20. McDonnell DP. The molecular determinants of estrogen receptor pharmacology. Maturitas. 2004 Aug 30;48 Suppl 1:S7-12.
21. Goldstein SR, Nanavati N. Adverse events that are associated with the selective estrogen receptor modulator levormeloxifene in an aborted phase III osteoporosis treatment study. Am J Obstet Gynecol. 2002 Sep;187(3):521-7.

Committee 8

Pharmacological Treatment of Urinary Incontinence

Chair

Karl-Erik Andersson (USA)

Members

Christopher R Chapple, (UK)

Linda Cardozo, (UK)

Francisco Cruz, (Portugal)

Christian Gratzke, (Germany)

Kyu-Sung Lee, (Korea)

Cara Tannenbaum, (Canada)

Alan J Wein (USA)

CONTENTS

A. Introduction

I. PUBLICATION SEARCHES

II. CENTRAL NERVOUS CONTROL

III. PERIPHERAL NERVOUS CONTROL

IV. PATHOGENESIS OF BLADDER CONTROL DISORDERS

V. BLADDER CONTRACTION

VI. MUSCARINIC RECEPTORS

B. Drugs used for treatment of overactive bladder symptoms/ detrusor overactivity

I. ANTIMUSCARINIC (ANTICHOLINERGIC) DRUGS

II. DRUGS ACTING ON MEMBRANE CHANNELS

III. α-ADRENOCEPTOR (AR) ANTAGONISTS

IV. β-ADRENOCEPTOR AGONISTS

V. PHOSPHODIESTERASE (PDE) INHIBITORS

VI. ANTIDEPRESSANTS

VII. CYCLOOXYGENASE (COX) INHIBITORS

VIII. TOXINS

IX. OTHER DRUGS

X. COMBINATIONS

XI. FUTURE POSSIBILITIES

C. Drugs used for treatment of stress incontinence in women

I. α-ADRENOCEPTOR AGONISTS

II. β-ADRENOCEPTOR AGONISTS

III. β–ADRENOCEPTOR ANTAGONISTS

IV. SEROTONIN-NORADRENALINE UPTAKE INHIBITORS

D. Stress urinary incontinence in men

E. Drugs to treat overflow incontinence/acute urinary retention

F. Hormonal treatment of urinary incontinence

I. OESTROGENS

II. OTHER HORMONES

III. DESMOPRESSIN

G. Considerations in the Elderly

I. ANTIMUSCARINIC AGENTS

II. DESMOPRESSIN – EFFICACY AND SAFETY IN THE ELDERLY

III. BOTULINUM TOXIN A IN OLDER ADULTS

IV. OTHER

REFERENCES

Pharmacological Treatment of Urinary Incontinence

Karl-Erik Andersson

Christopher R Chapple, Linda Cardozo, Francisco Cruz, Christian Gratzke, Kyu-Sung Lee, Cara Tannenbaum, Alan J Wein

A. Introduction

The function of the lower urinary tract (LUT) is to store and periodically release urine, and is dependent on the activity of smooth and striated muscles in the bladder, urethra, and pelvic floor. These structures form a functional unit, which is controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors [Andersson, 1993; de Groat and Yoshimura, 2001; Andersson and Wein, 2004; see, Andersson and Michel., 2011]. Malfunction at various levels may result in bladder control disorders, which roughly can be classified as disturbances of filling/storage or disturbances of voiding/emptying. Failure to store urine may lead to various forms of incontinence (mainly urgency and stress incontinence), and failure to empty can lead to urinary retention, which may result in overflow incontinence. A disturbed filling/storage function can, at least theoretically, be improved by agents decreasing detrusor activity, increasing bladder capacity, and/or increasing outlet resistance [Wein, 2012].

Many drugs have been tried, but the results are often disappointing, partly due to poor treatment efficacy and/or side effects. The development of pharmacologic treatment of the different forms of urinary incontinence has been slow, but several promising targets and drug principles have been identified [Andersson 2007; 2011c; Colli et al., 2007; Athanasopoulos and Cruz, 2011].

In this report, we update the recommendations from the 2008 International Consensus meeting [Andersson et al., 2009]. The most relevant information obtained since the last meeting is briefly reviewed and summarised. Agents specifically used for treatment of urinary tract infections and interstitial cystitis, have not been included. Our clinical drug recommendations are based on evaluations made using a modification of the Oxford system (**Table 1**). The terminology used is that recommended by the International Continence Society (ICS) [Abrams et al., 2002].

I. PUBLICATION SEARCHES

The review undertook a comprehensive search of all major literature databases and the abstract books from several major conferences: American Urological Association, ICS, European Association of Urology, International Urogynaecological Association, International Consultation of Incontinence and Societe Internationale d'Urologie. There were no restrictions on the inclusion of publications by

Table 1. ICI assessments 2008: Oxford guidelines (modified)

Levels of evidence

Level 1: Systematic reviews, meta-analyses, good quality randomized controlled clinical trials (RCTs)
Level 2: RCTs, good quality prospective cohort studies
Level 3: Case-control studies, case series
Level 4: Expert opinion

Grades of recommendation

Grade A: Based on level 1 evidence (highly recommended)
Grade B: Consistent level 2 or 3 evidence (recommended)
Grade C: Level 4 studies or "majority evidence"(optional)
Grade D: Evidence inconsistent/inconclusive (no recommendation possible) or the evidence indicates that the drug should not be recommended

language; publications in languages other than English were translated into English.

II. CENTRAL NERVOUS CONTROL

In the adult individual, the normal micturition reflex is mediated by a spinobulbospinal pathway, which passes through relay centers in the brain (**Figures1-4**). In infants, the central pathways seem to be organized as on-off switching circuits, but after the age of four to six years, voiding is initiated voluntarily by the cerebral cortex [de Groat et al., 1999; Beckel and Holstege, 2011]. Studies in humans and animals have identified areas in the brainstem and diencephalon (**Figure 5**) that are specifically implicated in micturition control, including Barrington's nucleus or the pontine micturition center (PMC) in the dorsomedial pontine tegmentum [Fowler et al., 2008]. These structures directly excite bladder motoneurons and indirectly inhibit urethral sphincter motoneurons via inhibitory interneurons in the medial sacral cord. The periaqueductal grey (PAG) receives bladder filling information, and the pre-optic area of the hypothalamus is probably involved in the initiation of micturition. According to PET-scan and functional imaging studies in humans, these supraspinal regions are active during micturition [Blok et al., 1998; Nour et al., 2000; Athwal et al., 2001; Griffiths et al., 2007; 2008; Hruz et al., 2008; Mehnert et al., 2008; Tadic et al., 2008; Griffiths, 2011].

III. PERIPHERAL NERVOUS CONTROL

Bladder emptying and urine storage involve a complex pattern of efferent and afferent signalling in ***parasympathetic***, sympathetic, somatic, and sensory nerves. These nerves are parts of reflex pathways, which either keep the bladder in a non-contracted state, enabling urine storage at low intravesical pressure, or which initiate micturition by relaxing the outflow region and contracting the bladder smooth muscle. Contraction of the detrusor smooth muscle and relaxation of the outflow region result from activation of parasympathetic neurones located in the sacral parasympathetic nucleus (SPN) in the spinal cord at the level of S2-S4 [de Groat et al., 1993; Beckel and Holstege, 2011]. The postganglionic neurones in the pelvic nerve mediate the excitatory input to the human detrusor smooth muscle by releasing acetylcholine (ACh) acting on muscarinic receptors. However, an atropine-resistant component has been demonstrated, particularly in functionally and morphologically altered human bladder tissue (see below). The pelvic nerve also conveys parasympathetic fibres to the outflow region and the urethra. These fibres exert an inhibitory effect and thereby relax the outflow region. This is mediated partly by release of nitric oxide [Andersson and Persson, 1993], although other transmitters might be involved [Bridgewater and Brading, 1993; Hashimoto et al., 1993; Werkström et al., 1995].

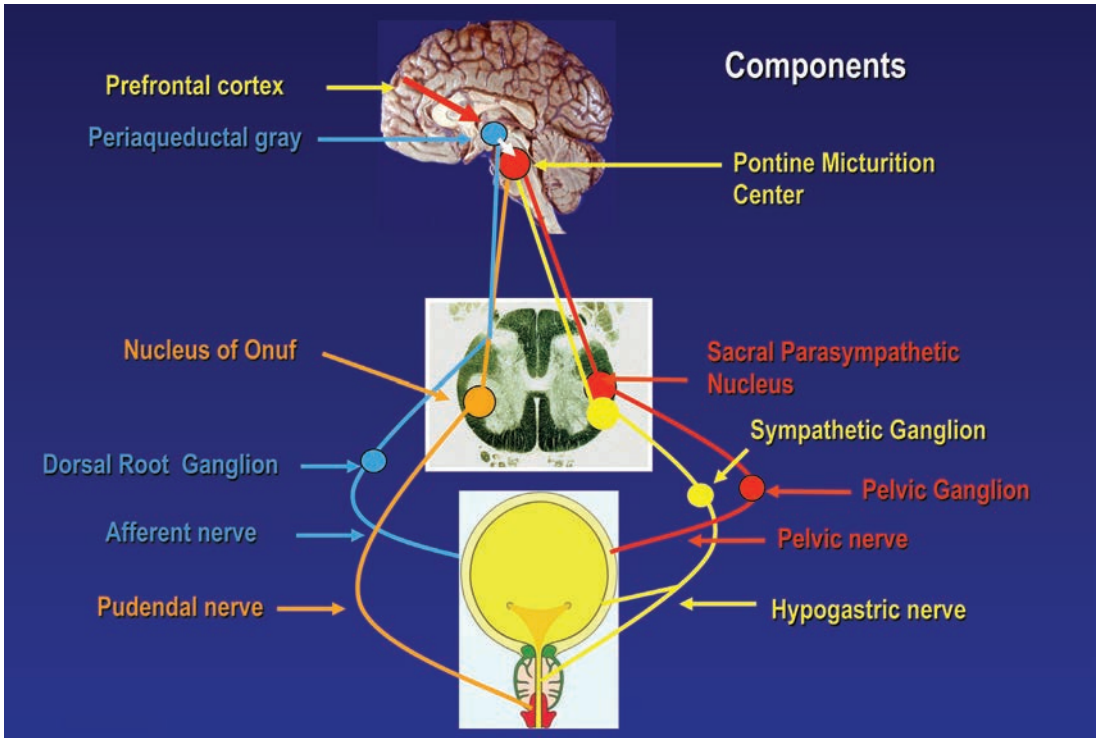


Figure 1 : Components of the micturition reflex.

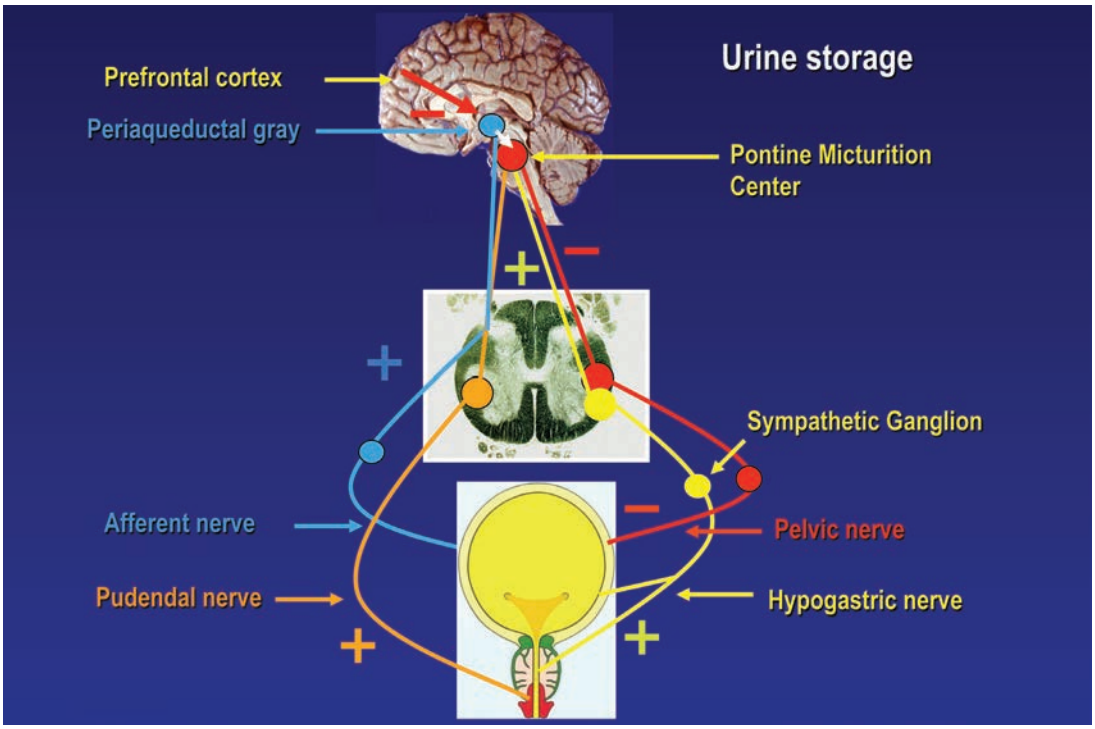


Figure 2 : Activity in the micturition reflex during storage. The pontine micturition center is inhibited by impulses from the prefrontal cortex, afferent impulses unable to initiate micturition. Activities in the hypogastric and pudendal nerves keep the bladder relaxed and the outflow region contracted.

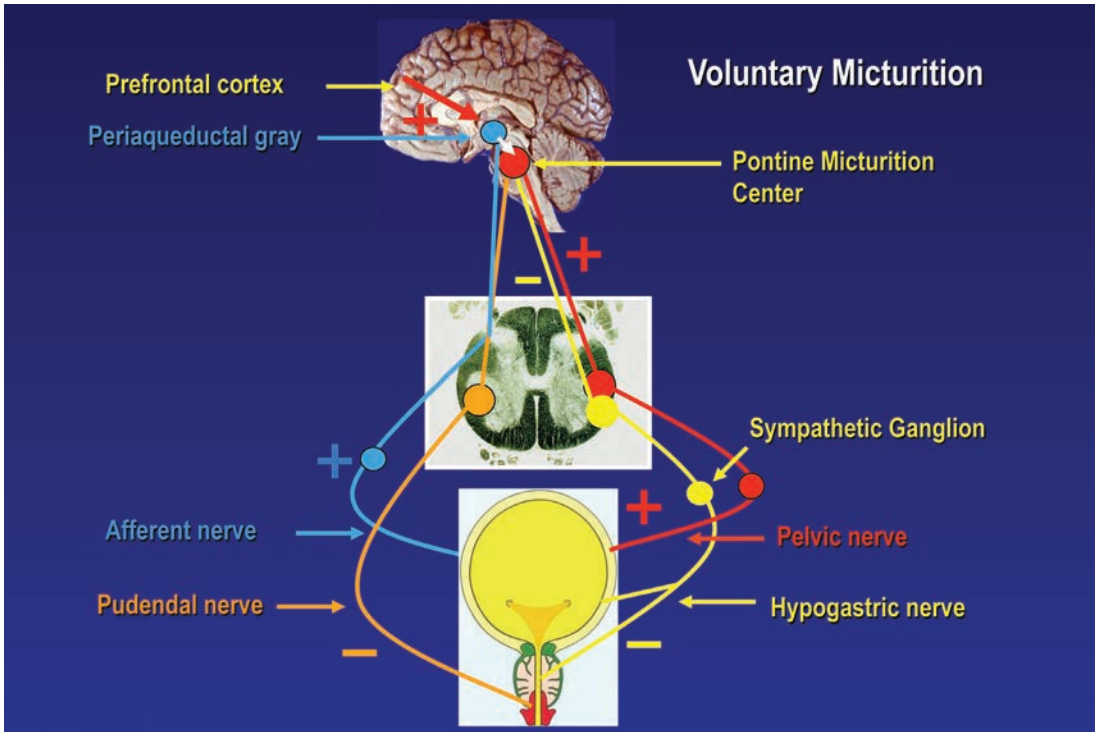


Figure 3 : Activity in the micturition reflex during voluntary voiding. The inhibitory impulses from the prefrontal cortex pontine micturition center are removed and afferent impulses are able to initiate micturition. Activities in the hypogastric and pudendal nerves are inhibited, the outflow region is relaxed, and the bladder is contracted by the activity in the pelvic nerve.

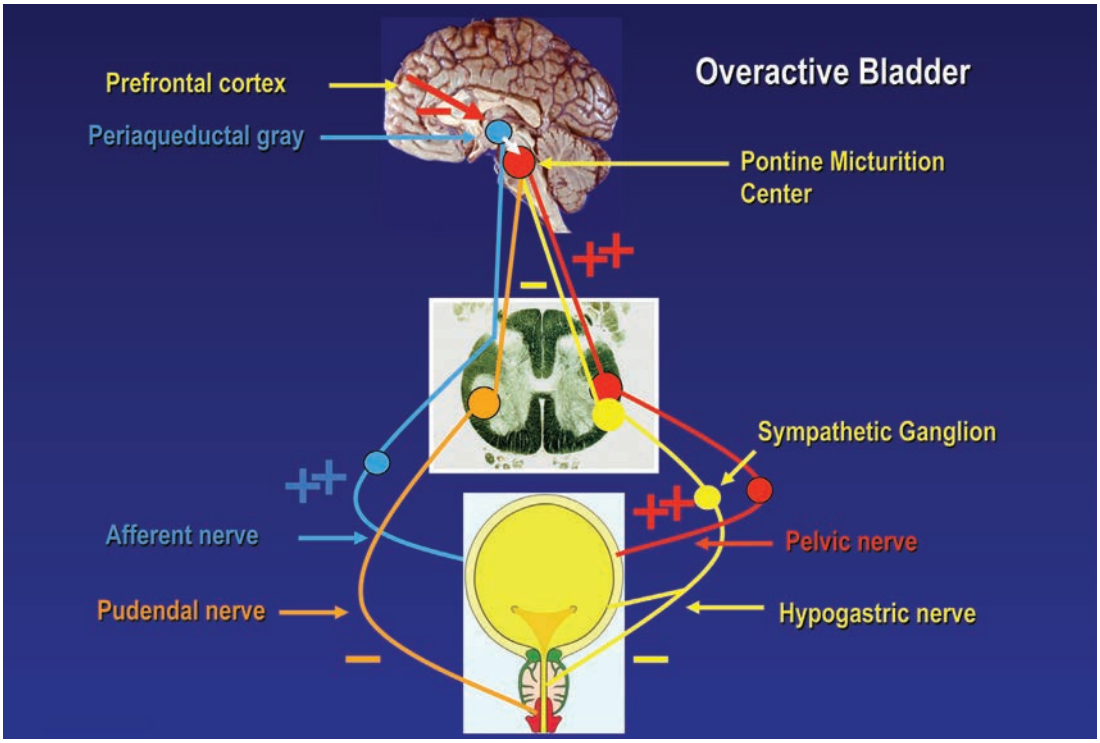


Figure 4 : Detrusor overactivity. Despite the inhibitory impulses from the prefrontal to the cortex pontine micturition center the enhanced (?) afferent impulses are able to initiate micturition.

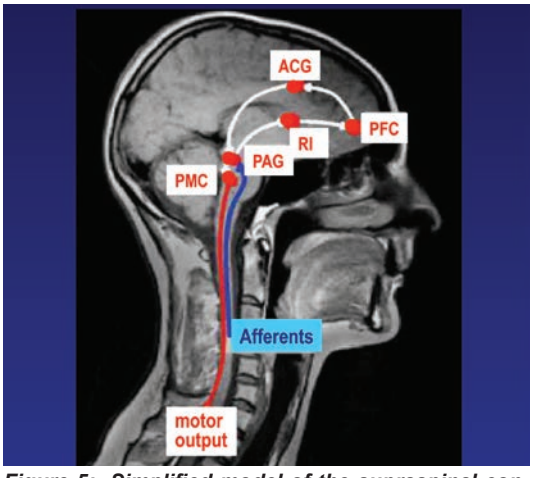


Figure 5: Simplified model of the supraspinal control system of micturition. Secondary bladder afferents synapse in the Periaqueductal Gray (PAG) and are relayed to the Insula (RI), forming the substrate for sensation. Insula representation may have slight right-sided predominance. The Anterior Cingulate Gyrus (ACG) is responsible for monitoring, arousal, and efferent output to the PAG and the Pontine Micturition Center (PMC). The prefrontal cortex (PFC) is involved in voluntary decision about voiding and generates efferent signals to control ACG and ultimately PMC. PMC provides motor output to cause voiding. Modified from Griffiths and Tadic, Neurourol Urodyn, 2008;27:466-474

Most of the ***sympathetic*** innervation of the bladder and urethra originates from the intermediolateral nuclei in the thoraco-lumbar region (T10-L2) of the spinal cord [Beckel and Holstege, 2011]. The axons travel either through the inferior mesenteric ganglia and the hypogastric nerve, or pass through the paravertebral chain and enter the pelvic nerve. Thus, sympathetic signals are conveyed in both the hypogastric and pelvic nerves [Lincoln and Burnstock, 1993].

The predominant effects of the sympathetic innervation of the lower urinary tract are inhibition of the parasympathetic pathways at spinal and ganglion levels (demonstrated in animals), and mediation of contraction of the bladder base and the urethra [shown in animals and man, see Andersson, 1993]. However, the adrenergic innervation of the bladder body is believed to inactivate the contractile mechanisms in the detrusor directly. Noradrenaline (norepinephrine) is released in response to electrical stimulation of detrusor tissues in vitro, and the normal response of detrusor tissues to released noradrenaline is relaxation [Andersson, 1993].

The ***somatic*** innervation of the urethral rhabdosphincter and of some perineal muscles (for exam-

ple compressor urethrae and urethrovaginal sphincter), is provided by the pudendal nerve [Beckel and Holstege, 2011]. These fibers originate from sphincter motor neurons located in the ventral horn of the sacral spinal cord (levels S2-S4) in a region called Onuf´s (Onufrowicz's) nucleus).

Most of the ***sensory*** innervation of the bladder and urethra reaches the spinal cord via the pelvic nerve and dorsal root ganglia [Kanai and Andersson, 2010]. In addition, some afferents travel in the hypogastric nerve. The sensory nerves of the striated muscle in the rhabdosphincter travel in the pudendal nerve to the sacral region of the spinal cord [Lincoln and Burnstock, 1993]. The most important afferents for the micturition process are myelinated Aδ-fibres and unmyelinated C-fibres travelling in the pelvic nerve to the sacral spinal cord, conveying information from receptors in the bladder wall to the spinal cord. The Aδ-fibres respond to passive distension and active contraction, thus conveying information about bladder filling [Janig and Morrison, 1986]. C-fibres have a high mechanical threshold and respond primarily to chemical irritation of the bladder mucosa [Habler et al., 1990] or cold [Fall et al., 1990]. Following chemical irritation, the C-fibre afferents exhibit spontaneous firing when the bladder is empty and increased firing during bladder distension [Habler et al., 1990]. These fibres are normally inactive and are therefore termed "silent fibres".

IV. PATHOGENESIS OF BLADDER CONTROL DISORDERS

As pointed out previously, bladder control disorders can be divided into two general categories: disorders of filling/storage and disorders of voiding [Wein, 2012]. Storage problems can occur as a result of weakness or anatomical defects in the urethral outlet, causing stress urinary incontinence. Failure to store also occurs if the bladder is overactive, as in the overactive bladder (OAB) syndrome. The prevalence varies with the criteria used for diagnosis, but according to Irwin et al. [2006], using the ICS definition of 2002 [Abrams et al., 2002], the overall prevalence of OAB, based on computer assisted telephone interviews (the EPIC study) was 11.8%; rates were similar in men and women and increased with age [Irwin et al., 2006]. A similar study based on a cross Canada telephone survey found the prevalence of OAB to be 13 % in men and 14.7% in women [Herschorn et al., 2008]. In a Finnish study, taking into account bother, the prevalence of clinically meaningful OAB was was much lower than reported in these studies [Vaughan et al., 2011].

OAB (symptomatic diagnosis) is often assumed to be caused by detrusor overactivity (DO; urodynamic diagnosis), even if this does not always seem to be the case [Hyman et al., 2001; Digesu et al., 2003; Hashim and Abrams, 2004; Aschkenazi et al., 2007]. DO/OAB can occur as a result of sensitization of afferent nerve terminals in the bladder or outlet region, changes of the bladder smooth muscle secondary to denervation, or consequent upon damage to the central nervous system (CNS) inhibitory pathways, as can be seen in various neurological disorders, such as multiple sclerosis, cerebrovascular disease, Parkinson's disease, brain tumors, and spinal cord injury [Andersson and Pehrson, 2003; Ouslander, 2004; Banakhar et al., 2012; Wein and Dmochowski, 2012]. Urinary retention and overflow incontinence can be observed in patients with urethral outlet obstruction (e.g. prostate enlargement), decreased detrusor contractility, or both), neural injury, and/or diseases that damage nerves (e.g. diabetes mellitus), or in those who are taking drugs that depress the neural control of the bladder or bladder smooth muscle directly [Wein, 2011].

V. BLADDER CONTRACTION

Normal bladder contraction in humans is mediated mainly through stimulation of muscarinic receptors in the detrusor muscle [Andersson and Wein, 2004] (**Figure 6**). Atropine resistance, i.e. contraction of isolated bladder muscle in response to electrical nerve stimulation after pretreatment with atropine, has been demonstrated in most animal species, but seems to be of little importance in normal human bladder muscle [Andersson, 1993; Bayliss et al., 1999]. However, atropine-resistant (non-adrenergic, non-cholinergic: NANC) contractions have been reported in normal human detrusor and may be caused mainly by adenosine triphosphate (ATP) [Andersson, 1993; Bayliss et al., 1999, Andersson and Wein, 2004; Kennedy et al., 2007]. ATP acts on two families of purinergic receptors: an ion channel family (P2X) and a G-protein-coupled receptor family (P2Y) [Ford and Cockayne, 2011]. Seven P2X subtypes and eight P2Y subtypes have been identified. In several species (rabbit, cat, rat, and human), various studies suggested that multiple purinergic excitatory receptors are present in the bladder [de Groat and Yoshimura, 2001; Ford and Cockayne, 2011]. Immunohistochemical experiments with specific antibodies for different P2X receptors showed that P2X1 receptors are the dominant subtype in membranes of rat detrusor muscle and vascular smooth muscle in the bladder. Excitatory receptors for ATP are present in parasympathetic ganglia, afferent nerve terminals, and urothelial cells [de Groat and Yoshimura, 2001]. P2X3 receptors, which have been identified in small-diameter afferent neurons in dorsal root ganglia, have also been detected immunohistochemically in the wall of the bladder and ureter in a suburothelial plexus

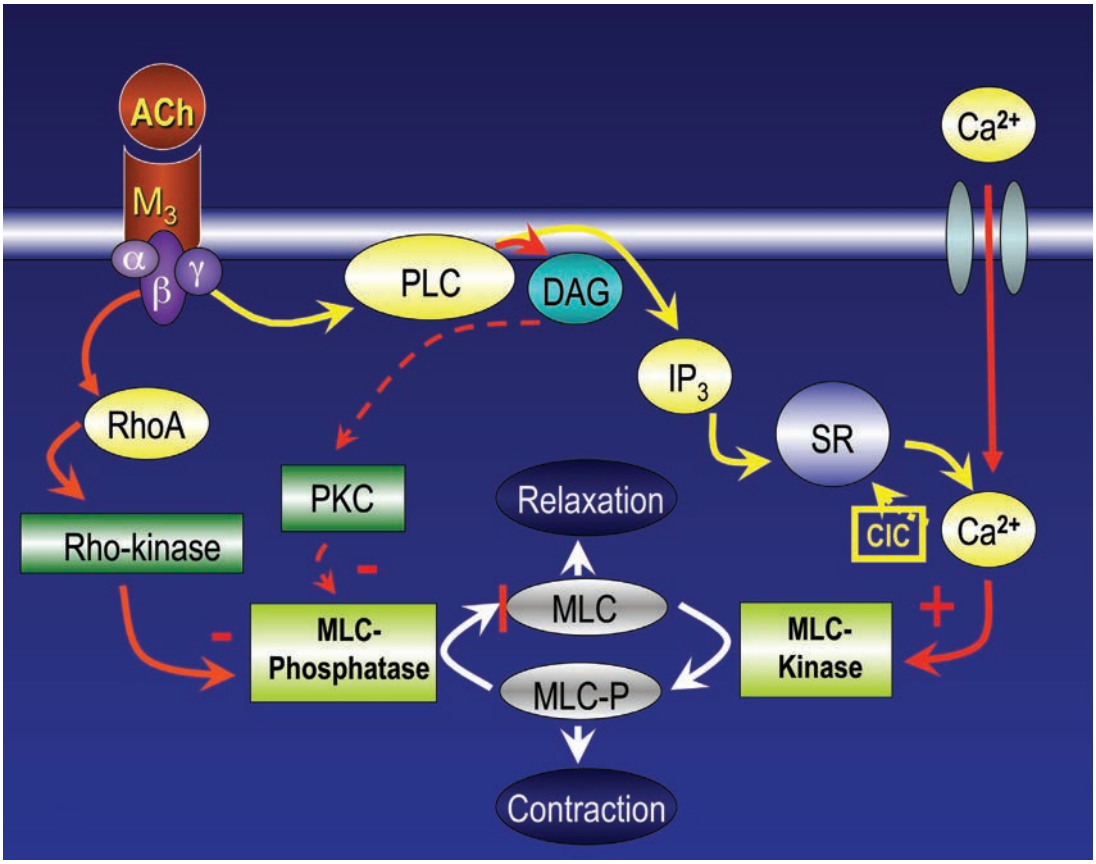


Figure 6: Muscarinic M3 receptor-mediated detrusor activation. Calcium influx and activation of the Rhokinase system are the main pathways mediating activation of the contractile system in the detrusor.

of afferent nerves. In P2X3 knockout mice, afferent activity induced by bladder distension was significantly reduced [Cockayne et al., 2000; Ford et al., 2006; Ruggieri et al., 2006; Ford and Cockeyne, 2011]. These data indicate that purinergic receptors are involved in mechanosensory signaling in the nonprimate mammalian bladder.

A significant degree of atropine resistance may exist in morphologically and/or functionally changed bladders, and has been reported to occur in hypertrophic bladders [Sjögren et al., 1982], interstitial cystitis [Palea et al., 1993], neurogenic bladders [Wammack et al., 1995], and in the aging bladder [Yoshida et al., 2001]. The importance of the NANC component to detrusor contraction in vivo, normally, and in different micturition disorders, remains to be established [Andersson, 2006].

VI. MUSCARINIC RECEPTORS

The neurotransmitter ACh acts on two classes of receptors, the nicotinic and the muscarinic receptors. While the former play a role in the signal transduction between neurones or between neurones and skeletal muscle (e.g. in the distal urethra), the signal transduction between parasympathetic nerves and smooth muscle of the detrusor involves muscarinic receptors [Abrams and Andersson, 2007]. Importantly, the endogenous muscarinic receptor agonist ACh is not necessarily derived only from parasympathetic nerves in the urinary bladder, but can also be formed and released non-neuronally by the urothelium [Bschleiper et al., 2007; Mansfield et al., 2005; Zarghooni et al., 2007, Andersson, 2011]. Five subtypes of muscarinic receptors have been cloned in humans and other mammalian species, which are designated M1-5 [Caulfield and Birdsall 1998]. Based upon structural criteria and shared preferred signal transduction pathways, the subtypes can be grouped into M1, M3 and M5 on the one hand and the subtypes M2 and M4 on the other. The former prototypically couple via pertussis toxin-insensitive Gq proteins to stimulation of a phospholipase C followed by elevation of intracellular calcium and activation of a protein kinase C, whereas the latter prototypically couple via pertussis toxin-sensitive Gi proteins

to inhibition of adenylyl cyclase and modulation of several ion channels [Caulfield and Birdsall 1998]. While sensitive molecular techniques such as reverse transcriptase polymerase chain reaction can detect mRNA for all five subtypes in the mammalian bladder [Abrams et al., 2006: Hegde, 2006], studies at the protein level, e.g. based upon radioligand binding, have typically detected only M2 and M3 receptors, with the former dominating quantitatively [Abrams et al., 2006: Hegde, 2006, Andersson, 2011]. Inhibitory pre-junctional muscarinic receptors have been classified as M2 in the rabbit and rat, and M4 in the guinea-pig, rat and human [d´Agostini et al., 2000; see Andersson, 2011] bladder. These receptors appear to be of the M1 subtype in the rat and rabbit urinary bladder, but have also been detected in human bladders. The muscarinic facilitatory mechanism seems to be upregulated (M3 receptors) in overactive bladders from chronic spinal cord transected rats.

Apparently, most muscarinic receptors in the bladder are found on the smooth muscle cells of the detrusor. While the detrusor expresses far more M2 than M3 receptors, it appears that detrusor contraction under physiological conditions is largely if not exclusively mediated by the M3 receptor [Hegde et al., 1997; Chess-Williams et al., 2001; Fetscher et al., 2002; Kories et al., 2003; Schneider et al., 2004a, b]. Studies in knock-out mice confirm this conclusion [Matsui et al., 2000; 2002; Stengel et al., 2002; Ehlert et al., 2007]. Under physiological conditions M2 receptor-selective stimulation causes little contraction [Schneider et al., 2005a], but rather appears to act mainly by inhibiting β-adrenoceptor-mediated detrusor relaxation [Hegde et al., 1997; Ehlert et al., 2007; Matsui et al., 2003]. It has been proposed that M2 receptors can also directly elicit bladder contraction under pathological conditions [Braverman et al., 1998; 2002; 2003; 2006; Pontari et al., 2003] , but such observations have not been confirmed by other investigators using distinct methodological approaches [Schneider et al., 2005a; b].

Based upon the prototypical signalling pathway of M3 receptors [Cauldfield and Birdsall, 1998] and the presence of phospholipase C stimulation by muscarinic agonists in the bladder [Kories et al., 2003; Schneider et al., 2005a] it had originally been believed that muscarinic receptor-mediated contraction is largely mediated by an activation of phospholipase C [Ouslander, 2004]. While some earlier data had supported this concept, it now appears clear that, at least in rat, mice and humans, muscarinic receptor-mediated bladder contraction occurs largely independent of phospholipase C [Schneider et al., 2004; Wegener et al., 2004; Frazier et al., 2007]. Rather, alternative signalling pathways such as opening of L-type calcium channels and activation of a rho-kinase (**Figure 6**) appear to contribute to muscarinic receptor-mediated bladder contraction in a major way [Frazier et al., 2008]. More recently, muscarinic receptors have also been identified in the urothelium [Chess-Williams, 2002; Kumar et al., 2005]. Similarly to the findings in bladder smooth muscle, the muscarinic receptors in the urothelium mainly belong to the M2 and M3 subtype, with the former dominating quantitatively [Mansfield et al., 2005; Bschleiper et al., 2007]. At present the functional role of muscarinic receptors in the urothelium has largely been studied indirectly, i.e. by investigating the effects of urothelium removal or of administration of pharmacological inhibitors. These data indicate that muscarinic stimulation of the urothelium causes release of an as yet unidentified factor which inhibits detrusor contraction [Hawthorn et al., 2000; Wuest et al., 2005; Sadananda et al., 2008]. Some data indicate that muscarinic receptors in the urothelium may partly act by releasing nitric oxide (NO) [Andersson et al., 2008a]. Muscarinic receptor blockade in urothelial cells may also reduce ATP release induced by strech [Young et al., 2012]. Thus, it appears that muscarinic receptors in the urothelium also contribute to the regulation of overall bladder function but their specific roles in health and disease have not been fully established.

Assuming an involvement of muscarinic receptors in physiological voiding contractions of the bladder, numerous studies have explored whether an overactivity of the muscarinic system may play a causative role in bladder dysfunction. This could involve, e.g., an enhanced expression of such receptors and/or an increased functional responsiveness. In vitro, an increased sensitivity to muscarinic receptor stimulation was found in both idiopathic and neurogenic overactive human detrusors [Stevens et al. 2006]. However, according to Michel and Barendrecht [2008] the overall balance of available studies suggests that the muscarinic receptor system is not hyperactive under conditions of DO and, if anything, can be even hypoactive [Michel and Barendrecht, 2008]. This does not exclude a contribution to DO of ACh and muscarinic receptor stimulation during bladder filling (see below). It appears that the contribution of muscarinic mechanisms to the overall regulation of bladder contractility decreases in favour of non-cholinergic mechanisms under pathological conditions [Yoshida et al., 2001; 2008; Rapp et al., 2005]. These observations may help to explain the moderate efficacy of muscarinic receptor antagonists relative to placebo in controlled clinical studies [Herbison et al., 2003; Chapple et al., 2005; 2008; Novara et al., 2008; Shamliyan et al., 2008].

B. Drugs used for treatment of overactive bladder symptoms/ detrusor overactivity

It has been estimated that more than 50 million people in the developed world are affected by urinary incontinence, and an abundance of drugs has been used for treatment (**Table 2**). Helfand and coworkers showed that in a cohort of 7,244,501 patients over 45 years with an OAB diagnosis, 24.4% of these were treated mainly with antimuscarinic agents; 75.6% went untreated. Only 25.6% of those treated were men. [Helfand et al., 2009]. As underlined by several other subcommittees, drugs may be efficacious in some patients, but they do have side effects, and frequently are not continued indefinitely. Hence it would be worth considering them as an adjunct to conservative therapy.

I. ANTIMUSCARINIC (ANTICHOLINERGIC) DRUGS

• Mechanism of action

Antimuscarinics block, more or less selectively, muscarinic receptors irrespective of location [Abrams and Andersson, 2007; Andersson 2011b] (**Figure 7**). The common view is that in OAB/DO, the drugs act by blocking the muscarinic receptors on the detrusor muscle, which are stimulated by ACh, released from activated cholinergic (parasympathetic) nerves. Thereby, they decrease the ability of the bladder to contract. However, antimuscarinic drugs act mainly during the storage phase, decreasing urgency and increasing bladder capacity, and during this phase, there is normally no parasympathetic input to the lower urinary tract [Andersson, 2004, 2007]. Furthermore, antimuscarinics are usually competitive antagonists. This implies that when there is a massive release of ACh, as during micturition, the effects of the drugs should be decreased, otherwise the reduced ability of the detrusor to contract would eventually lead to urinary retention. Undeniably, high doses of antimuscarinics can produce urinary retention in humans, but in the dose range used for beneficial effects in OAB/DO (**Figure 8**), there is little evidence for a significant reduction of the voiding contraction [Finney et al., 2006]. However, there is good experimental evidence that the drugs act during the storage phase by decreasing the activity in afferent nerves (both C- and Aδ -fibres) from the bladder [De Laet et al., 2006; Ijima et al., 2007] (**Figure 9**).

As mentioned previously, muscarinic receptors are found on bladder urothelial cells where their density can be even higher than in detrusor muscle. The role of the urothelium in bladder activation has attracted much interest [Andersson, 2002; Birder and de Groat, 2007], but whether the muscarinic receptors

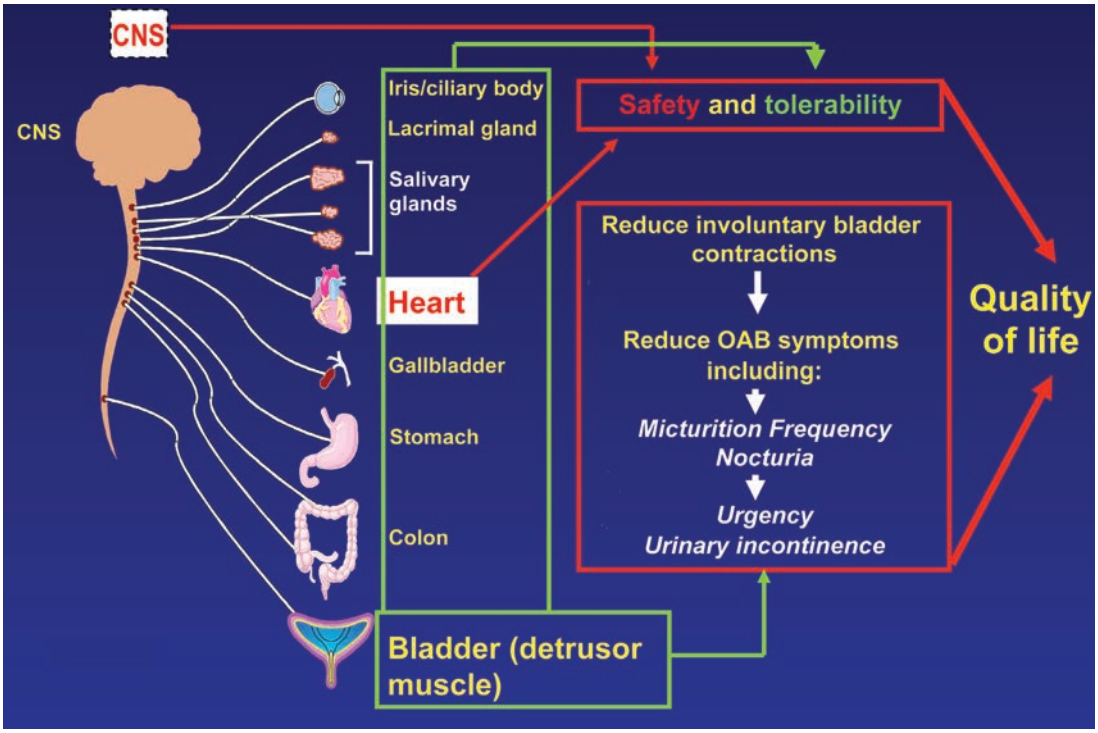


Figure 7: Important sites of action of antimuscarinics.

Table 2. Drugs used in the treatment of LUTS/OAB/ DO. Assessments according to the Oxford system (modified)

	Level of evidence	Grade of recommendation
Antimuscarinic drugs		
Atropine, hyoscyamine	3	C
Darifenacin	1	A
Fesoterodine	1	A
Imidafenacin	1	B
Propantheline	2	B
Solifenacin	1	A
Tolterodine	1	A
Trospium	1	A
Drugs with mixed actions		
Oxybutynin	1	A
Propiverine	1	A
Flavoxate	2	D
Drugs acting on membrane channels		
Calcium antagonists	2	D
K-Channel openers	2	D
Antidepressants		
Imipramine	3	C
Duloxetine	2	C
Alpha-AR antagonists		
Alfuzosin	3	C
Doxazosin	3	C
Prazosin	3	C
Terazosin	3	C
Tamsulosin	3	C
Silodosin	3	C
Naftopidil	3	C
Beta-AR antagonists		
Terbutaline (beta 2)	3	C
Salbutamol (beta 2)	3	C
Mirabegron (beta 3)	1	B
PDE-5 Inhibitors+		
(Sildenafil, Taladafil, Vardenafil)	1	B
COX-inhibitors		
Indomethacin	2	C
Flurbiprofen	2	C
Toxins		
Botulinum toxin (neurogenic)***	1	A
Botulinum toxin (idiopathic)***	1	B
Capsaicin (neurogenic)**	2	C
Resiniferatoxin (neurogenic)**	2	C
Other drugs		
Baclofen*	3	C
Hormones		
Estrogen	2	C
Desmopressin#	1	A

*+(male LUTS/OAB); * intrathecal; ** intravesical; *** bladder wall; #nocturia (nocturnal polyuria), caution hyponatremia, especially in the elderly!*

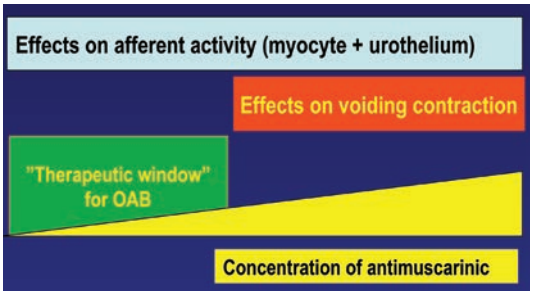


Figure 8: Rationale for use of antimuscarinics for treatment of OAB/DO. Blockade of muscarinic receptors at both detrusor and nondetrusor sites may prevent OAB symptoms and DO without depressing the contraction during voiding. The «Therapeutic window for OAB» can be obtained in most patients with recommended doses of antimuscarinics

on urothelial cells can influence micturition has not yet been established. Yoshida and colleagues [2004; 2006; 2008] found that there is basal ACh release in human bladder. This release was resistant to tetrodotoxin and much diminished when the urothelium was removed; thus, the released ACh was probably of non-neuronal origin and, at least partly, generated by the urothelium. There is also indirect clinical evidence for release of ACh during bladder filling. Smith and co-workers [1974] found that in patients with recent spinal-cord injury, inhibition of ACh breakdown by use of cholinesterase inhibitors could increase resting tone and induce rhythmic contractions in the bladder. Yossepowitch and colleagues [2001] inhibited ACh breakdown with edrophonium in a series of patients with disturbed voiding or urinary incontinence. They found a significant change in sensation and decreased bladder capacity, induction or amplification of involuntary detrusor contractions, or significantly decreased detrusor compliance in 78% of the patients with the symptom pattern of overactive bladder, but in no patients without specific complaints suggesting DO. Thus, during the storage phase, ACh and ATP may be released from both neuronal and non-neuronal sources (eg, the urothelium) and directly or indirectly (by increasing detrusor smooth muscle tone) excite afferent nerves in the suburothelium and within the detrusor. These mechanisms may be important in the pathophysiology of OAB/DO and represent possible targets for antimuscarinic drugs.

• Pharmacologic properties

Generally, antimuscarinics can be divided into tertiary and quaternary amines [Guay, 2003, Abrams and Andersson, 2007]. They differ with regards to lipophilicity, molecular charge, and even molecular size, tertiary compounds generally having higher lipophilicity and molecular charge than quaternary agents. Atropine, darifenacin, fesoterodine (and its active metabolite 5-hydroxymethyl-tolterodine), oxybutynin, propiverine, solifenacin, and tolterodine, are tertiary amines. They are generally well absorbed from the gastrointestinal tract and should theoretically be able to pass into the CNS, dependent on their individual physicochemical properties. High lipophilicity, small molecular size, and less charge will increase the possibilities to pass the blood brain barrier, but in some cases, such as darifenacin, that is compensated by active transport out of the CNS by the product of the MDR1 gene. Quaternary ammonium compounds, like propantheline and trospium, are not well absorbed, pass into the CNS to a limited extent, and have a low incidence of CNS side effects [Guay 2003]. They still produce well-known peripheral antimuscarinic side effects, such as accommodation paralysis, constipation, increases in heart rate, and dryness of mouth.

Many antimuscarinics are metabolized by the P450 enzyme system to active and/or inactive metabolites [Guay 2003]. The most commonly involved P450 enzymes are CYP2D6, and CYP3A4. The metabolic conversion creates a risk for drug-drug interactions, resulting in either reduced (enzyme induction) or increased (enzyme inhibition, substrate competition) plasma concentration/effect of the antimuscarinic and /or interacting drug. Antimuscarinics secreted by the renal tubules (eg trospium) may theoretically be able to interfere with the elimination of other drugs using this mechanism. Some antimuscarinics and their active metabolites are excreted in urine in amounts that may affect the mucosal muscarinic receptors from the luminal side. This has not yet been demonstrated to imply superior clinical efficacy [Andersson et al., 2008b].

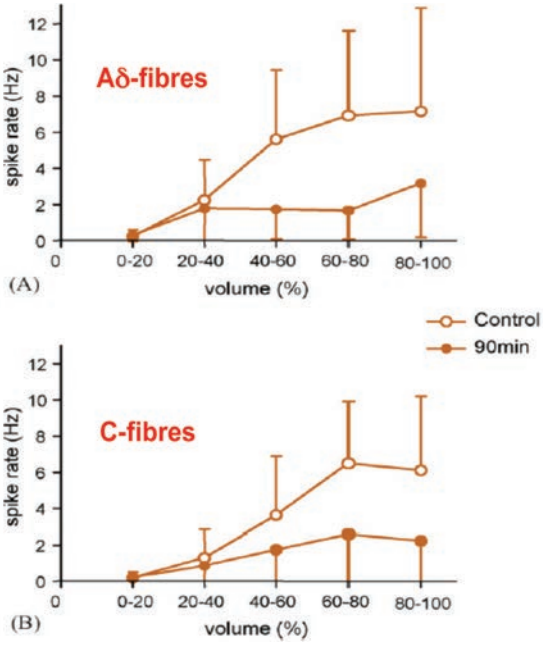


Figure 9: Influence of darifenacin on volume-related nerve activity in Aδ afferents (A) and C afferents (B) in the rat pelvic nerve. From Iijima et al. Eur Urol. 2007 Sep;52(3):842

Antimuscarinics are still the most widely used treatment for urgency and urgency incontinence [Andersson, 2004, Andersson et al., 2009]. However, currently used drugs lack selectivity for the bladder, and effects on other organ systems may result in side effects, which limit their usefulness. For example, all antimuscarinic drugs are contraindicated in untreated narrow angle glaucoma.

Theoretically, drugs with selectivity for the bladder could be obtained, if the subtype(s) mediating bladder contraction, and those producing the main side effects of antimuscarinic drugs, were different. Unfortunately, this does not seem to be the case. One way of avoiding many of the antimuscarinic side effects is to administer the drugs intravesically. However, this is practical only in a limited number of patients.

Several antimuscarinic drugs are and have been used for treatment of OAB/DO. For some of them, documentation of effects is not based on randomized controlled trials (RCTs) satisfying currently required criteria, and some drugs can be considered as obsolete (e.g., emepronium). Information on these drugs has not been included, but can be found elsewhere [Andersson, 1988; Andersson et al., 1999].

1. ANTIMUSCARINICS WITH "SPECIFIC" ACTION

Below data on the different antimuscarinics are presented. These drugs are assumed to block only muscarinic receptors (motivating the term "specific"). The amount of information for the individual drugs varies, and so does the degree of details from the different studies presented. However, the information has been chosen to give a reasonable efficacy and adverse effect profile of each individual drug.

a) Atropine sulfate

Atropine (dl-hyoscyamine) is rarely used for treatment of OAB/DO because of its systemic side effects, which preclude its use as an oral tratment. However, in patients with neurogenic DO, intravesical atropine may be effective for increasing bladder capacity without causing any systemic adverse effects, as shown in open pilot trials [Ekström et al., 1992; Glickman et al., 1995; Deaney et al., 1998; Enskat et al., 2001; Fader et al 2007]. It appears that intravesical atropine may be as effective as intravesical oxybutynin in patients with neurogenic DO [Fader et al., 2007].

The pharmacologically active antimuscarinic component of atropine is l-hyoscyamine.

Assessment

Although still used, few clinical studies are available to evaluate the antimuscarinic activity of l-hyoscyamine sulfate [Muskat et al., 1996]. For assessment, see **Table 2**.

b) Darifenacin hydrobromide

Darifenacin is a tertiary amine with moderate lipophilicity, well absorbed from the gastrointestinal tract after oral administration, and extensively metabolised in the liver by the cytochrome P450 isoforms CYP3A4 and CYP2D6, the latter saturating within the therapeutic range [Skerjanec, 2006]. UK-148,993, UK-73,689, and UK-88862 are the three main circulating darifenacin metabolites of which only UK-148,993 is said to have significant anti-muscarinic activity. However, available information suggests that various metabolites of darifenacin contribute little to its clinical effects [Michel and Hegde, 2006]. The metabolism of darifenacin by CYP3A4 suggests that co-administration of a potent inhibitor of this enzyme (e.g. ketoconazole) may lead to an increase in the circulating concentration of darifenacin [Kerbusch et al., 2003].

Darifenacin is a relatively selective muscarinic M3 receptor antagonist. In vitro, it is selective for human cloned muscarinic M3 receptors relative to M1, M2, M4 or M5 receptors. Theoretically, drugs with selectivity for the M3 receptor can be expected to have clinical efficacy in OAB/DO with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes [Andersson, 2002]. However, the clinical efficacy and adverse effects of a drug are dependent not only on its profile of receptor affinity, but also on its pharmacokinetics, and on the importance of muscarinic receptors for a given organ function.

Darifenacin has been developed as a controlled-release formulation, which allows once-daily dosing. Recommended dosages are 7.5 and 15 mg per day. The clinical effectiveness of the drug has been documented in several RCTs [Haab et al., 2004; Cardozo and Dixon 2005; Steers et al., 2005; Chapple et al., 2005; Foote et al., 2005; Hill et al., 2006; Haab et al., 2006; Zinner et al., 2006, Chapple et al., 2007; Abrams et al., 2008, Chancellor et al., 2008; Dwyer et al., 2008; for reviews, see Guay, 2005; Zinner, 2007; Novara et al., 2008; Chapple et al., 2008]. Haab et al. [2004] reported a multicentre, double-blind, placebo-controlled, parallel-group study which enrolled 561 patients (19−88 years; 85% female) with OAB symptoms for more than 6 months, and included some patients with prior exposure to antimuscarinic agents. After washout and a 2-week placebo run-in, patients were randomised [1:4:2:3]to once-daily oral darifenacin controlled-release tablets: 3.75 mg (n=53), 7.5 mg (n=229) or 15 mg (n=115) or matching placebo (n=164) for 12 weeks. Patients recorded daily incontinence episodes, micturition frequency, bladder capacity (mean volume voided), frequency of urgency, severity of urgency, incontinence episodes resulting in change of clothing or pads and nocturnal awakenings due to OAB using an electronic diary during weeks 2, 6 and 12 (directly preceding clinic visits). Tolerability data were evaluated from adverse event reports. Darifenacin 7.5 mg and 15 mg had a rapid onset of effect, with significant improvement compared with placebo being seen for most parameters at the first clinic visit (week 2). Darifenacin 7.5 mg and 15 mg, respectively, was significantly superior

to placebo for (median) improvements in micturition frequency (7.5 mg: -1.6; 15 mg: -1.7; placebo -0.8, frequency of urgency per day [-2.0; -2.0; -0.9], and number of incontinence episodes leading to a change in clothing or pads [-4.0; -4.7; -2.0]. There was no significant reduction in nocturnal awakenings due to OAB.The most common adverse events were mild-to-moderate dry mouth and constipation with a CNS and cardiac safety profile comparable to placebo. No patients withdrew from the study as a result of dry mouth and discontinuation related to constipation was rare (0.6% placebo versus 0.9% darifenacin).

In a dose titration study on 395 OAB patients, darifenacin, allowing individualized dosing (7.5 or 15 mg), was found to be effective and well-tolerated [Steers et al., 2005]. A 2-year open label extension study of these investigations [i.e., Haab et al., 2004; Steers et al., 2005], confirmed a favorable efficacy, tolerability and safety profile [Haab et al., 2006].

A review of the pooled darifenacin data from the three phase III, multicentre, double blind clinical trials in patients with OAB was reported by Chapple et al. [2005] After a 4-week washout/run-in period, 1,059 adults (85% female) with symptoms of OAB (urgency incontinence, urgency and frequency) for at least six months were randomized to once-daily oral treatment with darifenacin: 7.5 mg (n = 337) or 15 mg (n = 334) or matching placebo (n = 388) for 12 weeks. Efficacy was evaluated using electronic patient diaries that recorded incontinence episodes (including those resulting in a change of clothing or pads), frequency and severity of urgency, micturition frequency, and bladder capacity (volume voided). Safety was evaluated by analysis of treatment-related adverse events, withdrawal rates and laboratory tests. Relative to baseline, 12 weeks of treatment with darifenacin resulted in a dose-related significant reduction in median number of incontinence episodes per week (7.5 mg, –8.8 [–68.4%; placebo -54%, P<004]; 15 mg, –10.6 [–76.8%; placebo 58%, p<0.001]. Significant decreases in the frequency and severity of urgency, micturition frequency, and number of incontinence episodes resulting in a change of clothing or pads were also apparent, along with an increase in bladder capacity. Darifenacin was well tolerated. The most common treatment-related adverse events were dry mouth and constipation, although together these resulted in few discontinuations (darifenacin 7.5 mg 0.6% of patients; darifenacin 15 mg 2.1%; placebo 0.3%). The incidence of CNS and cardiovascular adverse events were comparable to placebo. The results were confirmed in other RCTs, including also a pooled analysis of three phase III studies in older patients (>65 years), showing that darifenacin (7.5 and 15 mg) had an excellent efficacy, tolerability and safety profile [Foote et al., 2005, Zinner et al., 2005; Hill et al. 2006].

The time-to effect with darifenacin was analyzed in a pooled analysis of efficacy and safety data fom 1,059 patients participating in three double-blind 12-week studies Khullar et al [2011]. Darifenacin significantly improved all OAB symptoms as early as 6 to 8 days.

One of the most noticeable clinical effects of antimuscarinics is their ability to reduce urgency and allow patients to postpone micturition. A study was conducted to assess the effect of darifenacin, on the 'warning time' associated with urinary urgency. Warning time was defined as the time from the first sensation of urgency to the time of voluntary micturition or incontinence. This was a multicenter, randomized, double-blind, placebo-controlled study consisting of 2 weeks' washout, 2 weeks' medication-free run-in and a 2-week treatment phase [Cardozo and Dixon, 2005]. Warning time was defined as the time from the first sensation of urgency to voluntary micturition or incontinence and was recorded via an electronic event recorder at baseline (visit 3) and study end (visit 4) during a 6-hour clinic-based monitoring period, with the subject instructed to delay micturition for as long as possible. During each monitoring period, up to three urgency-void cycles were recorded. Of the 72 subjects who entered the study, 67 had warning time data recorded at both baseline and study end and were included in the primary efficacy analysis (32 on darifenacin, 35 on placebo). Darifenacin treatment resulted in a significant (p<0.004) increase in mean warning time with a median increase of 4.3 minutes compared with placebo (darifenacin group from 4.4 to 1.8 minutes; placebo from 7.0 to -1.0 minutes). Overall, 47% of darifenacin-treated subjects compared with 20% receiving placebo achieved a ≥30% increase in mean warning time. There were methodological problems associated with this study; it utilized a dose of 30 mg (higher than the dose recommended for clinical use), the treatment period was short, it was conducted in a clinical-centred environment, the methodology carried with it a significant potential training effect, and the placebo group had higher baseline values than the treatment group. In another warning time study [Zinner et al., 2006] on 445 OAB patients, darifenacin treatment (15 mg) resulted in numerical increases in warning time, however, these were not significant compared to placebo.

Further studies have demonstrated that darifenacin treatment is associated with clinically relevant improvements on health related quality of life (HRQoL) in patients with OAB [Abrams et al., 2008], and such improvements were sustained as shown in a two-year extension study [Dwyer et al., 2008]. It was shown that neither the positive effects on micturition variables, nor on HRQoL produced by darifenacin (7.5 and 15 mg) were further enhanced by a behavioural modification programme including timed voiding, dietary modifications and Kegel exercises [Chancellor et al., 2008].

Since darifenacin is a substrate for the P-glycoprotein drug efflux transporter [Miller et al., 2011;

Chancellor et al., 2012], which is present both in the blood-brain and blood-ocular barriers, several clinical studies have been devoted to investigate possible effect of darifenacin on cognition. Neither in healthy volunteers (19-44 years) and healthy subjects (>60 years), nor in volunteers 65 years or older, could any effect of darifenacin (3.75-15mg daily) be demonstrated, compared to placebo [Kay and Wesnes, 2005; Lipton et al., Kay et al., 2006; Kay and Ebinger 2008; Chancellor et al., 2012].

To study whether darifenacin had any effect on QT/QTc intervals [Serra et al., 2005] performed a 7-day, randomized, parallel-group study (n = 188) in healthy volunteers receiving once-daily darifenacin at steady-state therapeutic (15 mg) and supratherapeutic (75 mg) doses, alongside controls receiving placebo or moxifloxacin (positive control, 400 mg) once daily. No significant increase in QTcF interval could be demonstrated compared with placebo. Mean changes from baseline at pharmacokinetic Tmax versus placebo were –0.4 and –2.2 milliseconds in the darifenacin 15mg and 75 mg groups, respectively, compared with +11.6 milliseconds in the moxifloxacin group (P < .01). The conclusion was that darifenacin does not prolong the QT/QTc interval.

Darifenacin 15 mg per day given to healthy volunteers did not change heart rate significantly compared to placebo [Olshansky et al., 2008].

Assessment

Darifenacin has a well-documented beneficial effect in OAB/DO (**Table 2**), and tolerability and safety seems acceptable.

c) Fesoterodine fumarate

Fesoterodine functions as an orally active prodrug that is converted to the active metabolite 5-hydroxymethyltolterodine (5-HMT) by non-specific esterases [Michel, 2008, Malhotra et al., 2009a]. This compound, which is is chemically identical to the 5-hydroxy metabolite of tolterodine, is a non-subtype selective muscarinic receptor antagonist [Ney et al., 2008]. All of the effects of fesoterodine in man are thought to be mediated via 5-HMT, since the parent compound remains undetectable upon oral dosing. 5-HMT is metabolized in the liver, but a significant part of 5-HMT is excreted renally without additional metabolism. Since the renal clearance of 5-HMT is about 250 mL/min, with >15% of the administered fesoterodine dose excreted as unchanged 5-HM, this raises the possibility that 5-HMT also could work from the luminal side of the bladder [Michel, 2008]. The bioavailability of fesoterodine, averaging 52%, was independent of food intake and the drug may be taken with or without a meal [Malhotra et al., 2009b]. Peak plasma concentration of 5-HMT is reached at 5 h following oral administration and has a half-life of 7–9 h [Malhotra et al., 2008]. The suggested starting dose, 4 mg/day, can be used in patients with moderately impaired renal or hepatic function due to the combination of renal excretion and hepatic metabolism of 5-HMT [Malhotra et al., 2009c; de Mey et al., 2011].

The clinical efficacy and tolerability of fesoterodine have been documented in several RCTs [Chapple et al., 2007; Nitti et al., 2007; Dmochowski et al., 2010; Herschhorn et al., 2010; Kaplan et al., 2010; Nitti et al., 2010; see Dell'Utri et al., 2012]. In a multicenter, double-blind, double-dummy RCT with tolterodine ER, 1132 patients were enrolled and received treatment [Chapple et al., 2007]. The trial showed that both the 4 and 8 mg doses of fesoterodine were effective in improving symptoms of OAB, with the 8 mg dose having a greater effect at the expense of a higher rate of dry mouth. There appeared to be little difference between fesoterodine 4 mg and tolterodine ER. Only one subject from the fesoterodine 8 mg group and one subject from the tolterodine ER group withdrew from the study due to dry mouth. The dose-response relationship was confirmed in another study that pooled data from two phase III RCTs [Khullar et al., 2008]. Fesoterodine 8 mg performed better than the 4 mg dose in improving urgency and urge UI as recorded by 3-day bladder diary, offering the possibility of dose titration.

A head to head placebo controlled trial has been completed comparing fesoterodine 8mg to tolterodine extended release 4mg and placebo [Herschorn et al., 2010]. The study randomized 1,590 patients to assess the primary outcome of reduced urgency incontinence episodes at 12 weeks. Fesoterodine produced statistically significant improvements in urgency incontinence episodes, complete dry rates (64.0% vs. 57.2%, p = 0.015), mean voided volume per void (+32.9 ml vs. +23.5 ml, p = 0.005), and in patients' assessments of bladder related problems as measured by OAB questionnaire (except sleep domain), Patient Perception of Bladder Condition (40% vs. 33% with > 2 point improvement, p < 0.001), and Urgency Perception Scale (46% vs. 40% with improvement, p = 0.014) compared with tolterodine. The clinical significance of these statistically significant findings is questionable as there was no difference between agents with respect to number of micturitions, urgency episodes, and frequency-urgency sum per 24 hours. The improved efficacy of fesoterodine came at the cost of greater dry mouth (27.8% vs. 16.4%), headache (5.6% vs. 3.4 %), constipation (5.4% vs. 4.1%), and withdrawal rates (6% vs. 4%). Nonetheless, this first head to head trial comparing two drugs in class supports the use of fesoterodine 8mg for additional benefit over tolterodine ER 4 mg.

Wyndaele et al. [2009] reported the first flexible-dose open-label fesoterodine trial, which was conducted at 80 different centres worldwide and comprised 516 participants (men and women) >18 years who self-reported OAB symptoms for at least 3 months

before screening and had been treated with either tolterodine or tolterodine ER within 2 years without symptom improvement. Approximately 50% opted for dose escalation to 8 mg at week 4. Significant improvements from baseline to week 12 were observed in micturitions, urgency urinary incontinence episodes, micturition-related urgency episodes and severe micturition-related urgency episodes per 24 h. Significant improvements from baseline were observed in QoL parameters. Dry mouth (23%) and constipation (5%) were the most common adverse events; no safety issues were identified.

The largest double-blind, double-dummy, flexible-dose fesoterodine RCT, which was conducted at 210 different centres with a total of 2,417 patients enrolled, was performed by Kaplan et al. [2010]. All patients were healthy, >18 years of age and self-reported OAB symptoms for at least 3 months. The 960 patients who received fesoterodine 8 mg showed significantly greater mean improvements at week 12 in most efficacy parameters (diary variables) than those receiving either tolterodine ER or placebo; UUI and urgency episodes, micturition frequency and MVV. No statistically significant changes were shown in reduction of nocturnal micturitions compared with the tolterodine group, whereas when comparing the mean changes in nighttime micturition with the placebo group a significant difference was found. This phase III study confirmed the superiority of fesoterodine 8 mg over tolterodine ER 4 mg for improving of UUI and urgency episodes and 24-h micturitions but not for MVV and nocturia. In another RCT of flexible-dose fesoterodine, Dmchowski et al. reported statistically significant improvements at week 12 in the mean number of micturition per 24 h and in both UUI and urgency episodes. Between groups, difference in nocturnal micturition was not statistically significant.

Nitti et al. [2010] determined whether the presence of DO in patients with OAB and urgency urinary incontinence was a predictor of the response to treatment with fesoterodine in a phase 2 randomized, multicentre, placebo-controlled trial. They concluded that regardless of the presence of DO, the response to fesoterodine treatment was dose-proportional and associated with significant improvements in OAB symptoms, indicating that the response to OAB pharmacotherapy in patients with UUI was independent of the urodynamic diagnosis of DO.

Kelleher et al. [2008] evaluated the effect of fesoterodine on HRQoL in patients with OAB syndrome. Pooled data from two randomized placebo-controlled phase III studies Chapple et al., 2007; Nitti et al., 2007] were analysed. Eligible patients were randomized to placebo or fesoterodine 4 or 8 mg for 12 weeks; one trial also included tolterodine extended release (tolterodine-ER) 4 mg. By the end of treatment, all active-treatment groups had significantly improved HRQoL compared with those on placebo. In a post hoc analysis of data pooled from these studies, significant improvements in all KHQ domains, ICIQ-SF scores, and bladder related problems were observed at months 12 and 24 compared to open label baseline [Kelleher et al., 2011]. The authors concluded that treatment satisfaction was high throughout the open-label treatment regardless of gender and age.

Malhotra et al. [2010] performed a thorough QT study to investigate the effects of fesoterodine on cardiac repolarization in a parallel-group study. Subjects were randomly assigned to receive double-blind fesoterodine 4 mg, fesoterodine 28 mg, or placebo or open-label moxifloxacin 400 mg (positive control) for 3 days. Electrocardiograms (ECGs) were obtained on Days -1 (baseline), 1, and 3. The primary analysis was the time-averaged changes from baseline for Fridericia's-corrected QT interval (QTcF) on Day 3. Among 261 subjects randomized to fesoterodine 4 mg (n = 64), fesoterodine 28 mg (n = 68), placebo (n = 65), or moxifloxacin 400 mg (n = 64), 256 completed the trial. The results indicated that fesoterodine is not associated with QTc prolongation or other ECG abnormalities at either therapeutic or supratherapeutic doses.

Assessment

Fesoterodine has a well-documented beneficial effect in OAB (**Table 2**), and the adverse event profile seems acceptable.

d) Imidafenacin

Imidafenacin (KRP-197/ONO-8025, 4-(2-methyl-1H-imidazol-1-yl)-2,2-diphenylbutanamide) is an antagonist for the muscarinic ACh receptor with higher affinities for M3 and M1 receptors than for the M2 receptor. Metabolites of imidafenacin (M-2, M-4 and M-9) had low affinities for muscarinic ACh receptor subtypes [Kobayashi, Yageta et al. 2007]. The drug blocks pre- as well as postjunctional muscarinic receptors and was shown to block both detrusor contractions and acetylcholine release [Murakami, Yoshida et al. 2003]. The receptor binding affinity of imidafenacin in vitro was found to be significantly lower in the bladder than submaxillary gland or colon [Yamada, Seki et al. 2011], and in rats orally administered imidafenacin distributes predominantly to the bladder and exerts more selective and longer-lasting effect here than on other tissues. Whether this can be translated to the human situation has to be established before claims of clinical bladder selectivity can be made.

Imidafenacin is well absorbed form the gastrointestinal tract and its absolute bioavailability in human is 57.8% [Ohmori, Miura et al. 2007; Ohno, Nakade et al. 2008]. It is rapidly absorbed with maximum plasma concentration occuring 1-3h after oral administration [Ohno, Nakade et al. 2008]. Metabolites in the plasma are produced mainly by

first-pass effects. The major enzymes responsible for the metabolism of the drug are CYP3A4 and UGT1A4. The oxidative metabolism is reduced by concomitant administration of CYP3A4 inhibitors. In contrast, imidafenacin and its metabolites have no inhibitory effect on the CYP-mediated metabolism of concomitant drugs [Kanayama, Kanari et al. 2007].

Kitagawa et al. [Kitagawa, Kuribayashi et al. 2011] reported that the subjective efficacy of imidafenacin was observed from 3 days after the commencement of administration and that mean total OABSS decreased gradually during 2 weeks after administration.

A randomized, double-blind, placebo-controlled phase II dose-finding study in Japanese OAB patients was performed to evaluate the efficacy, safety/tolerability, and dose-response relationship of imidafenacin [Homma, Yamaguchi et al. 2008]. Overall, 401 patients were enrolled and randomized for treatment with 0.1 mg of imidafenacin/day (99 patients), 0.2 mg of imidafenacin/day [100], 0.5 mg of imidafenacin/day [101], or a placebo [101]. After 12 weeks of treatment, the number of incontinence episodes was reduced in a dose-dependent manner, and a significant difference between the imidafenacin treatment and the placebo was observed ($P < 0.0001$). Compared with the placebo, imidafenacin caused significant reductions in urgency incontinence, voiding frequency, and urinary urgency, and a significant increase in the urine volume voided per micturition. Imidafenacin was also well tolerated. The incidence of dry mouth in the imidafenacin groups increased dose-dependently. Even though the percentage of patients receiving 0.5 mg/day who discontinued treatment due to dry mouth was high (8.9%), the percentages in the 0.1 mg/day and 0.2 mg/day groups (1.0% and 0.0%, respectively) were comparable with that in the placebo group (0.0%).

A randomized, double-blind, placebo- and propiverine-controlled trial of 781 Japanese patients with OAB symptoms were conducted by Homma et al.[Homma and Yamaguchi 2009]. They were randomized to imidafenacin (324), propiverine [310], or a placebo [147]. After 12 weeks of treatment, a significantly larger reduction in the mean number of incontinence episodes was observed in the imidafenacin group than in the placebo group ($P < 0.0001$). The non-inferiority of imidafenacin compared with propiverine was confirmed for the reduction in using incontinence episodes ($P = 0.0014$, non-inferiority margin: 14.5%). Imidafenacin was well tolerated. The incidence of adverse events with imidafenacin was significantly lower than with propiverine ($P = 0.0101$). Dry mouth, the most common adverse event, was significantly more common in the propiverine group than in the imidafenacin group. There were no significant increases in either the imidafenacin or placebo group in the mean QTc interval, whereas there was a significant increase in the mean QTc interval in the propiverine group ($P < 0.0001$). However, there were no clinical arrhythmia and clinical arrhythmic events in any of the treatment groups.

The long-term safety, tolerability, and efficacy imidafenacin was studied in Japanese OAB patients [Homma and Yamaguchi 2008], of whom 478 received treatment and 376 completed a 52-week program. Imidafenacin was well tolerated, the most common adverse event being a dry mouth (40.2% of the patients). Long-term treatment did not produce an increase in the frequency of adverse events compared with short-term treatment. A significant efficacy of the drug was observed from week 4 through week 52. After 52 weeks, imidafenacin produced mean changes from baseline in the number of incontinence episodes (-83.51%), urgency incontinence episodes (-84.21%), voiding frequency (-2.35 micturitions/day), urgency episodes (-70.53%), and volume voided per micturition (28.99 mL). There were also significant reductions from baseline in all domains of the King's Health Questionnaire. received the treatment and 376 patients completed the 52-week program. Imidafenacin had no significant effects on the corrected QT interval, vital signs, results from laboratory tests, or post-void residual volume.

A 52-week prospective, open randomized comparative study to evaluate the efficacy and tolerability of imidafenacin (0.2 mg/day) and solifenacin (5 mg/day) was conducted in a total of 41 Japanese patients with untreated OAB [Zaitsu, Mikami et al. 2011]. They were randomly assigned to imidafenacin and solifenacin groups. There was no difference in OABSS and KHQ scores between the two groups, but the severity and incidence of adverse events caused by the drugs showed increased differences between the groups with time. The severity of dry mouth and the incidence of constipation were significantly lower in the imidafenacin group ($P = 0.0092$ and $P = 0.0013$, resp.). An important limitation of this study is the low number of patients. Only 25 patients (17 males 8 females) were available for long-term analysis.

Assessment.

Imidafenacin seems to be effective and to have an acceptable tolerability. However, the documentation is relatively scarce and the drug is not yet available in the Western countries.

e) Propantheline bromide

Propantheline is a quaternary ammonium compound, non-selective for muscarinic receptor subtypes, which has a low (5 to 10%) and individually varying biological availability. It is metabolized (metabolites inactive) and has a short halflife (less than 2 h) [Beermann et al., 1972]. It is usually given in

a dose of 15 to 30 mg 4 times daily, but to obtain an optimal effect, individual titration of the dose is necessary, and often higher dosages are required. Using this approach in 26 patients with detrusor overactivitycontractions [Blaivas et al., 1980] in an open study obtained a complete clinical response in all patients but one, who did not tolerate more than propantheline 15 mg four times daily. The range of dosages varied from 7.5 to 60 mg four times daily. In contrast, Thüroff et al. [1991] comparing the effects of oxybutynin 5 mg three times daily, propantheline 15 mg three times daily, and placebo, in a randomized, double-blind, multicenter trial on the treatment of frequency, urgency and incontinence related to DO (154 patients), found no differences between the placebo and propantheline groups. In another randomized comparative trial with crossover design (23 women with idiopathic DO), and with dose titration, Holmes et al. [1991] found no differences in efficacy between oxybutynin and propantheline. Controlled randomized trials (n=6) reviewed by Thüroff et al [1998], confirmed a positive, but varying, response to the drug.

Assessment

Although the effect of propantheline on OAB/DO has not been well documented in controlled trials satisfying standards of today, it can be considered effective, and may, in individually titrated doses, be clinically useful (**Table 2**). No new studies on the use of this drug for treatment of OAB/DO seem to have been performed during the last decade.

f) Solifenacin succinate

Solifenacin succinate (YM905) is a tertiary amine and well absorbed from the gastrointestinal tract (absolute bioavailability 90%). The mean terminal half-life is 45-68 hours [Kuipers et al., 2002; Smulders et al., 2002; 2004]. It undergoes significant hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4). In subjects who received a single oral dose of 10 mg solifenacin on day 7 of a 20-day regimen of ketoconazole administration (200 mg) Cmax and AUC0-inf were increased by only approximately 40% and 56%, respectively [Swart et al., 2006]. Solifenacin has a modest selectivity for M3 over M2 (and M1) receptors [Abrams and Andersson, 2007]. Supporting an effect on sensory function by solifenacin, 15 women with DO receiving 10 mg/day of the drug showed an increase in the area under the bladder-volume sensation curve [Lowenstein et al., 2011] Solifenacin also increased maximum bladder capacity, a finding in agreement with other studies Tanaka et al., 2010; Hsiao et al., 2011].

Two large-scale phase 2 trials with parallel designs, comprising men and women, were performed [Chapple et al., 2004a, Smith et al., 2002]. The first dose-ranging study evaluated solifenacin 2.5 mg, 5 mg, 10 mg, and 20 mg and tolterodine (2 mg twice daily) in a multinational placebo-controlled study of 225 patients with urodynamically confirmed DO [Chapple et al., 2004a]. Patients received treatment for 4 weeks followed by 2 weeks of follow-up. Inclusion criteria for this and subsequent phase 3 studies of patients with OAB included at least 8 micturitions per 24 hours and either one episode of incontinence or one episode of urgency daily as recorded in 3-day micturition diaries. Micturition frequency, the primary efficacy variable, was statistically significantly reduced in patients taking solifenacin 5 mg (-2.21), 10 mg (-2.47), and 20 mg (-2.75), but not in patients receiving placebo (-1.03) or tolterodine (-1.79). This effect was rapid with most of the effect observed at the earliest assessment visit, 2 weeks after treatment initiation. In addition, there was numerically greater reductions in episodes of urgency and incontinence when compared with placebo. Study discontinuations due to adverse events were similar across treatment groups, albeit highest in the 20-mg solifenacin group. As the 5 mg and 10 mg doses caused lower rates of dry mouth than tolterodine, and superior efficacy outcomes relative to placebo, these dosing strengths were selected for further evaluation in large-scale phase 3 studies.

The second dose-ranging study of solifenacin 2.5 mg to 20 mg was carried out in the United States (USA) [Smith et al., 2002]. This trial included 261 evaluable men and women receiving solifenacin or placebo for 4 weeks followed by a 2-week follow-up period. Micturition frequency was statistically significantly reduced relative to placebo in patients receiving 10 mg and 20 mg solifenacin. The number of micturitions per 24 hours showed reductions by day 7 and continued to decrease through day 28; day 7 was the earliest time point tested in solifenacin trials and these findings demonstrate efficacy as early as one week. The 5 mg, 10 mg, and 20 mg dosing groups experienced statistically significant increases in volume voided; the 10 mg solifenacin dose was associated with statistically significant reductions in episodes of incontinence.

In one of the early RCTs, a total of 1077 patients were randomized to 5 mg solifenacin, 10 mg solifenacin, tolterodine (2 mg twice daily), or placebo [Chapple et al., 2004b]. It should be noted that this study was powered only to compare active treatments to placebo. Compared with placebo (-8%), mean micturitions/24 h were significantly reduced with solifenacin 10 mg (-20%), solifenacin 5 mg (-17%), and tolterodine (-15%). Solifenacin was well tolerated, with few patients discontinuing treatment. Incidences of dry mouth were 4.9% with placebo, 14.0% with solifenacin 5 mg, 21.3% with solifenacin 10 mg, and 18.6% with tolterodine 2 mg twice daily.

Cardozo et al. [2004] randomized 911 patients to 12-week once daily treatment with solifenacin 5 mg, solifenacin 10 mg or placebo. The primary efficacy variable was change from baseline to study end

point in mean number of micturitions per 24 hours. Secondary efficacy variables included changes from baseline in mean number of urgency, nocturia and incontinence episodes per 24 hours, and mean volume voided per micturition. Compared with changes obtained with placebo (-1.6), the number of micturitions per 24 hours was statistically significantly decreased with solifenacin 5 mg (-2.37) and 10 mg (-2.81). A statistically significant decrease was observed in the number of all incontinence episodes with both solifenacin doses (5 mg: -1.63, 61%; 10 mg: -1.57, 52%), but not with placebo (-1.25, 28%). Of patients reporting incontinence at baseline, 50% achieved continence after treatment with solifenacin (based on a 3-day micturition diary, placebo responses not given). Episodes of nocturia were statistically significantly decreased in patients treated with solifenacin 10 mg versus placebo. Episodes of urgency and mean volume voided per micturition were statistically significantly reduced with solifenacin 5 mg and 10 mg. Treatment with solifenacin was well tolerated. Dry mouth, mostly mild in severity, was reported in 7.7% of patients receiving solifenacin 5 mg and 23% receiving solifenacin 10 mg (vs 2.3% with placebo). A 40-week follow up of these studies [i.e., Chapple et al., 2004b and Cardozo et al., 2004] demonstrated that the favourable profile, both in terms of efficacy and tolerability was maintained over the study period [Haab et al., 2005].

The STAR trial [Chapple et al., 2005; 2007] was a prospective, double blind, double-dummy, two-arm, parallel-group, 12-week study was conducted to compare the efficacy and safety of solifenacin 5 or 10 mg and TOLT-ER 4 mg once daily in OAB patients. The primary effect variable was micturition frequency. After 4 weeks of treatment patients had the option to request a dose increase, but were dummied throughout as approved product labelling only allowed an increase for those on solifenacin. The results showed that solifenacin, with a flexible dosing regimen, was “non-inferior” to tolterodine concerning the primary effect variable, micturition freqency. However, solifenacin showed significant greater efficacy to tolterodine in decreasing urgency episodes (-2.85 vs -2.42), incontinence (-1.60 vs -.83), urgency incontinence (-1.42 vs -0.83), and pad usage (-1.72 vs -1.19). More solifenacin treated patients became continent by study endpoint (59 vs 49%) and reported improvements in perception of bladder condition (-1.51 vs -1.33) assessments. However, this was accompanied by an adverse event incidence which was greater with solifenacin than with tolterodine. Dry mouth and constipation (mild + moderate + severe) were the most common (solifenacin 30 and 6.4%, tolterodine 23 and 2.5%). The majority of side effects were mild to moderate in nature, and discontinuations were comparable and low (5.9 and 7.3%) in both groups.

Luo et al. [2012] performed a systematic review and meta-analysis of solifenacin RCTs and provided a comprehensive assessment regarding the efficacy and safety of the drug. Their results which largley confirmed what could be deduced from previouly published information, indicated that solifenacin could significantly decrease the number of urgency episodes per 24 h, micturitions per 24 h, incontinence episodes per 24 h, nighttime micturitions per 24 h, and UUI episodes per 24 h, and improve volume voided per micturitions compared with the placebo or tolterodine treatment.

A number of studies and reviews have further documented the effects of solifenacin [Cardozo et al., 2006; Chapple et al., 2006; 2007; Maniscalco et al., 2006, see also Chapple et al., 2008; Novara et al., 2008; Toglia et al., 2009; Vardy et al., 2009; Serels et al., 2010; Luo et al., 2012], including men with OAB without bladder outlet obstruction [Kaplan et al., 2010;] In a pooled analysis of four RCTs, Abrams and Swift (2005) demonstrated positive effects on urgency, frequency and nocturia symptoms in OAB dry patients. In an analysis of four phase III clinical trials, Brubaker and FitzGerald [2007] confirmed a significant effect of solifenacin 5 and 10 mg on nocturia in patients with OAB (reductions of nocturia episodes with 5 mg: -0.6, $p<0.025$; with 10 mg: -0.6, $p<0.001$vs placebo: -0,4) but without nocturnal polyuria. A positive impact on nocturia and sleep quality in patients with OAB treated with solifenacin has also been reported in other studies [Takao et al., 2011; Yokoyama et al., 2011] Kelleher et al. [2006] and Staskin and Te [2006] presented data showing efficacy in patients with mixed incontinence.

A pooled analysis of four studies confirmed the efficacy and tolerability of solifenacin 5 and 10 mg in elderly (> 65 years) patients, and also showed a high level of persistence in a 40 week extension trial [Wagg et al., 2005]. Post-hoc analysis of two12-week, open lable, flexible-dosing studies on 2645 patients over 65 years of age with OAB, revealed that solifenacin was associated with improvements in measures assessing patients’ perception of their bladder problems, symptom bother, and aspects of health-related quality of life [Capo et al., 2011]. Solifenacin was equally well tolerated in younger (<65 years) and older (>65 years) patients [Herschorn et al., 2001]. An exploratory pilot study with single doses of solifenacin 10 mg to 12 elderly volunteers suggested no clear propensity to impair cognitive functions [Wesnes et al., 2009].

Improvement of QoL by solifenacin treatment has been documented in several studies [Kelleher et al., 2005; Garely et al., 2006]. In 30 patients with mutiple sclerosis, van Rey and Heesakkers [2011] improved OAB symptoms as well as neurogenic disease-specific QoL measures.

Information on solifenacin treatment in children is scarce. In a prospective open label study in 72 children (27 with neurogenic bladders) Bolduc et al.[2010] improved urodynamic capacity and im-

proved continence.Chart review of 138 children with therapy resistant OAB treated with solifenacin increased mean voided volume and improved continence [Hoebeke et al., 2009]

In female volunteers, aged 19 to 79 years, the effect of 10 mg and 30 mg solifenacin on the QT interval was evaluated at the time of peak solifenacin plasma concentration in a multi-dose, randomized, double-blind, placebo and positive-controlled (moxifloxacin 400 mg) trial. The QT interval prolonging effect appeared greater for the 30 mg (8 msec, 4, 13: 90%CI) compared to the 10 mg (2 msec, -3, 6) dose of solifenacin. Although the effect of the highest solifenacin dose (three times the maximum therapeutic dose) studied did not appear as large as that of the positive control moxifloxacin at its therapeutic dose, the confidence intervals overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels.

Michel et al. [2008] studied cardiovascular safety and overall tolerability of solifenacin in routine clinical use in a 12-week, open-label, post-marketing surveillance study. They concluded that "in real-life conditions, i.e. with inclusion of large numbers of patients with cardiovascular co-morbidities and taking comedications, therapeutically effective doses of solifenacin did not increase heart rate or blood pressure".

Assessment

Solifenacin has a well-documented beneficial effect in OAB/DO (**Table 2**), and the adverse event profile seems acceptable.

g) Tolterodine tartrate

Tolterodine is is a tertiary amine, rapidly absorbed and extensive metabolized by the cytochrome P450 system (CYP 2D6). The major active 5-hydroxymethyl metabolite (5-HMT) has a similar pharmacological profile as the mother compound [Nilvebrant et al., 1997], and significantly contributes to the therapeutic effect of tolterodine [Brynne et al., 1997; Brynne et al., 1998]. Both tolterodine and 5-HMT have plasma half-lifes of 2-3 h, but the effects on the bladder seem to be more long-lasting than could be expected from the pharmacokinetic data. Urinary excretion of tolterodine accounted for <1-2.4 % of the dose; 5 – 14% of 5-HMT is eliminated in the urine [Brynne et al., 1997]. Whether or not the total antimuscarinic activity of unchanged tolterodine and 5-HMT excreted in urine is sufficient to exert any effect on the mucosal signaling mechanisms has not been established. However, the preliminary studies by Kim et al. [2005] and Chuang et al., [2008], do not support such an effect.

The relatively low lipophilicity of tolterodine and even lesser one of 5-HMT, implies limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects [Hills et al., 1998, Clemett et al., 2001; Salvatore et al., 2008]. However, tolterodine may disturb sleep in subjects unable to form the even less lipophilic 5-HMT due to a low activity of CYP 2D6 [Diefenbach et al., 2008].

Tolterodine has no selectivity for muscarinic receptor subtypes, but is claimed to have functional selectivity for the bladder over the salivary glands [Stahl et al., 1995; Nilvebrant et al. 1997b]. In healthy volunteers, orally given tolterodine in a high dose (6.4 mg) had a powerful inhibitory effect on micturition and also reduced stimulated salivation 1 hour after administration of the drug [Stahl et al., 1995]. However, 5 hours after administration, the effects on the urinary bladder were maintained, whereas no significant effects on salivation could be demonstrated.

Animal experiments have suggested that antimuscarinics may affect signaling from the bladder [Andersson, 2011b]. Cirfirming data in humans were found by Vijaya et al. [2012]. In a randomized, placebo-controlled study, they evaluated the effect of tolterodine on urethral and bladder afferent nerves in women with DO in comparison to placebo, by studying the changes in the current perception threshold (CPT). They found a significantly increased CPT value at 5 (described as urgency) and 250 Hz upon both urethral and bladder stimulation after 1 week of treatment. When compared with placebo, women taking tolterodine had significantly increased bladder CPT values at 5 Hz (P-value <0.05).

Tolterodine is available as immediate-release (TOLT-IR; 1 or 2 mg; twice daily dosing) and extended-release (TOLT-ER) forms (2 or 4 mg; once daily dosing). The ER form seems to have advantages over the IR form in terms of both efficacy and tolerability [Van Kerrebroeck et al. 2001].

Several randomised, double blind, placebo-controlled studies on patients with OAB/DO (both idiopathic and neurogenic DO), have documented a significant reduction in micturition frequency and number of incontinence episodes [Hills et al., 1998; Clemett et al., 2001; Salvatore et al., 2008]. Comparative RCTs such as the OBJECT (Overactive Bladder: Judging Effective Control and Treatment), and the OPERA (Overactive Bladder; Performance of Extended Release Agents) studies have further supported its effectiveness.

The OBJECT trial compared oxybutynin ER (OXY-ER) 10 mg once daily with TOLT-IR 2 mg twice daily [Appell et al., 2001] in a 12-week randomized, double blind, parallel-group study including 378 patients with OAB. Participants had between 7 and 50 episodes of urgency incontinence per week and 10 or more voids in 24 hours. The outcome measures were the number of episodes of urgency incontinence, total incontinence, and micturition frequency at 12 weeks adjusted for baseline. At the end of the study, OXY-ER was found to be significantly more effective than TOLT-IR in each of the main

outcome measures adjusted for baseline (see also below: oxybutynin chloride). Dry mouth, the most common adverse event, was reported by 33% and 28% of participants taking OXY-ER and TOLT-IR, respectively. Rates of central nervous system and other adverse events were low and similar in both groups. The authors concluded that OXY-ER was more effective than TOLT-IR and that the rates of dry mouth and other adverse events were similar in both treatment groups.

In the OPERA study [Diokno et al., 2003], OXY-ER at 10 mg/d or TOLT-ER at 4 mg/d were given for 12 weeks to women with 21 to 60 urgency incontinence episodes per week and an average of 10 or more voids per 24 hours. Episodes of incontinence (primary end point), total (urgency and non urgency) incontinence, and micturition were recorded in seven 24-hour urinary diaries at baseline and at weeks 2, 4, 8 and 12 and compared. Adverse events were also evaluated. Improvements in weekly urgency incontinence episodes were similar for the 790 women who received OXY-ER (n=391) or TOLT-ER (n=399). OXY-ER was significantly more effective than TOLT-ER in reducing micturition frequency, and 23.0% of women taking OXY-ER reported no episodes of urinary incontinence compared with 16.8% of women taking TOLT-ER. Dry mouth, usually mild, was more common with OXY-ER. Adverse events were generally mild and occurred at low rates, with both groups having similar discontinuation of treatment due to adverse events. The conclusions were that reductions in weekly urgency incontinence and total incontinence episodes were similar with the two drugs. Dry mouth was more common with OXY-ER, but tolerability was otherwise comparable; including adverse events involving the central nervous system.

In the ACET (Antimuscarinic Clinical Effectiveness Trial) [Sussman and Garely, 2002] study, which consisted of two trials, patients with OAB were randomized to 8 weeks of open-label treatment with either 2 mg or 4 mg of once-daily TOLT-ER (study one) and to 5 mg or 10 mg of OXY-ER (study two). A total of 1289 patients were included. Fewer patients prematurely withdrew from the trial in the TOLT-ER 4 mg group (12%) than either the OXY-ER 5 mg (19%) or OXY-ER 10 mg groups (21%). More patients in the OXY-ER 10 mg group than the TOLT-ER 4 mg group withdrew because of poor tolerability (13% vs. 6%). After 8 weeks, 70% of patients in the TOLT-ER 4 mg group perceived an improved bladder condition, compared with 60% in the TOLT-ER 2 mg group, 59% in the OXY-ER 5 mg group and 60% in the OXY-ER 10 mg group. Dry mouth was dose-dependent with both agents, although differences between doses reached statistical significance only in the oxybutynin trial (OXY-ER 5 mg vs. OXY-ER 10 mg; p=0.05). Patients treated with TOLT-ER 4 mg reported a significantly lower severity of dry mouth compared with OXY-ER 10 mg. The conclusion that the findings suggest improved clinical efficacy of TOLT-ER (4 mg) than of OXY-ER (10 mg) is weakened by the the open label design of the study.

Zinner et al. [2002] evaluated the efficacy, safety, and tolerability of TOLT-ER in older (> or =65) and younger (<65) OAB patients, in a 12-week RCT including 1015 patients with urgency incontinence and urinary frequency. Patients were randomized to treatment with TOLT-ER 4 mg once daily (n = 507) or placebo (n = 508) for 12 weeks. Efficacy, measured with micturition charts (incontinence episodes, micturitions, volume voided per micturition) and subjective patient assessments, safety, and tolerability endpoints were evaluated, relative to placebo. Compared with placebo, significant improvements in micturition chart variables with TOLT-ER showed no age-related differences. Dry mouth (of any severity) was the most common adverse event in both the TOLT-ER and placebo treatment arms, irrespective of age (<65: ER 22.7%, placebo 8.1%; > or =65: ER 24.3%, placebo 7.2%). A few patients (< 2%) experienced severe dry mouth. No central nervous system (cognitive functions were not specifically studied), visual, cardiac (per electrocardiogram), or laboratory safety concerns were noted in this study. Withdrawal rates due to adverse events on TOLT-ER 4 mg qd were comparable in the two age cohorts (<65: 5.5%; > or =65: 5.1%).

The central symptom in the OAB syndrome is urgency. Freeman et al. [2003] presented a secondary analysis of a double-blind, placebo-controlled study evaluating the effect of once-daily TOLT-ER on urinary urgency in patients with OAB. Patients with urinary frequency (eight or more micturitions per 24 hours) and urgency incontinence (five or more episodes per week) were randomized to oral treatment with TOLT-ER 4 mg once daily (n=398) or placebo (n=374) for 12 weeks. Efficacy was assessed by use of patient perception evaluations. Of patients treated with TOLT-ER, 44% reported improved urgency symptoms (compared with 32% for placebo), and 62% reported improved bladder symptoms (placebo, 48%). The proportion of patients unable to hold urine upon experiencing urgency was decreased by 58% with TOLT-ER, compared with 32% with placebo (P<.001).

In the IMprovement in Patients: Assessing symptomatic Control with Tolterodine ER (IMPACT) study [Elinoff et al., 2005], the efficacy of TOLT-ER for patients' most bothersome OAB symptom was investigated in an open label, primary care setting. Patients with OAB symptoms for >3 months received TOLT-ER (4 mg once daily) for 12 weeks. By week 12, there were significant reductions in patients' most bothersome symptom: incontinence, urgency episodes, nocturnal and daytime frequency. The most common adverse events were dry mouth (10%) and constipation (4%), and it was concluded that in primary care practice, bothersome OAB symptoms

can be effectively and safely treated with TOLT-ER, even in patients with comorbid conditions.

Various aspects of the efficacy and tolerability of tolterodine have been further documented in a number of RCTs [Dmochowski et al., 2007a; 2007; Barucha et al., 2008; Choo et al., 2008; Coyne et al., 2008; Rogers et al., 2008; Rovner et al., 2008a; see further: Novara et al, 2008, Chapple et al., 2008]. Importantly, the QTc effects of tolterodine were determined in a crossover-designed QT study of recommended (2 mg twice daily) and supratherapeutic (4 mg twice daily) doses of tolterodine, moxifloxacin (400 mg once daily), and placebo was performed. No subject receiving tolterodine exceeded the clinically relevant thresholds of 500 ms absolute QTc or 60ms change from baseline, and it was concluded that tolterodine does not have a clinically significant effect on QT interval [Malhotra et al., 2007].

Olshansky et al. [2008] compared the effects on heart rate of TOLT-ER 4 mg/day with those of darifenacin 15 mg/day in healthy volunteers. They found that tolterodine, but not darifenacin, significantly increased mean heart rate per 24 hours. The proportion of subjects with an increase >5 beats/min was significantly greater in those receiving TOLT-ER (25% than with darifenacin (8.9%).

Hsiao et al. [2011] compared the urodynamic effects, therapeutic efficacy and safety of solifenacin [5 mg] versus tolterodine ER [4 mg] treatment inwomen with the OAB syndrome. Both solifenacin and tolterodine had similar urodynamic effects, therapeutic efficacy and adverse events, however, tolterodine had a greater effect in increasing heart rate than solifenacin.

In a prospective, open study, Song et al. [2006] compared the effects of bladder training and/or tolterodine as first line treatment in female patients with OAB. One hundred and thirty-nine female patients with OAB were randomized to treatment with bladder training (BT), tolterodine (2 mg twice daily) or both for 12 weeks. All treatments were efficacious, however, combination therapy was the most effective. Mattiasson et al. [2003] compared the efficacy of tolterodine 2 mg twice daily plus simplified bladder training (BT) with tolterodine alone in patients with OAB in a multicenter single blind study. At the end of the study the median percentage reduction in voiding frequency was greater with tolterodine + BT than with tolterodine alone (33% vs. 25%; $p<0.001$), while the median percentage increase in volume voided per void was 31% with tolterodine + BT and 20% with tolterodine alone ($p<0.001$). There was a median of 81% fewer incontinence episodes than at baseline with tolterodine alone, which was not significantly different from that with tolterodine + BT (-87%). It was concluded that the effectiveness of tolterodine 2mg twice daily can be augmented by a simplified BT regimen. However, Millard et al. [2004] investigated whether the combination of tolterodine plus a simple pelvic floor muscle exercise program would provide improved treatment benefits compared with tolterodine alone in 480 patients with OAB. Tolterodine therapy for 24 weeks resulted in significant improvement in urgency, frequency, and incontinence, however, no additional benefit was demonstrated for a simple pelvic floor muscle exercise program. In a 16-week, multicenter, open label study tolterodine extended release plus behavioral intervention resulted in high treatment satisfaction and improved bladder diary variables in patients who had previously been treated and were dissatisfied with tolterodine or other antimuscarinics [Klutke et al., 2009].

Abrams et al. [2006] studied the safety and tolerability of tolterodine for the treatment of OAB symptoms in men with BOO. They found that tolterodine did not adversely affect urinary function in these men. Urinary flow rate was unaltered, and there was no evidence of clinically meaningful changes in voiding pressure and PVR or urinary retention. It was suggested that antimuscarinics can be safely administered in men with BOO. Lee et al. [2008] reviewed the safety and efficacy of antimuscarinic agents in treating men with BOO and OAB and emphasized their safety and efficacy. They also concluded that combination therapy of antimuscarinic and α1-AR antagonists improves the symptoms effectively without increasing the incidence of acute urinary retention.

The beneficial effect of TOLT-ER in men with benign prostatic enlargement (BPE) and LUTS, including OAB, has been well documented. Both as monotherapy, but in particularly in combination with α1-adenoceptor (AR) antagonist, TOLT-ER was found effective [Kaplan et al., 2006; Höfner et al., 2007; Kaplan et al., 2008a; 2008b; Rovner et al., 2008; Roehrborn et al., 2008]. This effect was obtained irrespective of prostate size, and was not associated with increased incidence of acute urinary retention (AUR) [Roehrborn et al., 2008]. A large, 26-week, multicenter, randomized, double-blind, placebo-controlled, three-period crossover study enrolled women aged ≥ 18 years that were diagnosed with OAB and reported ≥ 8 micturitions/24 hr and ≥ 4 urgency episodes/week on 5-day bladder diary at baseline [Marencak et al.2011]. Subjects were randomized to 1 of 10 treatment sequences and received three of five treatments, each for 4 weeks with 4-week washout periods: standard-dose pregabalin/tolterodine ER (150 mg twice daily [BID]/4 mg once daily [QD], n=102), pregabalin alone (150 mg BID, n=105), tolterodine ER alone (4 mg QD, n=104), low-dose pregabalin/tolterodine ER (75 mg BID/2 mg QD, n=105), and placebo (n=103). Subjects completed 5-day diaries at the end of treatment and washout periods. The primary endpoint was change from baseline to week 4 in mean voided volume (MVV) per micturition. Baseline-adjusted changes in MVV were significantly greater after

treatment with standard-dose pregabalin/tolterodine ER (39.5 ml) versus tolterodine ER alone (15.5 ml; P<0.0001), and with pregabalin alone (27.4 ml) versus tolterodine ER alone (P=0.005) and placebo (11.9 ml; P=0.0006). Treatments were generally well tolerated; discontinuation rates due to adverse events were 4%, 2%, 5%, 0%, and 1% with standard- and low-dose pregabalin/tolterodine ER, pregabalin,tolterodine ER, and placebo, respectively. See further section on Combinations].

Assessment

Both the IR and ER forms of tolterodine have a well-documented effect in OAB/DO (**Table 2**), and are well tolerated.

h) Trospium chloride

Trospium is a quaternary ammonium compound with a biological availability less than 10% [Fusgen and Hauri, 2000; Doroshyenko et al., 2005]. The drug has a plasma half-life of approximately 20 h, and is mainly (60% of the dose absorbed) eliminated unchanged in the urine. The concentration obtained in urine seems to be enough to affect the mucosal signaling system in a rat model [Kim et al., 2006]. Whether or not it contributes to the clinical efficacy of the drug remains to be established.

Trospium is not metabolized by the cytochrome P450 enzyme system [Beckmann-Knopp et al., 1999; Doroshyenko et al., 2005]. It is expected to cross the blood-brain to a limited extent since it is a substrate for the drug-efflux transporter P-glycoprotein, which restricts its entry into the brain [Gever et al., 2009]. This was demonstrated by Staskin et al. [2010], showing that trospium chloride levels in CSF samples were undetectable on Day 10 at steady-state peak plasma concentration concurrent with measureable peak plasma values. Clinically, trospium seems to have no negative cognitive effects [Fusgen and Hauri, 2000; Todorova et al., 2001; Widemann et al., 2002; Staskin et al., 2010; Chancellor et al., 2012].

Trospium has no selectivity for muscarinic receptor subtypes. In isolated detrusor muscle, it was more potent than oxybutynin and tolterodine to antagonize carbachol-induced contractions [Uckert et al., 2000].

Several RCTs have documented positive effects of trospium both in neurogenic [Stöhrer, et al., 1991; Madersbacher et al., 1995; Menarini et al., 2006] and non-neurogenic DO [Allousi et al., 1998; Cardozo et al., 2000; Junemann et al., 2000; Halaska et al., 2003; Zinner et al., 2004a; Rudy et al., 2006; Staskin et al., 2007; Dmochowski et al., 2008]. In a placebo-controlled, double blind study on patients with with neurogenic DO [Stöhrer et al, 1991], the drug was given twice daily in a dose of 20 mg over a 3-week period. It increased maximum cystometric capacity, decreased maximal detrusor pressure and increased compliance in the treatment group, whereas no effects were noted in the placebo group. Side effects were few and comparable in both groups. In another RCT including patients with spinal cord injuries and neurogenic DO, trospium and oxybutynin were equieffective; however, trospium seemed to have fewer side effects [Madersbacher et al., 1995].

The effect of trospium in urgency incontinence has been documented in several RCTs. Allousi et al. [1998] compared the effects of the drug with those of placebo in 309 patients in a urodynamic study of 3 weeks duration. Trospium 20 mg was given twice daily. Significant increases were noted in volume at first involuntary contraction and in maximum bladder capacity. Cardozo et al. [2000] investigated 208 patients with DO, who were treated with trospium 20 mg twice daily for two weeks. Also in this study, significant increases were found in mean volume at first unstable contraction (from 233 to 299 ml; placebo 254 to 255 ml) and in maximum bladder capacity (from 329 to 356 ml; placebo 345 to 335 ml) in the trospium treated group. Trospium was well tolerated with similar frequency of adverse effects as in the placebo group. Jünemann et al. [2000] compared trospium 20 mg twice daily with tolterodine 2 mg twice daily in a placebo-controlled double-blind study on 232 patients with urodynamically proven DO, urgency incontinence without demonstrable DO, or mixed incontinence. Trospium reduced the frequency of micturition, which was the primary endpoint, more than tolterodine and placebo, and also reduced the number of incontinence episodes more than the comparators. Dry mouth was comparable in the trospium and tolterodine groups (7 and 9%, respectively).

Halaska et al. [2003] studied the tolerability and efficacy of trospium chloride in doses of 20 mg twice daily for long-term therapy in patients with urgency syndrome. The trial comprised a total of 358 patients with urgency syndrome or urgency incontinence. After randomisation in the ratio of 3:1, participants were treated continuously for 52 weeks with either trospium chloride (20 mg twice daily) or oxybutynin (5 mg twice daily). Urodynamic measurements were performed at the beginning, and at 26 and 52 weeks to determine the maximal cystometric bladder capacity. Analysis of the micturition diary clearly indicated a reduction of the micturition frequency, incontinence frequency, and a reduction of the number of urgency episodes in both treatment groups. Mean maximum cystometric bladder capacity increased during treatment with trospium chloride by 92 ml after 26 weeks and 115 ml after 52 weeks (P=0.001). Further comparison with oxybutynin did not reveal any statistically significant differences in urodynamic variables between the drugs. Adverse events occurred in 65% of the patients treated with trospium and 77% of those treated with oxybutynin. The main symptom encountered in both treatment groups was dryness of the

mouth. An overall assessment for each of the drugs revealed a comparable efficacy level and a better benefit-risk ratio for trospium than for oxybutynin due to better tolerability.

Zinner et al. [2004] treated 523 patients with symptoms associated with OAB and urgency incontinence with 20 mg trospium twice daily or placebo in a 12-week, multicenter, parallel, double-blind, placebo controlled trial. Dual primary end points were change in average number of toilet voids and change in urgency incontinent episodes per 24 hours. Secondary efficacy variables were change in average of volume per void, voiding urgency severity, urinations during day and night, time to onset of action and change in Incontinence Impact Questionnaire. By week 12, trospium significantly decreased average frequency of toilet voids per 24 hours (-2.37) and urgency incontinent episodes 59% compared to placebo (-1.29; 44%). It significantly increased average volume per void (32 ml; placebo: 7.7) ml, and decreased average urgency severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 (-0.43; placebo: 0.17) - and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8%; placebo 6.5%), constipation (9.5%; placebo 3.8%) and headache (6.5%; placebo 4.6%). In a large US multicenter trial with the same design, and including 658 patients with OAB, Rudy et al. [2006] confirmed the data by Zinner et al [2004], both with respect to efficacy and adverse effects.

Dose escalation seems to improve therapeutic efficacy. In a 12-week, randomised, double-blind, phase IIIb study including 1658 patients with urinary frequency plus urgency incontinence received trospium chloride 15 mg TID (n = 828) or 2.5 mg oxybutynin hydrochloride TID (n = 830). After four weeks, daily doses were doubled and not readjusted in 29.2% (242/828) of patients in the trospium group, and in 23.3% (193/830) in the oxybuytnin group, until the end of treatment. At study end, there were no relevant differences between the “dose adjustment” subgroups and the respective “no dose adjustment” subgroups (trospium: P = 0.249; oxybutynin: P = 0.349). After dose escalation, worsening of dry mouth was higher in both dose adjusted subgroups compared to the respective “no dose adjustment” subgroups (P < 0.001). Worsening of dry mouth was lower in the trospium groups than in the oxybutynin groups [Bödeker et al., 2010].

An extended release formulation of trospium allowing once daily dosing, has been introduced [Silver et al., 2010], and and its effects tested in controlled trials [Staskin et al., 2008; Dmochowski et al., 2008; Chancellor et al., 2010; MacDiarmid et al., 2011; Sand et al., 2011a; b; c; Zinner et al., 2011]. These studies demonstrated similar efficacy as found with previous formulations, but include experiences in e.g., elderly patients (>75 years), obese patients, and in patients who use multiple concomitant medications. The most frequent side effects were dry mouth (12.9% ; placebo 4.6) and constipation (7.5%; placebo 1.8) [Dmochowski et al., 2008].

Intravesical application of trospium may be an interesting alternative. Frölich et al. [1998] performed a randomised, single-blind, placebo-controlled, mono-centre clinical trial in 84 patients with urgency or urgency incontinence. Compared to placebo, intravesical trospium produced a significant increase in maximum bladder capacity and a decrease of detrusor pressure accompanied by an increase of residual urine. There was an improvement in uninhibited bladder contractions. No adverse events were reported. Interestingly, intravesical trospium does not seem to be absorbed [Walter et al., 1999], thus offering an opportunity for treatment with minimal systemic antimuscuscarinic effects.

Assessment

Trospium has a well-documented effect in OAB/DO, and tolerability and safety seems acceptable (**Table 2**).

2. ANTIMUSCARINICS WITH “MIXED” ACTION

Some drugs used for treatment of the OABsyndrome/DO have been shown to have more than one mechanism of action. They all have a more or less pronounced antimuscarinic effect and, in addition, an often poorly defined “direct” action on bladder muscle. For several of these drugs, the antimuscarinic effects can be demonstrated at much lower drug concentrations than the direct action, which may involve blockade of voltage operated Ca2+ channels. Most probably, the clinical effects of these drugs can be explained mainly by an antimuscarinic action. Among the drugs with mixed actions was terodiline, which was withdrawn from the market because it was suspected to cause polymorphic ventricular tachycardia (torsade de pointes) in some patients [Connolly et al., 1991; Stewart et al., 1992].

a) Oxybutynin chloride

Oxybutynin is a tertiary amine that is well absorbed, and undergoes extensive upper gastrointestinal and first-pass hepatic metabolism via the cytochrome P-450 system (CYP3A4) into multiple metabolites. The primary metabolite, N-desethyloxybutynin (DEO) has pharmacological properties similar to the parent compound [Waldeck et al., 1997], but occurs in much higher concentrations after oral administration [Hughes et al., 1992]. It has been implicated as the major cause of the troublesome side effect of dry mouth associated with the administration of oxybutynin. It seems reasonable to assume that the effect of oral oxybutynin to a large extent is exerted by the metabolite. The occurrence of an active

metabolite may also explain the lack of correlation between plasma concentration of oxybutynin itself and side effects in geriatric patients reported by Ouslander et al. [1988]. The plasma half-life of the oxybutynin is approximately 2 hours, but with wide interindividual variation [Hughes et al., 1992; Douchamps et al, 1988].

Oxybutynin has several pharmacological effects in vitro, some of which seem difficult to relate to its effectiveness in the treatment of DO. It has both an antimuscarinic and a direct muscle relaxant effect, and, in addition, local anesthetic actions. The latter effect may be of importance when the drug is administered intravesically, but probably plays no role when it is given orally. In vitro, oxybutynin was 500 times weaker as a smooth muscle relaxant than as an antimuscarinic agent [Kachur et al., 1988]. Most probably, when given systemically, oxybutynin acts mainly as an antimuscarinic drug. Oxybutynin has a high affinity for muscarinic receptors in human bladder tissue and effectively blocks carbachol-induced contractions [Waldeck et al., 1997; Nilvebrant et al., 1988]. The drug was shown to have slightly higher affinity for muscarinic M1 and M3 receptors than for M2 receptors [Nilvebrant et al., 1986; Norhona-Blob et al., 1991], but the clinical significance of this is unclear.

The immediate release (IR) form of oxybutynin (OXY-IR) is recognized for its efficacy and most of the newer anti-muscarinic agents have been compared to it once efficacy over placebo has been determined. In general, the new formulations of oxybutynin and other anti-muscarinic agents offer patients efficacy roughly equivalent to that of OXY-IR, and the advantage of the newer formulations lies in improved dosing schedules and side-effect profile [Appell et al., 2001; Diokno et al., 2003; Dmochowski et al., 2002]. An extended release oxybutynin (OXY-ER) once daily oral formulation and an oxybutynin transdermal delivery system (OXY-TDS) are available. OXY-TDS offers a twice-weekly dosing regimen and the potential for improved patient compliance and tolerability. Some of the available formulations of oybutynin were overviewed by McCrery and Appell [2006].

Immediate-release oxybutynin (OXY-IR). Several controlled studies have have shown that OXY-IR is effective in controlling DO, including neurogenic DO [Yarker et al., 1995; Andersson and Chapple, 2001]. The recommended oral dose of the IR form is 5 mg three times daily or four times daily, even if lower doses have been used. Thüroff et al. [1998] summarized 15 randomized controlled studies on a total of 476 patients treated with oxybutynin. The mean decrease in incontinence was recorded as 52% and the mean reduction in frequency per 24 h was 33% (data on placebo not presented). The overall "subjective improvement" rate was reported as 74 % (range 61% - 100%). The mean percent of patients reporting an adverse effect was 70 (range 17% - 93%). Oxybutynin, 7.5 to 15 mg/day, significantly improved quality of life of patients suffering from overactive bladder in a large open multicenter trial. In this study, patients´ compliance was 97% and side effects, mainly dry mouth, were reported by only 8% of the patients [Amarenco et al., 1998]. In nursing home residents (n=75), Ouslander et al. [1995] found that oxybutynin did not add to the clinical effectiveness of prompted voiding in a placebo-controlled, double blind, cross-over trial. On the other hand, in another controlled trial in elderly subjects (n=57), oxybutynin with bladder training was found to be superior to bladder training alone [Szonyi et al., 1995].

Several open studies in patients with spinal cord injuries have suggested that oxybutynin, given orally or intravesically, can be of therapeutic benefit [Szollar et al., 1996; Kim et al., 1996].

The therapeutic effect of OXY-IR on DO is associated with a high incidence of side effects (up to 80% with oral administration). These are typically antimuscarinic in nature (dry mouth, constipation, drowsiness, blurred vision) and are often dose-limiting [Baigrie et al., 1988; Jonville et al., 1992]. The effects on the electrocardiogram of oxybutynin were studied in elderly patients with urinary incontinence [Hussain et al., 1998]; no changes were found. It cannot be excluded that the commonly recommended dose 5 mg x 3 is unnecessarily high in some patients, and that a starting dose of 2.5 mg x 2 with following dose-titration would reduce the number of adverse effects [Amarenco et al., 1998].

Extended release oxybutynin (OXY-ER). This formulation was developed to decrease liver metabolite formation of desethyloxybutynin (DEO) with the presumption that it would result in decreased side effects, especially dry mouth, and improve patient compliance with remaining on oxybutynin therapy [see Arisco et al., 2009]. The formulation utilizes an osmotic system to release the drug at a controlled rate over 24 hours distally primarily into the large intestine where absorption is not subject to first-pass metabolism in the liver. This reduction in metabolism is meant to improve the rate of dry mouth complaints when compared to OXY-IR. DEO is still formed through the hepatic cytochrome P-450 enzymes, but clinical trials have indeed demonstrated improved dry mouth rates compared with OXY-IR [Appell et al., 2003]. Salivary output studies have also been interesting. Two hours after administration of OXY-IR or TOLT-IR, salivary production decreased markedly and then gradually returned to normal. With OXY-ER, however, salivary output was maintained at predose levels throughout the day [Chancellor et al., 2001].

The effects of OXY-ER have been well documented [Siddiqui et al., 2004]. In the OBJECT study [Appell et al., 2001], the efficacy and tolerability of 10 mg OXY-ER was compared to a twice daily 2 mg dose

of TOLT-IR. OXY-ER was statistically more effective than the TOLT-IR in weekly urgency incontinence episodes (OXY-ER from 25.6 to 6.1%; TOLT-IR 24.1 to 7.8), total incontinence (OXY-ER from 28.6 to 7.1%; TOLT-IR 27.0 to 9.3), and frequency (OXY-ER from 91.8 to 67.1%; TOLT-IR 91.6 to 71.5) and both medications were equally well tolerated. The basic study was repeated as the OPERA study [Diokno et al., 2003] with the difference that this study was a direct comparison of the two extended-release forms, OXY-ER (10 mg) and TOLT-ER (4 mg) and the results were quite different. In this study there was no significant difference in efficacy for the primary endpoint of urgency incontinence, however, TOLT-ER had a statistically lower incidence of dry mouth. OXY-ER was only statistically better at 10 mg than TOLT-ER 4 mg in the reduction of the rate of urinary frequency. These studies made it clear that in comparative studies IR entities of one drug should no longer be compared with ER entities of the other.

Greater reductions in urgency and total incontinence have been reported in patients treated in dose-escalation studies with OXY-ER. In two randomized studies, the efficacy and tolerability of OXY-ER were compared with OXY-IR. In the 1999 study [Anderson et al., 1999], 105 patients with urgency or mixed incontinence were randomized to receive 5-30 mg OXY-ER once daily or 5 mg of OXY-IR 1-4 times/day. Dose titrations began at 5 mg and the dose was increased every 4-7 days until one of three endpoints was achieved. These were 1) the patient reported no urgency incontinence during the final two days of the dosing period; 2) the maximum tolerable dose was reached; the maximum allowable dose (30 mg for OXY-ER or 20 mg for OXY-IR) was reached. The mean percentage reduction in weekly urgency and total incontinence episodes was statistically similar between OXY-ER and OXY-IR but dry mouth was reported statistically more often with OXY-IR. In the 2000 study [Versi et al., 2000], 226 patients were randomized between OXY-ER and OXY-IR with weekly increments of 5 mg daily up to 20 mg daily. As in the 1999 study, OXY-ER again achieved a >80% reduction in urgency and total incontinence episodes and a significant percentage of patients became dry. A negative aspect of these studies is that there were no naïve patients included, as all patients were known responders to oxybutynin. Similar efficacy results have been achieved, however, with OXY-ER in a treatment-naïve population [Gleason et al., 1999].

In an RCT comparing different daily doses of oxybutynin (5, 10 and 15 mg), Corcos et al. [2006] found a significant dose-response relationship for both urgency incontinence episodes and dry mouth. The greatest satisfaction was with 15 mg oxybutynin/day.

In a multicentre, prospective, observational, flexible-dosing Korean study, Yoo et al. [2012] investigate the prescription pattern and dose distribution of OXY-ER in patients the OAB syndrome in actual clinical practice. The dosage of for each patient was adjusted after discussions of efficacy and tolerability between doctor and patient, over a 12 week treatment period. Efficacy was measured by administering the Primary OAB Symptom Questionnaire (POSQ) before and after treatment. Patients were also administered, the patient perception of treatment benefit (PPTB) questionnaire at the end of the study. Of the 809 patients enrolled, 590 (73.2%) continued to take study medication for 12 weeks. Most patients were prescribed 5–10 mg/day oxybutynin ER as both starting and maintenance doses, with a dose escalation rate of only 14.9%. All OAB symptoms evaluated by the POSQ were improved; 94.1% of patients reported benefits from treatment and 89.3% were satisfied.

Transdermal oxybutynin (OXY-TDS). Transdermal delivery also alters oxybutynin metabolism reducing DEO production to an even greater extent than OXY-ER. A study [Davila et al., 2001] comparing OXY-TDS with OXY-IR demonstrated a statistically equivalent reduction in daily incontinent episodes (from 7.3 to 2.3: 66% for OXY-TDS, and 7.4 to 2.6: 72% for OXY-IR), but much less dry mouth (38% for OXY-TDS and 94% for OXY-IR). In another study [Dmochowski et al., 2002] the 3.9-mg daily dose patch significantly (vs placebo) reduced the mean number of daily incontinence episodes (from 4.7 to 1.9; placebo from5.0 to 2.9), while reducing average daily urinary frequency confirmed by an increased average voided volume (from 165 to 198 ml; placebo from 175 to 182 ml). Furthermore, dry mouth rate was similar to placebo (7% vs 8.3%). In a third study [Dmochowski et al., 2003] OXY-TDS was compared not only to placebo but to TOLT-ER. Both drugs equivalently and significantly reduced daily incontinence episodes and increased the average voided volume, but TOLT-ER was associated with a significantly higher rate of antimuscarinic adverse events. The primary adverse event for OXY-TDS was application site reaction pruritis in 14% and erythema in 8.3% with nearly 9% feeling that the reactions were severe enough to withdraw from the study, despite the lack of systemic problems.

The pharmacokinetics and adverse effect dynamics of OXY-TDS (3.9 mg/day) and OXY-ER (10 mg/day) were compared in healthy subjects in a randomized, 2-way crossover study [Appell et al., 2003]. Multiple blood and saliva samples were collected and pharmacokinetic parameters and total salivary output were assessed. OXY-TDS administration resulted in greater systemic availability and minimal metabolism to DEO compared to OXY-ER which resulted in greater salivary output in OXY-TDS patients and less dry mouth symptomatology than when taking OXY-ER.

Dmochowski et al. [2005] analyzing the combined results of two RCTs concluded that transdermal

oxybutynin was shown to be efficacious and well tolerated. The most common sytemic side effect was dry mouth (7.0 % vs placebo 5.3%). Application site erythema occurred in 7% and pruritus in 16.1 %. Also Cartwright and Cardozo [2006], reviewing published and presented data concluded that transdermal oxybutynin has a good balance between efficacy and tolerability with a rate of systemic antimuscarinic side effects lower that with oral antimuscarinics – however, this benefit was offset by the rate of local skin reaction. The reviews of Sahai et al. [2008] and Staskin and Salvatore [2010] largely confirmed these conclusions, which also have been supported by further studies [Cartwright et al., 2011].

Oxybutynin topical gel. Given the efficacy and tolerability of the transdermal application, limited only by skin site reactions, a gel formulation was developed. oxybutynin topical gel (OTG) was approved by the US FDA in January 2009. OTG is applied once daily to the abdomen, thigh, shoulder, or upper arm area [Staskin et al., 2009]. The 1 gram application dose delivers approximately 4 mg of drug to the circulation with stable plasma concentrations and a "favorable" N-desethyloxybutynin metabolite: oxybutynin ratio believed to minimizing antimuscarinic side effects [Staskin and Robinson, 2009]. In a multicenter RCT, 789 patients (89% women) with urgency-predominant incontinence were assigned to OTG or placebo once daily for 12 weeks [Staskin et al., 2009]. The mean number of urgeny episodes, as recorded by 3-day voiding diary, was reduced by 3.0 episodes per day versus 2.5 in the placebo arm (P <0.0001). Urinary frequency decreased by 2.7 episodes per day and voided volume increased by 21 mL (versus 2.0 episodes [P = 0.0017] and 3.8 mL [P = 0.0018], respectively, in the placebo group). Dry mouth was reported in 6.9% of the treatment group versus 2.8% of the placebo group. Skin reaction at the application site was reported in 5.4% of the treatment group versus 1.0% in the placebo arm. It was felt that improved skin tolerability of the gel over the OXY transdermal patch delivery system was secondary to lack of adhesive and skin occlusion. The gel dries rapidly upon application and leaves no residue; person-to-person transference via skin contact is largely eliminated if clothing is worn over the application site [Dmochowski et al., 2011]. The evolution of the transdermal gel allows greater patient tolerability and improved compliance. This was confirmed by Sand et al. [2012] showing that in 704 women with OAB OTG significantly reduced the number (mean ± standard deviation) of daily incontinence episodes (OTG, -3.0 ± 2.8 episodes; placebo, -2.5 ± 3.0 episodes), reduced urinary frequency, increased voided volume, and improved select health-related quality-of-life domains vs placebo. Dry mouth was the only drug-related adverse event significantly more common with OTG (7.4%) than with placebo (2.8%).

Other administration forms. Rectal administration [Collas and Malone-Lee, 1997] was reported to have fewer adverse effects than the conventional tablets.

Administered intravesically, oxybutynin has in several studies been demonstrated to increase bladder capacity and produce clinical improvement with few side effects, both in neurogenic and in other types of DO, and both in children and adults [Lose and Norgaard, 2001; Fader et al., 2007; George et al., 2007; Guerra et al., 2008], although adverse effects may occur [Kasabian et al., 1994; Palmer et al., 1997].

Effects on cognition. Several studies have documented the possibility that oxybutynin may have negative effects on cognitive functions, particularly in the elderly population but also in children [see, e.g., Kay et al., 2006; Klausner al Steers, 2007; Kay and Ebinger, 2008]. This factor should be taken into consideration when prescribing the drug.

Assessment.

Oxybutynin has a well-documented efficacy in the treatment of OAB/DO (**Table 2**). Despite the adverse effect profile, it is still an established therapeutic option.

b) Propiverine hydrochloride

Several aspects of the preclinical, pharmacokinetic, and clinical effects of propiverine have been reviewed by Madersbacher and Murz [2001]. The drug is rapidly absorbed (tmax 2 h), but has a high first pass metabolism, and its biological availability is about 50%. Propiverine is an inducer of hepatic cytochrome P450 enzymes in rats in doses about 100-times above the therapeutic doses in man [Walter et al., 2003]. Several active metabolites are formed which quantitatively and qualitatively differ from the mother compound [Haustein et al., 1988; Muller et al., 1993; Wuest et al., 2006; Zhu et al., 2008; Sugiyama et al., 2008]. Most probable these metabolites contribute to the clinical effects of the drug, but their individual contributions have not been clarified [Michel and Hegde, 2006]. The half-life of propiverine itself is about 11-14 h. An extended release preparation was shown to be effective [Junemann et al., 2006; May et al., 2008]. Oral absorption of propiverine is sitedependent and influenced by dosage form and circadiantime– dependent elimination processes [May et al., 2008].

Propiverine has combined antimuscarinic and calcium antagonistic actions [Haruno, 1992; Tokuno et al., 1993]. The importance of the calcium antagonistic component for the drug´s clinical effects has not been established. Propiverine has no selectivity for muscarinic receptor subtypes. The effects of propiverine on cardiac ion channels and action potentials were investigated by Christ et al., [2008]. Propiverine blocked in a concentration-dependent manner HERG channels expressed in HEK293 cells, as well as native I(Kr) current in ventricular myocytes of guinea pig. However, action potential duration was not prolonged in guinea-pig and human ventricular

tissue, and the investigators concluded that their results did not provide evidence for an enhanced cardiovascular safety risk with the drug .

Propiverine has been shown to have beneficial effects in patients with DO in several investigations. Thüroff et al [1998] collected 9 randomized studies on a total of 230 patients, and found a 17% reduction in micturitions per 24 hours, a 64 ml increase in bladder capacity, and a 77% (range 33-80%) subjective improvement. Side effects were found in 14 % (range 8-42%). In patients with neurogenic DO, controlled clinical trials have demonstrated propiverine´s superiority over placebo [Stöhrer et al., 1999]. Propiverine also increased bladder capacity and decreased maximum detrusor contractions. Controlled trials comparing propiverine, flavoxate and placebo [Wehnert et al., 1989], and propiverine, oxybutynin and placebo [Wehnert et al., 1992; Madersbacher et al., 1999], have confirmed the efficacy of propiverine, and suggested that the drug may have equal efficacy and fewer side effects than oxybutynin. In a comparative RCT including 131 patients with neurogenic DO, propiverine and oxybutynin were compared [Stöhrer et al., 2007]. The drugs were found to be equally effective in increasing bladder capacity and lowering bladder pressure. Propiverine caused a significantly lower frequency of dry mouth than oxybutynin.

Also in children and adolescents with neurogenic DO, propiverine was found to be effective [Schulte-Baukloh et al., 2006; Grigoleit et al., 2006], with a low incidence rate of adverse events: <1.5% [Grigoleit et al., 2006]. A randomized, double-blind, placebo-controlled trial with parallel-group design in children aged 5–10 yr was performed by Marschall-Kehrel et al. [2009]. Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. Decrease in voiding frequency per day was the primary efficacy parameter; secondary endpoints included voided volume and incontinence episodes. There was a significant decrease in voiding frequency episodes for propiverine versus placebo. Superiority could also be demonstrated for voided volume and incontinence episodes per day. Propiverine was well-tolerated: 23% of side-effects were reported for propiverine and 20% for placebo.

In a randomised, double-blind, multicentre clinical trial, patients with idiopathic DO were treated with 15 mg propiverine twice daily or 2 mg TOLT-IR twice daily over a period of 28 days [Junemann et al., 2005]. The maximum cystometric capacity was determined at baseline and after 4 weeks of therapy. The difference of both values was used as the primary endpoint. Secondary endpoints were voided volume per micturition, evaluation of efficacy (by the investigator), tolerability, post void residual urine, and quality of life. It was found that the mean maximum cystometric capacity increased significantly ($p < 0.01$) in both groups. The volume at first urgency and the frequency/volume chart parameters also showed relevant improvements during treatment. The most common adverse event, dry mouth, occurred in 20 patients in the propiverine group and in 19 patients in the tolterodine group. The scores for the quality of life improved comparably in both groups.

Madersbacher et al. [1999] compared the tolerability and efficacy of propiverine (15 mg three times daily) oxybutynin (5 mg twice daily) and placebo in 366 patients with urgency and urgency incontinence in a randomized, double-blind placebo-controlled clinical trial. Urodynamic efficacy of propiverine was judged similar to that of oxybutynin, but the incidence of dry mouth and the severity of dry mouth were judged less with propiverine than with oxybutynin. Dorschner et al. [2000] investigated in a double-blind, multicentre, placebo-controlled, randomized study, the efficacy and cardiac safety of propiverine in 98 elderly patients (mean age 68 years), suffering from urgency, urgency incontinence or mixed urgency-stress incontinence. After a 2-week placebo run-in period, the patients received propiverine (15 mg three times daily) or placebo (three times daily) for 4 weeks. Propiverine caused a significant reduction of the micturition frequency (from 8.7 to 6.5) and a significant decrease in episodes of incontinence (from 0.9 to 0.3 per day). The incidence of adverse events was very low (2% dryness of the mouth under propiverine – 2 out of 49 patients). Resting and ambulatory electrocardiograms indicated no significant changes. The cardiac safety of propiverine was further studied by Donath et al. [2011] in two comprehensively designed mono-centric ECG studies (including 24 healthy females, followed by a second study on 24 male patients with coronary heart disease (CHD) and a pathological Pardee-Q-wave in the ECG). Both studies were placebo-controlled and compared the effects of single (30 mg s.i.d.) and multiple dosing (15 mg t.i.d.) of propiverine hydrochloride in a crossover design over 6 and 13 days, respectively., They were performed to investigate the influence of propiverine hydrochloride and its main metabolite propiverine-N-oxide on cardiac function with regard to QTc prolongation, QTc dispersion and T-wave shape. No negative effects on cardiac safety could be demonstrated.

Abrams et al. [2006] compared the effects of propiverine and oxybutynin on ambulatory urodynamic monitoring (AUM) parameters, safety, and tolerability in OAB patients. Patients (n=77) received two of the following treatments during two 2-week periods: propiverine 20 mg once daily, propiverine 15 mg three times daily, oxybutynin 5 mg three times daily, and placebo. They found that oxybutynin 15 mg was more effective than propiverine 20 mg in reducing symptomatic and asymptomatic involuntary detrusor contractions in ambulatory patients. Oxybutynin had a higher rate of dry mouth, and propiverine had

a more pronounced effect on gastrointestinal, cardiovascular, and visual function.

Yamaguchi et al. [2008] performed a multicentre, 12-week, double-blind phase III trial in Japanese men and women with OAB (1593 patients were randomized and 1584 were treated), comparing solifenacin 5 or 10 mg, propiverine 20 mg, and placebo. Changes at endpoint in number of voids/24 hours, urgency, incontinence, urgency incontinence and nocturia episodes, volume voided/void, restoration of continence and quality of life (QoL) were examined. It was found that at endpoint, there were greater reductions in mean (SD) voids/24 hours with all drug regimens than with placebo. All active treatments improved the volume voided and QoL vs placebo; solifenacin 10 mg reduced nocturia episodes and significantly improved urgency episodes and volume voided vs propiverine 20 mg, and solifenacin 5 mg caused less dry mouth. Solifenacin 10 mg caused more dry mouth and constipation than propiverine 20 mg. Wada et al. [2011] performed a prospective nonrandomized crossover study of female OAB patients, assigned alternately to treatment with propiverine (20 mg) for 8 weeks then solifenacin(5 mg) for 8 weeks or solifenacin for 8 weeks then propiverine for 8 weeks. At baseline, 8th week and 16th week, symptoms were assessed using overactive bladder symptom score (OABSS). Of the 121 patients enrolled 83 were analysed. Both drugs were effective. Urgency was further improved after switching from propiverine to solifenacin, but not after switching from solifenacin to propiverine. Solifenacin was better tolerated than propiverine.

In another multicentre, prospective, parallel, doubleblind, placebo-controlled trial, Lee et al. [2009] studied the effects of 30 mg propiverine/day in 264 OAB patients (mean age 52.2 years), 221 of whom had efficacy data available from baseline and at least one on-treatment visit with >75 compliance. The study was focused on improving urgency. Overall, among patients treated with propiverine, 39% rated their treatment as providing 'much benefit', compared with 15 % in the placebo group. Adverse events reported by 32 (22.5%) and 10 (12.7%) patients in the propiverine and placebo group were all tolerable.

Masumori et al. [2011] examined prospectively the efficacy and safety of propiverine in patients with overactive bladder (OAB) symptoms who poorly responded to previous treatment with solifenacin, tolterodine or imidafenacin. Of 73 patients enrolled (29 males and 44 females, median age 71 years), 52 completed the protocol treatment. The OABSS was significantly improved by propiverine treatment. The scores of OAB symptoms (nighttime frequency, urgency and urge incontinence) except daytime frequency also improved significantly. No increase in PVR was observed. The most frequent adverse event was dry mouth (13.7%), followed by constipation (6.8%).

In a non-controlled study in patients with wet OAB the efficacy of propiverine on symptoms and quality of life was confirmed [Komatsu et al. 2009].

Assessment

Propiverine has a documented beneficial effect in the treatment of OAB/DO (**Table 2**), and seems to have an acceptable side effect profile.

c) Flavoxate hydrochloride

Flavoxate is often discussed as a drug with mixed actions, however, its main mechanism of action may not be antimuscarinic.Flavoxate is well absorbed, and oral bioavailability appeared to be close to 100% [Guay, 2003]. The drug is extensively metabolized and plasma half-life was found to be 3.5 h [Sheu et al., 2001]. Its main metabolite (3-methylflavone-8-carboxylic acid, MFCA) has been shown to have low pharmacological activity [Cazzulani et al., 1988; Caine et al., 1991]. The main mechanism of flavoxate's effect on smooth muscle has not been established. The drug has been found to possess a moderate calcium antagonistic activity, to have the ability to inhibit phosphodiesterase, and to have local anesthetic properties; no antimuscarinic effect was found [Guarneri et al., 1994]. Uckert et al. [2000], on the other hand, found that in strips of human bladder, the potency of flavoxate to reverse contraction induced by muscarinic receptor stimulation and by electrical field stimulation was comparable, It has been suggested that pertussis toxin-sensitive G-proteins in the brain are involved in the flavoxate-induced suppression of the micturition reflex, since intracerebroventricularly or intrathecally administered flavoxate abolished isovolumetric rhytmic bladder contractions in anesthetized rats [Oka et al., 1996].

The clinical effects of flavoxate in patients with DO and frequency, urgency and incontinence have been studied in both open and controlled investigations, but with varying rates of success [Ruffman, 1988]. Stanton [1973] compared emepronium bromide and flavoxate in a double-blind, cross-over study of patients with detrusor overactivity and reported improvement rates of 83% and 66% after flavoxate or emepronium bromide, respectively, both administered as 200 mg 3 times daily. In another double-blind, cross-over study comparing flavoxate 1200 mg/day with that of oxybutynin 15 mg daily in 41 women with idiopathic motor or sensory urgency, and utilising both clinical and urodynamic criteria, Milani et al. [1993] found both drugs effective. No difference in efficacy was found between them, but flavoxate had fewer and milder side effects. Other investigators, comparing the effects of flavoxate with those of placebo, have not been able

to show any beneficial effect of flavoxate at dosages up to 400 mg three times daily [Briggs et al., 1980; Chapple et al., 1990; Dahm et al., 1995]. In general, few side effects have been reported during treatment with flavoxate. On the other hand its efficacy, compared to other therapeutic alternatives, is not well documented (**Table 2**).

• Assessment

No RCTs seem to have been performed with flavoxate during the last decade. The scarcity of documented clinical efficacy should be considered before using the drug.

3. CLINICAL USE OF ANTIMUSCARINICS

The clinical relevance of efficacy of antimuscarinic drugs relative to placebo has been questioned. Herbison et al. [2003] stated in a widely discussed article: "Anticholinergics produce significant improvements in overactive bladder symptoms compared with placebo. The benefits are, however, of limited clinical significance" Large meta-analyses of studies performed with the currently most widely used drugs [Chapple et al., 2005; 2008; Novara et al., 2008], clearly show that antimuscarinics are of significant clinical benefit. Novara et al. [2008] reviewed 50 RCTs and 3 pooled analyses, which they considered of good methodological quality. They concluded that still more clinical studies are needed to decide which of the drugs should be used as first-, second-, or third-line treatment. Reviewing information from more than 12,000 references, Chapple et al. [2008], based their conclusions ("antimuscarinics are efficacious, safe, and well tolerated treatments") on 73 RCTs selected for their meta-analysis. It was recommended that since the profiles of each drug (see below) and dosage differ, these factors should be considered in making treatment choices.

The durability of the effects of antimuscarinics is not known and the relapse rate of symptoms after discontinuation of treatment has not been systematically studied. In 173 women with OAB symptoms for >6 months, Lee et al.[2011] studied in a prospective, randomized, open-label, trial what happened 3 months after the patients had been successfully treated for 1, 3, or 6-months. The relapse rate was 62%, and the request for treatment was 65 %, indiretly suggesting an efficacy of treatment. None of the antimuscarinic drugs in common clinical use (darifenacin, fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin, tolterodine or trospium) is ideal as a first-line treatment for all OAB/DO patients. Optimal treatment should be individualized, implying that the patient´s co-morbidities and concomitant medications, and the pharmacological profiles of the different drugs, should be taken into consideration [Chapple et al., 2008].

To compare the effects of different antimuscarinic drugs for OAB symptoms, Madhuvrata et al. [2012] analyzed 86 trials, 70 with parallel and 16 with cross-over designs (31,249 adults). They concluded that when the prescribing choice is between oral immediate release oxybutynin or tolterodine, tolterodine might be preferred for reduced risk of dry mouth. ER preparations of oxybutynin or tolterodine might be preferred to immediate release preparations because there is less risk of dry mouth. Comparing solifenacin and immediate release tolterodine, solifenacin might be preferred for better efficacy and less risk of dry mouth. Fesoterodine might be preferred over ER tolterodine for superior efficacy, but has higher risk of withdrawal due to adverse events and higher risk of dry mouth.

Several studies have documented that the persistence with prescribed antimuscarinic therapy for overactive bladder is low [Kelleher et al., 2005; Basra et al.,2008; Sears et al; Wagg et al., 2012]. The most common causes seem to be lack of efficacy and adverse effects. However, there is some evidence suggesting that the tolerability of the different antimuscarinics may differ. Wagg et al. [2012] analysed prescription data for patients receiving antimuscarinics for treatment of the OAB syndrome over a 12-month period. At 12 months, they found that the proportions of patients still on their original treatment were: solifenacin 35%, tolterodine ER 28%, propiverine 27%, oxybutynin ER 26%, trospium 26%, tolterodine IR 24%, oxybutynin IR 22%, darifenacin 17%, and flavoxate 14%. The longest mean persistence was reported for solifenacin (187 days versus 77 − 157 days for the other treatments). Gomes et al. [2012] compared the persistence of oxybutynin or tolterodine therapy among older patients newly prescribed one of these drugs. This was a retrospective cohort study of Ontarians aged 66 years and older. Persistence with treatment was defined on the basis of refills for the drug within a grace period equal to 50% of the prescription duration. The authors identified 31,996 patients newly treated with oxybutynin and 24,855 newly treated with tolterodine. After 2 years of follow-up, persistence on oxybutynin (9.4%) was significantly lower than that on tolterodine (13.6%, $p < 0.0001$). The median time to discontinuation of oxybutynin and tolterodine was 68 and 128 days, respectively. Kessler et al. [2011] analyzed 69 trials enrolling 26,229 patients with OAB with the aim was to compare adverse events of antimuscarinics using a network meta-analytic approach that overcomes shortcomings of conventional analyses. They found similar overall adverse event profiles for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride, but not for oxybutynin orally administered when currently used starting dosages were compared. They concluded that most currently used antimuscarinics seem to be equivalent first choice drugs to start the treatment of OAB, except for oral oxybutynin dosages of ≥ 10 mg/day, which may have more unfavorable adverse event profiles.

Even if the use of antimuscarinics are associated with many adverse effects, they are generally

considered to be 'safe' drugs. However, among the more serious concerns related to their use is the risk of cardiac adverse effects, particularly QT prolongation and induction of polymorphic ventricular tachycardia (torsade de pointes), and increases in heart rate (HR) [Andersson and Olshansky, 2007; Andersson et al., 2011]. QT prolongation and its consequences are not related to blockade of muscarinic receptors, but rather linked to inhibition of the hERG potassium channel in the heart. However, the experiences with terodiline, an antimuscarinic drug that caused torsade de pointes in patients [Connolly et al., 1991; Stewart et al., 1992], have placed the whole drug class under scrutiny.

The parasympathetic actions on the heart (**Figure 10**) opposes the excitatory actions of the sympathetic nervous system, and slows the heart rate (**Figure 11**). An elevated resting HR has been linked to overall increased morbidity and mortality, particularly in patients with cardiovascular diseases. The prevalence of CV comorbidities was found to be significantly higher in patients with than without OAB [Andersson et al., 2010]. Since mean changes in HR reported in population studies might not be applicable to an individual patient, and particularly in patients at risk of cardiac disease, even moderate increases in HR might be harmful. The potential of the different antimuscarinic agents to increase HR and/or prolong the QT time has not been extensively explored for all agents in clinical use. Differences between drugs cannot be excluded, but risk assessments based on available evidence are not possible.

II. DRUGS ACTING ON MEMBRANE CHANNELS

1. CALCIUM ANTAGONISTS

Calcium channels play an important role in the regulation of free intracellular calcium concentrations and thereby contribute to the regulation of smooth muscle tone [Berridge, 2008] Two major groups of calcium channels include the voltage-gated [Caterall et al., 2003] and the store-operated channels [Leung et al., 2008]. While both can contribute to the maintenance of smooth tone in general, store-operated calcium channels apparently contribute only to a limited if any extent to the regulation of bladder smooth muscle tone [Schneider et al., 2004 a; b]. On the other hand, various types of voltage-operated calcium channels have been implicated in the regulation of bladder smooth muscle including Q-type [Frew and Lundy, 1995] and L-type channels [Wuest et al., 2007]. The latter appears to be of particular importance as inhibitors of L-type channels have repeatedly been shown to inhibit bladder contraction in

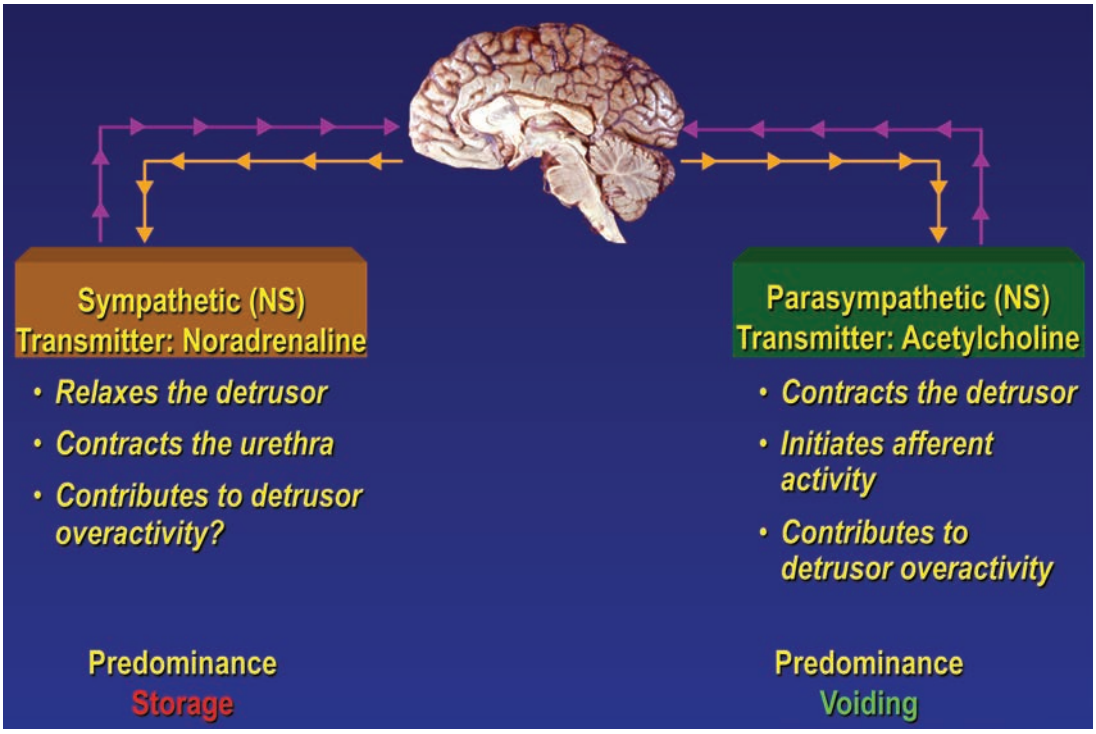


Figure 10 : Cardiac control via the autonomic nervous system. Acetylcholine, released from parasympathetic nerve terminals activate muscarinic receptors that mediate decrease in heart rate, decrease in force of contraction, and decrease in conduction velocity.

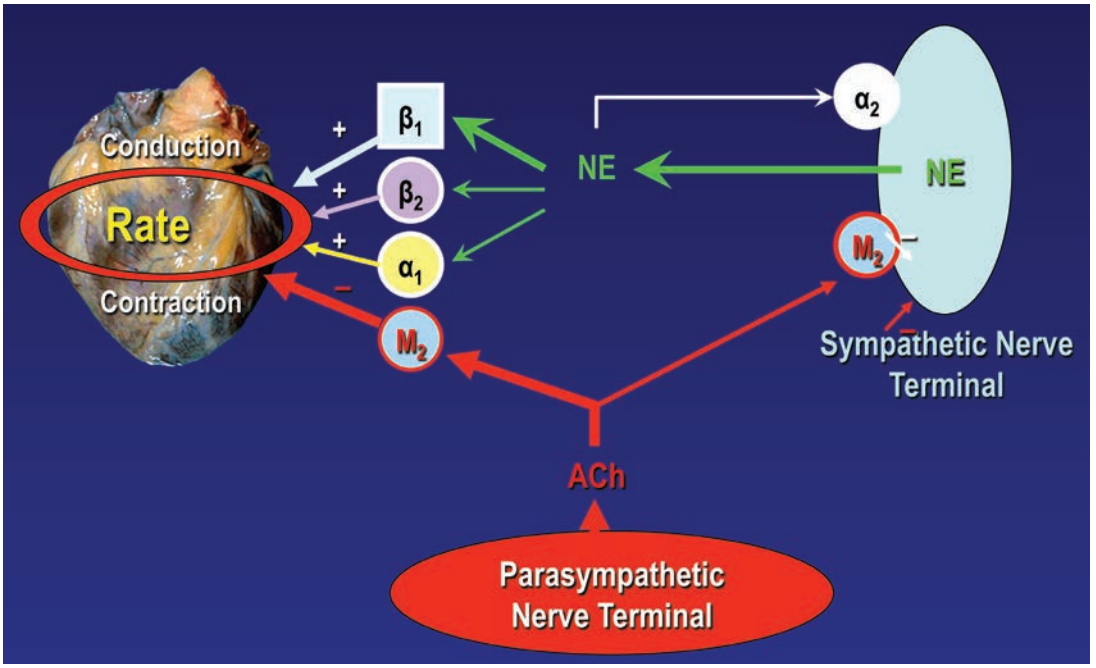


Figure 11: Autonomic receptors controlling heart rate. Acetylcholine, released form parasympathetic nerve terminals, activate muscarinic M2 receptors that mediate a decrease in heart rate. Inhibition of these receptors by antimuscarinics may increase heart rate.

vitro with tissue from multiple mammalian species, including humans [Frazier et al., 2008]. However, the relative importance of L-type channels may be somewhat less in humans than in other mammalian species [Wuest et al., 2007]. In confirmation of the role of L-type calcium channels, it has been shown that knock-out mice lacking a crucial subunit of this channel exhibit a markedly impaired bladder contractility [Wegener et al., 2004].

While these in vitro data suggest a possible role for calcium channel inhibitors, particularly those of L-type channels, in the treatment of DO and incontinence, only limited clinical studies are available in this regard. One urodynamic study compared the effects of intravesical installation of the calcium channel inhibitor verapamil, the muscarinic receptor antagonists oxybutynin and trospium and placebo to patients with urgency or urgency incontinence. While the two muscarinic receptor antagonists significantly increased bladder capacity, verapamil treatment was not associated with relevant changes in bladder function [Fröhlich et al., 1998]. In a clinical study of limited size the calcium channel inhibitor nimodipine (30 mg per day) did not significantly improve the number of incontinence episodes as compared to placebo [Naglie et al., 2002]. Larger studies with clinical endpoints related to effects of calcium channel inhibitors have not been reported in incontinent patients (based upon a Medline search using the MeSH terms “calcium channel blockers” and “urinary incontinence”). Moreover, it should be noted that despite a long-standing and wide-spread use of calcium channel inhibitors in the treatment of cardiovascular disease, there are no major reports on impaired bladder contractility as a side effect of such treatment. The reasons for the discrepancy between the promising in vitro and the lack of clinical data are not fully clear, but it may relate to pharmacokinetic properties of the currently used drugs which may insufficiently either reach or penetrate bladder tissue in therapeutically administered doses. At present, there is no clinical evidence to support a possible use of calcium channel inhibitors in the treatment of bladder dysfunction (**Table 2**). No new information has been added since the assessment in 2008 [Andersson et al., 2009].

2. POTASSIUM CHANNEL OPENERS

In a similar fashion to calcium channels, potassium channels also contribute to the membrane potential of smooth muscle cells and hence to the regulation of smooth muscle tone. Numerous types of potassium channels exist [Gutman et al., 2003; Petkov et al., 2012]. With regard to bladder function, ATP-dependent (KATP) and big calcium-activated (BKCa) channels have been studied most intensively. The BKCa channels also appear to be important physiologically as their activation can cause hyperpolarization of bladder smooth muscle cells and by this mechanism they can contribute to the relaxation of bladder smooth muscle by, e.g., β-adrenoceptor agonists [Frazier et al., 2008]. Openers of both KATP [Howe et al., 1995; Hu et al., 1997; Martin et al., 1997] and

BKCa channels [Hu et al., 1997; Sheldon et al., 1997] have been shown to induce bladder smooth muscle relaxation in various mammalian species, but the density of some types of potassium channels may differ markedly between species. Some potassium channel openers have also been shown to suppress non-voiding detrusor contractions in vivo in animal models of DO [Howe et al., 1995; Martin et al., 1997; Tanaka et al., 2003] and this also includes activators of the KCNQ type of potassium channels [Streng et al., 2004]. Although potassium channel openers are believed to mainly act directly on smooth muscle cells [Gopalakrishnan and Shieh, 2004; Petkov et al., 2012], they may also at least in part affect bladder function by modulating the activity of afferent neurones [Tanaka et al., 2003].

While the above data demonstrate the potential of potassium channel openers to inhibit non-voiding detrusor contractions, these channels are expressed not only in bladder, but also e.g. in vascular smooth muscle. Therefore, potassium channel openers may also affect cardiovascular function, and in effective doses may considerably lower blood pressure [Howe et al., 1995; Shieh et al., 2007]. While some compounds of this class have a certain degree of selectivity for the bladder as compared to the cardiovascular system, it remains unclear whether the degree of selectivity offers a sufficiently large therapeutic window for clinical use. This consideration has led to a considerable hesitancy to study potassium channel openers in OAB patients. Nevertheless, one randomized, placebo-controlled clinical study on the KATP opener ZD0947 has been reported [Chapple et al., 2006]. While ZD0947 at the chosen dose did not lower blood pressure or cause adverse events typical for a vasodilating drug, it also failed to achieve superiority relative to placebo for the treatment of OAB symptoms. Therefore, despite promising preclinical efficacy data, potassium channel openers at present are not a therapeutic option and may never become one due to a lack of selectivity for bladder over cardiovascular tissues (**Table 2**).

Another way to use potassium channels to normalize bladder function was suggested by Christ et al. [2001] in a rat model of detrusor hyperactivity. They injected “naked” hSlo/pcDNA3 (maxiK channel) into the bladder and found a significant amelioration of the hyperactivity. As to whether this principle can be therapeutically useful in man is currently under investigation.

III. α-ADRENOCEPTOR (AR) ANTAGONISTS

It is well documented that α1-AR antagonists can ameliorate lower urinary tract symptoms in men [Andersson, 2002; McVary et al., 2011; Oelke et al., 201l; Lepor et al., 2012]. Currently used α1-AR antagonists are considered effective for treatment of both storage and voiding symptoms in men with LUTS associated with or suggestive of BPH [Lepor et al., 2012]. However, in a study where tamsulosin was given alone, or together with tolterodine, to patients with male LUTS and OAB symptoms, monotherapy with the drug was not effective [Kaplan et al., 2006]. In an RCT from Korea, doxazosin monotherapy resulted in only minimal effects in IPSS storage subscore, urgency episodes and no improvement in the patient perception of bladder condition (PPBC) [Lee et al., 2011]. Thus, there is no convincing evidence that α-AR antagonists, given as monotherapy, are effective in patients with storage symptoms only.

A pivotal question is if better efficacy and/or tolerability can be obtained by highly subtype selective drugs than with the commonly used alternatives. α1-ARs include three receptor subtypes, α1A, α1B, and α1D, that are structurally and pharmacologically distinct and have different tissue distributions [Andersson and Gratzke, 2007]. α1A-ARs are the predominant subtype in the human prostate, where they mediate smooth muscle contraction. A fourth subtype, α1L, also present in human prostate, is derived from the same gene as α1A, but α1L- and α1A-receptors have different pharmacologic properties and bind some α-AR antagonists with different affinities. The precise structural relationship between the two subtypes remains to be elucidated.

Selectivity for α1B-AR has been considered disadvantageous from a cardiovascular point of view [Schwinn et al,, 2004; Schwinn and Roehrborn, 2008]. Kojima et al. [2008)] studied the expression of α1-AR in the transitional zone of prostates from 55 patients with BPH, comparing patients treated with tamsulosin presumed to block α1A-ARs and naftopidil presumed to block α1D-ARs. However, the selectivity of naftopidil for α1D- vs α1A-ARs is modest [Take et al., 1998] and its use as a tool to separate between α1-AR subtypes is questionable. Nevertheless, the tamsulosin and naftopidil groups were classified as α1A-AR dominant (22 and 12 patients) and α1D-AR dominant (11 and 16, respectively). The efficacy of tamsulosin and naftopidil differed depending on the dominant expression of the α1-AR subtype in the prostate. Tamsulosin was more effective in patients with dominant expression of the α1A-AR subtype, whereas naftopidil was more effective in those with dominant expression of the α1D-AR subtype. In another study, the same group assessed whether there was a direct correlation between the prostatic expression of α1-AR subtype mRNA and severity of LUTS or bladder outlet obstruction [Kojima et al., 2010]. They found no direct correlation between the expression of α1-AR subtype mRNA in the prostate and severity of LUTS or BOO, although there was a significant regression of this expression with patient age. Kojima et al. [2010] concluded that the expression level of α1-AR subtype mRNA in the prostate could be a predictor of the efficacy of subtype selective α1-AR antagonists in patients with BPH, and

suggested that genetic differences were responsible for the diverse responses to the drugs.

Silodosin (KD-3213), which has a high selectivity for α1A-ARs [Tatemichi et al., 2006a; b; Lepor and Hill, 2010; Yoshida et al., 2011], had clinically good effects on both voiding and storage symptoms in men with BPH [Kawabe et al., 2005; Yoshida et al., 2007; Marks et al., 2009a,b; Chapple et al., 2010; Morganroth et al., 2010; Yoshida et al., 2011]. Chapple et al. [2010] conducted a multicenter double-blind, placebo- and active-controlled parallel group study comparing silodosin, tamsulosin, and placebo. A total of 1228 men ≥50 yr of age with an International Prostate Symptom Score (IPSS) ≥13 and a urine maximum flow rate (Qmax) >4 and ≤15ml/s were selected at 72 sites in 11 European countries. The patients were entered into a 2-wk wash-out and a 4-wk placebo run-in period. A total of 955 patients were randomized (2:2:1) to silodosin 8 mg (n=381), tamsulosin 0.4 mg (n=384), or placebo (n=190) once daily for 12 wk. Its overall efficacy was not inferior to tamsulosin. Only silodosin showed a significant effect on nocturia over placebo. There was no significant difference between the two α1-AR antagonists and the placebo in terms of Qmax. There was also no difference between the two α-AR antagonists for the QoL parameter, whereas both were better than the placebo. Active treatments were well tolerated, and discontinuation rates due to adverse events were low in all groups (2.1%,1.0%, and 1.6% with silodosin, tamsulosin, and placebo, respectively).The most frequent adverse event with silodosin was a reduced or absent ejaculation during orgasm (14%), a reversible effect as a consequence of the potent and selective α1A-AR antagonism of the drug. The incidence was higher than that observed with tamsulosin (2%); however, only 1.3% of silodosin-treated patients discontinued treatment due to this adverse event. Silodosin treatment improved DO and obstruction grade by decreasing detrusor opening pressure, detrusor pressure at Qmax, bladder outlet obstruction index and Schafer´s obstruction class significantly [Yamanishi et al., 2009]. In a different open, nonblinded prospective study silodosin 8 mg lead to a significant increase in bladder capacity at first desire to void with no significant change in maximum cystometric capacity. In the voiding phase mean detrusor pressure at maximum flow significantly decreased, mean bladder outlet obstruction index decreased significantly and obstruction grade as assessed by the Schaefer nomogram improved significantly [Matsukawa et al., 2009].

It thus seems that selective blockade of α1A-ARs is a clinically effective approach, and silodosin is an effective and well-tolerated treatment for the relief of both voiding and storage symptoms in male patients with LUTS, even if treatment is associated with a high incidence of ejaculatory dysfunction.

Interest has also been focussed on the α1-ARs (α1D), specifically in the bladder [Schwinn et al., 2004; Schwinn and Roehrborn, 2008], assuming that these receptors were responsible for storage symptoms. However, the inter-relationship between the α1D-ARs in the human detrusor smooth muscle and the pathophysiology of LUTS is unclear. Naftopidil was shown to significantly improve the OAB symptom score [Sakai et al., 2011] and urgency episodes [Yokoyama et al., 2009]. Ikemoto et al. [2003] gave tamsulosin and naftopidil to 96 patients with BPH for 8 weeks in a crossover study. Whereas naftopidil monotherapy decreased the I-PSS for storage symptoms, tamsulosin monotherapy decreased the I-PSS for voiding symptoms. However, this difference (which was suggested to depend on differences in affinity for α1-AR subtypes between the drugs) could not be reproduced in a randomized head to head comparison between the drugs [Gotoh et al, 2005]. Based on available evidence, it therefore cannot be concluded that the α1D-ARs on the detrusor smooth muscle are the main therapeutic target. However, α1D-ARs may have effects on different locations in the bladder beside the detrusor smooth muscle: the detrusor vasculature, the urothelium, and the afferent and efferent nerve terminals and intramural ganglia [Andersson and Gratzke, 2007]. The importance and functional role of this observation remain to be established.

In females, treatment with OAB, α1-AR antagonists seem to be ineffective. In an RCT, comprising 364 women with OAB, no effect of tamsulosin vs placebo could be demonstrated [Robinson et al., 2007]. On the other hand, voiding symptoms in women with functional outflow obstruction, or LUTS, were treated (with modest success) with an α1-AR antagonist [Kessler et al., 2006, Low et al., 2008]. It should be remembered that in women, these drugs may produce stress incontinence [Dwyer and Teele, 1992].

In patients with neurogenic DO, treatment with a1-AR antagonists was moderately successful [Abrams et al., 2003].

IV. β-ADRENOCEPTOR AGONISTS

In isolated human bladder, non-subtype selective β-AR agonists like isoprenaline have a pronounced inhibitory effect, and administration of such drugs can increase bladder capacity in man [Andersson, 1993]. However, the β-ARs of the human bladder were shown to have functional characteristics typical of neither β1-, nor β2- ARs, since they could be blocked by propranolol, but not by practolol or metoprolol (β1) or butoxamine (β2) [Nergard et al., 1977; Larsen, 1979]. On the other hand, early receptor binding studies using subtype selective ligands, suggested that the β-ARs of the human detrusor are primarily of β2 subtype [Andersson

1993], and favourable effects on DO were reported in open studies with selective β2-AR agonists such as terbutaline [Lindholm and Lose, 1986]. In a double-blind investigation clenbuterol 0.01 mg 3 times daily was shown to have a good therapeutic effect in 15 of 20 women with DO [Gruneberger, 1984]. Other investigators, however, have not been able to show that non-subtype selective β-ARs agonists represent an effective therapeutic principle in elderly patients with DO [Castleden and Morgan, 1980], or in young patients with myelodysplasia and DO [Naglo et al, 1981].

However, three subtypes (β1, β2, and β3) have been identified in the detrusor of most species, including humans [Andersson and Arner, 2004; Michel and Vrydag, 2006]. Also the human urothelium contains all three receptor subtypes [Otsuka et al., 2008]. Studies, using real-time RT-PCR, have revealed a predominant expression of β3-AR mRNA in human detrusor muscle [Nomiya and Yamaguchi, 2003; Michel and Vrydag, 2006, , Igawa et al., 2010] and the functional evidence for an important role in both normal and neurogenic bladders is convincing [Fujumura et al., 1999; Igawa et al., 1999; Takeda et al., 1999; Morita et al., 2000; Igawa et al., 2001; 2010; Biers et al., 2006; Michel and Vrydag, 2006; Badawi et al., 2007; Leon et al., 2008]. The human detrusor also contains β2-ARs, and most probably both receptors are involved in the physiological effects (relaxation) of noradrenaline in this structure [Andersson and Arner 2004; Michel and Vrydag, 2006; Igawa et al., 2010].

The generally accepted mechanism by which β-ARs induce detrusor relaxation in most species, is activation of adenylyl cyclase with the subsequent formation of cAMP (**Figures 12 and 13**). However, there is evidence suggesting that in the bladder K+ channels, particularly BKCa channels, may be more important in β-AR mediated relaxation than cAMP [Hudman et al., 2000; Frazier et al., 2005; Uchida et al., 2005; Frazier et al., 2008]. Aizawa et al. [2010] showed that the β3-AR agonist, CL316,243, could inhibit filling-induced activity in mechanosensitive Aδ-fibers, but not in C-fiber primary bladder afferents of the rat bladder. However, the drug was able to inhibit prostaglandin (PG) E2-induced C-fiber mediated hyperactivity.

Since β-ARs are present in the urothelium, their possible role in bladder relaxation has been investigated [Murakami et al., 2007; Otsuka et al., 2008]. Murakami et al. [2007] found that the relaxation responses of the detrusor were not influenced

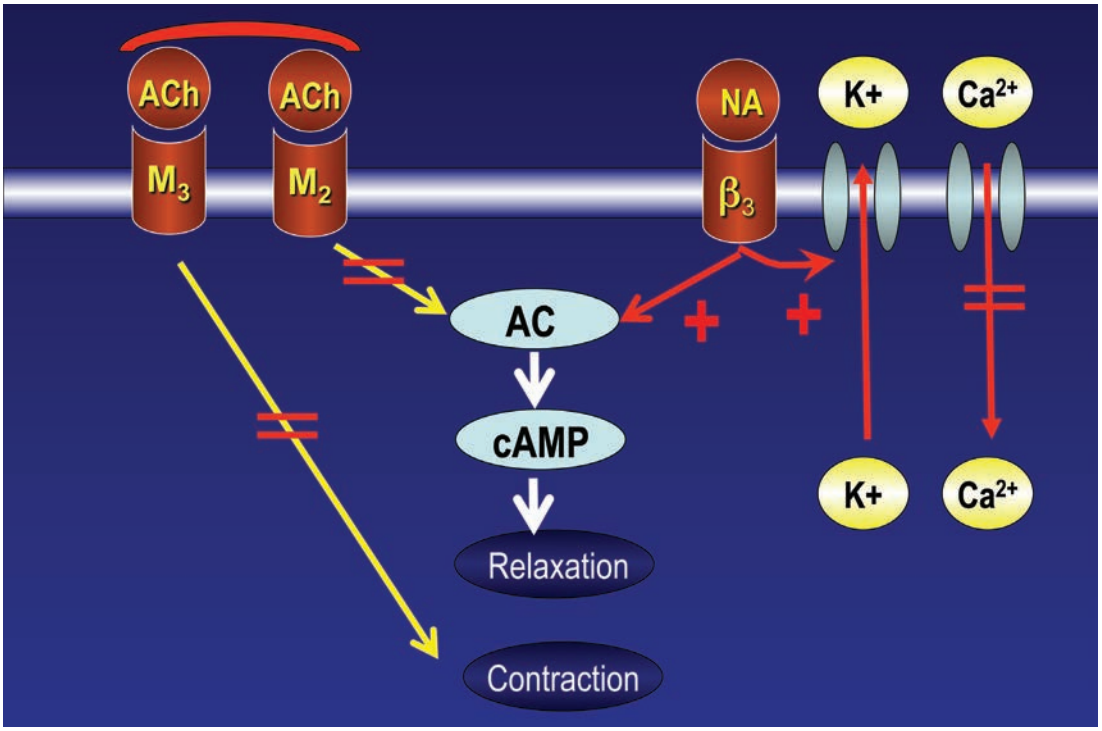


Figure 12 : During bladder filling, there is normally no parasympathetic nervous outflow to the bladder and no release of acetylcholine (ACh). The sympathetic nervous system is active and releases noradrenaline (NA) that via β3 adrenoceptors stimulates adenylyl cyclase (AC) and generation of cyclic AMP (cAMP) which mediates relaxation of the bladder. In addition, β3-adrenoceptor stimulation activate K+ channels, stimulating outflow of K+, which causes hyperpolarisation and inhibition of Ca2+ inflow.

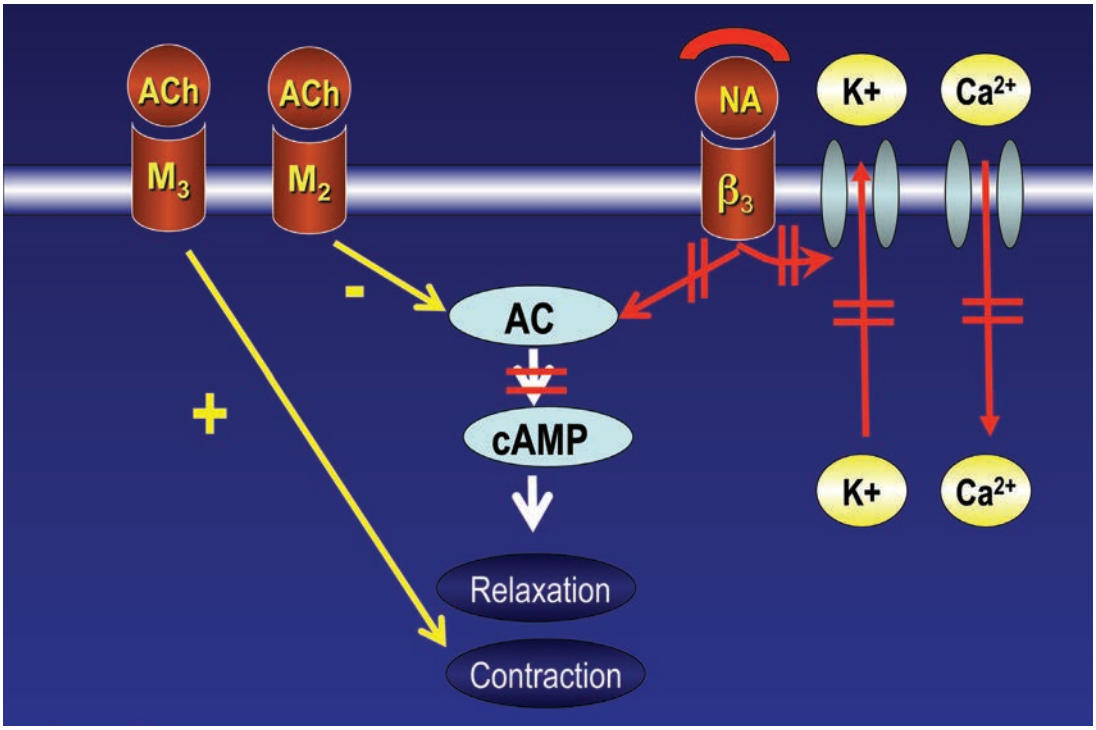


Figure 13: During voiding, the parasympathetic system is activated, releasing acetylcholine (ACh) which causes bladder contraction, directly via muscarinic M3 receptor stimulation, and indirectly by inhibition of adenylyl cyclase (AC) via stimulation of muscarinic M2 receptors. The sympathetic nerve activity is turned off. In vivo exogenous stimulation of the β3-adrenoceptors by β3-adrenoceptor agonists is not sufficient to inhibit the muscarinic receptor mediated activation, which implies that the voiding contraction is not compromised.

by the urothelium. However, isoprenaline was more potent at inhibiting carbachol contractions in the presence of the urothelium than in its absence. It was suggested that this might reflect the release of an inhibitory factor from the urothelium. Further support for this hypothesis was given by Otsuka et al. [2008]. However, to what extent a urothelial signaling pathway contributes in vitro and in vivo to the relaxant effects of β-AR agonists in general, and β3-AR agonists specifically, remains to be elucidated.

The in vivo effects of β3-AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), β3-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume [Fujimura et al., 1999; Woods et al., 2001; Takeda et al., 2002; Kaidoh et al., 2002; Igawa et al., 2010]. For example, Hicks et al. [2007] studied the effects of the selective β3-AR agonist, GW427353, in the anesthetized dog and found that the drug evoked an increase in bladder capacity under conditions of acid evoked bladder hyperactivity, without affecting voiding.

A number of β3-AR selective agonists are currently being evaluated as potential treatment for OAB in humans including GW427353 (solabegron) and YM178 (mirabegron) [Colli et al., 2007; Igawa et al., 2010; Saito et al., 2011; Tyagi and Tyagi, 2011] (**Figure 14**).

Mirabegron. Takusagawa et al. [2012] found that mirabegron was rapidly absorbed after oral administration. It circulates in the plasma as the unchanged form, its glucuronic acid conjugates and other metabolites. Of the administered dose, 55% is excreted in urine, mainly as the unchanged form, and 34% is recovered in feces, almost entirely as the unchanged form. Mirabegron is highly lipophilic and is metabolized in the liver via multiple pathways, mainly by cytochrome P450 3A4 and 2D6 (CYP2D6) [van Gelederen et al., 2009]. In a Phase I pharmacokinetic study, sixteen healthy volunteers, phenotyped as either poor or extensive metabolizers of CYP2D6 were enrolled The volunteers received a 160 mg single oral dose after overnight fasting. Poor metabolizers excreted a slightly higher urinary fraction of mirabegron (15.4±4.2%) than extensive metabolizers (11.7±3.0%). Tmax in both extensive and poor metabolizers was about

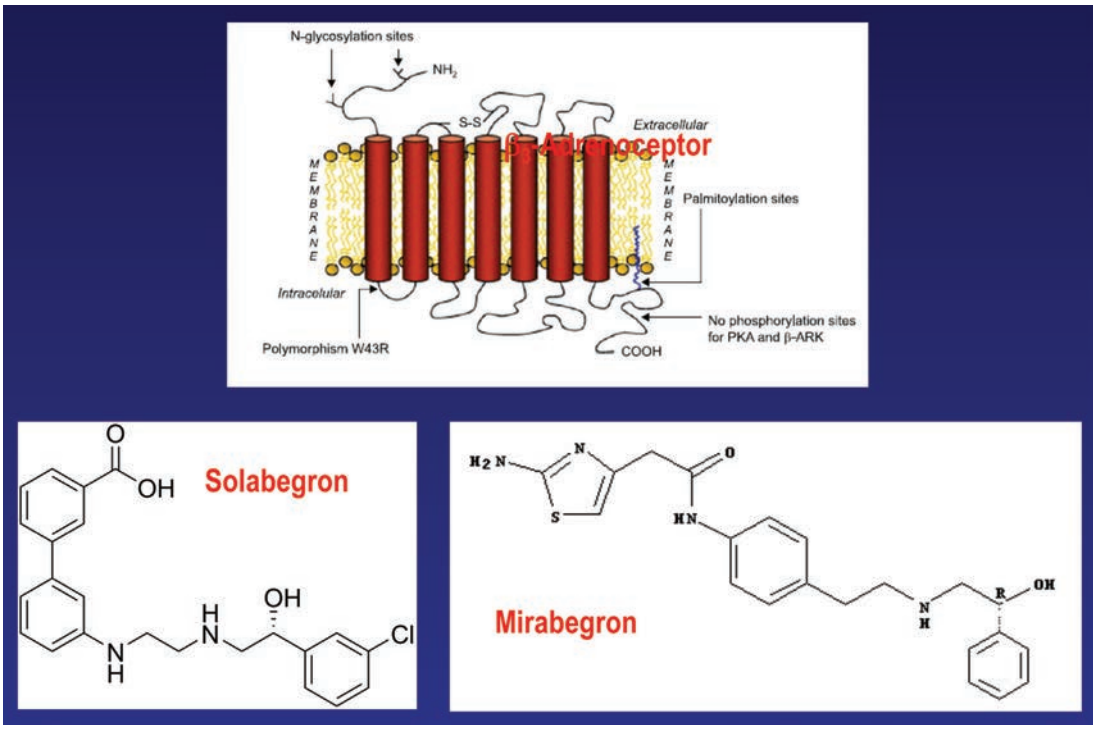


Figure 14: The β3-adrenoceptor is the predominating β-adrenoceptor subtype in the bladder. Stimulation by highly selective β3-adrenoceptor agonists like mirabegron and solabegron may inhibit symptoms of overactive bladder without affecting the ability to empty the bladder.

2 hours and the terminal elimination half-life (t1/2) approximately 23-25 hours.

Chapple et al. [2008] reported the results of a phase IIA trial of mirabegron in patients with OAB. The Blossom trial, conducted in several European countries, was a proof of concept study. It enrolled 314 patients with OAB symptoms - 262 patients were randomly assigned to 4 groups: placebo, mirabegron 100 mg bid, mirabegron 150 mg bid, and tolterodine 4 mg qd for a 4-week treatment period. The primary endpoint was efficacy, and the primary efficacy variable was the change in the mean number of micturitions per 24 hours as recorded on a frequency/volume chart. In both mirabegron groups significant improvements in the mean number of micturitions per 24 hours were found compared with the placebo group (−2.19 and −2.21 vs. −1.18, respectively). Mean volume voided was dose-dependently increased in the mirabegron groups, and the change reached significance in the mirabegron 150 mg group. Urgency episodes per 24 hours decreased significantly in both mirabegron groups compared with the placebo group. No severe adverse events were reported and treatment was generally well tolerated. A small, mean increase in pulse rate with mirabegron 150 mg (5 beats per minute) was demonstrated, but this was not associated with a clinically significant increase in adverse events such as tachycardia and palpitations. This successful phase IIA trial was followed by a phase IIB trial in OAB patients carried out in Europe [Chapple et al., 2010]. This trial was a dose-ranging study of once-daily mirabegron (an extended release formula of mirabegron) with multiple arms (placebo, mirabegron 25 mg, 100 mg, 150 mg, and 200 mg qd, for a 12-week treatment period), and the primary endpoint was to evaluate the dose-response relationship on efficacy. The mean number of micturitions per 24 hours decreased dose-dependently, and the decreases were statistically significant with mirabegron 50 mg, 150, and 200 mg compared with placebo. The mean volume voided per micturition increased dose-dependently, and the increases were significant with mirabegron 50 mg and more. Adverse events were experienced by 45.2% of the patients - the incidence of adverse events was similar among all treatment groups (placebo 43.2% vs. mirabegron 43.8-47.9%). The overall discontinuation rate owing to adverse events was 3.2% (placebo 3.0% vs. mirabegron 2.4-5.3%). The most commonly reported adverse events considered treatment-related was gastrointestinal disorders, including constipation, dry mouth, dyspepsia, and nausea. There was no patient-reported acute retention. No significant difference in ECG parameters between

the groups was demonstrated. However, a small but significant increase in mean pulse rate was observed after mirabegron 100 mg and 200 mg (1.6 and 4.1 beats per minute, respectively), although this was not in associated with an increase in cardiovascular adverse events.

Nitti et al. [2011] reported on a phase III multicentre, randomized, double-blind, parallel-group,placebo-controlled trial of mirabegron in North America. They enrolled 1328 patients ≥18 years with OAB symptoms for ≥3 months. Patients who completed a 2-week, single-blind, placebo run-in and had ≥8 micturitions/24 h and ≥3 urgency episodes/72 h (with or without incontinence) during a 3-day micturition diary period, were randomized to receive placebo, or mirabegron 50 or 100 mg once daily for 12 weeks. Co-primary endpoints were change from baseline to final visit (study end) in the mean number of incontinence episodes/24 h and micturitions/24 h. Efficacy was assessed according to patient micturition diaries and safety assessments included adverse event (AE) reporting. Patients were randomized and received study drug (placebo: n=453; mirabegron 50 mg: n=442; mirabegron 100 mg: n=433). Mean age was 60.1 years, 74.3% were female, 29.7% had urgency incontinence, 38.1% had mixed stress/urgency incontinence with urgency predominant and 32.2%had frequency without incontinence. At the final visit, mirabegron 50 and 100 mg showed statistically significant improvements in the co-primary efficacy endpoints and mean volume voided/micturition compared with placebo. Statistically significant benefits were achieved at the first-measured time point of Week 4. The incidence of AEs was similar across the placebo and mirabegron 50 and 100 mg groups (50.1, 51.6 and 46.9%, respectively). The most common (≥3%) AEs in any treatment group were hypertension (6.6, 6.1 and 4.9%, respectively), urinary tract infection (1.8, 2.7 and 3.7%), headache (2.0, 3.2 and 3.0%) and nasopharyngitis (2.9, 3.4 and 2.5%).

Khullar et al. [2011] performed a similarly designed study i Europe and Australia, enrolling 1978 patients, which included a fourth arm in which tolterodine SR 4 mg was used as a comparator. Like the American study, Khullar et al. [2011] found that mirabegron caused a statistically significant improvements from baseline compared with placebo in the number of urgency incontinence episodes and number of micturions per 24 hours. Mirabegrom 50 and 100 mg was numerically superior to tolterodine in these two key OAB symptoms, but the study was not powered for further analysis. Mirabegrom 50 and 100 mg was well tolerated, no differences being found between the placebo arm and the two mirabegron arms. In particular, the incidence of hypertension or UTI were identical. In contrast with tolterodine, no increased dry mouth incidence was observed with mirabegron.

Mirabegron has been shown to be effective in the treatment of the OAB syndrome and has been approved for clinical use on this indication in Japan. The Japanese label contains a warning: “Avoid administration to patients of reproductive age”. Mirabegron is currently under consideration for approval in Europe (EMA). In the US, the drug was approved in June 2012.

A positive effects of solabegron in patients with the OAB syndrome has also been documented in an RCT [Ohlstein et al., 2012].

V. PHOSPHODIESTERASE (PDE) INHIBITORS

Drugs stimulating the generation of cAMP are known to relax smooth muscles, including the detrusor [Andersson, 1999; Andersson and Wein, 2004]. It is also well established that drugs acting through the NO/cGMP system can relax the smooth muscle of the bladder outflow region [Andersson and Arner, 2004]. Use of PDE inhibitors to enhance the presumed cAMP- and cGMP-mediated relaxation of LUT smooth muscles (detrusor prostate, urethra) should then be a logical approach [Andersson et al., 1997; 2007; 2011]. There are presently 11 families of PDEs, some of which preferentially hydrolyse either cAMP or cGMP [Uckert et al., 2006] (**Figure 15**).

As a basis for PDE inhibitor treatment of LUTS, Uckert et al. [2006] investigated human bladder tissue, revealing messenger RNA for PDEs 1A, 1B, 2A, 4A, 4B, 5A, 7A, 8A, and 9A; most of these PDEs preferably inhibit the breakdown of cAMP. In vitro, human detrusor muscle responded poorly to sodium nitroprusside, and to agents acting via the cGMP system [Truss et al., 2000]. However, significant relaxation of human detrusor muscle, paralleled by increases in cyclic nucleotide levels, was induced by papaverine, vinpocetine (a low affinity inhibitor of PDE 1), and forskolin (stimulating the generation of cAMP), suggesting that the cAMP pathway and PDE 1 may be important in regulation of detrusor smooth muscle tone [Truss et al., 2001]. Significant dose-dependent relaxations were also induced by human cAMP analogs [Truss et al., 2001]. With these studies as a background, Truss et al. presented preliminary clinical data with vinpocetine in patients with urgency/urgency incontinence or low compliance bladders, and not responding to standard antimuscarinic therapy [Truss et al., 2000]. This initial open pilot study suggested a possible role for vinpocetine in the treatment of OAB. However, the results of a larger RCT in patients with DO showed that vinpocetine only showed statistically significant results for one parameter [Truss et al., 2001]. Studies with other PDE 1 inhibitors than vinpocetin (which may not be an optimal drug for elucidation the principle) do not seem to have been performed.

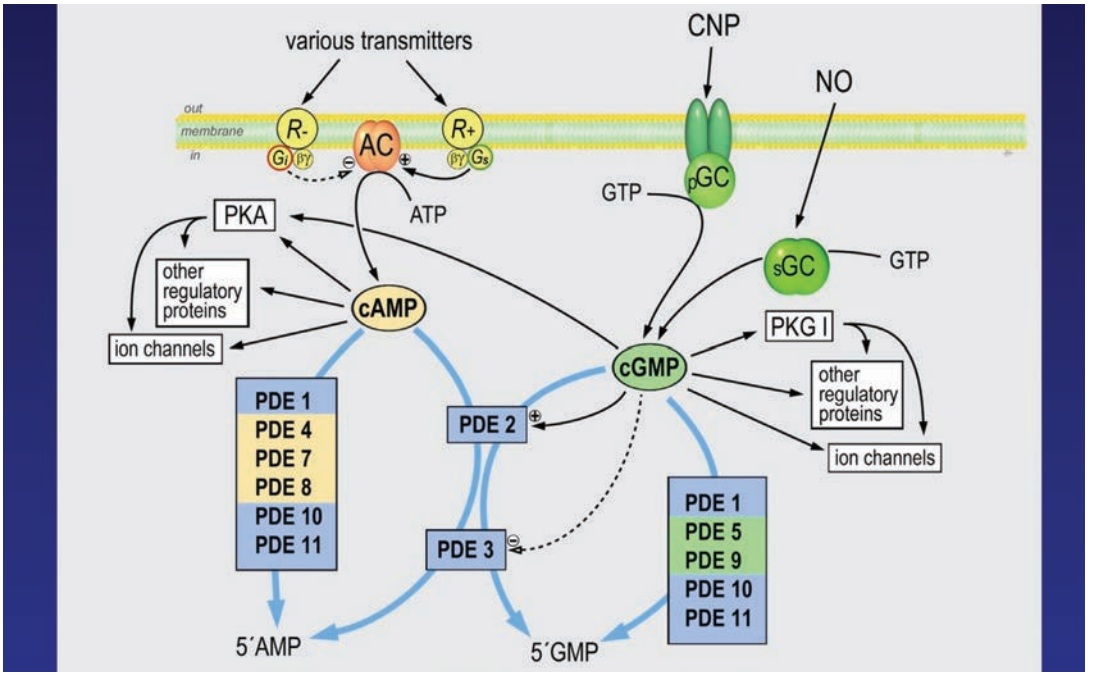


Figure 15: Families of phosphodiesterases (PDE). Inhibitors of both cyclic AMP and cyclic GMP may have inhibitory effects on bladder contraction. However, so far only inhibitors of PDE5 (inhibiting degradation of cyclic GMP) have been clinically useful for treatment of lower urinary symptoms in males.

PDE 4 (which also preferably hydrolyses cAMP) has been implicated in the control of bladder smooth muscle tone. PDE 4 inhibitors reduced the in vitro contractile response of guinea pig [Longhurst et al., 1997] and rat [Kaiho et al., 2008] bladder strips, and also suppressed rhythmic bladder contractions of the isolated guinea pig and rat bladder [Gillespie and Drak., 2004; Nishiguchi et al., 2007]. Previous experiences with selective PDE 4 inhibitors showed emesis to be a dose -limiting effect [Giembycz, 2005]. If this side action can be avoided, PDE 4 inhibition seems to be a promising approach.

Oger and co-workers showed that PDE5-inhibitor sildenafil-induced relaxation of human detrusor smooth muscle involved cGMP-, cAMP- and K(+) channel-dependent signalling pathways, with a minor contribution from NO [Oger et al., 2010]. In combination with the α1-AR antagonist doxazosin, sildenafil reduced adrenergic tone of prostatic and cavernosal smooth muscle and their combination provided a significant benefit when targeting relaxation of both tissues [Oger et al., 2008].

In-vivo, several studies have indicated a role for PDE5-inhibitors in the regulation of micturition function. Systemic vardenafil reduced both non-voiding contractions and bladder afferent nerve firing in unanesthetized, decerebrate, spinal cord injury rats, indicating potential mechanisms by which PDE5-Is improve storage symptoms in SCI patients [Behr-Roussel et al., 2010]. The effect of vardenafil on OAB-symptoms could be related to a cGMP-dependent RhoA/ROCK signaling inhibition, as shown in spontaneously hypertensive rats (SHR) [Morelli et al., 2009a; Morelli et al., 2009b]. Using the same animal model, bladder hypoxia was significantly reduced by acute vardenafil treatment [Morelli et al., 2009b]. Thus, besides relaxing muscular wall, PDE5 inhibition may positively affect urinary bladder blood perfusion. In the same respect, tadalfil was shown to increase prostate tissue oxygenation in SHR and human vesicular-deferential artery is characterized by a high expression and activity of PDE5, which was inhibited by tadalafil in vitro; these results suggest another possible mechanism through which PDE5i exert beneficial effects on LUT symptoms [Morelli et al., 2011].

NO has been demonstrated to be an important inhibitory neurotransmitter in the smooth muscle of the urethra and its relaxant effect is associated with increased levels of cyclic GMP [Andersson and Arner, 2004]. However, few investigations have addressed the cAMP- and cGMP-mediated signal transduction pathways and its key enzymes in the mammalian urethra. Morita et al. examined the effects of isoproterenol, prostaglandin E1 and E2, and SNP on the contractile force and tissue content of cAMP and cGMP in the rabbit urethra [Morita et al., 1994]. They concluded that both cyclic nucleotides can produce relaxation of the urethra. Werkström et al.[2006] characterized the distribution of PDE 5, cGMP and PKG1 in female pig and human urethra,

and evaluated the effect of pharmacological inhibition of PDE-5 in isolated smooth muscle preparations. After stimulation with the NO donor, DETA NO-NO-ate, the cGMP-immunoreactivity (IR) in urethral and vascular smooth muscles increased. There was a wide distribution of cGMP- and vimentin-positive interstitial cells between pig urethral smooth muscle bundles. PDE-5 IR could be demonstrated within the urethral and vascular smooth muscle cells, but also in vascular endothelial cells that expressed cGMP-IR. Nerve-induced relaxations of urethral preparations were enhanced at low concentrations of sildenafil, vardenafil and tadalafil, whereas there were direct smooth muscle relaxant actions of the PDE-5 inhibitors at high concentrations. Fibbi et al. [2009] confirmed that the highest expression and biological activity of PDE5 was found in bladder. However, a consistent PDE5 expression and activity was also found in prostatic urethra. In contrast, the prostate gland showed the lowest PDE5 abundance and cultures derived from this tissue were less sensitive to vardenafil. Using a different animal model associated with C-fibre afferent activation, it was shown that the NO/cGMP signalling pathway is involved in the regulation of the micturition reflex, with an action that seems more predominant on the sensory rather on the motor component of the micturition reflex [Caremel et al., 2010].

The observation that patients treated for erectile dysfunction with PDE5 inhibitors had an improvement of their LUTS, has sparked a new interest in using these drugs also for treatment of LUTS and OAB. After the report in an open study that treatment with sildenafil appeared to improve urinary symptom scores in men with ED and LUTS [Sairam et al., 2002], this observation has been confirmed in several well designed and conducted RCTs.

To date, 12 RCTs are available comparing the effect of PDE5 inhibitors alone to placebo and the combination of alpha-blockers and PDE5 inhibitors vs alpha-blockers alone [Bechara et al., 2008; Gacci et al., 2011; Kaplan et al., 2007; Liguori et al., 2009; McVary et al., 2007a; b; Porst et al., 2009; 2011; Roehrborn et al., 2008; Stief et al., 2008; Tamimi et al., 2010; Tuncel et al., 2010]. In these studies, different PDE5 inhibitors and different doses were administered.

PDE5-inhibitors significantly improve IPSS and IIEF scores, but not Qmax when compared to placebo. According to a recent meta-analysis by Gacci and co-workers, differences in IPSS score were significantly lower in older and obese patients [Gacci et al., 2011]. The combination of PDE5-inhibitors and alpha-blockers lead to significant improvements of the IPSS and IIEF score as well as Qmax when compared to the use of alpha-blockers alone. Recently, Dmochowski showed that tadalafil once daily for LUTS had no significant effect on bladder function as measured by detrusor pressure at maximum urinary flow rate or such as maximum detrusor pressure and bladder outlet obstruction index while improving IPSS [Dmochowski et al., 2010]. PDE5-inhibitors were generally shown to be safe and well tolerated.

The mechanism behind the beneficial effect of the PDE inhibitors on LUTS/OAB and their site(s) of action largely remain to be elucidated. If the site of action were the smooth muscles of the outflow region (and the effect relaxation), an increase in flow rate should be expected. In none of the trials referred to such an effect was found. (However, see Oelke et al.[2012]). On the other hand, there are several other structures in the LUT that may be involved, including those in the urothelial signaling pathway (urothelium, interstital cells, and suburothelial afferent nerves). In general, it is believed that major mechanisms contributing to LUTS include reduced nitric oxide/cyclic guanosine monophosphate signaling pathway, increased RhoA kinase pathway activity, autonomic overactivity, increased bladder afferent activity and pelvic ischemia [Andersson et al., 2011].

In practical considerations it has to be mentioned that only tadalafil has been recently approved for the the treatment of LUTS due to benign prostatic obstruction; long-term experience with PDE5 inhibitors in patients with LUTS is still lacking [Oelke et al., 2011]. In addition, insufficient information is available on the combination of PDE5 inhibitors with other LUTS medications such as 5-alpha-reductase-inhibitors.

VI. ANTIDEPRESSANTS

Several antidepressants have been reported to have beneficial effects in patients with DO [Lose et al., 1989; Martin and Schiff, 1984]. The use of antidepressants was shown to be an independent risk factor for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men (Krimpen Study) [Kok et al., 2009].

1. IMIPRAMINE

Imipramine is the only drug that has been widely used clinically to treat this disorder. Imipramine has complex pharmacological effects, including marked systemic antimuscarinic actions [Baldessarini, 1985] and blockade of the reuptake of serotonin and noradrenaline [Maggi et al., 1989], but its mode of action in DO has not been established [Hunsballe and Djurhuus, 2001]. Even if it is generally considered that imipramine is a useful drug in the treatment of DO, no good quality RCTs that can document this have been retrieved. It has been known for a long time that imipramine can have favourable effects in the treatment of nocturnal enuresis in children with a success rate of 10-70 % in controlled trials [Glazener et al., 2003; Hun-

sballe and Djurhuus, 2001]. It is well established that therapeutic doses of tricyclic antidepressants, including imipramine, may cause serious toxic effects on the cardiovascular system (orthostatic hypotension, ventricular arrhythmias). Imipramine prolongs QTc intervals and has an antiarrhythmic (and proarrhythmic) effect similar to that of quinidine [Bigger et al., 1977; Giardina et al., 1979]. Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants [Baldessarini, 1985]. The risks and benefits of imipramine in the treatment of voiding disorders do not seem to have been assessed. Very few studies have have been performed during the last decade [Hunsballe and Djurhuus, 2001; Natalin et al., 2009]. No good quality RCTs have documented that the drug is effective in the treatment DO. However, a beneficial effect has been documented in the treatment of nocturnal enuresis.

A prospective (no controls) study the impact of the "three-drug therapy" (antimuscarinic, alpha-blocker and tricyclic antidepressants) on the treatment of refractory detrusor overactivity (DO) showed a significant increase on bladder capacity and decreases on urgency, urge-incontinence and frequency. Objective urodynamic data as well as symptom score improved significantly with triple therapy [Natalin et al., 2009].

Selective serotonin-reuptake-inhibitors (SSRIs) have been tested with regard to their effects on OAB symptoms. Milnacipran hydrochloride, a serotonin-norepinephrine reuptake inhibitor (SNRI), or paroxetine hydrochloride, a selective serotonin reuptake inhibitor, were analyzed in a prospective open trial in neurogenic OAB-patients. Milnacipran reduced daytime urinary frequency, improved the quality of life index and increased bladder capacity as shown in urodynamic studies. No such changes were noted in the other categories of the lower urinary tract symptoms questionnaire or urodynamic studies, or in the paroxetine group [Sakakibara et al., 2008].

2. DULOXETINE

Duloxetine hydrochloride is a combined norepinephrine and serotonin reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function [Katofiasc et al., 2002; Thor and Katofiasc, 1995]. Bladder capacity was also increased in this model, both effects mediated centrally through both motor efferent and sensory afferent modulation [Fraser and Chancellor, 2003]. In a placebo-controlled study, the drug showed efficacy in patients with OAB [Steers et al., 2007]. The number of micturition episodes, the primary outcome, was reduced by 2 in the duloxetine arm and by 0.5 in the placebo arm. Episodes of urgency incontinence were also significantly reduced by duloxetine. These data have not been reproduced so far in another trial. However, the high withdrawal rate observed across all studies in which the drug was evaluated fou SUI, affecting 20-40% of the patients at short-term and up to 90% in long-term studies, do not predict clinical utility of duloxetine in OAB.

VII. CYCLOOXYGENASE (COX) INHIBITORS

Prostanoids (prostaglandins and thromboxanes) are synthesized by cyclooxygenase (COX) from a common precursor, arachidonic acid. Prostanoids may be involved in the control of bladder function under normal and pathological conditions, including DO and OAB. Human bladder mucosa has the ability to synthesize eicosanoids [Jeremy et al., 1987], and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma [Downie and Karmazyn, 1984; Leslie et al., 1984]. Even if prostaglandins cause contraction of human bladder muscle, it is still unclear whether prostaglandins contribute to the pathogenesis of unstable detrusor contractions. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling. Involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be effective. However, clinical evidence for this is scarce.

Cardozo et al. performed a double-blind controlled study of 30 women with DO using the prostaglandin synthesis inhibitor flurbiprofen at a dosage of 50 mg 3 times daily [Cardozo et al., 1980a]. The drug was shown to have favourable effects, although it did not completely abolish DO. There was a high incidence of side effects (43%) including nausea, vomiting, headache and gastrointestinal symptoms. Palmer studied the effects of flurbiprofen 50 mg x 4 versus placebo in a double-blind, cross-over trial in 37 patients with idiopathic DO (27% of the patients did not complete the trial) [Palmer, 1983]. Active treatment significantly increased maximum contractile pressure, decreased the number of voids and decreased the number of urgent voids compared to baseline. Indomethacin 50 to 100 mg daily was reported to give symptomatic relief in patients with DO, compared with bromocriptine in a randomized, single-blind, cross-over study [Cardozo and Stanton, 1980b]. The incidence of side effects was high, occurring in 19 of 32 patients.

Although these early clinical studies with nonselective COX inhibitors showed some promise in the treatment of these disorders, the drugs were not further developed for this indication mainly due to side effects. The interest in the use of selective COX-2 inhibitors was hampered by concerns about long-term cardiovascular toxicity with these drugs.

VIII. TOXINS

Intravesical pharmacological therapy for LUTS stems from the fact that circumventing systemic administration of active compounds offers two potential advantages. First, high concentrations of pharmacological agents can be given to the bladder tissue producing enhanced local effects. Second, drugs inappropriate for systemic administration due to off target effects can be safely used. Attractive as it may be, intravesical pharmacological therapy should still be considered as a second line treatment in patients refractory to oral therapy or patients who do not tolerate its systemic side effects. However, this statement is based on the assumption that intervention therapy should follow oral medication. Research aiming at defining if patients subgroups will benefit of intravesical therapy as first line is clearly necessary. An ongoing trial to define tolerability and cost effectiveness of daily antimuscarinic therapy versus a single intra-detrusor injection of 100U of BoNT/A for treatment of urgency urinary incontinence is at this moment under way [Visco et al., 2012].

1. BOTULINUM TOXIN

a) Mechanism of action of BONT

Botulinum toxin (BonT) is a neurotoxin produced by *Clostridium botulinum*, Of the seven subtypes of BONT, sub-type A (BONT-A) has the longest duration of action, making it is the most relevant clinically. BoNT/A is available in three different commercial forms, with the proprietary names of Botox®, Dysport®, Xeomin®, and Prosigne. Although the toxin is the same, it is wrapped by different proteins which modify the relative potency of each brand. This was the basis for the introduction of the non-proprietary names onabotulinum toxin A (onabotA), abobotulinum toxin A (abobotA) and incobotulinum toxin A (incobotA) for Botox®, Dysport® and Xeomin®, respectively. Prosigne is the proprietary name of a BoNT/A produced in China, which currently does not have a known non-proprietary name. Although potency of each one is usually expressed in units (U) the doses are not inter-changeable. Clinical dose conversion studies for the lower urinary tract do not exist. Available information indicates that onabotA is roughly three times more potent than abobotA and equivalent to incobotA. Nevertheless these equivalences should be approached with caution. Comprehensive reviews have been produced during the last few years. [Chapple and Patel., 2006; Nitti, 2006; Patel et al., 2006; Dinis et al., 2007; Karsenty et al., 2008; Apostolidis et al., 2009; Silva and Cruz, 2009; Dowson et al., 2010; Duthie et al., 2011; Mangera et al., 2011].

Most of the information available about intravesical application of BoNT/A derives from the use of onabotA (Botox®). However, in addition to sub-type A, some studies have investigated the effect of detrusor injection sub-type B, rimabotulinumtoxinB (proprietary names being Miobloc™ or Neurobloc™ according to countries). For further details see section 9.1.13 below.

BoNT consists of a heavy and a light chain linked by a disulphide bond. In the synaptic cleft the toxin binds to synaptic vesicle protein or SV2 [Dong et al., 2006] by the heavy chain before being internalized by the nerve terminal along with the recycling process of synaptic vesicles (**Figure 16**). The two chains are then

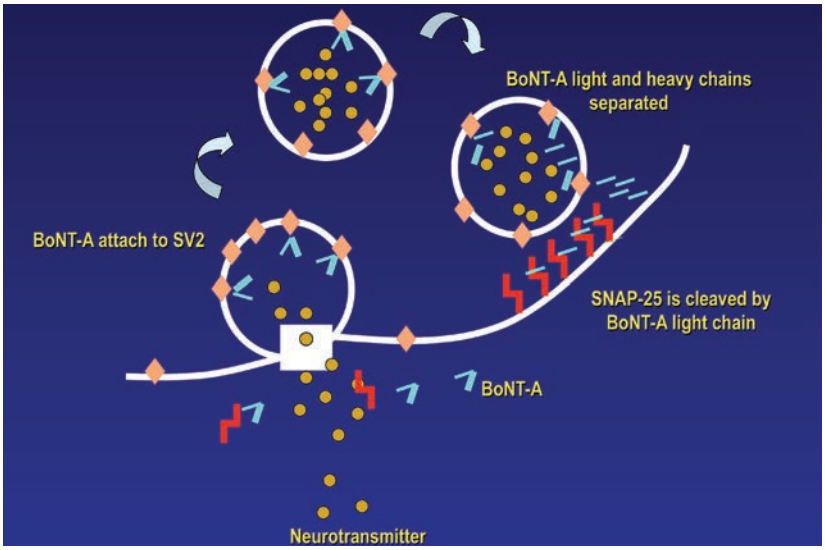


Figure 16 : Mechanism of action of botulinum toxin (BoNT). BoNT consists of a heavy and a light chain linked by a disulphide bond. In the synaptic cleft the toxin binds to synaptic vesicle protein or SV2 by the heavy chain before being internalized by the nerve terminal along with the recycling process of synaptic vesicles. The two chains are then cleaved and the light chain passes into the cytosol, where it cleaves the attachment proteins involved with the mechanism of fusion of synaptic vesicles to the cytoplasmatic membrane necessary for neurotransmitter release. Attachment protein (SNARE or soluble N-ethylmaleimidesensitive fusion attachment protein receptor) include synaptosome associated protein 25 kD (SNAP 25), synaptobrevin (vesicle associated membrane protein -VAMP) and syntaxin.

cleaved and the light chain passes into the cytosol, where it cleaves the attachment proteins involved with the mechanism of fusion of synaptic vesicles to the cytoplasmatic membrane necessary for neurotransmitter release. Attachment protein (SNARE or soluble N-ethylmaleimidesensitive fusion attachment protein receptor) include synaptosome associated protein 25 kD (SNAP 25), synaptobrevin (vesicle associated membrane protein -VAMP) and syntaxin. BonT/A cleaves SNAP 25 rendering the SNARE complex inactive [Humeau et al., 2000; Chancellor et al., 2008]. Subtype B, acts preferentially through the inactivation of VAMP [Humeau et al., 2000].

BonT/A application was extensively evaluated in striated muscle. In this tissue paralysis occurs by prevention of acetycholine (ACh) release from cholinergic motor nerve endings [Humeau et al., 2000]. Accumulation of neurotransmitter containing synaptic vesicles is followed by terminal axonal degeneration. Striated muscle paralysis recovers within 2 to 4 months time. During this time axons develope lateral sprouts and eventually regenerate completely [de Paiva et al., 1999].

In the human bladder SV2 and SNAP-25 expression has been demonstrated in parasympathetic, sympathetic and sensory fibers [Coelho et al., 2011]. Almost all parasympathetic nerves express the two proteins [Coelho et al., 2011]. As these nerves play a fundamental role for detrusor contraction during voiding, the blockade of ACh release is believed to play an essential role in detrusor hypo- or acontractility that follows BoNT/A injection in the bladder. In accordance with this view, it was shown that in normal or SCI animals BoNTA treatment decreased the bladder contractions evoked by electrical stimulation of spinal nerves without altering intrinsic contractions [Ikeda et al., 2012]. However cholinergic axon sprouting concomitant with clinical remission could not been documented in the detrusor [Haferkamp et al., 2004].

Bladder sensory impairment is also expected to play an important role in the final effect of BoNT/A bladder injection. About half of the peptidergic sensory fibers express SV2 and SNAP25 [Coelho et al, 2011]. BoNT/A inhibits the spinal cord release of glutamate, substance P (SP) and CGRP from sensory nerves [Purkiss et al., 2000; Aoki et al., 2005; Meng et al., 2007] as well as the release of neuropeptides at the peripheral extremities [Rapp et al., 2006; Lucioni et al, BJU Int, 2008]. BoNT/A has also been shown to reduce the suburothelial immunoreactivity for TRPV1 or P2X3 [Apostolidis et al., 2005]. Morenilla Palao et al. [2004] have shown that BonT/A impedes TRPV1 trafficking from intracellular vesicles to the neuronal membrane, a process that is also dependent on SNARE proteins. All these mechanisms may contribute to the recent observation that BoNT/A reduces afferent firing from bladder afferents and antidromic release of neuropeptides [Ikeda et al., 2012]. Although SV2 and SNAP-25 immunoreactivity has not been detected in urothelial cells [Coelho et al., 2011], urothelial function seems also compromised after BoNT/A administration. BonT/A has been shown to inhibit ATP release from urothelium in animal models of spinal cord injury [Khera et al.,2004; Smith et al., 2008]. Therefore, it is not surprising that administration of BoNT/A to inflamed rat bladders reduces spinal c-fos counts at the L6 and S1 spinal cord segments [Vemulakonda et al., 2005].

Cleaved, inactive SNAP-25 appears rapidly after BoNT/A injection. In the guinea-pig a robust expression of cleaved SNAP 25 could be detected already at 12 hours and maximum intensity could be detected at 24 hours with little changes afterwards. In guinea-pigs cleaved SNAP-25 expression was restricted to nerve fibers. Almost all parasympathetic fibers, either preganglionic and postganglionic were affected while less than half of the sensory fibers express the cleaved protein [Coelho et al., 2012a; b]. In the human urinary bladder cleaved SNAP 25 could be detected in NDO patients up to 11 months after BoNT/A injection. [Schulte-Baukloh et al., 2007]. The longer duration of cleaved SNAP 25 in the detrusor smooth muscle than in striated muscles, has no firm explanation at the moment. However the longer persistence of the inactive form of SNAP-25 plus the involvement of pre and postganglionicparasympathetic neurons may contribute to persistence of the BoNT/A effect in the bladder.

Interstitial cells (ICs) in the suburothelium form a syncytium through extensive coupling via the gap-junction protein connexin 43 and have close contacts with sensory nerves. These facts led to the hypothesis that ICs act as modulators of bladder behaviour [Wiseman et al., Apostolidis et al., 2006]. However, the expression of connexin 43 is not altered by BoNT/A [Roosen et al, 2009]. Hence, at the moment a firm evidence for the action of BoNT/A on ICs is scant.

BonT/A may decrease the levels of neurotrophic agents in the bladder tissue. Levels of Nerve Growth Factor (NGF) [Giannantoni et al.,; Liu et al., 2009] and Brain-derived Neurotrophic Factor (BDNF) [Pinto et al., 2010] have been shown to decrease in the bladder and/or urine following BoNT/A injections. As both neurotrophins have paramount roles for growth, maintenance and plasticity of peptidergic sensory nerves, these findings may point toward another mechanism whereby BonT/A acts upon the bladder.

b) BoNT/A effects on bladder histology

There is no evidence that repeated injections of onabotA into the detrusor muscle cause inflammatory infiltrates, fibrotic activity or apoptosis within the bladder wall [Comperat et al., 2006, Apostolidis et al., 2008, Kessler et al.]. Rather the reverse, one study demonstrated that NDO patients treated with BonT/A had less fibrosis than nontreated patients [Compérat et al., 2006]. The presence of eosinophilic infiltrate was shown to increase in specimens of patients receiving multiple treatments, a finding that could not be fully explained [Apostolidis et al., 2008].

c) BoNT/A injection protocol

When the treatment was first described in 1999 for NDO patients, onabotA was diluted in normal saline in order to obtain a concentration of 10 units/ml [Schurch et al., 2000]. Under visual control through a rigid cystoscope and a flexible 6 Fr injection needle, 30 injections of 1 ml (10 units of onabotA) were done in 30 different bladder wall locations above the trigone to prevent vesico-urethral reflux. Additional refinements have been added to this technique along the following years, including the use of a local anaesthetic agent (4% lidocaine) and a flexible cystoscope [Harper et al., 2003]. The recent demonstration that onabotA 200 U applied in 30 injections sites (1ml saline each) above the trigone is preferable to 300 U in NDO patients (200 U in 30 injections sites is the approved protocol by medical authorities) reduces the amount of onabotA per injection site to 6.66 U/ml. For abobotA larger studies used a similar technique albeit the number of injections was only 20 [del Popolo et al., 2008; Grise et al., 2010]. The number of units per injection site is obviously different taking in consideration that 500-1000 U are used [del Popolo et al., 2008]. The volume of saline at each injection site is commonly 1 ml but volumes so low as 0.25 ml per site were also used [Grise et al., 2010].

The effect of BONT/A after increasing the dose per injection site and decreasing the number of injected sites was investigated in one study. Patients were randomized to receive 300 U either in 10 or 30 sites [Karsenty et al., NAU, 2005]. The authors reported that 10 site injection was quicker and less painful and that no differences in efficacy between the two procedures could be detected up to 24 weeks. In accordance, it was found that patients receiving 300 U of onabotA distributed over 30 injection sites (30 ml of fluid in total) or the same dose of toxin distributed over 10 injection sites (10 ml of fluid in total) had a similar distribution of the fluid, as determined by MRI. About 1/3 to 1/4 of the total detrusor volume was covered by the two protocols, respectively [Mehnert et al, 2009].

When considering IDO or BPS/IC patients the most relevant aspects in the injection protocol is the smaller amount of toxin at each site, as most studies used onabotA 100 or 200 U or abobotA 500 U [see Mangera et al., 2011, Giannantoni et al., 2012 for reviews]. Another variable at stake is the trigone injection. The suggested risks of injecting bladder trigone were never demonstrated, whether onabotA or abobotA was used [Karsenty et al., 2007; Citeri et al., 2008; Mascarenhas et al., 2008; Pinto et al, 2010). A few studies have, therefore, compared trigonal vesus trigonal sparing protocols in IDO patients. A recent trial randomised 22 IDO patients to receive abobotA 500 U administration in 20 injections (1ml each) sparing the trigone against 15 off the trigone plus 5 injections in the trigone [Manecksha et al., 2011]. Mean postvoid residual volumes and clean intermittent self-catheterisation rates between the two groups were similar. However the change from baseline of the OABSS score was greater in the trigone injected group.

Another study compared 10 trigonal injections versus 40 detrusor or suburothelial injections of 100 U of onabotA in IDO patients [Kuo, 2007]. The most effective protocol was the 40 detrusor injections because it brought more robust symptomatic improvement which lasted longer. The trigone injection only protocol was the less effective and durable of the three, although the risk of urinary retention was null [Kuo, 2007].The suburothelial protocol brought intermediate results, worse than the detrusor but better than the trigone only technique [Kuo, 2007]. Pinto et al. [2010] injected 100 U distributed by 10 sites only in the trigone in 26 women with BPS/IC: No cases of voiding dysfunction were observed. PVR remained normal and bladder contractility index was not changed by onabotA.

Another variable of the injection technique is the volume of the saline used to reconstitute the toxin. Most studies used 1.0 mL per injection, although a few used 0.5 mL [Grosse et al., 2005; Schulte-Baukloh et al., 2005], 0.2 mL [Kuo et al., 2004], 0.25 ml [Grise et al., 2010] or even 0.1 mL per injection site [Rapp et al, Urology, 2004]. In a recent experimental study the amount of cleaved SNAP-25 induced by a fixed amount of onabotA was directly related with the volume of the injection [Coelho et al., 2012]. Thus more controlled studies designed to compare different number and locals of injection and the volume od each injection are necessary.

BoNT/A does not cross the urothelium if instilled in the bladder [Coelho et al., 2012]. Onabot/A instillation in the bladder encapsulated in liposomes may eventually overcome the urothelial barrier and induced distinctive bladder effects [Chuang et al., 2009]. However this technology has not yet been tested in humans. In contrast, electromotive administration seems to overtake this problem, at least in children. In 15 children with NDO due to myelomeningocele, a 10F indwelling catheter containing a silver spiral electrode was placed in the bladder, after providing a local transurethral anaesthesia with 2% lidocaine. The bladder was filled with saline and 10 U/kg of abobotA was added. A maximal current of 10 mA (100 mA increment/s) for 15 minutes was applied using abdominal pads [Kajbafzadeh et al., 2010]. The urodynamic and symptomatic results were excellent (see below). Skin erythema and burning sensation were de only side effects reported with this method. If this technique can be applied to adults it is not known. However, it would certainly simplify BoNT/A administration.

d) Effect of Bont/A on NDO adult patients

OnabotA 200 U is by now approved by FDA and by several European countries to treat NDO in SCI and MS patients. This was in part the consequence of the

findings of two large pivotal phase 3 studies where efficacy and safety of onabot A in about 700 patients with NDO was compared against placebo in patients with NDO and incontinence caused by multiple sclerosis (EDSS ≤ 6.5) or spinal cord injury below T1 [Cruz et al., 2011; Ginsberg et al., 2012]. About 60% of the patients were taking antimuscarinics and maintained the same dose throughout the study. Two doses, 200 and 300 U of onabotA were compared against placebo. Primary outcome measure was the change from baseline in week episodes of urinary incontinence at week 6 after treatment. Secondary outcome measures included the change from baseline in maximum cystometric capacity, maximum detrusor pressure during first involuntary detrusor contraction and quality of life using the I-QOL total score. Both studies yielded similar findings. In the first study [Cruz et al., 2011] onabotA significantly reduced UI and improved QOL in both MS and SCI patients, with no clinically relevant differences between the two doses. At week 6 mean change from baseline in weekly incontinence episodes was -21.8 in onabotA 200U, -19.4 with 300U and -13.2 with placebo ($p < 0.01$). At the same time point 7.6%, 38.0%, and 39.6% of patients in the placebo, 200U, and 300U onabotutA groups, respectively, were fully continent. The proportion of patients with no IDC was around 60% after onabotA 200 and 300 groups but only 17.4% after placebo. In the second study [Ginsberg et al., 2012], onabotA resulted in a 23,0%, 26,7% and 27,4% change from baseline in the incontinence episodes in the placebo, and 200 and 300 groups, respectively. Furthermore, 36% and 41% of patients in the 200 and 300 U groups, respectively, achieved dry status, contrasting with 10% in the placebo arm. In both studies, detrusor pressure and cystometric capacity increased significantly in the two onabotA groups, without clinically relevant differences between the two doses [Cruz et al., 2011; Ginsberg et al., 2012]. Patients could request a retreatment 12 weeks after initial treatment. Median time for saline treated patients was about 90 days days and 250 to 300 days for those treated with 200 or 300 onabotA, without differences between the two doses [Cruz et al., 2011; Ginsberg et al., 2012]. No diferences were found between patients with SCI or MS in terms of clinical response to onabotA [Cruz et al., 2011; Ginsberg et al., 2012].

The most common adverse event was UTI [Cruz et al., 2011; Ginsberg et al., 2012]. In the SCI population, the majority of which was performing CIC at baseline, the incidence was similar across all treatment groups (around 50%). In the MS population, it was highest in the onabotA 300 U arm (saline 32%, 200U: 58.5%, 300U: 70%) in the study by Cruz et al. [2011] whereas the incidence of UTI was similar, around 50%, after 200 and 300 onabotA doses in the study by Ginsberg et al., [2012]. This was related with dose dependent incidence of de novo CIC in MS patients (12.2% after saline, 29.5 after 200U, 42.2 after 300U [Cruz et al., 2011]. Ginsberg et al. [2012] observed that the incidence of CIC in patients not catheterizing at baseline was dose dependent, 10% on placebo, 35% on 200 U and 42% on 300 U, and mainly affected MS patients. The higher incidence of adverse events and the lack of clinically advantages of 300 U led to the approval of 200 U dose in NDO.

These pivotal phase 3 trials confirms observations coming from smaller trials. Schurch et al., [2005] randomized 59 NDO patients due to spinal cord injury to received onabotA 200 U, 300 U or placebo. OnabotA treated patients had a significant reduction in incontinence episodes and amelioration of urodynamic parameters versus placebo, that were still sustained 6 month post-treatment. In an additional subanalysis, onabotA also improved quality of life over placebo [Schurch et al., 2007]. No differences between onabotA 200 and 300 U were detected [Schurch et al., 2005]. A Canadian multicenter double-blind study [Herschorn et al., 2011] randomised 57 patients with NDO secondary to spinal cord injury or multiple sclerosis and urinary incontinence despite current antimuscarinic treatment to onabotA 300 U (28) or placebo (29). The mean daily number of incontinence episodes was significantly lower for onabotA than for placebo at week 6 (1.31 vs 4.76, $p<0.0001$). This effect was sustained at weeks 24 and 36. onabotA induced improvements were also seen in urodynamic and quality of life parameters and were maintained up to week 36.

Although not officially approved for NDO, abobotA has been the object of investigation in a few comparative clinical trials. A small study randomized a total of 31 NDO patients due to spinal cord injury, myelomeningocele, trauma at birth, multiple sclerosis and myelitis to intravesical injections of abobotA 500 U or placebo [Ehren et al., 2007]. Patients in the abobotA arm had a significantly higher cystometric capacity at 6 and 12 weeks, lower maximum detrusor pressure and episodes of urinary incontinence and less consumption of antimuscarinic drugs. Efficacy and safety of abotoA were, additionally, investigated in NDO patients that had abandoned antimuscarinic therapy. Two doses, 500 U (n = 39) or 750 U (n = 38) were compared. Complete continence at day 30 was observed in 22 patients (56.4%) and 28 patients (73.7%) receiving 500Uor 750U. The median delay in the reappearance of leakages was 168 days. Although there was a trend towards a greater improvement with 750 U, no statistically significant differences in terms of clinical and urodynamic variables and QoL were found between the treatment groups. Tolerability was excellent and equivalent for both doses.

The symptomatic improvement brought by BoNT/A injection in the bladder does not coincide with the moment of injection. The onset of BoNT/A effect was evaluated in a small open-label prospective study that specifically investigated the chronology of the symptomatic changes. Some improvement in urgency, nocturia and frequency could already be demonstrated as soon as 2 days after neurotoxin

injection in NDO patients [Kalsi et al., 2008]. In SCI and MS patients treated with onabotA, 200 or 300U, significant decrease in the number of incontinence episodes over placebo was first detected at week 2 after injection [Cruz et al., 2011].

A recent subanalysis of a phase 3 study showed that similar reductions in urinary incontinence episodes and proportion of patients fully dry were achieved, regardless of antimuscarinic use. Moreover, increment of maximal cystometric, decrease in detrusor pressure, improvement in quality of and median time to patient request for re-treatment were similar in anticholinergic users and non-users [Sievert et al., 2012] These observations go along with those made Reitz et al. [2004] and Grosse et al. [2005] who concluded that a substantial proportion of SCI patients could reduce or interrupt anti-muscarinic medication after BoNT/A injection.

Multiple Sclerosis patients represent a particular subgroup of patients in whom a careful analysis of the efficacy and safety of BoNT/A additional attention if voluntary voiding is present before treatment. Cohort studies clearly suggest that using onabotA 300 U reduces markedly episodes of urinary incontinence. Highly significant improvements in urgency, incontinence episodes, frequency, nocturia and urodynamic parameters (bladder capacity, volume to detrusor overactivity and maximal detrusor pressure) were observed. However, most of the patients required CIC to empty the bladder after receiving onabotA 300 U [Kalsi et al., 2007; Khan et al., 2011] In spite of this drawback, improvement in quality of life was quite remarkable indicating that patients may prefer CIC to incontinence [Kalsi et al., 2007; Khan et al., 2011]. A subanalysis of the large pivotal phase 3 study for 154 MS patients was recently reported [Cruz et al., 2011]. Fifty received saline injections, 51 onabotA 200U and 53 onabtA 300U. Weekly episodes of urinary incontinence decreased 18.1, 24.4 and 25.9 at week 6 after saline, 200 U and 300 U, respectively. About 40% of onabotA treated patients were dry at that visit, without relevant differences between the two doses. Quality of life and urodynamic parameters improved in both onabtA groups, also without relevant differences between 200 and 300 U. However, there was a dose dependent increase in post-void residual that led to CIC 2.6%, 24.3% and 37.5% of the patients after saline, 200U or 300U, respectively [Cruz et al., 2011]. Urinary infections were also higher after 200 U (58.5%) than after 300 U (70%). Therefore this subanalysis indicates that 200 U should be preferred to 300 U in for MS patients.

Whether lower that 200 U onabotA can still be effective in controlling urinary incontinence in MS patients without impairing pretreatment voluntary voiding, it is yet unclear. A pilot study with 12 MS patients with a mean EDSS of 5.0 (3.0-7.5) treated with onabotA 100 U seems to indicate that this is a valid alternative [Mehnert et al., 2010]. Daytime and night-time frequency, urgency and pad use significantly decreased while maximum bladder capacity increased. Post-void residual volume increased moderately during the initial 12 weeks but no patients required CIC. Median time to re-injection was 8 months. So, additional studies specifically designed to evaluated onabotA 100 U seems warranted in MS patients with voluntary voiding.

e) BONT/A and UTI in adult NDO patients

UTI are one of the most frequent adverse event of BoNT/A injection. In a phase 3 trial in SCI patients performing CIC, the incidence after saline or onabotA 200 and 300 U was similar, around 50%, reflecting the fact that most patients were on CIC across the three groups before treatment. In the MS population, the incidence of UTI was highest in the onabotA 300 U arm (saline 32%, 200U: 58.5%, 300U: 70%). This was eventually related with a dose dependent increase in post void residual and incidence of de novo CIC in MS patients receiving onabotA (12.2% after saline, 29.5 after 200U, 42.2 after 300U) [Cruz et al., 2011]. In a similar phase 3 trial, Ginsberg et al. [2012] found a similar incidence of UTI, of about 50%, in SCI and MS patients whether 200U or 300U were used. Although most of these infections were non-complicated, a careful exclusion of active UTI at the moment of injection and a cautious UTI screening after each BoNT/A bladder treatment seems justifiable.

A consequence of BONT/A treatment only recently noticed is a decrease in the incidence of severe urinary tract infections in NDO patients. In 30 SCI patients Gamé et al. [2008] observed that the number of pyelonephritis, orchitis and prostatitis in the 6 month before onabotA 300U, 1.75±1.87 per patient, decreased to 0.2±0.41 in the first 6 month after treatment. In 17 SCI patients that received onabotA injections for a period of 6 years, the number of urinary tract infection at the sixth year was 1.8±0.5 per year, significantly lower than at baseline, 6.7±2.1 [Giannantoni et al., 2008]. In a multicentre, cross-sectional retrospective cohort study, data from 214 NDO patients treated in 7 German centers were collected. The rate of urinary tract infections in 12 months proceeding and in the 12 months following onabotA was 68% and 28%, respectively [Boy et al., 2008]. The reason for these findings is unclear but may lie in a decreased maximum detrusor pressure resulting in less bladder wall ischemia and vesico-ureteral reflux [Wefer et al., 2009].

f) BONT/A in IDO patients

The enthusiasm of investigators rapidly produced a reasonable number of pilot studies investigating BoNT/A in patients with IDO refractory to antimuscarics. Although proper dose-escalating studies capable of defining ideal doses were lacking, investigators opted for the administration of BoNT/A in doses smaller than those initially used in NDO. That is the reason why most pilot studies used either onabot 200 U or abobot 500 U ([see list at the end, see also Mangera et al,, 2011] and 4 RCT trials compared

onabotA 200 U against placebo [Sahai et al., 2007; Brubaker et al., 2008; Flynn et al., 2009; Tincello et al., 2012]. Due to high incidence of voiding dysfunction associated with the use of onabotA 200U in IDO patients one large cohort, 100 patients, investigated the effect of onabot 100 U. Two dose escalating placebo controlled studies [Dmochowski et al., 2010; Rovner et al.,2011; Denys et al.,, 2012] investigated the ideal dose of onabotA. That dose seems to be 100 U. However, data from pivotal phase 3 studies with this dose are not yet available.

The largest placebo controlled RCT carried out until the moment was conducted in 8 centers in UK (the RELAX study) and randomised a total of 240 women with refractory DO to receive onabotA 200 U or placebo distributed by 20 bladder wall sites above the trigone (10 U/1ml) [Tincello et al., 2012]. Primary outcome was voiding frequency per 24 h at 6 months. Secondary outcomes included urgency and incontinence episodes and quality-of-life data. A total of 122 women received onabotA and 118 received placebo. Median leakage episodes were already significantly reduced by week 6 and at 6 months were 1.67 in onabotA vs 6.0 in the placebo group. Continence was more common after onabotA (31% vs 12%). Significant decreases also occurred in voiding frequency (8.3 vs 9.67) and in daily urgency episodes (3.83 vs 6.33). Quality of life scores were better in the toxin group. Urinary tract infections (31% vs 11%) and voiding difficulty requiring CIC (16% vs 4%) were more common after onabotA [Tincello et al., 2012].

Only one placebo controlled RCT on IDO [Sahai et al., 2007] included male patients (onabotA 200 U: 9 females and 7 males; Placebo 11 females and 8 males). Maximum cystometric capacity was the primary outcome measure and changes in overactive bladder symptoms, post-void residual, maximum detrusor pressure during filling cystometry, reflex detrusor volume and Quality of Life questionnaires were secondary outcome measures. Follow-up occurred at 4 and 12 weeks after injection, at which point the study was unblinded. Significant improvement in maximum cystometric capacity, urinary frequency and incontinence episodes were observed at 4 and 12 weeks in patients treated with BONT/A. Urgency was also significantly reduced over placebo only at 4 weeks. Post-void residual increased at 4 weeks but differences to placebo became insignificant by 12 weeks. Despite significant improvements in quality of life observed among patients treated with BONT/A, 37.5% of them required intermittent self-catheterization to empty the bladder. Two additional small RCT compared onabotA 200 U against placebo in women with IDO. Brubaker et al. [2008] randomized 28 women for onabotA 200 U and 15 for placebo. Approximately 60% of the women who received toxin had a clinical response based on the Patient Global Impression of Improvement. The median duration of their responses was 373 days, significantly longer than the 62 days for placebo. Post-void residual urine increased in 43% of the women in the BONT/A group (12 out of 26 women) and urinary tract infection developed in 75% of these women (9 of 12). These numbers exceeded by far the expected ranges and forced the suspension of the trial. Median duration of urinary retention after the first injection was approximately 2 month but increased to 5 months at a second injection [Brubaker et al., 2008].

Flynn et al. [2009] reported the preliminary results of a study comparing onabotA 200 or 300 U against placebo in patients with urinary incontinence. The primary outcome measure was the number of incontinence episodes per 24 hours whereas 24 hours pad weights, number of pads, voiding frequency, nocturia and urodynamic parameters at cystometry were secondary outcomes. Until the moment only 15 patients received onabot 200 or 300 U and 7 placebo, distributed by 10-12 sites above the trigone. Incontinence episodes were halved and pads per day were reduced by 2/3 in the onabotA group whereas no changes occurred in the placebo group. No changes were observed in nocturia, daily voiding frequency, peak flow or detrusor pressure in either group. Post-voiding residual over 200 ml was observed in the onabotA group. Four subjects experienced UTI, 2 in onabotA and 2 in the placebo group.

The obvious necessity of reducing micturition dysfunction in IDO patients treated with onabotA 200 U led to the investigation of the efficacy and safety of lower doses. Schmid et al. [2006] injected onabotA 100 U in 100 IDO patients refractory to antimuscarinic therapy. Treatment remained highly effective, incontinence and urgency sensation disappearing in 86% and 82% of patients, respectively, during an average period of 6 months. Temporary urinary retention only occurred in 4% of the cases, with additional 15% reporting moderate voiding difficulties.

The utterly necessary dose escalating studies were only recently accessible. Dmochowski et al. [2010] conducted a phase 2, multicenter, randomized, double-blind study were 288 females and 25 males with IDO experiencing ≥ 8 urgency incontinence episodes per week and ≥ 8 or more micturitions per day. They were randomized to receive 50, 100, 150, 200 or 300 U onabotA or placebo in 20 sites above the trigone (0.5 ml of fluid injected per site). A dose response was observed at week 12 for full continence (15.9%, 29.8%, 37.0%, 40.8%, 50.9% and 57.1% in the placebo, and 50, 100, 150, 200 and 300 U groups, respectively. However, during the full time course of the study, clear differentiation among doses of 100 to 300 U was not always apparent. MCC had small increases in placebo (49.5 ml), 50 U (50 ml) and 100 U (71 ml). At higher doses the increment become marked larger, 101 ml, 91 ml and 130 ml in 150 U, 200 U and 300 U groups [Dmochowski et al., 2010]. For other parameters like frequency and urgency, the magnitude of change was consistently less and a dose dependent response was not evident. A sustained response was absent in the placebo and 50 U

group compared to groups receiving 100 U or more. The proportion of patients with posttreatment PVR of 200 ml or greater was dose dependent and patients requiring CIC were 0%, 3,6%, 9,1% 12,7% 18,2% and 16,4 for placebo, and 50, 100, 150, 200 and 300 U groups, respectively. Another common adverse event were UTI, 16,3%, 33,9%, 44%, 48.1% and 34.5% for placebo, and 50, 100, 150, 200 and 300 U groups, respectively [Dmochowski et al., 2010]. The conclusions was that 100 U may be the dose that appropriately balances the symptom benefits with most common adverse events, in particular the risk of CIC due to increase post-void residual urine. Another dose-escalating study randomized 107 patients (87.9% women) for placebo or onabotA (50 U, 100 U or 150 U) applied through 15 injections of 1ml each above the trigone [Denys et al., 2011]. A >50% improvement in urgency and urgency incontinence versus baseline, the primary end point, was observed in 65% and 56% of patients who received 100 U and 150 U, the difference being only numerically superior to placebo. Complete continence was observed in 55% and 50% patients after 100 U and 150 U, respectively, Urodynamic improvements were consistent with 100 U and 150 U but not with 50U. The proportion of patients with a high PVR was low in all groups [Denys et al., 2011].

Two additional non-placebo controlled RCT also support onabotA 100 U as the ideal dose for IDO. Cohen et al [2009] randomized 44 OAB-dry and wet patients to receive 100 U or 150 U. No significant differences in clinical or urodynamic outcome measures were noted between the two doses. QOL was significantly improved in both groups with no difference between 100 U or 150 U. Altaweel et al. [2011]randomized 11 patients for onabotA 100U and 11 patients to onabotA 200U. No clinical or urodynamic differences were detected between the 2 groups at 3 months follow-up. Urinary retention occurred in 2 patients in the 200 U and in 1 patient in the 100 U arm.

Successful OAB treatment with onabotA does not appear to be related to the existence of DO. In a subanalysis of the dose finding study for onabotA, no differences in outcomes were found between those with and those without baseline DO [Rovner et al., 2011]. Likewise, in a cohort of 5 male and 27 female patients with OAB and without DO, improvement in frequency and urinary incontinence was observed after treatment with onabotA [Kanagarajah et al., 2011]. Two doses were tested, 100 and 150U, without no clinically relevant differences between them [Kanagarajah et al., 2011].

A small open-label prospective study specifically investigated the chronology of the onabot 200 U in IDO patients. Urgency, nocturia and frequency improved as soon as 4 days in IDO patients, therefore slightly later than in NDO cases [Kalsi et al., 2008].

These positive data must, nevertheless, be weighed against a recent negative trial for onabotA 100 U [Dowson et al., 2011]. The RCT enrolled 23 patients with a diagnosis of OAB without DO refractory to antimuscarinics to receive intradetrusor injections of either botn-A (100 U Botox) or saline (placebo). An interim analysis was performed and the trial halted as a result of poorly perceived patient benefit. Storage symptoms remained statistically unchanged following onabotA while 3 patients in the treatment arm initiated CIC [Dowson et al., 2011].

In IDO, BoNT/A is recommended for patients refractory to antimuscarinics, that is, patients that do not respond or do not tolerate the first line medication. In a retrospective analysis of the efficacy of 100-150 U of onabotA BTX-A injections in 85 patients, treatment was more successful in patients who did not tolerate anticholinergics than in those who abandoned the medication due to poor efficacy (86% vs. 60%, respectively) [Makovey et al., 2011].

g) BONT/A in children and elderly patients

In children, the dose of BONT/A should be calculated according to body weight. Doses of between 12 U/kg of weight up to a maximum dose of 300 U [Schulte-Baukloh et al., 2002] and 4 U/Kg [Corcos et al., 2002] have been used for onabotA. The maximum suggested for abobotA is 20 U/kg up to a maximum of 400 U [Altaweel et al., 2006; Akbar et al BJU Int 2007). BoNT/A has been essentially assayed in children with myelomeningocele [Schulte-Baukloh et al., 2002; 2003; Corcos et al., 2002; Riccabona et al., 2004; Kajbafzadeh et al., 2006; Altaweel et al., 2006]. Like in adults, the toxin increased bladder capacity and decreased maximal detrusor pressure. In 26 children with a mean age of 6,9 years, 19 of them (73%) became completely dry between clean intermittent catheterizations while 88% reported a global improvement in urine incontinence. Interestingly, in 11 (73%) out of the 15 children who had vesicoureteral reflux before injection, reflux either disappeared or decreased in grade. BONT/A also improved bowel function in 66% of the children with intestinal problems [Kajbafzadeh et al., 2006]. The success rate in terms of continence and cessation of antimuscarinic medication may, however, be substantially inferior to that seen in adults, potentially due to irreversible bladder wall changes associated with longstanding detrusor overactivity [Altaweel et al., 2006]. In a group of 20 children with myelomenigocele continence was achieved in only 13 children. At a second injection, this number also did not change appreciably [Altaweel et al., 2006].

Electromotive administration of BoNT/A may represent a substantial breakthrough among children. In 15 children with NDO due to myelomeningocele, electromotive administration of abobotA instilled in the bladder in a dose of 10 U/kg, proved very effective and safe. . The mean reflex volume (99 ± 35 ml to 216 ± 35 ml) and maximal bladder capacity (121 ±39 ml to 262 ± 41 ml) increased substantially while maximal detrusor pressure decreased

from 75 ± 16 cm H2O to 39 ± 10 cm H2O. Urinary incontinence improved in 12 patients (80%), [Kajbafzadeh et al., 2011].

To date, two case series have looked at the use of BoNT/A in children with non-neurogenic OAB refractory the anti-cholinergics. Both studies have shown an excellent response to treatment [Hoebeke et al., 2006; Marte et al., 2010]. Data have been updated recently [McDowell et al., 2011]. A total of 57 children of both gender received abobotA 12 U/kg up to a maximum dose of 480 U in multiple bladder sites. A total disappearance of OAB symptoms occurred in 66% and a partial improvement in 19% of the patients. About half of the cases had repeated injections after a mean time slightly exceeding 6 months No cases of voiding dysfunction or UTI were reported [McDowell et al., 2011].

Elderly patients represent, as well, a very special population where urgency and incontinence are not only very distressful but also particularly prevalent. Nevertheless, only 1 study specifically addressed efficacy and safety of BoNT/A in elderly patients. Twenty one patients with refractory IDO (18 females and 3 males) with a mean age of 81.2 years (range 75 to 92) received onabotA 200 U in 20 bladder sites [White et al , 2008]. A significant decrease in the number of daily voids, from 11.4 ± 1.67 to 5.19 ± 0.83 and incontinence pads per day, from 4.0 ± 0.89 to 1.3 ± 0.60, occurred. One month after treatment 16 of the 21 patients (76%) reported greater than 50% improvement in symptoms after 1 injection while only 3 did not show improvement after 2 injections [White et al., 2008]. Mean time to deterioration was 7.12 months. There were no treatment related complications.

h) Effect of BoNT/A on quality of life

Firm evidence that BoNT/A bladder injection in IDO patients increase quality of life can be extracted from several RCT in which QoL changes were in most cases secondary outcome parameters.

A multicenter, randomized, double blind placebo controlled trial by Schurch et al. [2007] which randomized 59 NDO patients with urinary incontinence for onabotA 200U or 300U or placebo. I-QOL scores improved significantly over placebo, at all time points whether 300U or 200U were used. A single center, double blind, placebo controlled study was performed by Ehren et al. [2007]. Thirty-one NDO patients with incontinence were randomized to abobotA 500 U or placebo. Patients in the abobotA group showed improved quality-of-life parameters compared to the placebo group. The Canadian multicenter double-blind study [Herschorn et al., 2011a] that randomised to onabotA 300 U or placebo 57 incontinent patients with NDO secondary to spinal cord injury or multiple sclerosis also found significant advantage of onabotA in terms of I-QoL score. One pivotal phase 3 study used the I-QoL questionnaire to evaluate quality of live changes in SCI and MS patients randomized to 200 and 300 U of onabotA or placebo. Change from baseline was 24 points for both onabotA doses ar 6 and 12 weeks but only 11 points at week 6 and 8 points at week 12 in the placebo group. The I-QoL questionnaires requires that a minimum change of 11 point occur in order to QoL to be detectable by patients, a barrier that was overcome by both onabotA doses [Cruz et al., 2011]. Improvements were present both in SCI and MS patients. In another large phase 3 trial these data were totally confirmed [Ginsberg et al., 2012]. Interestingly, a comparison in QoL in patients performing and non-performing CIC in the placebo, 200U and 300U arms did not show differences in patient perception, indicating that improvement in the continence condition was a more relevant outcome [Ginsberg et al., 2012].

Improvement in QoL was also found in a study that compared abobot 500 U versus /750 in a NDO population predominantly suffering from SCI. A disease- and organ-specific Qualiveen questionnaire with four domains (limitations, constraints, fears, and feelings) was used to assess the Specific Impact of Urinary Problems on QoL The initial evaluation was repeated at days 30, 90, 180, and 360. Identical improvements were detected for the two doses [Grise et al., 2010] The importance of continence for patients quality of life is also confirmed by the study of 43 MS patients treated with onabotA 300 U [Kalsi et al., 2007]. Although 98% of patients had to perform CIC after treatment, there were sustained improvements in all quality-of-life scores with a mean duration of effect was 9.7 months. Results were maintained with repeat treatments for 11.7 months. These results were confirmed in a larger MS cohort by Khan et al. [2011]. Urogenital Distress Inventory and Incontinence Impact Questionnaire 7 scores showed considerable improvement 4 weeks after onabotA 300 U treatment even when repeated 6 times. Again, the fact that 76% of the patients were dry seemed more relevant for QoL score than the necessity of CIC that was required by almost all patients [Khan et al., 2011].

Two RCT compared quality of life after BoNT/A administration to IDO patients. Sahai et al. [2009] used the King's Health Questionnaire (KHQ) at baseline and at 4 and 12 weeks, after injection of onabotA 200 U or saline in 16 and 18 patients of both genders. Overall QoL was significantly improved in the onabotA treated patients compared with placebo in the KHQ subdomains, 'Incontinence Impact', 'Emotions', 'Physical imitations', 'Social Limitations' and 'Severity Measures' at all time points. Other subdomains were improved only at some follow-up visits. The RELAX study that randomised a total of 240 women with refractory IDO to receive onabotA 200 U or placebo [Tincello et al., 2012] showed significant improvement in ICIQ-SF and I-QoL scores. However, none of the questionnaires were restored to the normal score (0 for ICIQ; 100 for IQOL)[Tincello et al. 2012]. The dose finding study by Dmochowski et al. [2010] in which placebo and onabtA 50, 100, 150, 200 and 300 U were compared showed a sustained improve-

ment in the King's Health Questionnaire score only in patients that received doses of 100 U or higher. In contrast, patients randomized to onabotA 50 U had changes similar to those observed after placebo [Dmochowski et al., 2010]. The dose finding study by Denys et al. [2011] showed an I-QoL improvement in patients receiving onabotA 100 U and 150 U, though at some time points scores were only numerically higher than in placebo or 50U groups. The general health status, as measured by the EQ-5D visual analogue scale also improved in patients that received 100 or 150 U [Denys et al., 2011].

i) Side effects of bladder wall injection of BoNT/A

The most frequent side effects reported after intradetrusor BonT/A injection are bladder pain and urinary infections [Karsenty et al., 2008; Del Popolo et al., 2008]. Hematuria may also occur, most of the times mild in nature. The most dangerous one, paralysis of the striated musculature due to circulatory leakage of the toxin has never been reported. Transient muscle weakness was, nevertheless, reported with abobotA application in several studies [Wyndaele and Van Dromme, 2002; Akbar et al., 2007; Del Popolo et al., 2008]. Among 199 NDO patients followed during 8 years, 5 developed hypostenia when injected with after abotbotA 1000 U [Del Popolo et al., 2008]. In another study with 44 patients, 3 adults also treated with 1000 units developed muscular weakness which subsided after 5 to 7 weeks [Akbar et al., 2007]. No such cases were reported with onabotA [Karsenty et al., 2008]. The reason for the lack of transient muscle weakness among Botox-treated patients is unclear but might be related with the larger size of its molecule which limits diffusion into the blood stream. Anyway, the risk of hyposthenia associated with abobotA might be avoided by using lower doses of the toxin, no more that 750 units for adults and 20 units/kg for children [Akbar et al., 2007, Del Popolo et al., 2008]. In addition, caution should be used in selecting high risk patients for botulism including children, patients with low pulmonary reserve or patients with myasthenia gravis. Aminoglycosides should be avoided during BoNT-A treatment since they might blockade motor plates and therefore enhance BoNT/A effect.

The risk of vesicoureteral reflux, which for long precluded trigonal injections [Schurch et al., 2000b, Reitz et al., 2004] seems unfounded [Karsenty et al, J Urol, 2007; Mascarenhas et al., 2008; Citeri et al., 2008; Eichel et al, 2008].

The most feared complication of BoNT/A application in patients with voluntary voiding is urinary retention and a transient necessity to perform CIC. It is, therefore, strongly recommended that in patients with spontaneous voiding BoNT/A administration is preceded by a complete information of this risk. Caregivers should ideally teach CIC to each patient before toxin injection.

In one cohort of 137 MS patients, 65% of whom relied on CISC to empty their bladder, repeated onabotA 300 U injections systematically increase that percentage to 95% [Khan et al., 2011]. In a subanalysis of MS patients with an EDSS around 5 included in the pivotal phase 3 RCT in which NDO patients were randomized for placebo, onabot 200 or 300 U the incidence of de novo CIC was dose dependent, 2.6%, 24.3% and 37.5%, respectively [Cruz et al., 2011]. A reduction of onabotA to 100 units might not be enough to solve the inconvenience. In a small cohort of 12 MS patients with a mean EDSS of 5, 25% of the patients required CIC or a suprapubic cathether to empty the bladder [Mehnert et al., 2010]. Future studies are needed in this area.

In IDO patients injected in the detrusor the rate of urinary retention or high post-voiding residuals requiring CIC is dose dependent [Dmochowski et al., 2010]. After injection of onabot 200 U 16-40% of the treated patients needed CIC [Kuo et al., 2004; 2005; Popat et al., 2005; Sahai et al., 2007; Brubaker et al., 2009; Dmochowski et al., 2010; Tincello et al., 2012). With onabotA 100 U the risk was substantially lower, from 4% to 13% [Schmid et al., 2006; Kuo, 2007; Dmochowski et al., 2010; Cohen et al., 2009]. Onabot 50 U was associated with the lower risk of increasing postvoid residuals and de novo CIC, 3,6%. [Dmochowski et al., 2010]. In contrast, detrusor injection of onabotA 100 U restricted to the trigone [Kuo et al., 2007; Kuo et al., 2010] were devoid of any risk of dysfunctional voiding. The same lack of dysfunctional voiding after trigonal injections of onabotA 100U was confirmed by Pinto et al. [2010] in BPS/IC women.

At this moment it is not possible to identify beforehand patients that will develop voiding difficulty after BoNT/A injection. The positive or negative status of the ice water test does not correlate with the risk of urinary retention after onabotA injection in NDO patients [Huwyler et al., WJU 2007]. A retrospective analysis of 217 patients receiving their first intravesical BoNTA injection for refractory IDO in a tertiary center concluded that risk factors for dysfunctional voiding and urinary retention included male gender ($p = 0.013$), baseline postvoid residual (PVR) > 100 ml ($p = 0.003$) and onabotA > 100 U ($p = 0.029$) [Kuo et al., 2010]. Also in a retrospective analysis of a cohort of 67 patients with IDO treated with onabotA 200 U CIC was necessary in 19 (28%). When compared to those not requiring CIC, those that started CIC had lower pretreatment maximum flow rate (15 vs 22 mL/s, P=0.003), lower projected isovolumetric pressure (43 vs 58, P=0.02) and lower bladder contractility índex (113 vs 180, P=0.001) [Sahai et al, BJU Int 2009].

Another common adverse event related with intradetrusor injection of BoNTA/ is UTI. In NDO patients due to SCI, almost all doing CIC at baseline, the risk of UTI in patients receiving onabotA, whether 200 U or 300 U was similar to those treated with placebo, slightly above 50% [Cruz et al., 2011]. The Canadian study randomised 57 NDO patients to placebo or

onabotA 300U. NDO was mostly due to SCI and the incidence of UTI was similar, 55% and 57%, respectively in the placebo and onabotA groups [Herschornet al., 2011]. However, in MS patients the risk was dose-dependent, 32%, 58.5% and 70%, respectively, eventually related with the increase in post-voiding urine residual volume and necessity of performing CIC in the MS population [Cruz et al., 2011]. In the cohort of 137 MS patients subjected to repeated injections of onabot 300 U and almost all emptying the bladder by CIC, after the 3-day prophylactic course further antibiotics for UTI were required in 9% of the total of 327 treatment sessions. Low dose long-term antibiotic prophylaxis was needed in additional 17% of the patients [Khan et al., 2011]. An word of caution shoukd however be left here. Most of these UTI were mild in nature. Severe infections like pyelonephritis, orquites or prostatitis seem to be substantially reduced after BoNT/A treatment of NDO [Game et al, 2008].

In IDO patients the risk of UTI is higher in males than in females [Kuo et al., 2010] and may well affect more than 1/3 of the patients. In RCT comparing placebo against onabot 200U the incidence of UTI was 0% vs 7% [Sahai et al., 2007], 22% vs 44% [Brubaker et al., 2009] or 11% vs 31% [Tincello et al., 2012], respectively. This adverse event seems to be dose related, eventually associated with the post-voiding urine volume increase. Domochowski et al. [2010] detected UTI in 16,3%, 33,9%, 44%, 48.1% and 34.5% of patients randomized for placebo, and 50, 100, 150, 200 and 300 U groups, respectively.

Although it is a concerned frequently rose by caregivers, at this moment there is no evidence that repeated BoNT/A injections cause detrusor atrophy or bladder wall fibrosis. Whether onabotA or abobotA were used, repeated injections in NDO patients in the short to medium term did not decrease bladder compliance which would presumably be the case if fibrosis were to develop [Reitz et al., 2007; Del Popolo et al., 2008]. Histological inspection of injected bladders did not show inflammatory changes, fibrosis, or dysplasia after repeated treatments and independently of the neurogenic or non-neurogenic origin of the detrusor overactivity [Haferkamp et al., 2004; Compérat et al., 2006; Apostolidis et al., 2008]. Rather the reverse, one study demonstrated that NDO patients treated with BonT/A had less fibrosis than nontreated patients [Compérat et al., 2006]. Curiously, the presence of eosinophilic infiltrate was shown to increase in specimens of patients receiving multiple treatments, a finding that could not be fully explained [Apostolidis et al., 2008].

j) Effectiveness of repeated injections in NDO and IDO patients

Median time for NOD patients due to SCI or MS to request a retreatment was around 300 days after onabotA 200 or 300 U but only 92 days after placebo [Cruz et al., 2011]. Therefore for patients that respond to BoNT/A a programme of reinjections is inevitable. The mean duration of the BoNT/A effect after repeated injections seems to remain stable, without any evidence of tachyphylaxis.

Three studies were identified that assessed the effect of repeated injections of onabotA and abobotA in NDO patients. A cohort of 199 patients with spinal cord lesions treated with abobotA 500 U to 1000 U was analyzed retrospectively, after 8 years of repeated injections. The intervals of between injections remained constant. Urodynamic improvements, patients satisfaction with treatment and number of pads or other protective devices was also constant after treatments [Del Popolo et al., 2008]. Intervals exceeded 12 months in 19.5% of the patients, ranged between 10-12 months in 40.2%, was < 10 months in 30.5% and < 6 months in only 10% of the patients [Del Popolo et al., 2088].

In another study, 20 consecutive NDO (SCI 18, MS 2) patients received at least five intradetrusor injections of onabotA 300 U in 30 sites above the trigone. Intervals between injections remained constant, between 193 and 199 days. Clinical continence improved significantly after the first injection and then remained constant after repeat injections. The median reflex volume increased from a 200 ml at baseline to values between 440 and 500 ml at follow-up studies. The presence of NDO decreased by 60–75%. Maximum cystometric capacity increased more than 2 folds and maximum detrusor pressure from a median of 70 cm H2O to values of about 20 cmH2O [Reitz et al., 2007].

In a MS cohort with137 patients who underwent detrusor onabot 300 U, 99 (72%) returned for a second treatment, and 47, 25, 14 and 5 returned for retreatments 3 to 6, respectively. The median interval for 1st, 2nd , 3rd, 4th, and 5th re-injections ranged between 12 and 13 months. The outcome in terms of continence did not differ among treatments [Khan et al., 2011].

Four studies were identified that analyzed repeated injections in IDO patients. In general, longer duration of BoNT/A effect and a relatively higher rate of treatment drop out is seen among IDO patients.

From a cohort of 34 IDO patients treated with onabotA 200 U, 58% received a 2nd injection and 26% received a 3rd and 4th injection. Significant improvements in OAB symptoms, QoL and urodynamic parameters were observed after each injection as compared with baseline, without differences in efficacy parameters between the 1st and last treatment. When analyzing the reasons why 20 out of the 34 patients abandoned the programme, the fear of CIC (25%) and poor response (20%) were the leading causes [Sahai et al., 2010].

This study was recently updated for 100 patients [Dowson et al., 2012]. A statistically significant reduction in frequency, urgency, and urge urinary

incontinence were seen following onabotA 200 U injection compared to baseline. Such improvement was again maintained after repeated injections. The mean inter-injection interval was 322 days. Interestingly, 37% of the patients stopped treatment after the first two injections, dropouts being rare thereafter. The most common reason for discontinuing treatment was poor efficacy (13%). CIC related issues was pointed out by 11% of patients in spite of the incidence of CIC after the first injection being 35% [Dowson et al., 2012].

In a prospective, observational study after 1 single onabotA 100 U injection, 26 patients were followed up for 2 years. One was a primary failure, 3 were lost to follow-up, and 11 patients had a repeated injection at 5–26 months. At 2 years 7 of the remaining 11 patients were recommended repeated injection or another treatment, and four required no other treatment.

Schmid et al. [2008] reported on 25 women and 5 men that received repeated [2] injections of onabotA for treatment of IDO. The interval between two subsequent treatments ranged between 4 and 26 months (mean 12 months). Improvement of OAB symptoms, quality of life and urodynamic parameters were observed after reinjection.

k) Cost-effectiveness of BoNT/A

Economic aspects of BonT/A are a concern due to the price of the drug and the need for repeated cystoscopies, very often performed under general anaesthesia and under close monitoring to detect and treat eventual episodes of autonomic dysreflexia. Nevertheless, In UK, in a cohort of 101 patients with detrusor overactivity, 63 of whom of neurogenic origin, BonT/A treatment was shown to be cost-effective in both NDO and IDO cases [Kalsi et al, 2006]. Costs were based on the resources used by typical patients in UK and in the cost-effectiveness of 200-300 U BoNT/A (Botox) compared with standard care [Kalsi et al., 2006]. In Germany a multicenter cost analysis showed that BonT/A (onabotA) treatment halved costs for incontinence aids and for urinary tract infection treatment in 214 NDO patients. In patients using incontinence aids, mean costs per patient decreased from €2 to €1 per day, whereas the mean cost of drugs to treat UTIs per patient decreased from €163 to €8 per year [Wefer et al., 2009].

Also in NDO patients, break-even point for BoNT/A and augmentation cystoplasty costs may be reached at five years. However BoNT/A may be substantially more cost-effective if the duration of effect of each injection is superior to 5 months or if the complications associated with augmentation cystoplasty overtake 40% of the patients [Padmanabhan et al., 2011].

For OAB/IDO, an assessment of costs, from a US payer perspective, extending up to 3 years, was made for 3 interventions, sacral neuromodulation, BoNTA, and augmentation cystoplasty in patients refractory to antimuscarinics. The initial treatment cost was $22,226, $1,313, and $10,252 for sacral neuromodulation, BoNTA, and augmentation cystoplasty respectively. Three years after initiating treatment, the cumulative cost was $26,269, $7651, and $14,337 respectively. Sensitivity analyses revealed that sacral neuromodulation persisted as the most costly intervention [Watanabe et al., 2010].

l) Comparisons between different BoNT/A brands

Systematic head-to-head comparisons between the different brands of BoNT/A are still lacking. Within each brand very few studies compared different doses for neurogenic or idiopathic DO. However, metanalysis and systematic reviews are already available which give some light on this important topic.

A recent metanalysis identified 19 randomised or quasi-randomised controlled trials for OAB/DO treatment in adults in which at least one management arm involved intravesical injection of botulinum toxin. Comparison interventions could include no intervention, placebo, lifestyle modification, bladder retraining, pharmacological treatments, surgery, bladder instillation techniques, neuromodulation, and different types, doses, and injection techniques of BoNT/A. Most patients in the studies had neurogenic DO, but some included patients with idiopathic DO. All studies demonstrated superiority of botulinum toxin to placebo. Lower doses of onabotA (100 to 150 U) appeared to have beneficial effects, but larger doses (300 U) may have been more effective and longer lasting, but with more side effects [Duthie et al., 2011].

Mangera et al. [2011] in a systematic review identified good-quality studies that evaluated onabotulinumtoxinA for all the indications in adults. However that was not the case with abobotA. Although this does not imply that onabotA is more effective than abobotA, it should be a consideration when counselling patients on the use of botulinum toxin in urologic applications. The two preparations should not be used interchangeably, either in terms of predicting outcomes or in determining doses to be used.

The only study available that compares two different brands used onabotA 200 or 300 U against the Chinese BoNT/A Presigne in the same dosage. Improvement in MCC was significantly greater with onabotA Botox versus Prosigne (+103.3% vs. +42.2%; P = 0.019). Continence was achieved by week 12 in 16 onabotA recipients (76.2%) and in 10 Presigne recipients (47.6%; P = 0.057) [Gomes et al., 2010]. Future studies seems, therefore, justified to assess the relative potencies of the different brands of BoNT/A.

m) BONT/B

Some humans repeatedly injected with BONT-A may develop resistance to the toxin, possibly due to antibody formation. Although this event seems very rare in the case of bladder injections, a minimum interval of 3 months between two BoNT/A injections is gener-

ally recommended to decrease its occurrence. If resistance appears, recent reports [Dykstra et al., 2003; Pistolesi et al., 2004; Reitz et al., 2004] investigated the replacement of BONT-A serotype by BONT-B. At this moment empiric doses of BoNT/B are being used as there is no clear potency equivalents for the two serotypes and between BoNT/B brands.

In 3 patients with spinal NDO, bladder injection of 5000 UI [Pistolesi et al., 2004] or 7500 UI [Reitz and Schurch, 2004) of BONT-B (Neurobloc ®) restored bladder function for 6 months [Reitz and Schurch, 2004]. Interestingly, 1 patient experienced dry mouth and dry eyes that resolved within 20 days. As this side effect was not reported after bladder BONT-A application, it is possible that different toxin serotypes have some different degrees of organ affinity. Dykstra et al. [2003] carried on a dose escalation study with BONT-B (rimabotB in 15 female patients with OAB. They used doses of 2500, 3750, 5000, 10,000, and 15,000 U injected at 10 sites. Only 1 patient failed to respond and a clear dose-dependent effect, was observed, with the longest response seen in those injected with 15,000 U. Two patients, both injected with 15,000 U, experienced dry mouth and general malaise. In another study involving IDO and NDO patients, in which rimabotB 5000 U were used, Hirst and coworkers [2007] observed a limited duration of action, with most of the symptomatic beneficial effects wearing off by 10 weeks in most of the patients. The short duration of action for BONT-B at safe doses may, therefore, limit the clinic usefulness of this serotype.

n) BONT/A in IC/PBS

BONT/A significantly inhibits the noxious sensory input from the bladder [Vemulakonda et al., 2005; Rapp et al., 2006; Lucione et al., 2008]. Therefore several pilot studies were carried out in the last few years. None is placebo controlled, a fact that limits the scientific value of the observations. On the other hand different techniques of administration have been assessed. These two facts may explain some heterogeneity of results.

The first pilot study with 13 females observed that, 9 (69%) had subjective improvement after onabotA 100 or 200 U injected in the trigone and above the trigone. Mean scores in the Interstitial Cystitis Symptom Index and the Interstitial Cystitis Problem Index improved by 71% and 69%, respectively. Daytime frequency, nocturia, and pain measured by a Visual Analogue Scale (VAS) decreased by 44%, 45%, and 79%, respectively. Symptom improvement lasted a mean of 3.7 months (range 1 to 8) [Smith and Chancellor, 2004]. In another pilot study with 15 patients, Giannantoni et al. [2006; 2008] reported similar obervations after bladder injection of onabotA 200 U (150U above the trigone, 50 U in the trigone). Subjective improvement at 1 and 3 month follow-up occurred in 86% of the patients but at 5-month only persisted in 26.6% . Importantly, 9 patients experienced moderate to severe voiding difficulties [Giannantoni et al., 2006; 2008] A third study could not demonstrate any effect of onabotA in 13 IC/PBS patients treated with onabotA 100–300 U in the bladder [Davies et al., 2006].

Three other studies, which added substantial modifications to the above protocol, reported, on the contrary, considerable improvement in clinical and urodynamic outcomes after BoNT/A adminitration.

A prospective, randomized study enrolled 67 patients with refractory IC/PBS Of these, 44 patients received suburothelial injection of onabotA 200 U [15] or 100 U [29] followed by cystoscopic hydrodistention 2 weeks later. The control group (23 patients) only received hydrodistention. The IC/PBS symptom score significantly decreased in all three groups, but VAS pain reduction and urodynamic improvement were only observed at 3 months in the arms that received onabotA, without any relevant differences between the two doses. A successful result at 12 and 24 months was reported in 55% and 30% of onabotA treated patients, respectively, compared with only 26% and 17% in the control group. The validity of these positive long-term results should however be interpreted with caution since all patients remained on baseline pentosan polysulphate throughout the study [Kuo and Chancellor, 2009].

Taking in consideration that most of the bladder nociceptors course in the trigone, Pinto et al. [2010] restricted 100 U onabotA injections to the trigone, in 10 sites (10 U/ 1 ml each. Twenty six women with positive findings at cystoscopy and biopsy were enrolled. All patients reported subjective improvement at 1- and 3-month follow-up in pain, daytime and nighttime voiding frequency, O'Leary-Sant score and QoL. Bladder volume to first pain and maximal cystometric capacity more than doubled. Treatment remained effective in >50% of the patients for 9 months. Retreatment was equally effective in all cases, with similar duration of the effect [Pinto et al., 2010]. No cases of dysfunctional voiding were reported after trigonal injections of onabotA 100U. Also PVR at urodynamics and bladder contractility index were not impaired [Pinto et al., 2010].

The third was a small placebo controlled trial comparing periurethral injections of onabotA 50U (n=9) versus saline (n=11). The rationale was to investigate the participation of periurethral somatic afferents to pain. The solution, 2 ml, was injected in the region of the bladder neck, at the 3 o'clock and 9 o'clock positions. Unfortunately, there was no differences between the onabotA and the at 3-month follow-up in terms of symptoms.

At this moment, without a well conducted placebo controlled RCT it is difficult to state how effective is BoNT/A in BPS/IC. However, taking in consideration the effects the toxin induces in nociceptors and in the urothelium and the favourable results of the two largest clinical trials, it is tempting to suggest that further assessments are warranted.

2. CAPSAICIN AND RESINIFERATOXIN (RTX)

a) Rationale for intravesical vanilloids

The rationale for intravesical vanilloid application in patients with detrusor overactivity (DO) was offered by the demonstration that capsaicin, following bladder C-fiber desensitization, suppresses involuntary detrusor contractions dependent upon a sacral micturition reflex [de Groat, 1997]. The C-fiber micturition reflex is usually inactive but it was shown that it is enhanced in patients with chronic spinal-cord lesions above sacral segments [de Groat, 1997] in those with chronic bladder outlet obstruction [Chai et al., 1998) and in those with IDO [Silva et al., 2002]. In the bladders of NDO patients, the enhancement of the micturition reflex is accompanied by an increase in the number of sub-urothelial C-fibers expressing TRPV1 [Brady et al., 2004]. Curiously, NDO patients who responded better to intravesical RTX exhibited a significant decrease in the density of TRPV1 immunoreactive fibers, whereas non-responders experience a non-significant variation [Brady et al., 2004]. A decrease in TRPV1 expression in urothelial cells of NDO patients was also demonstrated after intravesical application of RTX [Apostolidis et al., 2005; 2006].

Changes in sub-urothelial C-fibers expressing neuropeptides [Smet et al. 1997] or TRPV1 [Liu and Kuo, 2007] were also reported in patients with and sensory urgency. In IDO patients, responders to intravesical RTX are closely associated with the over-expression of the receptor in the bladder mucosa [Liu and Kuo, 2007]. In women with sensory urgency, TRPV1 mRNA expressed in trigonal mucosa was not only increased but also inversely correlated with the bladder volume at first sensation of filling during cystometry further indicating that TRPV1 play a role in premature bladder sensation [Liu et al., 2007].

b) Intravesical capsaicin

Intravesical capsacin for NDO was studied in 6 non-controlled [Fowler et al., 1992; Fowler et al., 1994; Geirsson et al., 1995; Das et al.,1996; Cruz et al., 1997, De Ridder et al., 1997] and 1 controlled clinical trial [de Seze et al., 1998]. Capsaicin was dissolved in 30% alcohol and 100-125 ml (or half of the bladder capacity if lower than that volume) of 1-2 mM solutions were instilled into the bladder and left in contact with the mucosa for 30 minutes. Best clinical results were found among patients with incomplete spinal cord lesions, in whom clinical improvement could be observed in up to 70-90% the patients [Fowler et al., 1994, Cruz et al., 1997; De Ridder et al., 1997]. In patients with complete spinal cord lesions the success rate was much lower [Geirsson et al., 1995].

Only one small randomized controlled study compared capsaicin against 30% ethanol, the vehicle solution. Ten patients received capsaicin and found a significant regression of the incontinence and urge sensation. In contrast, only 1 among the 10 patients that received ethanol had clinical improvement [de Seze et al., 1998].

The pungency of alcoholic capsaicin solutions has prevented the widespread use of this compound. In particular, the possibility of triggering autonomic dysreflexia with capsaicin, especially in patients with higher spinal cord lesions has progressively restrained its use. The relevance of capsaicin might however be back with a recent observation by de Séze et al.[2006] with a new capsaicin formulation. They conducted a double blind placebo controlled study with a glucidc solution of capsaicin in 33 NDO patients. The glucidic-capsaicin treated group showed improvement both in symptoms and urodynamic parameters above the comparator arm. The global tolerance of this new capsaicin formulation was excellent [de Sèze et al.,. 2006].

c) RTX in NDO

Resiniferatoxin (RTX) has the advantage over capsaicin in being much less pungent [Cruz et al., 1997]. Intravesical RTX application in NDO patients was evaluated in five small open-label studies (Cruz et al., 1997; Lazzeri et al., 1997; 1998; Silva et al., 2000; Kuo 2003). Different RTX concentrations, 10 nM, 50 nM, 100 nM and 10 μM were tested. RTX brought a rapid improvement or disappearance of urinary incontinence in up to 80% of the selected patients and a 30% decrease in their daily urinary frequency. Furthermore, RTX also increased the volume to first detrusor contraction and maximal cystometric capacity. In general, in patients receiving 50-100 nM RTX the effect was long-lasting, with a duration of more than 6 month being reported. In patients treated with 10 μM doses, transient urinary retention may occur [Lazzeri et al., 1998].

In a recent placebo-controlled study, the urodynamic effects of RTX in NDO patients was specifically evaluated. Only in the RTX arm a significant increase in first detrusor contraction and maximal cystometric capacity was found [Silva et al., 2005]. RTX also caused a significant improvement in urinary frequency and incontinence [Silva et al., 2005].

RTX, 600 nM was compared against BONT/A (Botox, 300U) in a study involving 25 patients with NDO due to chronic spinal cord injury. Both neurotoxins were capable of significantly reducing the number of daily incontinence episodes and improving maximum bladder capacity, although BONT/A turned out to be more effective.

d) RTX in IDO

The first study with intravesical RTX in IDO patients was designed as a proof-of-concept study and involved 13 patients. Intravesical RTX 50 nmol/L was associated with an improvement in volume to FDC from 170 ± 109 mL to 440 ± 153 mL at 30 days, and to 391 ± 165 mL at 90 days. An increase in mean MCC from 291 ± 160 mL to 472 ± 139 mL at 30 days and to 413 ± 153 mL at 90 days was also observed.

These improvements were accompanied by a decrease in episodes of urgency incontinence and of daily frequency [Silva et al., 2002]. Subsequent small open label studies confirmed these observations using either a single high (50-100 nM) or multiple low (10 nM) dose approaches [Kuo, 2003; Dinis et al, 2004; Kuo et al., 2005].

The effect of RTX on refractory IDO was evaluated in two randomized clinical trials [Kuo et al., 2006; Rios et al., 2007]. Kuo et al. [2006] randomised 54 patients to receive 4 weekly instillations of a low concentration RTX solutions (10 nmol/L) or the vehicle solution, 10% ethanol in saline [Kuo et al., 2006] Three months after completing the 4 intravesical treatments, the RTX treated group had 42.3% and 19.2% of patients feeling much better or improved, respectively. This was significantly more than in the placebo group, 14.2% and 7.1% respectively. At 6 months treatment remained effective in 50% patients in the RTX group but only in 11% in the placebo group [Kuo et al., 2006]. Such clinical and urodynamic findings could not be reproduced in another study in which patients were randomly assigned to receive a single intravesical dose of 100 ml of either RTX 50 nM or placebo. Patients were followed-up only for 4 weeks. During this period a single 50 nM intravesical dose of RTX was not better than placebo for the treatment of women with IDO and urgency incontinence [Rios et al., 2007].

e) RTX and urgency

The involvement of bladder C-fibers in IDO has led some investigators to explore the role of these sensory afferents to the genesis of urgency. In a non-controlled study involving 12 male patients with LUTS associated with BPH, mean IPSS halved following intravesical administration of RTX (50 nmol/L). The decrease in IPSS was largely due to improvements in scores related to urgency, in addition to improvement in nocturia and frequency [Dinis et al., 2005]. In another open-label study 15 patients with intractable urgency and frequency, with or without urgency incontinence or bladder pain/discomfort, and without urodynamic evidence of DO received one single 50 nM RTX solution. A trend towards an improvement of urgency was noticed [Apostolidis et al., 2006].

In a quasi-randomised study, 23 OAB patients with refractory urgency entered a 30 day run-in period in which medications influencing the bladder function were interrupted. At the end of this period patients filled a 7-day bladder diary. Then, patients were instilled with 100 ml of 10% ethanol in saline (vehicle solution) and 30 days later a second 7-day diary was collected. Finally, patients were instilled with 100 ml of 50 nM RTX in 10% ethanol in saline and additional bladder diaries were collected at 1 and 3 months. After vehicle instillation, the mean number of episodes of urgency per week was 56 ± 11. At 1 and 3 months after RTX instillation the number of episodes of urgency decreased to 39 ± 9 ($p = 0.002$) and 37 ± 6 ($p = 0.02$), respectively [Silva et al., 2007].

f) Intravesical RTX and IC/PBS

TRPV1 involvement in pain has stimulated the investigation of RTX as a treatment for bladder pain in IC/PBS. After desensitization of bladder C-fibers, RTX reduces the spinal expression of c-fos, a pain evoked gene, in animal models of cystitis [Dinis et al., 2004]. TRPV1 knock-out mice, which do not express the receptor in the bladder, do not experience an increase in the frequency of bladder reflex contractions or in the expression of c-fos in the spinal cord during cystitis [Charrua et al., 2007]. Patients with IC/PBS have more TRPV1 expressing sensory fibers in their bladder mucosa than normal individuals [Mukerji et al., 2006].

In a placebo-controlled study of 18 patients with IC/PBS, Lazzeri et al. [2000] reported an improvement in pain and urinary frequency after administration of intravesical RTX in 10 nmol/L concentration. This effect was short-lasting, eventually due to the use of a low dose of RTX. Chen and co-workers conducted a dose-escalating study and concluded that the most commonly reported adverse event with RTX was pain during instillation. However, at 10 or 5 nM RTX was safe and could improve bladder pain [Chen et al., 2005]. Additionally, 3 non-controlled studies have also reported bladder pain improvement after intravesical RTX [Lazzeri et al., 2004; Apostolidis et al., 2006; Peng and Kuo, 2007]. A randomized, double-blind study in 163 patients with IC/PBS, in which several doses of intravesical RTX (10 nmol/L, 50 nmol/L, and 100 nmol/L) were compared with placebo, failed, however, to show any advantage for the neurotoxin over placebo in terms of overall symptoms, pain, urgency, frequency, nocturia, or average voided volume during 12 weeks of follow up [Payne et al., 2005].

IX. OTHER DRUGS

1. BACLOFEN

Gamma-amino-butyric acid (GABA) is a ubiquitous inhibitory neurotransmitter in the CNS that can inhibit the micturition reflex at several points along its central pathway [de Groat, 1997; Pehrson et al., 2002]. Experimental data suggest the GABAergic system as an interesting target for bladder dysfunction therapy. Baclofen intrathecally attenuated oxyhemoglobin induced detrusor overactivity, suggesting that the inhibitory actions of GABA(B) receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fiber activation in the urothelium and/or suburothelium [Pehrson et al, 2002]. In spinal intact rats, intrathecal application of bicuculline induced detrusor-sphincter dyssynergia (DSD)-like changes whereas intrathecal application of baclofen induced urethral relaxation during isovolumetric bladder contractions [Miyazato et al., 2009]. After spinal cord injury (SCI), Miyazato et al.

[2009] found signs of hypofunction of the GABAergic system (glutamate decarboxylase 67 mRNA levels in the spinal cord and dorsal root ganglia were decreased), and showed that activation of GABA(A) and GABA(B) receptors in the spinal cord inhibited DO as evidenced by a reduction in non-voiding contractions. GABA(B) receptor activation preferentially reduced DO prior to inhibiting voiding contractions while GABA(A) receptor activation inhibited DO and voiding contraction at the same concentration.

As a GABA agonist on GABA(B) receptors, baclofen was used orally in IDO patients. However, its efficacy was poor, eventually dictated by the fact that baclofen does not cross the blood-brain barrier [Taylor and Bates, 1979]. Baclofen is one of the most effective drugs for the treatment of spasticity following spinal cord injury, traumatic or hypoxic brain injury, and cerebral palsy [Ochs, 1993], and intrathecal baclofen was shown to be useful in some patients with spasticity and bladder dysfunction [Bushman et al., 1993]. Baldo et al. [2000] found a rapid (24 hours) and persistent increment in the volume to first detrusor contraction and of the maximal cystometric whereas maximal detrusor pressure decreased. At ten days the volume to first detrusor contraction had increased from 143 ml to 486 ml. In selected patients with spasticity and bladder dysfunction, intrathecal baclofen seems to be an effective therapy.

X. COMBINATIONS

1. α_1-AR ANTAGONISTS WITH ANTIMUSCARINICS

Traditionally, male lower urinary tract symptoms (LUTS) were thought to result from benign prostatic obstruction (BPO) secondary to benign prostatic enlargement (BPE). However, male LUTS may arise from prostatic pathology, bladder dysfunction, or both. Thus, diagnosis and appropriate treatment of men with OAB symptoms are complex and difficult. α1-AR antagonists remain the most widely used pharmacologic agents for relief of bladder outflow resistance, as they relax prostatic and urethral smooth muscle tone, the dynamic component of BPO [Andersson and Gratzke, 2010; Lepor et al., 2012]. In contrast, antimuscarinics, which function by competitively blocking the muscarinic receptors, are the first-line pharmacologic treatment for OAB [Andersson et al., 2009]. Given the prevalence of combined voiding and OAB symptoms as well as the finding that the QoL of these patients is affected primarily by the symptoms of OAB, it might be logical for this category of patients to be given antimuscarinic drugs [Ruggieri et al., 2005].

A variety of such combinations have been evaluated. Several randomized, controlled trials demonstrated that the combination treatment of antimuscarinic drugs and α1-AR antagonist was more effective at reducing male LUTS than α1-AR antagonists alone in men with OAB and coexisting BPO [Saito et al., 1999; Athanasopoulos et al., 2003; Lee et al., 2004; 2005; Kaplan et al., 2006; 2008]. Therapeutic benefit of combining an antimuscarinic agent (propiverine) with α1-AR antagonists (tamsulosin), as compared to α1-AR antagonists alone, was reported by Saito and colleagues [Saito et al., 1999]. The rates of improvement in daytime frequency, incontinence, and urgency were greater in the combination group than the α1-AR antagonist-alone group. The postvoid residual (PVR) was unchanged in both groups, and there was only one case (1.5%) of acute urinary retention (AUR) with the combined treatment.

Subsequently, Lee et al. [2005] compared the efficacy and safety of combination therapy with propiverine and doxazosin in 211 men with urodynamically confirmed bladder outlet obstruction (BOO) and OAB symptoms for 8 weeks. Compared with the doxazosin arm, the patients in the combination therapy group showed greater improvement in urinary frequency, average micturition volume, and storage and urgency scores of international prostate symptom score (IPSS). Patient satisfaction was significantly higher in the combination group. There was also a significant increase in PVR (+20.7 mL) in the combination group, but no case of urinary retention was reported.

A large-scale, multicenter, randomized, double-blind, placebo-controlled trial (the TIMES study) demonstrated the efficacy and safety of tolterodine extended release (ER) alone, tamsulosin alone, and the combination of both in 879 men with OAB and BPO [Kaplan et al., 2006]. In the primary efficacy analysis, 172 men (80%) receiving tolterodine ER plus tamsulosin reported treatment benefits by week 12 ($p<0.001$ vs. placebo; $p=0.001$ vs. tolterodine ER; $p=0.03$ vs. tamsulosin). In the secondary efficacy analysis, patients receiving tolterodine ER plus tamsulosin compared with placebo experienced small but significant reductions in urgency incontinence, urgency episodes, daytime frequency, and nocturia. However, there were no significant differences between tamsulosin monotherapy and placebo for any diary variables at week 12. Patients receiving tolterodine ER plus tamsulosin demonstrated significant improvements in total IPSS (−8.02 vs. placebo, −6.19, $p=0.003$) and QoL (−1.61 vs. −1.17, $p=0.003$). Although there were significant improvements in the total IPSS among patients who received tamsulosin alone, the differences in total IPSS among patients that received tolterodine ER versus placebo were not significant. The combination of antimuscarinics and α1-AR antagonists may be the most effective therapy in men with OAB symptoms in the presence of BPO.

A subanalysis [Rovner et al., 2008] of data from the TIMES study focused on the urgency perception scale and concluded that the group of 217 men who received tolterodine plus tamsulosin showed

significantly improved urgency variables and patient-reported outcomes. Moreover, this group of patients reported increased satisfaction with the treatment as well as willingness to continue the treatment. Another subanalysis [Kaplan et al. 2008] of data from the TIMES study examined the effects of the drugs on urinary symptoms as assessed by the IPSS. Based on this subanalysis, the authors concluded that tolterodine ER plus tamsulosin was significantly more effective than placebo in treating storage LUTS, including OAB symptoms. However, these results should be considered with caution, as they were derived from post-hoc analysis of the TIMES data.

Maruyama et al. [2006] reported different results in their prospective, randomized, controlled study in which naftopidil (25-75 mg/day), an α1d-AR antagonist, alone or in combination with propiverine hydrochloride (10-20 mg/day) or oxybutynin hydrochloride (2-6 mg/day), was administered for 12 weeks to 101 BPH patients. In the study, the IPSS and QoL index improved significantly in both groups, with no marked differences between groups. Maximum flow rate (Qmax) and PVR tended to improve in both groups, again with no differences between groups. However, median post-therapeutic PVR was significantly larger in the combination group (45.0 mL) than in the monotherapy group (13.5 mL, $p = 0.021$). There were significantly more patients with increased residual urine volume relative to unchanged residuals in the combination therapy (22.9%) group versus the monotherapy group (5.0%, $p = 0.038$). The authors of this study concluded that combination therapy with a low-dose antimuscarinic agent was not more effective than monotherapy. Moreover, although they did not encounter any cases of urinary retention, the percentage of patients with increased residual urine volume was significantly greater in the combination therapy group than the monotherapy group.

The results of another study using low-dose antimuscarinic therapy was published by Kang et al. [2009]. They evaluated the efficacy and safety of combined treatment with tamsulosin 0.2 mg and propiverine hydrochloride 10 mg compared with tamsulosin monotherapy. After 3 months, both groups showed significant improvements in IPSS, QoL, voided volume, Qmax, and PVR, but only the QoL index was significantly different between groups in favor of the combination group. No cases of AUR were recorded in this low-dose study.

Medical therapy to reduce detrusor overactivity in a neurogenic bladder has focused on antimuscarinic therapy, which increases bladder capacity, decreases bladder filling pressure, and improves compliance [Goessl et al., 1998; Stohrer et al., 2007]. Although antimuscarinics combined with clean intermittent catheterization is the most commonly recommended medical therapy for neurogenic bladder, the results are sometimes unsatisfactory, and many patients continue to have poor bladder compliance and remain incontinent [Razdan et al., 2003]. MacGuire reported that α-AR antagonists decreased bladder pressure with filling and increased capacity, and that the addition of an antimuscarinic enhanced these effects, indicating that α-AR antagonists and the antimuscarinic had a synergistic effect on detrusor tone in the decentralized bladder [McGuire and Savastano, 1985]. This finding led to the widespread use of α1-AR antagonists in the treatment of neurogenic bladder [Chancellor et al., 1994; Swierzewski, Gormley et al. 1994; Abrams et al., 2003). Swierzewski treated 12 patients with spinal cord injury who had poor bladder compliance, despite therapy with clean intermittent catheterization and an antimuscarinic, with 5 mg terazosin for bladder management (Swierzewski et al., 1994). After 4 weeks, compliance increased by 73%, bladder pressure decreased by 36 cmH2O, and capacity increased by 157 mL. These results support the theory that α-AR antagonists and antimuscarinics have a synergistic effect on the bladder in the neurogenic population.

In a retrospective chart review, combination therapy with an antimuscarinic agent, an α1-AR antagonist, and imipramine produced superior results to those obtained using a single agent in patients with neurogenic bladder dysfunction [Cameron et al. 2009]. These patients showed significant improvement in clinical parameters and compliance, and decreased bladder pressures at capacity. It has been shown that in the decentralized human detrusor, there may be an increase in α-1-AR sites sites and a switch to α-1-AR mediated contractile function from the typical ß-AR mediated relaxation function during bladder filling [Sundin et al. 1977]. The tricyclic antidepressant imipramine is a muscarinic receptor agonist and a direct smooth muscle inhibitor that decreases bladder overactivity by blocking the reuptake of serotonin. Other effects include the peripheral blockade of noradrenaline, stimulating the ß ARs at the dome of the bladder, and decreasing bladder contractility [Hoebeke and Vande Walle, 2000]. These results suggest that targeting multiple receptors may maximize the effectiveness of pharmacological treatment of neurogenic bladder and should be considered in patients in whom treatment with antimuscarinics alone fails.

2. COMBINED ANTIMUSCARINICS

Although antimuscarinic agents are the first choice of treatment for patients with OAB symptoms, these drugs do not always lead to the desired effect of detrusor stability and continence, especially for patients with spinal cord injury or neurologic diseases such as multiple sclerosis or meningomyelocele. In these patients, the goal of urological therapy is to maintain continence and to reduce intravesical pressure. When antimuscarinic treatment fails,

however, invasive procedures such as the injection of botulinum toxin, intravesical application of drugs, or surgery are necessary.

A combined antimuscarinic regimen was evaluated as a non-invasive alternative by Amend and colleagues [Amend et al., 2008] for patients who had neurogenic bladder dysfunction with incontinence, reduced bladder capacity, and increased intravesical pressure. They added secondary antimuscarinics to the existing double-dosed antimuscarinics for patients who previously demonstrated unsatisfactory outcomes with double-dosed antimuscarinic monotherapy. The study drugs were tolterodine, oxybutynin, and trospium. After a 4-week combined regimen, incontinence episodes decreased and reflex volume, maximal bladder capacity, and detrusor compliance increased. Side-effects were comparable to those seen with normal-dosed antimuscarinics. Those positive findings were speculated to be due to: 1) synergistic activation of different muscarinic receptors or interactions of receptors on different parts of the bladder wall, 2) undiscovered faster metabolism of antimuscarinics requiring an increased dosage of different antimuscarinic drugs, and/or 3) down-regulation of subdivisions of antimuscarinic receptors under monotherapy that may lead to better susceptibility of other subdivisions when treated by the second drug. The combined regimen needs further investigation to verify its efficacy as a non-invasive alternative for patients in whom antimuscarinic monotherapy fails.

3. ANTIMUSCARINICS AND 5α-REDUCTASE INHIBITORS

The standard first-line medical therapy for men with moderate-to-severe LUTS is an α1-AR antagonist, a 5α-reductase inhibitor, or combination therapy with both. Both α1-AR antagonist and 5α-reductase inhibitors alleviate LUTS in men by reducing bladder outlet resistance. Alpha1-AR antagonists decrease smooth muscle tone in the prostate and bladder neck, while 5α-reductase inhibitors reduce prostate volume. As mentioned, several trials have demonstrated the efficacy and safety of the combination therapy of antimuscarinics and α1-AR antagonist for patients with OAB and coexisting BPO. However, post hoc analyses of the TIMES study [Kaplan et al., 2006] suggested that men with smaller prostates benefit more from antimuscarinic therapy than those with larger prostates [Roehrborn et al., 2008; Roehrborn, Kaplan et al., 2009]. Chung and coworkers conducted an open-label, fixed-dose study to assess the efficacy and safety of tolterodine ER in combination with dutasteride in men with a large prostate (≥30 g) and persistent OAB symptoms after α1-AR antagonist therapy who had been unsuccessfully treated with dutasteride alone [Chung et al. 2010]. At the start of the study, all patients had been on dutasteride 0.5 mg daily for at least 6 months and α1-AR antagonist therapy had failed. All patients were given 4 mg tolterodine ER daily for 12 weeks and had discontinued α1-AR antagonist before the start of the study. At 12 weeks, the frequency (-3.2/24hrs, $p < 0.02$), urgency (19.2%, $p < 0.03$), number of severe OAB episodes (71.4%, $p < 0.05$), and incidence of nighttime voiding (-0.9, $p < 0.003$) were found to have decreased significantly from baseline. The IPSS decreased with dutasteride treatment (from 19.3 to 14.3) and further decreased with the addition of tolterodine to 7.1 ($p < 0.001$). Storage symptoms decreased from 9.8 to 4.5 ($p < 0.001$). Dry mouth occurred in four (7.5%) subjects, constipation in one (2%), and decreased sexual function in two (3.9%). Post-void residual increased by 4.2 mL, Qmax decreased by 0.2 mL/s, and no patients went into retention. The authors concluded that the combination of tolterodine and dutasteride was effective, safe, and well-tolerated in men with large prostates with persistent OAB symptoms and LUTS secondary to BPO.

The results of this study indicate that antimuscarinics are safe and effective in selected patients with OAB and BPO when used in combination with 5α-reductase inhibitors. Further studies are required to verify the efficacy of antimuscarinics combined with 5α-reductase inhibitors in these patients.

4. α_1-AR ANTAGONISTS WITH 5A-REDUCTASE INHIBITORS

It has been well established that the combinations of α1-AR antagonists with 5-α reductase inhibitors (doxazosin finasteride: MTOPS; dutasteride+ tamsulosin: CombAT) can improve clinical outcomes and reduce the incidence of BPH and LUTS progression measured as symptom worsening, retention or progression to surgery [McConnell et al., 2003, Roehrborn et al., 2010].

XI. FUTURE POSSIBILITIES

1.PERIPHERALLY ACTING DRUGS

a) Vitamin D_3 receptor analogues

It is well known that vitamin D affects skeletal muscle strength and functional efficiency, and vitamin D insufficiency has been associated with notable muscle weakness. The levator ani and coccygeus skeletal muscles are critical components of the pelvic floor and may be affected by vitamin D nutritional status.Weakened pelvic floor musculature is thought to be associated with the development of urinary incontinence and fecal incontinence symptoms. Aging women are at increased risk for both pelvic floor dysfunction and vitamin D insufficiency. However, to date, only small case reports and observational studies have shown an association between insufficient vitamin D and pelvic floor dysfunction symptom severity (Parker-Autry et al., 2012). Rat and human bladders were shown to express receptors for vitamin D [Crescioli et al., 2005],

which makes it conceivable that the bladder may also be a target for vitamin D. Analogues of vitamin D3 have also been shown to inhibit benign prostatic hyperplasia (BPH) cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells [Crescioli et al., 2002; 2003; 2004]. Experiments in rats with bladder outflow obstruction [Schröder et al., 2006] showed that one of the analogues, BXL-628, at non-hypercalcemic doses, did not prevent bladder hypertrophy, but reduced the decrease in contractility of the bladder smooth muscle which occurred with increasing bladder weight [Schröder et al., 2006]. The mechanism of action for the effects has not been clarified. However, elocalcitol was shown to have an inhibitory effect on the RhoA/Rho kinase pathway [Morelli et al., 2007]. Upregulation of his pathway has been associated with bladder changes associated with diabetes, outflow obstruction, and DO [Peters et al., 2006; Christ and Andersson, 2007]. In rats with outflow obstruction, previous elocalcitol-treatment improved the effects of tolterodine on bladder compliance [Streng at al., 2012]. It was suggested that in rats elocalcitol exerted additional beneficial actions on outflow obstruction-induced functional changes during the filling phase of micturition. This supports combined therapy in BPH-related LUTS. If the results are valid in humans, combined therapy with the drug would be of value.

The effect of elocalcitol on prostate volume was evaluated in patients with BPH, and it was found that BXL628 was able to arrest prostate growth within 12 weeks in men aged>or=50 years with prostatic volume > or = 40 ml [Colli et al., 2006]. In an RCT enrolling 120 female patients with OAB, where the primary endpoint was an increase in the mean volume voided, a significant increase vs placebo (22% vs 11%) was demonstrated [Colli et al., 2007]. Whether or not vitamin D receptor agonism (monotherapy or in combination) will be a useful alternative for the treatment of LUTS/OAB, requires further RCTs. However, currently, the development of the drug seems to be stopped [Tiwari, 2009].

b) TRP channel antagonists

The transient receptor potential (TRP) channel superfamily has been shown to be involved in nociception and mechanosensory transduction in various organ systems, and studies of the LUT have indicated that several TRP channels, including TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1, are expressed in the bladder, and may act as sensors of stretch and/or chemical irritation [Araki et al., 2008; Everaerts et al., 2008; Andersson et al., 2010; Araki, 2011]. TRPV1 and TRPV4 channels have been found to be expressed in the urinary bladder [Tominaga et al., 1998; Birder et al., 2001; Gevaert et al., 2007]. TRPV1 is present and active both in the urothelium and in the nerve fibers of several species including humans [Ji et al., 2002; Charrua et al., 2009a]. TRPV4 was initially described in the urothelium of rodents and humans [Janssen et al., 2011]. Co-expression of the two receptors was observed in 20% of rat urothelial cells [Kullmann et al., 2009]. Recent observations indicate, however, that TRPV4 may also be expressed in bladder afferents. In fact, about 30% of L6 dorsal root ganglia neurons that project to the urinary bladder co-express TRPV1 and TRPV4 [Cao et al., 2009; Charrua et al., 2012a]. The physiological meaning of this observation is unclear.

TRPV1 KO mice have a normal or quasi-normal phenotype. In awake animals, the only change detected in TRPV1 KO mice was a smaller volume per void when compared with wild type (WT) controls [Birder et al., 2001]. In cystometries performed under anaesthesia, the TRPV1 KO mice phenotype seems also very benign. Some studies reported that this animals have totally normal cystometric traces [Charrua et al., 2007]. However, other studies showed that TRPV1 KO mice develop a few non-voiding contractions preceding the voiding contraction [Birder et al., 2001; Frias et al., 2012]. Accordingly, TRPV1 antagonists (GRC 6211) did not show any relevant effect on bladder activity of intact rodents [Charrua et al, 2009b]. In contrast with TRPV1 KO mice, the micturition phenotype of TRPV4 KO animals is clearly abnormal. TRPV4 KO mice are incontinent, most probably due to incomplete bladder emptying [Gevaert et al., 2007] Cystometric studies carried out under physiological conditions revealed that TRPV4 KO mice have an marked increase in the inter-contraction interval when compared to wild-type (WT) littermates. [Gevaert et al., 2007; Birder et al. 2002]. Likewise, TRPV4 antagonists (HC-067047) decreased the frequency of bladder contractions and increased the inter-contraction interval [Everaerts et al, 2010]. These observations indicated that TRPV4 has a role in the control of normal micturition reflex.

Indisputably, TRPV1 or TRPV4 have a role in the increase of micturition frequency associated with cystitis [Charrua et al., 2007; Everaerts et al., 2010]. While inflamed WT mice exhibit bladder hyperactivity and intense spinal Fos expression after different forms of bladder inflammation, including acetic acid or bacterial extracts, TRPV1 KO mice have normal cystometries and normal spinal c-fos expression [Charrua et al., 2007]). The The same holds true for TRPV4. In fact, TRPV4 KO mice exhibit significantly lower voiding frequencies and larger voided volumes than WT after inflammation with cyclophosphamide [Everaerts et al, 2010].

The blockade of TRPV1 and TRPV4 with specific antagonist confirm the observations carried out in knock-out animals. As a matter of fact, the TRPV1 antagonist GRC 6211 or the TRPV4 antagonist HC-067047 both abolish the increase of micturition frequency associated with chemical cystitis [Everaerts et al. 2010; Charrua et al., 2009b]. Recently,

it was shown that the systemic co-administration of TRPV1 and TRPV4 antagonist was more effective in treating the cystitis-induced increase of micturition frequency than the individual application of each antagonist [Charrua et al., 2012b]. In particular, the effect could be observed at very low doses of the TRPV1 and TRPV4 antagonists, which had no effect when given isolated. This observed effect might be the answer to overcome the eventual adverse events related with the application of some of these antagonists [Planells-Cases et al., 2011]. Just to mention a few, TRPV1 antagonists are associated with hyperthermia and increased risk of cardiac ischemia [Avelino et al., 2012] while TRPV4 antagonists may eventually precipitate urinary retention and overflow incontinence [Gevaert et al., 2007].

It is known for long that TRPV1 is involved in the emergence of neurogenic detrusor overactivity following spinal cord transaction [Avelino & Cruz, 2006]. Quite recently a TRPV1 antagonist GRC 6211 has been shown to decrease reflex detrusor overactivity in rats after chronic spinal cord transaction. With increasing doses it was possible to obtain a total suppression of bladder activity [Santos-Silva et al., 2012]. The clinical relevance of this finding will certainly be further investigated in the future.

There seem to be several links between activation of different members of the TRP superfamily and LUTS/DO/OAB, and further exploration of the involvement these channels in LUT function, normally and in dysfunction, may be rewarding. However, proof of concept studies in humans are still lacking.

c) Prostanoid receptor agonists/antagonists

Recent developments in the field of prostanoid receptors may open new possibilities to use selective prostanoid receptor antagonists for DO/OAB treatment [Aoki et al., 2009; Jones et al., 2009]. There is evidence suggesting that PGE2 contributes to the pathophysiology of DO/OAB: PGE2 infused into the bladder induces DO in humans and animals, increases PGE2 production in DO models and there are high concentrations of PGE2 in the urine of patients with OAB [McCafferty et al., 2008]. PGE2 is an agonist at EP receptors 1 to 4, all G-protein coupled, which mediate its physiological effects. Based on studies using knockout (KO) mice and EP1 receptor antagonists, it was suggested that the effects of PGE2 on bladder function were mediated through EP1 receptors [Schroder et al., 2004]. EP receptors can be found on urothelium/urothelium, in detrusor smooth muscle and in intramural ganglia [Wang et al., 2008; Rahnama'i et al., 2010; Rahnama'i et al., 2011]. Functionally, it has been proposed that modulation of bladder activity exerted via EP1 receptors occurs via an afferent mechanism. Schröder et al. [2004] found no difference in urodynamic parameters between unobstructed EP1 receptor KO and WT mice. However, EP1 receptor KO mice did not respond to intravesical PGE2 instillation, while WT mice developed DO. The lack of EP1 receptor did not prevent bladder hypertrophy due to partial bladder outflow obstruction but after obstruction WT mice had pronounced DO, while this was negligible in EP1 receptor KO mice.

Lee et al. [2008] found that in normal rats a selective EP receptor antagonist significantly increased bladder capacity, micturition volume and micturition intervals. The antagonist significantly decreased the stimulatory effects of PGE2, and decreased the frequency and amplitude of non-voiding contractions in animals with BOO. More recently it has been shown that also EP3 receptor KO mice have a diminished response to bladder infusion of PGE2, and demonstrate an enhanced bladder capacity under basal conditions [Jones et al., 2009]. This findings suggest an important contribution for EP3 receptors in the modulation of bladder function under physiological conditions as well as under conditions of enhanced PGE2 production evoking DO. Thus, EP1 and EP3 receptors may have a role in PGE2 mediated DO.

Interestingly, activation of EP3 receptors evoked diuresis and EP3 receptor antagonism was found to induce an antidiuretic effect [Jugus et al., 2009]. Thus, to modulate bladder activity, it appears that the EP3 receptor has a role in regulating urine production. Both effects may be useful for treatment of DO/OAB. It cannot be denied that EP1/EP3 receptors constitute interesting and promising targets for drugs aimed at DO/OAB treatment. However, a randomised, double-blind, placebo-controlled phase II study to investigate the efficacy and safety of the EP-1 receptor antagonist, ONO-8539, in patients with the overactive bladder syndrome suggests that the role of EP1 receptor antagonism in the management of OAB syndrome is minimal [Chapple et al., 2011].

d) Intraprostatic Injections of drugs

Intraprostatic injection therapy is probably the oldest minimally invasive surgical therapy for BPH and has been investigated for over 100 years with renewed interest recently. There are different injectables and various routes of administration, transperineal, transrectal and transurethral.

1. Ethanol

Ethanol injection is one of the most investigated intra-prostatic therapies and have been investigated for more than a decade [Goya et al., 1999]. However, the mechanism of action, patient selection and application of ethanol (the number of injection sites and the injection volume) have not been well investigated and long-term results are scarce. It seems that ethanol causes inflammation, coagulative necrosis with protein denaturation and cell membrane lysis, and, finally, sloughing of prostatic tissue resulting in cavity

formation [Plante et al., 2003]. The majority of trials demonstrated a significant reduction in symptoms and post-void residual volume as well as a significant improvement in Qmax and QoL and prostate volume also decreased significantly in the majority of studies [Goya et al., 2004; Grise et al., 2004; Plante et al., 2007; Sakr et al., 2009]. The durability of clinical effects beyond 1 year seems poor. One trial with a mean follow-up of 3 years showed a retreatment rate of 41% [Goya et al., 2004].

2. BoNT-A

BoNT-A investigation for the treatment of benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH) started in 2003 [Maria et al., 2003] after the experimental study by Doggweiler et al. [1998] demonstrating prostatic atrophy in the rat after intraprostatic injection of the neurotoxin. In an exploratory study, which involved injection of 200 U of onabotA in moderate to large prostate glands, a rapid prostate volume decrease was induced and still present at 12 months [Maria et al., 2003]. Following this study, Kuo [2005] reported similar findings when injecting prostate glands of 50 ml or larger. BoNT-A injection in smaller prostate glands caused a much lesser reduction in prostate volume, but a 15% reduction was still observed [Chuang et al., 2005; Chuang et al., 2006c). Independent of the extent of prostate volume reduction, improvement of LUTS and flow were consistently reported [Maria et al., 2003; Kuo, 2005; Chuang et al., 2005; Chuang et al., 2006c], while a decrease in total serum PSA were observed only in some studies [Maria et al., 2003; Guercini et al., 2005]. In a multicenter, double-blind, randomized phase II clinical trial of 100 and 300 unit doses of onabotA to treat the lower urinary tract symptoms of BPH, Crawford and coworkers concluded that intraprostatic injection of 100 or 300 units of onabotA passed predetermined criteria for treatment efficacy and safety (30% improvement from baseline to 3 months in American Urological Association symptom index and/or maximum urinary flow rate and safety). The ideal dose was not found, but it seemed that 100 unit dose may be preferable due to similar efficacy with reduced costs and adverse effects [Crawford et al., 2011]. Some serious adverse events were reported, including 3 cases of urosepsis related to the onabotA injection. Other minor adverse events reported were urinary tract infection, pelvic pain, urinary retention, macroscopic hematuria and hematospermia [Crawford ED et al., 2011].

Silva et al. [2008], selected a particular group of patients with high co-morbidity in which more invasive treatments were contraindicated. Intraprostatic BoNT-A injection was carried out transrectally, under ultrasound guidance. Twenty-one men with large BPE, 70±10 ml, on chronic indwelling catheter for at least 3 mo who were not candidates for surgery because of poor general condition received 200 U BoNT-A in the transition zone. Baseline prostate volume of decreased to 57±10 ml at 1mo and to 47±7ml at 3 months. At 1 month, 16 patients (76%) could resume voiding with a mean Qmax of 9.0±1.2 ml/s. At 3 months, 17 patients (81%) voided with a mean Qmax of 10.3±1.4 ml/s. Residual urine was not significant and mean serum total PSA showed a slight decrease [Silva et al. 2008]. The analysis of 11 patients of the initial cohort showed that the duration of prostate atrophy after the single injection of 200U of BoNT-A was found to be about 18 months [Silva et al., 2009b].

Intraprostatic injection of BoNT/A seems devoid of sexual adverse events. Sixteen sexually active men aged > 60 years with BPH/benign prostatic enlargement (BPE) refractory to standard medical therapy received 200U of BoNT/A by transrectal route. Erectile function was evaluated using the International Index of Erectile Function – Short Form (IIEF-5) questionnaire. Orgasmic/ejaculatory function and libido were evaluated using questions 9, 10, 11 and 12 of the IIEF – Long Form. Intraprostatic injection of BoNT-A did not cause deterioration of any domain of sexual function [Silva et al., 2011].

Although necrosis of the gland at the places of BoNT-A injection could explain the rapid volume reduction, transrectal ultrasound examination of the glands, performed in these or in previous studies [Maria et al., 2003; Kuo , 2005; Chuang et al., 2005; Silva et al., 2008, was unable to detect signs of cavitation that indirectly could suggest the presence of necrosis. Therefore, the reason for the decreased prostate volume should be more appropriately related to the widespread apoptosis detected in the gland after BoNT-A administration. Apoptosis was reported in rats, dogs, and humans, and affected both the epithelial and stromal components [Doggweiler et al., 1998; Chuang et al., 2005; Chuang et al., 2006b; Chuang et al., 2006d, Silva et al., 2009a].

Although until now, no important side-effects have been reported after intraprostatic injection of the neurotoxin in doses ranging between 100 and 300 U, a multicenter, double-blind, randomized phase II clinical trial of 100 and 300 unit doses of onabotA to treat the lower urinary tract symptoms of benign prostatic hyperplasia, was recently published [Crawford et al., 2011]. onabotA prostatic injection met the two safety criteria proposed, (a dose failed if: 1- a life threatening, disabling or fatal event was determined to be related to the onabotA injection, or 2- 40% or more of the participants reported a moderate or severe side effect related to the botulinum toxin injection). Nonetheless, some serious AEs were reported, including 3 cases of urosepsis related to the onabotA injection and the remaining events were judged not related to the injection. Other minor AEs reported were urinary tract infection,

pelvic pain, urinary retention, macroscopic hematuria and hematospermia [Crawford et al., 2011].

3. NX-1207

NX-1207 is a new drug under investigation for the treatment of LUTS associated with BPH. It is a new therapeutic protein of proprietary composition with selective pro-apoptotic properties [Shore , 2011]. The drug is injected directly into the directly into the transitional zone of the prostate as a single administration to induce focal cell loss in prostate tissue through apoptosis, leading to non-regressive prostate shrinkage and both short- and long-term symptomatic improvement. Information about the drugs is scarce and mostly published in abstract form and not yet in the peer-reviewed literature. Two US Phase II trials have been performed [Shore , 2011]. One of them was a multicenter, randomized, non-inferiority study involving 32 clinical sites with 85 subjects and two dose ranges (2.5 and 0.125 mg) and an active open-label comparator (finasteride). Subjects and investigators on NX-1207 were double-blind as to dosage. The primary endpoint was change in AUASI at 90 and 180 days for a single injection of NX-1207 as compared to finasteride on a non-inferiority basis. Inclusion criteria included an AUA Symptom Score ‡ 15, diminished peak urine flow (< 15 ml/s) and a prostate size of > 30 and < 70 mg. The mean AUA Symptom Score improvement after 90 days in the intent to- treat group was 9.71 points for 2.5 mg NX-1207 (n = 48) versus 4.13 points for finasteride (n = 24) (p = 0.001) and 4.29 for 0.125 mg NX-1207 (n = 7) (p = 0.034). The 180-day results also were positive (NX-1207 2.5 mg non-inferior to open-label finasteride).

No significant changes in serum testosterone or serum PSA levels in the NX-1207 cohorts. There were no reported adverse effects on sexual function. Two US multicenter, double-blind, placebo-controlled Phase III studies are currently underway. The results of such studies are needed to assess whether or not this therapeutic principle is a useful addition to the current treatment alternatives.

4. PRX302

PRX302 is a modified form of proaerolysin, a highly toxic bacterial pore-forming protoxin that requires proteolytic processing by prostate-specific antigen (PSA) [Sing et al., 2007]. The safety and efficacy of PRX302 was evaluated in men with moderate to severe BPH [Denmeade et al.,2010]. The patients were refractory, intolerant, or unwilling to undergo medical therapies for BPH and had an IPSS >12, a quality of life (QoL) score >3, and prostate volumes between 30 and 80 g. Fifteen patients were enrolled in phase 1 studies, and 18 patients entered phase 2 studies. Subjects received intraprostatic injection of PRX302 into the right and left transition zone via a transperineal approach in an office-based setting. Phase 1 subjects received increasing concentrations of PRX302 at a fixed volume; phase 2 subjects received increasing volumes per deposit at a fixed concentration. IPSS, QoL, prostate volume, Qmax), IIEF, serum PSA levels, pharmacokinetics, and adverse events were recorded at 30, 60, 90, 180, 270, and 360 days after treatment. Sixty percent of men in the phase 1 study and 64% of men in the phase 2 study treated with PRX302 had >30% improvement compared to baseline in IPSS out to day 360. Patients also experienced improvement in QoL and reduction in prostate volume out to day 360. Patients receiving >1 ml of PRX302 per deposit had the best response overall. There were no deleterious effect on erectile function. Adverse eventswere mild to-moderate and transient in nature. The major study limitation was the small sample size.The promising safety profile and evidence of efficacy in the majority of treated subjects in these phase 1 and 2 studies supports further development of PRX302 as a minimally invasive, targeted treatment for BPH. However, no further studies, verifying the initial data, seem to have been published.

e) Cannabinoids

There is increasing evidence that cannabinoids can influence micturition in animals as well as in humans, both normally and in bladder dysfunction [Ruggieri, 2011]. The effects of the cannabinoids are exerted via two types of well defined receptors, CB1 and CB2, distributed widely in the body. However, additional receptor subtypes cannot be excluded [Pertwee et al., 2010; Ruggieri 2011]. Both in the CNS and in peripheral tissues, CB1 and CB2 receptors have been identified; centrally CB1 and peripherally CB2 receptors seem to be predominant [Pertwee et al., 2010; Ruggieri, 2012] (**figure 17**). CBI as well as CB2 receptors have been identified in all layers of the human bladder [Merriam et al., 2008; Gratzke et al., 2009; Tyagi et al., 2009; Walczak et al., 2009]; their expression in the urothelium was found to be significantly higher than in the detrusor, and the expression of CB1 was higher than that of CB2 [Tyagi et al., 2009]. Gratzke et al. [2009] found higher expression of CB2 receptors, but not CB1 receptors, in the mucosa than in the detrusor. Compared to the detrusor, larger amounts of CB2receptor containing nerves that also expressed TRPV1 or CGRP were observed in the suburothelium. Nerve fibers containing CB2 receptors and VAChT (cholinergic neurons) were located in the detrusor. In general, activation of CB1 peripherally has been associated with vasodilation and motility changes via suppression of release of neurotransmitters, whereas activation of CB2 appears to induce anti-inflammatory, antinociceptive, and immunosuppressive actions [Pertwee et al., 2010; Ruggieri, 2011]. Several animal studies have suggested a modulatory role of CB2 receptors in both afferent signalling and cholinergic nerve activity [Gratzke et al., 2009; 2010; 2011]. Thus, in vivo the selective CB2 receptor agonist, cannabinor, increased micturition intervals and volumes, and

increased threshold and flow pressures, suggesting that peripheral CB2 receptors may be involved in sensory functions. In rats with partial urethral obstruction treated daily for 14 days with cannabinor, bladder weight was lower, the ability to empty the bladder was preserved and nonvoiding contraction frequency was low compared to those in controls.

The key enzyme for the degradation of anandamide and other endogenous cannabinoids, is fatty acid amide hydrolase (FAAH, **Figure 18**). FAAH was found to be expressed in rat and human urothelium and was coexpressed with CB2 receptors. In rats, a FAAH inhibitor altered urodynamic parameters that reflect sensory functions, suggesting a role for the endocannabinoid system in bladder mechanoafferent functions [Strittmatter et al., 2011].

It has not been established whether the effects of the cannabinoids are exerted in the CNS (brain, spinal cord) or peripherally. In a preliminay report Blywert et al. [2003] demonstrated an effect of combined CB1/CB2 receptor activation on detrusor overactivity in rats with spinal cord transection, which seemed to exclude the brain as a main site of action.

The clinical experiences the cannabinoid treatment of micturition disturbances inclung LUTS are limited [Ruggieri, 2011], but both open-label and placebo-controlled studies have demonstrated that orally administered cannabinoid modulators may alleviate neurogenic overactive bladder (OAB) symptoms refractory to first-line treatment [Brady et al., 2004; Freeman et al., 2006; Kavia et al., 2010]. Brady et al. [2004] evaluated the efficacy of 2 whole plant extracts (δ9-tetrahydrocannabinol and cannabidiol) of Cannabis sativa in patients with advanced MS and refractory LUTS. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia decreased significantly following treatment. Freeman et al. [2006] tested in a subanalysis of a multicenter trial (the CAMS study) whether cannabinoids could decrease urge incontinence episodes without affecting voiding in patients with MS. The CAMS study randomized 630 patients to receive oral administration of the cannabis extract δ9-tetrahydrocannabinol or matched placebo. Based on incontinence diaries a significant decrease in incontinence episodes was demonstrated.

Kavia et al. [2010] assessed the efficacy, tolerability and safety of Sativex(®) (nabiximols) as an add-on therapy in alleviating bladder symptoms in patients with MS. They performed a 10-week, double-blind, randomized, placebo-controlled, parallel-group trial on 135 randomized subjects with MS and overactive bladder (OAB). The primary endpoint, reduction in daily number of urinary incontinence episodes from baseline to end of treatment (8 weeks), showed little difference between Sativex and placebo. However, four out of seven secondary endpoints were significantly in favour of Sativex, including number of episodes of nocturia, number of voids/day, and number of daytime voids. The improvement in I-QOL was in favour of Sativex, but did not reach statistical significance.

Systemic cannabinoids have effects on the lower urinary tract that may have a therapeutic potential; local delivery (intravesical, spinal) may be possible, but more information is needed. The mechanisms of cannabinoid receptors in control of the human LUT

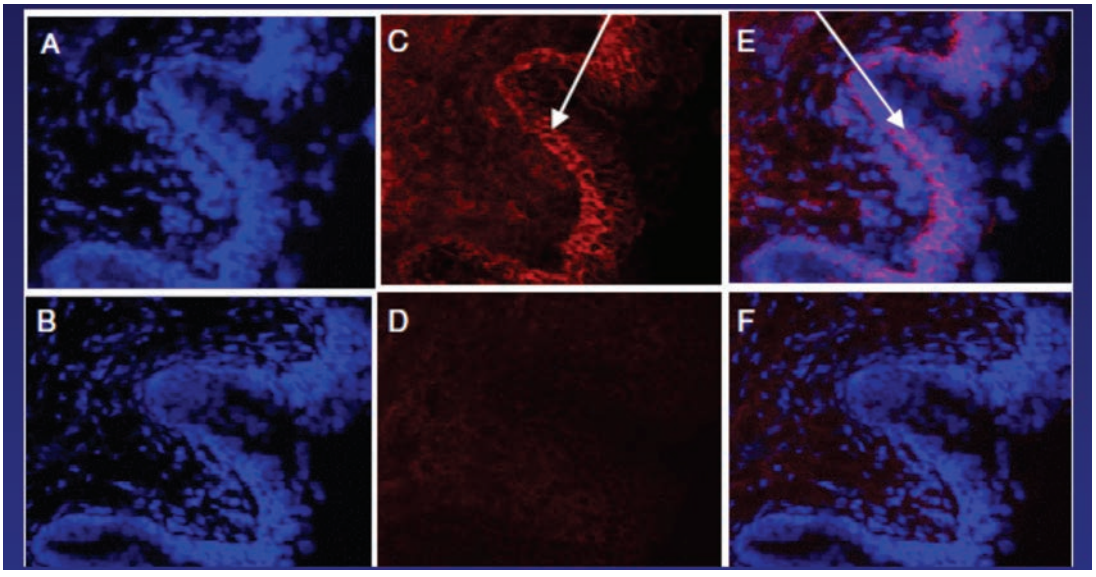


Figure 17 : CB2 receptors in the urothelium/lamina propria. The effects of the cannabinoids are exerted via two types of well defined receptors, CB1 and CB2, distributed widely in the body. Both in the CNS and in peripheral tissues, CB1 and CB2 receptors have been identified; centrally CB1 and peripherally CB2 receptors seem to be predominant.

is incompletely known, and further research is necessary for the development of novel cannabinoid drugs for treatment of LUT disorders.

2. CENTRALLY ACTING DRUGS

Many parts of the brain seem to be activated during storage and voiding [see, Griffiths 2007; Fowler et al., 2008; Griffiths and Tadic, 2008], and there is increasing interest in drugs modulating the micturition reflex by a central action [Andersson and Pehrson, 2003]. Several drugs used for pain treatment also affect micturition; morphine and some antiepileptic drugs being a few examples (**Figure 19**). However, central nervous mechanisms have so far not been preferred targets for drugs aimed to treat OAB, since selective actions may be difficult to obtain. Holstege [2005], reviewing some of the central mechnisms involved in micturition, including the periaqueductal gray (PAG) and the pontine micturition center (PMC), suggested that "the problem in OAB or urgency-incontinence is at the level of the PAG or PMC and their connections, and possible treatments for this condition should target the micturition pathways at that level."

a) Gonadotropin-releasing hormone antagonists

The beneficial effects of the 5α-reductase inhibitors, finasteride and dutasteride in the treatment of male LUTS are well documented. The efficacy of other hormonal treatments, for example, antiandrogens or gonadotropin-releasing hormone (GnRH; also known as luteinizing hormone-releasing hormone: LHRH) agonists is either poor or at the expense of unacceptable side effects such as medical castration associated with hot flushes, decrease of potency and libido, and negative effects on bone density following long-term androgen ablation [Schroeder et al., 1986; Peters et al., 1987; Bosch et al., 1989; Eri and Tveter, 1993]. With GnRH antagonists submaximal, non-castrating blockade of the androgen testosterone and consequently of dihydrotestosterone (DHT) can be achieved, thus avoiding medical castration. Several GnRH antagonists – such as cetrorelix, ozarelix and teverelix - have been tested in Phase IIA/IIB clinical trials for their ability to improve LUTS in patients with BPH [Colli and Tanko, 2011].

Debruyne et al. [2008] demonstrated in a phase 2 RCT that the LHRH antagonist cetrorelix, given subcutaneously weekly for 20 weeks to 140 men with LUTS (IPSS > 13, peak urinary flow rates 5-13 ml/s), rapidly caused a significant improvement in the mean IPSS: the peak decrease was -5.4 to -5,9 vs -2,8 for placebo. All dosage regimens tested were well tolerated, and the authors concluded that the drug offered a safe and effective treatment of male LUTS.

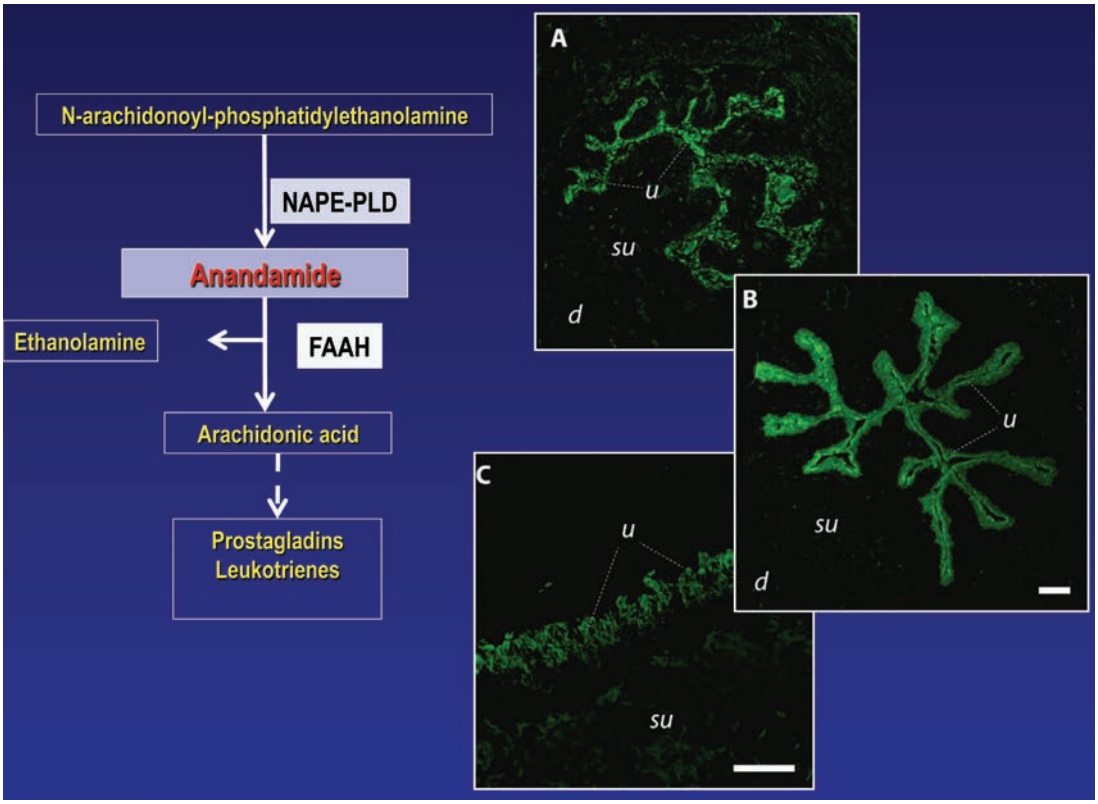


Figure 18: Metabolism of and distribution of fatty acid amide hydrolase (FAAH; cannabinoid degrading enzyme) immunoreactivity in the rat urothelium

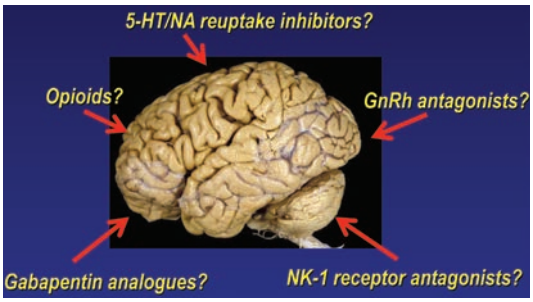


Figure 19 : OAB drugs with a central mode of action. Several principles seem to work, but currently used drugs have low efficacy and/or unacceptable side effects. However, there is great potential for further developments

Due to these results, two phase III studies were conducted in the United States and Europe [AEterna Zentaris] ; in the US study, 637 men were randomized to receive either two doses of placebo or cetrorelix on weeks 2 and 26. The drug showed no statistically significant benefit in improving IPSS. In addition, cetrorelix did not have a significant effect on peak flow rate or prostate volume versus placebo. It is difficult to reconcile this lack of efficacy given favorable prior results. A subsequent multicenter European trial also failed to show any treatment-related efficacy of cetrorelix. The experience with cetrorelix highlights the importance of randomized, placebo-controlled trials that are appropriately powered to show clinical benefit and safety.

b) Gabapentin

Gabapentin is one of the new first-generation antiepileptic drugs that expanded its use into a broad range of neurologic and psychiatric disorders [Striano and Striano 2008]. It was originally designed as an anticonvulsant GABA (y-aminobutyric acid) mimetic capable of crossing the blood-brain barrier [Maneuf et al., 2003]. The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial [Maneuf et al., 2003]. It has been suggested that it acts by binding to a subunit of the α2δ unit of voltage dependent calcium channels [Gee et al., 1996; Striano and Striano, 2008]. Gabapentin is also widely used not only for seizures and neuropathic pain, but for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

Carbone et al. [2006] reported on the effect of gabapentin on neurogenic DO. They found a positive effect on symptoms and significant improvement in urodynamic parameters, and suggested that the effects of the drug should be explored in further controlled studies in both neurogenic and non-neurogenic DO. Kim et al. [2004] studied the effects of gabapentin in patients with OAB and nocturia not responding to antimuscarinics. They found that 14 out of 31 patients improved with oral gabapentin. The drug was generally well tolerated, and the authors suggested that it can be considered in selective patients when conventional modalities have failed. It is possible that gabapentin and other α2δ ligands (e.g., pregabalin and analogs) will offer new therapeutic alternatives, but convincing RTC are still lacking.

c) Tramadol

Tramadol is a well-known analgesic drug [Grond and Sablotzski, 2004]. By itself, it is a weak μ-receptor agonist, but it is metabolized to several different compounds, some of them almost as effective as morphine at the μ-receptor. However, the drug (metabolites) also inhibits serotonin (5-HT) and noradrenaline reuptake [Grond and Sablotzski, 2004]. This profile is of particular interest, since both μ-receptor agonism and amine reuptake inhibition may be useful principles for treatment of LUTS/OAB/DO, as shown in a placobo controlled study with duloxetine [Steers et al., 2008].

In rats, tramadol abolished experimentally induced DO caused by cerebral infarction [Pehrson et al., 2003]. Tramadol also inhibited DO induced by apomorphine in rats [Pehrson and Andersson, 2003] – a crude model of bladder dysfunction in Parkinson´s disease. Singh et al. [2008] gave tramadol epidurally and found the drug to increase bladder capacity and compliance, and to delay filling sensations without adverse effects on voiding. Safarinejad and Hosseini [2006] evaluated in a double-blind, placebo-controlled, randomized study, the efficacy and safety of tramadol in patients with idiopathic DO. A total of 76 patients 18 years or older were given 100 mg tramadol sustained release every 12 h for 12 weeks. Clinical evaluation was performed at baseline and every two weeks during treatment. Tramadol significantly ($p<001$) reduced the number of incontinence periods per 24 hours from 3.2+/- 3.3 to 1.6+/-2.8) and induced improvements in urodynamic parameters. The main adverse event was nausea. It was concluded that in patients with non-neurogenic DO, tramadol provided beneficial clinical and urodynamic effects. Even if tramadol may not be the best suitable drug for treatment of LUTS/OAB, the study suggests efficacy for modulation of micturition via the μ-receptor.

d) NK1-receptor antagonists

The main endogenous tachykinins, substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), and their preferred receptors, NK1, NK2, and NK3, respectively, have been demonstrated in various CNS regions, including those involved in micturition control [Lecci and Maggi, 2001; Saffroy et al., 2003; Covenas et al., 2003]. NK1 receptor expressing neurons in the dorsal horn of the spinal cord may play an important role in DO, and tachykinin involvement via NK1 receptors in the micturition reflex induced by bladder filling has been demonstrated [Ishizuka et al., 1994] in normal, and more clearly, rats with bladder hypertrophy secondary to BOO. Capsaicin-induced detrusor overactivity was reduced by blocking NK1

receptor-expressing neurons in the spinal cord, using intrathecally administered substance P-saponin conjugate [Seki et al., 2002]. Furthermore, blockade of spinal NK1 receptor could suppress detrusor activity induced by dopamine receptor (L-DOPA) stimulation [Ishizuka et al., 1995a].

In conscious rats undergoing continuous cystometry, antagonists of both NK1 and NK2 receptors inhibited micturition, decreasing micturition pressure and increasing bladder capacity at low doses, and inducing dribbling incontinence at high doses. This was most conspicuous in animals with outflow obstruction [Gu et al., 2000]. Intracerebroventricular administration of NK1 and NK2 receptor antagonists to awake rats suppressed detrusor activity induced by dopamine receptor (L-DOPA) stimulation [Ishizuka et al., 2000]. Taken together, available information suggests that spinal and supraspinal NK1 and NK2 receptors may be involved in micturition control.

Aprepitant, an NK-1 receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting [Massaro and Lenz, 2005], significantly improved symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed incontinence (with predominantly urgency urinary incontinence), as shown in a well designed pilot RCT [Green et al., 2006]. The primary end point was percent change from baseline in average daily micturitions assessed by a voiding diary. Secondary end points included average daily total urinary incontinence and urgency incontinence episodes, and urgency episodes. Aprepitant significantly ($p<0.003$) decreased the average daily number of micturitions (-1.3+/-1.9) compared with placebo (-0.4+/-1.7) at 8 weeks. The average daily number of urgency episodes was also significantly ($p<0.047$) reduced (-23.2+/- 32%) compared to placebo (-9.3+/-40%), and so were the average daily number of urgency incontinence and total urinary incontinence episodes, although the difference was not statistically significant. Aprepitant was generally well tolerated and the incidence of side effects, including dry mouth, was low. Since this initial proof of concept study suggested that NK-1 receptor antagonism hold promise as a potential treatment approach for OAB symptoms, a randomized, double-blind, multicenter trial enrolled 557 adults with overactive bladder (8 or more average daily micturitions and 1 or more daily urge incontinence episodes) [Frenkl et al., 2010]. After a 1-week placebo run-in the patients were randomized to treatment with 8 weeks of daily 0.25, 1 or 4 mg serlopitant, 4 mg tolterodine extended release or placebo. Patients kept 7-day voiding diaries. The primary end point was change from baseline in micturitions per day. Secondary end points included urgency, total incontinence, urge incontinence episodes and incidence of dry mouth. Of the 557 patients randomized, 476 completed the trial and had valid efficacy data for analysis. Mean change from baseline in daily micturitions was significantly greater for 0.25 (-1.1) and 4 mg (-1.1) serlopitant, and for tolterodine (-1.5) than for placebo (-0.5), but not for 1 mg serlopitant (-0.8). No serlopitant dose response was demonstrated. Tolterodine was numerically superior to all doses of serlopitant in mean micturitions per day and secondary end points. The incidence of dry mouth on serlopitant (3.3%) was comparable to placebo (4.6%) and lower than tolterodine (8.8%). Serlopitant was generally well tolerated.

NK-1 receptor antagonists may have a role in the treatment of overactive bladder but at least the componds tested so far does not offer advantages in efficacy compared to tolterodine.

A different approach, modulation of neuropeptide release rather than NK receptor blockade, was tested in a pilot study with cizolirtine, which is a substance-P and CGRP release modulator at the spinal cord level. The modulation of substance-P and CGRP is probably related to the increase of extracellular levels of noradrenaline and serotonin. Cizolirtine 200 and 400 mg were compared to placebo in 79 OAB patients. Although the decrease in key OAB symptoms was significantly higher in the active arms, adverse events were reported in 68% and 81% of the patients on cizorlitine 200 and 400mg. More commonly reported side effects were gastro-intestinal in nature, including dry mouth and vomiting [Martınez-Garcıa et al., 2008]. No further developments of this compound have been reported.

C. Drugs used for treatment of stress incontinence in women

Many factors seem to be involved in the pathogenesis of stress urinary incontinence (SUI) in women: urethral support and function, bladder neck support and function of the nerves and musculature of the bladder, urethra, and pelvic floor [Delancey, 1997; Mostwin et al, 2005, Koelbl, Nitti et al, 2009; Chapple and Milsom, 2012]. Pure structural factors cannot be treated pharmacologically. However, SUI in women is generally thought to be characterized by decreases in urethral transmission pressure and, in most cases, resting urethral closure pressure [Henriksson et al, 1979; Hilton et al, 1983, Koelbl and Nitti, 2009]. It, therefore, seems logical that increasing urethral pressure should improve the condition.

Factors which may contribute to urethral closure include the tone of the urethral smooth and striated muscle (the rhabdosphincter) and the passive properties of the urethral lamina propria, in particular its vasculature. The relative contribution to intraurethral pressure of these factors is still subject to debate. However, there is ample pharmacological evidence that a substantial part of urethral tone is mediated through stimulation of α-ARs in the urethral smooth muscle by released noradrenaline [Andersson, 1993; Andersson and Wein, 2004; Andersson and Wein, 2012]. A contributing factor to SUI, mainly in elderly

women with lack of estrogen, may be lack of mucosal function. The pharmacological treatment of SUI (**Table 3**) aims at increasing intraurethral closure forces by increasing the tone in the urethral smooth and striated musculature, either directly or through increased motorneuron activity. Several drugs may contribute to such an increase [Andersson and Wein, 2012], but relative lack of efficacy or/and side effects have limited their clinical use.

I. α-ADRENOCEPTOR AGONISTS

Several drugs with agonistic effects on peripheral α-ARs have been used in the treatment of SUI. Relatively recently, a central role of noradrenaline (NA) in increasing the excitability of urethral rhabdosphincter motorneurons in the rat analogue of Onuf's nucleus, an effect due at least in part to α1-AR receptor dependent depolarization. This could contribute to the mechanism by which NA reuptake inhibitors improve SUI [Yashiro et al, 2010]. Ephedrine and norephedrine (phenylpropanolamine; PPA) seem to have been the most widely used [Andersson and Wein, 2012]. The original United States Agency for Healthcare Policy and Research Guidelines [Agency for Healthcare Policy and Research, 1992] reported 8 randomized controlled trials with PPA, 50 mg twice daily for SUI in women. Percent cures (all figures refer to percent effect on drug minus percent effect on placebo) were listed as 0% to 14%, percent reduction in continence as 19% to 60%, and percent side effects and percent dropouts as 5% to 33% and 0% to 4.3% respectively. The most recent Cochrane review on the subject [Alhasso et al, 2005, reprinted virtually unchanged in 2008] assessed randomized or quasi-randomized controlled trials in adults with stress urinary incontinence which included an adrenergic agonist drug in at least one arm of the trial. There were no controlled studies reported on the use of such drugs in men. Twenty-two eligible trials were identified, 11 of which were crossover trials, which included 1099 women, 673 of whom received an adrenergic drug (PPA in 11, midrodrine in 2, norepinephrine in 3, clenbuterol in 3, terbutaline in 1, eskornade in 1 and RO 115-1240 in 1). The authors concluded, "there was weak evidence to suggest that use of an adrenergic agonist was better than placebo in reducing the number of pad changes and incontinence episodes, as well as, improving subjective symptoms". There was not enough evidence to evaluate the merits of an adrenergic agonist compared with estrogen, whether used alone or in combination. Regarding adverse events, the review reported similar numbers with adrenergic, placebo, or alternative drug treatment. Over 25% of subjects reported such effects, but when these consisted of effects due to adrenergic stimulation, they caused discontinuation in only 4% of the total.

Ephedrine and PPA lack selectivity for urethral α-ARs and can increase blood pressure and cause sleep disturbances, headache, tremor, and palpitations [Andersson and Wein, 2012]. Kernan et al. [2000] reported the risk of hemorrhagic stroke to be 16 times higher in women less than 50 years of age who had been taking PPA as an appetite suppressant (statistically significant) and 3 times higher in women who had been taking the drug for less than 24 hours as a cold remedy (not statistically significant). There was no increased risk in men. PPA has been removed from the market in the United States. It is still allowed as a treatment for SUI in a few countries. Numerous case reports of adverse reactions due to ephedra alkaloids exist, and some [Bent et al., 2003) had suggested that sale of these compounds as a dietary supplement be restricted or banned. In December 2003, the Food and Drug Administration of the US decreed such a ban, a move which has survived legal appeal.

Midodrine and methoxamine stimulate α1-ARs with some degree of selectivity. According to the RCTs available, the effectiveness of these drugs is moderate at best, and the clinical usefulness seems to be limited by adverse effects [Alhasso et al., 2003; Radley et al., 2001; Weil et al., 1998].

Attempts continue to develop agonists with relative selectivity for the human urethra. Musselman et al. [2004] reported on a phase 2 randomized crossover study with RO 115-1240, a peripheral active selective α1A/1L-AR partial agonist [Blue et al., 2004] in 37 women with mild to moderate SUI. A moderate, positive effect was demonstrated, but side effects have apparently curtailed further development of the drug. PF-3774076, a CNS penetrating partial α1A-AR agonist, increased peak urethral pressure in dogs and was selective with respect to α1B and α1D receptors,

Table 3. Drugs used in the treatment of stress incontinence. Assessments according to the Oxford system (modified)

Drug	*Level of evidence*	*Grade of recommendation*
Clenbuterol	***3***	***C***
Duloxetine	***1***	***B***
Ephedrine	***3***	***D***
Estrogen	***2***	***D***
Imipramine	***3***	***D***
Methoxamine	***2***	***D***
Midodrine	***2***	***C***
Norephedrine (phenylpropanolamine)	***3***	***D***

but heart rate and blood pressure changes caused significant concern (Conlon et al., 2009). Furuta et al. [2009] reported that the α2-AR can inhibit the release of glutamate presynaptically in the spinal cord and proposed that α2-AR antagonists would be useful as a treatment for SUI. This hypothesis awaits testing.

II. β-ADRENOCEPTOR AGONISTS

Clenbuterol. β-AR stimulation is generally conceded to decrease urethral pressure [Andersson, 1993], but β2-AR agonists have been reported to increase the contractility of some fast contracting striated muscle fibers and suppress that of slow contracting fibers of others [Fellenius et al.,1980]. Some β-AR agonists also stimulate skeletal muscle hypertrophy – in fast twitch more so than slow twitch fibers [Kim et al., 1992]. Clenbuterol has been reported to potentiate the field stimulation induced contraction in rabbit isolated peri-urethral muscle preparations, an action which is suppressed by propanolol and greater than that produced by isoprotererol [Kishimoto et al, 1991]. These authors were the first to report an increase in urethral pressure with clinical use of clenbuterol and to speculate on its potential for the treatment of SUI. Yaminishi et al. [1994] reported an inotropic effect of clenbuterol and terbutaline on the fatigued striated urethral sphincter of dogs, abolished by β-AR blockade.

Yasuda et al. [1993] described the results of a double blind placebo controlled trial with this agent in 165 women with SUI. Positive statistical significance was achieved for subjective evaluation of incontinence frequency, pad usage per day, and overall global assessment. Pad weight decreased from 11.7± 17.9g to 6.0± 12.3g for drug and from 18.3± 29.0g to 12.6± 24.7g for placebo, raising questions about the comparability of the 2 groups. The “significant” increase in MUCP was from 46.0± 18.2 cm H2O to 49.3± 19.1 cm H2O, versus a change of -1.5 cm H2O in the placebo group. 56/77 patients in the clenbuterol group reported some degree of improvement versus 48/88 in the placebo group. The positive effects were suggested to be a result of an action on urethral striated muscle and/or the pelvic floor muscles. Ishiko et al. [2000] investigated the effects of Clenbuterol on 61 female patients with stress incontinence in a 12-week randomized study, comparing drug therapy to pelvic floor exercises. The frequency and volume of stress incontinence and the patient’s own impression were used as the basis for the assessment of efficacy. The improvement of incontinence was 76.9%, 52.6%, and 89.5% in the respective groups. In an open study, Noguchi et al [1997] reported positive results with clenbuterol (20 mg b.i.d. for 1 month) in 9 of 14 patients with mild to moderate stress incontinence after radical prostatectomy. No subsequent published reports have appeared. Further well-designed RTCs investigating effects of clenbuterol are needed to adequately assess its potential as a treatment for stress incontinence.

There have been no recent reports of clinical trials with α1- or β-AR agonists or antagonists for SUI.

III. β –ADRENOCEPTOR ANTAGONISTS

The theoretical basis for the use of β-AR antagonists in the treatment of stress incontinence is that blockade of urethral β-ARs may enhance the effects of noradenaline on urethral α-ARs. Propranolol has been reported to have beneficial effects in the treatment of stress incontinence [Gleason et al., 1974; Kaisary, 1984] but there are no RCTs supporting such an action. In the Gleason et al. [1974] study, the beneficial effects become manifest only after 4 to 10 weeks of treatment, a difficult to explain phenomenon. Donker and Van der Sluis [1976] reported that β-AR blockade did not change UPP in normal women. Although suggested as an alternative to α-AR agonists in patients with SUI and hypertension, these agents may have major potential cardiac and pulmonary side effects of their own, related to their therapeutic β-AR blockade.

IV. SEROTONIN-NORADRENALINE UPTAKE INHIBITORS

1. IMIPRAMINE

Imipramine, among several other pharmacological effects has classically been reported to inhibit the reuptake of noradrenaline and serotonin in adrenergic nerve endings. In the urethra this could be expected to enhance the contractile effects of noradrenaline on urethral smooth muscle. Gilja et al. [1984] reported in an open study on 30 women with stress incontinence that imipramine, 75 mg daily, produced subjective continence in 21 patients and increased mean maximal urethral closure pressure (MUCP) from 34 to 48 mm Hg. A 35% cure rate was reported by pad test and, in an additional 25%, a 50% or more improvement. Lin et al. [1999] assessed the efficacy of imipramine (25 mg imipramine three times a day for three months) as a treatment of genuine stress incontinence in 40 women with genuine stress incontinence. A 20-minute pad test, uroflowmetry, filling and voiding cystometry, and stress urethral pressure profile were performed before and after treatment. The efficacy of “successful treatment” was 60% (95% CI 11.8-75.2). There are no RCTs on the effects of imipramine on SUI. No subsequent published reports have appeared.

Interestingly, Gillman [2007] reported that clomipramine had far greater 5HT reuptake inhibition than imipramine and roughly similar NA reuptake inhibition. Desipramine and reboxetine had greater NA reuptake inhibition (desipramine superior), with less effects than imipramine on 5HT uptake (desipramine superior).

2. DULOXETINE

Duloxetine hydrochloride is a combined norepinephrine and serotonin reuptake inhibitor, which has been

shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function [Thor et al., 1995; Katofiasc et al., 2002]. Bladder capacity was also increased in this model, both effects mediated centrally through both motor efferent and sensory afferent modulation [Fraser et al., 2003]. The sphincteric effects were reversed by α1 adrenergic (praxosin) and 5HT2 serotonergic (LY 53857) antagonism, while the bladder effects were mediated by temporal prolongation of the actions of serotonin and norepinephrine in the synaptic cleft [Fraser et al., 2003]. Duloxetine is lipophilic, well absorbed, and extensively metabolized (CYP2D6). Its plasma half-life is approximately 12 h [Sharma et al., 2000].

Thor et al. [2007] described the mechanisms of action and the physiologic effects of duloxetine. 5HT (serotonin) and NA terminals are dense in spinal areas associated with lower urinary tract functioning especially around the pudendal nerve neurons in Onuf's nucleus. These are projections from separate areas in the brain stem. Glutamate is the primary excitatory neurotransmitter in the spinal cord, activating the pudendal neurons in Onuf's nucleus causing contraction of the urethral rhabdosphincter (**Figure 20**). The rhabdosphincter innervation is proposed as distinct from that of the levator ani [Thor and de Groat, 2010]. The responsiveness of the rhabdosphincter motor neurons to glutamate is modulated (facilitated) by 5HT (through 5HT2 receptors) and NA (through α1 -ARs). 5HT and NA, however, only modulate, and, when micturition occurs, glutamate excitation and the rhabdosphincter contraction cease. Excitatory effects on urethral sphincter activity are shared to a lesser extent by receptors for 5HT1A (indirect through a supraspinal stimulation), TRH, Vasopressin, NMDA and AMPA; inhibitory effects are similarly mediated by κ2 opioid, α1 ARs, GABA-A, GABA-B and glycine receptors [Thor and de Groat, 2010]. Some CNS penetrant selective 5HT2C agonists have been found to increase urethral muscle tone and inhibit micturition reflexes in animal models, and these are additional candidates for clinical development for the treatment of SUI [Brennan et al., 2009, Andrews et al., 2011].

Sevral RTCs have documented the effect of duloxetine i SUI [Norton et al., 2002; Dmochowski et al, 2003; Millard et al., 2004]. A Cochrane review of the effects of duloxetine for stress urinary incontinence in women is available, the last substantive amendment listed as 25 May 2005 [Mariappan et al., 2005]. Fifteen reports were deemed eligible for analysis, 9 primary studies and 6 additional reports related to 1 or 2 of the primary references. An additional analysis "performed under the auspices of the Cochrane Incontinence Group" was performed on just the 9 primary trials comparing duloxetine and placebo, and published separately [Mariappan et al., 2007]. The results can be summarized as follows. Subjective "cure" in the duloxetine 80 mg daily (40 mg b.i.d.) was higher than in the placebo group (10.8%

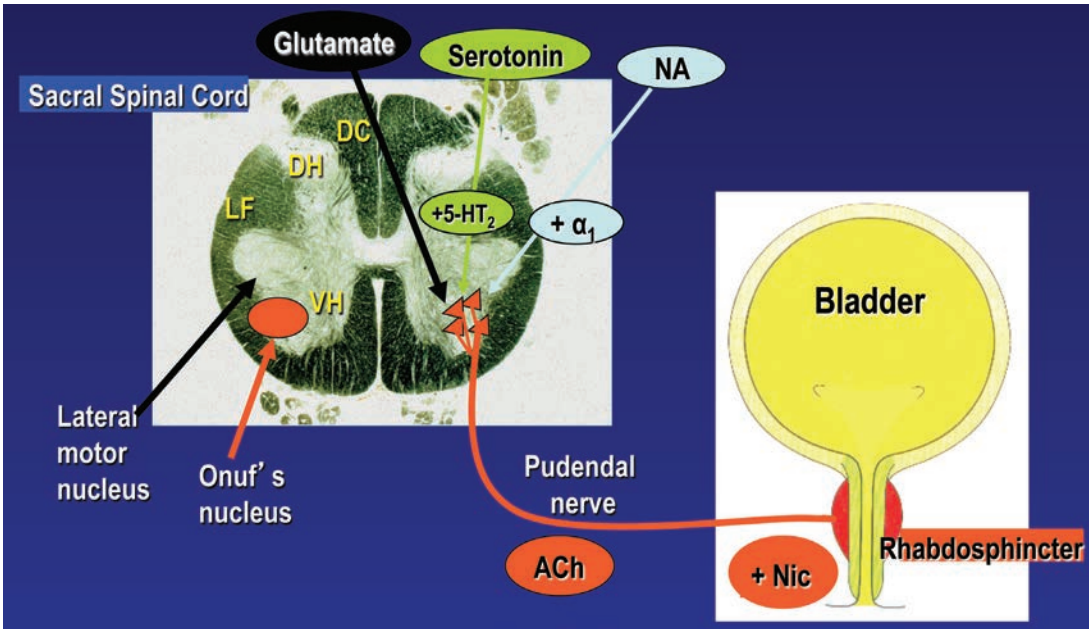


Figure 20: The striated urethral sphincter is innervated by the pudendal nerve, which contains the axons of motor neurons whose cell bodies are located in Onuf's nucleus. Glutamate exerts a tonic excitatory effects on these motor neurons, and this effect is enhanced by noradrenaline (NA) and serotonin (5-HT), acting on α1- adrenoceptors and 5-HT2-receptors, respectively. By inhibition of the reuptake of noradrenaline and serotonin, duloxetine increases the contractile activity in the striated sphincter (nicotinic receptors: + Nic). DC = dorsal commissure; DH = dorsal horn; VH = ventral horn; LF = lateral funiculus; ACh = acetylcholine

vs 7.7%, overall RR = 1.42; 95% CI, 1.02-1.98; p = 0.04). The estimated absolute size of effect was about 3 more patients cured of every 100 treated. Objective cure data, available from only 1 trial, showed no clear drug/placebo difference. Duloxetine showed greater improvement in I-QOL (WMD for 80 mg: 4.5; 95% CI 2.83-6.18, p<0.00001). Adverse effects in 6 trials were analyzed. These were reported by 71% of drug subjects and 59% of those allocated to placebo. Nausea was the most common adverse event and the incidence ranged from 23-25% and was the main reason for discontinuation. Other side effects reported were vomiting, constipation, dry mouth, fatigue, dizziness and insomnia, overall RR 1.30 (95% CI, 1.23-1.37). Across these 6 trials 17% in the drug group withdrew, 4% in the placebo arm. In the 2007 article, the authors conclude by saying that further research is needed as to whether management policies incorporating duloxetine are clinically effective and cost effective compared to other current minimally invasive and more invasive approaches in patients with varying severity of SUI, and that "longer term experience is now a priority to determine whether there is sustained efficacy during and after duloxetine use and to rule out complications".

Hurley et al. [2006] characterized the safety of duloxetine for treatment of SUI in women, using an integrated database generated from four published placebo-controlled clinical trials. The database included 1913 women randomized to duloxetine (N=958) or placebo (N=955), examining adverse events (AEs), serious adverse events (SAEs), vital signs, electrocardiograms, and laboratory analytes. AEs occurring initially or worsening during the double-blind treatment period were considered treatment-emergent (TEAE). Differences between duloxetine-treated and placebo-treated groups were compared statistically. Common TEAEs included: nausea (23.2%), dry mouth (13.4%), fatigue (12.7%), insomnia (12.6%), constipation (11.0%), headache (9.7%), dizziness (9.5%), somnolence (6.8%), and diarrhea (5.1%). Most TEAEs that emerged early were mild to moderate, rarely worsened, and resolved quickly. Overall AE discontinuation rates were 20.5% for duloxetine and 3.9% for placebo (P<.001). Most discontinuations (83%) occurred within the first month of treatment. SAEs were uncommon and did not differ between treatments. Statistically significant, but clinically unimportant mean increases in heart rate (2.4 bpm) and systolic and diastolic blood pressure (<or=2 mmHg) occurred. No arrhythmogenic potential was observed and any rare, transient, asymptomatic increases in hepatocellular enzymes normalized. The authors concluded that duloxetine was safe and tolerable, although transient AEs were not uncommon. Hashim and Abrams [2006] suggested, to reduce the risk of nausea, to begin with a dose of 20 mg twice daily for 2 weeks, then to increase to the recommended 40 mg b.i.d. dosage.

Ghoniem et al. [2005] randomized women with SUI to 1 of 4 treatment combinations: duloxetine alone (40 mg b.i.d.), pelvic floor muscle training, combination and placebo. Overall, drug with or without PFMT was superior to PFMT alone or placebo, while pad results and QOL data favored combination therapy to single treatment. Cardozo et al. [2004] reported that 20% of women awaiting continence surgery changed their minds while taking duloxetine. Duckett et al. [2006], offered a 4-week course to women awaiting a TVT operation. Thirty-seven percent (of 73) declined. Excluding women for whom concomitant prolapse surgery was planned, 8/33 (24%) scheduled for incontinence surgery alone came off the list. Sixteen (48%) discontinued duloxetine because of AEs, 9 (27%) found the drug ineffective.

Bent et al. [2008], reported on the effects of 12 weeks of duloxetine (40 mg b.i.d.) vs placebo in a large group of women with MUI. For SUI episodes, the mean IEF (incontinence episode frequency) per week decreased 58.9% with drug [7.69 to 3.93] vs 43.3% for placebo [8.93 to 6.05]. Interestingly, corresponding decreased for UUI episodes were 57.7% vs 39.6%. Both sets of values are statistically significant, but the baselines are different and the absolute change for SUI amounted to -3.76 episodes per week for drug, -2.87 for placebo. Nausea was reported by 18% of patients on drug, 4.5% on placebo. Corresponding percents for other AEs include, dry mouth (12 vs 2.8), dizziness (9.7 vs 2.4), constipation (8.3 vs 4.2), fatigue (6.7 vs 2.8). Nausea and dizziness were less common in a subgroup taking concurrent antidepressants. Women 65 years and older with SUI or stress predominant MUI (S-MUI) were given duloxetine (40 mg b.i.d. after a 2-week start on 20 mg b.i.d.) or placebo for 12 weeks by van Leeuwen et al [2008]. They conclude, "this study supports the use of duloxetine in elderly women with SUI or S-MUI". The data show an absolute change in SUI + S-MUI episodes of -11.7 and -6.9 IEF/week (drug and placebo) and median percent changes of -52.5% vs -36.7% from 24h diaries, both significant at p<0.001. However, the changes for SUI alone were -53% vs -42% (NS) while for S-MUI alone they were -51.6% vs -32.7% (p<0.001). Nausea was less than in other trials (7.5% vs 3.1%), perhaps due to the lower starting dose. Other AEs included fatigue (14.2% vs 5.4), constipation (10.4 vs 0.8), dizziness (9.0 vs 4.6), excess sweating (5.2 vs 0).

Schagen van Leeuwen et al. [2008] investigated efficacy and safety of duloxetine in elderly women with stress urinary incontinence or stress-predominant mixed urinary incontinence. Duloxetine-treated patients had a significantly greater decrease from baseline to endpoint in mean incontinence episode frequency/week than placebo-treated patients (-52.47% vs. -36.70%). The

responder rate (> or =50% reduction in incontinence episode frequency/week) was 57.1% in the duloxetine group and 35.2% in the placebo group (P<0.001). Significant benefits of duloxetine were also demonstrated for weekly continence pad usage, mean time between voids, incontinence quality of life questionnaire scores (P<0.001), and global impression of improvement ratings (P<0.001). Patients with depressive symptoms and cognitive impairments were few and changes were insignificant.

Persistence on duloxetine was studied by Vella et al. [2008] who found that only 31% of an original cohort of 228 were still taking drug beyond 4 weeks, 12% at 4 months, 10% at 6 months, and 9% at 1 year. Fifty-six percent of the discontinuations were attributed to side effects, 33% to lack of efficacy, Bump et al. [2008], however, reported that the positive effects of duloxetine were maintained in patients who continued treatment up to 30 months, but admitted that this subgroup was likely to include predominantly patients who had favorable responses. The number decreased from 1424 in this cohort at 3 months to 368 at 30 months Shaban et al. [2010] concluded that duloxetine is “optional second line for women not willing or unfit for surgery after warning against side effects as recommended by NICE guidelines in the UK”. Similar sentiments are expressed by Robinson and Cardozo [2010].

Duloxetine is licensed at 40 mg twice daily for the treatment of SUI in the European Union [European Medicines Agency, Scientific Discussion, 2005] in women with moderate to severe incontinence (defined as 15 or more episodes per week). It was withdrawn from the FDA consideration process in the United States for the treatment of SUI, but is approved for the treatment of major depressive disorder (20-30 mg b.i.d. initially, 60 mg once daily maintenance), diabetic peripheral neuropathic pain (60 mg once daily), generalized anxiety disorder (60 mg once daily, fibromyalgia (c0 mg once daily initially, 60b mg once daily maintenance) and chronic musculoskeletal pain (30 mg once daily initially,60 mg once daily as maintenance. The product information contains a “black box” warning of “increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders”, noting also that “depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide” [Prescribing Information, revised September 2011, Eli Lilly and Company, Indianapolis, Indiana 46285]. Other warnings and precautions in the U.S. in the United States Product Information for psychiatric indications, not SUI, include hepatotoxicity (not to be used in patients with substantial alcohol use or chronic liver disease), orthostatic hypotension, serotonin syndrome (general statement regarding SSRIs and SNRIs), abrupt discontinuation (may result in dizziness, paresthesias, irritability and headache), inhibitors of CYP1A2 (such as ciprofloxacin), thioridaxine (do not administer concomitantly) potent inhibitors of CYP2D6 (may increase concentration), and others. Adverse events for 6801 drug and 4487 placebo treated patients reported in the US Product Information (treatment for the indications mentioned) are nausea (24% vs 8%), dry mouth (13 vs 5), fatigue (10 vs 5), somnolence (10 vs 3), insomnia (10 vs 6), constipation (10 vs 4), dizziness (10 vs 5).

D. Stress urinary incontinence in men

Although a problem of significant magnitude, especially after radical prostatectomy (RP) for cancer, the pharmacologic treatment of male SUI is an area that has received relatively little attention.

Intrinsic sphincter function is the most important outlet factor maintaining continence in men. Urethral support is less important, and there is no entity similar to the hypermobility phenomenon in women. The proximal urethral sphincter extends from the bladder neck through the prostatic urethra. Its function is removed by radical prostatectomy. The distal urethral sphincter includes the rhabdosphincter, urethral smooth muscle and extrinsic paraurethral skeletal muscle, extending from the prostatic urethra below the verumontanum through the membranous urethra [Koelbl, Nitti et al, 2009]. Tsakiris et al [2008] searched for articles on drug treatment of male SUI published between 1966 and June 2007 and did a generalized database search in addition. Nine trials were identified using alpha adrenergic agonists, beta-2 antagonists or SNRSs. Only one of these included a comparison arm [Filocamo et al, 2007], 40 mg b.i.d. duloxetine plus pelvic floor exercise (PFE) vs PFE with placebo. The results suggested a positive effect of drug, but were a bit confusing. Of those patients completing the 4 month trial [92/112] 78% of the drug treated patients vs 52% of those in the placebo group were “dry”. However, one month after the end of the study, the corresponding figures were 46% vs 73%, a shift still observed 2 months later. The authors of the review article suggested further larger and well designed studies on duloxetine for this potential usage.

Cornu et al. [2011] reported a series of post RP men with SUI or MUI (stress predominant) randomized to duloxetine [l5] and placebo [16] after a 2-week placebo run in. Dosage was 20 mg b.i.d. for 7d, 40 mg b.i.d. for 67d, 20 mg for 14d. Subjects were at least 1 year post surgery. Outcome measures included percent decrease in IEF, 1h pad test and various QOL measures. Statistical significance for IEF percent decrease occurred only at week 8 & 12 [(-) 52.2 ± 38.6% vs (+)19 ± 43.5%] but there was clearly a trend at 4 weeks. There was no statistical difference in 1h pad test weights but there was in various QOL scores. A 50-100% decrease in IEF was seen at 12

weeks in over half of the patients. Adverse events for drug and placebo included fatigue (50 vs 13%), insomnia (25 vs 7), libido loss (19 vs 7), constipation (13 vs 7), nausea (13 vs 7), diarrhea (13 vs 7), dry mouth (6 vs 0), anorexia (6 vs 0), and sweating (25 vs 20). Drawbacks and concerns are the small number (the original proposed sample size was 90) and the lack of any placebo effect on IEF and QOL. There were 4 men with MUI in the drug group, 5 in the placebo group. Results for SUI and UUI were not separated. One would logically not expect improvement to continue after drug withdrawal unless a permanent change occurred in behavior, anatomy or neuromuscular function. In an uncontrolled usage study on men with post RP SUI, Serra et al [2011] reported that the benefit remained in 85% after the drug was stopped. In that series, 25% of patients withdrew because of AEs and 33% because of lack of effect.

Usage of duloxetine for SUI in the male is universally off label. A drug for this indication would be welcome. Larger controlled and better designed studies are necessary to provide conclusive positive or negative data on this subject.

E. Drugs to treat overflow incontinence/acute urinary retention

Urinary incontinence most often results from involuntary bladder contractions and/or too little resistance generated by the bladder outflow tract during the storage phase of the micturition cycle (urgency incontinence and stress incontinence, respectively). More rarely, incontinence can also occur because of too little pressure generation and/or too much outflow resistance, which can lead to a markedly distended bladder and urinary retention and, secondarily, overflow incontinence [Abrams et al., 2002].

Based upon theoretical reasoning, animal studies [Kamo et al., 2005; Gu et al., 2004], and reports of drugs that can cause overflow incontinence [Anders et al., 1985], a variety of medical approaches to the treatment of overflow incontinence have been proposed [Chutka and Takahashi, 1998; Diokno AC, 2004; Hampel et al., 2005]. Treatment may aim to increase bladder contractility, decrease bladder outlet resistance, or both. Theoretically, all drugs that improve decreased sensation (and increase afferent activity) or drugs that increase detrusor contractile force could be useful. Alternatively, agents that decrease outflow resistance, thereby restoring an appropriate balance between detrusor strength and urethral resistance, could be used.

These drugs include direct or indirect muscarinic receptor agonists, α1-AR antagonists, choline esterase inhibitors, prostaglandins (PG), and skeletal muscle relaxants [Diokno AC, 2004]. The use of muscarinic receptor agonists, such as bethanechol, to stimulate detrusor muscarinic receptors, or choline esterase inhibitors, such as distigmine, to reduce the degradation of acetylcholine, is based upon the idea that stimulation of muscarinic receptors may overcome a hypocontractile detrusor [Barendrecht et al., 2007]. However, a recent systematic review of controlled clinical studies that used direct and indirect parasympathetic agonists in patients with an underactive detrusor reported that these drugs do not provide consistent benefits and may even be harmful. The available information indicates that muscarinic receptor agonists and choline esterase inhibitors have little, if any, beneficial effects on preventing and treating detrusor underactivity. While there is a theoretical basis for the use of β-agonists to relax the sphincter, no definite improvements in symptoms have yet been demonstrated [Riedl et al., 2000; Dasgupta et al., 2003; Barendrecht et al., 2007; Ahmad et al. 2009]. As bethanechol exerts its effect on intact smooth muscle cells only, it is of limited use for the treatment of bladder atony. Idiopathic detrusor atony is poorly responsive to medical treatment [Noel et al. 2010].

The use of α1-AR antagonists has repeatedly been shown to be beneficial in patients with acute urinary retention due to benign prostatic enlargement[McNeill et al., 2004; 2005; Fitzpatrick et al., 2012]. These drugs are believed to facilitate bladder emptying by relaxing tone at the bladder neck. Administration of alfuzosin 10 mg daily almost doubles the likelihood of a successful trial without a catheter, even in patients who are elderly with a PVR > 100 mL. Continued use of alfuzosin significantly reduced the risk of BPH surgery in the first 3 months; however, this effect was not significant after 6 months [Fitzpatrick and Kirby, 2006; Emberton et al., 2008; Kalejaiye et al., 2009]. Thus, α1-AR antagonists provide rapid symptom relief from outlet obstruction caused by benign prostatic enlargement and delay the time to acute urinary retention; however, they do not decrease the overall risk of acute urinary retention or surgery [Emberton et al., 2008; Edwards, 2008; Fitzpatrick et al., 2012].

Acute urinary retention may ocur after surgery. Buckley and Lapitan [2010] reviewed drugs used for treatment of post-operative urinary retention either alone or in combination, assessing cholinergic agents, α1-AR blockers, sedatives and prostaglandins. A statistically significant association between intravesically administered prostaglandins and successful voiding was detected, but no such association was found for the other drugs investigated. When cholinergic agents were combined with sedative there was an improved likelyhood of spontaneous voiding compared with placebo.

There are some potential new agents for the treatment of an underactive bladder. Misoprostol, a cholinesterase inhibitor, and cholinergic agents are potential candidates for the treatment of the under-

active bladder, but their safety and lack of benefit is of concern. Novel muscarinic receptor manipulation using the presynaptic M2 receptor antagonist or postsynaptic allosteric receptor enhancement is promising. The prokinetics used in gastroenterology and the smooth muscle ionotropics used in cardiology warrant consideration. The use of trophic factors such as insulin-like growth factor and nerve growth factor may improve muscle and nerve function in the lower urinary tract. Furthermore, the use of stem cells, regenerative medicine, and gene therapy might facilitate improved contractility in a weak detrusor [Chancellor et al., 2008].

However, these agents have never been tested systematically in patients with overflow incontinence; there have been no randomized controlled trials to demonstrate the effectiveness and safety of these agents. Therefore, there is no empirical basis to select medical treatments for overflow incontinence and all previously recommended treatments must be rated as “expert opinion” at best. Better systemic studies are required to determine the best medical treatment for overflow incontinence. Any medical treatment for overflow incontinence should be compared to catherization or surgery.

F. Hormonal treatment of urinary incontinence

I. OESTROGENS

1. OESTROGENS AND THE CONTINENCE MECHANISM

The oestrogen sensitive tissues of the bladder, urethra and pelvic floor all play an important role in the continence mechanism. For women to remain continent the urethral pressure must exceed the intra-vesical pressure at all times except during micturition. The urethra has four oestrogen sensitive functional layers all of which have a role in the maintenance of a positive urethral pressure 1) epithelium, 2) vasculature, 3) connective tissue, 4) muscle.

Two types of oestrogen receptor, (α and β) have been identified in the trigone of the bladder, urethra and vagina as well as in the levator ani muscles and fascia and ligaments within the pelvic floor [Smith et al., 1990; Copas et al., 2001; Gebhardt et al., 2001]. After the menopause oestrogen receptor α has been shown to vary depending upon exogenous oestrogen therapy [Fu et al., 2003]. In addition exogenous oestrogens affect the remodeling of collagen in the urogenital tissues resulting in a reduction of the total collagen concentration with a decrease in the cross linking of collagen in both continent and incontinent women [Falconer et al., 1998; Keane et al., 1997]. Studies in both animals and humans have shown that oestrogens also increase vascularity in the peri-urethral plexus which can be measured as vascular pulsations on urethral pressure profilometry [Robinson et al., 1996; Endo et al., 2000; Versi and Cardozo, 1986].

2. OESTROGENS FOR STRESS URINARY INCONTINENCE

The role of oestrogen in the treatment of stress urinary incontinence has been controversial despite a number of reported clinical trials [Hextall, 2000]. Some have given promising results but this may have been because they were small observational and not randomised, blinded or controlled. The situation is further complicated by the fact that a number of different types of oestrogen have been used with varying doses, routes of administration and duration of treatment.

Fantl et al.[1996] treated 83 hypo-oestrogenic women with urodynamic stress incontinence and/or detrusor overactivity with conjugated equine oestrogens 0.625 mg and medroxyprogesterone 10 mg cyclically for three months. Controls received placebo tablets. At the end of the study period the clinical and quality of life variables had not changed significantly in either group. Jackson et al. [1996] treated 57 post menopausal women with urodynamic stress or mixed incontinence with Oestradiol 2 mg or placebo daily for six months. There was no significant change in objective outcome measures although both the active and placebo groups reported subjective benefit.

Two meta analyses of early data have been performed. In the first, a report by the Hormones and Urogenital Therapy (HUT) committee the use of oestrogens to treat all causes of incontinence in post menopausal women was examined [Fantl et al., 1994]. Of 166 articles identified, which were published in English between 1969 and 1992, only six were controlled trials and 17 uncontrolled series. The results showed that there was a significant subjective improvement for all patients and those with urodynamic stress incontinence. However, assessment of the objective parameters revealed that there was no change in the volume of urine lost, Maximum urethral closure pressure increased significantly but this result was influenced by only one study showing a large effect.

In the second meta-analysis Sultana and Walters [1990] reviewed eight controlled and 14 uncontrolled prospective trials and included all types of oestrogen treatment. They also found that oestrogen therapy was not an efficacious treatment for stress urinary incontinence but may be useful for the often associated symptoms of urgency and frequency. Oestrogen when given alone therefore does not appear to be an effective treatment for stress urinary incontinence.

Several studies have shown that oestrogen may have a role in combination with other therapies e.g. α-adrenoceptor agonists. However, phenylpropa-

malamine (the most widely used α-adrenoceptor agonist in clinical practice) has now been restricted or banned by the US Food and Drug Administration (FDA).

In a randomised trial Ishiko et al. [2001] compared the effects of the combination of pelvic floor exercise and oestriol (1 mg per day) in 66 patients with post menopausal stress urinary incontinence. Efficacy was evaluated every three months based on stress scores obtained from a questionnaire. They found a significant decrease in stress score in mild and moderate stress incontinent patients in both groups three months after the start of therapy and concluded that combination therapy with oestriol plus pelvic floor exercise was effective and could be used as first line treatment for mild stress urinary incontinence. Unfortunately this has not been reproduced in other clinical trials.

Thus even prior to the more recently reported secondary analyses of the heart and oestrogens/progestogen replacement study (HERS) [Grady et al., 2001] and women's health initiative (WHI) [Hendrix et al., 2005] it was already recognised that oestrogen therapy had little effect in the management of urodynamic stress incontinence [Al-Badr et al., 2003; Robinson and Cardozo 2003].

3. OESTROGENS FOR URGENCY URINARY INCONTINENCE AND OVERACTIVE BLADDER SYMPTOMS

Oestrogen has been used to treat post menopausal urgency and urge incontinence for many years but there have been few controlled trials to confirm that it is of benefit [Hextall, 2000]. A double blind multi centre study of 64 post menopausal women with "urge syndrome" failed to show efficacy [Cardozo et al., 1993]. All women underwent pre-treatment urodynamic investigation to ensure that they had either sensory urgency or detrusor overactivity. They were randomised to treatment with oral oestriol 3 mg daily or placebo for three months. Compliance with therapy was confirmed by a significant improvement in the maturation index of vaginal epithelial cells in the active but not the placebo group. Oestriol produced subjective and objective improvements in urinary symptoms but was not significantly better than placebo.

Another randomised controlled trial from the same group using 25 mg oestradiol implants confirmed the previous findings [Rufford et al., 2003], and furthermore found a high complication rate in the oestradiol treated patients (vaginal bleeding).

Symptoms of an overactive bladder increase in prevalence with increasing age and lower urinary tract symptoms and recurrent urinary tract infections are commonly associated with urogenital atrophy. Whilst the evidence supporting the use of oestrogens in lower urinary tract dysfunction remains controversial there are considerable data to support their use in urogenital atrophy and the vaginal route of administration correlates with better symptom relief by improving vaginal dryness, pruritis and dyspareunia, greater improvement in cytological findings and higher serum oestradiol levels [Cardozo et al 1998]. Overall vaginal oestradiol has been found to be the most effective in reducing patient symptoms although conjugated oestrogens produced the most cytological change and the greatest increase in serum oestradiol and oestrone. The most recent meta anlysis of intravaginal oestrogen treatment in the management of urogenital atrophy was reported by the Cochrane group in 2003 [Suckling et al 2003]. Overall 16 trials including 2129 women were included and intravaginal oestrogen was found to be superior to placebo in terms of efficacy although there were no differences between types of formulation. 14 trials compared safety between the different vaginal preparations and found a higher risk of endometrial stimulation with conjugated equine oestrogens as compared to oestradiol.

Thus theoretically there could be a role for combination treatment with an anti muscarinic agent and vaginal oestrogen in post menopausal women. However, the two clinical trials which have been reported to date differ in their outcome. Tseng et al.[2009] showed superior efficacy in terms of symptom improvement for the overactive bladder when Tolterodine was used with vaginal oestrogen cream as opposed to Tolterodine alone. However, Serati et al. [2009] found no difference between Tolterodine with or without topical oestrogen in women with symptomatic detrusor overactivity.

4. EVIDENCE REGARDING OESTROGENS AND INCONTINENCE FROM LARGE CLINICAL TRIALS

The HERS study included 763 post menopausal women under the age of 80 years with coronary heart disease and intact uteri [Grady et al., 2001]. It was designed to evaluate the use of oestrogen in secondary prevention of cardiac events. In a secondary analysis 1525 participants who reported at least one episode of incontinence per week at baseline were included. Participants were randomly assigned to 0.625 mg of conjugated oestrogens plus 2.5 mg of medroxyprogesterone acetate in one tablet (N=768) or placebo (N=757) and were followed for a mean of 4.1 years. Severity of incontinence was classified as improved, unchanged or worsened. The results showed that incontinence improved in 26% of the women assigned to placebo compared to 21% assigned to hormones whilst 27% of the placebo group worsened compared with 39% of the hormone group (P=0.001). This difference was evident by four months of treatment, for both urgency and stress urinary incontinence. The number of incontinence episodes per week increased an

average of 0.7 in the hormone group and decreased by 0.1 in the placebo group ($p< 0.001$). The authors concluded that daily oral oestrogen plus progestogen therapy was associated with worsening urinary incontinence in older post menopausal women with weekly incontinence and did not recommend this therapy for treatment of incontinence. However, it is possible that the progestogen component may have had an influence on the results of this study.

The Women's Health Initiative (WHI) was a multi centre double blind placebo controlled randomised clinical trial of menopausal hormone therapy in 27347 postmenopausal women age 50-79 years enrolled between 1992 and 1998 for whom urinary incontinence symptoms were known in 23296 participants at baseline and one year [Hendrix et al., 2005]. The women were randomised based on hysterectomy status to active treatment or placebo. Those with a uterus were given 0.625 mg per day of conjugated equine oestrogen (CEE) plus 2.5 mg per day of medroxyprogesterone Acetate (CEE+MPA), whereas those who had undergone hysterectomy received oestrogen alone (CEE). At one year hormone therapy was shown to increase the incidence of all types of urinary incontinence among women who were continent at baseline. The risk was highest for stress urinary incontinence CEE+MPA: RR, 1.7 95% continence interval) CI (1.61-2.18); CEE alone RR 2.15 mg, 95% CI, 1.77-2.62, followed by mixed urinary incontinence CEE+MPA: RR 1.49 95% CI 1.10-2.01. On CEE alone RR was 1.79 95% CI, 1.26-2.53. The combination of CEE and MPA had no significant effect on developing urge urinary incontinence RR, 1.15; 95% CI, 0.99-1.34 but CEE alone increased the risk RR 1.32; 95% CI, 1.10-1.58. For those women experiencing urinary incontinence at baseline frequency worsened in both active groups CEE+MPA; RR, 1.38 95% CI 1.28-1.49; CEE alone: RR, 1.47 95% CI, 1.35-1.61. Quantity of urinary incontinence worsened at one year in both active groups, CEE+MPA: RR, 1.20 95% CI, 1.06-1.76; CEE alone: RR, 1.59 95% CI, 1.39-1.82. Those women receiving hormone therapy were more likely to report that urinary incontinence limited their daily activities CEE+MPA: RR 1.18 95% CI, 1.06-1.32. CEE alone: RR 1.29 95% CI, 1.15-1.45 at one year. Thus based on this secondary analysis of data from a huge study conjugated equine oestrogen alone or in combination with Medroxyprogesterone Acetate was shown to increase the risk of urinary incontinence amongst continent women and worsen urinary incontinence amongst asymptomatic women after one year of therapy.

The Nurses Health Study [Grodstein et al., 2004] was a biennial postal questionnaire starting in 1976. In 1996 39436 post menopausal women aged 50-75 years was reported no urinary leakage at the start of the study were followed up for four years to identify incident cases of urinary incontinence. 5060 cases of occasional and 2495 cases of frequent incontinence were identified. The risk of developing urinary incontinence was increased amongst post menopausal women taking hormones compared to women who had never taken hormones (oral oestrogen: RR1.54 95% CI 1.44, 1.65; transdermal oestrogen: RR1.68, 95% CI 1.41, 2.00; oral oestrogen with progestin: RR1.34, 95% CI 1.24, 1.44; transdermal oestrogen with progestin: RR1.46, 95% CI 1.16, 1.84). After cessation of hormone therapy there was a decreased risk of incontinence such that 10 years after stopping hormones the risk was identical in women who had and who never had taken hormone therapy.

The most recent meta analysis of the effect of oestrogen therapy on the lower urinary tract has been performed by the Cochrane Group [Cody et al., 2009] and is notable as the conclusions are starkly different from those drawn from the previous review [Moehrer et al., 2003]. Overall 33 trials were identified including 19313 incontinent women (1262 involved in trials of local administration) of which 9417 received oestrogen therapy.

Systemic administration (of unopposed oral oestrogens – synthetic and conjugated equine oestrogens) resulted in worse incontinence than placebo (RR1.32; 95% CI: 1.17-1.48). Although this is heavily influenced by the size of the WHI study [Hendrix et al 2005]. When considering combination therapy there was a similar worsening effect on incontinence when compared to placebo (RR1.11; 95% CO: 1.04-1.08). There was some evidence suggesting that the use of local oestrogen therapy may improve incontinence (RR0.74; 95% CI: 0.64-0.86) and overall there were 1-2 fewer voids in 24 hours and less frequency and urgency.

The authors conclude that local oestorgen therapy for incontinence may be beneficial although there was little evidence of long term effect. The evidence would suggest that systemic hormone replacement using conjugated equine oestrogens may make incontinence worse. In addition they report that there are too few data to comment reliably on the dose type of oestrogen and route of administration.

II. OTHER HORMONES

Progesterone and progestogens are thought to increase the risk of urinary incontinence. Lower urinary tract symptoms especially stress urinary incontinence have been reported to increase in the progestogenic phase of the menstrual cycle [Hextall et al., 2001]. In similar studies progesterone has been shown to increase beta adrenergic activity leading to a decrease in the urethral closure pressure in female dogs [Raz et al., 1973]. However, in the WHI there appeared to be no difference whether or not progestin was given in addition to oestrogen [Hendrix et al., 2005].

Selective oestrogen receptor modulators (SERMS) have been reported to have varying effects. Each of the SERMS has receptor ligand conformations that are unique and have both oestrogenic and anti oestrogenic effects. In the clinical trials of levormeloxifene there was a fourfold increase in the incidence of incontinence leading to cessation of the clinical trial [Hendrix et al., 2001]. However raloxifene has not been shown to have any effect at all on urinary incontinence [Waetjen et al., 2004].There are no reported clinical trials evaluating the effect of androgens, and in particular Testosterone, on urinary incontinence in women.

Assessments, hormone treatment

Oestrogen has an important physiological effect on the female lower urinary tract and its deficiency is an aetiological factor in the pathogenesis of a number of conditions. However the use of oestrogen either alone or in combination with progestogen has yielded poor results. The current level 1 evidence against the use of oestrogen for the treatment of urinary incontinence comes from studies powered to assess their benefit in the prevention of cardiovascular events and therefore the secondary analyses have only been based on self reported symptoms of urinary leakage without any objective data. Despite this all of these large randomised controlled trials show a worsening of pre-existing urinary incontinence both stress and urgency and an increased new incidence of urinary incontinence with both oestrogen and oestrogen plus progestogen. However, the majority of subjects in all of these studies were taking combined equine oestrogen and this may not be representative of all oestrogens taken by all routes of administration.

In a systematic review of the effects of oestrogens for symptoms suggestive of an overactive bladder the conclusion was that oestrogen therapy may be effective in alleviating OAB symptoms, and that local administration may be the most beneficial route of administration [Cardozo et al., 2004]. It is quite possible that the reason for this is that the symptoms of urinary urgency, frequency and urge incontinence may be a manifestation of urogenital atrophy in older post menopausal women rather than a direct effect on the lower urinary tract [Robinson and Cardozo, 2003]. Whilst there is good evidence that the symptoms and cytological changes of urogenital atrophy may be reversed by low dose (local) vaginal oestrogen therapy there is currently no evidence that oestrogens with or without progestogens should be used in the treatment of urinary incontinence.

III. DESMOPRESSIN

The endogenous hormone vasopressin (also known as anti-diuretic hormone) has two main functions: it causes contraction of vascular smooth muscle and stimulates water reabsorption in the renal medulla. These functions are mediated by two specific vasopressin receptors of which there are two major subtypes, namely the V1 and V2 receptors. The V2 subtype is particularly important for the anti-diuretic effects of vasopressin. A genetic or acquired defect in making and secreting vasopressin leads to central diabetes insipidus, and genetic defects in the gene encoding the V2 receptor can cause nephrogenic diabetes insipidus [Insel et al., 2007]. Accordingly, decreased vasopressin levels are believed to be important in the pathophysiology of polyuria, specifically nocturnal polyuria, which can lead to symptoms such as nocturia [Matthiesen et al., 1996; Weiss et al., 2011a]. Nocturia is currently defined by the International Continence Society (ICS) as the complaint that an individual has to wake at night one or more times to void. It is, however, “an underreported, understudied, and infrequently recognized problem in adults” [Weiss et al., 2011b]. Nocturia leads to decreased quality of life [Kupelian et al., 2011], and has been associated with both increased morbidity and mortality [Nakagawa et al., 2010; Kupelian et al., 2012]. While it remains largely unknown in which fraction of patients nocturia can indeed be explained by too little vasopressin, the presence of nocturnal polyuria in the absence of behavioural factors explaining it (such as excessive fluid intake) is usually considered as an indication that a (relative) lack of vasopressin may exist. While it remains largely unknown in what fraction of patients nocturia is explained by too little vasopressin, the presence of nocturnal polyuria in the absence of behavioral factors that can explain it (e.g. excessive fluid intake) is usually considered to indicate decreased vasopressin levels [Bosch and Weiss., 2011, Weiss et al., 2011b]. Based upon these considerations, vasopressin receptor agonists have been used to treat nocturia, both in children and in adults. Desmopressin is the most common vasopressin analogue used to treat nocturia. Desmopressin shows selectivity for anti-diuretic over vasopressor effects. It has a more powerful and longer-lasting antidiuretic action than vasopressin. It is available in formulations for oral, parenteral, and nasal administration. It has a fast onset of action, with urine production decreasing within 30 minutes of oral administration [Rittig et al., 1998]. Because of symptomatic hyponatremia with water intoxication which is the only serious adverse event reported in children, occurred after intranasal or intravenous administration of desmopressin [Thumfart et al. 2005; Robson et al. 2007; Van de Walle et al. 2010], the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) removed the indication for the treatment of primary nocturnal enuresis from all intranasal preparations of desmopressin. An oral lyophilisate (MELT) formulation requiring no concomitant fluid intake is currently available. In a recent open-label, randomized, cross-over study, desmopressin MELT was shown to have similar levels of efficacy and safety at lower doses than the tablet formulation of desmopressin in children]. A recent study confirmed the superior pharmacodynamic charac-

teristics of desmopressin MELT to desmopressin tablets [De Guchtenaere et al., 2011].

The use of desmopressin in children with nocturnal enuresis was comprehensively reviewed by the Cochrane Collaboration in 2002 [Glazener et al. 2002]. These authors evaluated 47 randomized controlled trials involving 3448 children, of whom 2210 received desmopressin. According to their analysis, desmopressin was effective relative to placebo in reducing bed-wetting (e.g. a dose of 20 µg resulted in a reduction of 1.34 wets/night (95% CI 1.11; 1.57), and children were more likely to become dry with desmopressin (98%) than with placebo (81%). However, there was no difference between desmopressin and placebo after discontinuation of treatment, indicating that desmopressin suppresses symptom enuresis but does not cure the underlying cause. Additionally, not all children responded sufficiently to desmopressin monotherapy. The combination of desmopressin and an enuresis alarm resulted in a greatly improved short-term success rate and decreased relapse rates [Alloussi et al. 2011]. The combination of desmopressin and antimuscarinics resulted in better short- and long-term success rates as well as a lower relapse rate than desmopressin alone [Austin et al., 2008; Alloussi et al., 2009). For non-responders to desmopressin, replacement of desmopressin with other medications such as tricyclic antidepressants or loop diuretics could be of benefit, whereas muscarinic receptor antagonists may be ineffective in such children (De Guchtenaere et al., 2007; Neveus and Tullus, 2008).

Other studies have explored a possible treatment role for desmopressin in the treatment of nocturia in adults. A search for these studies in Medline using the terms “desmopressin” and “nocturia” was performed and limited to clinical studies of de novo nocturia, i.e. those that excluded subjects in whom childhood enuresis persisted into adulthood. Several previous studies investigated the use of desmopressin for the treatment of nocturia in the context of multiple sclerosis [Eckford et al., 1994;1995]. One study with single dose administration reported a reduction in nocturnal polyuria, but by design did not assess nocturia [Eckford et al., 1995]. Three placebo-controlled double-blind studies with a small patient number (16-33 patients total per study) reported a significant reduction in nocturia [Hilton et al., 1983; Eckford et al., 1994; Valiquette et al., 1996]. Other controlled studies of similar size, most with a crossover design, used micturition frequency within the first 6 h after desmopressin administration rather than nocturia as their primary endpoint. These studies consistently reported that desmopressin treatment for up to 2 weeks was efficacious [Kinn and Larsson, 1990; Fredrikson, 1996; Hoverd and Fowler, 1998]. While desmopressin treatment was generally well tolerated, 4 of 17 patients in one study discontinued treatment due to asymptomatic or minimally symptomatic hyponatremia [Valiquette et al., 1996]. Accordingly, desmopressin is now registered for the treatment of nocturia in multiple sclerosis patients [Cvetkovic and Plosker, 2005]. In a small open-label study, desmopressin was also reported to reduce nocturnal polyuria in spinal cord injury patients [Zahariou, Karagiannis et al. 2007].

Further studies have explored the use of desmopressin in adults with nocturia in the apparent absence of neurological damage. The recruited patient populations were based upon different criteria, including having at least two nocturia episodes per night or having nocturnal polyuria. Earlier studies mostly used a desmopressin dose of 20 µg given either orally [Asplund et al., 1999] or intranasally [Hilton and Stanton, 1982; Cannon et al., 1999], and tended to be very small (≤25 patients). Later studies, as part of the NOCTUPUS program, were considerably larger, involving a total of 1003 screened patients, and higher oral doses (0.1-0.4 mg) were administered for a period of 3 weeks of double-blind treatment in adults [Mattiasson et al., 2002; Lose et al., 2004; van Kerrebroeck et al., 2007]. A total of 632 patients entered the dose-titration phase and 422 patients entering the double-blind phase of the three NOCTUPUS trials. To counter the argument that the study was performed in desmopressin responders after the dose titration phase, all patients in the NOCTUPUS trials were washed-out following the dose-titration phase and in order to be randomized, it was a requirement that the patients returned to baseline nocturnal diuresis before inclusion in the double-blind phase. The trials showed that oral desmopressin (0.1, 0.2 or 0.4 mg) is effective in both men and women aged ≥ 18 years with nocturia. The number of nocturnal voids decreased from 3 to 1.7 in the desmopressin group compared to 3.2 to 2.7 in the placebo group. In women, the number of nocturnal voids in the desmopressin group decreased from 2.92 to 1.61, whereas that in the placebo group decreased from 2.91 to 2.36. When clinical response was defined as ≥ 50% reduction in nocturnal voids from baseline, 34% of men experienced clinical response with desmopressin, compared with 3% of men who received placebo. In women, 46% of desmopressin-treated patients experienced a clinical response, compared with 7% of patients on placebo.

The efficacy of desmopressin for the treatment of nocturia was confirmed in a long-term (10-12 months) open-label study involving 249 patients, which was an extension of the randomized studies in known desmopressin responders. However, a rebound effect was seen when treatment was withdrawn, confirming the association between continued treatment and response (Lose et al. 2004). An open-label pilot study in a nursing home setting also reported that desmopressin had beneficial effects [Johnson et al. 2006].

Around 75% of community-dwelling men and women with nocturia (≥2 voids/night) have nocturnal

polyuria (NP) [Rembratt et al., 2003; Swithinbank et al. 2004]. The key urological factors most relevant to nocturia are NP and OAB in women [Irwin, Abrams et al., 2008], and NP and benign prostatic hyperplasia (BPH) in men. About 74% of women with OAB have nocturia and 62% of patients with OAB and nocturia have NP. Among men with nocturia, 83% have NP; 20% have NP alone, and 63% have NP in combination with another factor such as a small nocturnal bladder capacity or bladder outlet obstruction [Chang et al., 2006]. Therefore, desmopressin combination therapy with α1-AR antagonists and/or antimuscarinics should be considered for patients with treatment–resistant nocturia. Seventy-three percent of α1-AR antagonist-resistant BPH patients experienced a ≥50% reduction in nocturnal voids with oral desmopressin [Rembratt et al., 2003; Yoong et al., 2005]. A randomized, double-blind, placebo-controlled study evaluating the long-term (1, 3, 6, and 12 months) efficacy and safety of low dose (0.1 mg) oral desmopressin in elderly (≥ 65 years) patients reported that low dose oral desmopressin led to a significant reduction in the number of nocturnal voids and nocturnal urine volume in patients with BPH [Wang, Lin et al. 2011].

Because nocturia can be caused by different factors, several studies have investigated whether desmopressin may be beneficial in patients with other symptoms in addition to nocturia. In a small, non-randomized pilot study of men believed to have BPH, desmopressin was reported to improve not only nocturia, but also to reduce the overall international prostate symptom score (IPSS) [Chancellor et al., 1999]. An exploratory, placebo-controlled double-blind study in women with daytime urinary incontinence reported that intranasal administration of 40 μg desmopressin increased the number of leakage-free episodes 4 hours after drug administration (Robinson et al., 2004). One double-blind, placebo-controlled pilot study in patients with OAB treated with 0.2 mg oral desmopressin reported a reduction in voids along with an improvement in quality of life (QoL) [Hashim et al., 2009]. While these data indicate that desmopressin may be effective in treating voiding dysfunction not limited to nocturia, they are too sparse to allow treatment recommendations.

Desmopressin was well tolerated in all the studies and resulted in significant improvements compared to placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. There was also an improvement in QoL. However, one of the main clinically important side-effects of demopressin usage is hyponatremia. Hyponatremia can lead to a variety of adverse events ranging from mild headache, anorexia, nausea, and vomiting to loss of consciousness, seizures, and death. Hyponatremia usually occurs soon after treatment is initiated. The risk of hyponatremia appears to increase with age, cardiac disease, and increasing 24-hour urine volume [Rembratt et al. 2003]. Based on a meta-analysis, the incidence is around 7.6% [Weatherall; 2004]. Increased age and female gender are well-known risk factors for the development of desmopressin-induced hyponatremia. Bae et al. [2007] assessed the effects of long-term oral desmopressin on serum sodium and baseline antidiuretic hormone secretion in 15 elderly male patients with severe nocturia (greater than 3 voids nightly), who did not show hyponatremia within 7 days of administration of 0.2 mg desmopressin. Desmopressin (0.2 mg) was administered orally nightly for 1 year. Before and 1 month after the 1-year medication 24-hour circadian studies were performed to monitor changes in antidiuretic hormone. Every 3 months during the 1-year medication, serum changes and timed urine chemistry were monitored. The results showed that long-term desmopressin administration gradually decreased serum sodium and induced statistically, but not clinically significant, hyponatremia after 6 months of treatment Administration of desmopressin for 1 year did not affect baseline antidiuretic hormone secretion. The authors recommended that for long-term desmopressin administration serum sodium should be assessed regularly, at least every 6 months.

Little focus has been on exploring gender differences in the antidiuretic response to desmopressin. Juul et al. [2011] found an increasing incidence of hyponatremia with increasing dose, and at the highest dose level of 100 μg decreases in serum sodium were approximately twofold greater in women over 50 yr of age than in men. A new dose recommendation stratified by gender was suggested in the treatment of nocturia: for men, 50- to 100 μg melt was suggested to be an efficacious and safe dose, while for women a dose of 25 μg melt was recommended as efficacious with no observed incidences of hyponatremia. Initiation of desmopressin is currently not indicated for patients aged ≥65 years. The mechanisms behind desmopressin-induced hyponatraemia are well understood, and serum sodium monitoring at baseline and early during treatment of older patients for whom treatment with desmopressin is indicated can greatly reduce their risk of developing the condition. Other advice regarding treatment administration, such as restriction of evening fluid intake and adherence to recommended dosing, should be followed to minimize the risk of hyponatremia [Vande Walle et al., 2007].

Desmopressin is useful for patients with nocturia as well as for children with nocturnal enuresis. The drug has been proven to be well-tolerated and effective by several randomized, placebo-controlled trials and is recommended as a first-line treatment (either as monotherapy or in combination with other agents) for patients who have been appropriately evaluated and whose nocturia is related to NP, whether or not this is accompanied by BPH or OAB. For assessment, see **Table 2**.

G. Considerations in the Elderly

I. ANTIMUSCARINIC AGENTS

1. EFFICACY AND TOLERABILITY

The efficacy of antimuscarinic agents for treating symptoms of overactive bladder and urge urinary incontinence in older people is similar to that observed in younger and middle-aged adults. Age-related pooled results or sub-analyses from randomized controlled trials of tolterodine [Malone-Lee et al., 2001, Zinner et al., 2002], solifenacin (Wagg et al., 2006), darifenacin [Foote et al., 2007], fesoterodine [Kraus et al., 2010, Sand et al., 2012], and trospium chloride [Sand et al., 2011] indicate that reductions of 25-75% in urgency urinary incontinence episodes can be expected with use of these agents in older (65+) adults. Higher doses may be needed in those over age 75 [Kraus et al., 2010]. In a post-marketing surveillance study of darifenacin, Michel et al. [2010] found that increasing age was negatively associated with improvements in urgency episodes and incontinence, with a statistically significant, but non-clinically relevant effect (0.01 more urgency episodes per year of age). Older adults may derive greater benefit from use of a combined drug and behavioural therapy regime as compared to treatment with drug therapy alone [Burgio et al., 2000]. Dry mouth is the most frequently reported treatment-related adverse event, however overall tolerance has been reported as good to excellent with fewer treatment-motivated withdrawals in recent trials of older patients persisting on antimuscarinic therapy [Sand et al., 2012, Sand et al., 2011]. Constipation is also common and may be particularly bothersome for older adults already suffering from chronic bowel dismotility [Meek et al., 2011, Gallegos-Orozco et al., 2012].

However, the therapeutic effectiveness and tolerability of antimuscarinic agents in the elderly in the real world practice setting may differ from the results obtained in randomized controlled trials for several reasons. First, research trials generally exclude individuals with concomitant consumption of other antimuscarinic agents. In practice, older adults are a heterogeneous group, often consuming many medications that may augment, desensitize or alter the response to antimuscarinic therapy. As well, there is a higher prevalence of comorbidity among the elderly, which can further reduce treatment efficacy and heighten the potential for side effects to occur (see the Section on Incontinence in the Frail Elderly). Failure to acknowledge the multifactorial nature of urinary incontinence in the elderly often leads to suboptimal treatment. Urgency symptoms may be exacerbated by consumption of caffeinated beverages, pelvic floor muscle weakness, diuretics or other functional and systemic dysfunctions. Treatment should therefore address all possible etiologies, and not be limited to a solitary intervention.

2. COGNITIVE SAFETY

A growing body of literature has emerged to address the concern that antimuscarinic agents used to treat symptoms of overactive bladder may cross the blood-brain barrier and provoke subtle or not so subtle cognitive impairment [Callegari et al, 2011; Jakobsen SM et al., 2011; Wagg et al., 2010; Pagoria et al., 2011]. Large randomized controlled trials were not designed to adequately measure central nervous system adverse events [Paquette et al, 2011]. As a result, evidence on the relative risk of different antimuscarinic agents for crossing the blood brain barrier and inducing changes in cognitive comes primarily from in-vitro studies and experimental studies using detailed neuropsychological testing.

Early studies suggested that administration of antimuscarinic agents such as scopolamine could impair memory and attention in older adults, and possibly induce hallucinations and confusion [Flicker et al., 1992; Sperling et al., 2002]. Oxybutynin in particular, due to its small molecular size and increased propensity to cross the blood-brain barrier, has consistently shown potential to elicit cognitive impairment in new users after a single high dose of this agent or at steady state, and should be avoided in the elderly [Donellan et al., 1997; Katz et al., 1998; Kay et al., 2008, Wesnes et al., 2009]. Katz et al. [1998] used a double-blind, placebo-controlled cross-over design to test a convenience sample of 12 healthy continent older adults, and revealed cognitive decrements on seven of fifteen cognitive measures resulting from oxybutynin use. Impairments were observed in verbal learning, memory, reaction time, attention, concentration and psychomotor speed. In a sleep study, oxybutynin was found to significantly alter EEG patterns compared to placebo [Todorova et al., 2001]. Oxybutynin was compared to darifenacin and placebo in a 3-week randomized multicentre double-blind parallel-group study in 150 healthy volunteers aged 60-83 [Kay et al., 2006]. Darifenacin produced no impairments compared to placebo at 3-weeks, but oxybutynin caused significant memory deterioration in delayed recall compared to the other two groups. Darifenacin was associated with significantly slower reaction times than placebo in the Divided Attention Test, but not in other tests of information processing speed. Oxybutynin also reduced accuracy scores for immediate recall in one of three tests. Wesnes et al. [2009] showed in a single-dose crossover study with 12 healthy older volunteers that oxybutynin IR 10 mg induced significant deficits in attention and memory compared to placebo, whereas solifenacin 10 mg did not.

Studies with the antimuscarinic agents solifenacin, trospium chloride ER and darifenacin suggest that these agents confer significantly lower cognitive risk than oxybutynin. Administration of trospium chloride ER to 12 cognitively intact adults with overactive bladder aged 65-75 was found to have no effect on memory testing with the Hopkins Verbal Learning

Test on day 10 post-administration compared to baseline, and was also found to be undetectable in the cerebral spinal fluid of participants [Staskin et al., 2010]. In a study of darifenacin among 129 older adults aged 65-84, no significant effects on cognition were observed (memory scanning sensitivity, speed of reaction time, and word recognition) compared with placebo [Lipton et al., 2005]. No data on fesoterodine and memory were found.

New onset delirium also does not appear to be a significant concern in patients taking antimuscarinic agents. Although several published case reports have documented the acute onset of delirium following initiation of tolterodine, in incontinent adults with and without dementia [Womack and Heilman, 2003; Salvatore et al., 2007; Edwards et al., 2002; Williams et al., 2004; Tsao et al., 2003], these deficits resolved upon discontinuation or dose reduction of tolterodine. In a randomized controlled study of extended-release oxybutynin in nursing-home residents with mild to severe dementia, there was no incidence of delirium over the duration of the study [Lackner et al., 2008]. Furthermore, more recent evidence puts into question the traditionally held belief that new use of anticholinergic agents provokes incident delirium in hospitalized older patients [Campbell et al., 2011; Luukkanen et al., 2011].

Taken together, increasing evidence suggests that with the exception of oxybutynin, use of the other antimuscarinic agents poses little or no cognitive risk to otherwise healthy older adults with symptoms of overactive bladder. However, two caveats apply. First, the integrity of the blood brain barrier may be compromised in many older adults with cerebrovascular disease, diabetes, or certain forms of dementia, with the results of studies in healthy older adults not generalizable to frailer individuals [Kay et al., 2005]. Second, long-term use of antimuscarinic agents over months or years may yield more detrimental cognitive effects than single dose or short-term use. A number of large observational studies have linked chronic consumption of antimuscarinic drugs with an increased risk of cognitive impairment, although most studies simultaneously examined the cumulative effect of drugs with any antimuscarinic properties rather than each drug class alone. [Ancelin et al., 2006; Campbell et al., 2009; Fox et al., 2011]. The Eugenia study of aging randomly recruited 372 adults 60 years and older from Montpellier, France, and showed that antimuscarinic drug users displayed significantly poorer reaction time, attention, immediate and delayed visuospatial memory, narrative recall, and verbal fluency than did non drug users [Ancelin et al., 2006]. A 2-year longitudinal study of 13,000 participants enrolled in the Medical Research Council Cognitive Function and Ageing Study also showed that use of medication with antimuscarinic effects was associated with a 0.33-point greater decline in the Folstein Mini Mental Status Exam score (95% confidence interval (CI)=0.03-0.64, P=.03) than not taking antimuscarinics. Two-year mortality was also greater for those taking (OR=1.68; 95% CI=1.30-2.16; P<.001) anticholinergics. Many commonly prescribed medications in the elderly possess antimuscarinic properties [Chew et al., 2008], so the results may not be specific to bladder antimuscarinics. Other antimuscarinic medication include, among others, amytriptyline, clozapine, olanzepine, paroxetine, furosemide, hydrocodone, lansoprazole, levofloxacin, and metformin.

Clinicians who remain wary of prescribing antimuscarinic agents for frail older adults with symptoms of overactive bladder are suggested to proceed with caution in prescribing these medications and fully weigh the risk-benefit ratio in light of other therapeutic options that can be equally effective for urgency and mixed incontinence in the elderly. If antimuscarinics are to be prescribed, a short cognitive screen (such as the Montreal Cognitive Assessment http://www.mocatest.org) or even a full neuropsychological test battery for those patients who are concerned or at risk, before and after initiating therapy might reveal whether subtle impairments have been induced. This is especially pertinent because patients are often unaware of their memory deficits [Kay et al., 2006]. A proxy informant, such as the patient's spouse or a relative, may be able to provide more reliable information on possible cognitive changes resulting from the drugs.

A frequently asked clinical question is whether antimuscarinic agents used to treat incontinence should be contraindicated in patients with dementia already taking cholinesterase inhibitors, as the mechanisms of these two medications are diametrically opposed. A number of small studies have shown that cholinesterase inhibitors used to improve cognition in Alzheimer's disease precipitate urinary incontinence [Hashimoto et al., 2000]. A Japanese study followed 94 patients with mild to moderate dementia treated with donepezil [Hashimoto et al., 2000]. Seven patients developed urinary incontinence, although the event was transient in most patients. In Scotland, among 216 patients with Alzheimer's disease initiating treatment with a cholinesterase inhibitor, incontinence was precipitated in 6.6%, and those with existing incontinence worsened [Starr, 2007]. Epidemiologic studies also show associations between cholinesterase inhibitors and incontinence [Gill et al., 2005; Roe et al., 2002]. In a large population-based cohort study of 44,884 adults with dementia carried out in Canada, those who were dispensed cholinesterase inhibitors were more likely to subsequently receive an antimuscarinic drug for incontinence compared to those not receiving cholinesterase inhibitors (hazard ratio 1.55, 95% confidence interval 1.39-1.72) [Gill et al., 2005]. This finding was confirmed by a separate study in the U.S. documenting a two-fold risk of taking oxybutynin in dementia patients treated with donepezil compared to those not treated with donepezil [Roe et al., 2002]. A Japanese study examined

the addition of a 3-month trial of propiverine 20 mg/day to donepezil in twenty-six cognitively impaired older adults, and found improved dryness rates with no deleterious effect on cognition [Sakakibara et al., 2009]. A 6-month study also compared the effects of trospium, galantamine, or trospium plus galantamine in 178 older adults with urge incontinence (n=99), dementia (n=43) or dementia and incontinence (n=36) respectively [Isik et al., 2009]. Treatment with 45-60 mg/day of trospium chloride and combined use of trospium with galantamine 24 mg/day was found to have no adverse effect on cognitive or physical function scores in this group of patients. A larger observational study of 3,563 long-term care residents with dementia also failed to document an increased rate of cognitive decline with combined use of a cholinesterase inhibitor and antimuscarinic therapy (oxybutynin or tolterodine) compared to cholinesterase therapy alone [Sink et al., 2008]. However, a 50% faster rate of physical function decline was observed in higher-functioning participants on dual therapy compared to cholinesterase inhibitor therapy alone. This evidence suggests the competing mechanisms of the antimuscarinics and cholinesterase inhibitors may indeed have clinical consequences in some, but not all patients.

3. Cardiac safety. Another serious side effect of antimuscarinic drugs in the elderly is the risk of cardiac adverse effects and increased mortality, particularly due to increases in heart rate, prolongation of the QT interval, and induction of polymorphic ventricular tachycardia. These have been previously discussed, and it has been noted that studies specific to the elderly are lacking [Andersson et al., 2011]. Only one study prospectively examined the effect of anticholinergic drug use in 400 community-dwelling older people (aged 75-90 years) with stable cardiovascular disease in Helsinki, Finland [Uusvaara et al., 2011]. Bladder antimuscarinic agents were not examined individually, but were considered in a cumulative assessment of all drugs with antimuscarinic properties being taken by the same individual. The unadjusted follow-up mortality was 20.7% and 9.5% among users and non-users of antimuscarinic drugs, respectively ($p = 0.010$). However, the use of drugs with antimuscarinic properties was not a significant predictor of mortality in multivariate analysis after adjustment for age, sex and other comorbidites (hazard ratio 1.57; 95% CI 0.78, 3.15).

4.Drug/drug interactions in the elderly. Rates of polypharmacy (> 5 drugs per patient) are high in the geriatric population, and cause potential for drug-drug interactions that increase toxicity or reduce the efficacy of antimuscarinic agents [Chancellor and Miguel, 2007]. The relationship between the number of drugs and potential drug-drug interactions in the elderly is alarming. Consumption of 5 to 7 and 8 to 10 drugs places older adults at a 4-fold and 8-fold increased risk of potentially serious drug-drug interactions respectively, compared with consumption of 2 to 4 drugs [Johnell & Klarin, 2007]. Drug drug interactions frequently involve isoenzymes of the hepatic cytochrome CYP450 system [Zakrzewski-Jakubiak et al., 2011]. Of the antimuscarinic drugs, tolterodine, darifenacin, solifenacin, and oxybutynin are extensively metabolized by CYP450 and are at greater risk of having altered drug metabolism due to hepatic-based drug-drug interactions. Trospium is eliminated renally as unchanged drug, suggesting that it has lower potential for CYP450 drug-drug interactions [Sand et al., 2011]. Trospium may therefore represent a safer treatment option in the context of polypharmacy in the elderly.

II. DESMOPRESSIN – EFFICACY AND SAFETY IN THE ELDERLY

Desmopressin (DDAVP) (0.1–0.2 mg) reduces nocturia in older persons [Rezakhaniha et al., 2011;Fu et al., 2011; Johnson et al., 2006], but has been associated with significant dose-related hyponatremia in 2-20% of older patients [Fu et al., 2011;Johnson et al., 2006; Weatherall 2004]. Both female sex and increasing age are risk factors for the development of hyponatremia [Callreus et al., 2005; Rembratt et al., 2006; Juul et al., 2010]. A lower starting dose (0.025 mg) for the melt form has been suggested for older women [Juul et al., 2010] but requires further study. Caution is recommended for the initiation of desmopressin in adults aged 65 years and older at the current time.

III. BOTULINUM TOXIN A IN OLDER ADULTS

To date no studies have stratified the results of trials using BoNTA for the treatment of urinary incontinence in patients with neurogenic bladder according to age. The risk of catheterization due to high post-void residual urine volumes following treatment with botulinum toxin may be higher in older adults, as they are at higher risk of elevated residuals, but this requires systematic investigation.

IV. OTHER

None of the other drug classes have undergone rigorous evaluation in the elderly, however a number of general guidelines apply. Use of α1-AR agonists and tricyclic antidepressants are discouraged in the elderly due to blood pressure considerations. Uncontrolled systolic hypertension could occur with the former agents and orthostatic hypotension leading to falls with the latter. There is no evidence that hormonal agents are of benefit for urgency or stress incontinence in older women, although local estrogens may be indicated to treat symptomatic vaginal atrophy. Finally, removal of any offending agents that could be contributing to incontinence should be considered.

REFERENCES

Abrams P, Amarenco G, Bakke A et al. Tamsulosin: efficacy and safety in patients with neurogenic lower urinary tract dysfunction due to suprasacral spinal cord injury. J Urol, 2003;170(4 Pt 1):1242

Abrams P, Andersson KE. Muscarinic receptor antagonists for overactive bladder. BJU Int. 2007 Nov;100(5):987

Abrams P, Andersson K-E, Buccafusco JJ, et al. Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. Br J Pharmacol 2006;148:565

Abrams P, Cardozo L, Chapple C et al. Comparison of the efficacy, safety, and tolerability of propiverine and oxybutynin for the treatment of overactive bladder syndrome. Int J Urol. 2006 Jun;13(6):692

Abrams P, Cardozo L, Fall M. et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn, 2002;21(2):167

Abrams P, Kaplan S, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. J Urol. 2006 Mar;175(3 Pt 1):999-1004;

Abrams P, Kelleher C, Huels J et al. Clinical relevance of health-related quality of life outcomes with darifenacin. BJU Int. 2008 Jul;102(2):208

Abrams P, Swift S. Solifenacin is effective for the treatment of OAB dry patients: a pooled analysis. Eur Urol. 2005 Sep;48(3):483

Agency for Healthcare Policy and Research. Urinary Incontinence Guideline Panel. Urinary Incontinence in Adults: Clinical Practice Guideline (AHCPR publication #92-0038). Rockville, MD, US Dept. of Health and Human Services, 1992.

Ahmad I, Krishna NS, Small DR, et al. Aetiology and management of acute female urinary retention Br J Med Surg Urol 2009;2:27-33

Akbar M, Abel R, Seyler TM et al. Repeated botulinum-A toxin injections in the treatment of myelodysplastic children and patients with spinal cord injuries with neurogenic bladder dysfunction. BJU Int. 2007 Sep;100(3):639

Al-Badr A, Ross S, Soroka D et al. What is the available evidence for hormone replacement therapy in women with stress urinary incontinence? J Obstet Gynecol Can, 2003;25(7):567

Alhasso A, Glazener CMA, Pickard R et al. Adrenergic drugs for urinary incontinence in adults. Cochrane Database Syst Rev. 2003:(2):CD001842

Alhasso A, Glazener CMA, Pickard R, N'Dow J: Adrenergic drugs for urinary incontinence in adults (Review). Cochrane Database for Systematic Reviews 2005, Issue 3, Art. No. CD001842. DOI: 10.1022/14651858. CD001842, pub 2. Reprinted in The Cochrane Library 2008, Issue 2.

Allousi S, Laval K-U, Eckert R. Trospium chloride (Spasmolyt) in patients with motor urge syndrome (detrusor instability): a double-blind, randomised, nulticentre, placebo-controlled study. J Clin Res 1998;1:439

Alloussi SH, Mürtz G, Lang C, et al. Desmopressin treatment regimens in monosymptomatic and nonmonosymptomatic enuresis: A review from a clinical perspective. J Pediatr Urol. 2011 Feb;7(1):10-20.

Alloussi SH, Mürtz G, Gitzhofer S, et al. Failure of monotherapy in primary monosymptomatic enuresis: a combined desmopressin and propiverine treatment regimen improves efficacy outcomes. BJU Int. 2009 Jun;103(12):1706-12.

Altaweel W, Jednack R, Bilodeau C et al. Repeated intradetrusor botulinum toxin type A in children with neurogenic bladder due to myelomeningocele. J Urol. 2006 Mar;175(3 Pt 1):1102

Altaweel W, Mokhtar A, Rabah DM. Prospective randomized trial of 100u vs 200u botox in the treatment of idiopathic overactive bladder. Urol Ann. 2011 May;3(2):66-70.

Amarenco G, Marquis P, McCarthy C et al. Qualité de vie des femmes souffrant d´mpériosité mictionelle avec ou sans fuites: étude prospective aprés traitement par oxybutinine (1701 cas). Presse Medicale, 1998;27:5

Amend B, Hennenlotter J, Schäfer T, et al. Effective treatment of neurogenic detrusor dysfunction by combined high-dosed antimuscarinics without increased side-effects. Eur Urol. 2008 May;53(5):1021-8.

Ancelin ML, Artero S, Portet F et al. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ 2006;332:455

Anders RJ, Wang E, Radhakrishnan J et al. Overflow urinary incontinence due to carbamazepine. J Urol 1985; 134: 758

Anderson RU, Mobley D, Blank B. et al. Once-daily controlled versus immediate-release oxybutynin chloride for urge urinary incontinence. OROS Oxybutynin Study Group. J Urol 1999;161:1809

Andersson K-E: Current concepts in the treatment of disorders of micturition. Drugs 1988;35:477

Andersson, K.-E. Pharmacology of lower urinary tract smooth muscles and penile erectile tissues. Pharmacol Rev, 45:253, 1993.

Andersson K-E. Pathways for relaxation of detrusor smooth muscle. In: Advances in Bladder Research, ed by Baskin LS and Hayward SW, Kluwer Academic/Plenum Publishers, New York 1999, p 241

Andersson KE. Bladder activation: afferent mechanisms. Urology. 2002 May;59(5 Suppl 1):43

Andersson K-E. Potential benefits of muscarinic M3 receptor selectivity. Eur Urol Suppl, 2002;1(4):23

Andersson K-E. Alpha-adrenoceptors and benign prostatic hyperplasia: basic principles for treatment with alpha-adrenoceptor antagonists. World J Urol 2002;19(6):390

Andersson KE. Antimuscarinics for treatment of overactive bladder. Lancet Neurol. 2004 Jan;3(1):46 .

Andersson KE. Treatment-resistant detrusor overactivity--underlying pharmacology and potential mechanisms. Int J Clin Pract Suppl. 2006 Dec;(151):8-16.

Andersson KE. LUTS treatment: future treatment options. Neurourol Urodyn. 2007 Oct;26(6 Suppl):934-47.

Andersson KE. Muscarinic acetylcholine receptors in the urinary tract. Handb Exp Pharmacol. 2011a;(202):319-44.

Andersson KE. Antimuscarinic mechanisms and the overactive detrusor: an update. Eur Urol. 2011b Mar;59(3):377-86

Andersson KE. Drugs and future candidates. Can Urol Assoc J. 2011c Oct;5(5 Suppl 2):S131-3.

Andersson KE, Appell R, Cardozo LD et al. The pharmacological treatment of urinary incontinence. BJU Int 1999 Dec;84(9):923

Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiol Rev. 2004 Jul;84(3):935-86.

Andersson K-E, Chapple CR, Cardozo L et al. Pharmacological treatment of urinary incontinence, in Abrams P, Khoury S, Wein A (Eds), Incontinence, 4rd International Consultation on Incontinence. Plymouth, Plymbridge Distributors Ltd, UK, Plymouth, p 633, 2009

Andersson KE, Campeau L, Olshansky B. Cardiac effects of muscarinic receptor antagonists used for voiding dysfunction. Br J Clin Pharm 2011;72:186-196.

Andersson K-E, Chapple CR. Oxybutynin and the overactive bladder. World J Urol 2001;19(5):319

Andersson KE, de Groat WC, McVary KT, et al. Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism(s) of action. Neurourol Urodyn. 2011 Mar;30(3):292-301

Andersson K-E, Fullhase C, Soler R. Urothelial effects of oral antimuscarinic agents. Current Urology Reports 2008b Nov;9(6):459

Andersson KE, Gratzke C. Pharmacology of alpha1-adrenoceptor antagonists in the lower urinary tract and central nervous system. Nat Clin Pract Urol. 2007 Jul;4(7):368-78.

Andersson KE, Gratzke C, Hedlund P. The role of the transient receptor potential (TRP) superfamily of cation-selective channels in the management of the overactive bladder. BJU Int. 2010 Oct;106(8):1114-27.

Andersson K-E, Michel MC. Urinary Tract. Handbook of Experimental Pharmacology. Springer-Verlag. Berlin Heidelberg 2011

Andersson KE, Pehrson R. CNS involvement in overactive bladder: pathophysiology and opportunities for pharmacological intervention. Drugs. 2003;63(23):2595

Andersson KE, Olshansky B. Treating patients with overactive bladder syndrome with antimuscarinics: heart rate considerations. BJU International 2007;100:1007

Andersson K-E, Persson K. The L-arginine/nitric oxide pathway and non-adrenergic, non-cholinergic relaxation of the lower urinary tract. 1993;Gen Pharmacol 24:833

Andersson K-E, Uckert S, Stief C et al. Phosphodiesterases (PDEs) and PDE inhibitors for treatment of LUTS. Neurourol Urodyn 1997 Oct;26(6Suppl):928

Andersson K-E, Wein AJ. Pharmacology of the lower urinary tract - basis for current and future treatments of urinary incontinence. Pharmacol Rev 2004 Dec; 56(4):581

Andersson KE, Sarawate C, Kahler KH, et al. Cardiovascular morbidity, heart rates and use of antimuscarinics in patients with overactive bladder. BJU Int. 2010 Jul;106(2):268-74.

Andersson K, Wein A. Pharmacologic management of lower urinary tract storage and emptying failure. In Campbell-Walsh Urology (Wein A, Kavoussi L, Novick A, Partin A, Peters C, eds), Elsevier Saunders, Philadelphia, 2012, pp1967-2002

Andersson MC, Tobin G, Giglio D. Cholinergic nitric oxide release from the urinary bladder mucosa in cyclophosphamide-induced cystitis of the anaesthetized rat. Br J Pharmacol 2008a;153:1438.

Andrews MD, Fish P v, Blagg J, et al. Pyrimido [4,5-d] azepines as potent and selective 5-HT2$_c$ receptor agonists:design, synthesis and evaluation of PF-3246799 as a treatment for urinary incontinence. Bioorg Med Chem Lett 2011;21(9):2715-2720

Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology. 2005 Oct;26(5):785

Aoki K, Hirayama A, Tanaka N, et al. A higher level of prostaglandin E2 in the urinary bladder in young boys and boys with lower urinary tract obstruction. Biomed Res. 2009 Dec;30(6):343-7.

Apostolidis A, Brady CM, Yiangou Y, et al. Capsaicin receptor TRPV1 in urothelium of neurogenic human bladders and effect of intravesical resiniferatoxin. Urology. 2005 Feb;65(2):400-5.

Apostolidis A, Gonzales GE, Fowler CJ, Effect of intravesical Resiniferatoxin (RTX) on lower urinary tract symptoms, urodynamic parameters, and quality of life of patients with urodynamic increased bladder sensation. Eur Urol. 2006 Dec;50(6):1299

Apostolidis A, Jacques TS, Freeman A, et al. Histological changes in the urothelium and suburothelium of human overactive bladder following intradetrusor injections of botulinum neurotoxin type A for the treatment of neurogenic or idiopathic detrusor overactivity. Eur Urol. 2008 Jun;53(6):1245-53

Apostolidis A, Kirana PS, Chiu G, et al. Gender and age differences in the perception of bother and health care seeking for lower urinary tract symptoms: results from the hospitalised and outpatients' profile and expectations study. Eur Urol. 2009 Dec;56(6):937-47.

Apostolidis A, Popat R, Yiangou Y et al. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol. 2005 Sep;174(3):977

Appell RA, Chancellor MB, Zobrist RH et al. Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral oxybutynin administration in healthy subjects. Mayo Clin Proc, 2003;78(6):696, 2003.

Appell RA, Sand P, Dmochowski R et al. Overactive bladder: judging effective control and treatment study group. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. Mayo Clin Proc, 2001;76(4):358

Araki I. TRP channels in urinary bladder mechanosensation. Adv Exp Med Biol. 2011;704:861-79.

Araki I, Du S, Kobayashi H, et al. Roles of mechanosensitive ion channels in bladder sensory transduction and overactive bladder. Int J Urol. 2008 Aug;15(8):681-7.

Arisco AM, Brantly EK, Kraus SR. Oxybutynin extended release for the management of overactive bladder: a clinical review. Drug Des Devel Ther. 2009 Sep 21;3:151-61.

Aschkenazi S, Botros S, Miller J et al. Overactive bladder symptoms are not related to detrusor overactivity. Neurourol Urodyn, 2007;26(5), abstract 35

Asplund R, Sundberg B, Bengtsson P. Oral desmopressin for nocturnal polyuria in elderly subjects: a double-blind, placebo-controlled randomized exploratory study. BJU Int 1999;83:591

Athanasopoulos A, Cruz F. The medical treatment of overactive bladder, including current and future treatments. Expert Opin Pharmacother. 2011 May;12(7):1041-55

Athanasopoulos A, Gyftopoulos K, Giannitsas K et al. G. Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. J Urol 2003; 169:2253

Athwal BS, Berkley KJ, Hussain I. et al. Brain responses to changes in bladder volume and urge to void in healthy men. Brain, 2001;124(Pt 2):369

Austin PF, Ferguson G, Yan Y, et al. Combination therapy with desmopressin and an anticholinergic medication for nonresponders to desmopressin for monosymptomatic nocturnal enuresis: a randomized, double-blind, placebo-controlled trial. Pediatrics. 2008 Nov;122(5):1027-32.

AvelinoA., Charrua A, Frias B, Cruz CD, Boudes M, de Ridder D., Cruz F. TRP channels in bladder function. 2012. Acta Physiol Scand (in press)

Avelino A, Cruz F. TRPV1 (vanilloid receptor) in the urinary tract: expression, function and clinical applications. Naunyn Schmiedebergs Arch Pharmacol. 2006 Jul;373(4):287-99.

Badawi JK, Seja T, Uecelehan H et al. Relaxation of human detrusor muscle by selective beta-2 and beta-3 agonists and endogenous catecholamines. Urology. 2007 Apr;69(4):785

Bae JH, Oh MM, Shim KS et al. The effects of long-term administration of oral desmopressin on the baseline secretion of antidiuretic hormone and serum sodium concentration for the treatment of nocturia: a circadian study. J. Urol 2007;178(1):200

Baigrie RJ, Kelleher JP, Fawcett DP et al. Oxybutynin: is it safe? Br J Urol, 1988;62:319 Jonville AP, Dutertre JP, Autret E et al. Effets indésirables du chlorure d´oxybutynine (Ditropan®). Therapie 1992;47:389

Baldessarini KJ. Drugs in the treatment of psychiatric disorders. In: Gilman et al. (Eds.) The pharmacological basis of therapeutics, 7th ed., McMillan Publishing Co., p387, 1985

Baldo A, Berger TH, Kofler M et al.: The influence of intrathecal baclofen on detrusor function. A urodynamic study. NeuroUrol Urodyn, 2000, 19, 444 (abstract 53).

Banakhar MA, Al-Shaiji TF, Hassouna MM. Pathophysiology of overactive bladder. Int Urogynecol J. 2012 Feb 7. [Epub ahead of print]

Barendrecht MM, Oelke M, Laguna MP et al. Is the use of parasympathomimetics for treating an underactive urinary bladder evidence-based? BJU Int 2007;99:749

Basra RK , Wagg A , Chapple C et al . A review of adherence to drug therapy inpatients with overactive bladder . BJU Int 2008 ; 102 : 774 – 9

Bayliss M, Wu C, Newgreen D et al. A quantitative study of atropine-resistant contractile responses in human detrusor smooth muscle, from stable, unstable and obstructed bladders. J Urol 1999;162:1833

Bechara A, Romano S, Casabe A et al. Comparative efficacy assessment of tamsulosin vs. tamsulosin plus tadalafil in the treatment of LUTS/BPH. Pilot study. J Sex Med 2008;5:2170-2178.

Beckel JM, Holstege G. Neuroanatomy of the lower urinary tract. Handb Exp Pharmacol. 2011;(202):99-116.

Beckmann-Knopp S, Rietbrock S, Weyhenmeyer R et al. Inhibitory effects of trospium chloride on cytochrome P450 enzymes in human liver microsomes. Pharmacol Toxicol, 1999;(6):299

Beermann B, Hellstrom K, Rosen A. On the metabolism of propantheline in man. Clin Pharmacol Ther, 1972; 13(2):212

Behr-Roussel D, Oger S, Caisey S, et al. Vardenafil decreases bladder afferent nerve activity in unanesthetized, decerebrate, spinal cord-injured rats. Eur Urol 2010;59: 272-279.

Bent A, Gousse A, Hendrix S. Duloxetine compared with placebo for the treatment of women with urinary incontinence. Neurourol Urodyn 2008;27(3):212-221

Bent S, Tiedt TN, Odden MC, et al. The relative safety of ephedra compared with other herbal products. Ann Intern Med. 2003;138(6):468

Berridge MJ. Smooth muscle cell calcium activation mechanisms. J Physiol. 2008 Nov 1;586(Pt 21):5047-61

Bharucha AE, Seide B, Guan Z et al. Effect of tolterodine on gastrointestinal transit and bowel habits in healthy subjects. Neurogastroenterol Motil. 2008 Jun;20(6):643

Biers SM, Reynard JM, Brading AF. The effects of a new selective beta3-adrenoceptor agonist (GW427353) on spontaneous activity and detrusor relaxation in human bladder. BJU Int. 2006 Dec;98(6):1310

Bigger JT, Giardina EG, Perel JM et al. Cardiac antiarrhythmic effect of imipramine hydrochloride. N Engl J Med 1977;296:206

Birder LA, de Groat WC. Mechanisms of disease: involvement of the urothelium in bladder dysfunction. Nat Clin Pract Urol. 2007 Jan;4(1):46-54.

Birder LA, Kanai AJ, de Groat WC, et al. Vanilloid receptor expression suggests a sensory role for urinary bladder epithelial cells. Proc Natl Acad Sci U S A. 2001 Nov 6;98(23):13396-401.

Birder LA, Nakamura Y, Kiss S, et al. Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci. 2002 Sep;5(9):856-60.

Blaivas JG, Labib KB, Michalik J et al. Cystometric response to propantheline in detrusor hyperreflexia: therapeutic implications. J Urol, 1980;124:259

Blok BF, Sturms LM, Holstege G. Brain activation during micturition in women. Brain, 1998;121 (Pt 11):2033

Blue DR, Daniels DV, Gever JR et al. Pharmacological characteristics of Ro 115-1240, a selective? 1A-1L- adrenoceptor partial agonist: a potential therapy for stress urinary incontinence. BJU Int 2004;93(1):162

Blyweert W, Van Der Aa F, De Ridder D. Cannabinoid therapy in detrusor overactivity: local versus systemic effect in a spinalised rat model. Neurourol Urodyn 2003;22:379–80.

Bödeker RH, Madersbacher H, Neumeister C, Zellner M. Dose escalation improves therapeutic outcome: post hoc analysis of data from a 12-week, multicentre, double-blind, parallel-group trial of trospium chloride in patients with urinary urge incontinence. BMC Urol. 2010 Sep 14;10:15.

Bolduc S, Moore K, Nadeau G, et al. Prospective open label study of solifenacin for overactive bladder in children. J Urol. 2010 Oct;184(4 Suppl):1668-73.

Bosch RJLH, Griffiths DJ, Blom JHM et al. Treatment of benign prostatic hyperplasia by androgen deprivation: effects on prostate size and urodynamic parameters. J Urol 1989;141:68

Bosch JL Weiss JP. The Prevalence and Causes of Nocturia. J Urol 2010;184(2): 440-446.

Boy S, Seif C, Braun PM et al. Retrospective Analysis of treatment outcomes and medical care of patients with neurogenic detrusor overactivity (NDO) receiving BOTOX therapy. European Urology Supplements, 2008;7 (3):212

Brady CM, Apostolidis AN, Harper M et al. Parallel changes in bladder suburothelial vanilloid receptor TRPV1 and pan-neuronal marker PGP9.5 immunoreactivity in patients with neurogenic detrusor overactivity after intravesical resiniferatoxin treatment. BJU Int. 2004 Apr;93(6):770

Brady CM, DasGupta R, Dalton C, et al. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Mult Scler 2004;10:425–33.

Braverman AS, Doumanian LR, Ruggieri MR, Sr. M2 and M3 muscarinic receptor activation of urinary bladder contractile signal transduction. II. Denervated rat bladder. J Pharmacol Exp Ther 2006;316:875

Braverman AS, Karlovsky M, Pontari MA et al. Aging and hypertrophy change the muscarinic receptor subtype mediating bladder contraction from M3 towards M2. J Urol 2002;167 Suppl.: Abstract #170.

Braverman AS, Kohn IJ, Luthin GR et al. Prejunctional M1 facilitatory and M2 inhibitory muscarinic receptors mediate rat bladder contractility. Am J Physiol 1998;274: R517

Braverman AS, Luthin GR, Ruggieri MR. M2 muscarinic receptor contributes to contraction of the denervated rat urinary bladder. Am J Physiol 1998;275:R1654

Braverman AS, Ruggieri MR, Sr. Hypertrophy changes the muscarinic receptor subtype mediating bladder contraction from M3 toward M2. Am J Physiol 2003;285:R701

Brennan PE, Whitlock GA, Ho DK, et al. Discovery of a novel azepine series of potent and selective 5-HT2_c agonists as potential treatments for urinary incontinence. Bioorg Med Chem Lett 2009;19:4999-5003

Bridgewater M, Brading AF. Evidence for a non-nitrergic inhibitory innervation in the pig urethra. Neurourol Urodyn 1993;12:357

Briggs KS, Castleden CM, Asher MJ. The effect of flavoxate on uninhibited detrusor contractions and urinary incontinence in the elderly. J Urol 1980;123:665

Brubaker L, FitzGerald MP. Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Jul;18(7):737

Brubaker L, Richter HE, Visco A et al. Pelvic Floor Disorders Network, Refractory idiopathic urge urinary incontinence and botulinum A injection. J Urol. 2008 Jul;180(1):217

Brynne N, Dalen P, Alvan G et al. Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine. Clin Pharmacol Ther 1998;63:529

Brynne N, Stahl MMS, Hallén B et al. J. Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. Int J Clin Pharmacol Ther 1997;35:287

Bschleipfer T, Schukowski K, Weidner W, et al. Expression and distribution of cholinergic receptors in the human urothelium. Life Sci 2007;80:2303

Buckley BS, Lapitan MC. Drugs for treatment of urinary retention after surgery in adults. Cochrane Database Syst Rev. 2010 Oct 6;(10):CD008023.

Bump RC, Voss S, Beardsworth A et al. Long-term efficacy of duloxetine in women with stress urinary incontinence. Br J Urol Int 2008;102:214

Burgio KL, Locher JL, Goode PS. Combined behavioral and drug therapy for urge incontinence in older women. J Am Geriatr Soc. 2000;48:370-4.

Bushman W, Steers WD, Meythaler JM, Voiding dysfunction in patients with spastic paraplegia: urodynamic evaluation and response to continuous intrathecal baclofen. Neurourol Urodyn. 1993;12(2):163

Caine M, Gin S, Pietra C et al. Antispasmodic effects of flavoxate, MFCA, and REC 15/2053 on smooth muscle of human prostate and urinary bladder. Urology 1991;37(4):390

Callegari E, Malhotra B, Bungay PJ, et al. A comprehensive nonclinical evaluation of the CNS penetration potential of antimuscarinic agents for the treatment of overactive bladder. Br J Clin Pharmacol 2011;72:235-46.

Callreus T, Ekman E, Andersen M. Hyponatremia in elderly patients treated with desmopressin for nocturia: a review of a case series. Eur. J. Clin. Pharmacol 2005;61(4):281

Cameron AP, Clemens JQ, Latini JM, McGuire EJ., Combination drug therapy improves compliance of the neurogenic bladder. J Urol. 2009 Sep;182(3):1062-7

Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. Clin Interv Aging. 2009;4:225-33.

Campbell N, Perkins A, Hui S, et al. Association between prescribing of anticholinergic medications and incident delirium: a cohort study. J Am Geriatr Soc. 2011;59 Suppl 2:S277-81.

Cannon A, Carter PG, McConnell AA et al. Desmopressin in the treatment of nocturnal polyuria in the male. BJU Int 1999; 84:20

Cao DS, Yu SQ, Premkumar LS. Modulation of transient receptor potential Vanilloid 4-mediated membrane currents and synaptic transmission by protein kinase C. Mol Pain. 2009 Feb 10;5:5.

Capo' JP, Lucente V, Forero-Schwanhaeuser S, He W. Efficacy and tolerability of solifenacin in patients aged ≥ 65 years with overactive bladder: post-hoc analysis of 2 open-label studies. Postgrad Med. 2011 Jan;123(1):94-104.

Carbone A, Palleschi G, Conte A et al. Gabapentin treatment of neurogenic overactive bladder. Clin Neuropharmacol. 2006 Jul-Aug;29(4):206

Cardozo LD, Bachmann G, McClish D, et al. Meta-analysis of oestrogen therapy in the management of urogenital atrophy in postmenopausal women: Second report of the Hormones and Urogenital Therapy Committee. Obstet Gynaecol 1998: 92: 722-727

Cardozo L, Castro-Diaz D, Gittelman M et al. Reductions in overactive bladder-related incontinence from pooled analysis of phase III trials evaluating treatment with solifenacin. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Sep;17(5):512

Cardozo L, Chapple CR, Toozs-Hobson P et al. Efficacy of trospium chloride in patients with detrusor instability: a placebo-controlled, randomized, double-blind, multicentre clinical trial. BJU Int 2000;85(6):659

Cardozo L, Dixon A. Increased warning time with darifenacin: a new concept in the management of urinary urgency. J Urol. 2005 Apr;173(4):1214

Cardozo L, Drutz HP, Baygari SK, et al. Pharmacological treatment of women awaiting surgery for stress urinary incontinence. Obstet Gynecol 2004;104(3):511-519

Cardozo L, Lisec M, Millard R et al. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. J Urol. 2004 Nov;172(5 Pt 1):1919

Cardozo L, Lose G, McClish D et al. A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder. Acta Obstetr Gynaecol Scand 2004;83:892

Cardozo L, Rekers H, Tapp A et al. Oestriol in the treatment of postmenopausal urgency: a multicentre study. Maturitas 1993;18:47

Cardozo LD, Stanton SL, Robinson H et al. Evaluation on flurbiprofen in detrusor instability. Br Med J 1980a;280:281

Cardozo LD, Stanton SL. A comparison between bromocriptine and indomethacin in the treatment of detrusor instability. J Urol 1980b;123:39

Caremel R, Oger-Roussel S, Behr-Roussel D et al. Nitric oxide/cyclic guanosine monophosphate signalling mediates an inhibitory action on sensory pathways of the micturition reflex in the rat. Eur Urol 2010;58:616-625.

Cartwright R, Cardozo L. Transdermal oxybutynin: sticking to the facts. Eur Urol. 2007 Apr;51(4):907.

Cartwright R, Srikrishna S, Cardozo L, Robinson D. Patient-selected goals in overactive bladder: a placebo controlled randomized double-blind trial of transdermaloxybutynin for the treatment of urgency and urge incontinence. BJU Int. 2011 Jan;107(1):70-6.

Castleden CM, Morgan B. The effect of ß-adrenoceptor agonists on urinary incontinence in the elderly. Br J Clin Pharmacol 1980;10:619

Catterall WA, Striessnig J, Snutch TP et al. International Unionv of Pharmacology. XL. Compendium of voltage-gated ion channels: calcium channels. Pharmacol Rev 2003;55:579

Caulfield MP, Birdsall NJM. International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. Pharmacol Rev 1998;50:279

Cazzulani P, Pietra C, Abbiati GA et al. Pharmacological activities of the main metabolite of flavoxate 3-methylflavone-8-carboxylic acid. Arzneimittelforschung, 1988;38(3):379

Chai TC, Gray ML, Steers WD, The incidence of a positive ice water test in bladder outlet obstructed patients: evidence for bladder neural plasticity. J Urol. 1998 Jul;160(1):34

Chancellor MB, Appell RA, Sathyan G et al. A comparison of the effects on saliva output of oxybutynin chloride and tolterodine tartrate. Clin Ther 2001;23(5):753

Chancellor MB, Atan A, Rivas DA et al. Beneficial effect of intranasal desmopressin for men with benign prostatic hyperplasia and nocturia: preliminary results. Tech Urol 1999;5:191

Chancellor MB, Erhard MJ, Hirsch IH, Stass WE Jr. Prospective evaluation of terazosin for the treatment of autonomic dysreflexia. J Urol. 1994 Jan;151(1):111-3.

Chancellor MB, de Miguel F. Treatment of overactive bladder: selective use of anticholinergic agents with low drug-drug interaction potential. Geriatrics 2007;62:15-24.

Chancellor MB, Fowler CJ, Apostolidis A et al. Drug Insight: biological effects of botulinum toxin A in the lower urinary tract. Nat Clin Pract Urol. 2008 Jun;5(6):319

Chancellor MB, Kaufman J. Case for pharmacotherapy development for underactive bladder J Urol2008;72(5):966-967

Chancellor MB, Kianifard F, Beamer E et al. A comparison of the efficacy of darifenacin alone vs. darifenacin plus a Behavioural Modification Programme upon the symptoms of overactive bladder. Int J Clin Pract. 2008 Apr;62(4):606

Chancellor MB, Oefelein MG, Vasavada S. Obesity is associated with a more severe overactive bladder disease state that is effectively treated with once-daily administration of trospium chloride extended release. Neurourol Urodyn. 2010 Apr;29(4):551-4.

Chancellor MB, Staskin DR, Kay GG, et al. Blood-brain barrier permeation and efflux exclusion of anticholinergics used in the treatment of overactive bladder. Drugs Aging. 2012 Mar 5. doi: 10.2165/11597530-000000000-00000. [Epub ahead of print]

Chang SC, Lin AT, Chen KK, Chang LS. Multifactorial nature of male nocturia. Urology. 2006 Mar;67(3):541-4.

Chapple CR, Abrams P, Andersson K-E, et al. Randomised, Double-blind, Placebo-controlled Phase II Study to Investigate the Efficacy and Safety of the EP-1 Receptor Antagonist, ONO-8539, in Idiopathic Overactive Bladder. AUA 2011

Chapple CR, Arano P, Bosch JL et al. Solifenacin appears effective and well tolerated in patients with symptomatic idiopathic detrusor overactivity in a placebo- and tolterodine-controlled phase 2 dosefinding study. 2004a;BJU Int, 93(1):71

Chapple CR, Cardozo L, Steers WD et al. Solifenacin significantly improves all symptoms of overactive bladder syndrome. Int J Clin Pract. 2006 Aug;60(8):959

Chapple C, DuBeau C, Ebinger U et al. Long-term darifenacin treatment for overactive bladder in patients aged 65 years and older: analysis of results from a 2-year, open-label extension study. Curr Med Res Opin. 2007 Nov;23(11):2697

Chapple CR, Fianu-Jonsson A, Indig M et al. STAR study group. Treatment outcomes in the STAR study: a subanalysis of solifenacin 5 mg and tolterodine ER 4 mg. Eur Urol. 2007 Oct;52(4):1195

Chapple C, Khullar V, Gabriel Z et al. The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis. Eur Urol 2005;48:5

Chapple CR, Khullar V, Gabriel Z et al. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol. 2008 Sep;54(3):543

Chapple CR, Martinez-Garcia R, Selvaggi L et al. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. Eur Urol. 2005 Sep;48(3):464

Chapple C, Milsom I. Urinary incontinence and pelvic prolapse: Epidemiology and pathophysiology. In Campbell-Walsh Urology (Wein A, Kavoussi L, Novick A, Partin A, Peters C, eds), Elsevier Saunders, Philadelphia, 2012, pp 1871-1908)

Chapple CR, Montorsi F, Tammela TLJ, et al. on behalf of the European Silodosin Study Group. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Eur Urol. 2011 Mar;59(3):342-52.

Chapple CR, Parkhouse H, Gardener C et al. Double-blind, placebo-controlled, cross-over study of flavoxate in the treatment of idiopathic detrusor instability. Br J Urol 1990;66:491

Chapple C, Patel A. Botulinum toxin--new mechanisms, new therapeutic directions? Eur Urol. 2006 Apr;49(4):606-8.

Chapple CR, Patroneva A, Raines SR. Effect of an ATP-sensitive potassium channel opener in subjects with overactive bladder: a randomized, double-blind, placebo-controlled study (ZD0947IL/0004). Eur Urol 2006; 49: 879

Chapple CR, Rechberger T, Al-Shukri, S et al. YM-905 Study Group. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU Int 2004b;93(3):303

Chapple C, Steers W, Norton P et al. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. BJU Int. 2005 May;95(7):993

Chapple CR, Van Kerrebroeck PE, Jünemann KP et al. Comparison of fesoterodine and tolterodine in patients with overactive bladder. BJU Int. 2008 Jul 21. [Epub ahead of print]

Chapple C, Van Kerrebroeck P, Tubaro A et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. Eur Urol. 2007 Oct;52(4):1204

Chapple CR, Yamaguchi O, Ridder A et al. Clinical proof of concept study (Blossom) shows novel _3 adrenoceptor agonist YM178 is effective and well tolerated in the treatment of symptoms of overactive bladder. Eur Urol Suppl 2008;7(3):239 (abstract 674)

Chapple C, Wyndaele JJ, van Kerrebroeck P, Radziszewski P, Dvorak V, Boerrigter P. Dose-ranging study of once-daily mirabegron (YM178), a novel selective β3 adrenoceptor agonist, in patients with overactive bladder (OAB). Eur Urol 2010;(Suppl 9):249.

Charrua A, Cruz CD, Cruz F, Avelino A. Transient receptor potential vanilloid subfamily 1 is essential for the generation of noxious bladder input and bladder overactivity in cystitis. J Urol. 2007 Apr;177(4):1537-41.

Charrua A, Cruz CD, Narayanan S, et al. GRC-6211, a new oral specific TRPV1 antagonist, decreases bladder overactivity and noxious bladder input in cystitis animal models. J Urol. 2009b Jan;181(1):379-86.

Charrua A, Reguenga C, Cordeiro JM, et al. Functional transient receptor potential vanilloid 1 is expressed in human urothelial cells. J Urol. 2009a Dec;182(6):2944-50.

Charrua A., Boudes M., de Ridder D., et al. TRPV1 and TRPV4 expression in bladder neurons during normal condition and during cystitis. 2012a´. Eur Urol Suppl. (in press)

Charrua A., Cruz CD., Cruz F. TRPV1 and TRPV4 antagonist have synergistic effect for treating bladder overactivity in rats. (2012b) Eur Urol Suppl. (in press)

Chen TY, Corcos J, Camel M, et al. Prospective, randomized, double-blind study of safety and tolerability of intravesical resiniferatoxin (RTX) in interstitial cystitis (IC). Int Urogynecol J Pelvic Floor Dysfunct. 2005 Jul-Aug;16(4):293-7.

Chess-Williams R. Muscarinic receptors of the urinary bladder: detrusor, urothelial and prejunctional. Auton Autacoid Pharmacol 2002;22:133

Chess-Williams R, Chapple CR, Yamanishi T et al. The minor population of M3-receptors mediate contraction of human detrusor muscle in vitro. J Auton Pharmacol 2001;21:243

Chew ML, Mulsant BH, Pollock BG et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc. 2008 May 26. Epub ahead of publication.

Choo MS, Doo CK, Lee KS. Satisfaction with tolterodine: assessing symptom-specific patient-reported goal achievement in the treatment of overactive bladder in female patients (STARGATE study). Int J Clin Pract. 2008 Feb;62(2):191

Christ GJ, Andersson KE. Rho-kinase and effects of Rho-kinase inhibition on the lower urinary tract. Neurourol Urodyn. 2007 Oct;26(6 Suppl):948

Christ GJ, Day NS, Day M, et al. Bladder injection of “naked” hSlo/pcDNA3 ameliorates detrusor hyperactivity in obstructed rats in vivo. Am J Physiol Regul Integr Comp Physiol. 2001 Nov;281(5):R1699-709.

Christ T, Wettwer E, Wuest M, et al. Electrophysiological profile of propiverine--relationship to cardiac risk. Naunyn Schmiedebergs Arch Pharmacol. 2008 Feb;376(6):431-40.

Chuang YC, Chiang PH, Huang CC, et al. Botulinum toxin type A improves benign prostatic hyperplasia symptoms in patients with small prostate. Urology, 2005;66: 775 – 779.

Chuang YC, Tu CH, Huang CC, et al. Intraprostatic injection of botulinum toxin type-A relieves bladder outlet obstruction in human and induces prostate apoptosis in dogs. BMC Urol, 2006b; 6:12.

Chuang YC, Chancellor MB. The application of botulinum toxin in the prostate. J Urol, 2006d;176: 2375 – 2382.

Chuang YC, Chiang PH, Yoshimura N, et al. Sustained beneficial effects of intraprostatic botulinum toxin type A on lower urinary tract symptoms and quality of life in men with benign prostatic hyperplasia. BJU Int, 2006c;98: 1033 – 1037.

Chuang YC, Thomas CA, Tyagi S, et al.: Human urine with solifenacin intake but not tolterodine or darifenacin intake blocks detrusor overactivity. Int Urogynecol J Pelvic Floor Dysfunct 2008 Oct;19(10):1353

Chuang YC, Tyagi P, Huang CC, et al. Urodynamic and immunohistochemical evaluation of intravesical botulinum toxin A delivery using liposomes. J Urol. 2009 Aug;182(2):786-92.

Chung DE, Te AE, Staskin DR, Kaplan SA. Efficacy and safety of tolterodine extended release and dutasteride in male overactive bladder patients with prostates >30 grams. Urology. 2010 May;75(5):1144-8.

Chutka DS, Takahashi PY. Urinary incontinence in the elderly. Drug treatment options. Drugs 1998; 56: 587

Citeri M, Spinelli M, Zanollo L et al. Botulinum tonix into the trigone in neurogenic overactive bladder non responder to detrusor injection. Eur Urol Suppl, 2008:7 (3):213

Clemett D, Jarvis B. Tolterodine: a review of its use in the treatment of overactive bladder. Drugs Aging, 2001;18(4):277

Cockayne DA, Hamilton SG, Zhu QM et al. Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X3-deficient mice. Nature, 2000;407(6807):1011

Cody JD, Richardson K, Moehrer B, et al. Oestrogen therapy for urinary incontinence in post-menopausal women, Cochrane Database of Systematic Reviews 2009, Issue 4. Art No: CD001405. DOI 10.1002/14651858.CD001405.pub2.

Coelho A, Dinis P, Pinto R, Gorgal et al. Distribution of the high-affinity binding site and intracellular target of botulinum toxin type A in the human bladder. Eur Urol. 2010 May;57(5):884-90.

Coelho A, Cruz F, Cruz CD, Avelino A. Spread of OnabotulinumtoxinA After Bladder Injection. Experimental Study Using the Distribution of Cleaved SNAP-25 as the Marker of the Toxin Action. Eur Urol. 2012a (in press)

Coelho A, Cruz F, Cruz CD, Avelino A. Effect of onabotulinumtoxinA on intramural parasympathetic ganglia: an experimental study in the guinea pig bladder. J Urol. 2012b; 187(3):1121-6.

Cohen BL, Barboglio P, Rodriguez D, Gousse AE. Preliminary results of a dose-finding study for botulinum toxin-A in patients

with idiopathic overactive bladder: 100 versus 150 units. Neurourol Urodyn. 2009;28(3):205-8.

Collado Serra A, Rubio-Briones J, Puvol Payás M, et al. Post-prostatectomy established stress urinary incontinence treated with duloxetine. Urology 2011;78(2):261-266

Collas D, Malone-Lee JG. The pharmacokinetic properties of rectal oxybutynin - a possible alternative to intravesical administration. Neurourol Urodyn 1997;16:346

Colli E, Digesu GA, Olivieri L. Overactive bladder treatments in early phase clinical trials. Expert Opin Investig Drugs. 2007 Jul;16(7):999-1007.

Colli E, Rigatti P, Montorsi F et al. BXL628, a novel vitamin D3 analog arrests prostate growth in patients with benign prostatic hyperplasia: a randomized clinical trial. Eur Urol. 2006 Jan;49(1):82

Colli E, Tankó LB. Gonadotropin-Releasing Hormone Antagonists: From Basic Science to the Clinic in Patients With Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms. Uro-Today Int J. 2010 Oct;3(5) doi:10.3834/uij.1944-5784.2010.10.14

Compérat E, Reitz A, Delcourt A et al. Histologic features in the urinary bladder wall affected from neurogenic overactivity--a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. Eur Urol. 2006 Nov;50(5):1058

Conlon K, Christy C, Westbrook S, et al. Pharmacological properties of 2-((R-5-chloro-4-methoxymethylindan-1-yl)-1H-imidazole (PF-3774076), a novel and selective alpha1$_A$-adrenergic partial agonist, in in vitro and in vivo models of urethral function. J Pharmacol Exp Ther 2009;330(3):892-901

Connolly MJ, Astridge PS, White EG, Morley CA, Cowan JC. Torsades de pointes ventricular tachycardia and terodiline. Lancet. 1991 Aug 10;338(8763):344

Copas PM, Bukovsky A, Asubyr B et al. Estrogen, progesterone and androgen receptor expression in levator ani muscle and fascia. J Womens Health Gend Based Med 2001;10(8):785

Corcos J, Al-Taweel W, Pippi Salle J et al. The Treatment of detrusor hyperreflexia using botulinum A toxin in myelomeningocele patients unresponsive to anticholinergic International Continence Society Annual Meeting. 2002: Abstract 39

Corcos J, Casey R, Patrick A et al. A double-blind randomized dose-response study comparing daily doses of 5, 10 and 15 mg controlled-release oxybutynin: balancing efficacy with severity of dry mouth. BJU Int. 2006 Mar;97(3):520

Cornu J-N, Merlet B, Ciofu C, et al. Duloxetine for mild to moderate postprostatectomy incontinence: preliminary results of a randomized, placebo-controlled trial. Eur Urol 2011;59(1):148-154

Covenas R, Martin F, Belda M et al. Mapping of neurokinin-like immunoreactivity in the human brainstem. BMC Neurosci Febr 4(1):3

Coyne KS, Elinoff V, Gordon DA et al. Relationships between improvements in symptoms and patient assessments of bladder condition, symptom bother and health-related quality of life in patients with overactive bladder treated with tolterodine. Int J Clin Pract. 2008 Jun;62(6):925

Crawford ED, Hirst K, Kusek JW, et al. Effects of 100 and 300 units of onabotulinum toxin A on lower urinary tract symptoms of benign prostatic hyperplasia: a phase II randomized clinical trial. J Urol, 2011;186: 965 – 970.

Crescioli C, Ferruzzi P, Caporali A et al. Inhibition of spontaneous and androgen-induced prostate growth by a nonhypercalcemic calcitriol analog. Endocrinology. 2003 Jul;144(7):3046

Crescioli C, Ferruzzi P, Caporali A et al. Inhibition of prostate cell growth by BXL-628, a calcitriol analogue selected for a phase II clinical trial in patients with benign prostate hyperplasia. Eur J Endocrinol. 2004 Apr;150(4):591

Crescioli C, Morelli A, Adorini L, et al. Human bladder as a novel target for vitamin D receptor ligands. J Clin Endocrinol Metab. 2005 Feb;90(2):962-72.

Crescioli C, Villari D, Forti G, et al. Des (1-3) IGF-I-stimulated growth of human stromal BPH cells is inhibited by a vitamin D3 analogue. Mol Cell Endocrinol. 2002 Dec 30;198(1-2):69-75.

Cruz F, Guimaräes M, Silva C et al. Suppression of bladder hyperreflexia by intravesical resiniferatoxin. Lancet. 1997 Aug 30; 350 (9078):640

Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2011 Oct;60(4):742-50.

Cruz et al, 2011, European Neurol Society

Cvetkovic RS, Plosker GL. Desmopressin in adults with nocturia. Drugs 2005;65:99

D'Agostino G, Barbieri A, Chiossa E et al. M4 muscarinic autoreceptor-mediated inhibition of [3H]acetylcholine release in the rat isolated urinary bladder. J Pharmacol Exp Ther 1997;283:750

Dahm TL, Ostri P, Kristensen JK et al. Flavoxate treatment of micturition disorders accompanying benign prostatic hypertrophy: a double-blind placebo-controlled multicenter investigation. Urol Int 1955;55:205

Das A, Chancellor MB, Watanabe T et al. Intravesical capsaicin in neurologic impaired patients with detrusor hyperreflexia. J Spinal Cord Med. 1996 Jul;19(3):190

Dasgupta R, Fowler CJ. The management of female voiding dysfunction:Fowler's syndrome-a contemporary update. Curr Op Urol 2003;13:293-9.

da Silva CM, Cruz F. Has botulinum toxin therapy come of age: what do we know, what do we need to know, and should we use it? Curr Opin Urol. 2009 Jul;19(4):347-52.

Davies AM, Chahal R, Inman R, Urwin G. Intravesical botulinum A toxin (Botox) - does it have a role in the management of interstitial cystitis? Eur Urol Suppl 2006; 5(2):222.

Davila GW, Daugherty CA, Sanders SW. A short-term, multicenter, randomized double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. J Urol 2001;166(1):140

Deaney C, Glickman S, Gluck T et al. Intravesical atropine suppression of detrusor hyperreflexia in multiple sclerosis. J Neurol Neurosurg Psychiatry 1998;65:957

Debruyne F, Gres AA, Arustamov DL. Placebo-controlled dose-ranging phase 2 study of subcutaneously administered LHRH antagonist cetrorelix in patients with symptomatic benign prostatic hyperplasia. Eur Urol. 2008 Jul;54(1):170

de Groat WC, A neurologic basis for the overactive bladder. Urology. 1997 Dec; 50 (6A Suppl):36-52; discussion 53

de Groat, WC, Booth AM, Yoshimura N. Neurophysiology of micturition and its modification in animal models of human disease. In: The Autonomic Nervous System. Vol. 6, Chapter 8, Nervous Control of the Urogenital System, ed. by C.A. Maggi. Harwood Academic Publishers, London, U.K., p. 227, 1993.

de Groat WC, Downie JW, Levin RM et al. Basic neurophysiology and neuropharmacology, in Abrams P, Khoury S, Wein A (Eds), Incontinence, 1st International Consultation on Incontinence. Plymouth, United Kingdom, Plymbridge Distributors Ltd, p. 105, 1999.

de Groat, W.C., and Yoshimura N. Pharmacology of the lower urinary tract. Annu Rev Pharmacol Toxicol, 41:691, 2001

De Guchtenaere A, Vande Walle C, Van Sintjan P et al. Desmopressin resistant nocturnal polyuria may benefit from furosemide therapy administered in the morning. J Urol 2007;178:2635

De Guchtenaere A, Van Herzeele C, Raes A, et al. Oral lyophylizate formulation of desmopressin: superior pharmacodynamics compared to tablet due to low food interaction. J Urol. 2011 Jun;185(6):2308-13

De Laet K, De Wachter S, Wyndaele JJ. Systemic oxybutynin decreases afferent activity of the pelvic nerve of the rat: new insights into the working mechanism of antimuscarinics. Neurourol Urodyn. 2006;25(2):156

DeLancey JOL. The pathophysiology of stress urinary incontinence in women and its implications for surgical treatment. World J Urol 1997;15:268

Dell'utri C, Digesu GA, Bhide A, Khullar V. Fesoterodine in randomised clinical trials: an updated systematic clinical review of efficacy and safety. Int Urogynecol J. 2012 Mar 13.

Denmeade SR, Egerdie B, Steinhoff G, et al. Phase 1 and 2 studies demonstrate the safety and efficacy of intraprostatic injection of PRX302 for the targeted treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol. 2011 May;59(5):747-54.

de Mey C, Mateva L, Krastev Z, et al. Effects of hepatic dysfunction on the single-dose pharmacokinetics of fesoterodine. J Clin Pharmacol. 2011 Mar;51(3):397-405.

de Paiva A, Meunier FA, Molgó J, et al. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. Proc Natl Acad Sci U S A. 1999 Mar 16;96(6):3200-5.

Del Popolo G, Filocamo MT, Li Marzi V et al. Neurogenic detrusor overactivity treated with english botulinum toxin a: 8-year experience of one single centre. Eur Urol. 2008 May;53(5):1013

Denys P, Le Normand L, Ghout I, et al.; VESITOX study group in France. Efficacy and safety of low doses of onabotulinumtoxinA for the treatment of refractory idiopathic overactive bladder: a multicentre, double-blind, randomised, placebo-controlled dose-ranging study. Eur Urol. 2012 Mar;61(3):520-9

De Ridder D, Chandiramani V, Dasgupta P et al. Intravesical capsaicin as a treatment for refractory detrusor hyperreflexia: a dual center study with long-term followup. J Urol. 1997 Dec;158(6):2087

de Sèze M, Gallien P, Denys P et al. Intravesical glucidic capsaicin versus glucidic solvent in neurogenic detrusor overactivity: a double blind controlled randomized study. Neurourol Urodyn. 2006;25(7):752

de Sèze M, Wiart L, Joseph PA et al. Capsaicin and neurogenic detrusor hyperreflexia: a double-blind placebo-controlled study in 20 patients with spinal cord lesions. Neurourol Urodyn. 1998;17(5):513

Diefenbach K, Jaeger K, Wollny A et al. Effect of tolterodine on sleep structure modulated by CYP2D6 genotype. Sleep Med 2008Jul;9(5)579

Digesu GA, Khullar V, Cardozo L, Salvatore S. Overactive bladder symptoms: do we need urodynamics? Neurourol Urodyn. 2003;22(2):105

Dinis P, Charrua A, Avelino A, Cruz F. Intravesical resiniferatoxin decreases spinal c-fos expression and increases bladder volume to reflex micturition in rats with chronic inflamed urinary bladders. BJU Int. 2004 Jul;94(1):153-7.

Dinis P, Charrua A, Avelino A, et al. The distribution of sensory fibers immunoreactive for the TRPV1 (capsaicin) receptor in the human prostate. Eur Urol. 2005 Jul;48(1):162-7.

Dinis P, Silva J, Ribeiro MJ et al. Bladder C-fiber desensitization induces a long-lasting improvement of BPH-associated storage LUTS: a pilot study. Eur Urol. 2004Jul;46(1):88

Diokno AC. Medical management of urinary incontinence.Gastroenterology. 2004 Jan;126(1 Suppl 1):S77-81

Diokno AC, Appell RA, Sand PK et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. Mayo Clin Proc 2003;78(6):687

Dmochowski R, Abrams P, Marschall-Kehrel D et al. Efficacy and tolerability of tolterodine extended release in male and female patients with overactive bladder. Eur Urol. 2007 Apr;51(4):1054

Dmochowski RR, Davila GW, Zinner NR et al. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. J Urol 2002;168(2):580

Dmochowski R, Kreder K, MacDiarmid S et al. The clinical efficacy of tolterodine extended-release is maintained for 24 h in patients with overactive bladder. BJU Int. 2007 Jul;100(1):107

Dmochowski RR, Miklos JR, Norton PA et al. Duloxetine vs. placebo in the treatment of North American women with stress urinary incontinence. J Urol 2003;170:1259.

Dmochowski RR, Newman DK, Sand PK, et al. Pharmacokinetics of oxybutynin chloride topical gel: effects of application site, baths, sunscreen and person-to-person transference. Clin Drug Investig. 2011;31(8):559-71.

Dmochowski RR, Nitti V, Staskin D et al. Transdermal oxybutynin in the treatment of adults with overactive bladder: combined results of two randomized clinical trials. World J Urol. 2005 Sep;23(4):263

Dmochowski RR, Peters KM, Morrow JD, et al. Randomized, double-blind, placebo-controlled trial of flexible-dose fesoterodine in subjects with overactive bladder. Urology. 2010 Jan;75(1):62-8.

Dmochowski R, Roehrborn C, Klise S et al. Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: a randomized, placebo controlled 12-week clinical trial. J Urol 2010;183:1092-1097.

Dmochowski RR, Sand PK, Zinner NR et al. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. Urology, 2003;62(2):237

Dmochowski RR, Sand PK, Zinner NR et al. Trospium 60 mg once daily (QD) for overactive bladder syndrome: results from a placebo-controlled interventional study. Urology 2008 Mar;71(3):449

Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol. 2010 Dec;184(6):2416-22

Doggweiler R, Zermann DH, Ishigooka M, et al. Botox-induced prostatic involution. Prostate, 1998;37: 44 – 50.

Donath F, Braeter M, Feustel C. The influence of propiverine hydrochloride on cardiac repolarization in healthy women and cardiac male patients. Int J Clin Pharmacol Ther. 2011 Jun;49(6):353-65.

Dong M, Yeh F, Tepp WH et al. SV2 is the protein receptor for botulinum neurotoxin A. Science. 2006 Apr 28;312(5773):592

Donker P, Van der Sluis C. Action of beta adrenergic blocking agents on the urethral pressure profile. Urol Int 1976;31:6

Donnellan CA, Fook L, McDonald P et al. Oxybutynin and cognitive dysfunction. BMJ 1997;315:1363

Doroshyenko O, Jetter A, Odenthal KP et al. Clinical pharmacokinetics of trospium chloride. Clin Pharmacokinet. 2005;44(7):701

Dorschner W, Stolzenburg JU, Griebenow R et al. Efficacy and cardiac safety of propiverine in elderly patients - a double-blind, placebo-controlled clinical study. Eur Urol 2000;37:702

Douchamps J, Derenne F, Stockis A et al. The pharmacokinetics of oxybutynin in man. Eur J Clin Pharmacol, 1988;35:515

Downie JW, Karmazyn M. Mechanical trauma to bladder epithelium liberates prostanoids which modulate neurotransmission in rabbit detrusor muscle. J Pharmacol Exp Ther 1984;230: 445

Dowson C, Sahai A, Watkins J, et al. The safety and efficacy of botulinum toxin-A in the management of bladder oversensitivity: a randomised double-blind placebo-controlled trial. Int J Clin Pract. 2011 Jun;65(6):698-704.

Dowson C, Watkins J, Khan MS, et al. Repeated botulinum toxin type a injections for refractory overactive bladder: medium-term outcomes, safety profile, and discontinuation rates. Eur Urol. 2012 Apr;61(4):834-9.

Duckett J, Aggarwal I, Patil A. Duloxetine treatment for women awaiting continence surgery. Int Urogynecol J Pelvic Floor Dysfunct 2006;17(6):563-565

Duthie JB, Vincent M, Herbison GP, Wilson DI, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Database Syst Rev. 2011 Dec 7;12:CD005493

Dwyer P, Kelleher C, Young J et al. Long-term benefits of darifenacin treatment for patient quality of life: results from a 2-year extension study. Neurourol Urodyn. 2008;27(6):540

Dwyer PL, Teele JS. Prazosin: a neglected cause of genuine stress incontinence. Obstet Gynecol 1992;79:117

Dykstra D, Enriquez A, Valley M. Treatment of overactive bladder with botulinum toxin type B: a pilot study. Int Urogynecol J Pelvic Floor Dysfunct. 2003 Dec;14(6):424

Eckford SD, Carter PG, Jackson SR et al. An open, in-patient incremental safety and efficacy study of desmopressin in women with multiple sclerosis and nocturia. Br J Urol 1995;76:459

Eckford SD, Swami KS, Jackson SR et al. Desmopressin in the treatment of nocturia and enuresis in patients with multiple sclerosis. Br J Urol 1994;74:733

Edwards JL. Diagnosis and management of benign prostatic hyperplasia. Am Fam Physician. 2008;77:1403-1410.

Edwards KR, O'Connor JT. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. J Am Geriatr Soc 2002;50:1165

Ehlert FJ, Ahn S, Pak KJ, et al. Neuronally release acetylcholine acts on the M2 muscarinic receptor to oppose the relaxant effect of isoproterenol on cholinergic contractions in mouse urinary bladder. J Pharmacol Exp Ther 2007; 322:631

Ehren I, Volz D, Farrelly E et al. Efficacy and impact of botulinum toxin A on quality of life in patients with neurogenic detrusor overactivity: a randomised, placebo-controlled, double-blind study. Scand J Urol Nephrol. 2007;41(4):335

Eichel R, Lang C, Alloussi SH et al. Botulinum Toxin A (DYSPORT®), A safe modern treatment regime in the therapy of drug refractorical detrusor overactivity, 5 years of clinical experience. Eur Urol Suppl, 2008;7(3):213.

Ekström B, Andersson K-E, Mattiasson A. Urodynamic effects of intravesical instillation of atropine and phentolamine in patients with detrusor hyperactivity. J Urol 1992;149:155

Elinoff V, Bavendam T, Glasser DB et al. Symptom-specific efficacy of tolterodine extended release in patients with overactive bladder: the IMPACT trial. Int J Clin Pract. 2006 Jun;60(6):745

Emberton M, Cornel EB, Bassi PF, et al. Benign prostatic hyperplasia as a progressive disease : a guide to the risk factors and options for medical management. Int J ClinPract. 2008;62:1076-1086.

Emberton M, Fitzpatrick J. The Reten-World survey of the management of acute urinary retention: preliminary results. BJU Int 2008;101(Suppl 3):27-32.

Endo RM, Girao MJ, Sartori MG et al. Effect of estrogen-progestogen hormonal replacement therapy on periurethral and bladder vessels. Int Urogynecol J Pelvic Floor Dysfunct 2000;11(2):120

Enskat R, Deaney CN, Glickman S. Systemic effects of intravesical atropine sulphate. BJU Int 2001;87:613

Eri LM, Tveter KJ. A prospective, placebo-controlled study of the luteinizing hormone-releasing hormone agonist leuprolide as treatment for patients with benign prostatic

hyperplasia. J Urol 1993;150:359

Everaerts W, Gevaert T, Nilius B, De Ridder D. On the origin of **bladder** sensing: Tr(i)ps in urology. Neurourol Urodyn. 2008;27(4):264-73.

Everaerts W, Zhen X, Ghosh D, et al. Inhibition of the cation channel TRPV4 improves bladder function in mice and rats with cyclophosphamide-induced cystitis. Proc Natl Acad Sci U S A. 2010 Nov 2;107(44):19084-9.

Fader M, Glickman S, Haggar V et al. Intravesical atropine compared to oral oxybutynin for neurogenic detrusor overactivity: a double-blind, randomized crossover trial. J Urol 2007 Jan;177(1)208

Falconer C, Ekman-Ordeberg G, Blomgren B et al. Paraurethral connective tissue in stress incontinent women after menopause. Acta Obstetr Gynaecol Scand 1998;77(1)95

Fall M, Lindstrom S, Mazieres L. A bladder-to-bladder cooling reflex in the cat. J Physiol, 1990;427:281

Fantl JA, Bump RC, Robinson D et al. Efficacy of estrogen supplementation in the treatment of urinary incontinence. Obstet Gynaecol 1996;88:745

Fantl JA, Cardozo L, McClish DK Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta –analysis. Frist report of the Hormones and Urogenital Therapy Committee. Obstet Gynaecol 1994;83:12

Fellenius E, Hedberg R, Holmberg E et al. Functional and metabolic effects of terbutaline and propranolol in fast and slow contracting skeletal muscle in vitro. Acta Physiol Scand, 1980;109:89

Fetscher C, Fleichman M, Schmidt M et al. M3 muscarinic receptors mediate contraction of human urinary bladder. Br J Pharmacol 2002; 136: 641

Fibbi B, Morelli A, Vignozzi L et al. Characterization of phosphodiesterase type 5 expression and functional activity in the human male lower urinary tract. J Sex Med 2009; 7:59-69.

Filocamo MT, LiMarzi V, Del Popoilo G et al. Pharmacologic treatment in postprostatectomy stress urinary incontinence. Eur Urol 2007;51:1559

Finney SM, Andersson KE, Gillespie JI, Stewart LH. Antimuscarinic drugs in detrusor overactivity and the overactive bladder syndrome: motor or sensory actions? BJU Int. 2006 Sep;98(3):503

Fitzpatrick JM, Desgrandchamps F, Adjali K, Gomez Guerra L, Hong SJ, El Khalid S, Ratana-Olarn K; Reten-World Study Group. Management of acute urinary retention: a worldwide survey of 6074 men with benign prostatic hyperplasia. BJU Int. 2012 Jan;109(1):88-95.

Fitzpatrick J, Kirby R. Management of acute urinary retention. BJU Int 2006;97(Suppl 2):16-20.

Flicker C, Ferris SH, Serby M. Hypersensitivity to scopolamine in the elderly. Psychopharmacol (Berl) 1992;107:437

Flynn MK, Amundsen CL, Perevich M, Liu F, Webster GD. Outcome of a randomized, double-blind, placebo controlled trial of botulinum A toxin for refractory overactive bladder. J Urol. 2009 Jun;181(6):2608-15

Foote J, Glavind K, Kralidis G et al. Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of darifenacin, an M3 selective receptor antagonist. Eur Urol. 2005 Sep;48(3):471

Ford AP, Gever JR, Nunn PA et al. Purinoceptors as therapeutic targets for lower urinary tract dysfunction. Br J Pharmacol. 2006 Feb;147 Suppl 2:S132

Ford AP, Cockayne DA. ATP and P2X purinoceptors in urinary tract disorders. Handb Exp Pharmacol. 2011;(202):485-526.

Fowler CJ, Beck RO, Gerrard S et al. Intravesical capsaicin for the treatment of detrusor hyperreflexia. J Neurol Neurosurg Psychiatry 1994;57:169

Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008 Jun;9(6):453-66

Fowler CJ, Jewkes D, McDonald WI et al. Intravesical capsaicin for neurogenic bladder dysfunction. Lancet. 1992 May 16;339(8803):1239.

Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. J Am Geriatr Soc. 2011;59:1477-83.

Fraser MO, Chancellor MB: Neural control of the urethra and development of pharmacotherapy for stress urinary incontinence. BJU Int 2003;91(8):743

Frazier EP, Braverman AS, Peters SLM et al. Does phospholipase C mediate muscarinic receptor-induced rat urinary bladder contraction? J Pharmacol Exp Ther 2007; 322: 998

Frazier EP, Mathy MJ, Peters SL et al. Does cyclic AMP mediate rat urinary bladder relaxation by isoproterenol? J Pharmacol Exp Ther. 2005 Apr;313(1):260

Frazier EP, Peters SLM, Braverman AS et al. Signal transduction underlying control of urinary bladder smooth muscle tone by muscarinic receptors and _-adrenoceptors. Naunyn-Schmiedeberg's Arch Pharmacol 2008;377: 449

Fredrikson S. Nasal spray desmopressin in treatment of bladder dysfunction in patients with multiple sclerosis. Acta Neurol Scand 1996;94:31

Freeman RM, Adekanmi O, Waterfield MR, et al. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebocontrolled trial (CAMS-LUTS). Int Urogynecol J Pelvic Floor Dysfunct 2006;17:636–41.

Freeman R, Hill S, Millard R et al. Tolterodine Study Group. Reduced perception of urgency in treatment of overactive bladder with extended-release tolterodine. Obstet Gynecol 2003;102(3):605

Frenkl TL, Zhu H, Reiss T, et al. A multicenter, double-blind, randomized, placebo controlled trial of a neurokinin-1 receptor antagonist for overactive bladder. J Urol. 2010 Aug;184(2):616-22.

Frew R, Lundy PM. A role for Q type Ca2+ channels in neurotransmission in the rat urinary bladder. Br J Pharmacol 1995;116:1595

Frias B, Charrua A, Avelino A, Michel MC, Cruz F, Cruz CD. TRPV1 mediates NGF-induced bladder hyperactivity and noxious input. 2012. BJU Int, in press

Fröhlich G, Burmeister S, Wiedemann A et al. Intravesical instillation of trospium chloride, oxybutynin and verapamil for relaxation of the bladder detrusor muscle. A placebo controlled, randomized clinical test. Arzneimittelforschung. 1998;May;48(5):486. (German).

Fu FG, Lavery HJ, Wu DL. Reducing nocturia in the elderly: a randomized placebo-controlled trial of staggered furosemide and desmopressin. Neurourol Urodynam 2011;30:312-316.

Fu X, Rezapour M, Wu X et al. Expression of estrogen receptor alpha and beta in anterior vaginall walls of genuine stress incontinence women. Int Urogynaecol J Pelivc Floor Dysfunc 2003;14(4)276, discussion 281

Fujimura T, Tamura K, Tsutsumi T et al. Expression and possible functional role of the beta3-adrenoceptor in human and rat detrusor muscle. J Urol. 1999 Feb;161(2):680

Furuta A, Naruoka T, Suzuki Y, et al: _2-Adrenoceptor as a new target for stress urinary incontinence. LUTS 2009;1:526-529

Fusgen I, Hauri D. Trospium chloride: an effective option for medical treatment of bladder overactivity. Int J Clin Pharmacol Ther, 2000;38(5):223

Gacci M, Vittori G, Tosi N, et al. A randomised, placebo-controlled study to assess safety and efficacy of vardenafil 10 mg and tamsulosin 0,4 mg versus tamsulosin 0,4 mg alone in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Sex Med. 2011

Gallegos-Orozco JF, Foxx-Orenstein AE, Sterler SM, Stoa JM. Chronic constipation in the elderly. Am J Gastroenterol. 2012 ;107:18-25.

Gamé X, Castel-Lacanal E, Bentaleb Y, et al. Botulinum toxin A detrusor injections in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infections. Eur Urol. 2008 Mar;53(3):613-8.

Gamé X, Castel-Lacanal E, Bentaleb Y et al. Botulinum toxin A detrusor injections in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infections. Eur Urol. 2008 Mar;53(3):613

Garely AD, Kaufman JM, Sand PK et al. Symptom bother and health-related quality of life outcomes following solifenacin treatment for overactive bladder: the VESIcare Open-Label Trial (VOLT). Clin Ther. 2006 Nov;28(11):1935

Gebhardt J, Richard D, Barrett T. Expression of estrogen receptor isoforms alpha and beta messengera RNA in vaginal tissue of premenopausal and postmenopausal women. Am J Obstetr Gynaecol 2001;185:1325

Gee NS, Brown JP, Dissanayake VU et al. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. J Biol Chem. 1996 Mar 8;271(10):5768

Geirsson G, Fall M, Sullivan L. Clinical and urodynamic effects of intravesical capsaicin treatment in patients with chronic traumatic spinal detrusor hyperreflexia. J Urol. 1995 Nov;154(5):1825

George J, Tharion G, Richar J et al. The effectiveness of intravesical oxybutynin, propantheline, and capsaicin in the management of neuropathic bladder following spinal cord injury. ScientificWorldJournal. 2007 Oct 22;7:1683

Gevaert T, Vriens J, Segal A, et al. Deletion of the transient receptor potential cation channel TRPV4 impairs murine bladder voiding. J Clin Invest. 2007 Nov;117(11):3453-62.

Ghoneim GM, Van Leeuwen JS, Elser DM et al. A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment, and no treatment in women with stress urinary incontinence. J Urol 2005;173:1647

Giannantoni A, Bini V, Dmochowski R, et al. Contemporary management of the painful bladder: a systematic review. Eur Urol. 2012 Jan;61(1):29-53

Giannantoni A, Di Stasi SM, Nardicchi V et al. Botulinum-A toxin injections into the detrusor muscle decrease nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity. J Urol. 2006 Jun;175(6):2341

Giannantoni A, Di Stasi SM, Stephen RL et al. Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study. J Urol 2004;172:240

Giannantoni A, Serva MR, Proietti S, et al. Six year follow-up of intradetrusorial injections of botulinum toxin type A in patients with refractory neurogenic detrusor overactivity: clinical and urodynamic results - Abstract 567. Eur Urol Supplements. 2008;7:212

Giardina EG, Bigger JT. Jr, Glassman AH et al. The electrocardiographic and antiarrhythmic effects of imipramine hydrochloride at therapeutic plasma concentrations. Circulation 1979;60:1045

Giembycz MA. Life after PDE4: overcoming adverse events with dual-specificity phosphodiesterase inhibitors. Curr Opin Pharmacol. 2005 Jun;5(3):238

Gilja I, Radej M, Kovacic M et al. Conservative treatment of female stress incontinence with imipramine. J Urol 1984;132:909

Gill SS, Mamdani M, Naglie G et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. Arch Intern Med 2005;165:808

Gillespie JL. Phosphodiesterase-linked inhibition of non-micturition activity in the isolated bladder. BJU Int. 2004 Jun;93(9):1325

Gillespie JI, Drake MJ. The actions of sodium nitroprusside and the phosphodiesterase inhibitor dipyridamole on phasic activity in the isolated guinea-pig bladder. BJU Int 2004;93:851-858.

Gillman P. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br J of Pharmacol 2007;151(6):737-748

Glazener CMA, Evans JHC. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev 2002;3:CD002112. 2008.

Gleason DM, Reilly SA, Bottacini MR, et al. The urethral continence zone and its relation to stress incontinence. J Urol 1974;112:81

Gleason DM, Susset J, White C et al. Evaluation of a new once-daily formulation of oxybutynin the treatment of urinary urge incontinence. The Ditropan XL Study Group. Urology 1999;54:420

Glickman S, Tsokkos N, Shah PJ. Intravesical atropine and suppression of detrusor hypercontractility in the neuropathic bladder. A preliminary study. Paraplegia 1995;33:36

Goessl C, Knispel HH, Fiedler U, et al. Urodynamic effects of oral oxybutynin chloride in children with myelomeningocele and detrusor hyperreflexia. Urology. 1998 Jan;51(1):94-8.

Gomes CM, Castro Filho JE, Rejowski RF, et al. Experience with different botulinum toxins for the treatment of refractory neurogenic detrusor overactivity. Int Braz J Urol. 2010 Jan-Feb;36(1):66-74.

Gomes T, Juurlink DN, Mamdani MM. Comparative adherence to oxybutynin or tolterodine among older patients. Eur J Clin Pharmacol. 2012 Jan;68(1):97-9.

Gopalakrishnan M, Shieh C-C. Potassium channel subtypes as molecular targets for overactive bladder and other urological disorders. Expert Opin Ther Targets 2004; 8: 437

Gotoh M, Kamihira O, Kinikawa T, et al. Comparison of _1A-selective adrenoceptor antagonist, tamsulosin, and _1D-selective adrenoceptor antagonist, naftopidil, for efficacy and safety in the treatment of benign prostatic hyperplasia: a randomized controlled trial. BJU Int. 2005 Sep;96(4):581-6.

Goya N, Ishikawa N, Ito F, et al. Ethanol injection therapy of the prostate for benign prostatic hyperplasia: preliminary report on application of a new technique. J Urol, 1999;162: 383 - 386.

Goya N, Ishikawa N, Ito F, et al. Transurethral ethanol injection therapy for prostatic hyperplasia: 3-year results. J Urol, 2004;172: 1017 - 1020.

Grady D, Brown JS, Vittinghoff E et al. Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. Obstet Gynaecol 2001;97:116

Gratzke C, Streng T, Park A, et al. Distribution and function of cannabinoid receptors 1 and 2 in the rat, monkey and human bladder. J Urol 2009;181:1939–48.

Gratzke C, Streng T, Stief CG, et al. Cannabinor, a selective cannabinoid-2 receptor agonist, improves bladder emptying in rats with partial urethral obstruction. J Urol 2011;185:731–6.

Gratzke C, Streng T, Stief CG, et al. Effects of cannabinor, a novel selective cannabinoid 2 receptor agonist, on bladder function in normal rats. Eur Urol. 2010 Jun;57(6):1093-100.

Griffiths D. Imaging bladder sensations. Neurourol Urodyn. 2007 Oct;26(6 Suppl):899

Griffiths D, Tadic SD. Bladder control, urgency, and urge incontinence: evidence from functional brain imaging. Neurourol Urodyn. 2008;27(6):466

Griffiths DJ. Use of functional imaging to monitor central control of voiding in humans. Handb Exp Pharmacol. 2011;(202):81-97

Grise P, Plante M, Palmer J, et al. Evaluation of the transurethral ethanol ablation of the prostate (TEAP) for symptomatic benign prostatic hyperplasia (BPH): a European multi-center evaluation. Eur Urol, 2004;46: 496 - 501.

Grise P, Ruffion A, Denys P, et al. Efficacy and tolerability of botulinum toxin type A in patients with neurogenic detrusor overactivity and without concomitant anticholinergic therapy: comparison of two doses. Eur Urol. 2010 Nov;58(5):759-66.

Green SA, Alon A, Ianus J et al. Efficacy and safety of a neurokinin-1 receptor antagonist in postmenopausal women with overactive bladder with urge urinary incontinence. J Urol. 2006 Dec;176(6 Pt 1):2535

Grigoleit U, Mürtz G, Laschke S et al. Efficacy, tolerability and safety of propiverine hydrochloride in children and adolescents with congenital or traumatic neurogenic detrusor overactivity--a retrospective study. Eur Urol. 2006 Jun;49(6):1114

Grise P, Ruffion A, Denys P, et al. Efficacy and tolerability of botulinum toxin type A in patients with neurogenic detrusor overactivity and without concomitant anticholinergic therapy: comparison of two doses. Eur Urol. 2010 Nov;58(5):759-66.

Grodstein F, Lifford K, Resnick NM et al., Curham GC. Postmenopausal hormone therapy and risk of developing urinary incontinence. Obstet Gynaecol 2004;103(2):254

Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet. 2004;43(13):879

Grosse J, Kramer G, Stöhrer M. Success of repeat detrusor injections of botulinum a toxin in patients with severe neurogenic detrusor overactivity and incontinence. Eur Urol. 2005 May;47(5):653

Grüneberger A. Treatment of motor urge incontinence with clenbuterol and flavoxate hydrochloride. Br J Obstet Gynaecol 1984;91:275

Gu B, Fraser MO, Thor KB et al. Induction of bladder sphincter dyssynergia by _-2 opioid receptor agonists in the female rat. J Urol 2004; 171: 472

Gu BJ, Ishizuka O, Igawa Y et al. Role of supraspinal tachykinins for micturition in conscious rats with and without bladder outlet obstruction. Naunyn Schmiedebergs Arch Pharmacol. 2000 May;361(5):543

Guercini, F, Giannantoni A, Bard RL et al. Intraprostatic botox - an injection in patients with severe benign prostatic hyperplasia. A multicenter study. Eur Urol Suppl, 2005;4: 150.

Guarneri L, Robinson E, Testa R. A review of flavoxate: pharmacology and mechanism of action. Drugs Today, 1994;30:91

Guerra LA, Moher D, Sampson M et al. Intravesical oxybutynin for children with poorly compliant neurogenic bladder: a systematic review. J Urol. 2008 Sep;180(3):1091

Guay DR. Clinical pharmacokinetics of drugs used to treat urge incontinence. Clin Pharmacokinet. 2003;42(14):1243

Gutman GA, Chandy KG, Adelman JP, et al. International Union of Pharmacology. XLI. Compendium of voltage-gated ion channels: potassium channels. Pharmacol Rev 2003; 55: 583

Haab F, Cardozo L, Chapple C et al. Solifenacin Study Group. Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome. Eur Urol. 2005 Mar;47(3):376

Haab F, Corcos J, Siami P et al. Long-term treatment with darifenacin for overactive bladder: results of a 2-year, open-label extension study. BJU Int. 2006 Nov;98(5):1025

Haab F, Stewart L, Dwyer P. Darifenacin, an M3 selective receptor antagonist, is an effective and well-tolerated oncedaily treatment for overactive bladder. Eur Urol, 2004;45(4):420

Habler HJ, Janig W, Koltzenburg, M. Activation of unmyelinated afferent fibres by mechanical stimuli and inflammation of the urinary bladder in the cat. J Physiol, 1990;425:545

Haferkamp A, Schurch B, Reitz A et al. Lack of ultrastructural detrusor changes following endoscopic injection of botulinum toxin type a in overactive neurogenic bladder. Eur Urol. 2004 Dec; 46(6): 784

Halaska M, Ralph G, Wiedemann A et al. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. 2003;World J Urol 20(6):392

Hampel C, Gillitzer R, Pahernik S et al. Medikamentöse Therapie der weiblichen Harninkontinenz. Urologe A 2005; 44: 244

Harper M, Popat RB, Dasgupta R et al. A minimally invasive technique for outpatient local anaesthetic administration of intradetrusor botulinum toxin in intractable detrusor overactivity. BJU Int. 2003 Aug;92(3):325

Haruno A. Inhibitory effects of propiverine hydrochloride on the agonist-induced or spontaneous contractions of various isolated muscle preparations. Arzneim-Forsch /Drug Res 1992;42:815

Hashim H, Abrams P. Do symptoms of overactive bladder predict urodynamics detrusor overactivity? NeuroUrol Urodyn 2004;23(5/6):484

Hashim H, Abrams P. Pharmacologic management of women with mixed urinary incontinence. Drugs 2006;66(5):591

Hashim H, Malmberg L, Graugaard-Jensen C et al. Desmopressin, as a "designer-drug," in the treatment of overactive bladder syndrome. Neurourol Urodyn. 2009;28(1):40-6.

Hashimoto M, Imamura T, Tanimukai S et al. Urinary incontinence: an unrecognised adverse effect with donepezil. Lancet 2000;356:568.

Hashimoto S, Kigoshi S, Muramatsu I. Nitric oxidedependent and -independent neurogenic relaxation of isolated dog urethra. Eur J Pharmacol 1993;231: 209

Haustein KO, Huller G. On the pharmacokinetics and metabolism of propiverine in man. Eur J Drug Metab Pharmacokinet 1988;13(2):81

Hawthorn MH, Chapple CR, Cock M et al. Urothelium-derived inhibitory factor(s) influences on detrusor muscle contractility in vitro. Br J Pharmacol 2000;129:416

Hegde SS. Muscarinic receptors in the bladder: from basic research to therapeutics. Br J Pharmacol 2006;147:S80

Hegde SS, Choppin A, Bonhaus D, et al. Functional role of M2 and M3 muscarinic receptors in the urinary bladder of rats in vitro and in vivo. Br J Pharmacol 1997;120: 1409

Helfand BT, Evans RM, McVary KT. A comparison of the frequencies of medical therapies for overactive bladder in men

and women: analysis of more than 7.2 million aging patients. Eur Urol. 2010 Apr;57(4):586-91

Hendrix SL, Cochrane BB, Nygaard IE et al. Effects of estrogen with and without progestin on urinary incontinence. JAMA 2005;293(8):935

Hendrix SL, McNeeley SG. Effect of selective estrogen receptor modulators on reproductive tissues other than endometrium. Ann N Y Acad Sci 2001;949:243

Henriksson L, Andersson K-E, Ulmsten U. The urethral pressure profiles in continent and stress incontinent women. Scand J Urol Nephrol 1979;13:5

Herbison P, Hay-Smith J, Ellis G et al. Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. Br Med J 2003;326:841

Herschorn S, Gajewski J, Ethans K, et al. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: a randomized, double-blind trial. J Urol. 2011a Jun;185(6):2229-35.

Herschorn S, Gajewski J, Schulz J, Corcos J. A population-based study of urinary symptoms and incontinence: the Canadian Urinary Bladder Survey. BJU Int. 2008 Jan;101(1):52

Herschorn S, Pommerville P, Stothers L, et al. Tolerability of solifenacin and oxybutynin immediate release in older (> 65 years) and younger (≤ 65 years) patients with overactive bladder: sub-analysis from a Canadian, randomized, double-blind study. Curr Med Res Opin. 2011b Feb;27(2):375-82.

Herschorn S, Swift S, Guan Z, et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. BJU Int. 2010 Jan;105(1):58-66.

Hextall A. Oestrogens and lower urinary tract function. Maturitas 2000;36:83

Hextall A, Bidmead J, Cardozo L et al. The impact of the menstrual cycle on urinary symptoms and the results of urodynamic investigation. BJOG 2001;108(11)1193

Hicks A, McCafferty GP, Riedel E et al. GW427353 (solabegron), a novel, selective beta3-adrenergic receptor agonist, evokes bladder relaxation and increases micturition reflex threshold in the dog. J Pharmacol Exp Ther. 2007 Oct;323(1):202

Hill S, Khullar V, Wyndaele JJ et al. Dose response with darifenacin, a novel once-daily M3 selective receptor antagonist for the treatment of overactive bladder: results of a fixed dose study. Int Urogynecol J Pelvic Floor Dysfunct. 2006 May;17(3):239

Hills CJ, Winter SA, Balfour JA. Tolterodine. Drugs 1998;55:813

Hilton P, Hertogs K, Stanton SL. The use of desmopressin (DDAVP) for nocturia in women with multiple sclerosis. J Neurol Neurosurg Psychiatry 1983;46:854

Hilton P, Stanton SL. The use of desmopressin (DDAVP) in nocturnal urinary frequency in the female. Br J Urol 1982;54:252

Hilton P, Stanton SL. Urethral pressure measurement by microtransducer: the results in symptom free women and in those with genuine stress incontinence. Br J Obstet Gynaecol 1983 Oct;90(10):919-33.

Hirst GR, Watkins AJ, Guerrero K et al. MG, Botulinum toxin B is not an effective treatment of refractory overactive bladder. Urology 2007 Jan;69(1):69

Hoebeke P, De Caestecker K, Vande Walle J, et al. The effect of botulinum-A toxin in incontinent children with therapy resistant overactive detrusor. J Urol. 2006 Jul;176(1):328-30

Hoebeke P, De Pooter J, De Caestecker K, et al. Solifenacin for therapy resistant overactive bladder. J Urol. 2009 Oct;182(4 Suppl):2040-4.

Hoebeke PB, Vande Walle J. The pharmacology of paediatric incontinence. BJU Int. 2000 Sep;86(5):581-9.

Höfner K, Burkart M, Jacob G et al. Safety and efficacy of tolterodine extended release in men with overactive bladder symptoms and presumed non-obstructive benign prostatic hyperplasia. World J Urol. 2007 Dec;25(6):627

Holmes DM, Montz FJ, Stanton SL. Oxybutinin versus propantheline in the management of detrusor instability. A patient regulated variable dose trial. Br J Obstet Gynaecol 1989;96: 607

Holstege G. Micturition and the soul. J Comp Neurol. 2005 Dec 5;493(1):15-20

Homma Y, Yamaguchi O; Imidafenacin Study Group. A randomized, double-blind, placebo- and propiverine-controlled trial of the novel antimuscarinic agentimidafenacin in Japanese patients with overactive bladder. Int J Urol. 2009 May;16(5):499-506.

Homma Y, Yamaguchi O. Long-term safety, tolerability, and efficacy of the novel anti-muscarinic agent imidafenacin in Japanese patients with overactive bladder. Int J Urol. 2008 Oct;15(11):986-91.

Homma Y, Yamaguchi T, Yamaguchi O. A randomized, double-blind, placebo-controlled phase II dose-finding study of the novel anti-muscarinic agentimidafenacin in Japanese patients with overactive bladder. Int J Urol. 2008 Sep;15(9):809-15.

Hoverd PA, Fowler CJ. Desmopressin in the treatment of daytime urinary frequency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 1998;65:778

Howe BB, Halterman TJ, Yochim CL, et al. Zeneca ZD6169: a novel KATP channel opener with in vivo selectivity for urinary bladder. J Pharmacol Exp Ther 1995; 274: 884

Hruz P, Lövblad KO, Nirkko AC et al. Identification of brain structures involved in micturition with functional magnetic resonance imaging (fMRI). J Neuroradiol. 2008 Jul;35(3):144-9.

Hsiao SM, Chang TC, Wu WY, Chen CH, Yu HJ, Lin HH. Comparisons of urodynamic effects, therapeutic efficacy and safety of solifenacinversus tolterodine for female overactive bladder syndrome. J Obstet Gynaecol Res. 2011 Aug;37(8):1084-91.

Hu S, Kim HS. Modulation of ATP sensitive and large-conductance Ca2+-activated K+ channels by Zeneca ZD6169 in guinea pig bladder smooth muscle cells. J Pharmacol Exp Ther 1997;280:38

Hudman D, Elliott RA, Norman RI. K(ATP) channels mediate the beta(2)-adrenoceptor agonist-induced relaxation of rat detrusor muscle. Eur J Pharmacol. 2000 May 26;397(1):169

Hughes KM, Lang JCT, Lazare R et al. Measurement of oxybutynin and its N-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. Xenobiotica, 1992;22:859

Humeau Y, Doussau F, Grant NJ et al. How botulinum and tetanus neurotoxins block neurotransmitter release. Biochimie. 2000 May;82(5):427

Hunsballe JM, Djurhuus JC. Clinical options for imipramine in the management of urinary incontinence. Urol Res 2001;29:118

Hurley DJ, Turner CL, Yalcin I et al. Duloxetine for the treatment of stress urinary incontinence: an integrated analysis of safety. Eur J Obstet Gynecol Reprod Biol 2006; 125:120

Hussain RM, Hartigan-Go K, Thomas SHL et al. Effect of oxybutynin on the QTc interval in elderly patients with urinary incontinence. Br J Clin Pharmacol 1994;37:485P

Huwyler M, Schurch B, Knapp PA, Reitz A. Can the ice-water test predict the outcome of intradetrusor injections of botulinum toxin in patients with neurogenic bladder dysfunction? World J Urol. 2007 Dec;25(6):613-7.

Hyman MJ, Groutz A, Blaivas JG. Detrusor instability in men: correlation of lower urinary tract symptoms with urodynamic findings. J Urol. 2001 Aug;166(2):550

Igawa Y, Aizawa N, Homma Y. Beta3-adrenoceptor agonists: possible role in the treatment of overactive bladder. Korean J Urol. 2010 Dec;51(12):811-8.

Igawa Y, Komiyama I, Nishizawa O et al. Intravesical capsaicin inhibits autonomic dysreflexia in patients with spinal cord injury. Neurourol Urodyn 1996; 15: 374 (abst).

Igawa Y, Yamazaki Y, Takeda H et al. Functional and molecular biological evidence for a possible beta3-adrenoceptor in the human detrusor muscle. Br J Pharmacol. 1999 Feb;126(3):819

Igawa Y, Yamazaki Y, Takeda H et al. Relaxant effects of isoproterenol and selective beta3-adrenoceptor agonists on nor-

mal, low compliant and hyperreflexic human bladders. J Urol. 2001 Jan;165(1):240

Iijima K, De Wachter S, Wyndaele JJ. Effects of the M3 receptor selective muscarinic antagonist darifenacin on bladder afferent activity of the rat pelvic nerve. Eur Urol. 2007 Sep;52(3):842

Ikeda Y, Zabbarova IV, Birder LA, et al. Botulinum Neurotoxin Serotype A Suppresses Neurotransmitter Release from Afferent as Well as Efferent Nerves in the Urinary Bladder. Eur Urol. 2012 Mar 23.

Ikemoto I, Kiyota H, Ohishi Y, et al. Usefulness of tamsulosin hydrochloride and naftopidil in patients with urinary disturbances caused by benign prostatic hyperplasia: a comparative, randomized, two-drug crossover study. Int J Urol. 2003 Nov;10(11):587-94.

Insel PA, Tang C-M, Hahntow I et al. Impact of GPCRs in clinical medicine: genetic variants and drug targets. Biochim Biophys Acta 2007;1768:994

Irwin DE, Abrams P, Milsom I, et al; EPIC Study Group. Understanding the elements of overactive bladder: questions raised by the EPIC study. BJU Int. 2008 Jun;101(11):1381-7.

Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol. 2006 Dec;50(6):1306

Ishiko O, Hirai K, Sumi T et al. Hormone replacement therapy plus pelvic floor muscle exercise for postmenopausal stsress incontinence. A randomized controlled trial, J Reprod Med 2001;46:213

Ishiko O, Ushiroyama T, Saji F et al. Beta(2)-Adrenergic agonists and pelvic floor exercises for female stress incontinence. Int J Gynaecol Obstet 2000;71:39

Ishizuka O, Igawa Y, Lecci A et al. Role of intrathecal tachykinins for micturition in unanaesthetized rats with and without bladder outlet obstruction. Br J Pharmacol. 1994 Sep;113(1):111

Ishizuka O, Igawa Y, Nishizawa O et al. Role of supraspinal tachykinins for volume- and L-dopa-induced bladder activity in normal conscious rats. Neurourol Urodyn. 2000;19(1):101

Ishizuka O, Mattiasson A, Andersson KE. Effects of neurokinin receptor antagonists on L-dopa induced bladder hyperactivity in normal conscious rats. J Urol. 1995 Oct;154(4):1548

Isik AT, Celik T, Bozoglu E, Doruk H. Trospium and cognition in patients with late onset Alzheimer disease. J Nutr Health Aging 2009;13:672-676.

Jacobsen SM, Kerstein H, Molden E. Evaluation of brain anticholinergic activities of urinary spasmolytic drugs using a high-throughput radio receptor bioassay. J Am Geriatr Soc 2011;59:501-505.

Jackson S, Shepherd A, Abrams P. The effect of oestradiol on objective urinary leakage in postmenopausal stress incontinence: a double blind placebo controlled trial. Neurourol Urodyn 199615:322

Janig W, Morrison JF. Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. Prog Brain Res, 1986;67:87

Janssen DA, Hoenderop JG, Jansen KC, et al. The mechanoreceptor TRPV4 is localized in adherence junctions of the human bladder urothelium: a morphological study. J Urol. 2011 Sep;186(3):1121-7.

Jeremy JY, Tsang V, Mikhailidis DP et al. Eicosanoid synthesis by human urinary bladder mucosa: pathological implications. Br J Urol 1987;59:36

Ji RR, Samad TA, Jin SX, et al. p38 MAPK activation by NGF in primary sensory neurons after inflammation increases TRPV1 levels and maintains heat hyperalgesia. Neuron. 2002 Sep 26;36(1):57-68.

Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interaction in the elderly. Drug Safety 2007;30:911-918.

Johnson TMII, Miller M, Tang T et al. Oral ddAVP for nighttime urinary incontinence in characterized nursing home residents: a pilot study. J Am Med Dir Assoc 2006;7:6

Jones, R.L., Giembycz, M.A., Woodward, D.F., 2009. Prostanoid receptor antagonists: development strategies and therapeutic applications. Br J Pharmacol 158, 104-145.

Jonville AP, Dutertre JP, Autret E, Barbellion M. [Adverse effects of oxybutynin chloride (Ditropan). Evaluation of the official survey of Regional Pharmacovigilance Centers]. Therapie. 1992 Sep-Oct;47(5):389-92.

Jugus MJ, Jaworski JP, Patra PB, et al. Dual modulation of urinary bladder activity and urine flow by prostanoid EP3 receptors in the conscious rat. Br J Pharmacol 2009;158: 372-381.

Juul KV, Klein BM, Sandstrom R et al. Gender difference in antidiuretic response to desmopressin. Am J Physiol Renal Physiol 2011;300:F1116-F1122.

Jünemann KP, Al-Shukri S. Efficacy and tolerability of trospium chloride and tolterodine in 234 patients with urge-syndrome: a double-blind, placebo-controlled multicentre clinical trial. Neurourol Urodyn 2000;19:488

Jünemann KP, Halaska M, Rittstein T et al. Propiverine versus tolterodine: efficacy and tolerability in patients with overactive bladder. Eur Urol. 2005 Sep;48(3):478

Jünemann KP, Hessdörfer E, Unamba-Oparah I, et al. Propiverine hydrochloride immediate and extended release: comparison of efficacy and tolerability in patients with overactive bladder. Urol Int. 2006;77(4):334

Kachur JF, Peterson JS, Carter JP et al. R and S enantiomers of oxybutynin: pharmacological effects in guinea pig bladder and intestine. J Pharmacol Exp Ther, 1988;247: 867

Kaidoh K, Igawa Y, Takeda H et al. Effects of selective beta2 and beta3-adrenoceptor agonists on detrusor hyperreflexia in conscious cerebral infarcted rats. J Urol. 2002 Sep;168(3):1247

Kaiho Y, Nishiguchi J, Kwon DD et al. The effects of a type 4 phosphodiesterase inhibitor and the muscarinic cholinergic antagonist tolterodine tartrate on detrusor overactivity in female rats with bladder outlet obstruction. BJU Int. 2008 Mar;101(5):615

Kaisary AV. Beta adrenoceptor blockade in the treatment of female stress urinary incontinence. J d'Urol (Paris) 1984;90:351

Kajbafzadeh AM, Moosavi S, Tajik P et al. Intravesical injection of botulinum toxin type A: management of neuropathic bladder and bowel dysfunction in children with myelomeningocele. Urology, 2006 Nov; 68(5):1091

Kajbafzadeh AM, Nikfarjam L, Mahboubi AH, Dianat S. Antibody formation following botulinum toxin type A (Dysport) injection in children with intractable bladder hyper-reflexia. Urology. 2010 Jul;76(1):233-7.

Kajbafzadeh AM, Montaser-Kouhsari L, Ahmadi H, Sotoudeh M. Intravesical electromotive botulinum toxin type A administration: part I--Experimental study. Urology. 2011 Jun;77(6):1460-4.

Kalejaiye O, Speakman MJ. Management of acute and chronic retention in men. Eur Urol 2009;Suppl 8:523-9.

Kalsi V, Apostolidis A, Gonzales G et al. Early effect on the overactive bladder symptoms following botulinum neurotoxin type A injections for detrusor overactivity. Eur Urol. 2008 Jul;54(1):181

Kalsi V, Gonzales G, Popat R et al. Botulinum injections for the treatment of bladder symptoms of multiple sclerosis. Ann Neurol. 2007 Nov;62(5):452

Kalsi V, Popat RB, Apostolidis A et al. Cost-consequence analysis evaluating the use of botulinum neurotoxin-A in patients with detrusor overactivity based on clinical outcomes observed at a single UK centre.Eur Urol. 2006 Mar; 49(3):519

Kamo I, Chancellor MB, De Groat WC et al. Differential effects of activation of peripheral and spinal tachykinin neurokinin$_2$ receptors on the micturition reflex in rats. J Urol 2005; 174: 776

Kanagarajah P, Ayyathurai R, Caruso DJ, et al. Role of botulinum toxin-A in refractory idiopathic overactive bladder patients without detrusor overactivity. Int Urol Nephrol. 2012 Feb;44(1):91-7.

Kanai A, Andersson KE. Bladder afferent signaling: recent findings. J Urol. 2010 Apr;183(4):1288-95.

Kanayama N, Kanari C, Masuda Y, et al. Drug-drug interactions in the metabolism of imidafenacin: role of the human cytochrome P450 enzymes and UDP-glucuronic acid transferases, and potential of imidafenacin to inhibit human cytochrome P450 enzymes. Xenobiotica. 2007 Feb;37(2):139-54.

Kang I S, Sung ZH, et al. The efficacy and safety of combination therapy with alpha-blocker and low-dose propiverine hydrochloride for benign prostatic hyperplasia accompanied by overactive bladder symptoms. Korean J Urol 2009;**50**: 1078-82.

Kaplan SA, Goldfischer ER, Steers WD, et al. Solifenacin treatment in men with overactive bladder: effects on symptoms and patient-reported outcomes. Aging Male. 2010 Jun;13(2):100-7.

Kaplan SA, Gonzalez RR, Te AE. Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. Eur Urol 2007;51:1717-1723.

Kaplan SA, Roehrborn CG, Rovner ES et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA 2006 Nov 15;296(19):2319

Kaplan SA, Roehrborn CG, Chancellor M et al. Extended-release tolterodine with or without tamsulosin in men with lower urinary tract symptoms and overactive bladder: effects on urinary symptoms assessed by the International Prostate Symptom Score. BJU Int. 2008 Nov;102(9):1133-9.

Kaplan SA, Schneider T, Foote JE, et al. Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial. BJU Int. 2011 May;107(9):1432-40.

Kaplan SA, Walmsley K, Te AE. Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol. 2008a May;179(5 Suppl):S82

Karsenty G, Boy S, Reitz A et al. Botulinum toxin A (BTA) in the treatment of neurogenic detrusor overactivity incontinence (NDOI)- a prospective randomized study to compare 30 vs 10 injections sites. Neururol Urodyn. 2005: 24 (5/6): 547-548 (abstract 93).

Karsenty G, Denys P, Amarenco G, et al.. Botulinum toxin A (Botox) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. Eur Urol. 2008 Feb;53(2):275

Karsenty G, Elzayat E, Delapparent T et al. Botulinum toxin type a injections into the trigone to treat idiopathic overactive bladder do not induce vesicoureteral reflux. J Urol. 2007 Mar;177(3):1011

Kasabian NG, Vlachiotis JD, Lais A et al. The use of intravesical oxybutynin chloride in patients with detrusor hypertonicity and detrusor hyperreflexia. J Urol 1994;151:944

Katofiasc MA, Nissen J, Audia JE, et al: Comparison of the effects of serotonin selective norepinephrine selective, and dual serotonin and norepinephrine reuptake inhibitors on lower urinary tract function in cats. Life Sci 2002;71(11):1227

Katz IR, Prouty Sands L, Bilker W et al. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. J Am Geriatr Soc 1998;46:8

Kavia R, De Ridder D, Constantinescu S, et al. Randomised controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. Mult Scler 2010;16:1349–59.

Kawabe K, Yoshida M, Homma Y; Silodosin Clinical Study Group. Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. JU Int. 2006 Nov;98(5):1019-24.

Kay G, Crook T, Rekeda L et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. Eur Urol. 2006 Aug;50(2):317

Kay GG, Ebinger U. Preserving cognitive function for patients with overactive bladder: evidence for a differential effect with darifenacin. Int J Clin Pract. 2008 Aug 11. [Epub ahead of print]

Kay GG, Wesnes KA. Pharmacodynamic effects of darifenacin, a muscarinic M selective receptor antagonist for the treatment of overactive bladder, in healthy volunteers. BJU Int. 2005 Nov;96(7):1055

Keane DP, Sims TJ, Abrams P et al. Analysis of collagen status in premenopausal nulliparous women with genuine stress incontinence. Br J Obstet and Gynaecol 1997;104(9)994

Kelleher CJ , Cardozo L , Chapple CR , Haab F , Ridder AM. Improved quality of life in patients with overactive bladder symptoms treated with solifenacin . B JU Int 2005 ; 9 5 : 81 – 5

Kelleher C, Cardozo L, Kobashi K et al. Solifenacin: as effective in mixed urinary incontinence as in urge urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Jun;17(4):382

Kelleher CJ, Dmochowski RR, Berriman S, et al. Sustained improvement in patient-reported outcomes during long-term fesoterodine treatment for overactive bladder symptoms: pooled analysis of two open-label extension studies. BJU Int. 2011 Nov 30.

Kelleher CJ, Tubaro A, Wang JT et al. Impact of fesoterodine on quality of life: pooled data from two randomized trials. BJU Int. 2008 Jul;102(1):56

Kennedy C, Tasker PN, Gallacher G et al. Identification of atropine- and P2X1 receptor antagonist-resistant, neurogenic contractions of the urinary bladder. J Neurosci 2007 Jan 24;27(4):845

Kerbusch T, Wahlby U, Milligan PA et al. M.O. Population pharmacokinetic modelling of darifenacin and its hydroxylated metabolite using pooled data, incorporating saturable first-pass metabolism, CYP2D6 genotype and formulation-dependent bioavailability. Br J Clin Pharmacol 2003;56(6):639

Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med 200;343(25):1826

Kessler TM, Khan S, Panicker JN, et al. In the human urothelium and suburothelium, intradetrusor botulinum neurotoxin type A does not induce apoptosis: preliminary results. Eur Urol. 2010 May;57(5):879-83.

Kessler TM, Studer UE, Burkhard FC. The effect of terazosin on functional bladder outlet obstruction in women: a pilot study. J Urol. 2006 Oct;176(4 Pt 1):1487

Khan S, Game X, Kalsi V, Gonzales et al. Long-term effect on quality of life of repeat detrusor injections of botulinum neurotoxin-A for detrusoroveractivity in patients with multiple sclerosis. J Urol. 2011 Apr;185(4):1344-9.

Khera M, Somogyi GT, Kiss S et al. Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. Neurochem Int. 2004 Dec;45(7):987

Khullar V, Cambronero J, Ströberg P, et al. The efficacy and tolerability of mirabegron in patients with overactive bladder - results from a European-Australian Phase III trial. Presented at the 26th Annual Congress of the European Association of Urology, Vienna, Austria, 18-22 March 2011.

Khullar V, Foote J, Seifu Y, Egermark M. Time-to-effect with darifenacin in overactive bladder: a pooled analysis. Int Urogynecol J. 2011 Dec;22(12):1573-80.

Khullar V, Rovner ES, Dmochowski R et al. Fesoterodine dose response in subjects with overactive bladder syndrome. Urology. 2008 May;71(5):839

Kim YH, Bird ET, Priebe M et al. The role of oxybutynin in spinal cord injured patients with indwelling catheters. J Urol 1996;158:2083

Kim YT, Kwon DD, Kim J et al. Gabapentin for overactive bladder and nocturia after anticholinergic failure. Int Braz J Urol. 2004 Jul-Aug;30(4):275

Kim YS, Sainz RD. Beta adrenergic agonists and hypertrophy of skeletal muscles. Life Sci 1992;50:397

Kim Y, Yoshimura N, Masuda H et al.: Intravesical instillation of human urine after oral administration of trospium, tolterodine and oxybutynin in a rat model of detrusor overactivity. BJU Int 2006, 97:400

Kinn AC, Larsson PO. Desmopressin: a new principle for symptomatic treatment of urgency and incontinence in patients with multiple sclerosis. Scand J Urol Nephrol 1990;24:109

Kishimoto T, Morita T, Okamiya Y et al. Effect of clenbuterol on contractile response in periurethral striated muscle of rabbits. Tohoko J Exp Med 1991;165(3):243

Klausner AP, Steers WD. Antimuscarinics for the treatment of overactive bladder: a review of central nervous system effects. Curr Urol Rep. 2007 Nov;8(6):441

Klutke CG, Burgio KL, Wyman JF, et al. Combined effects of behavioral intervention and tolterodine in patients dissatisfied with overactive bladder medication. J Urol. 2009 Jun;181(6):2599-607.

Kobayashi F, Yageta Y, Yamazaki T, et al. Pharmacological effects of imidafenacin (KRP-197/ONO-8025), a new bladder selective anti-cholinergic agent, in rats. Comparison of effects on urinary bladder capacity and contraction, salivary secretion and performance in the Morris water maze task. Arzneimittelforschung. 2007;57(3):147-54.

Koelbl H, Nitti, V, Baessler K, et al. Pathophysiology of urinary incontinence, faecal incontinence and pelvic organ prolapse. In Incontinence (Abrams P, Cardozo L, Khoury S, Wein A, eds), Health Publication, Limited, Editions 21, Paris, 2009, pp 255-330

Kojima Y, Sasaki S, Imura M, et al. Correlation between expression of alpha-adrenoceptor subtype mRNA and severity of lower urinary tract symptoms or bladder outlet obstruction in benign prostatic hyperplasia patients. BJU Int. 2010 Aug 26

Kojima Y, Sasaki S, Kubota Y, et al. Expression of alpha1-adrenoceptor subtype mRNA as a predictor of the efficacy of subtype selective alpha1-adrenoceptor antagonists in the management of benign prostatic hyperplasia. J Urol. 2008 Mar;179(3):1040-6.

Kok ET, Schouten BW, Bohnen AM et al. Risk factors for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men: the Krimpen Study. J Urol 2009;181:710-716.

Komatsu, T, Gotoh M, Funahashi Y, et al. Efficacy of propiverine in improving symptoms and quality of life in female patients with wet overactive bladder. LUTS 2009;1:22-24

Kories C, Czyborra C, Fetscher C et al. Gender comparison of muscarinic receptor expression and function in rat and human urinary bladder: differential regulation of M2 and M3? Naunyn-Schmiedeberg's Arch Pharmacol 2003;367:524

Kraus SR, Ruiz-Cerdá JL, Martire D, et al. Efficacy and tolerability of fesoterodine in older and youngersubjects with overactive bladder. Urology 2010;76:1350-7.

Kuipers M, Tran D, Krauwinkel W et al. Absolute bioavailability of YM905 in healthy male volunteers. A single-dose randomized, two-period crossover study. Presented at the 32nd International Continence Society Annual Meeting, Heidelberg, Germany, August 2002

Kullmann FA, Shah MA, Birder LA, de Groat WC. Functional TRP and ASIC-like channels in cultured urothelial cells from the rat. Am J Physiol Renal Physiol. 2009 Apr;296(4):F892-901.

Kumar V, Cross RL, Chess-Williams R et al. Recent advances in basic science for overactive bladder. Curr Opin Urol 2005;15:222

Kuo HC. Effectiveness of intravesical resiniferatoxin in treating detrusor hyper-reflexia and external sphincter dyssynergia in patients with chronic spinal cord lesions. BJU Int. 2003 Oct;92(6):597

Kuo HC. Urodynamic evidence of effectiveness of botulinum A toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents. Urology. 2004 May;63(5):868-72.

Kuo HC. Clinical effects of suburothelial injection of botulinum A toxin on patients with nonneurogenic detrusor overactivity refractory to anticholinergics. Urology. 2005 Jul;66(1):94

Kuo HC. Multiple intravesical instillation of low-dose resiniferatoxin is effective in the treatment of detrusor overactivity refractory to anticholinergics. BJU Int. 2005 May;95(7):1023

Kuo HC. Prostate botulinum A toxin injection – an alternative treatment for benign prostatic obstruction in poor surgical candidates. Urology, 2005;65: 670 - 674.

Kuo HC. Comparison of effectiveness of detrusor, suburothelial and bladder base injections of botulinum toxin a for idiopathic detrusor overactivity. J Urol. 2007 Oct;178(4 Pt 1):1359

Kuo HC, Chancellor MB. Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int. 2009 Sep;104(5):657-61.

Kuo HC, Liao CH, Chung SD. Adverse events of intravesical botulinum toxin a injections for idiopathic detrusor overactivity: risk factors and influence on treatment outcome. Eur Urol. 2010 Dec;58(6):919-26.

Kuo HC, Liu HT, Yang WC. Therapeutic effect of multiple resiniferatoxin intravesical instillations in patients with refractory detrusor overactivity: a randomized, double-blind, placebo controlled study. J Urol. 2006 Aug;176(2):641

Kupelian V, Fitzgerald MP, Kaplan SA, Norgaard JP, Chiu GR, Rosen RC. Association of Nocturia and Mortality. Results from the Third National Health and Nutrition Examination Survey. J Urol 2011;185 (2): 571-577

Kupelian V, Wei J, O'Leary M, Norgaard JP, Rosen R, McKinlay J. Nocturia and Quality of Life: Results from the Boston Area Community Health Survey. Eur Urol. 2012 Jan; 61(1):78-84.

Lackner TE, Wyman JF, McCarthy TC, et al. Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin in cognitively impaired nursing home residents with urge urinary incontinence. J Am Geriatr Soc 2008;56:862-70.

Larsen JJ. alpha And beta-adrenoceptors in the detrusor muscle and bladder base of the pig and beta-adrenoceptors in the detrusor muscle of man. Br J Pharmacol 1979;65(2):215

Lazzeri M, Beneforti P, Spinelli M, et al. Intravesical resiniferatoxin for the treatment of hypersensitive disorder: a randomized placebo controlled study. J Urol. 2000 Sep;164(3 Pt 1):676-9.

Lazzeri M, Beneforti P, Turini D, et al Urodynamic effects of intravesical resiniferatoxin in humans: preliminary results in stable and unstable detrusor. J Urol 1997 Dec;158(6):2093

Lazzeri M, Spinelli M, Beneforti P et al. Intravesical resiniferatoxin for the treatment of detrusor hyperreflexia refractory to capsaicin in patients with chronic spinal cord diseases. Scand J Urol Nephrol. 1998 Sep;32(5):331

Lazzeri M, Spinelli M, Beneforti P, et al. Intravesical infusion of resiniferatoxin by a temporary in situ drug delivery system to treat interstitial cystitis: a pilot study. Eur Urol. 2004 Jan;45(1):98-102.

Lecci A, Maggi CA. Tachykinins as modulators of the micturition reflex in the central and peripheral nervous system. Regul Pept. 2001 Sep 15;101(1-3):1-18.

Lee T, Andersson K-E, Streng T, Hedlund P. Simultaneous registration of intraabdominal and intravesical pressures during cystometry in conscious rats--effects of bladder outlet obstruction and intravesical PGE2. Neurourol Urodyn 2008;27:88-95.

Lee KS, Choo MS, Kim DY et al. Combination treatment with propiverine hydrochloride plus doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder and coexisting benign prostatic obstruction: a prospective, randomized, controlled multicenter study. J Urol. 2005 Oct;174(4 Pt 1):1334

Lee, S.H., Chung, B.H., Kim, S.J., Kim, J.H., Kim, J.C., Lee, J.Y., 2011. Initial combined treatment with anticholinergics and alpha-blockers for men with lower urinary tract symptoms related to BPH and overactive bladder: a prospective, randomized, multicenter, double-blind, placebo-controlled study. Prostate Cancer Prostatic Dis 14, 320-325.

Lee JY, Kim HW, Lee SJ et al.Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. BJU Int. 2004 Oct;94(6):817

Lee KS, Lee HW, Choo MS, et al. Urinary urgency outcomes after propiverine treatment for an overactive bladder: the 'Propiverine study on overactive bladder including urgency data'. BJU Int. 2010 Jun;105(11):1565-70.

Lee KS, Lee HW, Han DH. Does anticholinergic medication have a role in treating men with overactive bladder and benign

prostatic hyperplasia? Naunyn Schmiedebergs Arch Pharmacol. 2008 Jun;377(4-6):491

Lepor H, Hill LA. Silodosin for the treatment of benign prostatic hyperplasia: pharmacology and cardiovascular tolerability. Pharmacotherapy. 2010 Dec;30(12):1303-12.

Lepor H, Kazzazi A, Djavan B. α-Blockers for benign prostatic hyperplasia: the new era. Curr Opin Urol. 2012 Jan;22(1):7-15.

Leslie CA, Pavlakis AJ, Wheeler JS Jr et al. Release of arachidonate cascade products by the rabbit bladder: neurophysiological significance? J Urol 1984;132:376

Leung FP, Yung LM, Yao X, et al. Store-operated calcium entry in vascular smooth muscle. Br J Pharmacol. 2008 Mar;153(5):846-57.

Liguori G, Trombetta C, De Giorgi G. et al. Efficacy and safety of combined oral therapy with tadalafil and alfuzosin: an integrated approach to the management of patients with lower urinary tract symptoms and erectile dysfunction. Preliminary report. J Sex Med 2009;6:544-552.

Lin HH, Sheu BC, Lo MC et al. Comparison of treatment outcomes for imipramine for female genuine stress incontinence. Br J Obstet Gynaecol 1999;106:1089

Lincoln J, Burnstock G. Autonomic innervation of the urinary bladder and urethra. In The Autonomic Nervous System. Vol. 6, Chapter 2, Nervous Control of the Urogenital System, ed. CA Maggi, London: Harwood Academic Publisher, p. 33, 1993.

Lipton RB, Kolodner K, Wesnes K. Assessment of cognitive function of the elderly population: effects of darifenacin. J Urol 2005;173:493-498.

Liu HT, Chancellor MB, Kuo HC. Urinary nerve growth factor levels are elevated in patients with detrusor overactivity and decreased in responders to detrusor botulinum toxin-A injection. Eur Urol. 2009 Oct;56(4):700-6

Liu HT, Kuo HC. Increased expression of transient receptor potential vanilloid subfamily 1 in the bladder predicts the response to intravesical instillations of resiniferatoxin in patients with refractory idiopathic detrusor overactivity. BJU Int. 2007 Nov;100(5):1086

Liu L, Mansfield KJ, Kristiana I, et al. The molecular basis of urgency: regional difference of vanilloid receptor expression in the human urinary bladder. Neurourol Urodyn. 2007;26(3):433-8

Lecci A, Maggi CA. Tachykinins as modulators of the micturition reflex in the central and peripheral nervous system. Regul Pept. 2001 Sep 15;101(1-3):1

Leon LA, Hoffman BE, Gardner SD et al. Effects of the beta 3-adrenergic receptor agonist disodium 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate (CL-316243) on bladder micturition reflex in spontaneously hypertensive rats. J Pharmacol Exp Ther. 2008 Jul;326(1):178

Leung FP, Yung LM, Yao X et al. Store-operated calcium entry in vascular smooth muscle. Br J Pharmacol 2008; 153: 846

Lindholm P, Lose G. Terbutaline (Bricanyl) in the treatment of female urge incontinence. Urol Int 1986;41(2):158

Lipton RB, Kolodner K, Wesnes K. Assessment of cognitive function of the elderly population: effects of darifenacin. J Urol. 2005 Feb;173(2):493

Longhurst PA, Briscoe JA, Rosenberg DJ et al. The role of cyclic nucleotides in guinea-pig bladder contractility. Br J Pharmacol. 1997 Aug;121(8):1665

Lose G, Jorgensen L, Thunedborg P. Doxepin in the treatment of female detrusor overactivity: A randomized double-blind crossover study. J Urol 1989;142:1024

Lose G, Lalos O, Freeman RM et al. Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. Am J Obstet Gynecol 2003;189:1106

Lose G, Mattiasson A, Walter S et al. Clinical experience with desmopressin for long-term treatment of nocturia. J Urol 2004;172:1021

Lose G, Norgaard JP. Intravesical oxybutynin for treating incontinence resulting from an overactive detrusor. BJU Int 2001;87:767

Low BY, Liong ML, Yuen KH et al. Terazosin therapy for patients with female lower urinary tract symptoms: A randomized, double-blind, placebo controlled trial . J Urol. 2008 Apr;179(4):1461

Lowenstein L, Kenton K, Mueller ER, et al. Solifenacin objectively decreases urinary sensation in women with overactive bladder syndrome. Int Urol Nephrol. 2011 Oct 13. [Epub ahead of print]

Lucioni A, Bales GT, Lotan TL et al. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. BJU Int. 2008 Feb;101(3):366 .

Luukkanen MJ, Uusvaara J, Laurila JV, et al. Anticholinergic drugs and their effects on delirium and mortality in the elderly. Dement Geriatr Cogn Dis Extra. 2011;1(1):43-50.

MacDiarmid SA, Ellsworth PI, Ginsberg DA, et al. Safety and efficacy of once-daily trospium chloride extended-release in male patients with overactive bladder. Urology. 2011 Jan;77(1):24-9.

Madersbacher H, Halaska M, Voigt R et al. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. BJU Int 1999;84:646

Madersbacher H, Mürz G. Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic). World J Urol, 2001;19:324

Madersbacher H, Stohrer M, Richter R ET AL. Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyper-reflexia. Br J Urol 1995;75(4):452

Madhuvrata P, Cody JD, Ellis G, et al. Which anticholinergic drug for overactive bladder symptoms in adults. Cochrane Database Syst Rev. 2012 Jan 18;1:CD005429.

Maggi CA, Borsini F, Lecci A et al. The effect of acute and chronic administration of imipramine on spinal and supraspinal micturition reflexes in rats. J Pharmacol Exp Ther, 1989;248:278

Makovey I, Davis T, Guralnick ML, O'Connor RC. Botulinum toxin outcomes for idiopathic overactive bladder stratified by indication: lack of anticholinergic efficacy versus intolerability. Neurourol Urodyn. 2011 Nov;30(8):1538-40

Malhotra BK, Glue P, Sweeney K et al. Thorough QT study with recommended and supratherapeutic doses of tolterodine. Clin Pharmacol Ther. 2007 Mar;81(3):377

Malhotra B, Gandelman K, Sachse R, et al. The design and development of fesoterodine as a prodrug of 5-hydroxymethyl tolterodine (5-HMT), the active metabolite of tolterodine. Curr Med Chem. 2009a;16(33):4481-9.

Malhotra B, Sachse R, Wood N. Influence of food on the pharmacokinetic profile of fesoterodine. Int J Clin Pharmacol Ther. 2009b Jun;47(6):384-90.

Malhotra B, Gandelman K, Sachse R, Wood N. Assessment of the effects of renal impairment on the pharmacokinetic profile of fesoterodine. J Clin Pharmacol. 2009c Apr;49(4):477-82.

Malhotra B, Guan Z, Wood N, Gandelman K. Pharmacokinetic profile of fesoterodine. Int J Clin Pharmacol Ther. 2008 Nov;46(11):556-63.

Malhotra B, Wood N, Sachse R, Gandelman K. Thorough QT study of the effect of fesoterodine on cardiac repolarization., Int J Clin Pharmacol Ther. 2010 May;48(5):309-18.

Malone-Lee JG, Walsh JB, Maugourd MF et al. Tolterodine: a safe and effective treatment for older patients with overactive bladder. J Am Geriatr Soc 2001;49:700

Maneuf YP, Gonzalez MI, Sutton KS et al. Cellular and molecular action of the putative GABA-mimetic, gabapentin. Cell Mol Life Sci. 2003 Apr;60(4):742

Manecksha RP, Cullen IM, Ahmad S, et al. Prospective Randomised Controlled Trial Comparing Trigone-Sparing versus Trigone-Including Intradetrusor Injection of AbobotulinumtoxinA for Refractory Idiopathic Detrusor Overactivity. Eur Urol. 2011 Nov 7. [Epub ahead of print]

Mangera A, Andersson KE, Apostolidis A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). Eur Urol. 2011 Oct;60(4):784-95.

Maniscalco M, Singh-Franco D, Wolowich WR et al. Solifenacin succinate for the treatment of symptoms of overactive bladder. Clin Ther. 2006 Sep;28(9):1247

Mansfield KJ, Liu L, Mitchelson FJ et al. Muscarinic receptor subtypes in human bladder detrusor and mucosa, studied by radioligand bindingand quantitative competitive RT-PCR: changes in ageing. Br J Pharmacol 2005;144:1089

Maria G, Brisinda G, Civello IM, et al. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo- controlled study. Urology, 2003;62: 259 – 264.

Mariappan P, Ballantyne Z, N'Dow JMO et al: Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults (review). Cochrane Database of Systemic Reviews 2005, Issue 3, Art. No: CD 004742. DOI: 10.1002/14651858. CD 0043742. pub 2. Also published in The Cochrane Library 2007, issue 3

Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Rapid efficacy of the highly selective a1A-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. J Urol 2009a;181:2634–40.

Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study. Urology 2009b; 6:1318–22.

Marschall-Kehrel D, Feustel C, Persson de Geeter C, et al. Treatment with propiverine in children suffering from nonneurogenic overactive bladder and urinary incontinence: results of a randomized placebo-controlled phase 3 clinical trial. Eur Urol. 2009 Mar;55(3):729-36.

Marte A, Borrelli M, Sabatino MD, et al. Effectiveness of botulinum-A toxin for the treatment of refractory overactive bladder in children. Eur J Pediatr Surg. 2010 May;20(3):153-7.

Martin SW, Radley SC, Chess-Williams R et al. Relaxant effects of potassium-channel openers on normal and hyper-reflexic detrusor muscle. Br J Urol 1997; 80: 405

Martin MR, Schiff AA. Fluphenazine/nortriptyline in the irritative bladder syndrome: a double-blind placebo-controlled study. Br J Urol 1984;56:178

Martínez-García R, Abadías M, Arañó P, et al. Cizolirtine citrate, an effective treatment for symptomatic patients with urinary incontinence secondary to overactive bladder: a pilot dose-finding study. Eur Urol. 2009 Jul;56(1):184-90.

Maruyama O, Kawachi Y, Hanazawa K, et al. Naftopidil monotherapy vs naftopidil and an anticholinergic agent combined therapy for storage symptoms associated with benign prostatic hyperplasia: A prospective randomized controlled study. Int J Urol. 2006 Oct;13(10):1280-5.

Mascarenhas F, Cocuzza M, Gomes CM et al. Trigonal injection of botulinum toxin-A does not cause vesicoureteral reflux in neurogenic patients. Neurourol Urodyn. 2008;27(4):311

Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. Ann Pharmacother. 2005 Jan;39(1):77

Masumori N, Miyamoto S, Tsukamoto T, et al. The efficacy and safety of propiverine hydrochloride in patients with overactive bladder symptoms who poorly responded to previous anticholinergic agents. Adv Urol. 2011;2011:714978.

Matsukawa Y, Gotoh M, Komatsu T, et al. Efficacy of silodosin for relieving benign prostatic obstruction: prospective pressure flow study. J Urol 2009;182:2831-2835.

Mattiasson A, Abrams P, van Kerrebroeck P et al. Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. BJU Int 2002;89:855

Mattiasson A, Blaakaer J, Hoye K et al. Tolterodine Scandinavian Study Group. Simplified bladder training augments the effectiveness of tolterodine in patients with an overactive bladder. BJU Int 2003;91(1):54

Matsui M, Griffin MT, Shehnaz D et al. Increased relaxant action of forskolin and isoproterenol against muscarinic agonist-induced contractions in smooth muscle from M2 receptor knockout mice. J Pharmacol Exp Ther 2003; 305:106

Matsui M, Motomura D, Fujikawa T, et al. Mice lacking M2 and M3 muscarinic acetylcholine receptors are devoid of cholinergic smooth muscle contractions but still viable. J Neurosci 2002; 22:10627

Matsui M, Motomura D, Karasawa H, et al. Multiple functional defects in peripheral autonomic organs in mice lacking muscarinic acetylcholine receptor gene for the M3 subtype. Proc Natl Acad Sci U S A. 2000 Aug 15;97(17):9579-84.

Matthiesen TB, Rittig S, Norgaard JP et al. Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. J Urol 1996;156:1292

May K, Westphal K, Giessmann T et al. Disposition and antimuscarinic effects of the urinary bladder spasmolytics propiverine: influence of dosage forms and circadian-time rhythms. J Clin Pharmacol. 2008 May;48(5):570

McCafferty GP, Misajet BA, Laping NJ, et al. Enhanced bladder capacity and reduced prostaglandin E2-mediated bladder hyperactivity in EP3 receptor knockout mice. Am J Physiol Renal Physiol 2008;295: F507-514

McConnell JD, Roehrborn CG, Bautista OM et al. Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med. 2003 Dec 18;349(25):2387

McCrery RJ, Appell RA. Oxybutynin: an overview of the available formulations. Ther Clin Risk Manag. 2006 Mar;2(1):19

McDowell DT, Noone D, Tareen F, Waldron M, Quinn F. Urinary incontinence in children: botulinum toxin is a safe and effective treatment option. Pediatr Surg Int. 2012 Mar;28(3):315-20.

McGuire EJ, Savastano JA. Urodynamics and management of the neuropathic bladder in spinal cord injury patients. J Am Paraplegia Soc. 1985 Apr;8(2):28-32.

McNeill SA, Hargreave TB. Alfuzosin once daily facilitates return to voiding in patients in acute urinary retention. J Urol 2004;171:2316

McNeill SA, Hargreave TB, Roehrborn CG. Alfuzosin 10 mg once daily in the management of acute urinary retention: results of a double-blind placebo-controlled study. Urology 2005;65:83

McVary KT, Monnig W, Camps JL Jr et al. Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. J Urol. 2007b Mar;177(3):1071

McVary KT, Roehrborn CG, Kaminetsky JC et al. Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Urol. 2007a Apr;177(4):1401

McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 2011;185:1793-1803.

Meek PD, Evang SD, Tadrous M, Roux-Lirange D, Triller DM, Gumustop B.Overactive bladder drugs and constipation: a meta-analysis of randomized, placebo-controlled trials. Dig Dis Sci. 2011;56:7-18.

Mehnert U, Birzele J, Reuter K, Schurch B. The effect of botulinum toxin type a on overactive bladder symptoms in patients with multiple sclerosis: a pilot study. J Urol. 2010 Sep;184(3):1011-6.

Mehnert U, Boy S, Schmid M, et al. A morphological evaluation of botulinum neurotoxin A injections into the detrusor muscle using magnetic resonance imaging. World J Urol. 2009 Jun;27(3):397-403.

Mehnert U, Boy S, Svensson J et al. Brain activation in response to bladder filling and simultaneous stimulation of the dorsal clitoral nerve - an fMRI study in healthy women. Neuroimage 2008 Jul 1;41(3):682-9.

Menarini M, Del Popolo G, Di Benedetto P et al. Trospium chloride in patients with neurogenic detrusor overactivity: is dose titration of benefit to the patients? Int J Clin Pharmacol Ther. 2006 Dec;44(12):623

Meng J, Wang J, Lawrence G et al. Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by

botulinum toxins reflects their anti-nociceptive potential J Cell Sci. 2007 Aug 15;120(Pt 16):2864

Merriam FV, Wang ZY, Guerios SD, Bjorling DE. Cannabinoid receptor2 is increased in acutely and chronically inflamed bladder of rats. Neurosci Lett 2008;445:130–4.

Michel MC. Fesoterodine: a novel muscarinic receptor antagonist for the treatment of overactive bladder syndrome. Expert Opin Pharmacother. 2008 Jul;9(10):1787

Michel MC, Barendrecht MM. Physiological and pathological regulation of the autonomic control of urinary bladder contractility. Pharmacol Ther 2008;117:297

Michel MC, Hegde SS. Treatment of the overactive bladder syndrome with muscarinic receptor antagonists: a matter of metabolites? Naunyn Schmiedebergs Arch Pharmacol. 2006 Nov;374(2):79

Michel MC, Vrydag W. Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol. 2006 Feb;147 Suppl 2:S88

Michel MC, Wetterauer U, Vogel M et al. Cardiovascular safety and overall tolerability of solifenacin in routine clinical use: a 12-week, open-label, post-marketing surveillance study. Drug Saf. 2008;31(6):505

Milani R, Scalambrino S, Milia R et al. Double-blind crossover comparison of flavoxate and oxybutynin in women affected by urinary urge syndrome. Int Urogynecol J, 1993;4:3Millard RJ. Asia Pacific Tolterodine Study Group. Clinical efficacy of tolterodine with or without a simplified pelvic floor exercise regimen. Neurourol Urodyn 2004;23(1):48

Millard RJ, Moore K, Rencken R et al. Duloxetine versus placebo in the treatment of stress urinary incontinence: a four continent randomized clinical trial. BJU Int 2004;93:311

Miller DW, Hinton M, Chen F. Evaluation of drug efflux transporter liabilities of darifenacin in cell culture models of the blood-brain and blood-ocular barriers. Neurourol Urodyn. 2011 Nov;30(8):1633-8.

Miyazato M, Sasatomi K, Hiragata S, et al. GABA receptor activation in the lumbosacral spinal cord decreases detrusor overactivity in spinal cord injured rats. J Urol. 2008 Mar;179(3):1178-83.

Montreal Cognitive Assessment homepage. Accessed at http://www.mocatest.org on June 4, 2011.

Morelli A, Filippi S, Comeglio P et al. Acute vardenafil administration improves bladder oxygenation in spontaneously hypertensive rats. J Sex Med 2009a;7:107-120.

Morelli A, Filippi S, Sandner P et al. Vardenafil modulates bladder contractility through cGMP-mediated inhibition of RhoA/Rho kinase signaling pathway in spontaneously hypertensive rats. J Sex Med 2009b;6:1594-1608.

Morelli A, Sarchielli E, Comeglio P et al. Phosphodiesterase type 5 expression in human and rat lower urinary tract tissues and the effect of tadalafil on prostate gland oxygenation in spontaneously hypertensive rats. J Sex Med 2011;8:2746-2760

Morelli A, Vignozzi L, Filippi S et al. BXL-628, a vitamin D receptor agonist effective in benign prostatic hyperplasia treatment, prevents RhoA activation and inhibits RhoA/Rho kinase signaling in rat and human bladder. Prostate. 2007 Feb 15;67(3):234

Morenilla-Palao C, Planells-Cases R, García-Sanz N et al. Regulated exocytosis contributes to protein kinase C potentiation of vanilloid receptor activity. Biol Chem. 2004 Jun 11;279(24):25665

Morganroth J, Lepor H, Hill LA, et al. Effects of the selective a_{1A}-adrenoceptor antagonist silodosin on ECGs of healthy men in a randomized, double blind, placebo-moxifloxacin-controlled study. Clin Pharmacol Ther 2010;87:609–13.

Morita T, Ando M, Kihara K, et al. Effects of prostaglandins E1, E2 and F2alpha on contractility and cAMP and cGMP contents in lower urinary tract smooth muscle. Urol Int 1994;52:200

Morita T, Iizuka H, Iwata T et al. Function and distribution of beta3-adrenoceptors in rat, rabbit and human urinary bladder and external urethral sphincter. J Smooth Muscle Res. 2000 Feb;36(1):21

Mostwin J, Bourcier A, Haab F et al. Pathophysiology of urinary incontinence, fecal incontinence and pelvic organ prolapse. In, Abrams P, Cardozo L, Khoury S, Wein A (eds): Incontinence. Plymouth, UK, Health Publications, pp 423, 2005

Mukerji G, Yiangou Y, Agarwal SK, Anand P. Transient receptor potential vanilloid receptor subtype 1 in painful bladder syndrome and its correlation with pain. J Urol. 2006 Aug;176(2):797-801.

Muller C, Siegmund W, Huupponen R et al. Kinetics of propiverine as assessed by radioreceptor assay in poor and extensive metabolizers of debrisoquine. Eur J Drug Metab Pharmacokinet 1993;18(3):265

Murakami S, Chapple CR, Akino H et al. The role of the urothelium in mediating bladder responses to isoprenaline. BJU Int. 2007 Mar;99(3):669

Murakami S, Yoshida M, Iwashita H, et al. Pharmacological effects of KRP-197 on the human isolated urinary bladder. Urol Int. 2003;71(3):290-8.

Muskat Y, Bukovsky I, Schneider D et al. The use of scopolamine in the treatment of detrusor instability. 1996;J Urol 156:1989

Musselman DM, Ford AP, Gennevois DJ, et al. A randomized crossover study to evaluate Ro 115-1240, a selective alpha 1 A/1L-adrenoceptor partial agonist in women with stress urinary incontinence. BJU Int 2004Jan;93(1):78

Naglie G, Radomski SB, Brymer C et al. A randomized, double-blind, placebo controlled crossover trial of nimodipine in older persons with detrusor instability and urge incontinence. J Urol 2002;167:586

Naglo AS, Nergardh A, Boreus LO. Influence of atropine and isoprenaline on detrusor hyperactivity in children with neurogenic bladder. Scand J Urol Nephrol 1981;15(2):97

Nakagawa H, Niu K, Hozawa A, et al. Impact of nocturia on bone fractures and mortality in older people: A Japanese longitudinal cohort study. J Urol 2010;184: 1413-1418.

Natalin R, Reis LO, Alpendre C et al. Triple therapy in refractory detrusor overactivity: a preliminary study. World J Urol 2009;28:79-85.

Nergardh A, Boreus LO, Naglo AS. Characterization of the adrenergic beta-receptor in the urinary bladder of man and cat. Acta Pharmacol Toxicol (Copenh) 1977;40(1):14

Neveus T, Tullus K. Tolterodine and imipramine in refractory enuresis: a placebo-controlled crossover study. Pediatr Nephrol 2008;23:263

Ney P, Pandita RK, Newgreen DT et al. Pharmacological characterization of a novel investigational antimuscarinic drug, fesoterodine, in vitro and in vivo. BJU Int. 2008 Apr;101(8):1036

Nilvebrant L, Andersson K-E, Gillberg PG. Tolterodine—a new bladder-selective antimuscarinic agent. Eur J Pharmacol, 1997b;327(2-3):195

Nilvebrant L, Gillberg PG, Sparf B. Antimuscarinic potency and bladder selectivity of PNU-200577, a major metabolite of tolterodine. Pharmacol Toxicol, 1997a;81(4):16

Nilvebrant L, Sparf B. Dicyclomine, benzhexol and oxybutynin distinguish between subclasses of muscarinic binding sites. Eur J Pharmacol 1986;123:133

Nilvebrant L, Sparf B. Receptor binding profiles of some selective muscarinic antagonists. Eur J Pharmacol. 1988 Jun 22;151(1):83-96.

Nishiguchi J, Kwon DD, Kaiho Y et al. Suppression of detrusor overactivity in rats with bladder outlet obstruction by a type 4 phosphodiesterase inhibitor. BJU Int. 2007 Mar;99(3):680

Nitti VW. Botulinum toxin for the treatment of idiopathic and neurogenic overactive bladder: state of the art Rev Urol. 2006 Fall;8(4):198

Nitti VW, Dmochowski R, Sand PK, et al. Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. J Urol. 2007 Dec;178(6):2488-94.

Nitti V, Herschorn S, Auerbach S, et al. The efficacy and safety of mirabegron in patients with overactive bladder syndrome -

results from a North-American Phase III trial. Presented at the 26th Annual Congress of the European Association of Urology, Vienna, Austria, 18-22 March 2011.

Nitti VW, Rovner ES, Bavendam T. Response to fesoterodine in patients with an overactive bladder and urgency urinary incontinence is independent of the urodynamic finding of detrusor overactivity. BJU Int. 2010 May;105(9):1268-75.

Noel S, Claeys S, Hamaide A. Acquired urinary incontinence in the bitch: Update and perspectives from human medicine. Part 1: The bladder component, pathophysiology and medical treatment. Vet J 2010;186:10-17

Noguchi M, Eguchi Y, Ichiki J et al. Therapeutic efficacy of clenbuterol for urinary incontinence after radical prostatectomy. Int J Urol 1997;4:480

Nomiya M, Yamaguchi O. A quantitative analysis of mRNA expression of alpha 1 and beta-adrenoceptor subtypes and their functional roles in human normal and obstructed bladders. J Urol. 2003 Aug;170(2 Pt 1):649

Norhona-Blob L, Kachur JF. Enantiomers of oxybutynin: in vitro pharmacological characterization at M1, M2 and M3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydriasis and salivary secretion in guinea pigs. J Pharmacol Exp Ther 1991;256:562

Norton PA, Zinner NR, Yalcin I et al. Duloxetine versus placebo in the treatment of stress urinary incontinence. Am J Obstet Gynecol 2002;187:40

Nour S, Svarer C, Kristensen JK, Paulson OB, Law I. Cerebral activation during micturition in normal men. Brain. 2000 Apr;123 (Pt 4):781-9.

Novara G, Galfano A, Secco S et al. Systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol. 2008 Oct;54(4):740-63.

Ochs GA. Intrathecal baclofen. Baillieres Clin Neurol. 1993 Apr;2(1):73-86.

Oelke M, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L. HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/22297243" Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. Eur Urol. 2012 May;61(5):917-25.

Oger S, Behr-Roussel D, Gorny D, et al. Signalling pathways involved in sildenafil-induced relaxation of human bladder dome smooth muscle. Br J Pharmacol 2010;160:1135-1143.

Ohlstein EH, Michel MC, Von Keitz A. The beta-3 adrenoceptor agonist solabegron is safe and effective for improving symptoms of overactive bladder. Eur Urol. 2012 Jun 5. [Epub ahead of print]

Ohmori S, Miura M, Toriumi C, et al. Absorption, metabolism, and excretion of [14C]imidafenacin, a new compound for treatment of overactive bladder, after oral administration to healthy male subjects. Drug Metab Dispos. 2007 Sep;35(9):1624-33.

Ohno T, Nakade S, Nakayama K, et al. Absolute bioavailability of imidafenacin after oral administration to healthy subjects. Br J Clin Pharmacol. 2008 Feb;65(2):197-202.

Oka M, Kimura,Y, Itoh Y et al. Brain pertussis toxin-sensitive G proteins are involved in the flavoxate hydrochloride-induced suppression of the micturition reflex in rats. Brain Res 1996;727(1-2):91

Olshansky B, Ebinger U, Brum J et al. Differential pharmacological effects of antimuscarinic drugs on heart rate: A randomized, placebo-controlled, double-blind, crossover study with tolterodine and darifenacin in healthy participants >=50 Years. J Cardiovasc Pharmacol Ther. 2008 Dec;13(4):241-51.

Otsuka A, Shinbo H, Matsumoto R et al. Expression and functional role of beta-adrenoceptors in the human urinary bladder urothelium. Naunyn Schmiedebergs Arch Pharmacol. 2008 Jun;377(4-6):473

Ouslander JG. Management of overactive bladder. New Engl J Med, 350:786, 2004.

Ouslander JG, Blaustein J, Connor A et al. Pharmacokinetics and clinical effects of oxybutynin in geriatric patients. J Urol 1988;140:47

Ouslander JG, Schnelle JF, Uman G et al. Does oxybutynin add to the effectiveness of prompted voiding for urinary incontinence among nursing home residents? A placebo-controlled trial. J Am Geriatr Soc 1995;43:610

Padmanabhan P, Scarpero HM, Milam DF, et al .Five-year cost analysis of intra-detrusor injection of botulinum toxin type A and augmentation cystoplasty for refractory neurogenic detrusor overactivity. World J Urol. 2011 Feb;29(1):51-7.

Pagoria D, O'Connor RC, Guralnick ML. Antimuscarinic drugs: review of the cognitive impact when used to treat overactive bladder in elderly patients. Curr Urol Rep 2011;12:351-357.

Palea S, Artibani, W, Ostardo, E et al. Evidence for purinergic neurotransmission in human urinary bladder affected by interstitial cystitis. J Urol, 1993;150(6):2007

Palmer J. Report of a double-blind crossover study of flurbiprofen and placebo in detrusor instability. J Int Med Res 1983;11 Supplement 2:11

Palmer LS, Zebold K, Firlit CF et al. Complications of intravesical oxybutynin chloride therapy in the pediatric myelomeningocele population. J Urol 1997;157:638

Parker-Autry CY, Burgio KL, Richter HE. Vitamin D status: a review with implications for the pelvic floor. Int Urogynecol J. 2012 Mar 14. [Epub ahead of print]

Patel AK, Patterson JM, Chapple CR. Botulinum toxin injections for neurogenic and idiopathic detrusor overactivity: A critical analysis of results. Eur Urol. 2006 Oct;50(4):684

Paquette A, Gou P, Tannenbaum C. Systematic review and meta-analysis: do clinical trials testing antimuscarinic agents for overactive bladder adequately measure central nervous system adverse events? J Am Geriatr Soc 2011;59:1332-9.

Payne CK, Mosbaugh PG, Forrest JB, et al., ICOS RTX Study Group (Resiniferatoxin Treatment for Interstitial Cystitis). Intravesical resiniferatoxin for the treatment of interstitial cystitis: a randomized, double-blind, placebo controlled trial. J Urol. 2005 May;173(5):1590-4.

Pehrson R, Andersson KE. Tramadol inhibits rat detrusor overactivity caused by dopamine receptor stimulation. J Urol. 2003 Jul;170(1):272

Pehrson R, Andersson KE. Effects of tiagabine, a gamma-aminobutyric acid re-uptake inhibitor, on normal rat bladder function. J Urol. 2002 May;167(5):2241

Pehrson R, Stenman E, Andersson KE. Effects of tramadol on rat detrusor overactivity induced by experimental cerebral infarction. Eur Urol. 2003 Oct;44(4):495

Peng CH, Kuo HC. Multiple intravesical instillations of low-dose resiniferatoxin in the treatment of refractory interstitial cystitis. Urol Int. 2007;78(1):78-81.

Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. Pharmacol Rev 2010;62: 588–631.

Peters SL, Schmidt M, Michel MC. Rho kinase: a target for treating urinary bladder dysfunction? Trends Pharmacol Sci. 2006 Sep;27(9):492

Peters CA, Walsh PC. The effect of nafarelin acetate, a luteinizing-hormone-releasing hormone agonist, on benign prostatic hyperplasia. N Engl J Med 1987;317:599.

Planells-Cases R, Valente P, Ferrer-Montiel A, et al. Complex regulation of TRPV1 and related thermo-TRPs: implications for therapeutic intervention. Adv Exp Med Biol. 2011;704:491-515

Plante MK, Gross AL, Kliment J, et al. Intraprostatic ethanol chemoablation via transurethral and transperineal injection. BJU Int, 2003;91: 94 - 98.

Plante MK, Marks LS, Anderson R, et al. Phase I/II examination of transurethral ethanol ablation of the prostate for the treatment of symptomatic benign prostatic hyperplasia. J Urol, 2007;177: 1030 - 1035.

Pinto R, Lopes T, Frias B, et al. Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/interstitial cystitis. Eur Urol. 2010 Sep;58(3):360-5.

Pistolesi D, Selli C, Rossi B et al. Botulinum toxin type B for type A resistant bladder spasticity. J Urol. 2004 Feb;171(2 Pt 1):802

Pontari MA, Braverman AS, Ruggieri MR, Sr. The M2 muscarinic receptor mediates in vitro bladder contractions from patients with neurogenic bladder dysfunction. Am J Physiol 2004;286:R874

Popat R, Apostolidis A, Kalsi V et al. A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. J Urol. 2005 Sep;174(3):984

Porst H, Kim ED, Casabe AR et al. Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial. Eur Urol 2011;60:1105-1113.

Porst H, McVary KT, Montorsi F et al. Effects of once-daily tadalafil on erectile function in men with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. Eur Urol 2009;56:727-735.

Purkiss J, Welch M, Doward S et al. Capsaicin-stimulated release of substance P from cultured dorsal root ganglion neurons: involvement of two distinct mechanisms. Biochem Pharmacol. 2000 Jun 1;59(11):1403

Radley SC, Chapple CR, Bryan NP et al. Effect of methoxamine on maximum urethral pressure in women with genuine stress incontinence: a placebo-controlled, double-blind crossover study. Neurourol Urodyn 2001;20(1):43

Rahnama'i MS, de Wachter SG, van Koeveringe GA, et al. The relationship between prostaglandin E receptor 1 and cyclooxygenase I expression in guinea pig bladder interstitial cells: proposition of a signal propagation system. J Urol. 2011 Jan;185(1):315-22.

Rahnama'i MS, van Koeveringe GA, Essers PB, et al. Prostaglandin receptor EP1 and EP2 site in guinea pig bladder urothelium and lamina propria. J Urol. 2010 Mar;183(3):1241-7.

Rapp DE, Lucioni A, Katz EE et al. Use of botulinum-A toxin for the treatment of refractory overactive bladder symptoms: an initial experience. Urology. 2004 Jun;63(6):1071

Rapp DE, Lyon MB, Bales GT et al. A role for the P2X receptor in urinary tract physiology and in the pathophysiology of urinary dysfunction. Eur Urol 2005;48:303

Rapp DE, Turk KW, Bales GT et al. Botulinum toxin type a inhibits calcitonin gene-related peptide release from isolated rat bladder. J Urol. 2006 Mar;175(3 Pt 1):1138

Razdan S, Leboeuf L, Meinbach DS, et al. Current practice patterns in the urologic surveillance and management of patients with spinal cord injury. Urology. 2003 May;61(5):893-6.

Raz S, Zeigler M, Caine M. The effect of progesterone on the adrenergic receptors of the urethra. Br J Urol 1973;45(2)131

Reitz A, Denys P, Fermanian C et al. Do repeat intradetrusor botulinum toxin type a injections yield valuable results? Clinical and urodynamic results after five injections in patients with neurogenic detrusor overactivity. Eur Urol. 2007 Dec;52(6):1729

Reitz A, Schurch B., Botulinum toxin type B injection for management of type A resistant neurogenic detrusor overactivity. J Urol. 2004 Feb;171(2 Pt 1):804

Reitz A, Stöhrer M, Kramer G et al. European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol. 2004 Apr;45(4):510

Rembratt A, Norgaard JP, Andersson KE. Desmopressin in elderly patients with nocturia: short-term safety and effects on urine output, sleep and voiding patterns. BJU. Int. 2003;91(7), 642

Rembratt A, Riis A, Norgaard JP. Desmopressin treatment in nocturia; an analysis of risk factors for hyponatremia. Neurourol Urodyn 2006;25(2):105

Rezakhaniha B, Arianpour N, Siroosbakhat S. Efficacy of desmopressin in treatment of nocturia in elderly men. J Res Med Sci 2011;16:516-23.

Riccabona M, Koen M, Schindler M, et al. Botulinum-A toxin injection into the detrusor: a safe alternative in the treatment of children with myelomeningocele with detrusor hyperreflexia. J Urol. 2004 Feb;171(2 Pt 1):845-8;

Riedl CR, Stephen RL, Daha LK, et al. Electromotive administration of intravesical bethanechol and the clinical impact on acontractile detrusor management: introduction of a new test. J Urol. 2000 Dec;164(6):2108-11.

Rios LA, Panhoca R, Mattos D Jr et al. Intravesical resiniferatoxin for the treatment of women with idiopathic detrusor overactivity and urgency incontinence: A single dose, 4 weeks, double-blind, randomized, placebo controlled trial. Neurourol Urodyn 2007;26(6):773

Rittig S, Jensen AR, Jensen KT, Pedersen EB. Effect of food intake on the pharmacokinetics and antidiuretic activity of oral desmopressin (DDAVP) in hydrated normal subjects. Clin Endocrinol (Oxf). 1998 Feb;48(2):235-41.

Robinson D, Cardozo L. The role of estrogens in female lower urinary tract dysfunction. Urology 2003;62(4 Suppl 1):45

Robinson D, Cardozo L. New drug treatments for urinary incontinence. Maturitas 2010;65(4):340-347

Robinson D, Cardozo L, Akeson M et al. Antidiuresis: a new concept in managing female daytime urinary incontinence. BJU Int 2004;93:996

Robinson D, Cardozo L, Terpstra G et al. A randomized double-blind placebo-controlled multicentre study to explore the efficacy and safety of tamsulosin and tolterodine in women with overactive bladder syndrome. BJU Int. 2007 Oct;100(4):840

Robinson D, Rainer RO, Washburn SA et al. Effects of estrogen and progestin replacement on the urogenital tract of the ovariectomized cynomolgus monkey. Neurourol Urodyn 1996;15(3):215

Robson WL, Leung AK, Norgaard JP. The comparative safety of oral versus intranasal desmopressin for the treatment of children with nocturnal enuresis. J Urol. 2007 Jul;178(1):24-30.

Roe CM, Anderson MJ, Spivack B. Use of anticholinergic medications by older adults with dementia. J Am Geriatr Soc 2002;50:836

Roehrborn CG, Kaplan SA, Kraus SR, et al. Effects of serum PSA on efficacy of tolterodine extended release with or without tamsulosin in men with LUTS, including OAB. Urology. 2008 Nov;72(5):1061-7;

Roehrborn CG, Kaplan SA, Jones JS et al. Tolterodine extended release with or without tamsulosin in men with lower urinary tract symptoms including overactive bladder symptoms: effects of prostate size. Eur Urol. 2009 Feb;55(2):472-9

Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup, L. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. J Urol 2008;180:1228-1234.

Roehrborn CG, Siami P, Barkin J, et al. CombAT Study Group. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol. 2010 Jan;57(1):123-31.

Rogers R, Bachmann G, Jumadilova Z et al. Efficacy of tolterodine on overactive bladder symptoms and sexual and emotional quality of life in sexually active women. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Nov;19(11):1551

Roosen A, Datta SN, Chowdhury RA,et al. Suburothelial myofibroblasts in the human overactive bladder and the effect of botulinum neurotoxin type A treatment. Eur Urol. 2009 Jun;55(6):1440-8.

Rovner E, Kennelly M, Schulte-Baukloh H, et al. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. Neurourol Urodyn. 2011 Apr;30(4):556-62

Rovner ES, Kreder K, Sussman DO et al. Effect of tolterodine extended release with or without tamsulosin on measures of urgency and patient reported outcomes in men with lower urinary tract symptoms. J Urol. 2008 Sep;180(3):1034

Rovner ES, Rackley R, Nitti VW et al. Tolterodine extended release is efficacious in continent and incontinent subjects with overactive bladder. Urology. 2008 sept;72(3):488

Rudy D, Cline K, Harris R et al. Multicenter phase III trial study-

ing trospium chloride in patients with overactive bladder. Urology 2006 Feb;67(2):275

Rufford J, Hextall A, Cardozo L et al. A double blind placebo controlled trial on the effects of 25 mg estradiol implants on the urge syndrome in postmenopausal women. Int Urogynecol J Pelvic Floor Dysfunct 2003;14(2):78

Ruffmann R. A review of flavoxate hydrochloride in the treatment of urge incontinence. J Int Med Res 1988;16:317

Ruggieri MR Sr. Mechanisms of disease: role of purinergic signaling in the pathophysiology of bladder dysfunction. Nat Clin Pract Urol. 2006 Apr;3(4):206

Ruggieri MR Sr. Cannabinoids: potential targets for bladder dysfunction. Handb Exp Pharmacol. 2011;(202):425-51.

Ruggieri MR Sr, Braverman AS, Pontari MA. Combined use of alpha-adrenergic and muscarinic antagonists for the treatment of voiding dysfunction. J Urol. 2005 Nov;174(5):1743

Sadananda P, Chess-Williams R, Burcher E. Contractile properties of the pig bladder mucosa in response to neurokinin A: a role for myofibroblasts? Br J Pharmacol 2008; 153:1465

Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of idiopathic detrusor overactivity: a double-blind, placebo-controlled, randomized study. Br J Clin Pharmacol. 2006 Apr;61(4):456

Saffroy M, Torrens Y, Glowinski J et al. Autoradiographic distribution of tachykinin NK2 binding sites in the rat brain: comparison with NK1 and NK3 binding sites. Neuroscience. 2003;116(3):761

Sahai A, Dowson C, Khan MS, Dasgupta P. Improvement in quality of life after botulinum toxin-A injections for idiopathic detrusor overactivity: results from a randomized double-blind placebo-controlled trial. BJU Int. 2009 Jun;103(11):1509-15.

Sahai A, Khan MS, Dasgupta P, Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial J Urol. 2007 Jun;177(6):2231

Sahai A, Mallina R, Dowson C et al. Evolution of transdermal oxybutynin in the treatment of overactive bladder. Int J Clin Pract. 2008 Jan;62(1):167

Sairam K, Kulinskaya E, McNicholas TA et al. Sildenafil influences lower urinary tract symptoms. BJU Int. 2002 Dec;90(9):836

Saito M, Dimitriadis F, Ohmasa F, et al. A β3 Agonist, Mirabegron for the Treatment of Overactive Bladder. UroToday Int J. 2011 Dec;4(6): art 70. http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03

Saito H, T, Yamada T, et al. A comparative syudy of the efficacy and safety of tamsulosin hydrochloride alone and combination of propiverine hydrochloride and tamsulosin hydrochloride in the benign prostatic hypertrophy with pollakisuria and/or urinary incontinence. Jpn J Urol Surg 1999;12: 525-36.

Sakai, H., Igawa, T., Onita, T., et al. Efficacy of naftopidil in patients with overactive bladder associated with benign prostatic hyperplasia: prospective randomized controlled study to compare differences in efficacy between morning and evening medication. Hinyokika Kiyo 57, 7-13.

Sakakibara R, Ito T, Uchiyama T et al. Effects of milnacipran and paroxetine on overactive bladder due to neurologic diseases: a urodynamic assessment. Urol Int 2008;81:335-339.

Sakakibara R, Ogata T, Uchiyama T, et al. How to manage overactive bladder in elderly individuals with dementia? Combined use of donepezil, a central acetylcholinesterase inhibitor, and propiverine, a peripheral muscarine receptor antagonist. J Am Geriatr Soc 2009;57:1515-1517

Sakr M, Eid A, Shoukry M, et al. Transurethral ethanol injection therapy of benign prostatic hyperplasia: four-year follow-up. Int J Urol, 2009;16: 196 - 201.

Salvatore S, Serati M, Cardozo L et al. Cognitive dysfunction with tolterodine use. Am J Obstet Gynecol 2007;197:e8.

Salvatore S, Serati M, Bolis P. Tolterodine for the treatment of overactive bladder. Expert Opin Pharmacother. 2008 May;9(7):1249

Sand PK, Davila GW, Lucente VR, et al. Efficacy and safety of oxybutynin chloride topical gel for women with overactive bladder syndrome. Am J Obstet Gynecol. 2012 Feb;206(2):168.e1-6

Sand PK, Johnson Ii TM, Rovner ES, et al. Trospium chloride once-daily extended release is efficacious and tolerated in elderly subjects (aged ≥ 75 years) with overactive bladder syndrome. BJU Int 2011;107:612-20.

Sand PK, Rovner ES, Watanabe JH, Oefelein MG. Once-daily trospium chloride 60 mg extended release in subjects with overactive bladder syndrome who use multiple concomitant medications: Post hoc analysis of pooled data from two randomized, placebo-controlled trials. Drugs Aging. 2011;28(2):151-60.

Sand PK, Heesakkers J, Kraus SR, et al. Long-term safety, tolerability and efficacy of fesoterodine in subjects with overactive bladder symptoms stratified by age: pooled analysis of two open-label extension studies. Drugs Aging 2012;29:119-31.

Santos-Silva A, Charrua A, Cruz CD, et al. Rat detrusor overactivity induced by chronic spinalization can be abolished by a transient receptor potential vanilloid 1 (TRPV1) antagonist. Auton Neurosci. 2012 Jan 26;166(1-2):35-8.

Schagen van Leeuwen JH, Lange RR, Jonasson AF et al. Efficacy and safety of duloxetine in elderly women with stress urinary incontinence or stress-predominant mixed urinary incontinence. Maturitas. 2008 Jun 20;60(2):138

Schmid DMS, Roy-Guggenbuehl SG, Werner MW et al. The Zurich experiences including 6 year results of 200 cases treated with Botulinum-A toxin injections into the detrusor muscle for overactive bladder refractory to anticholinergics. Eur Urol Suppl , 2008:7(3):212.

Schmid DM, Sauermann P, Werner M et al. Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. J Urol. 2006 Jul;176(1):177

Schneider T, Fetscher C, Krege S et al. Signal transduction underlying carbachol-induced contraction of human urinary bladder. J Pharmacol Exp Ther 2004a; 309:1148

Schneider T, Hein P, Bai J et al. A role for muscarinic receptors or rho-kinase in hypertension associated rat bladder dysfunction? J Urol 2005b;173:2178

Schneider T, Hein P, Michel MC. Signal transduction underlying carbachol-induced contraction of rat urinary bladder. I. Phospholipases and Ca2+ sources. J Pharmacol Exp Ther 2004b; 308:47

Schneider T, Hein P, Michel-Reher M et al. Effects of ageing on muscarinic receptor subtypes and function in rat urinary bladder. Naunyn-Schmiedeberg's Arch Pharmacol 2005a;372:71

Schröder A, Colli E, Maggi M et al. Effects of a vitamin D3 analogue in a rat model of bladder outflow obstruction. BJU Int 2006; 98:637

Schroder, A., Newgreen, D., Andersson, K.E., 2004. Detrusor responses to prostaglandin E2 and bladder outlet obstruction in wild-type and Ep1 receptor knockout mice. J Urol 172, 1166-1170.

Schroeder FH, Westerhof M, Bosch RJLH, Kurth KH. Benign prostatic hyperplasia treated by castration or the LH-RH analogue buserelin: a report on 6 cases. Eur Urol 1986;12:318

Schulte-Baukloh H, Knispel HH, Stolze T et al. Repeated botulinum-A toxin injections in treatment of children with neurogenic detrusor overactivity. Urology. 2005 Oct;66(4):865

Schulte-Baukloh H, Michael T, Schobert J, Stolze T, Knispel HH. Efficacy of botulinum-a toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. Urology. 2002 Mar;59(3):325-7;

Schulte-Baukloh H, Michael T, Stürzebecher B, Knispel HH. Botulinum-a toxin detrusor injection as a novel approach in the treatment of bladder spasticity in children with neurogenic bladder. Eur Urol. 2003 Jul;44(1):139-43.

Schulte-Baukloh H, Mürtz G, Henne T et al. Urodynamic effects of propiverine hydrochloride in children with neurogenic detrusor overactivity: a prospective analysis. BJU Int. 2006 Feb;97(2):355

Schulte-Baukloh H, Zurawski TH, Knispel HH et al. Persistence of the synaptosomal-associated protein-25 cleavage product after intradetrusor botulinum toxin A injections in patients with my-

elomeningocele showing an inadequate response to treatment. BJU Int. 2007 Nov;100(5):1075

Schurch B, Denys P, Kozma CM et al. Botulinum toxin A improves the quality of life of patients with neurogenic urinary incontinence. Eur Urol. 2007 Sep;52(3):850

Schurch B, de Sèze M, Denys P et al. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol. 2005 Jul;174(1):196

Schurch B, Schmid DM, Stöhrer M. Treatment of neurogenic incontinence with botulinum toxin A. N Engl J Med. 2000a Mar 2;342(9):665

Schurch B, Stöhrer M, Kramer G et al. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol. 2000b Sep;164(3 Pt 1):692

Schwinn DA, Price DT, Narayan P. alpha1-Adrenoceptor subtype selectivity and lower urinary tract symptoms. Mayo Clin Proc. 2004 Nov;79(11):1423-34.

Schwinn DA, Roehrborn CG. Alpha1-adrenoceptor subtypes and lower urinary tract symptoms. Int J Urol. 2008 Mar;15(3):193-9.

Sears CL, Lewis C, Noel K, Albright TS, Fischer JR. Overactive bladder medication adherence when medication is free to patients . J Urol 2010;183:1077 – 81

Seki S, Erickson KA, Seki M et al. Elimination of rat spinal neurons expressing neurokinin 1 receptors reduces bladder overactivity and spinal c-fos expression induced by bladder irritation. Am J Physiol Renal Physiol. 2005 Mar;288(3):F466

Serati M, Salvatore S, Uccella S, et al. Is there a synergistic effect of topical oestrogens when administered with antimuscarinics in the treatment of symptomatic detrusor overactivity? Eur Urol. 2009 Mar;55(3):713-9.

Serels SR, Toglia MR, Forero-Schwanhaeuser S, He W. Impact of solifenacin on diary-recorded and patient-reported urgency in patients with severe overactive bladder (OAB) symptoms. Curr Med Res Opin. 2010 Oct;26(10):2277-85.

Serra DB, Affrime MB, Bedigian MP et al. QT and QTc interval with standard and supratherapeutic doses of darifenacin, a muscarinic M3 selective receptor antagonist for the treatment of overactive bladder. J Clin Pharmacol. 2005 Sep;45(9):1038

Shaban A, Drake M, Hashim H. The medical management of urinary incontinence. Autonomic Neuroscience: Basic and Clinical 2010;152(1-2):4-10

Shamliyan TA, Kane RL, Wyman J et al. Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. Ann Int Med 2008;148:459

Sharma A, Goldberg MJ, Cerimele BJ: Pharmacokinetics and safety of duloxetine, a dual- serotonin and norepinephrine reuptake inhibitor. J Clin Pharmacol 2000;40(2):161

Sheldon JH, Norton NW, Argentieri TM. Inhibition of guinea pig detrusor contraction by NS-1619 is associated with activation of BKCa and inhibition of calcium currents. J Pharmacol Exp Ther 1997; 283: 1193

Sheu MT, Yeh GC, Ke WT et al. Development of a high-performance liquid chromatographic method for bioequivalence study of flavoxate tablets. J Chromatogr B Biomed Sci Appl 2001;751(1):79

Shieh C-C, Brune ME, Buckner SA, et al. Characterization of a novel ATP-sensitive K+ channel opener, A-251179, on urinary bladder relaxation and cystometric parameters. Br J Pharmacol 2007; 151: 467

Shore N. NX-1207: a novel investigational drug for the treatment of benign prostatic hyperplasia. Expert Opin Investig Drugs. 2010 Feb;19(2):305-10

Siddiqui MA, Perry CM, Scott LJ. Oxybutynin extended- release: a review of its use in the management of overactive bladder. Drugs, 2004;64(8):885

Sievert K.D., Heesakkers J., Ginsberg D., et al. Efficacy of onabotulinumtoxinA in neurogenic detrusor overactivity is independent of concomitant anticholinergic use. Eur Uro; Suppl. 2012;11:e461

Silva J, Pinto R, Carvallho T, et al. Mechanisms of Prostate atrophy after glandular botulinum neurotoxin type A Injection: An experimental study in the rat. Eur Urol, 2009a;56: 134 – 141.

Silva J, Pinto R, Carvalho T, et al. Intraprostatic Botulinum Toxin Type A injection in patients with benign prostatic enlargement: duration of the effect of a single treatment. BMC Urol, 2009b;15; 9: 9.

Silva J, Pinto R, Carvalho T, et al. Intraprostatic botulinum toxin type A administration: evaluation of the effects on sexual function. BJU Int, 2011;107: 1950 – 1954.

Silva C, Ribeiro MJ, Cruz F. The effect of intravesical resiniferatoxin in patients with idiopathic detrusor instability suggests that involuntary detrusor contractions are triggered by C-fiber input. J Urol. 2002 Aug;168(2):575

Silva C, Rio ME, Cruz F, Desensitization of bladder sensory fibers by intravesical resiniferatoxin, a capsaicin analog: long-term results for the treatment of detrusor hyperreflexia. Eur Urol. 2000 Oct;38(4):444

Silva C, Silva J, Castro H et al. Bladder sensory desensitization decreases urinary urgency. BMC Urol. 2007 Jun;11(7):9

Silva C, Silva J, Ribeiro MJ et al. Urodynamic effect of intravesical resiniferatoxin in patients with neurogenic detrusor overactivity of spinal origin: results of a double-blind randomized placebo-controlled trial. Eur Urol. 2005 Oct; 48 (4):650

Silva J, Silva C, Saraiva L, et al. Intraprostatic botulinum toxin type a injection in patients unfit for surgery presenting with refractory urinary retention and benign prostatic enlargement. Effect on prostate volume and micturition resumption. Eur Urol, 2008;53: 153 – 159.

Silver N, Sandage B, Sabounjian L, et al Pharmacokinetics of once-daily trospium chloride 60 mg extended release and twice-daily trospium chloride20 mg in healthy adults. J Clin Pharmacol. 2010 Feb;50(2):143-50.

Singh SK, Agarwal MM, Batra YK, et al. Effect of lumbar-epidural administration of tramadol on lower urinary tract function. Neurourol Urodyn. 2008;27(1):65

Singh R, Browning JL, Abi-Habib R, et al.. Recombinant prostate-specific antigen proaerolysin shows selective protease sensitivity and cell cytotoxicity. Anticancer Drugs. 2007 Aug;18(7):809-16.

Sink KM, Thomas J, Xu H, Craig B, Kritchebsky S, Sands LP. Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes. J Am Geriatr Soc 2008;56:847-853.

Sjögren C, Andersson K-E, Husted S et al. Atropine resistance of the transmurally stimulated isolated human bladder. J Urol 1982;128:1368

Skerjanec A. The clinical pharmacokinetics of darifenacin. Clin Pharmacokinet. 2006;45(4):325

Smet PJ, Moore KH, Jonavicius J. Distribution and colocalization of calcitonin gene-related peptide, tachykinins, and vasoactive intestinal peptide in normal and idiopathic unstable human urinary bladder. Lab Invest. 1997 Jul;77(1):37

Smith CP, Chancellor MB. Emerging role of botulinum toxin in the management of voiding dysfunction. J Urol. 2004 Jun;171(6 Pt 1):2128-37

Smith PH, Cook JB, Prasad EW.The effect of ubretid on bladder function after recent complete spinal cord injury. Br J Urol. 1974 Apr;46(2):187

Smith CP, Gangitano DA, Munoz A et al. Botulinum toxin type A normalizes alterations in urothelial ATP and NO release induced by chronic spinal cord injury. Neurochem Int. 2008 May;52(6):1068

Smith N, Grimes I, Ridge S et al. YM905 is effective and safe as treatment of overactive bladder in women and men: Results from phase II study. ICS Proceedings. Heidelberg, Germany: 138 (abstract 222), 2002

Smith P, Heimer G, Norgren A et al. Steroid hormone receptors in pelvic muscles and ligaments in women. Gynecol Obstet Investig 1990;30(1):27

Smulders RA, Krauwinkel WJ, Swart PJ et al. Pharmacokinetics

and safety of solifenacin succinate in healthy young men. J Clin Pharmacol. 2004 Sep;44(9):1023

Smulders R, Tan H, Krauwinkel W et al. A placebo-controlled, dose –rising study in healthy male volunteers to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of single oral doses of YM905. Presented at the 32nd International Continence Society Annual Meeting, Heidelberg, Germany, August 2002

Song C, Park JT, Heo KO et al. Effects of bladder training and/or tolterodine in female patients with overactive bladder syndrome: a prospective, randomized study. J Korean Med Sci. 2006 Dec;21(6):1060

Sperling R, Greve D, Dale A et al. Functional MRI detection of pharmacologically induced memory impairment. Proc Natl Acad Sci USA 2002;99:455

Stahl MM, Ekstrom B, Sparf B et al. Urodynamic and other effects of tolterodine: a novel antimuscarinic drug for the treatment of detrusor overactivity. Neurourol Urodyn, 1995;14(6):647

Stanton SL. A comparison of emepronium bromide and flavoxate hydrochloride in the treatment of urinary incontinence. J Urol 1973;110:529

Starr JM. Cholinesterase inhibitor treatment and urinary incontinence in Alzheimer's disease. J Am Geriatr Soc 2007;55:800

Staskin DR, Dmochowski RR, Sand PK, et al. Efficacy and safety of oxybutynin chloride topical gel for overactive bladder: a randomized, double-blind, placebo controlled, multicenter study. J Urol. 2009 Apr;181(4):1764-72.

Staskin D, Kay G, Tannenbaum C, et al. Trospium chloride has no effect on memory testing and is assay undetectable in the central nervous system of older patients with overactive bladder. Int J Clin Pract. 2010;64(9):1294-1300.

Staskin DR, Robinson D. Oxybutynin chloride topical gel: a new formulation of an established antimuscarinic therapy for overactive bladder. Expert Opin Pharmacother. 2009 Dec;10(18):3103-11.

Staskin DR, Salvatore S. Oxybutynin topical and transdermal formulations: an update. Drugs Today (Barc). 2010 Jun;46(6):417-25

Staskin D, Sand P, Zinner N et al. Trospium Study Group. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. J Urol 2007 Sep;178(3 Pt 1):978

Staskin DR, Te AE. Short- and long-term efficacy of solifenacin treatment in patients with symptoms of mixed urinary incontinence. BJU Int. 2006 Jun;97(6):1256

Steers W, Corcos J, Foote J et al. An investigation of dose titration with darifenacin, an M3-selective receptor antagonist. BJU Int. 2005 Mar;95(4):580

Steers WD, Herschorn S, Kreder KJ et al. Duloxetine compared with placebo for treating women with symptoms of overactive bladder. BJU Int. 2007 Aug;100(2):337

Stengel PW, Yamada M, Wess J et al. M3-receptor knockout mice: muscarinic receptor function in atria, stomach fundus, urinary bladder, and trachea. Am J Physiol Regul Integr Comp Physiol 2002; 282: R1443

Stevens LA, Chapple CR, Chess-Williams R. Human idiopathic and neurogenic overactive bladders and the role of M2 muscarinic receptors in contraction. Eur Urol. 2007 Aug;52(2):531-8.

Stewart DA, Taylor J, Ghosh S et al. Terodiline causes polymorphic ventricular tachycardia due to reduced heart rate and prolongation of QT interval. Eur J Clin Pharmacol. 1992;42(6):577

Stief CG, Porst H, Neuser D et al. A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol. 2008 Jun;53(6):1236

Stöhrer M, Bauer P, Giannetti BM et al. Effect of trospium chloride on urodynamic parameters in patients with detrusor hyperreflexia due to spinal cord injuries: a multicentre placebo controlled double-blind trial. Urol Int 1991;47:138

Stöhrer, M., Madersbacher, H., Richter, R. et al. Efficacy and safety of propiverine in SCI-patients suffering from detrusor hyperreflexia—a double-blind, placebo-controlled clinical trial. Spinal Cord 1999:37:196

Stöhrer M, Mürtz G, Kramer G et al. Propiverine compared to oxybutynin in neurogenic detrusor overactivity--results of a randomized, double-blind, multicenter clinical study. Eur Urol. 2007 Jan;51(1):235

Streng T, Christoph T, Andersson K-E. Urodynamic effects of the K+ channel (KCNQ) opener retigabine in freely moving, conscious rats. J Urol 2004; 172: 2054

Streng T, Andersson KE, Hedlund P, et al. Effects on bladder function of combining elocalcitol and tolterodine in rats with outflow obstruction. BJU Int. 2012 Jan 30. doi: 10.1111/j.1464-410X.2011.10838.x. [Epub ahead of print]

Striano P, Striano S. Gabapentin: a Ca2+ channel alpha 2-delta ligand far beyond epilepsy therapy. Drugs Today (Barc). 2008 May;44(5):353

Strittmatter F, Gandaglia G, Benigni F, et al. Expression of fatty acid amide hydrolase (FAAH) in human, mouse, and rat urinary bladder and effects by FAAH inhibition on bladder function in awake rats. Eur Urol 2012;61:98–106.

Suckling J, Lethaby An, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 2003; (4) CD001500

Sugiyama Y, Yoshida M, Masunaga K et al. Pharmacological effects of propiverine and its active metabolite, M-1, on isolated human urinary bladder smooth muscle, and on bladder contraction in rats. Int J Urol. 2008 Jan;15(1):76

Sultana CJ, Walters MD. Estrogen and urinary incontinence in women. Maturitas 1990;20:129

Sundin T, Dahlström A, Norlén L, Svedmyr N. The sympathetic innervation and adrenoreceptor function of the human lower urinary tract in the normal state and after parasympathetic denervation. Invest Urol. 1977 Jan;14(4):322-8.

Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). Curr Med Res Opin 2002;18 (4):177

Swart PJ, Krauwinkel WJ, Smulders RA et al. Pharmacokinetic effect of ketoconazole on solifenacin in healthy volunteers. Basic Clin Pharmacol Toxicol. 2006 Jul;99(1):33.

Swithinbank LV, Vestey S, Abrams P. Nocturnal polyuria in community-dwelling women. BJU Int. 2004 Mar;93(4):523-7.

Swierzewski SJ 3rd, Gormley EA, Belville WD, Sweetser PM, Wan J, McGuire EJ. The effect of terazosin on bladder function in the spinal cord injured patient. J Urol. 1994 Apr;151(4):951-4.

Szonyi G, Collas DM, Ding YY et al. Oxybutynin with bladder retraining for detrusor instability in elderly people: a randomized controlled trial. Age Aging, 1995;24:287

Szollar SM, Lee SM. Intravesical oxybutynin for spinal cord injury patients. Spinal Cord, 1996;34:284

Tadic SD, Griffiths D, Schaefer W et al. Abnormal connections in the supraspinal bladder control network in women with urge urinary incontinence. Neuroimage 2008 Feb 15;39(4):1647-53.

Takasu T, Ukai M, Sato S et al. Effect of (R)-2-(2-aminothiazol-4-yl)-4'-{2-[(2-hydroxy-2-phenylethyl)amino]ethyl} acetanilide (YM178), a novel selective beta3-adrenoceptor agonist, on bladder function. J Pharmacol Exp Ther. 2007 May;321(2):642

Takao T, Tsujimura A, Yamamoto K, et al. Solifenacin may improve sleep quality in patients with overactive bladder and sleep disturbance. Urology. 2011 Sep;78(3):648-52. Epub 2011 Jun 15.

Take H, Shibata K, Awaji T, et al. Vascular alpha1-adrenoceptor subtype selectivity and alpha1-blocker-induced orthostatic hypotension. Jpn J Pharmacol. 1998 May;77(1):61-70

Takeda M, Obara K, Mizusawa T et al. Evidence for beta3-adrenoceptor subtypes in relaxation of the human urinary bladder detrusor: analysis by molecular biological and pharmacological methods. J Pharmacol Exp Ther. 1999 Mar;288(3):1367

Takeda H, Yamazaki Y, Igawa Y et al. Effects of beta(3)-adrenoceptor stimulation on prostaglandin E(2)-induced bladder hyper-

activity and on the cardiovascular system in conscious rats. Neurourol Urodyn. 2002;21(6):558

Takusagawa S, van Lier JJ, Suzuki K, Nagata M. Absorption, Metabolism and Excretion of [14C]Mirabegron (YM178), a Potent and Selective β3-Adrenoceptor Agonist, after Oral Administration to Healthy Male Volunteers. Drug Metab Dispos. 2012 Jan 23. [Epub ahead of print]

Tamimi NA, Mincik I, Haughie S. et al. A placebo-controlled study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with lower urinary tract symptoms associated with clinical benign prostatic hyperplasia. BJU Int 2010;106:674-680.

Tanaka Y, Masumori N, Tsukamoto T. Urodynamic effects of solifenacin in untreated female patients with symptomatic overactive bladder. Int J Urol. 2010 Sep;17(9):796-800.

Tanaka M, Sasaki Y, Kimura Y et al. A novel pyrrole derivative, NS-8, suppresses the rat micturition reflex by inhibiting afferent pelvic nerve activity. BJU Int 2003; 92: 1031

Tatemichi S, Tomiyama Y, Maruyama I, et al. Uroselectivity in male dogs of silodosin (KMD-3213), a novel drug for the obstructive component of benign prostatic hyperplasia. Neurourol Urodyn. 2006;25(7):792-9;

Tatemichi S, Akiyama K, Kobayashi M, et al. A selective alpha1A-adrenoceptor antagonist inhibits detrusor overactivity in a rat model of benign prostatic hyperplasia. J Urol. 2006 Sep;176(3):1236-41.

Taylor MC, Bates CP, A double-blind crossover trial of baclofen--a new treatment for the unstable bladder syndrome. Br J Urol. 1979 Dec;51(6):504

The Montreal Cognitive Assessment homepage. Accessed at http://www.mocatest.org on June 4, 2008

Thor KB, de Groat WC. Neural control of the female urethral and rhabdosphincteris and pelvic floor muscles. Am J Physiol Regul Integr Comp Physiol 2010;299(2):R416-438

Thor K, Katofiasc MA. Effects of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, on central neural control of lower urinary tract function in the chloralose-anesthetized female cat. J Pharmacol Exp Ther 1995;274(2):1014

Thor K, Kirby M, Viktrup L. Serotonin and noradrenaline involvement in urinary incontinence, depression and pain: scientific basis for overlapping clinical efficacy from a single drug. Int J Clinical Practice 2007;61(8):1349-1355

Thumfart J, Roehr CC, Kapelari K, et al. Desmopressin associated symptomatic hyponatremic hypervolemia in children. Are there predictive factors? J Urol. 2005 Jul;174(1):294-8; discussion 298.

Thüroff JW, Bunke B, Ebner A et al. Randomized, double-blind, multicenter trial on treatment of frequency, urgency and incontinence related to detrusor hyperactivity: oxybutynin versus propantheline vesus placebo. J Urol, 1991;145:813

Thüroff JW, Chartier-Kastler E, Corcus J, et al. Medical treatment and medical side effects in urinary incontinence in the elderly. World J Urol. 1998;16 Suppl 1:S48-61.

Tincello DG, Kenyon S, Abrams KR, et al. Botulinum Toxin A Versus Placebo for Refractory Detrusor Overactivity in Women: A Randomised Blinded Placebo-Controlled Trial of 240 Women (the RELAX Study). Eur Urol. 2012 Jan 5.

Tiwari A.. Elocalcitol, a vitamin D3 analog for the potential treatment of benign prostatic hyperplasia, overactive bladder and male infertility. IDrugs. 2009 Jun;12(6):381-93.

Todorova A, Vonderheid-Guth B, Dimpfel W. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. J Clin Pharmacol 2001;41(6):636

Toglia MR, Serels SR, Laramée C, et al. Solifenacin for overactive bladder: patient-reported outcomes from a large placebo-controlled trial. Postgrad Med. 2009 Sep;121(5):151-8.

Tokuno H, Chowdhury JU, Tomita T. Inhibitory effects of propiverine on rat and guinea-pig urinary bladder muscle. Naunyn-Schmiedeberg´s Arch Pharmacol, 1993;348:659

Tominaga M, Caterina MJ, Malmberg AB, et al. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron. 1998 Sep;21(3):531-43.

Truss MC, Stief CG, Uckert S et al. Initial clinical experience with the selective phosphodiesterase-I isoenzyme inhibitor vinpocetine in the treatment of urge incontinence and low compliance bladder. World J Urol 2000;18:439

Truss MC, Stief CG, Uckert S et al. Phosphodiesterase 1 inhibition in the treatment of lower urinary tract dysfunction: from bench to bedside. World J Urol 2001;19:344

Tsakiris P, de la Rosette JJ, Michel M et al. Pharmacologic treatment of male stress urinary incontinence: systemic review of the literature and levels of evidence. European Urology 2008;53:53-59

Tsao JW, Heilman KM. Transient memory impairment and hallucinations associated with tolterodine use. N Engl J Med 2003;349:2274

Tseng LH, Wang AC, Chang YL, et al. Randomised comparison of tolterodine with vaginal oestrogen cream versus tolterodine alone for the treatment of postmenopausal women with overactive bladder syndrome. Neurourol Urodyn 2009 28 (1) 47-51

Tuncel A, Nalcacioglu V, Ener K et al. Sildenafil citrate and tamsulosin combination is not superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. World J Urol 2010;28:17-22.

Tyagi V, Philips BJ, Su R, et al. Differential expression of functional cannabinoid receptors in human bladder detrusor and urothelium. J Urol 2009;181:1932–8.

Tyagi P, Tyagi V. Mirabegron, a Beta3-adrenoceptor agonist for the potential treatment of urinary frequency, urinary incontinence or urgency associated with overactive bladder. IDrugs 2010: 13: 713-722

Uchida H, Shishido K, Nomiya M et al. Involvement of cyclic AMP-dependent and -independent mechanisms in the relaxation of rat detrusor muscle via beta-adrenoceptors. Eur J Pharmacol. 2005 Aug 22;518(2-3):195

Uckert S, Hedlund P, Andersson KE, et al. Update on phosphodiesterase (PDE) isoenzymes as pharmacologic targets in urology: present and future. Eur Urol. 2006 Dec;50(6):1194-207

Uckert S, Kuthe A, Jonas U et al. Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. J Urol 2001;166:2484

Uckert S, Stief CG, Odenthal KP et al. Responses of isolated normal human detrusor muscle to various spasmolytic drugs commonly used in the treatment of the overactive bladder. Arzneimittelforschung, 2000;50(5):456

Uusvaara J, Pitkala KH, Kautiainen H, et al. Association of anticholinergic drugs with hospitalization and mortality among older cardiovascular patients: A prospective study. Drugs Aging 2011;28:131-8.

Valiquette G, Herbert J, Maede-D'Alisera P. Desmopressin in the management of nocturia in patients with multiple sclerosis. A double-blind, crossover trial. Arch Neurol 1996;53:1270

Vande Walle JGJ, Bogaert GA, Mattsson S et al. A new fast-melting oral formulation of desmopressin: a pharmacodynamic study in children with primary nocturnal enuresis. BJU Int 2006;97:603

Van de Walle J, Van Herzeele C, Raes A.Is there still a role for desmopressin in children with primary monosymptomatic nocturnal enuresis?: a focus on safety issues. Drug Saf. 2010 Apr 1;33(4):261-71.

van Gelderen EM, Li Q, Meijer J, et al. An exploratory comparison of the single dose pharmacokinetics of the beta3-adrenoceptor agonist mirabegron in healthy CYP2D6 poor and extensive metabolizers. Clin Pharmacol Ther. 2009;85:S88.

Van Kerrebroeck P, Abrams P, Lange R et al. Duloxetine vs. placebo in the treatment of European and Canadian women with stress urinary incontinence. Br J Obstet Gynaecol 2004;111:249

Van Kerrebroeck P, Kreder K, Jonas U et al. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. Urology, 2001;57(3):414

van Kerrebroeck P, Rezapour M, Cortesse A et al. Desmopressin in the treatment of nocturia: a double-blind, placebo-controlled study. Eur Urol 2007;52:221

van Leeuwen J, Lange R, Jonasson A, et al. Efficacy & safety in elderly women with stress urinary incontinence or stress predominant mixed urinary incontinence. Maturitas 2008;60(2):138-147

van Rey F, Heesakkers J. Solifenacin in multiple sclerosis patients with overactive bladder: a prospective study. Adv Urol. 2011;2011:834753. Epub 2011 May 5.

Vardy MD, Mitcheson HD, Samuels TA, et al. Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient-reported outcomes: results from VIBRANT - a double-blind, placebo-controlled trial. Int J Clin Pract. 2009 Dec;63(12):1702-14.

Vaughan CP, Johnson TM 2nd, Ala-Lipasti MA, et al. The prevalence of clinically meaningful overactive bladder: bother and quality of life results from the population-based FINNO study. Eur Urol. 2011 Apr;59(4):629-36.

Vella M, Duckett J, Basu M. Duloxetine 1 year on: the long term outcome of a cohort of women prescribed duloxetine. Int Urogynecol J Pelvic Floor Dysfunct 2008;19(7):961-964

Vemulakonda VM, Somogyi GT, Kiss S, et al. Inhibitory effect of intravesically applied botulinum toxin A in chronic bladder inflammation. J Urol. 2005 Feb;173(2):621-4.

Versi E, Appell R, Mobley D et al. Dry mouth with conventional and controlled-release oxybutynin in urinary incontinence. The Ditropan XL Study Group. Obstet Gynecol, 2000;95(5):718-721

Versi E, Cardozo LD. Urethral instability: diagnosis based on variations in the maximum urethral pressure in normal climacteric women. Neurourol Urodynamics 1986;5(6):535

Vijaya G, Digesu GA, Derpapas A, et al. Antimuscarinic effects on current perception threshold: a prospective placebo control study. Neurourol Urodyn. 2012 Jan;31(1):75-9.

Visco AG, Brubaker L, Richter HE, et al.; Pelvic Floor Disorders Network. Anticholinergic versus botulinum toxin A comparison trial for the treatment of bothersome urge urinary incontinence: ABC trial. Contemp Clin Trials. 2012 Jan;33(1):184-96.

Wada N, Watanabe M, Kita M, et al. Efficacy and safety of propiverine and solifenacin for the treatment of female patients with overactive bladder: a crossover study. LUTS 2011;3:36-42

Waetjen LE, Brown JS, Modelska K et al. Effect of raloxifene on urinary incontinence: a randomized controlled trial. Obstet Gynaecol 2004;103(2)261

Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. BJU Int. 2012 Mar 12. doi: 10.1111/j.1464-410X.2012.11023.x. [Epub ahead of print]

Wagg A, Verdejo C, Molander U. Review of cognitive impairment with antimuscarinic agents in elderly patients with overactive bladder. Int J Clin Pract 2010;64:1279-1286.

Wagg A, Wyndaele JJ, Sieber P. Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: a pooled analysis. Am J Geriatr Pharmacother. 2006 Mar;4(1):14

Wang CJ, Lin YN, Huang SW, Chang CH. Low dose oral desmopressin for nocturnal polyuria in patients with benign prostatic hyperplasia: a double-blind, placebo controlled, randomized study. J Urol. 2011 Jan;185(1):219-23.

Walczak JS, Cervero F. Local activation of cannabinoid CB1 receptors in the urinary bladder reduces the inflammation-induced sensitization of bladder afferents. Mol Pain 2011;7:31–42.

Waldeck K, Larsson B, Andersson K-E. Comparison of oxybutynin and its active metabolite, N-desethyl-oxybutynin, in the human detrusor and parotid gland. J Urol, 1997;157:1093

Walter P, Grosse J, Bihr AM et al. Bioavailability of trospium chloride after intravesical instillation in patients with neurogenic lower urinary tract dysfunction: A pilot study. Neurourol Urodyn. 1999;18(5):447-53.

Walter R, Ullmann C, Thummler et al. Influence of propiverine on hepatic microsomal cytochrome p450 enzymes in male rats. Drug Metab Dispos 2003;31(6):714

Wammack R, Weihe, E., Dienes, H.-P., and Hohenfellner, R. Die Neurogene Blase in vitro. Akt Urol, 1995;26:16

Wang, X., Momota, Y., Yanase, H., Narumiya, S., Maruyama, T., Kawatani, M. Urothelium EP1 receptor facilitates the micturition reflex in mice. Biomed Res 2008;29, 105-111.

Watanabe JH, Campbell JD, Ravelo A, et al. Cost analysis of interventions for antimuscarinic refractory patients with overactive bladder. Urology. 2010 Oct;76(4):835-40.

Weatherall M. The risk of hyponatremia in older adults using desmopressin for nocturia: a systematic review and meta-analysis. Neurourol Urodyn 2004;23(4):302

Wefer B, Ehlken B, Bremer J, et al. Treatment outcomes and resource use of patients with neurogenic detrusor overactivity receiving botulinum toxin A (BOTOX) therapy in Germany. World J Urol. 2010 Jun;28(3):385-90.

Wegener JW, Schulla V, Lee T-S, et al. An essential role of CaV1.2 L-type calcium channel for urinary bladder function. FASEB J 2004; 18: 1159

Wegener JW, Schulla V, Lee T-S, et al. An essential role of CaV1.2 L-type calcium channel for urinary bladder function. FASEB J 2004; 18: 1159

Wehnert J, Sage S. Comparative investigations to the action of Mictonorm (propiverin hydrochloride) and Spasuret (flavoxat hydrochloride) on detrusor vesicae. Z Urol Nephrol, 1989;82:259

Wehnert J, Sage S. Therapie der Blaseninstabilität und Urge-Inkontinenz mit Propiverin hydrochlorid (Mictonorm®) und Oxybutynin chlorid (Dridase®) - eine randomisierte Crossover- Vergleichsstudie. Akt Urol, 1992;23:7

Weil EH, Eerdmans PH, Dijkman GA et al. Randomized double-blind placebo controlled multicenter evaluation of efficacy and dose finding of midodrine hydrochloride in women with mild to moderate stress urinary incontinence: a phase II study. Int Urogynecol J Pelvic Floor Dysfunct 1998;9(3):145

Wein AJ. Pathophysiology and classification of lower urinary tract dysfunction. In, Wein, AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA (eds): Campbell-Walsh Urology, tenth Edition, volume 3, Elsevier Saunders, pp. 1834-1846, 2012

Wein AJ, Dmochoski RR. Neuromuscular dysfunction of the lower urinary tract. In, Wein, AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA (eds): Campbell-Walsh Urology, tenth Edition, volume 3, Elsevier Saunders, pp 1909-1946

Weiss JP, van Kerrebroeck PE, Klein BM, Nørgaard JP. Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia. J Urol. 2011b Oct;186(4):1358-63.

Weiss JP, Blaivas J, Bliwise D, et al. The Evaluation and Treatment of Nocturia: A Consensus Statement. BJU Int 2011a;108(1):6-21

Werkström V, Persson K, Ny L et al. Factors involved in the relaxation of female pig urethra evoked by electrical field stimulation. Br J Pharmacol 1995;116:1599

Werkström V, Svensson A, Andersson KE et al. Phosphodiesterase 5 in the female pig and human urethra: morphological and functional aspects. BJU Int. 2006 Aug;98(2):414

Wesnes KA, Edgar C, Tretter RN, Bolodeoku J. Exploratory pilot study assessing the risk of cognitive impairment or sedation in the elderly following single doses of solifenacin 10 mg. Expert Opin Drug Saf. 2009;8(6):615-626.

White WM, Pickens RB, Doggweiler R, Klein FA. Short-term efficacy of botulinum toxin a for refractory overactive bladder in the elderly population. J Urol. 2008 Dec;180(6):2522-6. Wiedemann A, Füsgen I, Hauri D. New aspects of therapy with trospium chloride for urge incontinence. Eur J Geriatrics 2002;3:41

Williams SG, Staudenmeier J. Hallucinations with tolterodine. Psychiatr Serv 2004;55:1318

Wiseman OJ, Fowler CJ, Landon DN. The role of the human bladder lamina propria myofibroblast. BJU Int. 2003 Jan;91(1):89-93.

Womack KB, Heilman KM. Tolterodine and memory: dry but forgetful. Arch Neurol 2003;60:771

Woods M, Carson N, Norton NW et al. Efficacy of the beta3-adrenergic receptor agonist CL-316243 on experimental bladder hyperreflexia and detrusor instability in the rat. J Urol. 2001 Sep;166(3):1142

Wuest M, Hiller N, Braeter M et al. Contribution of Ca2+ influx to carbachol-induced detrusor contraction is different in human urinary bladder compared to pig and mouse. Eur J Pharmacol 2007; 565: 180

Wuest M, Kaden S, Hakenberg OW et al. Effect of rilmakalim on detrusor contraction in the presence and absence of urothelium. Naunyn-Schmiedeberg's Arch Pharmacol 2005; 372:203.

Wuest M, Weiss A, Waelbroeck M et al. Propiverine and metabolites: differences in binding to muscarinic receptors and in functional models of detrusor contraction. Naunyn Schmiedebergs Arch Pharmacol. 2006 Nov;374(2):87

Wyndaele JJ, Goldfischer ER, Morrow JD, et al. Effects of flexible-dose fesoterodine on overactive bladder symptoms and treatment satisfaction: an open-label study. Int J Clin Pract. 2009 Apr;63(4):560-7.

Wyndaele JJ, Van Dromme SA, Muscular weakness as side effect of botulinum toxin injection for neurogenic detrusor overactivity. Spinal Cord. 2002 Nov;40(11):599

Yamada S, Seki M, Ogoda M, et al. Selective binding of bladder muscarinic receptors in relation to the pharmacokinetics of a novel antimuscarinic agent, imidafenacin, to treat overactive bladder. J Pharmacol Exp Ther. 2011 Feb;336(2):365-71.

Yamaguchi O, Marui E, Kakizaki H et al. Randomized, double-blind, placebo- and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder. BJU Int. 2007 Sep;100(3):579

Yamanishi T, Mizuno T, Tatsumiya K, et al. 2009. Urodynamic effects of silodosin, a new alpha 1A-adrenoceptor selective antagonist, for the treatment of benign prostatic hyperplasia. Neurourol Urodyn 2009;29: 558-562

Yaminishi T, Yasuda K, Tojo M et al. Effects of beta-2 stimulants on contractility and fatigue of canine urethral sphincter. J Urol 1994;151:1073

Yarker YE, Goa KL, Fitton A. Oxybutynin - A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. Drugs Aging, 1995;6:243

Yashiro K, Thor K, Burgard E. Properties of urethral rhabdosphincter motoneurons and their regulation by noradrenaline. J Physiol 2010;588(Pt 24);4951-4967

Yasuda K, Kawabe K, Takimoto Y et al. A double blind clinical trial of a beta-2 adrenergic agonist in stress incontinence. Int. Urogynecol J, 1993;4:146

Yokoyama, T., Uematsu, K., Watanabe, T et al. Naftopidil and propiverine hydrochloride for treatment of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia and concomitant overactive bladder: a prospective randomized controlled study. Scand J Urol Nephrol 2009;43:307-314.

Yokoyama O, Yamaguchi O, Kakizaki H, et al. Efficacy of solifenacin on nocturia in Japanese patients with overactive bladder: impact on sleep evaluated by bladder diary. J Urol. 2011 Jul;186(1):170-4.

Yoo DS, Han JY, Lee KS, Choo MS. Prescription pattern of oxybutynin ER in patients with overactive bladder in real life practice: a multicentre, open-label, prospective observational study. Int J Clin Pract. 2012 Feb;66(2):132-8.

Young JS, Matharu R, Carew MA, Fry CH. Inhibition of stretching-evoked ATP release from bladder mucosa by anticholinergic agents. BJU Int. 2012 Feb 28. doi: 10.1111/j.1464-410X.2012.10966.x. [Epub ahead of print]

Yoshida M, Homma Y, Inadome A et al. Age-related changes in cholinergic and purinergic neurotransmission in human isolated bladder smooth muscles. Exp Gerontol 2001;36(1):99

Yoshida M, Homma Y, Kawabe K. Silodosin, a novel selective alpha 1A-adrenoceptor selective antagonist for the treatment of benign prostatic hyperplasia. Expert Opin Investig Drugs. 2007 Dec;16(12):1955-65.

Yoshida M, Inadome A, Maeda Y et al. Non-neuronal cholinergic system in human bladder urothelium. Urology. 2006 Feb;67(2):425

Yoshida M, Masunaga K, Satoji Y et al. Basic and clinical aspects of non-neuronal acetylcholine: expression of non-neuronal acetylcholine in urothelium and its clinical significance. J Pharmacol Sci. 2008 Feb;106(2):193

Yoshida M, Miyamae K, Iwashita H et al. Management of detrusor dysfunction in the elderly: changes in acetylcholine and adenosine triphosphate release during aging. Urology. 2004 Mar;63(3 Suppl 1):17

Yoshida M, Kudoh J, Homma Y, Kawabe K. Safety and efficacy of silodosin for the treatment of benign prostatic hyperplasia. Clin Interv Aging. 2011;6:161-72.

Yossepowitch O, Gillon G, Baniel J et al. The effect of cholinergic enhancement during filling cystometry: can edrophonium chloride be used as a provocative test for overactive bladder? J Urol. 2001 May;165(5):1441

Yoong HF, Sundaram MB, Aida Z. Prevalence of nocturnal polyuria in patients with benign prostatic hyperplasia. Med J Malaysia. 2005 Aug;60(3):294-6.

Zahariou A, Karagiannis G, Papaionnou P et al. The use of desmopressin in the management of nocturnal enuresis in patients with spinal cord injury. Eura Medicophys 2007;43:333

Zaitsu M, Mikami K, Ishida N, Takeuchi T. Comparative Evaluation of the Safety and Efficacy of Long-Term Use of Imidafenacin and Solifenacin in Patients with Overactive Bladder: A Prospective, Open, Randomized, Parallel-Group Trial (the LIST Study). Adv Urol. 2011;2011:854697.

Zakrzewski-Jakubiak H, Doan J, Lamoureux P, et al. Detection and prevention of drug-drug interactions in the hospitalized elderly: utility of new cytochrome p450-based software. Am J Geriatr Pharmacother 2011;9(6):461-70.

Zarghooni S, Wunsch J, Bodenbenner M et al. Expression of muscarinic and nicotinic acetylcholine receptors in the mouse urothelium. Life Sci 2007;80:2308

Zhu HL, Brain KL, Aishima M et al. Actions of two main metabolites of propiverine (M-1 and M-2) on voltage-dependent L-type Ca2+ currents and Ca2+ transients in murine urinary bladder myocytes. J Pharmacol Exp Ther. 2008 Jan;324(1):118

Zinner NR, Dmochowski RR, Staskin DR, et al. Once-daily trospium chloride 60 mg extended-release provides effective, long-term relief of overactive bladder syndrome symptoms. Neurourol Urodyn. 2011 Sep;30(7):1214-9.

Zinner N, Gittelman M, Harris R et al. Trospium Study Group. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. J Urol 2004a;171(6 Pt 1):2311

Zinner NR, Mattiasson A, Stanton SL. Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. J Am Geriatr Soc 1002;50(5):799

Zinner N, Susset J, Gittelman M et al. Efficacy, tolerability and safety of darifenacin, an M(3) selective receptor antagonist: an investigation of warning time in patients with OAB. Int J Clin Pract. 2006 Jan;60(1): 119.dorsal horn; VH = ventral horn; LF = lateral funiculus; ACh = acetylcholine.

Committee 9

Diagnosis and Management of Urinary Incontinence in Childhood

Chair

Rien Nijman (The Netherlands)

Members

Serdar Tekgul (Turkey)

Janet Chase (Australia)

An Bael (Belgium)

Paul Austin (USA)

Alexander von Gontard (Germany)

CONTENTS

A. Introduction

I. NORMAL DEVELOPMENT OF BLADDER AND SPHINCTER CONTROL

II. NORMAL VALUES

B. Evaluation in children who wet

I. HISTORY TAKING

II. PHYSICAL EXAMINATION

III. URINALYSIS

IV. NON-INVASIVE DIAGNOSTIC TECHNIQUES

V. CLASSIFICATION SCHEME OF URINARY INCONTINENCE IN CHILDREN

C. Nocturnal enuresis

I. DEFINITION

II. SEVERITY

III. PREVALENCE

IV. INHERITANCE

V. GENDER AND MONOSYMPTOMATIC NE

VI. CLASSIFICATION

VII. PATHOPHYSIOLOGY OF MONO-SYMPTOMATIC NE

VIII. TREATMENT OF NOCTURNAL ENURESIS

D. Children with both day and night time incontinence

I. PREVELANCE

II. INTRODUCTION TO CLINICAL ASSESSMENT

III. CONFOUNDING FACTORS: LOWER URINARY TRACT DYSFUNCTION, RECURRENT URINARY TRACT INFECTION AND VESICOURETERIC REFLUX (VUR)

IV. CLASSIFICATION

V. PRINCIPLES OF NON PHARMACOLOGICAL TREATMENT FOR ALL DIFFERENT STATES

VI. PHARMACOLOGICAL TREATMENT

VII. CONCLUSION CHILDREN WITH BOTH DAY AND NIGHT TIME INCONTINENCE

E. Neurogenic detrusor-sphincter dysfunction

I. INTRODUCTION

II. PRESENTATION OF NEUROGENIC DETRUSOR SPHINCTER DYSFUNCTION IN CHILDREN

III. CLASSIFICATION: PATTERN RECOGNITION

IV. MANAGEMENT

F. Surgical management of urinary incontinence in children

I. ABNORMALITIES OF STORAGE

II. ABNORMALITIES OF SPHINCTERIC FUNCTION

III. BYPASS OF SPHINCTERIC MECHANISM

IV. EVALUATION AND DIAGNOSIS

V. INDICATIONS FOR SURGICAL PROCEDURES TO CORRECT URINARY INCONTINENCE

VI. BLADDER RESERVOIR CONSTRUCTION

VII. BLADDER OUTLET SURGERY

VIII. COMPLICATIONS OF CONTINENCE SURGERY IN CHILDREN

IX. CONSENSUS STATEMENT ON SURGICAL TREATMENT OF URINARY INCONTINENCE IN CHILDREN

G. Psychological aspects of urinary incontinence, enuresis and faecal incontinence

I. INTRODUCTION

II. CLINICAL BEHAVIOURAL DISORDERS

III. CLINICAL BEHAVIORAL DISORDERS IN CHILDREN WITH ENURESIS AND URINARY INCONTINENCE

IV. CLINICAL BEHAVIORAL DISORDERS IN CHILDREN WITH FAECAL INCONTINENCE

V. SUBCLINICAL SIGNS AND SYMPTOMS OF WETTING CHILDREN

VI. GENERAL PRINCIPLES:

VII. CONCLUSION AND SUMMARY

REFERENCES

Diagnosis and Management of Urinary Incontinence in Childhood

Rien Nijman

Serdar Tekgul, Janet Chase, An Bael, Paul Austin,Alexander von Gontard

A. Introduction

In this chapter the diagnostic and treatment modalities of urinary incontinence in childhood will be discussed. In order to understand the pathophysiology of the most frequently encountered problems in children, the normal development of bladder and sphincter control will be discussed.

The underlying pathophysiology will be outlined and the specific investigations for children will be discussed. For general information on epidemiology and urodynamic investigations the respective chapters are to be consulted.

I. NORMAL DEVELOPMENT OF BLADDER AND SPHINCTER CONTROL

Normal bladder storage and voiding involve low-pressure and adequate bladder volume filling followed by a continuous detrusor contraction that results in bladder emptying, associated with adequate relaxation of the sphincter complex. This process requires normal sensation and normal bladder outlet resistance. The neurophysiological mechanisms involved in normal bladder storage and evacuation include a complex integration of sympathetic, parasympathetic and somatic innervations which is ultimately controlled by a complex interaction between spinal cord, brain stem, midbrain and higher cortical structures [1].

Achievement of urinary control is equally complex and as yet not fully understood: various developmental stages have been observed [2,3].

In newborns the bladder has been traditionally described as “uninhibited”, and it has been assumed that micturition occurs automatically by a simple spinal cord reflex, with little or no mediation by the higher neural centres. However, studies have indicated that even in full-term foetuses and newborns, micturition is modulated by higher centres and the previous notion that voiding is spontaneous and mediated by a simple spinal reflex is an oversimplification [4]. Foetal micturition seems to be a behavioural state-dependent event: intrauterine micturition is not randomly distributed between sleep and arousal, but occurs almost exclusively while the foetus is awake [4].

During the last trimester the intra-uterine urine production is much higher than in the postnatal period (30ml/hr) and the voiding frequency is approximately 30 times every 24 hours [5].

Immediately after birth voiding is very infrequent during the first few days of life. The first void may only take place after 12 to 24 hours. After the first week frequency increases rapidly and peaks at the age of 2 to 4 weeks to an average of once per hour. It then decreases and remains stable after 6 months to about 10 to 15 times per day. After the first year it decreases to 8 to 10 times per day, while voided volumes increase by three- to fourfold.

During the postnatal period, micturition control mechanisms undergo further changes and extensive modulation. Using ambulatory bladder monitoring techniques in conjunction with polysomnographic recordings it has been shown that even in newborns the bladder is normally quiescent and micturition does not occur during sleep[6].

This inhibition (or lack of facilitation) of detrusor contractions during sleep is also observed in infants with neurogenic bladder dysfunction who have marked detrusor overactivity while they are awake. In response to bladder distension during sleep, an infant nearly always exhibits clear electro-encephalographic evidence of cortical arousal, facial grimaces or limb movements, or actual awakening. Sleeping infants are always seen to wake up before the bladder contracts and voiding occurs. This arousal period may be transient and the infant may cry and move for a brief period before micturition and then shortly afterward go back to sleep. Because this wakening response is already well established in newborns, it follows that the control of micturition probably involves more complicated neural pathways and higher centres than has been appreciated. There is also strong evidence that a pronounced reorganisation of pre-existing synaptic connections and neural pathways

involved in bladder control occurs during the early postnatal period.

In newborns micturition occurs at frequent intervals and may have an intermittent pattern although bladder emptying efficiency is usually good. In over 80 percent of voids the bladder empties completely [7].

During infancy voiding pressures are much higher than in adults. It has also been noted that these pressures are higher in boys than in girls (mean pdet max of 118 vs. 75 cm H2O, respectively) [8,9].

These higher detrusor pressures decrease progressively with increasing age. In up to 70 percent of infants (up to the age of 3 years) with normal lower urinary tracts, intermittent patterns of voiding were observed. They tend to disappear with increasing age, and are thought to represent variations between individual infants in the maturation of detrusor and sphincteric co-ordination during the first 1 to 2 years of life. Videourodynamic studies have confirmed these findings [6,8,9,10,11].

Between the age of 1 and 2, conscious sensation of bladder filling develops. The ability to void or inhibit voiding voluntarily at any degree of bladder filling commonly develops in the second and third years of life. Central inhibition is crucial to obtain continence.

During the second and third year of life, there is progressive development towards a socially conscious continence and a more voluntary type of micturition control develops. The child becomes more aware of the sensation of bladder distension and the need to urinate, as well as social norms and embarrassment associated with urinary incontinence. Through an active learning process, the child acquires the ability to voluntarily inhibit and delay voiding until a socially convenient time, then actively initiate urination even when the bladder is not completely full, and allows urination to proceed to completion. During the first years of life, gradual development to an adult type of voluntary micturition control that conforms to the social norms depends on an intact nervous system, in addition to at least three other events occurring concomitantly:

- a progressive increase in functional storage capacity.
- maturation of function and control over the external urinary sphincter.
- and most importantly achievement of volitional control over the bladder-sphincteric unit so that the child can voluntarily initiate or inhibit a micturition reflex [12].

The final steps are usually achieved at the age of 3 to 4 years when most children have developed the adult pattern of urinary control and are dry both day and night. The child has learned to inhibit a micturition reflex and postpone voiding and voluntarily initiate micturition at socially acceptable and convenient times and places. This development is also dependent on behavioural learning and can be influenced by toilet training, which in turn depends on cognitive perception of the maturing urinary tract.

It is understandable that this series of complex events is highly susceptible to the development of various types of dysfunction. Various functional derangements of the bladder-sphincter-perineal complex may occur during this sophisticated course of early development of normal micturition control mechanisms. These acquired “functional” disorders overlap with other types of bladder functional disturbances that may have a more organic underlying pathophysiological basis.

II. NORMAL VALUES

1. NORMAL BLADDER CAPACITY

The bladder capacity increases during the first 8 years of life roughly with 30 ml per year, so with an average capacity of 30 ml in the neonatal period, a child’s bladder volume can be calculated as Y = 30 + 30 X, where Y = capacity in ml and X = age in years (**Figure 1**) [13].

Hjälmås described a linear correlation that could be used up to 12 years of age: in boys, Y = 24.8 X + 31.6, in girls Y = 22.6 X + 37.4, where Y is capacity in ml, and X is age in years [14].

It should be noted that these data were obtained during cystometric investigations. Cystometric capacity is generally less than normal bladder volumes. Obviously, the relation between age and bladder capacity is not linear for all ages, nor is the relation between body weight and bladder capacity [15].

Another formula to calculate bladder capacity in infants is: bladder capacity (ml) = 38 + (2.5 x age (mo)) [11].

Kaefer and co-workers demonstrated that a nonlinear model was the most accurate for the relation between age and bladder capacity, and they determined two practical linear equations:

Y = 2 X + 2 for children less than 2 years old, and Y = X/2+6 for those 2 years old or older; Y = capacity in ounces, X = age in years (**Figure. 2**) [16].

None of these formulas have been acquired from a population based study and do not reflect normal bladder capacity. Normal bladder capacity should be regarded as the maximum voided volume of urine and shows huge variation. Recent work of Rittig et al looked at Maximum Voided Volumes (MVV). 2836 daytime voids showed a reasonably good correlation with the Koff Formula, if first morning voids were neglected [17].

Girls were found to have a larger capacity than boys, but the rate of increase with age was not

significantly different between them. Data on 'normal' bladder capacity have been obtained in continent children undergoing cystography, with retrograde filling of the bladder.

Data obtained from the International Reflux Study indicate that there is not a linear relation between age and capacity and that there is a huge variability. (**Figure 3**) [18].

2. NORMAL VOIDING

The micturition frequency of the foetus during the last trimester is approximately 30 per 24 hours. It decreases to 12 during the first year of life, and after that it is gradually reduced to an average of 5±1 voidings per day [11, 16].

The normal range for the micturition frequency at age seven is 3 to 7 [19].

By age 12, the daily pattern of voiding includes 4-6 voids per day [20].

Mattson and Lindström emphasize the enormous variability of voiding frequencies in children: also in individual children, the weight-corrected diuresis could vary up to 10-fold [21].

3. NORMAL VOIDING PRESSURES

Bladder dynamics in children have demonstrated developmental changes with age. Detrusor pressures at voiding in children after the age of 2 years are similar to adults, with a mean maximum pressure of 66 cm H2O in boys, and 57 cm H2O in girls [22].

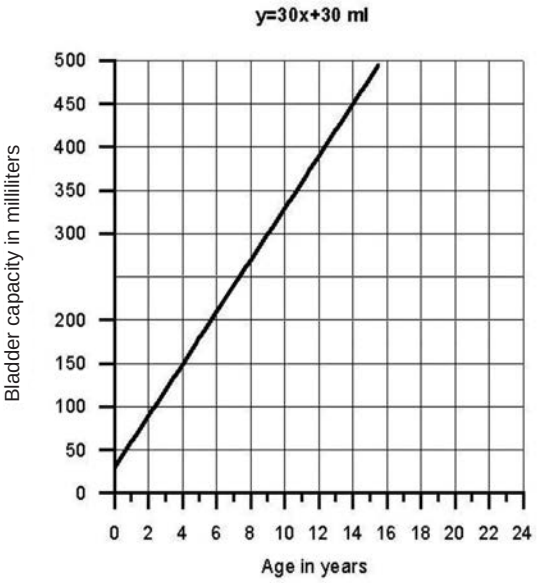


Figure 1: Bladder capacity using the formula
Y = 30 + 30X
(Y = capacity in ml, X=age in years)

These pressures are lower than those reported in infancy by Yeung et al, who found boys having pressures of 118 cm H2O and girls 75 cm H2O [6].

4. NORMAL URINARY FLOW RATES

Urinary flow rates in normal children have been only minimally described. Szabo et al published nomograms for flow rates vs. age in normal children [23].

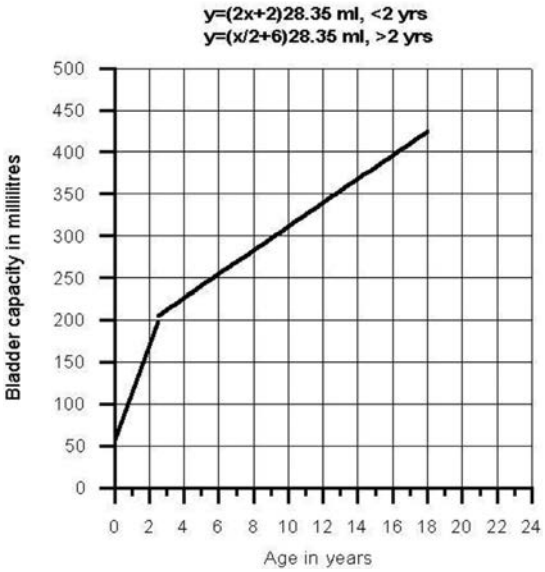


Figure 2: Bladder capacity using the formula
Y = (2X + 2) x 28.35ml < 2 years
Y = (X/2 + 6) x 28.35ml > 2 years
(Y = capacity in ml. X=age in years)

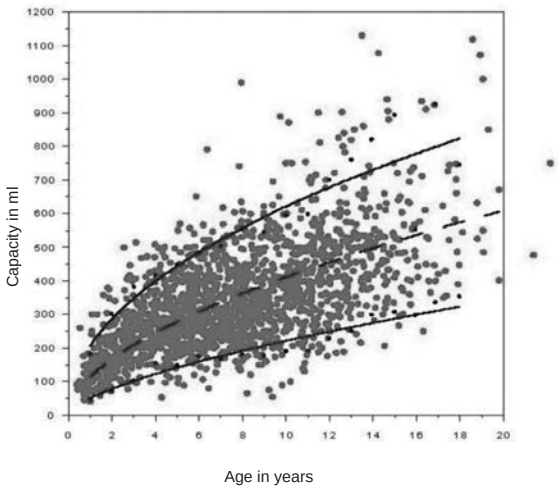


Figure 3: Bladder capacities determined by VCUG in the International Reflux Study.

As in adults, flow rates are clearly dependent upon voided volume, and normal values can only be applied to flow rates that have been registered when voiding at a bladder volume approximating the normal capacity for age [21,24].

B. Evaluation in children who wet

Even with clear definitions, the approach to history-taking and physical examination has to be structured. The child's complaints at presentation are not synonymous with the signs and symptoms that have to be checked to arrive at a diagnosis. Also, sociocultural aspects and psychomotor development will distort the presentation.

The International Children's Continence Society has provided two standardization documents on the diagnostic evaluation of children with daytime incontinence as well as on the evaluation of and treatment for monosymptomatic enuresis [1,2].

Standardization reports on urodynamic studies of the lower urinary and on initial diagnostic evaluation, follow-up and therapeutic intervention in congenital neurogenic bladder and bowel dysfunction in children will be available soon.

Validated questionnaires are very helpful in structuring the history-taking; they at least provide checklists [3].

With a structured approach the diagnosis of monosymptomatic nocturnal enuresis can be made with confidence.

When ultrasound imaging of kidneys and bladder, recording of urinary flow, and measurement of postvoid residual are added to history and physical examination, the clinical entities caused by functional disturbances of the bladder and sphincter mechanism (non-neurogenic detrusor and pelvic floor dysfunction) can be diagnosed accurately in the majority of cases, and a high level of suspicion can be maintained towards incomplete bladder emptying in both neurogenic pelvic floor dysfunction and structurally caused incontinence. This is important in view of the potential these conditions have to cause irreversible loss of kidney function.

In a minority of incontinent children the non-invasive assessment yields equivocal results, or results suggesting gross deviations from normal function. Only in these situations is there an indication for invasive investigations, such as:

- Voiding cystourethrography.
- Invasive urodynamics (cystometry, pressure/flow/EMG studies, videocystometry).
- Renal scans or intravenous urography.
- Cystourethroscopy.

I. HISTORY TAKING

For the paediatric age group, where the history is jointly obtained from parents and child, and where the failure to develop bladder control generates specific problems, a structured approach is recommended, with a questionnaire [3,4].

Level of evidence: 3.

Grade of recommendation: B

Many signs and symptoms related to voiding and wetting are new to the parents, and they should be specifically asked for, using the questionnaire as checklist. If possible the child should be addressed as the patient and questioned directly, as the symptoms prompting the parents to seek consultation may be different from those are problematic for the child.

A voiding diary is mandatory to determine the child's voiding frequency and voided volumes. Checklists and frequency volume chart can be filled out at home, and checked at the first visit to the clinics. History-taking should also include assessment of bowel function; a similar pro-active process using a questionnaire should be followed for defecation and faecal soiling [5].

The general history-taking should include questions relevant to familial disorders, neurological and congenital abnormalities, as well as information on previous urinary infections, relevant surgery and menstrual and sexual functions (in pubertal and older children). Information should be obtained on medication with known or possible effects on the lower urinary tract.

At times it is helpful to more formally evaluate the child's psychosocial status and the family situation, e.g. using validated question forms such as CBCL (Achenbach) or the Butler forms [6,7].

A short screening instrument for psychological problems in enuresis (SSIPPE) and a disease specific quality of life questionnaire for children with LUTD called PinQ are also validated tools available to the clinician [8,9].

Child abuse is very often signalled first by symptoms of vesico-urethral dysfunction [10].

At present there are no validated questionnaires to diagnose the cause of incontinence in children.

Level of evidence: 4.

Grade of recommendation: C

II. PHYSICAL EXAMINATION

Apart from a general paediatric examination, the physical examination should include the assessment of perineal sensation, the perineal reflexes supplied by the sacral segments S1-S4 (standing on toes, bulbocavernosus) and anal sphincter tone and control. Special attention should be paid to inspection of the male or female genital region, and of the urethral meatus. Asymmetry of buttocks, legs or feet, as well as other signs of occult neurospinal dysraphism in the lumbosacral area (subcutaneous lipoma, skin discoloration, hair growth and abnormal gait) should be looked for specifically [11].

In examining the abdomen for the presence of a full bladder, full sigmoid or descending colon which is a significant finding with a history of constipation.

Detailed questioning of the parents' observation of the child's voiding habits is essential as is direct observation of the voiding, if possible. Children may have their voiding dysfunction ameliorated or even eliminated by correcting anomalies of body position detected when observing the child's micturition. Children may void in awkward positions, e.g. with their legs crossed or balancing on the toilet without proper support of the legs, thereby preventing the pelvic floor relaxation and obstructing the free flow of urine [12] (**Figure 4**).

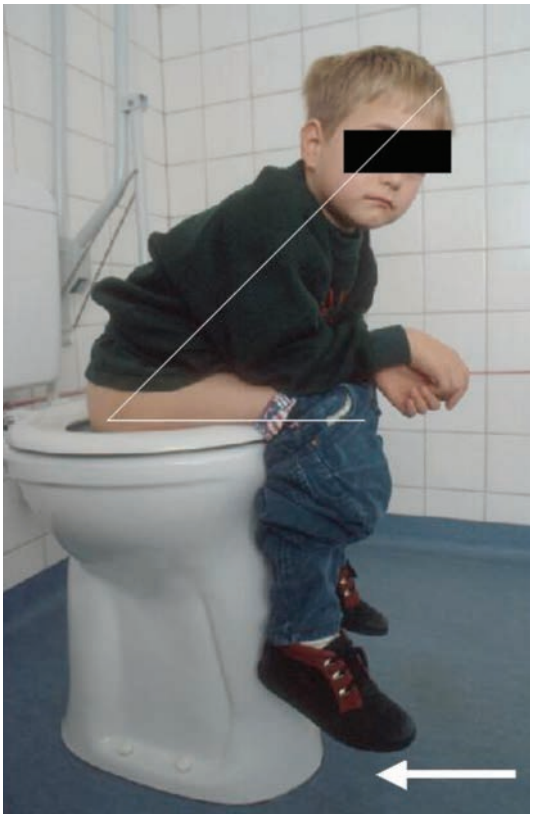


Figure 4: Improper position for voiding: the feet are not supported (unbalanced position) and the boy is bent forward. Support of the feet will correct this and will allow the pelvic floor muscles to relax properly.

Level of evidence: 4.

Grade of recommendation: D

III. URINALYSIS

In order to be comprehensive, physical examination should include urinalysis to identify patients with urinary tract infection, diabetes mellitus, diabetes insipidus and hypercalciuria if indicated [13].

IV. NON-INVASIVE DIAGNOSTIC TECHNIQUES

1. FREQUENCY / VOLUME CHARTS: BLADDER DIARY

The frequency/volume chart is a detailed diary recording each void by time and urine output over 24-hour periods. The chart gives objective information on the number of voidings, the distribution of day and night voids, along with the voided volumes and episodes of urgency and leakage, or dribbling. In order to obtain a complete picture, defecation frequency and/or soiling are often also recorded: Then, this becomes termed as bladder-bowel diary due to its complexity.

From the frequency/volume chart the child's "functional" bladder capacity may be assessed as the largest voided volume, with the exception of the morning micturition, which actually represents nighttime bladder capacity. Whenever possible, filling out the chart is the responsibility of the child: the parents provide assistance and support. Ideally the chart should cover 3 complete days, but in reality completion over a weekend restricts the record to 2 days.

The frequency volume chart is a reliable non-invasive measure of maximum bladder storage capacity and can be used as an outcome measure in children with bladder dysfunction if care is taken to minimise confounding factors and sources of error during chart completion [14].

The amount of urine voided by a non-supervised child during the day varies considerably since the child's voidings are dictated more by social circumstances and /or bladder activity rather than by

bladder capacity. Children with bladder symptoms void smaller volumes of urine than may be expected from traditional estimates [14].

This is unrelated to either gender, type of presenting incontinence or a positive family history of bladder dysfunction. The only significant influence upon voided volumes recorded on a frequency volume chart is the age effect, and voided volumes, even in incontinent children, increase incrementally with age. The frequency volume chart is useful when comparing the mean voided volume and standard deviation by a child's age 15,16].

Validation and test/retest data on frequency/volume charts whilst scarce indicate that voiding interval is the most variable parameter. Data in normal children and in children with different categories of incontinence are available for comparison [14,17,18].

In order to obtain a complete picture it is better to ask for a bladder diary: fluid intake as well as voiding frequency, voided volumes, incontinence episodes and defecation frequency and/or soiling are recorded.

Test/retest evaluation is not available; trend analyses of frequency/volume charts can be extracted from currently available data.

Level of evidence: 3.

Grade of recommendation: B

2. QUANTIFICATION OF URINE LOSS

Subjective grading of incontinence may not indicate reliably the degree of dysfunction. For objective grading, 12-hour pad test and frequency/volume charts are validated instruments [18-20]. One should be aware that children tend to do their utmost best when filling out diaries and doing padtests: underestimation is more the case than overestimation [21].

In children, the 12-hour pad test should also give information about fluid intake. The pad test is complementary to the bladder diary, which denotes more the frequency of incontinence and the distribution of wetting episodes than the quantities of urine lost.

The amount of urine lost during sleep can be determined by weighing diapers or absorbent pads, before and after sleep. To obtain a measure of the total nocturnal urine output, the volume of the early-morning voiding should be added to the amount lost during sleep.

3 SCORING SYSTEMS

At present three scoring systems, based on validated questionnaires have been described. Specific scores correlated with lower urinary tract dysfunction with a specificity and sensitivity of about 90% [22-24].

The value of these scoring systems to determine the cause of incontinence seems to be of limited value to the individual patient, but can be very useful in studies to determine and compare treatment outcome.

Level of evidence: 3.

Grade of recommendation: C

4. QUANTIFICATION OF CONSTIPATION

Scoring a plain X-ray of the abdomen (Barr score) yields inconsistent results in grading constipation. [17-19] Reproducibility seems to be best using the method described by Leech [28-30].

A better way to match clues from the medical history with signs and symptoms is the measurement of colonic transit time.

As many children with an overactive bladder habitually use their pelvic floor as an "emergency brake", anomalous defecation frequency and constipation have a high prevalence in this group.

Diagnosing constipation is important: we recommend to use the Rome III criteria listed in the table below [31].

A non-invasive way to determine fecal retention is the estimation of rectal diameter on ultrasound. In children without constipation the mean diameter was 2, 2.1 and 2.4 cm in three different studies respectively [32-34]. In children with constipation the rectal diameter was on average 3.4 cm in the first, 4.9 in the second and 4.2 cm in the third study, significantly different from the non-constipated children. Joensson et al. also re-measured constipated children 4 weeks after treatment with laxatives finding the rectal diameters in the constipation group were significantly reduced ($p < 0.001$) [34].

Finding a dilated and filled rectum on ultrasound while the child feels no need to defecate probably can replace a digital rectal examination.

Overt constipation should be dealt with before embarking on treatment of incontinence or bladder and pelvic floor dysfunction [35,36].

Level of evidence 3.

Grade of recommendation: B

5. URINARY FLOW

Voiding should be analysed in detail in all incontinent children with the exception of monosymptomatic bedwetting where voiding, as far as we know, is normal.

Graphic registration of the urinary flow rate during voiding is a standard office procedure. Flow

patterns and rates should be repeated to allow for evaluation, and several recordings are needed to obtain consistency.

Approximately 1% of school children have a voiding that can be labelled abnormal with flattened or intermittent flow curves. The remaining 99% have a bell-shaped flow curve [37]. It should be noted that a normal flow does not exclude a voiding disturbance, nor does an abnormal flow pattern automatically means a bladder or voiding dysfunction, as in asymptomatic normal schoolchildren abnormal patterns were also found [38,39].

Flow recordings with a voided volume of less than 50% of the functional capacity are not consistent: they represent voiding on command, and many children will try to comply by using abdominal pressure. On the other hand, overdistension of the bladder can result in abnormal uroflow recordings also [40].

A helpful tool in this respect is the use of transabdominal ultrasound (e.g. bladder scan) before micturition in order to assess the bladder volume [41,42]. If the bladder is still nearly empty the child should be asked to drink some water until the bladder is full enough for a reliable flow.

Urinary flow may be described in terms of rate and pattern and may be continuous, intermittent (in fractions), or staccato (fluctuating). An intermittent flow pattern shows a interrupted flow, whereas in staccato voiding the flow does not stop completely, but fluctuates due to incomplete relaxation of the sphincter.

Measurement of urinary flow is performed as a solitary procedure, with bladder filling by diuresis (spontaneous or forced), or as part of a pressure/flow study, with bladder filling by catheter. Patterns and rates should be consistent to allow for evaluation, and several recordings are needed to obtain consistency [43,44].

The same parameters used to characterise continuous flow may be applicable, if care is exercised, in children with intermittent, or staccato flow patterns (**Figure 5-8**). In measuring flow time, the time intervals between flow episodes are disregarded. Voiding time is total duration of micturition, including interruptions.

6. ULTRASOUND IMAGING OF UPPER AND LOWER URINARY TRACT

In most clinical settings, ultrasound-imaging techniques are routinely used in children with incontinence. Upper tract abnormalities such as duplex kidney, dilatation of the collecting system, and gross reflux nephropathy can be readily detected, but detection of the more subtle expressions of these abnormalities requires urological expertise on the part of the ultrasound operator [45].

Lower urinary tract abnormalities are even more difficult to assess for the inexperienced, aside from bladder wall thickness: a bladder wall cross-section of more than 3-4 millimetres, measured at 50% of expected bladder capacity, is suspicious of detrusor overactivity [46,47]. Because only a few studies have been conducted to compare bladder wall thickness in normal children without complaints and in children with lower urinary tract dysfunction, more studies need to be performed to validate these non-invasive techniques [48,49].

Another possibility is to assess bladder volume and bladder wall thickness to calculate the Bladder Volume / Bladder Wall Thickness index. In children with nocturnal enuresis this index correlated well with response to treatment [50].

Functional constipation

Must include ≥ *2* of the following in a child with a developmental age of ≥ *4* years with insufficient criteria for diagnosis of IBS:

- ≤ 2 defecations per week
- ≥ 1 episode of fecal incontinence per week
- History of retentive posturing or excessive volitiotnal stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large diameter stools that obstruct the toilet

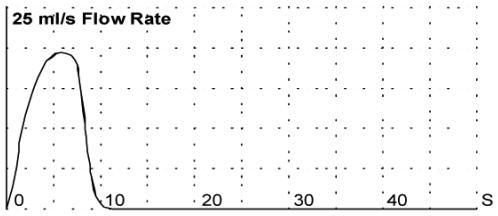
a) Post-void residual volume

Except in small infants, the normal bladder will empty completely at every micturition [51].

The identification or exclusion of post-void residual is therefore an integral part of the study of micturition. However, an uneasy child voiding in unfamiliar surroundings may yield unrepresentative results, as may voiding on command with a partially filled or overfilled bladder. When estimating residual urine, voided volume and the time interval between voiding and estimation of post-void residual should be recorded. This is of particular importance if the patient is in a diuretic phase. In patients with gross vesicoureteral reflux, urine from the ureters may enter the bladder immediately after micturition and may falsely be interpreted as residual urine. The absence of residual urine is an observation of clinical value, but does not exclude bladder outlet obstruction or sphincter / pelvic floor overactivity with absolute certainty. An isolated finding of residual urine requires confirmation before being considered significant, especially in infants and young children.

b) Ultrasound-flow-ultrasound

This combination of imaging and non-invasive urodynamics is a standardised procedure used to obtain representative data on flow rate and flow pattern, as well as post-void residual volumes.



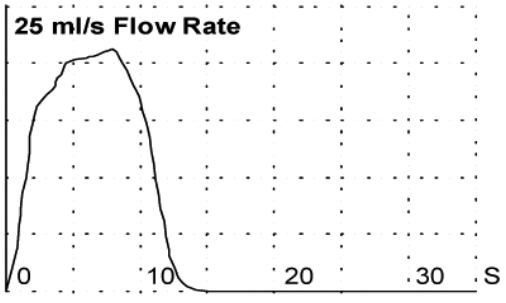


Figure 5: normal urinary flow curves of 2 childtren

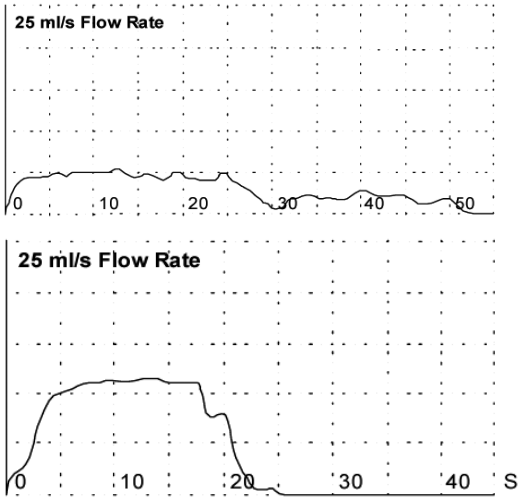


Figure 6: flow curves of 2 children with a static, anatomic obstruction; the curve is continuous but the flow is lower than normal and extended in time

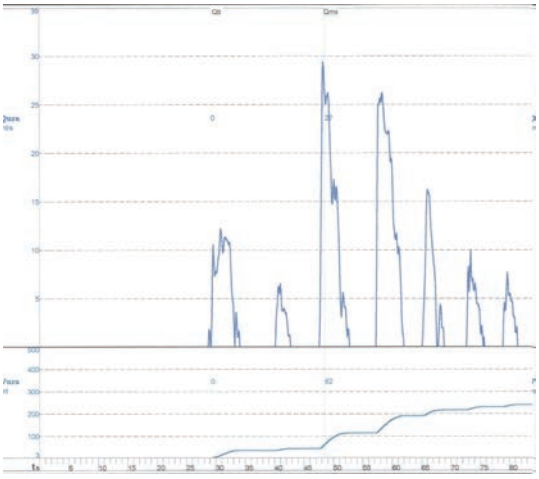


Figure 7: intermittent flow curve in a child voiding with abdominal straining

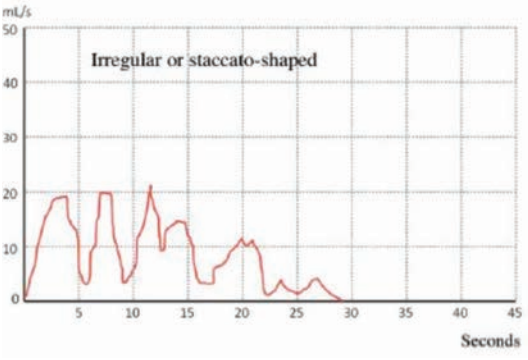


Figure 8: Staccato voiding in a child

With ultrasound, bladder filling is assessed and when the bladder capacity is equal to the functional or expected bladder capacity for age, the child is asked to void into the flowmeter. After recording the flow, post-void residual is assessed again.

This procedure avoids the registration of flow rates at unrealistic bladder volumes.

Alternatively children can be asked to use a flowmeter at home: a special flowmeter has been designed to use at home [52]. For those children who have difficulty voiding in a strange environment, this option can be useful.

7. INVASIVE DIAGNOSTIC TECHNIQUES

The important question (for the incontinent child) "whether invasive diagnostic procedures are necessary" is decided by the results of the non-invasive procedures.

At present there are no studies indicating that a VCUG is useful in children with incontinence, but without urinary tract infections.

In general urodynamic studies will only be done if the outcome will alter the management, and this will also depend on whether the possible treatments being considered are invasive. The diagnostic information needed is that which is necessary to find the correct treatment. Indicators include, straining or manual expression during voiding, a weak urinary stream, previous febrile urinary tract infection, continuous dribbling incontinence or pronounced apparent stress incontinence, or previously identified dilating vesicoureteral reflux.

The finding of genitourinary abnormalities or signs of occult spinal dysraphism at physical examination also indicate the need for further diagnostics. Urinary flow registration will detect the plateau-shaped flow curve typical for structural bladder outlet obstruction, and an intermittent flow suggesting detrusor –sphincter- pelvic floor dys-coordination [43].

A clinically significant post-void residual on repeated occasions clearly points to incomplete bladder emptying. The pad test will detect the cases with obvious stress and urgency incontinence, or continuous dribbling. Ultrasound imaging will raise suspicion of an ectopic ureter.

In short, invasive diagnostics are indicated when the non-invasive testing raises suspicion of neurogenic detrusor-sphincter dysfunction (occult spinal dysraphism), obstruction (especially posterior urethral valves), genitourinary abnormalities (e.g. epispadias), advanced non-neurogenic detrusor-sphincter- pelvic floor dysfunction (as in children with vesicoureteral reflux and upper tract dilatation and/or febrile urinary tract infections), or significant post void residuals.

To diagnose the complex of non-neurogenic detrusor-sphincter dysfunction, recurrent urinary tract infections and vesicoureteral reflux, urodynamic studies are needed in only a minority of all children.

a) Voiding Cystourethrogram

1. Technique of VCUG in children

Cleanse and rinse the external genitalia with lukewarm water: do not use detergents. Use a feeding tube with side holes and a rounded tip (Ch 06-08) or balloon catheter to catheterise the bladder; check the urine for infection. Empty the bladder completely before filling. Use a radio-opaque dye of maximum 30% concentration, at body temperature, and fill the bladder by slow-drip infusion, with a hydrostatic pressure of not more than 40 cm H2O. Note the volume of the contrast medium instilled. Use fluoroscopy during filling at regular intervals.

Take spot-films (70mm or 90mm camera) with the child in supine position, with partial filling and at the end of filling, in AP projection, of the complete urinary tract. Upper and lower tract should be visible.

When voiding is imminent, change the position of the child so that spot films of bladder and urethra in 3/4 projection can be taken during voiding. Also take a spot film of the upper urinary tract during voiding, as the degree of vesicoureteral reflux (VUR) may change with the pressure generated by the detrusor muscle during voiding. Post-void residual volumes vary very considerably with VCUG. The voiding phase is critically important to VCUG, both for reflux detection and for assessment of voiding dynamics. Without a voiding phase the VCUG is incomplete.

Prophylactic antibiotics are indicated in all children, to minimise the risk for post-VCUG urinary tract infection especially in children with an anatomic abnormality.

2. Indications for VCUG

A VCUG is an invasive procedure and should only be done if the outcome will influence the management. It is indicated in children with recurrent urinary tract infections in order to detect reflux, in children with a dilated system on ultrasound and in children with an abnormal flow pattern to detect bladder outlet abnormalities (like valves, strictures or a syringocele).

In children with incontinence the lateral projection during voiding is the most important part of the study. Especially in children with stress incontinence or a neurogenic bladder the position and configuration of the bladder neck during filling and voiding should be noted.

In children with non-neurogenic detrusor-sphincter- pelvic floor dysfunction as well as in children with neurogenic detrusor-sphincter dyssynergia, the proximal urethra may show the so-called 'spinning top' configuration, during filling and during voiding. With detrusor and pelvic floor muscles contracting at the same time, the force of the detrusor contraction will dilate the proximal urethra down to the level of the forcefully closed striated external sphincter. The resulting 'spinning top' configuration used to be seen as a sure sign of distal urethral stenosis, a concept held responsible for recurrent urinary tract infections in girls, with urethral dilatation or blind urethrotomy as the obvious therapy. However, urodynamics made it clear that the 'spinning top' will only appear when detrusor and pelvic floor contract synchronously, which makes it a functional anomaly, not an anatomical one [53,54].

Women often recall their experience with VCUG as young girls in terms bordering on abuse. The use of VCUG in children should be limited to the absolutely necessary.

b) (Video)-Urodynamics

In children urodynamic investigations should only be performed if the outcome will have consequences for treatment [55-57]. Furthermore like VCUG it may be considered when invasive or surgical interventions are planned. The main question is whether the urodynamic study will provide new information that cannot be obtained otherwise and will influence the further management. From the few studies that have addressed this issue it can be concluded that urodynamic studies in the majority of cases do not provide significant additional information to justify this type of investigation as a routine procedure in children [58-60].

Both children and parents need careful preparation and adequate information before the study is done. It is an invasive procedure and artefacts may occur. Because of the invasiveness of the investigations all children are anxious and this may be reflected in the outcome of the study. Especially during the first filling cycle, when the child does not know what to expect, detrusor overactivity may be seen and the voiding phase can be incomplete due to contraction or incomplete relaxation of the pelvic floor muscles during voiding. Once the child knows that filling and voiding are not painful a subsequent filling and voiding cycle may show a completely different pattern. The study should be repeated at least 2 or 3 times. Only if during the first filling cycle, no detrusor contractions are seen and also the voiding phase is in accordance with history and uroflow, it is probably sufficient to do only one complete filling and voiding cycle [61].

Still the results may not always be reproducible and it should be stressed that the primary objective is to treat the child and not a "urodynamic abnormality" per se.

Special attention should be given to a pleasant surrounding for the child: one or both parents should be present and young children may be given a bottle. Older children may be distracted by watching a video movie. The child should be awake, unanaesthetised and neither sedated nor taking any drugs that affect bladder function.

During the study the investigator has the opportunity to observe the child and discuss various findings and correlate them to what the child feels and/or normally would do in such circumstances.

In children, the transition from filling phase to voiding phase is not as marked as in adults. To avoid missing this important transition, cystometry and pressure-flow/EMG measurements are performed as one continuous study in paediatric urodynamics.

Electromyography of the pelvic floor muscles is assumed to evaluate the activity of the striated urethral sphincter, in the filling phase and in the voiding phase. Surface skin electrodes are usually used to record the EMG. In children the pelvic floor EMG is probably of much more importance than in adults as it helps to differentiate the different voiding disorders.

Filling the bladder can be achieved by diuresis (natural fill cystometry) or retrograde by catheter. For retrograde filling by catheter, saline 0.9% or contrast medium at body temperature is recommended in children. Especially in young children some urodynamic parameters, such as capacity and detrusor activity are influenced by the temperature of the filling fluid. Although the clinical relevance is as yet unknown, it is recommended to fill the bladder with fluid of body temperature [62].

When filling by catheter, slow fill cystometry (5 – 10 percent of expected bladder capacity per minute (based on the voiding diary), or < 10ml/min) is recommended in children, as certain cystometric parameters, notably compliance, may be significantly altered by the speed of bladder filling.

Involuntary detrusor contractions may be provoked by rapid filling, alterations of posture, coughing, walking, jumping, and other triggering procedures.

The presence of these contractions does not necessarily imply a neurologic disorder. In infants, detrusor contractions often occur throughout the filling phase. (**figure 9**)

Bladder sensation is difficult to evaluate in children. Only in toilet-trained cooperative children is it a relevant parameter. Normal desire to void

is not relevant in the infant, but can be used as a guideline in children of 4 years and older. Normal desire to void should be considered the volume at which some unrest is noted, e.g. wriggling the toes; this usually indicates voiding is imminent. In the older child, the volume may be small with the first cystometry, for fear of discomfort. Also involuntary detrusor contractions occur more often during the first filling cycle [62]. This is the reason that in paediatric urodynamics at least two cycles of filling are recommended.

Maximum cystometric capacity (MCC) is the volume in the bladder at which the infant or child starts voiding. The value for maximum cystometric capacity is derived from volume voided plus residual volume. Values for MCC should be interpreted in relation to normal values for age.

Compliance indicates the change in volume for a change in pressure. For children with neurogenic detrusor-sphincter dysfunction, data are available relating poor compliance to the risk of upper urinary tract damage [64].

The urethral closure mechanism during storage may be normal or incompetent. The normal urethral closure mechanism maintains a positive urethral closure pressure during filling, even in the presence of increased abdominal pressure or during detrusor overactivity (guarding reflex) [63].

Immediately prior to micturition the normal closure pressure decreases to allow flow.

Bladder outlet obstruction, recorded with a pressure / flow study, may be anatomical or functional in nature. An *anatomical obstruction* may be present at the bladder neck or in the urethra as a stenosis or a stricture when there is a small and fixed urethral diameter that does not dilate during voiding. As a result, the flow pattern is plateau shaped, with a low and constant maximum flow rate, despite high detrusor pressure and complete relaxation of the urethral sphincter. In a *functional obstruction,* it is the active contraction of the urethral sphincter or pelvic floor during passage of urine, that creates the narrow urethral segment as a constant or intermittent obstruction. To differentiate anatomical from functional obstruction, information is needed about the activity of the urethral sphincter during voiding. This information can be obtained, and recorded together with pressure and flow, by monitoring the urethral pressure at the level of the urethral sphincter, or by recording a continuous electromyogram of the pelvic floor, as in clinical practice the urethral sphincter is not readily accessible, and the electromyogram of the external anal sphincter is often used to monitor activity of the striated urethral sphincter. This corresponds to activity of the pelvic floor muscles. Also the use of video urodynamics can be very helpful in this respect, as contractions of the pelvic floor muscles can actually be seen during the voiding phase (**Figure 9 and 10**).

In infants and small children, pelvic floor muscle overactivity during voiding (with post-void residuals) is not uncommon: in all probability it is a normal developmental feature [65, 66].

c) Cystoscopy

In by far the majority of children cystoscopy is not indicated. In boys with therapy resistant incontinence, an abnormal flow pattern, especially in combination with a history of (recurrent) urinary tract infection is suspicious of infra-vesical obstruction such as bladder neck obstruction, urethral valves, syringocele etc. A VCUG may not always show these abnormalities and pressure flow curves may be equivocal [67].

In girls the flow may be directed upward, indicating an abnormal meatal position or stenosis. A dorsal meatotomy generally solves this problem. It has been postulated that in girls the abnormal direction of the stream triggers the bulbocavernosus reflex resulting in dysfunctional voiding [68].

Grade of recommendation: for all diagnostic procedures level B

C. Nocturnal enuresis

I. DEFINITION

Nocturnal enuresis (NE) is involuntary voiding of urine during sleep, at least three times a week, in children over 5 years of age in the absence of congenital or acquired defects of the central nervous system [1].

Parental concern and child distress affect the clinical significance of the problem [2]. While most children who wet at night after age five are considered nocturnal enuretics, the child's development level is also important. The age criterion of five is arbitrary but reflects the natural course of achieving bladder control [4]. Verhulst et al argue for flexibility due to different age at which boys develop nighttime continence compared with girls [4]. Extrapolation from Verhulst's figures suggests that the prevalence of nighttime wetting for 8-year-old boys equals that for girls at 5 years [4].

Monosymptomatic NE is bedwetting without daytime symptoms. **Non-monosymptomatic** or polysymptomatic NE describes children with both day and nighttime wetting [5].

II. SEVERITY

Nocturnal enuretics vary in wetting frequency. Although fifteen percent wet each night, most children wet less frequently [4,6]. In a population survey of nearly 1,800 Irish children aged 4 –14 years, Devlin found the frequency of wetting as

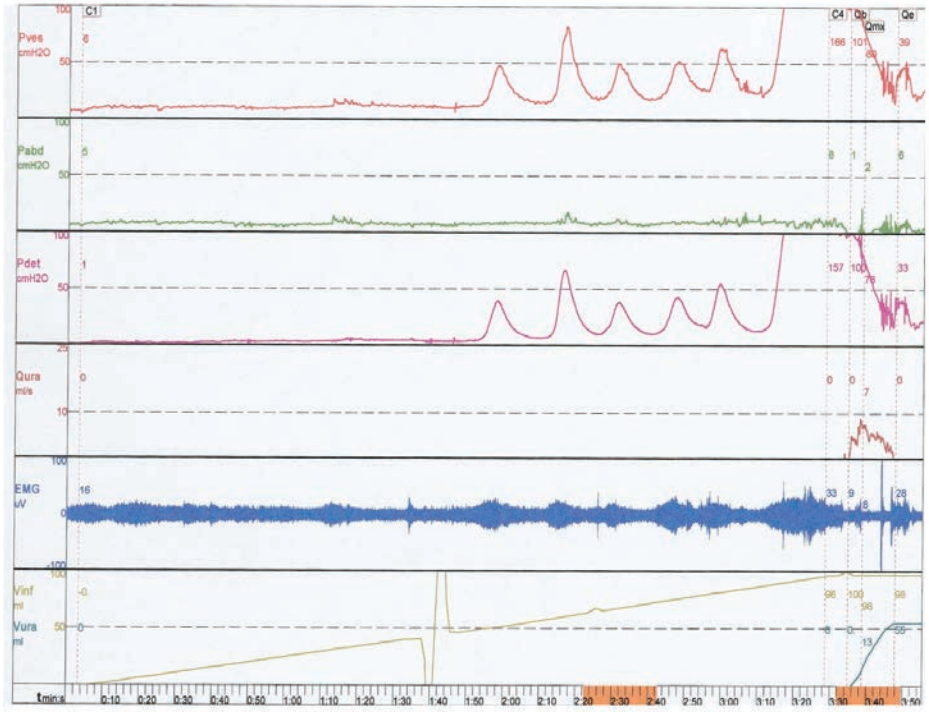


Figure 9: Urodynamic study illustrating involuntary detrusor contractions, counter action of pelvic floor muscles (guarding reflex) and incomplete pelvic floor relaxation during voiding resulting in post void residual urine (detrusor overactivity + dysfunctional voiding) [63]

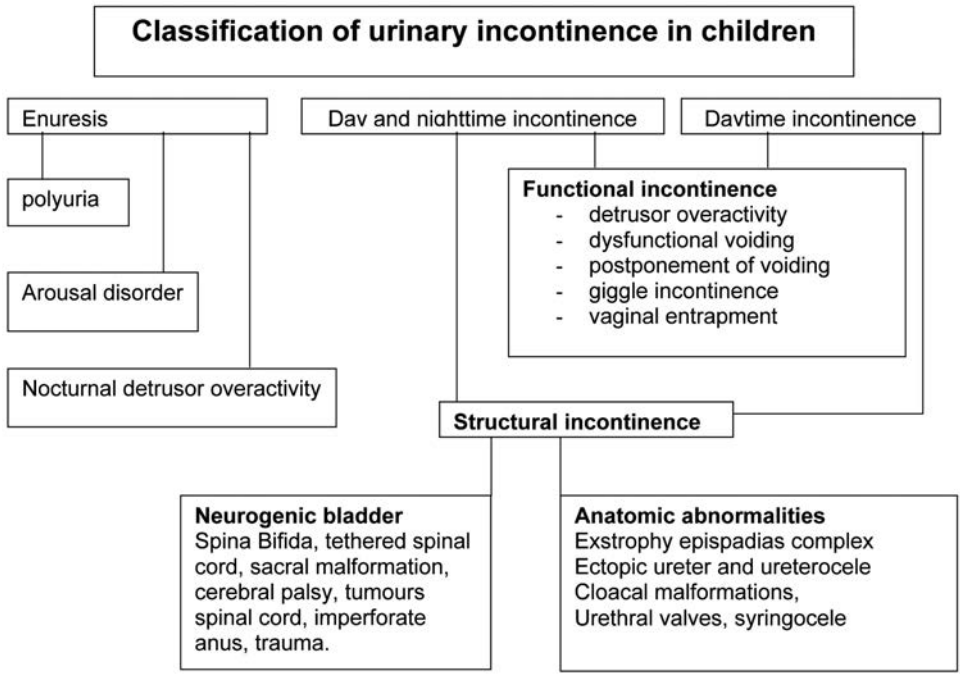


Figure 10: Classification of urinary incontinence in children

(Over)activity of the urethral sphincter- pelvic floor may occur during the voiding contraction of the detrusor in neurologically normal children; this set of events is termed dysfunctional voiding.

Grade of recommendation: for all diagnostic procedures level B

follows: less than once per week in 33 percent, once per week in 11 percent and 2 to 4 times per month in 25 percent [7]. Some children and parents are concerned about an occasional wet bed, while others accept regular wetting. Clinically severity can be defined as: infrequent (1-2 wetting episodes per week), moderately severe (3 – 5 wetting episodes per week) or severe (6 – 7 wetting episodes per week) [7].

III. PREVALENCE

Bedwetting is common. In the United Kingdom, estimates approximately 750,000 children and young people over 7 years regularly wet the bed. In the United States 5 to 7 million children regularly experience primary NE [8,9,10].

The prevalence of bedwetting varies regionally. In China, where parents take children out of diapers earlier, bedwetting seems to resolve more quickly. For example, in a large survey from Shandon, the proportion of children attaining nocturnal urinary control before age 2 was 7.7%; by age 3, this had increased to 53.1%, and by age 5 to 93%. The overall prevalence of NE was 4.3%, with a significantly higher prevalence in boys than girls. There was no additional decrease in the prevalence of enuresis between 6 and 16 years [11]. This suggests that structured awakening and toileting is effective treatment for monosymptomatic NE, even in small children.

Bedwetting becomes less common with advancing age. In the West, 15 per cent of children each year develop nocturnal bladder control [12]. By adulthood, bedwetting is rare. Hirasing et al sampled over 13,000 adults [18-64 years] and found an overall prevalence rate of NE at 0.5% [13]. Of these, 12 percent of men and 29 percent of women had daytime incontinence. Despite persistence of wetting into adulthood, 50 percent of men and 35 percent of the women never seek help for their problem. The enuresis prevalence of 0.5% in otherwise healthy adults in Hirasing's study refers to a largely untreated population. Fifty percent of the men had primary enuresis and had never been consistently dry at night. Assuming a prevalence of enuresis of 8 percent in 7-year-old boys, the risk for an enuretic boy to remain so for the rest of his life is 3 percent. [12.14]. Many believe adult enuretics represent a "hard core" group with worse symptoms. These individuals are likely to have associated diurnal enuresis or voiding symptoms. One study included 18 males and 29 females with a mean age of 20 years with persistent NE. Of these patients 37 (79%) had moderate or severe symptoms and 17 (38%) also had daytime urinary symptoms. Thirty patients had urodynamics including 12 males and 16 females, and 93% had detrusor overactivity. In addition, 73% of patients had urodynamic evidence of functional bladder outflow obstruction, including dysfunctional voiding and detrusor sphincter or detrusor pelvic floor discoordination. Two male patients (6.7%) had an obstructive pattern on urodynamics and subsequent cystoscopic examination confirmed the presence of congenital urethral stricture/valves. Sixteen patients (53%) had significantly reduced bladder capacity of less than 300 ml. [15-18]. These and other studies suggest that persistent NE after childhood is a serious adult problem requiring some investigation and considerable effort to treat.

IV. INHERITANCE

Bedwetting runs in the family of many children who suffer from bedwetting. In one study, A positive family history was found in 94 families (23%) of 411 probands with PNE, including 49% of fathers, 9% of mothers, 6% of both parents, 6% of the siblings and 30% of grandfathers or (and) mothers. Among the probands the ratio of male to female was 1.3:1 excluding sex-linked inheritance. Autosomal dominant inheritance was in 15%, and autosomal recessive inheritance was consistent in 1.46% of families[19]. Thus, the mode of inheritance is usually autosomal dominant; if both parents were nocturnal enuretics as children, the risk for their children is from 65 to 85 % [20]. If only one parent has NE the risk is about 45 percent [21].

Molecular studies have clearly shown that NE is a complex disease with locus heterogeneity and no clear genotype-phenotype association.

Linkage studies to determine the location of the genetic changes have suggested foci on several genes. Linkage studies to markers on chromosomes 8, 12 and 13 demonstrate both clinical, as well as genetic heterogeneity in nocturnal enuresis [22]. But these have not been consistently reported in other studies [23]. So far, there has been no reported association of the genotype with a particular phenotype of enuresis [24].

V. GENDER AND MONOSYMPTOMATIC NE

Boys suffer nocturnal enuresis more frequently. In a population survey of 706 families in London, Weir found a higher prevalence for boys than girls, at age 3 years, with 56 percent of boys and 40 percent of girls being wet at night more than once a week [25]. More recent studies are consistent [26]. Surveys of monosymptomatic NE undertaken in Great Britain, Holland, New Zealand and Ireland suggest that the prevalence for boys is 13-19% at 5 years, 15-22% at 7 years, 9-13% at 9 years and 1-2% at 16 years. For girls the prevalence rates are reported to be about half that rate: 9-16% at 5 years, 7-15% at 7 years, 5-10% at 9 years and 1-2% in the late teenage years [4,7,27,28]. Although

monosymptomatic NE is more common in young boys, by adolescence the incidence in males is the same as in females [16,29]

VI. CLASSIFICATION

1. PRIMARY VERSUS SECONDARY NOCTURNAL ENURESIS

Children who have never been free of bedwetting for 6 months have **primary NE**. Secondary NE is the re-emergence of wetting after a period of being dry for at least six months. A birth cohort of 1265 New Zealand children studied over 10 years by Fergusson et al found an increased risk of secondary nocturnal enuresis with age [30]. The proportion of children who developed secondary enuresis was 3.3 percent at 5 years, 4.7 percent at 6 years, 6.2 percent at 7 years, 7.0 percent at 8 years, 7.5 percent at 9 years and 7.9 percent at 10 years.

Secondary NE is associated with a higher incidence of stressful events particularly parental separation, disharmony between parents, birth of a sibling, early separation of the child from parents and psychiatric disturbance in a parent [22, 30,31].

Von Gontard and colleagues found children with secondary enuresis had significantly more emotional difficulties compared to those with primary NE. Their evidence also suggests children with secondary enuresis, compared to those with primary enuresis, are more likely to have behavioural problems, a finding which corresponds to that of McGee et al [32].

Both Jarvelin and Fergusson et al argue that primary and secondary enuretics are similar [30,31]. They believe the two share a common etiological basis. The rate the child acquires primary control influences his or her risk of secondary enuresis. The primary form is the consequence of a delay in maturation of the physiological mechanisms. The child's capacity to sustain and maintain nocturnal bladder control is manifest in the rate at which he or she acquires control. On the other hand, this capacity determines the child's susceptibility to lapsing back to night wetting when exposed to stress.

Other sources of secondary enuresis must be excluded prior to proceeding with treatment for enuresis. These include sleep apnea from obstructive airway disease, obesity, constipation and infrequent or dysfunctional voiding. Treatment of sleep apnea from obstructive airway has been shown to improve or eliminate NE in some children following surgery or medical management [34,35]. Obesity has been associated with nocturnal enuresis both independently [36] and in the context of sleep apnea. [37]

2. MONO-SYMPTOMATIC VERSUS NON-MONO-SYMPTOMATIC NE

Mono-symptomatic NE refers to those children who report no other bladder or voiding problems associated with wetting. Non-mono-symptomatic NE refers to bedwetting, that is associated with detrusor overactivity or voiding problems such as urgency and bladder holding during the day [5].

This classification becomes important when considering the most appropriate treatment intervention. Many parents are unaware of daytime symptoms when seeking help for bedwetting and when identified these symptoms should be treated prior to intervention for the NE. Between 10-28% of children with NE have associated daytime wetting. If so, these children should be considered day and night incontinent. In these cases, night time incontinence is not any longer an isolated phenomenon but part of the symptomatology of day and night time incontinence. These children are more resistant to treatment and more vulnerable to relapse [38]. These boys and girls are more appropriately managed in the context of the primary bladder problem.

VII. PATHOPHYSIOLOGY OF MONOSYMPTOMATIC NE

NE stems from a mismatch of bladder capacity, nocturnal urine output and the ability for the child to arouse during sleep. Night wetting is normal until age 5. Delayed maturation in one or more of the following systems results in NE: a lack of stability in bladder function, a lack of arginine vasopressin (AVP) release or response, or relative increased solute excretion during the night [39,40] , or an inability to wake from sleep to full bladder sensations [41,42]. Combinations of all three problems may be present.

A unifying and simplistic concept with important clinical implications, is that NE is caused by a mismatch between nocturnal bladder capacity and the amount of urine produced during the night, combined with delayed or incomplete arousal response to the afferent neurological stimulus of the full bladder (**Figure 11**).

1. INCREASED NOCTURNAL URINE OUTPUT

In normal children, the circadian rhythm of urine production results in a nocturnal reduction in diuresis to approximately 50% of daytime levels [43,44]. In children this is the result of nocturnal release of hormones that regulate free water excretion (arginine vasopressin, (AVP) or solute excretion (angiotensin II and aldosterone) and may result from circadian changes in glomerular filtration [45]. In the normal child, this results in increased urine concentration and reduced urine

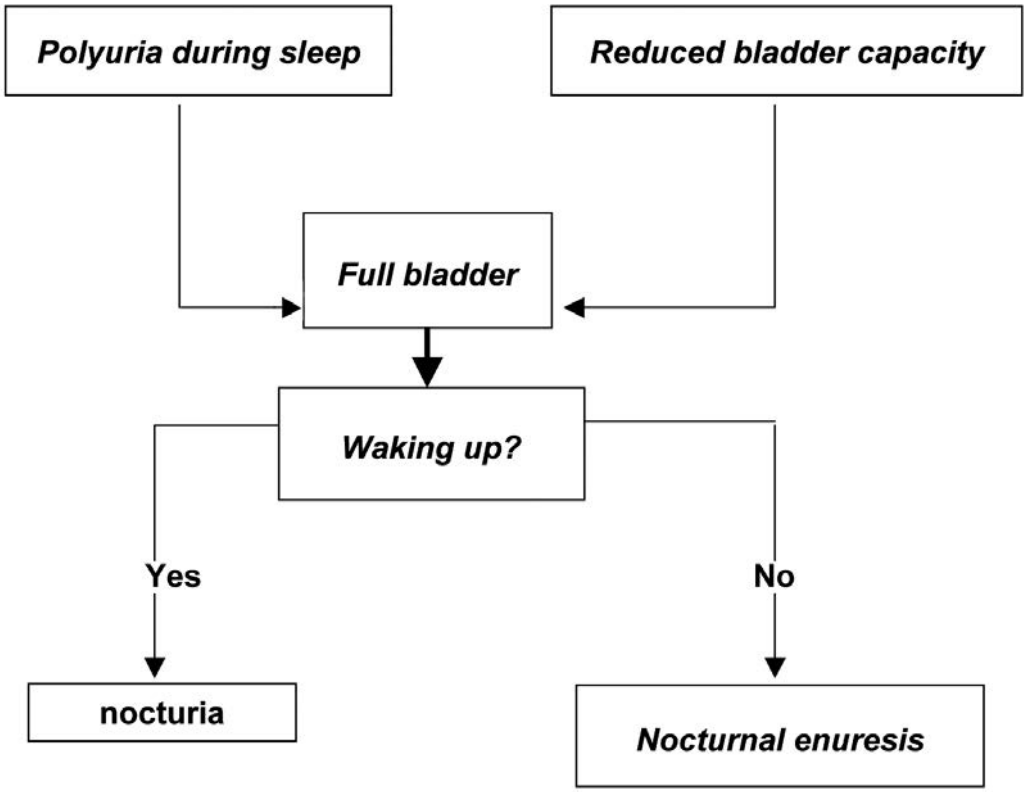


Figure 11: Basic pathophysiology of NE or nocturia. When the bladder is full because of (relative) polyuria and/ or a reduced bladder capacity, the child either wakes up to void (nocturia) or voids while sleeping (NE)

volume during sleep. This is why children who are not enuretic sleep through the night without being wet and do not need to rise to void.

Two thirds of patients with mono-symptomatic NE have been found to have a lack of circadian rhythm of vasopressin, resulting in high nocturnal urine production, which exceeds bladder capacity [46,47,48]. Rittig et al and Norgaard et al demonstrated abnormalities in the circadian rhythm of AVP secretion resulting in increased nocturnal urine output that exceeded bladder capacity in children with nocturnal enuresis [46,47]. These children make more urine at night, and often overcome their bladder capacity and wet early in the night. Abnormalities can also be intrinsic, related to reduced nocturnal circadian changes in glomerular filtration rate (GFR) [45] or in sodium and calcium excretion[49].

Detection of low plasma vasopressin levels, GFR assessments or specific sodium and calcium excretion are difficult to measure. Instead, we look for clinical signs of low vasopressin during the assessment interview. Weighing the diapers and adding the first morning void provides the total nocturnal urine output. if this total exceeds the child's functional bladder capacity this may indicate nocturnal polyuria. Nocturnal urine output varies appreciably from night to night [50], but seems larger in children with NE who respond best to desmopressin (dDAVP).

By the time the child becomes an adolescent, the circadian rhythm is less prominent. In adolescents and adults with nocturnal enuresis, there is no diurnal rhythm of plasma vasopressin concentration. The changes in urine production at night occur from a decrease in the urinary sodium excretion that is not due to differences in concentration of AVP but due to a lack of sensitivity to AVP [51] with resultant increased urine output [39].

There may be a small sub-group of children with impaired renal sensitivity to vasopressin or desmopressin [40,52]. Recent work by Devitt et al suggests that 18 percent of children have 'normal' levels of plasma vasopressin release but remain enuretic [48]. These children all failed to respond to a therapeutic dosage of desmopressin. This finding could indicate renal insensitivity to vasopressin but could also be indicative of detrusor overactivity or a small functional bladder capacity. Total urine output during the night could be helpful in differentiating between the two conditions. The subgroup of patients with NE and increased nocturnal urine output generally has a normal func-

tional bladder capacity and a favourable response to dDAVP [53].

2. DETRUSOR OVERACTIVITY DURING THE NIGHT

The detrusor, in order to function appropriately, needs to be relaxed during filling and allow an appropriate functional capacity. Detrusor overactivity usually causes small voided volumes resulting in a decreased functional bladder capacity [54].

Watanabe and his colleagues, employing EEG and cystometry recording during sleep, discovered that 32 percent of children with NE had involuntary detrusor contractions that resulted in enuresis [60-62]. These children had smaller functional bladder capacities at the point of wetting, than children with enuresis who did not have detrusor overactivity. Functional bladder capacity – defined as the largest daytime void on a frequency- volume (F/V) chart, after excluding the first morning void, may give a reasonably accurate assessment of daytime functional bladder capacity (FBC). Reduced functional bladder capacity, when below 70% of predicted FBC for age, is likely to result in poor response to dDAVP treatment [55]. Daytime bladder capacity is smaller than night time capacity in children without NE [56].

The pattern may be different at night. Yeung et al reported that 44 percent of treatment failures [with desmopressin or the enuresis alarm] have normal daytime bladder function but marked detrusor overactivity during sleep resulting in enuresis [63,64]. Almost none of these children had nocturnal polyuria. Ultrasound studies of the bladder furthermore revealed an increased bladder wall thickness in these children [57].

When further segregated prior to treatment, increased bladder wall thickness and bladder volume predicted the response to therapy in children with their primary nocturnal enuresis (more than three nights weekly). In one study, Yeung, et al, [58] correlated ultrasound measured parameters and urodynamic findings. Of 35 children with frequent NE, bladder wall index was normal in only eight patients. It was less than 70% of predicted in 24, and more than 130% in three. When bladder volume and wall thickness index was correlated with ultrasound, 87% of the patients with a normal index exhibited a normal bladder pattern on imaging and 96% of patients with an index less than 70 exhibited detrusor over activity on ultrasound. All the children with a normal index either had a complete or good response to conventional treatment for nocturnal enuresis, whereas 62% of those with an index less than 70 % did not respond to treatment. With longer follow-up, bladder dysfunction had resolved in 38% of the children with an initial index of less than 30, all of whom had a good response to treatment. The bladder dysfunction persisted in the 63% of children who had partial or no response to treatment. What this means is that ultrasound measured bladder parameters may segregate children, prior to management of primary nocturnal enuresis, into groups that have a favorable outcome and those that do not, following conventional treatment. These studies will become more and more important in helping to predict response of various treatment regiments in the future.

This approach may be even more important in adults with refractory monosymptomatic nocturnal enuresis. Bower, et al. [15] found that in 56 consecutive adolescents and adults compared with 293 normal adults, there were significantly higher childhood scores of urgency, frequency, urgency incontinence, infrequent voiding and small volume voids than their normal non-enuretic counterparts. This suggests that adolescents and adults with persistent nocturnal enuresis may have a more significant bladder component, particularly since the majority of patients with adult type nocturnal enuresis do not seem to exhibit the nocturnal polyuria problem seen more commonly in the smaller children.

3. LACK OF AROUSAL FROM SLEEP/CNS FUNCTION

The fundamental mechanism resulting in nocturia or NE is that the bladder fills to its capacity during sleep and needs to empty (**figure 11**). Bladder fullness is due to nocturnal polyuria and/or a reduction of the bladder capacity due to detrusor overactivity during sleep. These factors do not fully explain why the enuretic child does not wake up during the night to the sensation of a full or contracting bladder. Regardless of whether the child has detrusor overactivity or nocturnal polyuria, the enuresis event results from the child's inability to awaken from sleep to empty prior to the wetting episode.

There is a widely held belief amongst parents and some clinicians that enuretics are deep sleepers. This is logical, since many of the children exposed to alarm therapy sleep through the alarm while family members awaken. Nevéus reviewed by questionnaire 1413 schoolchildren between the ages of six and ten and noted that enuresis was associated with subjectively high threshold arousal and significant confusion upon awakening from sleep [42]. Wolfish in a study of 15 enuretic and 18 control boys and girls found that enuretics wet most frequently during the first two-thirds of the night and that arousal attempts were less successful in enuretics than in normals[59]. This might explain why the most heavily endorsed view of both children and parents, regarding the aetiology of NE is a belief in deep sleep [60].

More recently Frietag, et al studied brainstem evoked potentials in 37 children with nocturnal enuresis and compared these aged 8 to 14 years, with 40 controls, mean age 10 years, and found that interpeak latencies of the brainstem evoked potentials were increased in children with nocturnal enuresis, suggesting that a maturational deficit of the brainstem was present in children with nocturnal enuresis. Differences in visually evoked potential latencies might point to a reason behind functional cortical differences in children with family history of nocturnal enuresis [61].

Feittag's study would suggest that a maturational effect is present; however, overnight studies in enuretic children with simultaneous sleep electroencephalographic and cystometry have revealed marked detrusor overactivity, only occuring after sleep at night and not during wakeful periods during the day [62]. Because this pattern has not been observed in normal non-enuretic subjects, even during the newborn period, one may hypothesize that this could be due to a small neurologic lesion affecting a tiny area in the vicinity of the pontine micturition center, the posterior hypothalamus (responsible for secretion of antidiuretic hormone) or the locus coeruleus which may be the cortical arousal center [63].

Another interesting study by Baeyens et al. [64] showed a convincingly significant difference between children with enuresis and control groups, and the startled eye blink reflex which improved with maturation but did not seem to correlate with resolution of enuresis. Clearly there is considerable work that is required to further unravel the mechanisms behind perceived differences in arousal between enuretic and non-enuretic children.

However a raft of evidence counters such a belief. Sleep patterns of children with NE are no different from children who do not have NE [65].

Enuretic episodes occur during all stages of sleep in proportion to the amount of time spent in that stage and appear to occur independent of sleep stage but occur when the bladder is at a volume equivalent to the maximal daytime functional capacity [66-69].

Bedwetting children sleep normally but are unable to suppress nocturnal detrusor contractions or awaken in response to them or to bladder fullness.

Waking becomes easier as the night progresses. However, several authors have found that children with NE are also more likely to wet in the first third of the night, often in the first two hours following sleep [59,66,67,70,71]. Thus the point of bladder fullness for most enuretic children coincides with a time of night where they find it most difficult to wake from sleep.

Children who do wake up but are afraid to go to the bathroom, and therefore wet their bed should be identified as treatment is completely different for obvious reasons.

VIII. TREATMENT OF NOCTURNAL ENURESIS

The age at which the child and his or her parent begins to be concerned about bedwetting varies. In an important review article, Hjalmas, et al. noted that, "for successful treatment of nocturnal enuresis, the child must be brought to the physician by the parents who are concerned and the physician must have the necessary knowledge about the condition and be motivated to start treatment [43]. In order to fulfill the requirements, parents, teachers, and nurses in primary care need to understand nocturnal enuresis and be ready to treat the child, regardless of age.

Nocturnal enuresis is thought of as a social problem and less of a medical problem; therefore, since the majority of children stop wetting as they mature and since no ill health follows bedwetting in most cases, there is a tendency for many practitioners to take a "wait and see" approach despite the fact that the family and the child in many cases are quite disturbed. In one study, 3803 French school children age five to ten years noted the prevalence of primary nocturnal enuresis to be 9.2%. The majority of the children noted that bedwetting bothered them and hoped that a doctor could help them. In this survey, a questionnaire was addressed to mothers of enuretic children, 100 school teachers and 100 school doctors. The mothers had a relatively tolerant attitude but two-thirds had consulted a doctor. Most of the doctors had proposed no solution or a "wait and see" attitude or treatment with a drug rather than an alarm. From this study, we may conclude that considerable work needs to be done to help educate not only parents but teachers and even physicians about the importance of treatment of nocturnal enuresis as well as supportive care [72].

The actual timing of treatment for nocturnal enuresis may vary depending on the needs of the child and the parent. Toilet training age may be different in different societies. For example, toileting in Asia may begin earlier than in North America or other parts of the world [72,73,74]. Toilet training should be started when both the child and parents are ready. Most studies appear to show that children start training between 24 and 36 months of age with a current trend toward later completion than in previous generations. This is markedly different than noted in some Asian cultures where training

appears to begin much earlier. Toilet training should occur in an environment that is comfortable for the child. Unfortunately, toilets in most household bathrooms are adult sized, making it difficult for the child who needs to climb to the top of the toilet to relax. In these cases, a potty chair to toilet train the child, and once the child is old enough, he or she should be transitioned to an over-the-toilet seat with a footstool to allow optimal posture for voiding. Parents should encourage children to relax and take time to completely empty the bladder [43].

It is essential that both the child and his or her parents understand bedwetting pathophysiology and treatment philosophy. The clinician should give the child general advice such as what to eat and drink and to void regularly during the day, abstain from drinking too much during the late afternoon and evening and have relaxed routines at bedtime. The clinician should stress that NE is common and usually represents a delay in maturation without any psychopathological undertone. Up to 19 percent of children will become dry within the next 8 weeks without any further treatment besides good counselling [43,73,74].

1. EVALUATION

Hjalmas, et al. have recommended a careful history which we will summarize in these next few paragraphs (**Figure 12**). This approach, which has been recommended by the International Children's Continence Society, provides an excellent guide toward the taking of a history for a child with nocturnal enuresis [43].

a) The frequency volume chart (FVC). Parents are asked to record a two-day three-night record. This includes recording the child's fluid intake and urine output, frequency of micturition and the frequency and pattern of voiding. The largest single micturition is considered the functional bladder capacity. This chart can be performed beginning on a Friday evening and concluding on Sunday on any weekend.

b) Symptoms of nocturnal enuresis. A careful history should include questions about the age of onset of nocturnal enuresis, length and circumstances of dry spells, number and time of episodes of nocturnal enuresis or nocturia, presence of daytime voiding symptoms or urinary tract infection, posture while voiding, daytime and evening fluid intake, sleep habits, frequency and consistency of bowel movements and psychosocial situation. One must establish whether or not symptoms represent primary or secondary nocturnal enuresis. It is critical to search for new psychological problems that might cause secondary nocturnal enuresis, particularly when the child presents with nocturnal enuresis after a prolonged period of dryness. The personality of the child, family situation, school environment, and presence of alternate care givers might have an appreciable impact on voiding habits and will influence management options [43]. Children may drink large volumes of fluid in the hours before sleep and this may result in nocturnal enuresis or nocturia.

It is helpful to determine the number of hours of sleep and to compare this to standard charts of average duration of sleep by age. Morning fatigue may be the result of obstructive sleep apnea. Other symptoms of sleep apnea include mouth breathing, snoring, and restless sleep [43].

It is important to rule out symptoms of anatomical or physiologic urologic conditions that may lead to

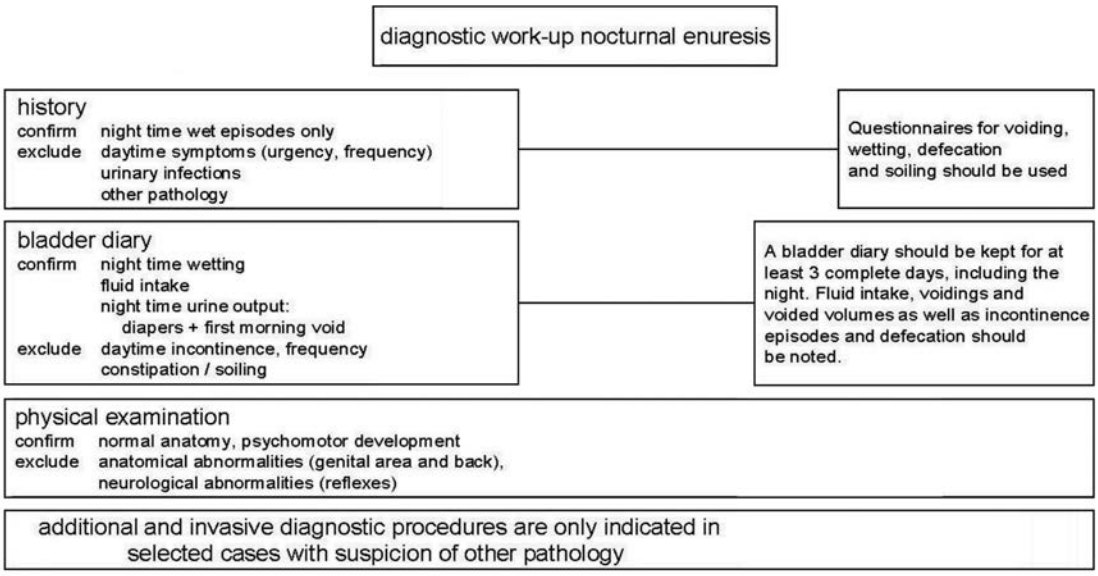


Figure 12 : Schematic work-up in patients presenting with night-time wetting only

nocturnal enuresis. Many of these conditions are covered in other parts of this section, and include a failure to store urine or failure to empty urine. Storage symptoms include increased frequency, urgency, and urgency incontinence including squatting behavior, daytime incontinence and the sensation to need to void again. The clinician must carefully assess daytime wetting, particularly in older children. In many cases, the child may hide these symptoms from the clinician and the family.

Children void four to seven times a day or about every two to three hours [75]. If the child is voiding significantly more frequently than eight or more times a day, this may suggest incomplete emptying or overactive bladder symptoms. Urgency is present in many children and posturing, including squeezing or crossing the legs, squirming while standing or sitting, or physically compressing the genital area with a hand is all suggestive of overactive bladder due to detrusor overactivitiy which may or may not be associated with dysfunctional voiding. Other causes include urinary tract infection, polyuria from diabetes mellitus or diabetes insipidus, which can also cause more frequent voiding [43]. Treatment for these symptoms is covered in other sections within this chapter.

Additional symptoms during the daytime include continuous dribbling between voids that can come from an ectopic ureter bypassing sphincter mechanisms, or from failing to empty the bladder or sphincter incompetence. Also continous leakage can result from neurologic causes or anatomical causes such as epispadias, or a closed bladder exstrophy or urogenital sinus.

Lastly, children may have incomplete emptying from true dysfunctional voiding which results from the sphincter or pelvis floor contracting at the same time as the detrusor contracts during micturition. In addition, detrusor underactivity may result from neuropathy from diabetes mellitus and in some cases conditions such as the prune belly syndrome will result in detrusor underactivity. Lastly, urethral strictures may result in incontinence due to detrusor overactivity with poor bladder emptying. Boys with posterior urethral valves or Cobb's collar may also have incomplete emptying. Lastly, the clinician should be alert for symptoms of constipation and faecal incontinence. It is a common misconception that if a child is stooling once per day then he or she is not constipated. In fact, the best symptom of constipation is the infrequent or painful passage of hard small pellet-like stools. Faecal incontinence may also be present, the principal sign of this being faecal material in the underwear. Excessive stool retention may result in bladder dysfunction. In these cases [76], this may result in increased urethral sphincter and pelvic floor activity and explain the association of voiding dysfunction with incomplete voiding. Treatment of constipation may result in improvement in enuresis.

2. PHYSICAL EXAMINATION

Anatomic and behavioral causes for enuresis may be identified through a careful physical examination. Evidence of improper gait, spinal deformities, and foot abnormalities including asymmetry, high-arched feet, or hammer toes are signs of sacral neuropathy. Physical signs of occult spinal abnormalities such as dimples, tufts of hair, skin discoloration, lipoma, asymmetrical buttocks and gluteal clefts are also important. A careful abdominal examination with particular emphasis on the left lower quadrant may identify the colon full of firm stool. In most cases, a rectal examination is not performed but in some cases this may also be indicated. Occult feacal impaction, poor perineal sensation and reduced anal sphincter tone can be indicative of neuropathy.

In boys, marked narrowing of the urethral meatus (when the meatal lips are separated and no mucosa is seen), must be identified and carefully noted. If these signs are present, the boy should be asked to void so the clinician can witness and record the flow rate and residual urine. Narrowed or displaced urinary stream is suggestive of meatal stenosis.

In girls, the introitus should be identified for the position of the urethra. Evidence of wetting or irritation of the labia or vagina should be identified, as this could be suggestive of post-void dribbling or incomplete emptying with incontinence due to either detrusor overactivity or sphincter weakness [77].

3. LABORATORY EXAMINATION

There is very little laboratory examination that is required in patients with nocturnal enuresis other than a urinalysis to rule out UTI and evidence of glycosuria and a urine culture if the urinalysis is suggestive of infection.

Urodynamics and imaging are rarely important in the child with monosymptomatic nocturnal enuresis. If there is any suggestion, however, that daytime wetting is occurring, and then a full evaluation of the daytime problem should precede the evaluation for nocturnal enuresis.

4. THE MANAGEMENT of NE depends on:

- the child's motivation to participate in treatment.
- exclusion of confounding psychosocial factors.
- providing information and instruction about daily habits, underlining the importance of having regular fluid intake, regular voidings, and relaxed routines at bedtime.
- regular review of the new intervention.

The therapist should convey a sense of understanding and compassion to both the child and the

family. Education about the problem and a realistic discussion about the prognosis will help instil competence in the treatment offered which may improve both compliance and outcome [78]. What follows is taken in part from the excellent review article by Hjalmas et al [43].

5. EVIDENCE BASED RECOMMENDATIONS FOR TREATMENT

First line treatment and preliminary steps: primary and secondary forms of nocturnal enuresis are treated the same. If faecal incontinence, constipation or daytime wetting is present, these should be treated first [76].

Although treatment modalities like lifting, fluid restriction, dry-bed training, retention control training, psychotherapy, acupuncture, hypnosis all have been used, there is not sufficient data in the literature to strongly recommend any of these [93-100]. However, non invasive behavioural modifications such as resisting over hydration in the evening are appropriate recommendations at the initiation of therapy. The child must void before bed. Excessive calcium or sodium intake should be avoided as well [79].

During the day the child should be instructed to void regularly, not to hold urine until the last minute, and to relax and take time to completely empty. If deemed important by the parents, a letter should be sent to the school to explain this.

Timing of treatment for the child who wets is dependent on the family's desire and the child's desire. As a good rule of thumb, children should be six to eight years of age. Some children, however, may want to wait until later. Others may be ready closer to age six. It is important for the parents to know that relapses can occur. The successful treatment of children with nocturnal enuresis has a foundation of realistic expectations and a motivated family [43].

Before starting treatment, a "baseline" meeting with counselling, provision of information, positive reinforcement, reassurance that 15% of children resolve each year, and increasing motivation should occur first. Children are asked to fill out a calendar or chart depicting the wet and dry nights. Children became significantly drier in two non-randomized trials associated with fewer wet nights simply by focusing them more on record keeping and true reward charts [80].

6. PHARMACOLOGICAL TREATMENT

Based on the three main causes of enuresis, namely nocturnal polyuria, detrusor overactivity, and disorder of arousal, the pharmacological treatment is designed to address these three areas.

a) Desmopressin.

Arginine vasopressin (AVP) or antidiuretic hormone (ADH) is normally produced in the hypothalamus and released in the pituitary in response to hyperosmolality or hypovolemic conditions. Vasopressin acts on the collecting ducts and distal tubules to enhance water absorption. AVP by virtue of an independent vasoconstrictor effect is also a potent vasopressor. Desmopressin (or dDAVP) is an analog of vasopressin created by deaminating the cystine residue at position 1 and substituted D-argenine for L -argenine at position 8. These changes result in significantly increased antidiuretic activity but loss of vasopressor activity. The half-life of Desmopressin is 1.5 to 3.5 hours. In a larger portion of children with monosymptomatic nocturnal enuresis, the normal circadian variation in urine production with nocturnal rise of vasopressin is absent. In these cases, dDAVP would seem to be particularly appropriate. Desmopressin is easy to administer and the clinical effects appear immediately. The usual dose is 0.2 to 0.4 mg orally, or 20-40 micrograms intranasally at bedtime. The intranasal form is no longer recommended for nocturnal enuresis in many places around the world. Some patients have a delayed response and a small group of children who do not respond to desmopressin in ordinary dosage will become dry when the dose is increased [81].

With meal combination desmopressin melt formulation has a superior pharmacodynamic profile to tablets, making it more suitable for the younger age group with a limited interval between meal and drug administration [82]

Desmopressin may be particularly beneficial in the child with limited numbers of wet episodes per month who wants added security on special nights such as a sleepover, etc.

Nocturnal polyuria is a characteristic of children that respond the best to desmopressin [83].

But detrusor overactivity associated enuresis does not easily respond as well to desmopressin treatment. The presence of daytime urgency or daytime incontinence is common in this group, and constipation or faecal incontinence is a regular finding, and these must be treated before offering dDAVP. In the short term, desmopressin is reported to produce more rapid improvement than alarm therapy. The results of various long-term studies which have followed children for six to 24 months after treatment cessation, indicate an annual cure rate in children on long-term treatment of approximately 30% [84,85].

1. Tolerability and Safety

Large amounts of liquid should not be consumed the nights when the drug is taken. There have been several reports that note Desmopressin toxicity [86,87].

This data would suggest that a fairly rigid regimen

of water restriction must be enforced for two hours prior to bedtime and to allow one eight-ounce (300 ml) glass of water at dinner and nothing for the two hours prior to bedtime.

The results of numerous clinical trials have shown that desmopressin is well tolerated even during long-term treatment and associated with a low risk of adverse events. In the SWEET study, only six of 242 children (2.5%) withdrew during the long-term treatment because of very mild adverse events following the administration of intranasal desmopressin. With the exception of water intoxication, which can be serious, this drug seems to be tolerated quite well.

In a survey on hyponatremia in patients with nocturnal enuresis, by Robson and Norgard in 1996, it was found that in the majority of children water intoxication was due to considerable intake of water during the time the child was actually taking the desmopressin.

2. Predictors of Response:

The SWEET study found that those who improved or became dry during desmopressin were older (greater than 8 years), had fewer wet nights during baseline, and had only one wet episode during the week and responded initially to the smallest dose of desmopressin used in the study [88,89].

The practical approach, however, is to offer the treatment to enuretic children since it is difficult to absolutely predict those that will respond.

There is considerable evidence that desmopressin works better than placebo. In one study, patients on desmopressin were 4.6 times more likely to achieve 14 consecutive dry nights compared with placebo [90].

However, relapse after short-term treatment is common. Sixty-one percent of 399 patients six to 12 years of age recruited from a primary care in one study responded to desmopressin initially [83]. Using intention to treat analysis 19% (77 of the 399) remained dry off medication and 18% were dry while still on desmopressin, thus not significantly better than the spontaneous cure rate. This suggests that desmopressin, by reducing the urine output over night, reduces nocturnal enuresis but does not significantly affect the resolution rate over time above the spontaneous rate.

Although several studies have shown that dDAVP is a well tolerated and safe drug, even during long-term usage, one has to be aware that dDAVP is a potent antidiuretic drug and that there have been reports of severe water retention with hyponatremia and convulsions, but these are infrequent [91-97].

Level of evidence: 1.

Grade of recommendation: A

b) Antimuscarinic drugs for OAB

Antimuscarinic drugs should not theoretically be efficacious in children with monosymptomatic nocturnal enuresis. However, because there is considerable misdiagnosis of monosymptomatic nocturnal enuresis, a number of children with mild daytime symptoms of overactive bladder may have symptoms of overactive bladder at night. Moreover, it has been shown that on Urodynamics, 73% of adults with primary nocturnal enuresis have some form of functional bladder outlet outflow obstruction classified as [1] “primary bladder neck dysfunction” or “detrusor sphincter dyssynergia”. [18]. That would suggest then that antimuscarinic drugs might be a useful alternative in some children who are unresponsive to DDAVP. It is also indicated in combined day and nighttime incontinence [52,98,99].

In general, antimuscarinic drugs are well tolerated but there are some side effects, namely dryness of the mouth, constipation and vertigo (rare). Constipation can also pose a problem since antimuscarinics may lead to constipation and the development of constipation may aggravate detrusor overactivity and thus counteract the beneficial effects of the drug. Antimuscarinics may also result in increased residual volumes which may make it difficult for the child to empty prior to bedtime. Antimuscarinic treatment in conjunction with desmopressin may have a role in cases with suspected day and night time detrusor overactivity.

Level of evidence : 2.

Grade of recommendation: B.

In those children who have NE due to detrusor overactivity during the night, treatment with an antimuscarinic drug should be considered [100]. Because it is difficult to perform a night time cystometry in these children, it may be tried in children who have more than 2 wetting episodes per night and who do not respond to dDAVP or be given in combination with alarm or dDAVP [101,99]. At present no studies have been performed to demonstrate its efficacy in this circumstance.

Level of evidence: 3.

Grade of recommendation: C

c) Tricyclic antidepressants

Although tricyclic antidepressant drugs, imipramine in particular, have worked in a number of children, most of the studies that recommend this drug are relatively old. The major drawbacks to imipramine therapy are cardiotoxic side effects, in some cases even with therapeutic doses, and the possibility of death with overdose.

Because imipramine and other drugs of the same family have potential cardiotoxic side effects they

cannot be generally recommended for treatment of this non-lethal disorder [102].

Although treatment with tricyclic drugs is associated with a decrease of one wet night per week, the lasting cure rate of only 17 percent restricts the use of these drugs [103].

Only in selected cases (like adolescent boys with Attention Deficit Hyperactivity Disorder and persistent NE) it should be considered [104].

In addition to dDAVP and imipramine, other drugs, such as carbamazine and indomethacin have been investigated as well: based on study design as well as study outcomes, these drugs are not recommended at this stage [105-107].

Level of evidence: 1.

Grade of recommendation: C (due to potential cardiotoxicity).

7. ENURESIS ALARM

The enuresis alarm is the most effective means of facilitating arousal from sleep and remains the most effective way to treat mono-symptomatic NE [107,108]. Intervention with an alarm is associated with nine times less likelihood of relapse than antidiuretic therapy. Relapse rates in the 6 months following treatment are in the order of 15 - 30 %. Alarm therapy has been shown in a meta-analysis to have a 43 percent lasting cure rate [109,110]. Alarm therapy should be considered in every patient. There is an average success rate of nearly 68% with efficacy increasing with the duration of therapy.

Better results occur with optimal motivation of the child and family and higher frequency of wet nights. Reduced efficacy is associated with the lack of concern shown by the child, lack of supervision, inconsistent use, family stress, abnormal scores on behaviour system checklists, psychiatric disorder of the child, failure to awaken in response to the alarm, unsatisfactory housing conditions and more than one wetting episode per night. Enuresis alarms require several months of continuous use and are, therefore, unsuitable for some families [111-112].

For optimal results, alarm therapy requires a motivated family and child with significant commitment to time and effort. The impact on other family members should be considered. In some families, alarm therapy may wake other members of the family and may increase parental annoyance and place a child at increased risk for physical or emotional abuse. Close follow-up is important to sustain motivation, troubleshoot technical problems and otherwise monitor the therapy [43].

The exact mechanisms for alarm treatment are not known. The effects are not due to classical conditioning as stimulus awakening occurs after and not before wetting. Instead it is clearly an operant type of behavioural approach, i.e. a learning program with positive reinforcement that includes aversive elements. Dryness is reached either by waking up leading to “nocturia” in 35% of children or by sleeping through the night with a full bladder in 65%. Body worn (vibrating) alarms are as effective as bedside alarms [113].

The family should continue alarm therapy for at least 14 consecutive dry nights – or a maximum of 16 weeks before discarding it as ineffective [114-116]. Compliance remains a problem: drop-out rates are rarely disclosed in reported studies. Proper guidance and instructions are mandatory.

The key to success is not the stimulus intensity of the alarm triggering, but the child’s preparedness to awake and respond to the signal. Comparison of the different types of alarm did not show significant outcomes.

In general it can be stated that alarm treatment is more effective than other forms of treatment and the lasting cure rate about twice as high [117,118].

Level of evidence 1.

Grade of recommendation A

In some cases, alarm therapy can be enhanced using the alarm in addition to other behavioral components. Overlearning (giving extra fluids at bedtime after successfully becoming dry using an alarm) and avoiding penalties may further reduce the relapse rate [108].

8. DRY BED TRAINING

This is a package of behavioural procedures used in conjunction with the enuresis alarm first described by Azrin et al [119]. It incorporates:

- the enuresis alarm
- cleanliness training (encouraging the child to take responsibility for removing of wet night clothes and sheets, re-making the bed and resetting the alarm)
- waking schedules – to ease arousability from sleep as described above and involving:

  1 for the first night, waking the child each hour, praising a dry bed, encouraging the child to decide at the toilet door whether he or she needs to void, and on returning to bed the child is encouraged to have a further drink .

  2 On the second night the child is awakened and taken to the toilet 3 hours after going to sleep. For each dry night, the waking time is advanced by 30 minutes. If the child is wet on any night, the waking time stays at the time of the previous evening. The waking schedule is restarted if the child begins wetting twice or more in any week, stating again 3 hours after sleep.

High success rates and low drop out have been reported although relapse rates are no different than enuresis alarm treatment alone. Modifications are advocated to remove some of the more punitive elements of the programme but at best, it is a complex, time consuming and a demanding technique [113,120,121]

Hirasing et al found 80 % success with group administered dry bed training. Girls responded better than boys [122]. The majority of parents were satisfied with the programme but opinions of the children were divided. Factors not related to success were the child's age, bedwetting frequency, secondary enuresis or family history.

In another study they found a positive effect on behavioural problems [123].

An important component analysis by Bollard & Nettelbeck found that the enuresis alarm accounted for most of the success achieved through dry bed training. They believe that a large proportion of the components of the procedure can be eliminated without sacrificing much of its overall effectiveness and that the waking schedule coupled with the enuresis alarm is as effective as the complete dry bed-training programme [124].

Level of evidence: 2.

Grade of recommendation D (no more effective than alarm treatment alone)

9. AROUSAL TRAINING

Arousal training entails reinforcing appropriate behaviour [waking and toileting] in response to alarm triggering. The aim is to reinforce the child's rapid response to the alarm triggering, not on 'learning to keep the bed dry'.

The instructions involve:

- setting up the alarm before sleep
- when the alarm is triggered the child must respond by turning it off within 3 minutes
- the child completes voiding in the toilet, returns to bed and re-sets the alarm
- when the child reacts in this fashion he is rewarded with 2 stickers
- when the child fails to respond in this way the child pays back one sticker

Van Londen et al first described this procedure with a group of 41 children, aged 6-12 years, with predominantly primary enuresis [125].

They reported 98 percent success [14 consecutive dry nights] compared to 73 percent success with alarm monotherapy. The difference was significant [p<0.001]. Ninety two per cent remained dry after 2 ½ years: a very low relapse rate. An extraordinary aspect of this study was the lack of contact between therapist and parents. All those included were parents who had ordered an alarm from a rental agency and were given the instructions with the alarm. The authors conclude that arousal training is 'definitely the treatment of choice for enuretic children between 6 and 12 years'. Compared with other studies, and considering experience of daily practice, one may question the very high success rate in this particular group of patients.

Level of evidence: 3.

Recommendation: grade C

The enuresis alarm remains the most effective means of facilitating arousal from sleep. The key to success is not the stimulus intensity of the alarm triggering, but the child's preparedness to awake and respond to the signal.

10. ACUPUNCTURE:

In one randomised controlled trial that examined acupuncture, 40 children were allocated either to dDAVP or acupuncture, 75% of children were dry after 6 month of therapy (while still on medication), while 65% of patients were completely dry after a mean of 12 sessions. From this study it is concluded that as an alternative, cost-effective and short-term therapy, acupuncture should probably be counted among available treatment options. Another metaanalysis provides some evidence for the efficacy of acupuncture for the treatment of childhood nocturnal enuresis [126].

Comparison of treatment outcome and cure rates is difficult because of the inconsistent use of definitions, the inclusion of children with daytime symptoms, and the variable follow-up periods in most studies. For a pragmatic approach, see **Figure 3**.

Level of evidence: 4

Recommendation: grade D

11. COMBINED TREATMENT WITH ALARM AND DESMOPRESSIN

Combined treatment may be superior to alarm alone especially for non-responders of each individual treatment. In this approach, treatments are started at the same time: the rapid action of dDAVP is believed to facilitate the child's adaptation to the alarm [127,128]. After 6 weeks the dDAVP is discontinued while the alarm treatment is continued until the child becomes completely dry. Compared with either therapy alone, the combination is particularly effective in children with high wetting frequencies and behavioural problems.

Combination with full-spectrum therapy may even yield higher success rates [129-130].

Van Kampen et al reported their results of 'full-

spectrum' therapy in 60 patients: they were treated for 6 months with a combination of alarm, bladder training, motivational therapy and pelvic floor muscle training: 52 patients became dry [129].

The combination of alarm with six weeks of 40ug Desmopressin intranasally was better than alarm treatment alone, especially with high micturition frequency and comorbid behavioural symptoms [127]. In a Chinese study comparing alarm, Desmopressin and a combined therapy, the latter had the highest rate of sustained response (40.6%). However, there was a high relapse rate after discontinuing medication [131].

In another randomised-controlled, double blind study, the addition of 3 weeks of 40ug and 3 weeks of 20ug Desmopressin to alarm use, lead to temporary, short-term reduction of wet nights compared to controls on alarm and placebo [128]. The long-term success rate did not differ between the two groups and were low (36% and 37%, respectively). In the subgroup of Desmopressin non-responders, the combination of alarm plus Desmopressin was not more successful (51.5% remission) than alarm plus placebo (48.1% remission), so that this cannot be recommended as a routine strategy [132].

Also, theorectically, the combination of alarm and Desmopressin makes little sense: alarm treatment is an operant type of behavioural therapy that requires a certain number of wet nights to be effective: by reducing the number of wet nights through Desmopressin, the child will have less opportunity to 'practice' and 'learn' continence by the alarm therapy.

Also, the combination of alarm and anticholinergics should be considered if an overactive bladder is suspected. If the alarm is set off several times per night, indicative of overactive bladder, this combination has been proven to be successful. For example, 5 mg of Oxybutinin in the evening combined with alarm could be tried in these cases. If higher levels of anticholinergics are required, several doses should be given over the day.

In conclusion, based on current evidence, alarm treatment alone should be started first. As an adjunct programme, arousal treatment is easy to perform and effective. Also, the combination of alarm and Oxybutinin can be indicated. Alarm and Desmopressin are the two first line alternatives, but their combination cannot be recommended. Other programmes such as 'full spectrum treatment' remain treatment forms that are reserved for therapy-resistant cases. In certain cases, alarm treatment will not be possible: this is the prime indication for desmopressin.

12. INHIBITORS OF PROSTAGLANDIN SYNTHESIS

Because nocturnal polyuria in children with NE may not be entirely attributed to a defect in free water excretion, but rather to an increase in nocturnal excretion of sodium, cyclo-oxygenase inhibitors tlike diclofenac), which reduce urinary sodium excretion, have been tried and in a randomised double blind placebo controlled study proved to be effective [133]. Further studies need to be done to elucidate the role of these drugs.

13. NON RESPONDERS

About one third of children do not respond to treatment with alarm and/or dDAVP. The majority of these children are likely to have a small nocturnal bladder capacity and suffer from "detrusor dependent NE". These children may void more frequently than their peers or have urgency and day-time urgency incontinence. They are also often constipated. Prescription of dDAVP plus antimuscarinics should be considered, although evidence from the literature is lacking. Most likely, the reduced urinary output during the night leads to a lower filling rate which may reduce the nocturnal involuntary detrusor contractions and enhance the action of antimuscarinic drugs. Treatment success is usually noted between 1-2 months. Treatment should be continued for 6 -12 months, but clinical evidence is lacking.

On the other hand some of these children may have day time incontinence, which was not discovered during the initial workup. They should be given a strict voiding regimen and a combination of dDAVP with the alarm [54].

Some children who remain non-responders to desmopressin in combination with alarm and / or anticholinergic drugs, may have absorptive nocturnal hypercalciuria which may be responsible for the NE in some of these patients. With an appropriate (low calcium) diet these patients can became desmopressin responders [134].

NE is a symptom, not a homogeneous disorder. A really efficient treatment will never become possible until we have clarified all the different pathophysiological subgroups that go under the heading of NE.

14. CONCLUSION

Response and cure of different treatment modalities

Full response (while on medication) and Cure rates (6 months after cessation of treatment) of Nocturnal Enuresis

	Full response	Cure
Alarm treatment	**65%**	**43%**
Desmopressin	**31%**	**22%**
Dry-bed training	**40%**	**18%**
Imipramine		**17%**

- Gaining the confidence of the child and the family is paramount. The development of structure in the child's life, early bedtime, careful diary keeping,

avoidance of fluids late in the day, are critical.

- Secondly, identifying compounding psychological or physiologic factors of the child such as constipation and diurnal enuresis are critical.
- Third, alarm treatment should probably be recommended as the first choice of treatment with the modifications listed above. Single parents have a difficult time with the effort that is required to awaken with the child for the alarm management, and, in some cases, when children are not frequently wet, dDAVP may provide effective therapy for the last few years that they are at risk. In general, those that do the best with the alarm therapy are those with frequent bedwetting, normal estimated bladder volume, parents who are willing to participate, and true monosymptomatic nocturnal enuresis.
- Desmopressin seems to work best in children who are unable to participate in alarm therapy, who have truly monosymptomatic nocturnal enuresis, who are wetting only once on a wet night and are relatively devoid of OAB symptoms.
- If the initial treatment does not provide satisfactory results in two months, the child can switch to another. In some cases, using both the alarm and Desmopressin can be effective [127,135].
- Lastly, combinations of therapy including Desmopressin plus an antimuscarinic can be used in some cases, if detrusor overactivity at night is suspected.

D. Children with both day and night time incontinence

Urinary incontinence in children may be caused by a congenital anatomical or neurologic abnormality, such as ectopic ureter, bladder exstrophy or myelomeningocele (MMC). In many children, however, there is no such obvious cause for the incontinence and they are referred to as having "functional incontinence."

Becoming continent is a complicated process: there is a progressive development towards normal storage and emptying of the bladder at a socially accepted place and time, mostly achieved by age 3-4.

Bladder control is believed to be under the influence of the central nervous system. The pontine region is considered to be responsible for detrusor sphincter coordination while the cortical area is responsible for inhibition of the micturition reflex and voluntary initiation of micturition (detrusor overactivity control). Formerly it was believed that bladder maturation followed maturation of cortical inhibition processes, However, recent work of CK Yeung suggests bi-directional maturation of both the coordinating influence on the bladder and the pons may be implicated. This implies that a condition such as detrusor overactivity would be the result of loss of cortical control or of deficiency in cortical control, while dysfunctional voiding would be the result of non maturation of the coordination.

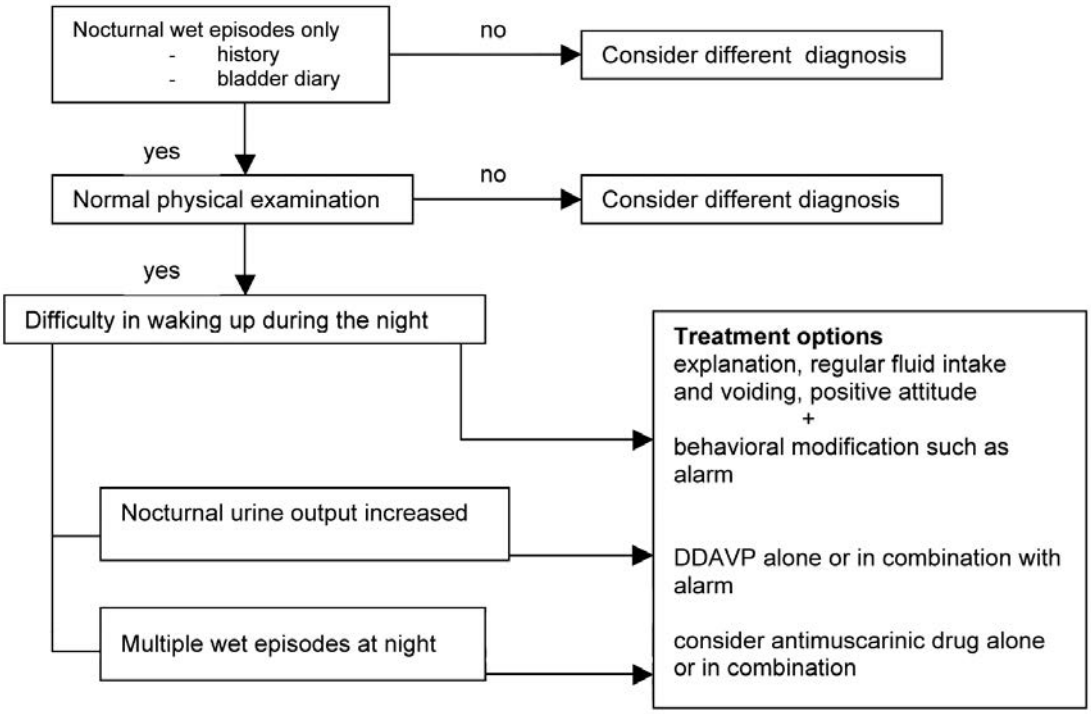


Figure 13. Pragmatic approach to the diagnosis and treatment of nocturnal enuresis

With the emergence of functional MRI, future studies will be able to illuminate this enigma.[1] This opens an era of corticocentric thinking on lower urinary tract dysfunction, moving away from the current trend of vesicocentric thinking. Detrusor overactivity may be a symptom of a centrally located dysfunction affecting bladder, bowel, sexual function and even mood and behaviour.[2] Indeed many studies indicate that there exists a link between lower urinary tract dysfunction and ADHD (attention deficit and hyperkinesia) [3-5].

The desire to void is a sensation which, in the developing child, is incorporated into daily life so that voiding takes place at an appropriate time and place. Problems with training or psychological difficulties possibly have a great impact on the results of training: some parents send their child to the toilet many times, though his/her bladder may be empty [6]. Voiding in these circumstances can only be achieved by abdominal straining. The positive reinforcement that the child receives by voiding even a small amount may lead to the development of an abnormal voiding pattern. The same is true when children receive negative feedback related to voiding [7]. Urinary incontinence in children may be due to disturbances of the filling phase, the voiding phase or a combination of both. . In the ICCS terminology document, these conditions are termed functional bladder disorders or Lower Urinary tract (LUT) conditions. They are divided into either overactive bladder (OAB) or dysfunctional voiding [8]. While the former condition is a filling disorder the latter is considered an emptying disorder. They can of course coincide and one may even be causative of the other.

Detrusor overactivity may lead to disturbances in the filling phase characterized by urgency, frequency and at times urgency incontinence. Girls present with OAB symptoms more often than boys. In addition to the urinary symptoms, children with functional urinary incontinence may also have recurrent urinary tract infections (UTI) and constipation.

Incomplete relaxation or tightening of the sphincteric mechanism and pelvic floor muscles during voiding results in an interupted or staccato voiding pattern, that may be associated with elevated bladder pressures and post-void residuals. Such individuals with dysfunctional voiding are also prone to constipation and recurrent UTIs [9]. Bladder function during the filling phase in these children may be essentially normal, alternatively OAB may be present. In children with a underactive detrusor, voiding occurs with reduced or minimal detrusor contractions with post-void residuals, and incontinence is a characteristic symptom.

I. PREVELANCE

For more detailed information on the prevalence of daytime incontinence the Chapter on Epidemiology should be consulted, where an overview is presented on the currently available data. The main problem is that it is impossible to draw any conclusions from the presented data as different studies have used definitions and criteria that differ from others. Furthermore, it is virtually impossible to identify the prevalence of detrusor overactivity or dysfunctional voiding as the studies tended to look primarily at daytime versus nighttime incontinence and made no effort to evaluate the type of daytime incontinence.

Daytime or combined daytime and nighttime incontinence at least once a week seems to occur in about 2-4 percent of 7-year old children and is more common in girls than in boys [10]. Overall the rates of prevalence vary from 1 to 10 percent, but in general for 6 to 7 year old children the prevalence is somewhere between 2 and 4 percent, and rapidly decreases during the following years [11-17]. Sureshkumar et al in a population based survey of over 2000 new entrant primary school children [age 4-6 years] in Sydney, Australia noted an overall prevalence of daytime wetting of 19.2% defined as at least one daytime wetting episode in the prior 6 months with 16.5% having experienced more than one wetting episode and only 0.7% experiencing wetting on a daily basis [17,18]. Multivariate analysis showed that recent stress, a history of daytime wetting along the paternal line, and a history of wetting among male siblings were independent risk factors for moderate to severe daytime wetting. Because this was a cross-sectional study recall bias may have resulted in an overestimate of risk of daytime wetting being caused by such factors as emotional stress and family history. In addition, urine cultures were not obtained so occult UTIs could not be identified.

Chung comes to the same percentage of OAB (16,6%) in 19,240 Korean children. In this study OAB was differentiated in ‘dry’ OAB and ‘wet’ OAB: children with OAB do not always have incontinence [19].

In a questionnaire based study, supplemented by telephone calls, Hellstrom assessed the prevalence of urinary incontinence in 7 year old Swedish school entrants [20]. Diurnal incontinence was more frequent in girls than boys, 6.7% vs 3.8%, respectively. Wetting every week was reported in 3.1% girls and 2.1% of boys. The majority of children with diurnal incontinence had concomitant symptoms: urgency was reported in 4.7% girls and 1.3% boys. Nocturnal incontinence combined with daytime wetting was equally common in males versus females, 2.2% versus 2%, respectively. At the age of 17 years daytime wetting, at least once a week, was found in 0.2 % of boys and 0.7% of girls. A limitation of this study is its dependency on recall. Children with daytime or mixed wetting were found to suffer from urgency in 50.7 %, with 79.1 % wetting themselves at least once in 10 days [21]. Urgency symptoms seem to peak at age 6–9 years and diminish towards puberty, with an assumed spontaneous cure rate for daytime wetting of about 14% per year [21,22].

Most children are toilet-trained by the age of 3 years, although the mean age may range from 0.75 to 5.25 years, with girls being trained earlier [2.25 years] than boys (2.56 years) [23]. A Turkish study, in 2008, reported day dryness at a mean age of 28 months [24]. The age of commencing toilet training has increased [25].

This is thought to be associated with higher education levels in parents and the popularity of the child-oriented approach rather than parent-initiated methods [26]. Children who exhibited elimination signals for voiding became dry sooner than those who did not show such signs. There is huge social and cultural variation in toilet training practices with some of the implicated issues being, availability of inside toilet, washable versus disposable diapers, working or home-based mothers, rural or urban location and use or not of punishment methods [23].

It appears that initiating toilet training after 24 months of age may be associated with problems attaining and maintaining bladder control and that early training is not associated with bladder dysfunction [25,26].

Da Fonseca found no such association between children with combined bladder and bowel dysfunction and the time of toilet training compared to healthy children [27].

Swithinbank et al have found a prevalence of day wetting [including also "occasional" wetting] in 12.5% in children age 10-11 years which decreases to 3.0% at age 15-16 years [28]. Based on these findings, it seems that the prevalence of all kinds of daytime incontinence diminishes by 1-2% per year from age 10-11 to age 15-16 years, while daytime incontinence, at least once a week, seems to diminish by 0.2% per year from age 7 to age 17 years. Because of treatment interventions the studies may not recount the true natural history.

A more recent cohort study of all school children in the first and fourth grades in the city of Eskilstuna (Sweden), daytime urinary incontinence (at least once a month) was reported in 6.3% of the first graders and 4.3% of the fourth graders, while bedwetting (at least once a month) was reported in 7.1% and 2.7% and faecal incontinence in 9.8% and 5.6%, respectively. This study demonstrates that soiling and daytime urinary incontinence often coexist [29].

The natural history of detrusor overactivity in children is not well understood. It is no longer held that detrusor overactivity in children is idiopathic or due to a maturational delay but more likely to be associated with feed forward loops from the generation of a high pressure system during voiding or filling. Both the interplay of neural drive with motor control and the dynamic nature of the growing bladder could be causative. This is in contrast to the adult population, where detrusor overactivity is considered a chronic condition whose origin is unrelated to functional use. There is no long-term data to determine if childhood detrusor overactivity predicts detrusor overactivity as an adult.

There is evidence that genetic influences affect adult urinary symptoms and that suffering lower urinary tract conditions in childhood increases the risk for these conditions in adult woman [30-33]. Recent research points to a link between deficits in the brain and functional urinary problems [5].

By the age of 5 years, unless organic causes are present, the child is normally able to void at will and to postpone voiding in a socially acceptable manner. After this age, night-time and daytime involuntary wetting become a social problem and a cause for therapeutic intervention. In children who present with a change in voiding habits, such as a new onset of voiding dysfunction, one should consider the possibility of child sexual abuse [37]. A more recent study found no significant differences in the presence of lower urinary tract symptoms between children and adolescents who had experienced sexual abuse and controls [33]. Nevertheless this should be kept in mind, especially when invasive diagnostic and therapeutic procedures are contemplated. One may want to simply ask the parent or caregiver if there were any precipitating events or concerns that they feel may have led to the changes in the child's voiding habits. The appropriate individuals should be contacted if there is a high index of suspicion. Of adult women with complex urinary symptoms, a significant proportion report sexual abuse as a child.

II. INTRODUCTION TO CLINICAL ASSESSMENT

The International Children's Continence Society has published standardisation documents on the diagnostic evaluation of children with daytime incontinence as well as on the management of dysfunctional voiding in children. They also assessed psychological and psychiatric issues in urinary and fecal incontinence [34-36].

The evaluation of daytime wetting is based on the medical and voiding history, a physical examination, a urinalysis, bladder diaries and uroflowmetry with post void residual. The upper urinary tract should be evaluated in children with recurrent infections and dysfunctional voiding. Uroflowmetry can be combined with pelvic floor electromyography to demonstrate overactivity of the pelvic floor muscles. Urodynamic studies are usually reserved for patients with therapy resistant dysfunctional voiding and those not responding to treatment who are being considered for invasive treatment [38-41].

Treatment is usually a combination of 'standard therapy' (see below), behaviour therapy, bladder training, physiotherapy and medical treatment. Surgery is rarely needed for the management of daytime

wetting in the absence of a structural abnormality. The roles of neuromodulation, botulinum toxin and intravesical therapies in the management of pediatric urinary incontinence are less well-defined. Clean intermittent self-catheterization is sometimes necessary in children with poor bladder emptying, due to underactivity of the detrusor and subsequent large residuals, who do not respond to a more conservative approach. The importance of treatment during childhood was pointed out in a general population study of 1333 adult women. Fifty percent reported symptoms of stress incontinence and 22 percent reported symptoms of urgency incontinence. Eight percent noted severe symptoms. Women who at age six years had wet episodes during the day or were wet several nights per week, were more likely to suffer from severe incontinence and report urgency symptoms: occasional bedwetting was not associated with an increased risk in adult life [42].

III. CONFOUNDING FACTORS: LOWER URINARY TRACT DYSFUNCTION, RECURRENT URINARY TRACT INFECTION AND VESICOURETERIC REFLUX (VUR)

The relationship between detrusor dysfunction and VUR associated with a urodynamic anomaly was first described by Allen and Koff and has been confirmed by several authors [43-46]. Koff demonstrated that treatment of detrusor overactivity reduced the incidence of infection and resulted in a 3 fold increase in the rate of reflux resolution. In a study by Sillen of children with gross bilateral reflux, extreme detrusor overactivity without signs of bladder outlet obstruction was found in boys. Infant girls with gross bilateral reflux did not show the same degree of detrusor overactivity [46]. Other investigators assessing high grade VUR in newborns noted similar findings. Van Gool et al noted that 40% of 93 girls and boys evaluated for urgency incontinence and recurrent UTIs had reflux [47].

These studies in infants and the association of combined bladder and bowel dysfunction with reflux and infection in older children support the suggestion that, in some individuals, vesicoureteral reflux is a secondary disorder related more to abnormal detrusor function than to a primary anatomic defect at the ureterovesical junction. It has been shown that increased intravesical pressure, without reflux, may be detrimental for the upper tracts: renal scarring without reflux was described by Vega at al recently [48].

In support of this concept is the common finding of vesicoureteral reflux in children with neuropathic bladders and detrusor-sphincter dyssynergia. In such children, the institution of clean intermittent catheterization and anticholinergic therapy leads to the resolution of VUR in a large number of cases. It is believed that the decrease of detrusor overactivity and restoration of functional capacity in combination with regular and complete emptying of the bladder are the responsible co-factors [49]

Koff et al. evaluated the effects of antimuscarinic therapy in 62 children with a history of recurrent UTIs, VUR and detrusor overactivity, and compared these children with an age-matched control group with a normal urodynamic study [50]. The overall small sample size and the small number of compliant patients limit the study, however, it did demonstrate a statistically significant difference in the resolution rate of VUR between the treated group and the control group. The overall infection rate was lower in the treated group [16%] compared to the non-medically treated group [63%] and the age-matched control group [71%]. Several authors have documented the relationship between detrusor overactivity and dysfunctional voiding with recurrent UTIs .

Proposed etiologies for the increased incidence of UTIs in these patient populations include a milk back phenomenon whereby bacteria in the proximal urethra are “milked back” into the bladder during contraction of the pelvic floor muscles. Alternatively, decreased blood flow and relative hypoxia during periods of increased detrusor pressure such as during involuntary detrusor contractions and voiding against functional obstruction, may induce transient bladder mucosal injury.

Constipation is prevalent among children with bladder symptoms, but often poorly identified by parents [51]. It is a risk factor for recurrent UTIs. Contrary to expectations, findings from the European Bladder Dysfunction Study suggested that symptoms of disordered defecation did not influence the cure rate of treatment for bladder symptoms [52]. In a prospective non-randomized clinical series of day wetting children, a strong correlation was found between recurrent urinary tract infections, detrusor overactivity and detrusor-sphincter dysfunction [53]. In a study by Hansson et al, symptoms of detrusor overactivity, such as urgency and daytime incontinence were found in a high percentage of girls with asymptomatic bacteriuria [54].

In the majority of children with dysfunctional voiding the recurrent infections disappeared following successful treatment of the voiding dysfunction. This finding confirms the hypothesis that dysfunctional voiding is the main factor responsible for the infections [and to a lesser extent vice versa] [55,56],. Additionally, since such children typically have coexistent constipation, attempts at restoring normal bowel habits will also contribute to decreasing the risk of UTIs. At present, current opinion is that vesicoureteral reflux as such does not predispose to UTI: however it may facilitate renal involvement [causing pyelonephritis] once bacteriuria has been established in the bladder. This concept has not been scientifically validated and the incidence of renal scars as a consequence of pyelonephritis is reportedly the same, regardless of whether reflux has been documented

or not [57]. Those children with VUR in association with detrusor overactivity and/or voiding dysfunction may be at increased risk for upper tract damage given their increased risk of developing UTIs. With this in mind, aggressive treatment of the underlying filling/voiding disorder, the addition of prophylactic antibiotics, and attention to their bowel habits should be given in an effort to decrease the risk of UTIs in this higher risk group [58-61].

In a recent study evaluating retrospectively a large group of children with LUT conditions it was shown that in patients who had urinary tract infection the presence of reflux increased the rate of renal cortical abnormalities. [62]

IV. CLASSIFICATION

Numerous classifications have been used for children who present with varying degrees of 'functional' urinary symptoms, unrelated to apparent disease, injury or congenital malformation. In 2006, the International Children's Continence Society (ICCS) released a standardized terminology to provide guidelines for the classification and communication about LUTS in children [8]. Symptoms are classified according to their relation to the voiding and or storage phase of bladder function.

In addition to gaining a comprehensive history, observing micturition and examining the child forms the basis of assessment: the information derived from a 48-72 hour bladder diary, stool record, voiding uroflowmetery and lower urinary tract ultrasonography is also essential in making the initial diagnostic classification [34]. Urodynamic investigations elucidate the basis of clinical findings but are first line evaluation techniques only in tertiary referral centers where children have not responded to previous treatment or have symptoms suggestive of neural involvement or anatomical anomalies.

The ICCS has classified daytime LUT conditions into groups that currently align with understanding of underlying pathophysiology. The groups commonly overlap and allocation is based on the 4 symptoms of urinary incontinence, frequency of volitional voiding, micturition volumes and fluid intake.

Over active bladder (OAB) including urgency incontinence

Dysfunctional voiding

Underactive bladder

The symptom-specific conditions of

Voiding postponement

Vaginal reflux

Giggle incontinence

Extraordinary daytime urinary frequency

Elimination syndrome

The term 'non-neurogenic dysfunction' is commonly encountered in the literature and describes the whole spectrum, from simple bladder overactivity to severe cases with deterioration of the upper tracts. The fact that a neurologic deficit is not demonstrated at the time of evaluation, does not, however exclude the possibility that a neurologic abnormality was present at the onset of the problem. It has been postulated that detrusor overactivity may eventually lead to poor bladder emptying due to underactivity of the detrusor or severe dyscoordination between detrusor, sphincter and pelvic floor. However, the natural history of many of these children does not confirm this hypothesis, nor the early onset of severe pathology in some of them. Hoebeke et al found no evidence for this dysfunctional voiding sequence: children with functional incontinence have different primary diseases, but all have a common risk of incontinence, UTI, VUR [15%] and constipation [17%] [63].

1. OVERACTIVE BLADDER IN CHILDREN

The term bladder overactivity is used to describe the symptom complex of urgency, which may or may not be associated with urgency incontinence and is not a direct result of known neurological damage. Recent suggestions describe OAB as a symptom of corticocentral dysfunction that affects multiple systems rather than a dysfunction isolated to the urinary bladder [64],.Urgency syndrome is characterized clinically by frequent episodes of an urgent need to void, countered by contraction of the pelvic floor muscles (guarding reflex) and holding manoeuvres, such as squatting and the Vincent curtsey sign. The term urgency refers to a sudden compelling desire to void that is often difficult to defer, unlike the need to void which is experienced by all individuals and may be intense if one holds one's urine for a prolonged period of time. The symptoms arise from detrusor overactivity during the filling phase, causing urgency. These detrusor contractions are countered by voluntary contraction of the pelvic floor muscles to postpone voiding and minimize wetting. The detrusor contractions can be demonstrated urodynamically, as can the increased activity of the pelvic floor muscles during each contraction.

The voiding phase is essentially normal, but detrusor contraction during voiding may be extremely powerful. The flow rate reaches its maximum quickly and may level off ('tower shape'). Such strong bladder and pelvic floor muscle contractions have been postulated to result in damage to the bladder mucosa increasing the risk of UTIs. In addition, these children may note suprapubic or perineal pain. A cohort of patients presenting with nighttime pain syndromes based on pelvic floor spasms was described by Hoebeke et al. Good response to pelvic floor relaxation biofeedback is described in this study [65]

Overactive bladder (OAB) should also be considered in "continent" children with recurrent UTI and vesicoureteral reflux. Depending on fluid intake and

urine production, the complaints of incontinence become worse towards the end of the day, due to loss of concentration and fatigue and may also occur during the night. Children usually diminish their fluid intake to minimize wetting, and therefore incontinence may not be the main complaint or symptom, but on careful questioning urgency becomes apparent.

Frequent voluntary contractions of the pelvic floor muscles may also lead to postponement of defecation. Constipation and fecal incontinence (soiling) are often found in children with detrusor overactivity [66]. The constipation is aggravated by the decreased fluid intake. Constipation contributes to an increased risk of UTIs and may exacerbate the detrusor overactivity. An investigation of the natural history of combined emptying dysfunction of bladder and bowel, using an elimination score in women with and without urogynaecological problems, demonstrated that childhood lower urinary tract dysfunction may have a negative impact on bladder and bowel function in later life [67].

A careful history, physical examination and scrutiny of the child's bladder diary will identify symptoms of detrusor overactivity. Urine flow rate registration and post-void residual urine measurement help to identify co-exsisting dysfunctional voiding. Thus in the majority of children, invasive studies such as urodynamic studies are not indicated as part of the initial evaluation. Such studies are reserved for those children with a question of an underlying neurologic defect and those who fail to improve with medical and behavioral therapy, if invasive therapies are being considered.Those children with a history of recurrent UTIs should undergo assessment with a renal/bladder ultrasound and depending on the age of the child, and the severity of the UTI(s), a voiding cystourethrogram (VCUG) to assess reflux is occasionally performed [68,69]. By adopting a structured approach to history and physical examination, the diagnosis of urgency syndrome can be made in the majority of children without the need for invasive diagnostic procedures.

Treatment:

The treatment of urgency syndrome involves a multimodal approach, involving strategies such as behavioral modification, antimuscarinic medication, adjunctive biofeedback and neuromodulation. Underlying and potentially complicating conditions such as constipation and UTIs are managed prior to intervention.

Level of evidence: 3.

Grade of recommendation: C

2. DYSFUNCTIONAL VOIDING

Dysfunctional voiding refers to an inability to fully relax the urinary sphincter or pelvic floor muscles during voiding. There is no identified underlying neurologic abnormality. Children with dysfunctional voiding usually present with incontinence, urinary tract infections and constipation and demonstrate a intermittent, or fluctuating pattern referred ot as staccato flow (by ICCS definition) during repeated uroflowmetry.

No clear data are available on the possible causes of dysfunctional voiding. It may be that detrusor overactivity eventually leads to overactivity of the pelvic floor muscles, with subsequent insufficient relaxation during voiding [70]. Alternatively, poor relaxation of the pelvic floor muscles during voiding may be a learned condition during the toilet training years, adopted following episodes of dysuria due to UTI, or constipation or occuring secondary to sexual abuse [71]. The child's environment, in particular toilet conditions and privacy issues, can trigger or exacerbate voiding anomalies [72]. In some girls, anatomical anomalies of the external urethral meatus seem to be associated with a higher incidence of dysfunctional voiding. The urine stream may be deflected anteriorly and cause stimulation of the clitoris with subsequent reflex activity of the bulbocavernosus muscle causing intermittent voiding [73]. Since no true structural obstruction can be identified the intermittent incomplete pelvic floor relaxation that occurs during abnormal voiding is termed a functional disorder.

Abnormal flow patterns seen in children with dysfunctional voiding:

- Fluctuating (Staccato) voiding: continuous urine flow with periodic reductions in flow rate precipitated by bursts of pelvic floor activity. Voids are commonly prolonged and incomplete.
- Interrupted voiding: characterized by unsustained detrusor contractions resulting in infrequent and incomplete voiding, with micturition in separate fractions. Bladder volume is usually larger than age-expected capacity. Residual urine is often present. Detrusor overactivity may be seen but it may also be absent [56, 68, 74].

Sustained alteration of voiding is associated with subsequent filling phase anomalies such as phasic detrusor overactivity and inappropriate urethral relaxation [75]. Urinary tract infections and kidney damage are common sequelae[76]. Over time, routine incomplete bladder emptying can progress to detrusor over-distension associated with chronic urinary retention. The child with this presentation is often classified as having poor bladder emptying due to detrusor underactivity .

Urinary symptoms associated with dysfunctional voiding range from urgency to complex incontinence patterns during the day and night [77]. Children with dysfunctional voiding have a higher rate of recurrent urinary tract infections than children with no voiding abnormality and also demonstrate increased incidence of higher grades of VUR [63, 78]. Symptoms are significantly more common in children with Attention Deficit Disorder than in 'normal' children [79].

Signs of dysfunctional voiding reflect initial "compensatory" overactivity of the detrusor along with poor emptying ability. They may include small bladder capacity, increased detrusor thickness, decreased detrusor contractility, impaired relaxation of the external urinary sphincter/ pelvic floor during voiding, weak or interrupted urinary stream and large post-void residual volumes of urine. There may also be ultrasound abnormalities, secondary vesicoureteric reflux, fecal incontinence or constipation [63, 80,81].

Treatment:

Symptoms are often refractory to standard therapy of hydration, bowel management, timed voiding and basic relaxed voiding education. Effective intervention requires combination therapy, generally with a sizeable investment of time over a long period. Treatment is aimed at optimizing bladder emptying and inducing full relaxation of the urinary sphincter or pelvic floor prior to and during voiding.

Specific goals are:

- consistent relaxation of the pelvic floor throughout voiding,
- normal flow pattern,
- no residual urine and
- resolution of both storage and voiding symptoms.

Strategies to achieve these goals include pelvic floor muscle awareness and timing training, repeated sessions of biofeedback visualization of pelvic floor activity and relaxation, clean intermittent self-catheterization for large post-void residual volumes of urine, and antimuscarinic drug therapy if detrusor overactivity is present. If the bladder neck is implicated in increased resistance to voiding, alpha-blocker drugs may be introduced. Recurrent urinary infections and constipation should be treated and prevented during the treatment period.

Treatment efficacy can be evaluated by improvement in bladder emptying and resolution of associated symptoms [82]. Controlled studies of the various interventions are needed. As with detrusor overactivity, the natural history of untreated dysfunctional voiding is not well delineated and optimum duration of therapy is poorly described.

Level of evidence: 4.

Grade of recommendation: C

3. DETRUSOR UNDERACTIVITY

Children with detrusor underactivity may demonstrate low voiding frequency and an inability to void to completion using detrusor pressure alone. Voiding is of long duration, low pressure, intermittent and often augmented with abdominal straining.

Children with this condition usually present with urinary tract infections and incontinence. Urodynamically, the bladder has a larger than normal capacity, a normal compliance and reduced or no detrusor contraction during voiding. Abdominal pressure is the driving force for voiding. The previously used term 'lazy bladder' is incorrect and is no longer used.

A correct diagnosis can only be made by urodynamic evaluation. Renal function studies, renal ultrasound and VCUG should be performed to assess the extent of renal damage and reflux. Long-standing overactivity of the pelvic floor may in some children be responsible for decompensation of the detrusor, leading to a non-contractile detrusor. However, no data are available to support this theory.

Treatment:

Treatment is aimed at optimizing bladder emptying after each void. Clean intermittent (self) catheterization is the procedure of choice to promote complete bladder emptying, in combination with treatment of infections and constipation [which may be extreme in these patients]. Intravesical electrostimulation has been described, but at this time it is still not recommended as a routine procedure for children.

Level of evidence 4

Grade of recommendation C

4. VOIDING POSTPONEMENT

Voiding postponement is a condition in which children postpone imminent micturition until overwhelmed by urgency, resulting in urgency incontinence [83] . A recent study comparing children with typical OAB to those with voiding postponement revealed a significantly higher frequency of clinically relevant behavioral symptoms in postponers than in children with OAB, suggesting that voiding postponement is an acquired or behavioral disorder [83]. In the children with voiding postponement only 20% exhibit a fluctuating voiding pattern. It remains to be determined whether or not voiding postponement can develop in the setting of a perfectly normal urinary tract or whether OAB is a necessary precursor.

Level of evidence 4

Grade of recommendation C

5. GIGGLE INCONTINENCE

In some children giggling can trigger partial to complete bladder emptying well into their teenage years, and intermittently into adulthood [84]. The condition occurs in girls and occasionally in boys and is generally self-limiting. The etiology of giggle incontinence is not defined. Urodynamic studies fail to demonstrate any abnormalities, there is no anatomic dysfunction, the upper tracts appear normal on ultrasound, the urinalysis is normal and there are no neurologic abnormalities [85,86]. It is postulated that laughter induces a generalized hypotonic state with urethral relaxation, thus predisposing an individual to incontinence, however the effect has not been

demonstrated on either smooth or skeletal muscle. It has also been suggested that giggle incontinence is due to laughter triggering the micturition reflex and overriding central inhibitory mechanisms. One small study hinted at an association with cataplexy (a state of excessive daytime sleepiness), suggesting involvement of central nervous structures, however with only 7 subjects further evidence is needed [87]. Since the etiology of giggle incontinence is not known it is difficult to determine the appropriate form of treatment. Positive results have been reported with conditioning training, methylphenidate and imipramine [85- 91]. Others have tried antimuscarinic agents and alpha-sympathomimetics. There is no acceptable evidence that any form of treatment is superior to no intervention.

Level of evidence 3

Grade of recommendation D

6. VESICOVAGINAL ENTRAPMENT

Urinary leakage that occurs in girls a short time after voiding to completion, that is not associated with any strong desire to void, may be the result of vesicovaginal reflux [92]. Urine may become entrapped in the vagina during voiding due to labial adhesions, a funnel shaped hymen, or an inappropriate position on the toilet. The classic presentation is that of a girl who does not spread her legs apart during voiding and who is not sitting all the way back on the toilet seat, but who is rather sitting near the end of the toilet seat tilting forward. Obesity may be an associated risk factor. Changes in voiding position and treatment of labial adhesions will lead usually to resolution of the urine leakage.

Level of evidence 4. Grade of recommendation C

7. ELIMINATION SYNDROME

This is a term used to describe dysfunctional emptying of bowel and/or bladder presenting with symptoms of OAB, constipation and sometimes infrequent voiding.

The term is misleading as the combined bladder and bowel dysfunction involves dysfunction of both emptying and storage.

The genitourinary tract and the gastrointestinal system are interdependent, sharing the same embryologic origin, pelvic region and sacral innervation. Although children with voiding disturbances often present with bowel dysfunction, until recently this co-existence was considered coincidental. However, it is now accepted that dysfunction of emptying of both systems, in the absence of anatomical abnormality or neurological disease, is inter-related. The common neural pathways, or the mutual passage through the pelvic floor musculature, may provide a theoretical basis for this relationship, as may the acquisition of environmental and developmental learning. The latter can be influenced by episodes of urinary tract infection, constipation, anal pain or trauma, childhood stressors, reluctance to toilet and poor toilet facilities [66,72,93].

There is also evidence to suggest that in severe cases symptoms may have a neurological basis.

The Elimination Syndrome [ES] is seen more frequently in girls than boys and is significantly associated with the presence of both VUR and UTI [94]. VUR is slower to resolve and breakthrough urinary tract infections are significantly more common in children with ES when compared to those without the diagnosis. Infections do not ameliorate with antibacterial prophylaxis. Age of first febrile UTI does not appear to be an etiological factor [84], however, recurrence of UTI in children older than 5 years is associated with the presence of ES [95,96].

Abnormal recruitment of the external anal sphincter during defecation or at call to stool is considered causative, in that it elicits concomitant urethral sphincter and pelvic floor co-contractions. Thus in both systems a functional obstruction to emptying is generated. In the case of the urinary system, high pressures generated by the detrusor muscle to overcome a decrease in urethral diameter can stimulate detrusor hypertrophy, detrusor overactivity, and lead to incompetence of the vesicoureteric junctions. In the early stages of defecation disorders, bowel emptying is incomplete, infrequent and poorly executed. As the dysfunction progresses stool quality becomes abnormal, the child develops distension of the rectum and descending colon, seems to lose normal sensation and develops fecal retentive incontinence. If constipation was not present as a predisposing factor, it rapidly develops [93].

Children with elimination syndrome commonly complain of urinary incontinence, non-monosymptomatic nocturnal enuresis, recurrent urinary tract infections, imperative urgency to void (OAB) and exceptionally urinary frequency. On investigation, they are often noted to have poor voiding efficiency, vesicoureteric reflux, constipation, fecal incontinence, no regular bowel routine and infrequent toileting. The incidence of children with elimination syndrome and sub-clinical signs and symptoms is unknown.

Assessment follows the same process as for other aspects of pediatric bladder dysfunction, with the addition of a 2 week bowel diary and relevant symptom score. The inclusion of an ultrasound rectal diameter measure, either via the perineum or when assessing the bladder, has been shown to be discriminative for children with elimination syndrome. Urinary flow curve, perineal EMG and post void residual urine estimate, when considered in isolation, are not conclusive for the diagnosis of elimination syndrome. There is no evidence to suggest that anorectal manometry is warranted as a first line investigation in these children. Recently a symptom scale for ES has been developed providing objective assessment for diagnosis and quantification of severity [97].

Treatment:

Treatment aims at assisting a child to become clean and dry in the short term, by retraining appropriate bladder and bowel awareness and teaching dynamic elimination skills. As bowel dysfunction is more socially isolating than urinary incontinence, and in the light of evidence that amelioration of underlying constipation can relieve bladder symptoms, most clinicians begin with treatment of the bowel. Strategies include disimpaction [if needed], prevention of stool reaccumulation, and post-prandial efforts to empty the bowel while maintaining optimal defecation dynamics. Once stools are being passed regularly, treatment focuses on teaching awareness of age appropriate fullness in the bladder, and training unopposed emptying (without straining or pelvic floor muscle recruitment), at pre-scheduled times. Pelvic floor awareness training and biofeedback therapy are integral.

There are few studies of the efficacy of treatment in children with elimination syndrome. Several authors have evaluated the outcome of constipation management on bladder symptoms, however the baseline characteristics of subjects were not described adequately enough to allow clear diagnosis of elimination syndromes [66, 97]

A review on the effectiveness of biofeedback for dysfunctional elimination syndrome reports that 80% of children benefited from biofeedback but that the level of evidence was low due to poor study designs [99].

Level of evidence 4.

Grade of recommendation C

V. PRINCIPLES OF NON PHARMACOLOGICAL TREATMENT FOR ALL DIFFERENT STATES

Treatment of the over active bladder focuses on both the involuntary detrusor contractions and the child's response to these. The initial treatment of daytime urinary incontinence involves a behavioral and cognitive approach. The child and parent[s]/caregiver(s) are educated about normal bladder function and responses to urgency. Voiding regimens are instituted and UTIs and any constipation are managed. Additional treatment involves pharmacotherapy, pelvic floor muscle relaxation techniques and biofeedback, either alone or in combination.

Although there are many studies reported in the literature assessing the effects of various forms of therapy on daytime incontinence and urinary symptoms, many of these are case series rather than being randomized or controlled trials. The paucity of studies evaluating basic standard therapy initiatives has precluded double-blinded trials of novel and multimodal interventions. Whilst clinically important benefits are commonly described, patient numbers, objective outcome measures and length of follow-up are sub-optimal.

The main objectives of treatment are to normalise the micturition pattern, normalize bladder and pelvic floor overactivity and cure the incontinence, infections and constipation. Traditional therapy for day-wetting children is cognitive and behavioural. Children learn to recognize the desire to void and to suppress this by normal central inhibition instead of resorting to holding manoeuvers [i.e. immediate voiding without postponement] to generate urethral compression. Children with dysfunctional voiding learn to initiate voiding with a completely relaxed pelvic floor and to pass urine in association with a detrusor contraction rather than via generation of abdominal pressure. Dietary changes and bowel regimens are used to treat the constipation [98]. Antibiotic prophylaxis may prevent recurrent UTIs, however, data to support this is limited.

"Bladder training" is used widely, but the evidence that it works is variable [50, 88]. Some authors contend that in less severely affected children a thorough explanation of the underlying causes and the expected progress of resolution is sufficient treatment in itself [47] . More active conventional management involves a combination of cognitive, behavioral, physical and pharmacological therapy methods. Common modes of treatment include parent and child reassurance, bladder retraining (including timed toileting), pharmacotherapy, pelvic floor muscle relaxation and the use of biofeedback to inhibit rises in detrusor pressure associated with urinary incontinence [29, 100-102]. Further treatment options include suggestive or hypnotic therapy and acupuncture. A combination of bladder training programs and pharmacological treatment, aimed specifically at reducing detrusor contractions, is often useful and sometimes necessary.

1. BLADDER REHABILITATION AND UROTHERAPY

Initial intervention for OAB and dysfunctional voiding uses a non-pharmacologic approach. This is often termed Urotherapy. Despite its use for many years there is no set format to urotherapy and many clinical studies utilize differing combinations of therapies, which makes it difficult to evaluate the results [29, 60, 101]. The aim of urotherapy is to normalize the micturition pattern and to prevent further functional disturbances. This is achieved through a combination of patient education, cognitive, behavioral and physical therapy methods.

A Danish report of the outcome of standard urotherapy in 240 children with daytime incontinence noted achievement of dryness in 126 children (55%). Alarm therapy has traditionally been used for the treatment of nocturnal enuresis but was recently used in management of daytime wetting. When a time watch was utilized as a reminder to void at regular intervals 70%

of children became dry. An earlier study of a contingent alarm [which sounded when the child wets] versus a noncontingent alarm system (which sounded at intermittent intervals to remind the child to void) over 3 months in 45 children [103] was equally successful for the achievement of continence. Predictors for dryness included a low voiding frequency, larger volumes voided in relation to age-expected storage and fewer incontinent episodes per week [104].

There is evidence that for children who are therapy-resistant, timed voiding assisted by a timer watch added to urotherapy is effective [105].

Following a 3 month training programme, 42.8% of daywetting children were cured at 1 month, 61.9% by 6 months, and 71.4% by 1 year [106]. Allen et al [107] reported that urotherapy patients with good compliance with timed voiding were significantly more likely to improve their continence than those with poor compliance. It has recently been highlighted however, that there is frequently conflict between school rules, routines and toilet facilities and the urotherapy programme components. Adaptive coping techniques added to urotherapy training may enhanced gains in dryness.

In children with OAB and dysfunctional voiding the pelvic floor muscles relaxation is impaired during voiding. Physiotherapy is concerned with re-training of specific muscle groups. Adjunctive physiotherapeutic input offers children different strategies to achieve pelvic floor relaxation during micturition.

Several centers offer intensive urotherapy called voiding schools or even inpatient rehabilitation. A prospective evaluation of 38 Belgian children who underwent this approach showed improvement in 90% of the children with 42% becoming dry, whilst no child on the waiting list improved during the 6 months [108]. Long-term follow-up of 75 incontinent children who underwent intensive urotherapy 16-22 years later showed a good result in 84%and the authors concluded that if the original outcomes of pediatric intensive inpatient urotherapy were good, they tend to remain so over time in most patients [109].

Level of evidence 3.

Grade of recommendation C

2. ADJUNCTIVE BIOFEEDBACK

Biofeedback is a technique in which physiological activity is monitored, amplified and conveyed to the patient as visual or acoustic signals, thereby providing the patient with information about unconscious physiological processes. Biofeedback may be utilized for the management of both filling phase (detrusor overactivity) and voiding phase (dysfunctional voiding due to pelvic floor muscle overactivity) abnormalities.

Biofeedback can help children to identify how to relax their pelvic floor muscles or recognize involuntary detrusor contractions.

Training with biofeedback can be used as a single treatment [110,111], or in conjunction with a comprehensive rehabilitation program [112,113]. It may be performed by a cystometrogram during which the child is taught to recognize and inhibit involuntary detrusor contractions by watching the pressure curve during cystometry. This is invasive and a time consuming process with limited application as a routine treatment.

More commonly pelvic floor muscle relaxation is taught through the use of EMG biofeedback and real-time uroflow. The child sits on a toilet with a flow transducer, watching both the flow curve and EMG on a computer display, and attempts to empty completely in one relaxed void. Ultrasound may be used to determine the post void residual and demonstrate complete emptying. Interactive computer games are commonly used to make biofeedback training more attractive to children [114,115], however care should be taken that posture and muscle recruitment approximates that of the voiding position.

The results of biofeedback are commonly reported as case series rather than RCTs. Results are generally positive but overall may not be superior to high quality standard urotherapy. The group receiving adjunctive biofeedback in the Vasconcelos study [106] did not achieve greater continence rates at the study end point, although a greater proportion of subjects achieved earlier dryness. Furthermore, the post void residual volumes were significantly reduced in the biofeedback group compared to the standard therapy only group.

Long duration follow-up, whilst desirable, confounds results of intervention in children who are continually growing and maturing. Hellstrom et al report results of a 6 week bladder rehabilitation program inclusive of biofeedback [101] and note that at 3 years, 71% of the children with detrusor overactivity, 70% of those with dysfunctional voiding and 73% of those with a combined disturbance had a normal micturition pattern. The potential for bias from intercurrent events and interventions precludes statements about the efficacy of biofeedback alone.

Level of evidence: 3

Grade of recommendation C

3. CLEAN INTERMITTENT (SELF) CATHETERISATION

In children with an underactive detrusor, bladder emptying can be achieved with timed and double voiding. If this does not adequately empty the bladder clean intermittent self-catheterization (CISC) may be tried [116-118]. This requires careful guidance for both the child and the parents. Sometimes it is necessary to give the child a suprapubic catheter for a while and gradually prepare him/her to accept CISC. Once the infections have cleared and the child is continent it will become easier for both the parents and the child to accept. The frequency of CISC depends on the

severity of the problem and may vary between four times a day and once a day before going to bed.

Level of evidence 4.

Grade of recommendation C

4. NEUROMODULATION

Neuromodulation has been used in adults for a variety of lower urinary tract symptoms and has been applied in children. The use of transcutaneous stimulation with surface electrodes stimulating the sacral root (S3) has shown promising results, especially when tested as part of a randomized controlled trial [119]. Transcutaneous and percutaneous neuromodulation delivered over either the sacral outflow or peroneal region of the ankle at a frequency between 10-25 Hz, has proven a useful adjunctive treatment in children with detrusor overactivity. Intravesical stimulation can impact function of an underactive detrusor and potentially improve detrusor contractility and enhance bladder emptying [120,121]].

Electrical current directly affects the central nervous system by artificially activating neural structures; facilitating both neural plasticity and normative afferent and efferent activity of the lower urinary tract. For children with structural abnormalities, for example imperforate anus, electrostimulation is one method of facilitating strength gains in the skeletal muscle and its fascial attachments. Treatment is particularly useful in patients with very little pelvic floor awareness to stimulate muscle recruitment. Once neural efficiency has improved, training is augmented by active pelvic floor contractions.

In 2011, three papers were published reviewing the use of neuromodulation in children [122-124]. This highlights the level of interest in this modality for treating LUTD and also bowel dysfunction. A literature search revealed 18 reports of the use of neuromodulation in children with non-neurogenic bladder dysfunction. Only three of these studies were randomized and controlled, one a randomised crossover study whilst the rest were case series. However parasacral TENS has been shown to be more effective than sham in randomized trials in treating OAB. Use of neuromodulation in children with neurogenic LUT dysfunction has been reported in 9 studies, 3 of which were randomized controlled trials.

Of note is the fact that most studies have looked at the use of electrical neuromodulation in children whose symptoms have been refractory to all other interventions, whereas using it as first-line treatment may prove beneficial. Also studies using intravesical, transcutaneous and implantable electrodes have noted improved bowel function. One randomised placebo-controlled trial using interferential current transcutaneously showed significant improvements in colonic transit times,decreased soiling and abdominal pain and increased quality of life in children with severe constipation [125].

From **Table 1 and 2** it is clear that different modes of application have been trialed in mostly small series of children. There is minimal standardization of populations, application parameters or outcome measures. Thus evidence is largely drawn from low quality studies. Clearly neuromodulation in children warrants larger, controlled and randomized studies, including its use as first-line intervention and in children with combined bladder and bowel dysfunction. Despite the slow pace of research the reviewers of the articles mentioned above agree that there is a positive role for neuromodulation in children with LUTD, and that it is adjunctive to other interventions, with no known predictors of efficacy at the present time, but also rare and minor adverse events. Neuromodulation of the bowel shows promise.

Tables 1: Study parameters in paediatric neuromodulation trials (Neurogenic and Non Neurogenic bladder dysfunction)

Author and year of publication	Population	Design	N	Mode of application	Outcome measure
Guys 2004	Neurogenic (Spina bifida)	RCT	42	Sacral implant	n/s difference from controls for continence
Marshall 1997	Neurogenic (MMC)	RCT	50	Transcutaneous	n/s difference from controls for continence
Johnston 2005	Neurogenic (spinal cord injury)	Series	2	FES implant	Suppression of detrusor overactivity in 1 pt
Han 2004	Neurogenic (MMC)	Series	24	Intravesical	Significant ↓ in faecal incontinence
De Gennaro 2004	Neurogenic and Non neurogenic	Series	6 17	Percutaneous tibial nerve	n/s difference in neuropathic pts 5/9 with incontinence cured
Gladh 2003	Neurogenic and Non neurogenic	Series	20 24	Intravesical	40% cure neurogenic 83% cure non neurogenic
Hagerty 2007	Neurogenic	series	405	IVES	61% gained sensation >UD bladder capacity 77%
Balcolm 1997	Neurogenic	series	29	Transcutaneous	Sensation improved >bladder capacity ($p<0.05$)
Kajbafzadeh	Neurogenic	series	30	Transcutaneous IFT	MMDP, PVR, and DSD improved to sham ($p<0.05$) Also frequency and enuresis ($p<0.05$)

Table 2: Study parameters in paediatric neuromodulation trials (Non Neurogenic bladder dysfunction)

Author and year of publication	Population	Design	N	Mode of application	Outcome measure
Tanagho 1992	Non neurogenic	Series	6	Sacral implant	Resolution 4/6
Trsinar 1996	Non neurogenic	Controlled trial (sham)	73	Anal plug	+ve gains in active group
Bower 2001	Non neurogenic	Series	17	Transcutaneous sacral	73% improved continence
Gladh 2001	Non neurogenic (DI diagnosis)	Series	48	Anal plug	18/48 cured
Hoebeke 2001	Non neurogenic	Series	41	Transcutaneous sacral	56% cured after 1 year
Hoebeke 2002	Non neurogenic	Series	32	Percutaneous tibial nerve	25% cured, 35% improved UD>MVV
Gladh 2003	Non neurogenic	Series	24	Intravesical	Normalized voiding 83%
Lee 2005	Non neurogenic (infrequent voiding)	Series	12	Intravesical	Signif - max flow rate, signif ¯ PVR
Barroso 2006	Non neurogenic (urge syndrome)	Series	36	Transcutaneous sacral	12/19 “complete” improvement
Humphreys 2006	Non neurogenic (severe DES)	Series	23	Sacral implant	Improvements: Day 83% Urgency 75% Freq’y 73% Bowel 80% Retent’n 60%
Malm-Buatsi 2007	Non neurogenic	Series	18	Transcutaneous sacral	13 cured
Roth 2008	Non Neurogenic (DES)	Series	20	Sacral implant	Resolution constipation in 71%
Hagstroem 2008	Non neurogenic	RCT (sham)	25	Transcutaneous sacral	8/13 partial response
Lordelo 2009	Non neurogenic	Series	49	Transcutaneous sacral	2yr later 73% cured
Capitanucci 2009	Non neurogenic	Series	33	Percutaneous tibial nerve	Complete /partial response 78% 2 yrs later
Lordelo 2010	Non neurogenic	RCT (sham)	21 (test) 16(control)	Transcutaneous sacral	62% cured test group. None in control ($p<0.001$)
Haddad 2010	Non neurogenic	RCT crossover	33	Sacral implant	Effective ($p<0.001$) Improvements: 75% for urinary 81% bowel
Lordelo 2010	Non neurogenic (NMNE)	Series	19	Transcutaneous sacral	42% resolved 21% improved

Reported changes on bladder function with neuromodulation include: significantly increased bladder capacity, decreased severity of urgency, improved continence, and decreased frequency of urinary tract infection. Significant improvement in urodynamic parameters of bladder compliance, number of involuntary contractions, and bladder volume at first detrusor contraction have also been noted.

More recently the first reports on sacral nerve stimulation with implantable electrodes have been published. In a group of 20 patients between 8 and 17 years old followed prospectively. Urinary incontinence, urgency and frequency, nocturnal enuresis and constipation were improved or resolved in 88% (14 of 16), 69% (9 of 13), 89% (8 of 9), 69% (11 of 16) and 71% (12 of 17) of subjects, respectively. Complications were seen in 20% of patients [126] . Due to the uncontrolled design the level of evidence is low. Experience from adults offered this treatment modality suggests future positive development in children to be likely.

Level of evidence: 3.

Grade of recommendation C

5. ALARM TREATMENT

Alarm therapy has traditionally been used for the treatment of nocturnal enuresis and has rarely been used for daytime wetting. Only one randomised clinical trial has been published to establish the efficacy of this form of treatment. Halliday et al compared a contingent alarm which sounded when the child wets with a noncontingent alarm system (which sounded at intermittent intervals to remind the child to void) [103]. Forty-four children participated in the study, 50% were assigned to each form of therapy for a 3 month period. Success was measured as 6 consecutive weeks without daytime wetting. Nine children in the non-contingent group and 6 children in the contingent group had persistent wetting. Although the risk of persistent wetting with the contingent alarm was 67% of the risk of persistent wetting with the noncontingent alarm, the difference in the reduction in wetting between the groups was not significant (RR 0.67, 95% CI 0.29 to 1.56). In a more recent retrospective review by Van Laecke et al, a cure rate of 35% after the use of a daytime alarm was described[127]. Due to the retrospective design of the study the level of evidence is low.

Level of evidence: 3

Grade of recommendation C

6. CONCLUSION

Most clinical studies describe combinations of therapies rather than single interventions, which makes it difficult to evaluate the results. Physiotherapy and biofeedback both focus on the pelvic floor. Relaxation of the pelvic floor during voiding is essential for normal voiding and most of these patients are unable to relax their pelvic floor muscles. Biofeedback is important for showing the children the effect of their relaxation efforts. Most studies only state the clinical responses, and do not provide information on urodynamic parameters before and after treatment. A 'normal' flow curve may not mean normal voiding if no information is provided on post-void residual urine. In most papers the inclusion and exclusion criteria are not clearly documented, and it may very well be that the more difficult patients with both storage and voiding dysfunction were included in the study population. Furthermore, different series may describe different groups of patients due to poor definitions and an inadequate classification system. In children with a suspected bladder outlet obstruction, endoscopic investigations should be performed. Most often the anatomic abnormality causing abstruction can be treated at the same time. In girls, a meatal web may cause a deflection of the stream upwards [causing stimulation of the clitoris and bulbocavernosus reflex. A meatotomy may cure this problem, though no information on the long-term effects is available [73].

VI. PHARMACOLOGICAL TREATMENT

1. ANTIMUSCARINIC THERAPY

Antimuscarinic therapy remains one of the common forms of therapy for detrusor overactivity. Its use is predicated on the concept that parasympathetic mediated stimulation of muscarinic receptors in the bladder causes detrusor overactivity, which is responsible for the symptoms of detrusor overactivity. Antimuscarinic agents have been demonstrated to increase bladder capacity, increase bladder compliance and decrease detrusor contractions in neurogenic detrusor overactivity. Detrusor overactivity is believed to play a role in many children with functional incontinence, vesicoureteral reflux and urinary tract infections [128]. More commonly, pharmacotherapy is instituted when behavioral therapy has failed to achieve a satisfactory outcome. Some clinicians use pharmacologic therapy as a first line therapy in children with moderate to severe daytime incontinence [60].

Despite the frequent use of anticholinergic therapy, often in conjunction with a behavioral therapy regimen, the outcome of pharmacologic therapy for daytime urinary incontinence is "unpredictable and inconsistent" and there are few randomized studies available to assess drug safety and efficacy.

a) Oxybutynin

Currently the pharmacologic therapy most widely used in children with detrusor overactivity is oxybutynin [129]. More recently, a long-acting formulation, Oxbutynin- XL, has been approved by the FDA for use in children [130]. Historically, oxybutynin use has been limited by its adverse effect profile with such

side effects as dry mouth, constipation, facial flushing and CNS effects. The incidence of side effects seems to be dose-related, both for oral and intravesical administration [131]. The CNS effects are related to the ability for oxybutynin to cross the blood brain barrier. Oxybutynin- XL utilizes a novel delivery system, which results in absorption in the large intestine, thereby bypassing the first pass metabolism in the liver. This leads to a decrease in the amount of active metabolite [produced in the liver]: resulting in a more favorable tolerability profile. The delivery system requires an intact tablet and thus it cannot be cut or crushed to facilitate swallowing. Another method of delivery of oxybutynin is intravesical therapy. This method of delivery also avoids the first pass effect and leads to increased amounts of oxybutynin available compared to immediate release oxybutynin. Its use in the neurologically intact patient is limited by the need for catheterization [132].

There are only a few studies, none randomized and double blinded, assessing the efficacy of oxybutynin in detrusor overactivity in children. Curran et al, in a retrospective review assessed the efficacy of several agents, primarily oxybutynin in children with non-neurogenic detrusor overactivity, confirmed by urodynamics, who were refractory to behavioral therapy. Some children were treated with combination therapy. Eighty percent had complete resolution or a significant improvement in their urinary symptoms. The authors noted an average time to resolution of symptoms of 2.7 years [range 0.2 to 6.6], however patients were not followed frequently [133]. In a study by Van Hoeck et al, holding exercises with and without oxybutynin showed no beneficial effect on bladder volume of adding oxybutynin.[134].

Level of evidence: 3.

Grade of recommendation C

b) Tolterodine

Tolterodine, a nonselective antimuscarinic is currently being used for the treatment of detrusor overactivity in adults. It is the first antimuscarinic agent designed specifically for use in detrusor overactivity and is felt to be “bladder selective”. It’s affinity for the bladder compared to other organ systems leads to an improved tolerability profile. The chemical nature of tolterodine makes it less likely to penetrate the blood brain barrier, which is supported by EEG studies [135]. The delivery system of the long acting preparation is such that the capsule may be cracked and “sprinkled” on food. Tolterodine has not been approved for use in children but there are several studies, which evaluate its safety and efficacy in children with detrusor overactivity. Hjålmas reported the results of an open label, dose escalation study using immediate release tolterodine in 33 children [136]. Doses ranged from 0.5 mg po BID to 2 mg po BID for 14 days. The results demonstrated a 21% (23% with 2 mg po BID) mean decrease from baseline in micturition frequency and a 44% mean decrease from baseline for the number of incontinence episodes in children treated with 1 mg and 2 mg po BID. Bolduc et al reported on a prospective crossover study of 34 children followed for > 1 year who were crossed over from oxybutynin to tolterodine because of adverse effects with oxybutynin [137]. Detrusor overactivity was confirmed in 19/20 who had urodynamic studies performed prior to therapy. Children received either 1 mg or 2 mg po BID and the median treatment period was 11.5 months. Efficacy was assessed by a questionnaire and was comparable for oxybutynin and tolterodine. Sixty-eight percent noted a > 90% reduction in wetting episodes at 1 year and an additional 15% noted a > 50% reduction in wetting episodes. Fifty nine percent reported no side effects with tolterodine and 18% reported the same side effect as with oxybutynin, but felt it was less severe. Eight patients [24%] discontinued tolterodine.

Munding et al reported on the use of tolderodine in children with “dysfunctional voiding” manifested as daytime wetting, frequency or urgency [138]. There was no documentation of uroflow studies to make the diagnosis of “dysfunctional voiding” and from the symptoms these children appeared to have detrusor overactivity. Children were started on behavioral modification for 4-6 weeks and pharmacologic therapy was instituted if they failed or had only slight improvement with behavioral therapy. A minimum of 1 month’s follow-up was needed for inclusion, but the mean follow-up was only 5.2 months. Doses ranged from 1 mg po BID to 4 mg po BID. Assessment of results was made by telephone survey. Thirty three percent had > 90% reduction in daytime and nighttime wetting episodes and 60% had > 50% reduction. Four patients [13.3%] had side effects, constipation in 2, dry mouth in 1 and diarrhea in 1.

Reinberg et al performed an open label parallel group retrospective study of the efficacy and safety of immediate release and long acting tolterodine and extended release oxybutynin [139]. Children started out with the lowest possible dose, 2 mg tolterodine and 5 mg oxybutynin and titrated up according to response and side effects. Children were arbitrarily assigned to therapy based on the formulary restrictions of the health plan and there was an uneven distribution of patients in the treatment groups. Final dose and duration of treatment were not noted. Study nurses asked about side effects and a voiding diary was used to assess efficacy. The authors concluded that extended release tolterodine [$p<0.05$] and oxybutynin [$p<0.01$] were more effective than immediate release tolterodine in improving urinary incontinence symptoms and that extended release oxybutynin was more effective than extended release tolterodine in resolving diurnal incontinence ($p<0.05$) Long term tolerability of tolterodine extended release in a large pediatric population has been shown. [140]

Level of evidence: 3.
Grade of recommendation C

c) Terodiline

One of the drugs which has been investigated in a randomized placebo controlled trial was terodiline [141,142]. Because of serious cardiac side effects terodiline has been withdrawn from the market. Trospium chloride is another agent, which has been used in small series in children. It is currently available in a twice a day dosing formulation. In the adult population, there is a 16% intra-individual variability in bioavailability and 36% inter-individual variability. Absorption is affected by food intake. Trospium's chemical structure make it unlikely to penetrate the blood brain barrier as supported by EEG studies [135]. Lopez Periera et al evaluated the use of trospium in 62 children with documented detrusor overactivity and absence of 'detrusor sphincter dyssynergia' [143]. Children were randomly assigned to 10, 15, 20 or 25 mg of trospium administered in 2 divided doses or placebo. Fifty-eight children were evaluated. Response rates were assessed by incontinence episodes and urodynamic parameters. Overall, 32% had an excellent response, 42% a good response and 8% a fair response. Detrusor overactivity completely resolved in 35%. Four children had medication related adverse effects including headache, dizziness, abdominal cramps and dry mouth.

Level of evidence: 3.
Grade of recommendation C

d) Trospium and propiverine

Like trospium, propiverine has been used in children, but results are variable and inclusion and outcome criteria were not in accordance with ICCS definitions making comparison with other studies difficult. Recently a randomized, double-blind, placebo-controlled phase 3 trial with propiverine in children aged 5-10 yr was performed. Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. The primary efficacy parameter showed a decrease in voiding frequency (-2.0 episodes for propiverine versus -1.2 for placebo; p=0.0007). Superiority could also be demonstrated for increase in voided volume (31.4 vs. 5.1ml; p<0.0001) and reduction in incontinence episodes (-0.5 vs. -0.2 episodes per d; p=0.0005. This clinical trial showed superior efficacy of propiverine over placebo and good tolerability for the treatment of children suffering from DO and urinary incontinence.[144,145] This is the first study with level of evidence 1 that shows beneficial effect of anticholinergic therapy.

Level of evidence: 1.
Grade of recommendation B/C (only single study)

e) Solifenacin

Solifenacin is the last antimuscarinic agent recently used in children with OAB: Hoebeke et al treated 139 children with therapy resistant OAB, with favourable results, and few side effects [146].

Some authors try combinations of anticholinergics for refractory OAB: Bolduc et all treated 33 children with a combination of oxybutinin and solifenacin or tolterodine with good success [147].

f) Botulinum toxin

Botulinum toxin is currently being used in children, mainly with neurogenic detrusor overactivity. Initial results seem promising, but more studies need to be done. In children. 300 Units on average, are injected in 30-40 spots [`148]. The trigone should not be injected, as there is an increased risk of reflux developing. The results last about 6-9 months. Botulinum toxin is not registered for injection in the detrusor or the sphincter in children. It is off label used and further prospective studies are needed before a general recommendation can be made [149].

One prospective uncontrolled study by Hoebeke et all shows beneficial effects of botulinum toxin in 70% of children with therapy resistant detrusor overactivity [150]. Injection of botulinum toxin is also possible into the external sphincter, but the results are more variable and last only 3-4 months [151] Radojici et al describe excellent results in the treatment of dysfunctional voiding. In 20 children good results are described for 17 patients. [152] In a retrospective study by Franco et al, similar results are described in 16 children, however using a higher dosage. [153]

Less invasively, botulinum toxin can be administered electromotively: a small study in 15 children shows the administration is feasible, safe, and results in considerable improvement on urinary incontinence [154].

Level of evidence: 3
Grade of recommendation C

g) Alpha-adrenergic blockade

Treatment of the overactive pelvic floor and sphincter is much more difficult. Treatment with alpha-adrenergic blockade seems promising, but from the presented studies it is difficult to draw firm conclusions: as most series are small, not randomized and describe a mixed patient population [155-157].

In a more recent uncontrolled study by Donohoe et al a total of 26 patients with Primary Bladder Neck Dysfunction (20 males, 6 females, mean age 12.8 years) were treated with alpha-blockers. Mean average and maximum uroflow rates improved from 5.5 to 12.6 cc per second and from 10.3 to 19.7 cc per second, respectively, while mean EMG lag time decreased from 24.4 to 5.7 seconds and post-void residual urine volume from 98.9 to 8.9 cc (all p <0.001). Mean follow-up was 31 months and no major adverse side effects were observed.[158] Further randomized controlled studies are needed to define the place of alpha-blockers.

Level of evidence: 3.
Grade of recommendation C

VII. CONCLUSION CHILDREN WITH BOTH DAY AND NIGHT TIME INCONTINENCE

Because there is much variability in presenting symptoms as well as the underlying pathology an individual approach is advisable: a step by step algorithm has been developed by Marschall-Kehrel, which seems to deal with many of these variables [159].

Level of evidence 3.

Grade of recommendation B/C

The limited number of identified randomized controlled trials does not allow a reliable assessment of the benefits and harms of different methods of management in children. Further work is required in this difficult clinical area. The establishment of outcome measures is needed, to facilitate randomized controlled trials of routine therapy. Interventions that would benefit from further investigations include: bladder and voiding education, bladder retention training, bowel management, hypnotherapy and alternative therapies, psychology, prophylactic antibiotic medication, neuromodulation, biofeedback therapy and pelvic floor muscle awareness and specific relaxation. Only then can the efficacy of new interventions be measured in children with detrusor overactivity or dysfunctional voiding.

In summary, while there is a wide therapeutic choice available to clinicians, many of the commonly used treatments are of dubious value and have not been rigorously evaluated in careful clinical trials with an appropriate study design. Children who suffer this distressing condition, and their families, and those who care for them clinically, need clear guidance as to which treatments are of proven value. They need access to treatments which work, and they need protection from treatments which do not work.

Children who present with urinary symptoms may have been victims of sexual abuse. In these cases, the use of invasive diagnostic procedures (VCUG and urodynamic studies) must be regarded as contraindicated, as must the use of invasive intra-anal treatment devices. Development of less invasive methods of diagnosis and treatment should therefore be encouraged.

E. NEUROGENIC DETRUSOR-SPHINCTER DYSFUNCTION

I. INTRODUCTION

Neurogenic detrusor-sphincter dysfunction (NDSD) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of lower urinary tract dysfunction which may lead to incontinence, urinary tract infections (UTIs), vesicoureteral reflux (VUR), and renal scarring. Surgery may be required to establish adequate bladder drainage, and potentially, if not managed properly, NDSD can cause renal failure, requiring dialysis or transplantation.

Management of neurogenic detrusor sphincter dysfunction in children has undergone major changes over the years. While the use of diapers, permanent catheters, external appliances and various forms of urinary diversion were acceptable treatment modalities; these are now reserved for only a small number of resistant patients [1]. Initially, long term renal preservation was the only aim of therapy and early diversion had the best long term results for preserving renal function. Despite some of the complications of ileal conduits and cutaneous urostomies requiring secondary surgery, this form of treatment offered the best outcome for renal preservation with socially acceptable continence [2].

Introduction of clean (self) intermittent catheterization revolutionized the management of children with NDSD. It, not only made conservative management a very successful treatment option, but also made surgical creation of continent reservoirs a very effective alternative with a good quality of life [3].

The most common cause of NDSD in children is neurospinal dysraphism and this condition presents with various patterns of detrusor-sphincter dysfunction within a wide range of severity. About 15 % of neonates with myelodysplasia have no signs of lower urinary tract dysfunction (LUTD) when initially studied [4]. However there is a high chance of progressive changes in the dynamics of the neurological lesion in time and even babies with normal LUT function at birth have a 1 in 3 risk of developing either detrusor sphincter dyssynergia or acontractile detrusors by the time they reach puberty [5]. Nearly 60 % of the neonates with neurospinal dysraphism may develop upper tract deterioration due to increased detrusor filling pressures and infections, with or without reflux [6,7].

As our understanding of urodynamic studies has evolved it allowed us to understand the nature and severity of the problems and administer management in a more rational manner differing according to the functional characteristics of each detrusor sphincter unit. Although the last quarter century has witnessed a remarkable progress in understanding pathophysiology, pathogenesis and the management of these children, the main goals of treatment remained the same i.e. the prevention of urinary tract deterioration and the achievement of continence at an appropriate age.

II. PRESENTATION OF NEUROGENIC DETRUSOR SPHINCTER DYSFUNCTION IN CHILDREN

Neurogenic detrusor sphincter dysfunction can develop as a result of a lesion at any level in the ner-

vous system, including the cerebral cortex, spinal cord or the peripheral nervous system. The type and degree of detrusor sphincter dysfunction is poorly correlated with the type and spinal level of the neurologic lesion.

The closure of spinal canal in utero takes place in caudad direction from cephalic end and is completed at around 35 days of gestation. The failure of mesodermal in-growth over the developing spinal canal results in an open lesion most commonly seen in the lumbosacral area. The degree of this closure deficiency contributes to a variable presentation of neural injury with varying degrees of LUTD and lower extremity problems. Developmental anomalies that result from defects in neural tube closure are termed as myelodysplasia. This term includes a group of lesions like spina bifida occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental. Traumatic and neoplastic spinal lesions of the cord are less frequent in children. [8]

The neurologic lesions produced by myelodysplasia are variable and contingent on the neural elements that protrude within the meningocele sac. The bony vertebral level correlates poorly with the neurologic lesions produced. Additionally, different growth rates between the vertebral bodies and the elongating spinal cord can introduce a dynamic factor to the lesion, and scar tissue surrounding the cord at the site of meningocele closure can tether the cord during growth [9-10].

In occult myelodysplasia, the lesions are not overt and often with no obvious signs of neurologic lesion. The diagnosis of this condition has increased since the advent of spinal ultrasonography and magnetic resonance imaging. Yet, in nearly 90% of patients, a cutaneous abnormality overlies the lower spine and this condition can easily be suspected by simple inspection of the lower back. These cutaneous lesions can vary from a dimple or a skin tag to a tuft of hair, a dermal vascular malformation, or an obvious subdermal lipoma. [8] Alterations may be found in the arrangement or configuration of the toes, along with discrepancies in lower extremity muscle size and strength with weakness or abnormal gait. Back pain and an absence of perineal sensation are common symptoms in older children.

Incidence of abnormal lower urinary tract function in patients with spina bifida occulta is as high as 40%. Occult lesions may also become manifest with tethering of the cord later in life. This can lead to changes in bowel, bladder, sexual and lower extremity function.

Sacral agenesis is a rare congenital anomaly that involves absence of part or all of one or more sacral vertebrae. Perineal sensation is usually intact and lower extremity function is usually normal and the diagnosis is made when a flattened buttock and a short gluteal cleft is seen on physical examination. This lesion may produce variable degrees and patterns of LUTD.

Cerebral palsy patients may also present with varying degrees of LUTD usually in the form of overactive detrusor and wetting.

Imperforate anus is a rare anomaly and presents with a closed rectum that does not open onto anal skin verge. These children may present with accompanying spinal cord pathology. This is more common when the rectum ends above the pelvic floor muscles and they should undergo a MR imaging for detection. Early detection of this problem in imperforate anus patients is important to improve the child's chance of maintaining healthy kidneys and becoming continent.

III. CLASSIFICATION: PATTERN RECOGNITION

The purpose of any classification system is to facilitate the understanding and management of the underlying pathology. There are various systems of classification of the neurogenic bladder.

Most systems of classification were formulated primarily to describe those types of dysfunction secondary to neurologic disease or injury. Such systems are based on the localization of the neurologic lesion and findings of the neuro-urologic examination. These classifications have been of more value in adults as neurogenic lesions are usually due to trauma and more readily identified.

In children, the spinal level and extent of congenital lesion is poorly correlated with the clinical outcome. Indeed, severe detrusor sphincter dysfunction has been associated with minimal bony defects. Various possible neuropathologic lesions of the spinal cord including syringomyelia, hydromyelia, tethering of the cord and dysplasia of the spinal cord are the causes of these disparities and they may actually extend several segments above and below the actual site of the myelomeningocele. Therefore urodynamic and functional classifications have been more practical for defining the extent of the pathology and planning treatment in children.

The detrusor and sphincter are two units working in harmony to make a single functional unit. The initial approach should be to evaluate the state of each unit and define the pattern of bladder and sphincter dysfunction. Determined by the nature of the neurologic deficit, they may be either in an overactive or in an inactive state. The detrusor may be overactive with increased contractions during filling, with a diminished bladder capacity

and compliance or be underactive with no effective contractions during voiding; the bladder outlet (urethra and sphincter) may be independently overactive causing functional obstruction or paralyzed with no resistance to urinary flow leading stress incontinence.

These conditions may exist in any combination [9-14].

Urodynamic evaluation (preferably in combination with fluoroscopy) makes pattern recognition possible. Four major types are usually used to describe the detrusor-sphincter dysfunction:

1. Detrusor overactivity with overactivity of the sphincter (mostly dyssynergia),
2. Detrusor overactivity with normal or underactivity of the sphincter,
3. Detrusor underactivity with sphincter overactivity and
4. Detrusor underactivity with sphincter underactivity.

Besides these 4 patterns, one can use the ICS classification: overactive detrusor, underactive detrusor, overactive sphincter and underactive sphincter. Sometimes this is more helpful, as the detrusor may be overactive during filling, but underactive during 'voiding'.

The urodynamic investigation is considered normal when there is suitable age appropriate capacity, good compliant bladder with no overactivity and normal innervation of the sphincter with normal sacral reflexes and an increase in pelvic floor activity during filling and no activity during voiding. Presence of detrusor overactivity during filling with or without decreased capacity and compliance, is usually seen when there is upper motor neuron lesion and this is usually accompanied by overactivity of the sphincter and failure to relax during voiding. A lower motor neuron lesion is considered when the voiding detrusor contractions are weak or lost and the sphincter is underactive. Urodynamic investigations make it possible to establish a management plan for each individual patient.

Evidence level 3

Grade of recommendation B

For the very young child the combination of an overactive detrusor and sphincter is potentially dangerous because of the high intravesical filling pressures, which will put the upper tract at risk (vesicoureteral reflux and hydronephrosis), whereas an underactive detrusor and a paralysed sphincter is relatively safe, providing a low-pressure reservoir [15-17].

Level of evidence: 2

IV. MANAGEMENT

The main aim in management of NDSD in children is to ensure and maintain a reservoir with normal age-matched capacity and good compliance that can be emptied completely at low pressures and at regular intervals.

1. ASSESSMENT

In the first years of life, the kidneys are highly susceptible to backpressure and infection. In this period, emphasis will be on documenting the pattern of neurogenic detrusor- sphincter dysfunction and assessing the potential for functional obstruction and whether or not there is vesicoureteral reflux [17,18]. Ultrasound studies and a VCUG or video-urodynamics to exclude reflux have to be performed soon after birth. Measurement of residual urine during both ultrasound and cystography should also be done. These studies provide a baseline for the appearance of the upper and lower urinary tracts, can facilitate the diagnosis of hydronephrosis or vesicoureteral reflux, and can help identify children at risk for upper urinary tract deterioration and impairment of renal function.

A urodynamic evaluation can be done after some weeks and needs to be repeated at regular intervals, in combination with evaluation of the upper tracts [19].

Level of evidence 3.

Grade of recommendation: B

2. TREATMENT

Overwhelming experience gained over the years with early management of neurogenic bladder in infants has lead to a consensus that children do not develop upper tract deterioration when managed early with CIC and antimuscarinic medication [19-22]. Therefore initial treatment should consist of **oral or intravesical antimuscarinic drugs in combination with clean intermittent catheterisation**, to start soon after birth in all babies and especially in those with signs of possible outlet obstruction [23-27].

Level of evidence 2.

Grade of recommendation: B

The **early initiation of intermittent catheterization** in the newborn period, makes it easier for parents to master it and for children to accept it as they grow older [28,29].

With early management not only are upper tract changes less, but also bladders are better protected and incontinence rates are much lower.

It has been suggested that increased bladder pressures due to detrusor sphincter dyssynergia cause

secondary changes of the bladder wall. These fibroproliferative changes in the bladder wall may cause further loss of elasticity and compliance: resulting in a small non-compliant bladder with progressively elevated pressures. It is believed that early institution of intermittent catheterization and anticholinergic drugs may prevent this in some patients [30-32].

Level of evidence 3.

Retrospective evaluation of patients has also shown that significantly fewer bladder augmentations were required in patients with early start of CIC [23,24].

Level of evidence 4

The main disadvantage of CIC is bacteriuria which is found in 60% of the patients, but symptomatic UTIs are less common (20%) with CIC when compared to the group without CIC (40%). Since the risk of reflux is similarly lower with CIC the renal scar rates are lower. CIC alone, when begun in infancy can achieve continence at a rate of 60 %. When combined with newer and more potent antimuscarinic drugs continence rates approach 75-80%. [33-36]

At present oxybutynin, tolterodine, trospium and propiverine are the most frequently used anticholinergic drugs to treat detrusor over activity in children. Some clinical studies are available, but no randomised placebo controlled studies have been performed [31,37-41].

A prospective controlled trial evaluating trospium in children reports that trospium is effective and safe in correcting detrusor overactvity in children but this study does not include patients with a neurogenic bladder [42].

Two different forms of tolterodine have been investigated in children with neurogenic bladder and extended release formulation of tolterodine is found to be as efficient as the instant release form with the advantages of being single dosage and less expensive [43].

Level of evidence 3. Grade of recommendation: B

Use of medication in children with neurogenic bladder to facilitate emptying has not been studied well in the literature. Few studies investigating the use of alpha-adrenergic blockade in children with neurogenic bladder report good response rates but they are non-controlled studies and long-term follow-up is lacking [44-46].

Level of evidence 4.

Use of **intravesical oxybutynin** in children with poorly compliant neurogenic bladder has been investigated in some studies and incontinence has been shown to be improved significantly in most studies, with “dry and improved” rates ranging from 61% to 83% [47]. Use of lidocain intravesically also has been shown to be effective to improve bladder capacity and compliance and decrease overactivity in children with neurogenic bladder [48]. None of these studies are randomized controlled trials and evidence available is insufficient to strongly recommend this therapy. There are no data available on long term use.

Level of evidence 3.

Grade of recommendation: C

In neurogenic bladders that are refractory to antimuscarinics and still remain to be in a small capacity and high-pressure state, **injection of botulinum toxin** into the detrusor has been introduced to be a new treatment alternative [49-50]. Initial promising results in adults have also initiated its use in children. So far pediatric studies have been open-label studies and prospective controlled trials are lacking [51-53]. Injection of botulinum toxin in therapy resistant bladders seems to be an effective and safe treatment alternative. This treatment seems to be more effective in bladders with evidence of detrusor overactivity, while non-compliant bladders without obvious detrusor contractions are unlikely to respond to this treatment. Dosage in children should be determined by body weight, with caution regarding total dose if also being used for treatment of spasticity, and minimum age [54-57].

Level of evidence 3.

Grade of recommendation C

In a single study urethral sphincter botulinum-A toxin injection has been shown to be effective in decreasing urethral resistance and improve voiding.The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases [58].

Intravesical electrical stimulation of the bladder was introduced more than four decades ago and it has been tested in some open clinical trials in children since 1984. Its practice is limited to a few centres who have reported varying results. The nature of this type of treatment (time consuming and very dedicated personal) does not make it attractive for the majority of treatment centres [59].

Level of evidence 3.

Grade of recommendation C

Children with neurogenic bladder also have **disturbances of bowel function.** Fecal incontinence in these children is frequently unpredictable; it is related to the loss of lower bowel sensation and function, altered reflex activity of the external sphincter and the consequent failure to fully empty the rectum [60].

The majority of children with a neurogenic bladder also have **constipation** and this is managed most commonly with laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel

contents. A regular and efficient bowel emptying regimen is often necessary to maintain fecal continence and this may have to be started even at a very young age. With antegrade or retrograde enemas, the majority of these children's constipation can be managed and they may attain some degree of fecal continence [61-65].

Level of evidence 3.

Grade of recommendation C

Biofeedback training *programs* to strengthen the external anal sphincter have not been shown to be more effective than a conventional bowel management program in achieving fecal continence [66]. Electrostimulation of the bowel may also offer a variable improvement in some patients [67].

Level of evidence 3.

Grade of recommendation D

Urinary tract infections are common in children with neurogenic bladders. In the absence of reflux, patients with urinary tract infections should be treated if symptomatic. There is strong evidence not to prescribe antibiotics to patients with bacteriuria without clinical symptoms [68-71]. Bacteriuria is seen in more than half of the children on clean intermittent catheterization (CIC), but patients who are asymptomatic do not need treatment.

Level of evidence 3.

Grade of recommendation B

Patients with **vesicoureteral reflux and urinary tract infection** often should be placed on prophylactic antibiotics to reduce the incidence of pyelonephritis, which can potentially lead to renal damage [72].

Sexuality, while not an issue in childhood, becomes progressively more important as the patient gets older. This issue has historically been overlooked in individuals with myelodysplasia. Patients with myelodysplasia have sexual encounters, and studies indicate that at least 15-20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. Therefore counseling patients regarding sexual development is important in early adolescence.

Children with a good response to antimuscarinic treatment and an overactive sphincter may be continent in between catheterizations. Bladder pressure and (normal) development of the upper tracts will determine whether additional treatment is necessary.

Children with therapy resistant overactivity of the detrusor, or small capacity and poor compliance will usually need additional surgical treatment such as **bladder augmentation.**

Children with detrusor overactivity but with underactive sphincters will be in a better shape in terms of protecting their upper tracts, but they may be severely handicapped because of their incontinence. Initial treatment will be **intermittent catheterization** (as it may reduce the degree of incontinence and offers a much better control over urinary infections) in combination with antimuscarinic drugs. At a later age the outlet resistance has to be increased in order to render them continent [73]. There is no medical treatment of proven efficacy that increases bladder outlet resistance. Alpha-receptor stimulation of the bladder neck has not been very effective. Surgical procedures need to be considered for maintaining continence [75-77].

It is important to establish **adequate bowel emptying** before attempting to correct bladder dysfunction surgically or medically.

Patients with a neurogenic bladder require **lifelong supervision and monitoring of renal function** is extremely important. Periodic investigation for upper tract changes, renal function and bladder status is mandatory. Therefore repeat urodynamic studies are needed more frequently at younger ages and less frequently at later ages. A repeat urodynamic study is warranted when the patient has a change in symptoms or undergoes any neurosurgical procedure. In case of any apparent changes both in the upper and lower urinary tract or any changes of neurological symptoms, a more detailed examination including urodynamics and MRI of the spine is indicated. Renal failure usually progresses slowly but may occur with startling rapidity in these children.

F. Surgical management of urinary incontinence in children

Intermittent catheterization and drug therapy are usually sufficient in the majority of cases for maintaining continence and preserving upper tracts. Surgical procedures should be considered if conservative measures fail to achieve continence between catheterizations or preserve upper tracts.

Surgical intervention is required for congenital and acquired diseases interfering with the function of the storage function of the bladder, the sphincter mechanisms or which bypass normal sphincter mechanisms. A plethora of different surgical procedures has been proposed to maintain continence by using different mechanisms. Various procedures using different mechanisms for maintaining continence may be used in the same patient.

In many cases measures such as intermittent catheterization and drug therapy are needed in addition to surgery since most of the surgical procedures can achieve 'dry- ness', but rarely restore normal voiding.

Patients with bladder neck incompetence pose a real challenge and require a different approach. All surgical procedures to "reconstruct" the bladder neck have one thing in common; an obstruction is created

to enhance bladder outlet resistance. Even if successful, normal spontaneous voiding with low pressures without external help is not possible in most patients. Considering the long-term outcome, it may be better not to void spontaneously when bladder outlet resistance is increased because longstanding outlet resistance may cause secondary changes of the bladder wall.

The rarity and complexity of the conditions associated with congenital incontinence in children precludes the establishment of higher levels of evidence because of the rarity and spectrum of the pathology. Results are highly dependent on the skills of the individual surgeon. Therefore graded recommendations for specific procedures cannot be provided. There are no randomized controlled trials (level 1 and 2 evidence). Based on the available literature most studies have a level of evidence 3-4 and grade of recommendation C or D.

I. ABNORMALITIES OF STORAGE

Bladder Exstrophy*:* The incidence of bladder exstrophy is 1 per 30,000 live births. (male to female ratio 2:3.1-6.1). Closure of the bladder is generally performed within the first days of life; pelvic osteotomies facilitate reconstruction of the abdominal wall and may improve ultimate continence [1,2,3]. Some children will develop more or less normal capacities. Even after successful closure there will be some children who end up with a poorly compliant small bladders, requiring later bladder enlargement or urinary diversion (ureterosigmoidostomy) [4,5,6,7]. Patients with a good bladder template who develop sufficient bladder capacity after successful primary closure and epispadias repair can achieve acceptable continence without bladder augmentation and intermittent catheterization [8,9,10].

Reconstruction of the bladder neck can either be done at the time of bladder closure or at a later stage. Early reconstruction may facilitate normal bladder function, but should be attempted only at centers experienced with such surgery [11,12]. Continence rates vary from center to center and may range between 43 to 87% [13,14].

Cloacal Exstrophy*:* The incidence of cloacal exstrophy is 1 per 200,000 live births. This is a much more complex deformity that requires an individual approach. Most of these children have anomalies of the nervous system, upper urinary tract and gastrointestinal tract that can adversely affect urinary tract reconstruction. Before reconstructive procedures are considered, an extensive evaluation has to be carried out.

Agenesis and duplication of the bladder are both extremely rare. Agenesis is rarely compatible with life. In bladder duplication other associated congenital anomalies are often observed such as duplication of external genitalia or lower gastrointestinal tract.

Abnormal storage function in combination with other anomalies is usually caused by a neurologic deficit or is secondary to bladder outlet obstruction. Sacral anomalies are frequently seen with cloacal malformations and imperforate anus [15, 16, 17,18].

Posterior urethral valves may cause severe hypertrophy of the detrusor with a small poorly compliant bladder [19,20] .

Unfortunately, following valve ablation, these bladders may not return to normal function [21,22] .

II. ABNORMALITIES OF SPHINCTERIC FUNCTION

Epispadias (without exstrophy): incidence 1 in 60,000 live births, male to female ratio: 3-5:1. All patients with bladder exstrophy also have complete epispadias.

In male patients with complete epispadias and all females, the sphincteric mechanism is deficient and the child has complete incontinence. Reconstruction of the bladder neck is either performed at the time of epispadias repair or at a later stage. The bladder function may or may not be normal in these patients [23,24].

Malformation of the Urogenital Sinus occurs exclusively in phenotypic females. The incidence is 1 in 50,000 live births. In patients with classical urogenital sinus or cloaca, the sphincteric mechanism is insufficient and due to associated neurological abnormalities the bladder function may be abnormal.

Ectopic ureteroceles protruding into the urethra may be responsible for a partial defect of the bladder neck. In these rare cases, sphincteric incontinence may be the result.

Sphincter abnormalities secondary to spina bifida and other neurologic disorders are of particular importance. The sphincter may be overactive (like in detrusor sphincter dyssynergia) or underactive. Overactivity of the sphincter causes secondary changes of the bladder wall (increased collagen type III with decreased elasticity and compliance). Continence is usually achieved with antimuscarinic drug treatment or bladder augmentation (using the overactivity of the sphincter for continence). In cases of incompetence of the sphincter, different types of surgical intervention are possible to enhance the sphincteric mechanism. In general all patients with a neurogenic bladder need Clean Intermittent Catherization (CIC). In patients bound

to a wheelchair a suprapubic channel can be created (Mitrofanoff) to facilitate CIC.

III. BYPASS OF SPHINCTERIC MECHANISM

Ectopic Ureter is an abnormally located terminal portion of the ureter. Instead of the ureter opening in the bladder, it opens in the urethra, vagina, or uterus. Ectopic ureters occur more frequently in girls and are commonly part of a duplex system: in girls the ectopic orifice of the upper pole moiety drains into the urethra below sphincteric level or vaginal vestibule, thus causing incontinence [25].

When the ectopic ureter represents a single system, the trigone is usually asymmetrical and not well developed. These children may suffer from continuous incontinence as well as a deficient sphincteric mechanism: this is particularly true in bilateral ectopia of single systems. In these patients the trigone and bladder neck are functionally abnormal and treatment includes surgical reconstruction of the bladder neck. When the upper pole ureter opens in the mid or distal female urethra or outside the urinary tract (i.e. vulva or vagina) incontinence results. Upper pole nephrectomy or ipsilateral uretero-ureterostomy solves the problem.

A rare and a challenging condition is when there are bilateral ectopic ureters. Since the bladder is hypoplastic, in these children achieving normal bladder capacity and function may require additional procedures to ureteric reimplantation [26,27,28] .

Urethral duplications. Most patients with urethral duplication will leak urine from the abnormal meatus during voiding. In rare cases, when the urethra bypasses the sphincteric mechanisms, continuous leakage may be present [29] .

Vesicovaginal fistulas. Acquired fistulas may be traumatic or iatrogenic, following procedures on the bladder neck.

IV. EVALUATION AND DIAGNOSIS

A detailed history and physical examination in combination with imaging studies and urodynamic evaluation are the corner stones for successful management. Imaging studies are essential to define the anatomical abnormalities responsible for and associated with incontinence. Ultrasonography of bladder and kidneys as well as a voiding cystourethrogram are the basic studies. In infants and small children sacral ultrasonography can demonstrate normal position and mobility of the spinal cord.The scout film of the contrast voiding cystourethrogram (VCUG) assesses the lower spine and sacrum, intersymphyseal distance, and fecal retention. The contrast films will show bladder configuration, presence of vesicoureteral reflux, incomplete voiding, bladder neck competence, urethral anatomy, and vaginal reflux. Occasionally, an intravenous urogram will provide the clearest assessment of the urinary tract. MRI and CT scanning can be helpful in defining spinal abnormalities as well as congenital abnormalities in the urinary tract.

In addition to imaging studies, urodynamic studies (cystometrography, and when needed, electromyography of the sphincters and urinary flow studies) are useful for all patients with neurogenic incontinence, and after surgery in some cases of bladder exstrophy and after posterior urethral valves resection to help define the mechanism of any continued incontinence. However in many patients much useful information on the function of the lower urinary tract can be obtained with very basic studies including ultrasound and cystometry.

V. INDICATIONS FOR SURGICAL PROCEDURES TO CORRECT URINARY INCONTINENCE

1. STORAGE FUNCTION

Reduced bladder capacity is the main indication for simple bladder augmentation. Reduced capacity can be congenital (bilateral single ectopic ureters, bladder exstrophy) or caused by previous surgery e.g. bladder neck reconstruction in exstrophy patients, where a part of the bladder is used to create an outlet resistance. Other indications are low functional bladder capacity as it may be present in neurogenic detrusor overactivity, or poor bladder compliance (meningomyelocele), or bladder scarring from previous surgery or obstruction. Bladder scarring from bilharzia remains common in endemic areas and is increasingly common with immigration to the developed world. In all such cases surgery is indicated when conservative treatment has failed.

Several studies suggest that aggressive early intervention with CIC and anticholinergic therapy improves bladder compliance and may protect children from augmentation surgery [30,31].

Yet in a recent survey has reported that there has been no change in augmentation rates during the last 5 years: they demonstrated significant inter-institutional variability [32].

2. SPHINCTER FUNCTION DURING STORAGE

Most of the diseases in childhood requiring surgical repair for incontinence not only have an influence on bladder capacity but also on sphincter function.

Conservative measures to improve sphincter function have limited value and surgery is required in many cases. There are different surgical options; either to increase outlet resistance or to create or implant a new sphincter mechanism. In neurologically normal patients such as classic exstrophy patients, early anatomic reconstruction may allow 'normal' bladder and sphincter function. Sling procedures are indicated when the residual sphincter function is not sufficient to avoid incontinence. This may be the case in patients with neurogenic bladder disturbances and urethral incontinence. If there is no residual sphincter function or outlet resistance, an autologous tape or colposuspension in girls, and an artificial sphincter in boys, may be required. Primary urinary diversion (rectal reservoirs / continent stoma) offers an alternative solution to this problem.

3. PROCEDURES TO BYPASS THE SPHINCTER

If bladder outlet surgery fails or urethral catheterization is not possible, a continent stoma may be constructed. Some patients prefer catheterizing through a continent stoma rather than through the sensate urethra. The continent stoma (Mitrofanoff principle) may be combined with bladder augmentation and/or bladder neck reconstruction or closure. An alternative to such procedures would be the use of the anal sphincter for urinary continence with the use of colon as the storage reservoir.

VI. BLADDER RESERVOIR CONSTRUCTION

1. URETEROSIGMOIDOSTOMY

This type of continent urinary reconstruction may be utilized in reconstruction for bladder exstrophy, an incontinent urogenital sinus or the traumatic loss of the urethral sphincter. As this reconstruction is totally dependent on the normal function of the anal sphincter, contraindications include incompetence of the anal sphincter, anal prolapse, previous anal surgery, and irradiation. Because of the potential for electrolyte resorption, renal insufficiency is also a contraindication.

Low pressure rectal reservoirs are superior to simple ureterosigmoidostomy because the augmented or reconfigured rectal bladder achieves lower pressure storage and accordingly, enhances continence.

There are two techniques which have been utilized:

a) The augmented rectal bladder in which.the rectosigmoid is opened on its antimesenteric border and augmented by an ileal segment. The sigmoid may be invaginated to form a nipple valve to avoid reflux of urine into the descending colon and thus to minimize metabolic complications.

b) The sigma-rectum pouch (Mainz pouch II) in which there is an antimesenteric opening of the recto-sigmoid and a side to side detubularization anastomosis. Ureteral reimplantation of normal sized ureters is by a standard submucosal tunnel (Goodwin, Leadbetter). If the ureter is dilated the technique utilizing a serosa lined extramural tunnel may be more appropriate [33,34].

As reported by D'elia et al, the results of these low-pressure rectal reservoirs are excellent with day and night continence better than 95% and complications related to the surgical procedure range from 0 -10% with the sigma-rectum pouch to 34% for the augmented rectal bladder [35]. Late complications for the sigma-rectum pouch range from 6-12.5% and the late complications for the augmented rectal bladder are 17%. Early complications include pouch leakage while late complications are mainly related to the ureteral implantation into the bowel and pyelonephritis. Metabolic acidosis also occurs (69% of the patients had a capillary base excess of –2.5 mmol/L and used oral alkalinizing drugs to prevent hyperchloraemic acidosis).

Periodic follow-up studies are important to check the upper urinary tract and prevent metabolic acidosis. Due to the risk of malignancy at the ureterointestinal anastomosis, colonoscopy should be performed annually beginning at postoperative year 10 [30,36,37,38,39].

Level of evidence : 3.

Grade of recommendation: B

2. BLADDER AUGMENTATION, BLADDER REPLACEMENT AND CONTINENT URINARY DIVERSION, USING INTESTINE

The indication for bladder augmentation, replacement of the bladder, or the creation of a continent urinary diversion, is either the morphological or functional loss of normal bladder function. The main goal of this surgery is to relieve high pressure and low capacity of the urinary bladder and create a new reservoir with low storage pressures that can be emptied periodically. It is particularly important that the patients understand that spontaneous voiding will not be possible after such surgery and life long intermittent catheterization will be required.

Before deciding on what type of procedure can be performed some significant factors must be addressed. These are:

1. Physical and mental capacity of the patient to do intermittent catheterization.
2. Previous surgery (on urinary tract and bowel)
3. Renal function status (including acid base state)
4. Absence or presence of reflux

5. Outlet resistance

6. The need for a catheterizable channel

The different technical approaches to bladder augmentation or replacement are dependent on the clinical presentation of the patient:

- a simple bladder augmentation using intestine may be carried out if there is any bladder tissue, a competent sphincter and/or bladder neck, and a catheterizable urethra,

- an augmentation with additional bladder outlet procedures such as bladder neck reconstruction or other forms of urethral reconstruction are required when both the bladder and outlet are deficient. This occurs most commonly in spina bifida or bladder exstrophy. It must be appreciated that bladder outlet procedures may complicate transurethral catheterization.

- augmentation with surgical closure of the bladder neck may be required primarily, or as a secondary procedure in certain rare clinical situations. In this situation a continent stoma will be required. Most urologists however prefer to leave the bladder neck and urethra patent as a safety precaution: when the bladder is very full leakage will occur and it allows transurethral manipulations such as catheterization if the continent reservoir cannot be emptied through the suprapubic catheterizable channel.

- an augmentation with additional continent stoma is utilized primarily following failure of previous bladder outlet surgery. It is advisable also when it can be anticipated that there will be an inability to catheterize transurethrally. An abdominal wall continent stoma may be particularly beneficial to the wheelchair bound spina bifida patient who often can have difficulty with urethral catheterization or who is dependent on others to catheterize the bladder. For continence with augmentation and an abdominal wall stoma, it is essential that there be an adequate bladder outlet mechanism to maintain continence.

- total bladder replacement in anticipation of normal voiding in children is very rare, as there are infrequent indications for a total cystectomy, with preservation of the bladder outlet and a competent urethral sphincter. This type of bladder replacement is much more common in adult urologic reconstruction.

The main contraindications are the inability of the patient to be catheterized, or perform CIC him or herself and the anticipation of poor patient compliance. When there is reduced renal function generally with a creatinine above 2 mg/dl or a creatinine clearance below 40 ml./min/1.73 m2, there is a relative contraindication to the use of ileum or colon because of metabolic acidosis secondary to reabsorption. The stomach with its excretion of acid may be used with a low creatinine clearance possibly in preparation for transplantation. It is, however, not wise to use stomach in any voiding patient or one with any questions of an incompetent bladder outlet because of the severe skin irritation that the acid urine may produce (hematuria-dysuria syndrome).

3. WHICH INTESTINAL SEGMENT SHOULD BE UTILIZED?

a) Stomach

Stomach has limited indications primarily because of the complications that have been seen. It is the only intestinal segment suitable in patients with significantly reduced renal function [40,41,42].

Additionally, when no other bowel may be available, as after irradiation or there exists the physiology of a short bowel syndrome, as in cloacal exstrophy, this may be the only alternative remaining.

b) Ileum / Colon

Clinically these two intestinal segments appear to be equally useful. In children, sigmoid colon is widely used except in those who have been treated for imperforate anus. Use of the ileocecal region can be associated with transient and sometimes prolonged diarrhea. This segment should be avoided in patients with a neurogenic bowel such as in myelomeningocele or who have been subject to previous pelvic irradiation. If the ileocecal valve must be used, it can easily be reconstructed at the time of performing the ileo-colonic anastomosis. The ileum can be satisfactorily used for bladder augmentation: however because of its smaller diameter a longer segment of ileum is required to create a comparable reservoir to that created from colon. Colon has greater flexibility for ureteral implantation and construction of a continent catheterizable channel.

c) General principles

There are several important principles for bladder augmentation and replacement that should be respected:

- use the minimal amount of bowel and if available use hindgut segments or conduits from previous surgical procedures,

- a low-pressure large capacity reservoir is essential. This requires detubularization of any intestinal segment used.

- for colonic reservoirs a sigmoid segment of 20-30 cm is generally satisfactory. A slightly longer segment of ileum is generally used. The

length of the segments can be scaled down in smaller children. Care should be taken not to use more than 50 to 60 cm of ileum in adolescents and comparable lengths in younger children because of reduction of the intestinal resorptive surface.

- the jejunum is contraindicated in intestinal reconstruction of the urinary tract because of its metabolic consequences (hyponatremia, hypercalcemia, and acidosis).
- it is wise to strive to achieve an anti-reflux ureteral anastomosis into the reservoir to avoid the potential for reflux and consequently ascending infection: in high pressure bladders with reflux the reflux usually disappears spontaneously following augmentation [43,44].
- a reliable continence mechanism (continent urinary outlet) must be assured.
- because of the risk of stone formation only resorbable sutures and staples should be used in bladder augmentation and reservoir construction.

d) Bladder augmentation techniques

1. In gastric augmentation a 10-15 cm wedge-shaped segment of stomach is resected. Most commonly this is based on the right gastroepiploic artery but can be based on the left one as an alternative. The segment is brought down to the bladder easily in the retroperitoneal space along the great vessels.
2. When using large or small bowel the segment to be utilized is opened on the antimesenteric border and detubularized prior to anastomosis to the bladder remnant. The anastomosis of the intestinal segment to the bladder remnant and to itself is usually carried out in one running layer of inverting absorbable sutures.
3. The techniques for urinary diversion with continent stoma (Mainz pouch, Indiana pouch, Kock pouch) are covered in the chapter on urinary diversion in adults [45,46,47].

Currently, augmentation cystoplasty is the standard treatment for low capacity and/or low compliance bladders secondary to neurogenic, congenital and inflammatory disorders. Due to the relatively high morbidity of conventional augmentation there is renewed interest in alternative methods [48, 49,50,51,52,53]. These alternative techniques try to avoid the contact between urine and intestinal mucosa and include gastrocystoplasty, bladder auto-augmentation, seromuscular augmentation, alloplastic or biodegradable scaffolds grafted with autologous urothelium developed in cell culture, and ureterocystoplasty.

e) Auto-augmentation

The principle of auto-augmentation of the bladder is the excision of a great portion of the detrusor while leaving the urothelium intact, creating a large diverticulum for the storage of urine at lower pressures. This urine stored at a low pressure can be drained by intermittent catheterization. The theoretical advantages of this procedure are the low complication rates of the surgery, reduced operative morbidity with shorter stay in the hospital, absence of urine salt resorption, less mucous production in the urine and possibly absence of carcinogenic potential. Although some series showed good results with this procedure [54,55,56,57], most authors have been unable to achieve previously reported success [58].

Long-term results have been rather disappointing: MacNeily et al concluded that of 17 patients with neurogenic bladder following auto-augmentation, 71% were clinical failures and 14 out of 15 were urodynamic failures [59]. Similar findings have been reported by others [60,61]. The inability of this procedure to achieve long-term good results may be due to the regeneration of nerve fibers divided during the surgery as well as the ischemic atrophy of the mucosa.

Although there are many potential advantages to this approach to a small poorly compliant bladder the inconsistency of success make it a less favorable option at this time. It is generally felt that pressures can be lowered but that capacity remains unchanged.

More recently, some authors have proposed the laparoscopic auto-augmentation as a minimally invasive procedure for the treatment of low capacity/ low compliance bladder. [62,63]. Despite the indifferent results some still suggest its consideration before a standard augmentation because of the reasons listed above [64,65,66].

Level of evidence 4.

Grade of recommendation C

f) Seromuscular patch

To overcome one of the major disadvantages of a conventional augmentation that is mucus formation several techniques have been developed to use intestinal segments free of mucosa. The first attempts at using intestinal segments free of mucosa to improve bladder capacity resulted in viable seromuscular segments covered with urothelial mucosa [67,68]. The intense inflammatory response and shrinkage observed in the intestinal segment discouraged its use in humans [69]. Further attempts consisted of using the association between demucosalized intestinal segments and auto-augmentation. In the

initial model using sheep, the animals tolerated the demusculization procedure poorly, reflected by inflamed, hemorrhagic colonic segments in the animals sacrificed within one month. In addition, colonic mucosa regrowth occurred in one third of the animals[70] . Follow-up studies in a dog model with previously reduced bladder capacity suggested that the contraction of the intestinal patch in seromuscular enterocystoplasty can be avoided by the preservation of both the bladder urothelium and lamina propria, together with the submucosa and muscularis mucosa of the intestinal patch [71,72] . This form of bladder augmentation was shown to prevent absorption of toxic substances like ammonium chloride [73]. Other authors using the same technique to line de-epithelialized gastric patches in the mini-pig model found it useless due to the fibrotic changes and decreased surface of the patch [74].

The initial experience in treating humans with colocystoplasty lined with urothelium were reported by Gonzales and Lima who developed a slightly different technique independently [75,76] . Bladder capacity increased significantly while bladder pressures decreased. Biopsies demonstrated urothelium covering the augmented portion of the bladder in the majority of cases.

Longer term follow-up is now available and although the results are very encouraging, the results seem to be highly operator dependent and the way the mucosa is removed seems to be a crucial factor. Lima et al do no longer preserve the bladder urothelium and use a silicone balloon to prevent the augmented segment from contracting (they remove the balloon after 2 weeks: urine is diverted using ureteral stents): in 123 patients no ruptures were found and only 10% were regarded as failures [77].

Gonzalez et al found seromuscular colocystoplasty in combination with an artificial urinary sphincter successful in 89% of their patients and that it effectively achieves continence with no upper tract deterioration, and concludes that this is their preferred method of augmentation when adverse bladder changes occur after implanting the AUS [78].

Although more authors have now reported their results it still remains a more complex form of augmenting the bladder. This procedure has not receive a general acceptance among the paediatric urological community but is being done in some designated centres [79,80,81,82]. A recent comparison of the long term outcome of this technique with standard intestinocystoplasty has indicated that most of the risks and benefits of augmentation cystoplasty performed using intestine and seromuscular patch appear similar .

Level of evidence 3.

Grade of recommendation C

g) Ureteral bladder augmentation

Another alternative to avoid the morbidity of intestinal bladder augmentation is the use of ureteral segments to improve bladder capacity and/or compliance. Megaureters associated with poorly or nonfunctioning kidneys provide an excellent augmentation material with urothelium and muscular backing, free of potential electrolyte and acid base disturbance, and mucus production [83,84].

Another alternative in patients with ureteral dilation and good ipsilateral renal function, is to combine transureteroureterostomy with ureterocystoplasty [85].Another alternative in bilateral dilated ureters with preserved renal function is bilateral reimplantation and the use of bilateral distal ends for detubularized bladder augmentation [86,87].

Bladder augmentation with ureter may be effective in a small sub group of patients with ureteral dilatation and poor bladder capacity. Overall long-term results are good and remain so over a longer period of time [88,89,90,91,92,93].

In a recent evaluation of the long term functional outcome of this technique it is reported that ureterocystoplasty provides durable functional urodynamic improvement, yet some patients (4 out of 17 in this series) would eventually need a standard intestinal cystoplasty [94].

Level of evidence 3.

Grade of recommendation B

It has been shown that this type of augmentation can also be employed in children who require a kidney transplantation [95,96,97].

h) Experimental Methods

The artificial bladder has been the topic of speculation and experiment that remains still outside the bounds of clinical application. Somewhat nearer to clinical application may be the concept of tissue engineering using autologous urothelium and bladder muscle cells. These cells may be grown on biodegradable scaffolds—both naturally derived and synthetic—for the temporary support of growing tissues and then can be used for augmenting the bladder. A number of synthetic materials and natural matrices have been used in experimental and clinical settings and major improvement have been gained in techniques of cell harvest, culture, and expansion as well as polymer design.

A range of applications of engineered bladder tissues are at different stages of development. There have been a few in preclinical trials, recent progress suggests that engineered bladder tissues may have an expanded clinical applicability in the future.

Clinical trials with these methods are not far away [98-110].

Although this field of research may represent the future of bladder reconstructive surgery, currently only few experimental studies are available and it may be some time before all this knowledge can be used clinically. We strongly encourage further research in this field.

VII. BLADDER OUTLET SURGERY

1. URETHRAL ENHANCEMENT

In those children where sphincteric incompetence is the only cause of incontinence or plays a mayor role in association with decreased bladder capacity or compliance, surgical procedures to enhance outlet resistance should be considered. In many cases bladder outlet surgery needs to be combined with other procedures aimed at creating a large low pressure storage reservoir.

2. BULKING AGENTS

The injection of bulking substances in the tissues around the urethra and bladder neck to increase outlet resistance in children dates back to at least 1985. However, concern about distant migration of the injected substance and risk of granuloma formation prevented this technique from gaining widespread acceptance [111,112].

The search for safer, biocompatible substances to create periurethral compression has first led to the use of cross-linked bovine collagen, with initially reported success in about 20-50% of children [113,114,115].

Collagen injection appeared to effectively improve urethral resistance, but this did not always translate into satisfactory dryness, besides, the effect of the injection is of short duration and repeated injections were often necessary [116,117]. Because of this collagen is no longer recommended for this indication.

At present the following substances are available and have been tested in children with incontinence: dextranomer / hyaluronic acid copolymer (a nontoxic, nonimmunogenic, non-migrant synthetic substance) and polydimethylsiloxane.

Usually the substance is injected endoscopically in the bladder neck area (finding the best spot is often the most difficult part of the procedure): more than one procedure may be necessary. On average 2.8 – 3.9 ml is injected. More than 50% of patients need more than one injection. Initial results of 75% success have been reported, but after 7 years there is a gradual decrease and only 40% remained dry [118,119,120].

Others have reported success rates of 0 - 70% [121-128].

Despite limited success it remains an option for all patients who are poor surgical candidates and those who want to avoid extensive BN reconstruction.

An alternate route may be the injection around the urethra using laparoscopy [129].

Level of evidence : 3.

Grade of recommendation C

3. ARTIFICIAL URINARY SPHINCTER

Since its introduction in 1973 the AUS has undergone major transformations over the years. Different devices are currently in use: one of the most frequently used devices is the AS800-T that has been in use for almost 20 years [130]. It consists of an inflatable cuff, a pressure regulating balloon and a unit containing a pump and control mechanisms. The inflatable cuff can only be implanted around the bladder neck in females and pre-pubertal males. In post-pubertal males the bulbar urethral placement is possible but not recommended for wheelchair patients or those who perform intermittent catheterization [131]. In patients who have had extensive urethral surgery (exstrophy and epispadias) it may also not be technically feasible.

Implantation of an AUS requires special training and difficulties may be encountered in the dissection of the space around the bladder neck in obese, post-pubertal males or in patients with a history of previous bladder neck procedures. A 61-70 cm H_2O pressure balloon is used exclusively when the cuff is around the bladder neck and a lower pressure balloon when it is around the bulbous urethra. Although high in cost, the artificial sphincter remains the most effective means or increasing urethral resistance and preserving the potential for voiding.

The ideal candidate for AUS implantation is a patient with pure sphincteric incompetence who voids spontaneously and has good bladder capacity and compliance. Unfortunately only a small proportion of children with sphincteric incontinence meet the criteria. The AUS may also be used in patients dependent on clean intermittent catheterization. The compatibility of the AUS with intermittent catheterization and enterocystoplasty is well documented [132,133,134].

The ability to empty the bladder spontaneously or by Valsalva maneuver may be preserved after AUS implantation. In series reporting children with AUS, the majority having neurogenic incontinence, 25% void spontaneously [135]. When the AUS is implanted before puberty, the ability to void spontaneously may be lost after puberty.

Overall, 40 to 50% of neurogenic patients require a bladder augmentation concomitantly or subsequently to the AUS implantation [133,136,137,138].

The continence rate ranges from 63 to 97% [139-146].

Herndon et al reported a success rate of 86% (of 134 patients): 22% voided, 11% had to perform CIC after voiding, 48% only performed CIC through the urethra, 16% performed CIC through a continent channel and 3% used diversion [147]. Mechanical problems occurred in 30% of patients who had an 800 model implanted (versus 64% in the old model). Revisions (in 16%) were significantly less in the 800 model. Erosion occurred in both groups (16%). A major complication was perforation of the augmented bladder in this group (it occurred in 10 patients). In 28% a secondary bladder augmentation was necessary.

Another interesting aspect of the AUS is that in some children the device is either deactivated or no longer functions but they remain dry: others have reported that placing a cuff only without activation is all that is required to make them dry [148].

The complications most commonly encountered in patients with AUS are mechanical failures. The longevity of the present devices is expected to exceed 10 years, although Spiess et al reported a mean lifetime of only 4.7 years [149].

The second most common problem is the development of reduced bladder compliance with time. This may result from an error in the preoperative evaluation or the reaction of the detrusor to obstruction (a reaction noted in some patients with spina bifida). These changes can be seen after many years of follow-up. The results of decreased capacity and compliance may be incontinence, upper tract deterioration, or the development of vesicoureteral reflux. Therefore long term follow-up with ultrasound, renal scintigraphy and if indicated urodynamics is mandatory in all patients with an AUS.

Infection of the prosthesis should occur in no more than 15% of all cases. Erosions of the tissues in contact with the prosthesis are rather infrequent. Bladder neck erosions are practically non-existent when the sphincter is implanted around a “virgin” bladder neck. When the AUS is used as a salvage procedure following bladder neck reconstruction, the erosion rate may be as high as 30% [137]. Despite the high complication and revision rate, AUS results show that acceptable continence rates can be achieved in the long-term. For this reason AUS implantation may be better considered as the initial treatment in selected cases [150].

4. FASCIAL SLINGS

Fascial slings constructed with the fascia of the anterior rectus muscle have been used to increase outlet resistance in incontinent children, particularly those with neurogenic dysfunction since 1982 [151]. The sling is used to elevate and compress the bladder neck and proximal urethra. The dissection around the urethra may be facilitated by a combined vaginal and abdominal approach, however, this option is limited to post-pubertal females [152].

Several technical variations of the sling have been reported. The fascial strip may be a graft or a flap based on the rectus sheath on one side. The fascial strip can be crossed anteriorly or wrapped around the bladder neck to enhance urethral compression.

Although the short-term success rate reported by most authors is encouraging, there are no series reporting detailed results at 5 years [153-154]. Most authors report a greater success when fascial slings are used in conjunction with bladder augmentation and success seems more likely in females than in males [155-158]. In patients with neurogenic incontinence postoperative CIC is recommended.

The pubovaginal sling in girls may also be placed through the vagina: in 24 girls with spina bifida this procedure was successful in 19, while another 3 became dry following additional injections with bulking agent around the bladder neck via a suprapubic needle introduction. CIC was possible in all patients. One patient developed a vesicovaginal fistula [159].

Complications of sling procedures include difficulties with intermittent transurethral catheterization, erosion of the urethra and persistent incontinence. Overall, the increase in outlet resistance provided by slings seems less than that provided by the artificial sphincter. Experience with these procedures suggests an overall success between 50 and 80% in females.

Numerous alternatives are being used nowadays: small intestinal submucosa has been used in 20 children and showed equivalent rates of continence. The advantage being that it is available off-the-shelf. Results were better in girls than in boys (85 vs 43% being dry) [160,161,162].

When combining bladder augmentation with a Gore-tex sling in 19 children the results were bad: because of erosion the sling had to be removed in 14 patients, all except one also had a bladder stone. In this respect this type of sling should not be used [163].

From the data published it presently seems that the AUS provides more consistent results in boys and for girls capable of spontaneous voiding who have not had previous bladder neck surgery. Bladder neck slings may be used for the enhancement of bladder outlet resistance in the

majority of patients with neurogenic bladder who need augmentation cystoplasty and whom we do not expect will be capable of voiding spontaneously. Sling procedures are probably equally effective for girls dependant on intermittent catheterization and in conjunction with bladder augmentation. At present, given the cost and lack of effectiveness of injection procedures, their use does not appear justified in incontinent children. The cost of the AUS may restrict its use.

Level of evidence 2.

Grade of recommendation B

It is important that one should be aware of the fact that these patients who undergo bladder outlet surgery need long-term follow-up not only because of the complications but also because their bladder behavior may undergo unexpected clinically asymptomatic changes that could negatively affect their upper tracts if augmentation is not performed at the same time[164].

5. BLADDER NECK CLOSURE

In 'desperate' cases the bladder neck may be closed, the indication being persistent leakage despite several attempts to enhance outlet resistance by bulking agents or other surgical procedures. Although initial results are acceptable, long-term results are usually disappointing: persistent urinary leakage, stomal stenosis and leakage or stone formation (in up to 40%) [165,166]. One of the most important factors seems to be compliance with intermittent catheterization and bladder irrigation.

6. BLADDER OUTLET RECONSTRUCTION

Surgical procedures to achieve urinary continence are dictated by functional and anatomic deficiencies and by the ultimate goal of either continence (with normal voiding) or dryness (dependent on intermittent catheterization).

Construction of a functional urethra for continence usually implies an anatomic defect without a neurogenic component (epispadias / esxtrophy) and includes urethral and bladder neck narrowing and urethral lengthening [167-172].

Such procedures may initially require intermittent catheterization or occasional post voiding catheterization, but bladder empting by voiding is anticipated.

Urethral reconstruction for dryness, however, mandates intermittent catheterization. The goal in surgery to achieve dryness is to create a urethra suited to catheterization, which has closure such that intra-luminal pressures always exceed intravesical pressure. The most dependable procedures for dryness utilize a flap valve or tunnel to achieve urethral closure, although urethral slings, wraps and injections have also been used [173].

Level of evidence 3.

Grade of recommendation C

Reconstruction to achieve **continence** is based on the principle that proximal reduction of the caliber of the urethra supports the inherent proximal sphincteric mechanism of the bladder neck and proximal urethra. The narrowing must be dynamic to permit closure for continence and yet permit opening with funneling during voiding. Several techniques have been described to achieve this goal [3, 166-176]. Young [1922] performed a "double sphincter technique" that involved the excision of a wedge of tissue at the anterior bladder neck, as well as removal of a wedge of tissue just proximal to the epispadiac meatus (external sphincter). Dees [1949] added the concept of lengthening the urethral tube to that of narrowing. In his procedure parallel incisions were made through the existing bladder neck area which created a posterior urethral plate from what had previously been the trigone of the bladder. This is tubularized to give added length to the proximal urethra. The added length provides increased potential for urethral closure and moves the bladder neck and proximal urethra into the abdominal cavity. Leadbetter [1964] modified the Young-Dees procedure by creating muscular flaps from the area of the bladder neck and proximal urethra which were used to wrap the newly created proximal tube. This procedure was popularized by Jeffs [1983] who applied it to a staged repair of exstrophy. He supported a lengthened urethra by a suspension. They report their long term continence rate with this procedure as greater than 80%, without the need for CIC or augmentation [177].

Presently, this represents the gold standard for reconstruction for continence, however, modifications of the technique have reported similar or improved results. Most urethral lengthening procedures utilizing the posterior urethra and bladder neck require ureteral reimplantation and preservation of the posterior urethral plate. Because part of the bladder is used to create the functional lengthening of the urethra, bladder capacity decreases following the procedure. It also remains to be seen whether the created urethra is actually a functioning urethra: in many patients fibrosis around the urethra prevent it from being really 'functional': in these patients it may act as an anatomic obstruction and long-term follow-up is necessary to follow not only the bladder but also the upper tract.

Surgery for **dryness** is dependent on the effectiveness of intermittent catheterization and is usually reserved for patients with neurogenic dysfunction or multiple previous surgeries. Procedures to

achieve dryness usually create a urethral closure pressure that exceeds bladder pressure.

A flap valve can be constructed by using an anterior or posterior bladder flap (full thickness) to construct a tube that is placed in a submucosal tunnel [171,175,176].

The major disadvantage of these procedures (flap valves) is that the valve will not allow leakage with high intravesical pressures, potentiating renal damage. Therefore, these procedures can be dangerous to the patient who is not totally committed to follow catheterization recommendations.

Unfortunately, the ideal procedure for surgical reconstruction of the bladder neck does not exist. The surgical approach to urinary incontinence in the child must be multifaceted because of the inherent complex and varied nature of the problem.

Recent data would support the concept that very early reconstruction in the exstrophy / epispadias group may result in physiologic bladder cycling which facilitates normal bladder and urethral development. This results in higher potential for continence without the need for bladder augmentation and bladder neck reconstruction (Level 3). More work and clinical experience in this area is strongly recommended. (Grade A)

7. ALTERNATIVE CONTINENCE CHANNELS

In the surgical treatment of incontinence in children every effort must be made to preserve the natural upper and lower urinary tract. The bladder is the best urinary reservoir, the urethra the best outlet and the urethral sphincters the best control mechanism. If the bladder is partly or wholly unusable it may be augmented or replaced by a variety of techniques.

Urethral failure may occur either because the sphincters are incompetent or because it is overactive and does not allow spontaneous voiding. It would be preferable for the former to be treated by one of the techniques described above and the latter by intermittent catheterization (CIC). If all of these fail, continent supra pubic diversion is indicated.

a) The Mitrofanoff principle.

Mitrofanoff's name is given to the principle of burying a narrow tube within the wall of the bladder or urinary reservoir whose distal end is brought to the abdominal wall to form a catheterizable stoma suitable for intermittent catheterization [178]. The technique is simple and familiar to all urologists who are accustomed to re-implanting ureters. Several narrow tubes are available for the Mitrofanoff conduit [179,180]. In the original description, the appendix was used. However, even if the appendix is still present, it may be unusable in 31% of patients [181].

If no suitable tube is found, a good tube can be formed by tailoring ileum transversely so that only 2-3cm of ileum can be made into a 7-8 cm conduit. This modification was originally described by Yang in humans and by Monti in experimental animals[182,183]. It is increasingly used though great care must be taken in its construction to avoid an internal fistula [184].

The ureter may be used but there may be some difficulty in achieving sufficient

calibre with a previously normal ureter. Earlier reports that the Fallopian tube could be used have not stood the test of time.

The Mitrofanoff system achieves reliable continence which is maintained in long term follow-up, for a high proportion of patients. Long-term follow-up data shows that in the original series of Paul Mitrofanoff of 23 patients after a mean follow-up of 20 years, 1 patient had died, but in the other 22 patients no metabolic changes were noted. The bladder neck was closed in 21 patients. Secondary bladder augmentation had to be performed in 8, while in 4 children a non-continent diversion was created. With time the need for additional surgery decreased and after 20 years 16 patients had a good and stable continent diversion [185].

The pressure generated within the lumen of the conduit is 2 to 3 times higher than that within the reservoir so that continence is preserved even when the intra abdominal pressure is raised by straining. Conversely, the pressure in the lumen of a Kock nipple is only slightly higher than that in the reservoir so that continence is less reliable[186,187].

The conduit may be buried either between the mucosal and muscle layers of the reservoir, or may be completely imbrocated in the full thickness of the reservoir wall. Any well supported tunnel of about 2- 4 cm will suffice. The choice depends both on the nature of the reservoir and on the conduit [188].

Continence rates of 90-100% with the Mitrofanoff Principle are reported, regardless of diagnosis, reservoir or conduit type [188,189]. Follow-up for at least ten years has shown that the system is resilient [190,191,192].

A modified technique of vesicostomy is described using a gastrostomy button, which could be used as a continent urinary stoma in children with incomplete voiding. Button vesicostomy is a useful addition to the options available for a catheterizable continent urinary stoma in children in the short or medium term [193].

Although perfect continence seems attractive, it may not be in the child's best interests. A 'pop-off' valve may be in the interest of the child if catheterization is impossible or forgotten.

b) The Ileo-cecal valve.

The ileo-cecal valve is an obvious sphincter to combine with cecum and ascending colon as the reservoir and the terminal ileum as the conduit. The early continence rate of 94% was not sustained because of high pressures in the tubular reservoir and weakness of the valve [194,195,196].

The Indiana system is based on the competence of the ileo-caecal valve but with a detubularized reservoir [197]. The valve itself is reinforced with non-absorbable plicating sutures and the terminal ileum which forms the conduit is tailored. The best reported continence rate is 96% with a 2% rate of catheterization difficulties.

In the complete Mainz I pouch a length of terminal ileum is intussuscepted through the ileo-cecal valve as a Kock nipple [198]. It is impossible to say whether the nipple or the ileocecal valve (or both) produce the continence which is reported in 96% of patients.

Both these systems work well as complete reconstructions and are widely used as bladder replacements in children. The sacrifice of the ileo-cecal valve may cause gastro-intestinal complications.

c) Kock pouch

The first workable continent diversion was the Kock pouch [42]. The reservoir is made from 40cm ileum reconfigured to reduce the intrinsic pressure. The continence mechanism is formed by intussusception of 12cm of ileum. In a complete form it requires 72cm of ileum which may be more than can be spared from the gastro-intestinal tract.

Although first described as a mechanism for a continent ileostomy in children the Kock pouch is now not commonly used in children because of the problem with large amount of bowel needed, stone formation and mediocre success with dryness of the catheterizable stoma [199,200].

d) Artificial Sphincter

As a last resort, the AUS may be considered to give continence to a reconstructed outlet. Experimental evidence suggests that AUS cuffs can be placed safely around intestine providing the cuff pressure is low [201]. The AUS has been used successfully around large bowel, in three of four children with follow-up to 11 years [202].

e) Where to place the cutaneous stoma

In patients with spina bifida, particularly non-walkers, the site must be chosen with particular care. The natural tendency is for the spine to collapse with time so that the lower half of the abdomen becomes more pendulous and beyond the range of vision. A low site may seem appropriate in the child, but will become unusable in the adult. It is best to use a high, midline site, preferably hidden in the umbilicus. The site should be determined in a sitting position and marked before surgery because in the supine position the position will change dramatically. In some patients the best position may not be in the midline at all: special care must be taken that the patient can manage bladder emptying and irrigation him/herself.

For most other patients, the site of the stoma should be chosen by cosmetic criteria. The umbilicus can be made into a very discrete stoma; the risk of stenosis is low and it is a readily identifiable landmark. Otherwise, the stoma should be as low on the abdominal wall as possible and certainly below the top of the underpants. However, many surgeons find the best results by placing the catheterizable stoma in the umbilicus.

The problem of stomal stenosis remains ever present. It can occur at any time so that only follow up of many years could determine whether any system of anastomosis to the skin is better than any other. The published rate of stomal stenosis is between 10 and 20%. The multi-flap V.Q.Z. stoma is claimed to have the lowest rate but follow up is short and it may well not pass the test of time [203].

VIII. COMPLICATIONS OF CONTINENCE SURGERY IN CHILDREN

1. STORAGE AND EMPTYING COMPLICATIONS

In the short term, it has been shown that the continent diversions can store urine and can be emptied by clean intermittent catheterization (CIC). It is apparent that there is a constant need for review and surgical revision. This observation mirrors the late complications of augmentation cystoplasty for neuropathic bladder where the median time to revision surgery is as long as ten years [204,205].

In general, once continent, they remain continent, although there are occasional reports of late development of incontinence. The problem lies more in difficulties with catheterization, particularly stenosis and false passages which may occur in up to 34% of patients[188]. In a recent retrospective evaluation of 500 augmentations over 25 years with a median follow-up of 13.3 years, the cumulative risk of further surgery at the bladder level was 0.04 operations per patient per year of augmentation and 34 % of the patients needed further surgery for complications. Bladder perforation occurred in 43 patients (8.6%) with a total of 53 events and 125 surgeries done for bladder stones in 75 cases [206].

The principal complications arise because the reservoir is usually made from intestine. Ideally, urothelium should be used and preservation of the bladder epithelium gives fewer complications than enterocystoplasty [207].

Combinations of detrusor myomectomy and augmentation with de-mucosalised colon have given promising results in the short term. The surgery is difficult as the bladder epithelium must not be damaged and the intestinal mucosa must be removed completely. When achieved there are no metabolic problems and many patients can void [207].

When augmentation can be done with a dilated ureter, the results are good and the complication rate low even in children with compromised renal function or transplantation [208].

All intestinal reservoirs produce mucus. The amount is difficult to measure and most estimates are subjective. No regime has been shown to dependably reduce mucus production [209].

2. RESERVOIR RUPTURE

The incidence of spontaneous rupture varies between different units. There may be delay in diagnosis although the history of sudden abdominal pain and diminished or absent urine drainage should make it obvious. The patient rapidly becomes very ill with symptoms of generalized peritonitis [210,211]. A 'pouchogram' may not be sensitive enough to demonstrate a leak. Diagnosis is best made by history, physical examination, ultrasonography and a CT cystogram. If diagnosed early, catheterization and broad spectrum antibiotics may sometimes lead to recovery. If the patient fails to respond within 12 hours on this regime or if the patient is ill, laparotomy should be performed at once. If there is any instability of the patient laparotomy should be considered as an immediate necessity as bladder rupture in this clinical situation can be lethal.

Level of evidence 2.

Grade of recommendation A

Figures are not available on the incidence of this complication in reservoirs made only of bowel but come from patients with intestinal segments in the urinary tract. Most papers report small numbers. In a multicentre review from Scandinavia an incidence of 1.5% was noted. There were eight patients with neurogenic bladder which was said to be disproportionately high [210]. In a series of 264 children with any sort of bowel reservoir or enterocystoplasty, 23 perforations occurred in 18 patients with one death [211]. Therefore, as this complication is more common in children it becomes a very important consideration [212]. A review of 500 bladder augmentation procedures performed during the preceding 25 years, spontaneous perforations occurred in 43 patients (8.6%), for a total of 54 events. The calculated risk was 0.0066 perforations per augmentation-year [213].

Patients and their families should be warned of this possible complication and advised to return to hospital at once for any symptoms of acute abdomen, especially if the reservoir stops draining its usual volume of urine. All young patients with urinary reconstructions including intestinocystoplasty should carry suitable information to warn attending physicians of their urinary diversion in case of emergency.

3. METABOLIC COMPLICATIONS

Metabolic changes are common when urine is stored in intestinal reservoirs and must be carefully monitored. It is uncertain whether they are commoner in children or whether they just live longer and are more closely monitored.

Nurse et al found that all patients absorbed sodium and potassium from the reservoirs but the extent was variable [214]. A third of all patients (but 50% of those with an ileocecal reservoir) had hyperchloremia. All patients had abnormal blood gases, the majority having metabolic acidosis with respiratory compensation. The findings were unrelated to renal function or the time since the reservoir was constructed.

In 183 patients of all ages at St Peter's Hospitals who had any form of enterocystoplasty, hyperchloraemic acidosis was found in 25 (14%) and borderline hyperchloraemic acidosis in an additional 40 (22%) patients. The incidence was lower in reservoirs with ileum as the only bowel segment compared to those containing some colon (9% v 16%). When arterial blood gases were measured in 29 of these children a consistent pattern was not found [215].

In a series of 23 patients, Ditonno et al found that 52% of patients with a reservoir of right colon had hyperchloraemic acidosis [216]. In ileal reservoirs, Poulsen et al found mild acidosis but no patients with bicarbonate results outside the reference range [217].

Many authors do not distinguish between patients with normal and abnormal renal function. All of 12 patients in one series with a pre-operative serum creatinine above 2.0mg% developed hyperchloraemic acidosis within 6 months of enterocystoplasty[218]. It is prudent to monitor patients for metabolic abnormalities, especially hyperchloraemic acidosis, and to treat them when found [219].

With increasing experience, it has become clear that there is a risk of developing vitamin B12 defi-

ciency, sometimes after many years of follow up. It is likely that resection of ileum in children leads to an incomplete absorption defect. Stores of B12 may last for several years before the serum level becomes abnormal. At a mean follow up of six years, low levels of B12 have been found in 14% of children. There was a corresponding rise in the serum methyl malonic acid which is a metabolite that accumulates in B12 deficiency suggesting that the finding was clinically significant. Similarly, in adults, 18.7% have B12 deficiency at five years. In the adults the mean B12 level was significantly lower when the ileo caecal segment as opposed to ileum alone had been used (413 ng/ml compared to 257 ng/ml) [220,221]. In order to avoid the serious neurological complications, regular monitoring of B12 levels is essential.

In a review of 500 augmentations starting at 7 years postoperatively, 6 of 29 patients (21%) had low B12 values, while 12 of 29 (41%) had low-normal values [222].

Pediatric patients who have undergone ileal enterocystoplasty are at risk for development of vitamin B12 deficiency. These patients are at the highest risk beginning at 7 years postoperatively, and the risk increases with time. An annual serum B12 value in children beginning at 5 years following bladder augmentation is recommended.

Level of evidence 2.

Grade of recommendation B

The stomach has had a checkered career as a urinary reservoir. Its non-absorptive role in the gastro intestinal tract has made it particularly useful in reconstruction of children with inadequate intestine, such as those with cloacal exstrophy. There is little effect on gastro intestinal function. Metabolically, the acid production leading to hypochloraemic alkalosis may be positively beneficial in children with renal failure. It produces no mucus and the acidic urine is less easily infected and seldom grows stones. However about a third of children have had serious long term complications, often multiple. The quite severe dysuria / haematuria and the skin complications from the acid urine, particularly, have limited its use [223,224].

4. EFFECTS ON THE GASTROINTESTINAL TRACT

Little attention has been paid to the effects on gastro intestinal motility of removing segments of ileum or cecum for urinary reconstruction in children. In adults, disturbance of intestinal function has been found to be more frequent and more debilitating than might be expected.

Disturbance of bowel habit does not mean diarrhoea alone. It also includes urgency, leakage and nocturnal bowel actions. It is clear that quality of life may be seriously undermined by changes in bowel habit [225].

It is known that the bowel has a considerable ability to adapt, especially in young animals, when parts are removed. Nonetheless, reconstruction should be undertaken with the smallest length of bowel possible. Particular care should be taken in children with neurologic abnormality in whom rectal control is already poor. Poorly controlled fecal incontinence may occur in a third of patients [226,227].

5. RENAL FUNCTION

Obstruction and high pressures in the bladder during storage have devastating effects on the upper urinary tract. Bladder augmentation eliminates these high pressures. Urinary diversion with recurrent urinary tract infections and stone formation also may have deleterious effects on renal function. It is therefore of utmost importance to evaluate renal function in young children who have undergone undiversion or continent diversion. In the follow-up so far available, these procedures do not seem to affect renal function. When function has improved after such surgery it is likely to be the result of eliminating obstruction or high bladder storage pressure.

In rats with near complete nephrectomy the rate of progression of renal failure is no worse in those with ileocystoplasty compared to those with normal bladder [228]. This suggests, experimentally, that storage of urine in small intestine is not, on its own, harmful to renal function.

Clinically, in the longer term, renal deterioration has been related to obstruction, reflux and stone formation. In one long-term study of Kock pouch patients, these complications occurred at the same rate as that found in patients with ileal conduits: 29% at five to 11 years [229]. Similarly, in a prospective follow-up to a minimum of 10 years, it was found that the deterioration in glomerular filtration rate (GFR), that was found in 10 of 53 patients, was due to a ‘surgical’ cause in all but one [230].

Although a more complicated procedure, a renal transplant can be anastomosed to an intestinal reservoir with similar long term results as those using an ileal conduit [231,232].

6. INFECTIONS AND STONES

The incidence of bladder reservoir stones varies between 12 and 25%. This is higher in children compared to adults. Palmer et al reported an incidence of 52.5% during a follow-up of four years[233]. Renal stones are uncommon, occurring in about 1.6% of patients, an incidence which would be expected in a group with congenital urinary tract anomalies.

In a series comparing the Kock pouch with the Indiana pouch (which does not have staples), 43.1% of 72 Kock reservoirs formed stones compared to 12.9% of 54 Indiana reservoirs[234]. Furthermore, no patient with an Indiana pouch formed a stone after 4 years, but patients with Kock pouches continued to do so at a steady rate up to eight years.

Apart from the presence of a foreign body, several factors have been blamed for the high stone risk. Almost all reservoir stones are triple phosphate on analysis, though Terai et al found carbonate apatite, urate and calcium oxalate in up to 50% of stones from patients with an Indiana pouch[235]. This suggests that infection rendering the urine alkaline is a key factor. Micro-organisms that produce urease and split urea to form ammonia are the main culprits. The incidence of infection in reservoirs is high, 95% in one series, and yet the majority of patients do not form stones, suggesting that there are predisposing factors other than infection and the anatomical abnormality of the urine reservoirs [236].

It has been suggested that the immobility associated with spina bifida may be responsible, but this seems to have been in series with a predominance of such patients and was not confirmed in other studies[237].

The production of excess mucus has also been blamed. The problem is that the measurement of mucus is difficult.

The finding of a spectrum of stone formation from mucus, through calcification to frank stone lends some support to this aetiology. However, it could be a secondary event, with mucus becoming adherent to a stone that has already formed. Many surgeons encourage patients to wash out their reservoirs vigorously with water two or three times a week. There seem to be fewer stones in those that claim to practice regular washing. In a prospective study a regime of weekly washouts did not improve the incidence of stones in 30 children compared to historical controls [238].

Mathoera et al found an incidence of 16% during a follow-up of 4.9 years in 90 patients: girls were more frequently affected than boys and concomitant bladder neck reconstruction, recurrent infections and difficulties with CIC were other risk factors identified, while the frequency of irrigation did not appear to be a risk factor [239].

Mucins are an important component of the epithelial barrier and protect the epithelium from mechanical and chemical erosion. Mucins are known to act as important adhesion molecules for bacteria. Mucins may also enhance the formation of crystals[240]. Mucin expression changes after incorporating the intestinal segment in the bladder. Upregulation of MUC1 and MUC4 expression occurs in transposed ileal segments resembling normal epithelium, whereas ileal segments in enterocystoplasty showed an upregulation of MUC2,3,4 and 5AC expression towards the site of anastomosis with the ileal segment. These changes which may be due to exposure to urine coincide with a change from ileal sialomucins to colonic sulfomucins by a change in glycosylation. The mucins bind calcium and may form a template resembling the crystal structure on which crystals are formed and grow. From these studies it is concluded that inhibition of bacterial adhesion (by using different irrigation fluids based on sugars) could be of eminent importance in the prevention of certain types of infection stones.

An interesting comparison has been made between children with a native bladder alone and those with an augmentation, all of whom were emptying by self catheterization. There was no significant difference in the incidence of stones with or without an augmentation[241].

Stones are associated with inadequate drainage in the sense that CIC through the urethra, the most dependent possible drainage, has the lowest stone rate. Patients with the most ‘up hill’ drainage, that is with a Mitrofanoff channel entering the upper part of an orthotopic reservoir have a higher incidence of stones [239].

Kronner et al made the observation, that the incidence of stones was statistically associated with abdominal wall stomas and a bladder outlet tightening procedure (21.1% compared to 6% in patients with augmentation alone)[236].

Once a bladder stone has been diagnosed it has to be removed: several methods are available, but ESWL should be avoided as it is difficult to remove all fragments (and small particles may get trapped in mucus and the pouch wall), which may form the focus of a new calculus. Because of the recurrent nature of these stones the least invasive method should be recommended [242,243].

Because of the high incidence of stones following enterocystoplasty several measures should be recommended to the patients and their parents. Regular CIC under hygienic circumstances with adequate fluid intake and irrigation seem to be the most important [244]. It is unclear whether prophylactic antibiotics are useful, but a clinical infection should be treated adequately. Maybe in the future different types of irrigation fluid may prove helpful.

7. GROWTH

The suggestion that enterocystoplasty delayed growth in height seems to have been ill founded. In a group of 60 children reported in 1992 it was stated that 20% had delayed growth [245]. Current follow up of the same group has shown that all have caught up and achieved their final predicted height. Furthermore, measurements in a group of

123 children from the same unit have shown no significant delay in linear growth [246].

Enterocystoplasty may have an effect on bone metabolism even if growth is not impaired. At least in rats with enterocystoplasty there is significant loss of bone mineral density especially in the cortical compartment where there is endosteal resorption. These changes are not associated with HCA and are lessened by continuous antibiotic administration [247,248].

More recent follow-up data shows either no effect on growth or a decreased linear growth [249-252].

8. PREGNANCY

When reconstructing girls it is essential to have a future pregnancy in mind. The reservoir and pedicles should be fixed on one side to allow enlargement of the uterus on the other.

Pregnancy may be complicated and requires the joint care of obstetrician and urologist [253]. Particular problems include upper tract obstruction and changes in continence as the uterus enlarges.

Pregnancy with an orthotopic reconstruction appears to have a good outcome but chronic urinary infection is almost inevitable and occasionally an indwelling catheter is needed in the third trimester [254]. With a suprapubic diversion, catheter drainage for incontinence or retention may be needed in the third trimester [255].

Except in patients with an artificial urethral sphincter and extensive bladder outlet reconstruction, vaginal delivery is usual and caesarean section should generally be reserved for purely obstetric indications (distorted pelvis in spina bifida patients). During the delivery the bladder reservoir should be empty and an artificial sphincter deactivated. The urologist should be present during Caesarean section to ensure protection for the reservoir, the continent channel and its pedicles.

9. MALIGNANCY

The possibility of cancer occurring as a complication of enterocystoplasty is a constant source of worry. Currently cancer following augmentation cystoplasty is a recognized risk factor. It is known to be a frequent complication of ureterosigmoidostomy after 20 to 30 years of follow up. Animal evidence suggests that faecal and urinary streams must be mixed in bowel for neoplasia to occur. However, if it is chronic mixed bacterial infection, rather than the faeces per se, then all bowel urinary reservoirs are at risk.

In patients with colonic and ileal cystoplasties high levels of nitrosamines have been found in the urine of most patients examined [256]. Clinically significant levels probably only occur in chronically infected reservoirs [257]. Biopsies of the ileal and colonic segments showed changes similar to those that have been found in ileal and colonic conduits and in ureterosigmoidostomies. More severe histological changes and higher levels of nitrosamines correlated with heavy mixed bacterial growth on urine culture [258].

In a review by Filmer et al, 14 cases of pouch neoplasm were identified [259]. Special features could be found in nearly all the cases. Ten patients had been reconstructed for tuberculosis; four tumors were not adenocarcinomas; one patient had a pre-existing carcinoma; six patients were over 50 years old. Cancer was found in bowel reservoirs at a mean of 18 years from formation. This is a few years earlier than the mean time at which malignant neoplasms are seen in ureterosigmoidostomies.

In a review of 260 patients with a follow-up of more than 10 years, Soergel et al found 3 malignancies (all transitional cell carcinoma): 2 following ileocecal and 1 after cecal augmentation. The age at augmentation was 8, 20 and 24 years respectively: the tumors were found when they were 29, 37 and 44 years old. All had metastatic desease and died. The incidence of malignancy in this group was 1.2%: considering that the development of tumors usually takes 20-25 years the probable incidence of malignancy following enterocystoplasty may be as high as 3.8 % [260].

Hussmann et studied a group of 153 patients with a mean follow-up of 27 years (10-52 yrs)after augmentation cystoplasty. In those with a Neurogenic bladder (n=97) they found 2 patients with transitional cell carcinoma (both smokers), in 38 patients with bladder exstrophy 3 multifocal adenocarcinomas in the augmented segment were found and in 2 of 18 patients with urethral valves an adenocarcinoma was discovered. The overall risk of cancer was 4.5% after a median period of 32 years. Of the 7 patients 5 died suggesting that these tumors are very aggressive and metastazise early [261].

This was also confirmed by Sung [262].

Patients who undergo bladder augmentation with a gastric remnant are at increased risk for malignancy, probably similar to that in patients with enterocystoplasty. In a review of 119 patients underwent augmentation cystoplasty with stomach in 2 institutions, three patients had gastric adenocarcinoma, while the other had poorly differentiated transitional cell carcinoma. Each case progressed to malignancy more than 10 years after augmentation [263-265).

If cancer is going to be a common problem, there will be some difficulty in monitoring the patients at risk [266]. Endoscopy with a small instrument through a stoma may not be sufficient. Ultrasound may not be able to distinguish between tumors and folds of mucosa. Three dimensional reconstruction of computerised tomography may be helpful, though the equipment is expensive and not widely

available at present [267]. At present it is advised to perform an annual endoscopic evaluation in all patients following enterocystoplasty starting 10 years after surgery.

10. PSYCHOLOGICAL CONSEQUENCES AND QUALITY OF LIFE

The main justification for performing a bladder reconstruction or continent diversion is to improve the individual's Quality of Life (QoL).

It would seem logical that continent urinary diversion would be better than a bag. This is not always the case. In adults the only sure advantage is cosmetic. Validated QoL surveys in children have not been reported, primarily because of the lack of suitable instruments [268]. Our prejudice is that reconstruction does, indeed, improve the lives of children. Supporting evidence is very thin and based on experience in adults.

The ileal conduit has been a standard part of urological surgery for over 50 years. It has well known complications but few would seriously suggest that they were more troublesome than those of the complex operations for bladder replacement. In an early investigation into quality of life issues, Boyd et al investigated 200 patients, half with an ileal conduit and half with a Kock pouch: there was little difference between the groups except that those with a Kock pouch engaged in more physical and sexual contact. The only patients that were consistently 'happier' were those who had had a conduit and subsequently were converted to a Kock pouch [269].

In a recent QoL survey in adults, a wide range of complications were considered to be acceptable, although an ordinary urological clinic would be full of patients trying to get rid of such symptoms: mild incontinence (50%), nocturia (37%), bladder stones (12%), urinary infections (9%), hydronephrosis (5%). Nonetheless, their QOL was judged to be good, primarily because 70% had experienced no adverse effect on their normal daily lives [270].

Quality of life does not mean absence of disease or a level of complications acceptable to the reviewing clinician. It is a difficult concept to measure because lack of validated instruments, difficulties in translating from one culture or language to another, and the difficulties in selecting control groups and variations in clinical situations. Gerharz et al have constructed their own 102 item instrument and compared 61 patients with a continent diversion and 131 with an ileal conduit. Patients with a continent diversion did better in all stoma related items indicating that containment of urine within the body and voluntary emptying is of major importance. In addition they had better physical strength, mental capacity, social competence and used their leisure time more actively. There was little difference in satisfaction with professional life, financial circumstances and in all interactions within the family including sexual activity [271].

IX. CONSENSUS STATEMENT ON SURGICAL TREATMENT OF URINARY INCONTINENCE IN CHILDREN

Forms of urinary incontinence in children are widely diverse, however, a detailed history and physical and voiding diary obviate the need for further studies. These should identify that limited group that may require surgery. Many patients in this group will have obvious severe congenital abnormalities.

Because of the spectrum of problems the specific treatment is usually dictated by the expertise and training of the treating physician. The rarity of many of these problems precludes the likelihood of any surgeon having expertise in all areas. Furthermore, nuances in surgical procedures develop gradually and often are tested without rigorous statistics.

Nevertheless it may be that newer forms of very early aggressive surgical approach to severe complex anomalies such as exstrophy, myelodysplasia and urethral valves may provide a successful model for significant impact on the ultimate continence in such patients. Ultimately this may provide a basis for randomized studies to determine the most specific and effective mode of therapy.

The committee would encourage vigorous research in the molecular basis of bladder development and also support the development of surgical and treatment strategies which would utilize the natural ability of the bladder to transform in the early months of development and immediately after birth. Furthermore efforts to promote bladder healing, and protecting and achieving normal bladder function should be supported. Such studies and research may lead to earlier and more aggressive treatment of many of the complex anomalies now treated by the surgical procedures outlined in this report.

G. PSYCHOLOGICAL ASPECTS OF URINARY INCONTINENCE, ENURESIS AND FAECAL INCONTINENCE

LIST OF ABBREVIATIONS

ADHD	Attention-Deficit/Hyperactivity Disorder
CBCL	Child Behavior Checklist
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – IV
DW	Daytime wetting (urinary incontinence)
HKD	Hyperkinetic Disorder
ICD-10	International Classification of Diseases – 10
NW	Nighttime wetting (nocturnal enuresis)
ODD	Oppositional Defiant Disorder

Since the publication of the ICI report in 2009 [1] an increasing body of studies has been published on psychological factors of incontinence in children including some comprehensive reviews [2-7]. This part includes an update based on the recent literature and especially the ICCS standardisation document on psychological aspects in urinary and faecal incontinence [8].

I. INTRODUCTION

Children with urinary incontinence, enuresis and faecal incontinence carry a higher risk for manifest behavioural disorders, as well as for subclinical emotional and behavioural symptoms. It is important to assess and integrate psychological factors in treatment for two reasons:

1. As can be seen in **table 3**, the rate of comorbid behavioural and emotional disorders is much higher than possible organic causes [7,8]. The same care used to exclude organic causes should be applied to the assessment of behavioural aspects. Therefore, even paediatricians and urologists should have a basic understanding of psychological principles in order to treat their young patients adequately.

2. In functional elimination disorders, provision of information, cognitive therapy and behavioural modification are the most effective, first-line approaches to treatment. Medication can be helpful in many cases, but are usually not the mainstay of treatment. Surgery is rarely indicated. As most of the techniques used in "urotherapy" are based on cognitive-behavioural psychotherapy, it is essential to be acquainted with the basic psychological principles.

This chapter provides information on comorbid manifest clinical disorders, as well as symptoms which might be emotionally distressing for children and parents, but do fulfil the criteria for a disorder. Often, these will resolve upon attaining continence, while manifest disorders usually do not. In addition, children with psychological disorders are less compliant, and this explains why the failure rate of children's incontinence treatment is much higher. It is recommended that both incontinence and any comorbid psychological disorder are treated separately to ensure effective therapy.

Also, the relevance of psychological factors for the different subtypes of incontinence will be considered. The terminology of the ICCS for enuresis and urinary incontinence as well as of the Rome-III classification for faecal incontinence will be used [9,10].

II. CLINICAL BEHAVIOURAL DISORDERS

The rate of clinically relevant behavioural disorders in children and adolescents lies between 12.0% (ICD-10 criteria) and 14.3% (DSM-IV) [11-13]. The rate of comorbid behavioural disorders is increased in children with all types of incontinence. Comorbidity denotes the co-occurrence of two or more disorders at the same time (concurrent comorbidity) or in sequence (sequential comorbidity). The focus on comorbidity allows a descriptive approach without making reference to possible causal associations. Basically, four combinations are possible:

- A behavioural disorder can be a consequence of the wetting problem,
- A behavioural disorder can precede and induce a relapse when a genetic disposition for enuresis is present, for example in secondary nocturnal enuresis,

Table 3: Organic causes and comorbidity of clinically relevant psychological disorders or symptom scores*

Nocturnal enuresis	
Organic causes	< 1%
Behavioural comorbidity*	20-30%
Urinary incontinence	
Organic causes	<10%
Behavioural comorbidity*	20-40%
Faecal incontinence with constipation	
Organic causes	< 5%
Behavioural comorbidity*	30-50%
Faecal incontinence without constipation	
Organic causes	< 1%
Behavioural comorbidity*	30-50%

- Wetting and a behavioural disorder can both be due to a common neurobiological dysfunction (such as in nocturnal enuresis and ADHD),

- With such common disorders, no causal relationship can be present and the two may co-exist by chance.

Psychological disorders (synonyms: psychiatric, psychic, mental disturbances) indicate that there is "a clinically significant behavioural or psychological syndrome or pattern (not a variant of normal behaviour) that occurs in an individual, that it is associated with present distress, disability or impairment and carries a risk for the future development of the individual" (DSM-IV)[12].

Clinically relevant disorders can be assessed by two basic methods: the categorical and the dimensional approach. The categorical method is based on a detailed diagnostic process (including: history, observation, exploration, mental state examination, questionnaires, testing, physical examination and other procedures) and are professional diagnoses according to standardised classification schemes: ICD-10 [11] or DSM-IV [12]. Dimensional assessment is based on symptom scores by questionnaires, but do not represent diagnoses. Cut-offs are defined to delineate a clinical (and sub-clinical) range.

One can differentiate:

- externalising or behavioural disorders with outwardly-directed, visible behaviour (examples: conduct disorders and ADHD),

- internalising, i.e. inwardly-directed, intrapsychic disorders such as emotional disorders (examples: separation anxiety, social anxiety, phobias, sibling rivalry and depressive disorders),

- and other disorders that do not fit into the two categories, such as anorexia nervosa, tic disorders and autistic syndromes.

III. CLINICAL BEHAVIORAL DISORDERS IN CHILDREN WITH ENURESIS AND URINARY INCONTINENCE

Children with urinary incontinence show a higher rate of comorbid behavioural and emotional problems than non-wetting children, in both epidemiological and in clinical studies. The overall relative risk is 1.4 – 4.5 times higher (**table 2**) [7].

1. EPIDEMIOLOGICAL STUDIES

Epidemiological studies have the advantage of revealing representative associations. They often cannot differentiate well between subgroups.

Not all epidemiological studies on enuresis actually assess behavioural problems in a standardised form [14]. Only those studies that clearly define the group of clinically deviant children are reported in **table 4**. If a control group is reported, the relative risk for a behavioural problem can be calculated; otherwise the normative data is used.

a) Nocturnal Enuresis

In the Isle-of Wight study, 25%-28% of enuretics were seen by their parents to show problematic behaviour according to the Rutter Child Scale, 3-4 times more often than the controls [15]. Using the same instrument, the longitudinal Study from Christchurch (New Zealand) came to similar rates for the primary children with nocturnal enuresis, while the children with secondary nocturnal enuresis showed a much higher rate of 52% [16]. The same study assessed rates of DSM-III diagnoses at a later age, with marked differences between the primary and the secondary children with nocturnal enuresis [17].

In the Dutch study by Hirasing et al [19], 23% of children with enuresis scored in the clinical range of the CBCL total problem scale. In the cross-sectional Chinese study by Liu et al [18], a third of all wetting children were in the clinical range, 3.6-4.5 more often than controls. The US-Study by Byrd et al [13] used the 32-item-BPI (Behavior Problem Index), which is modelled after CBCL. The rates are lower than in the other studies, but included infrequent wetters, with as few as one wetting episode per year.

In a British population-based study of 8242 children at the age of 7 ½ years, children with enuresis were affected by: separation anxiety (8.0%), social anxiety (70%), specific phobia (14.1%), generalised anxiety (10.5%), depression (14.2%), ODD (8.8%), conduct disorders (8.5%) and ADHD (17.6%) [21,22].

In summary, the epidemiological studies show clearly that, depending on definitions and instruments used, 20-30% of all **nocturnal enuretic children** show clinically relevant behavioural problems, 2 to 4 times higher than non-wetting children.

Children with **primary nocturnal enuresis** were not different from controls in epidemiological studies [17]. **Secondary nocturnal enuresis** was preceded by a higher rate of weighted life-events [23] and was significantly associated with a higher rate of DSM-III psychiatric disorders, which can persist into adolescence [17]. By adolescence, the attainment of dryness after the age of 10 years increased the risk for behavioural problems, independently of the primary or secondary status [14].

The only epidemiological study addressing monosymptomatic nocturnal enuresis included 8242 children aged 7 ½ years [24]. Though not adhering to the ICCS criteria, children with monosymptomatic nocturnal enuresis showed fewer behavioural symptoms than those with daytime problems (i.e. the non-monosymptomatic forms), although the differences did not reach significance.

Table 4: Epidemiological studies: Percentage of children with clinically relevant behavioural problems in comparison to controls and their relative risk*

Study	Age (years)	N	Type of wetting	Incontinent children	Controls	Relative risk
				Rutter Child Scale; cut-off > 13		
Rutter 1973 [15]	5-14	4481	NW/DW	Boys: 25.6% Girls: 28.6%	7.9% 7.8%	3.2 3.7
McGee 1984 [16]	7-9	1037	NW	Primary: 30.8% Secondary: 51.9%	21.6%	1.4 2.4
				DSM-III diagnoses		
Feehan 1990 [17]	11-15	1037	NW	Total: 23.4% Primary: 0% Secondary: 42.3%	9.5%	2.5 4.5
				CBCL Total > 90th p.		
Liu 2000 [18]	6-18	3344	NW	30.3%	9.1%	4.3
Hirasing 1997 [19]	9	1652	NW	23.0%	10.0%	2.3
				BPI > 90th p.		
Byrd 1996 [13]	5-17	10960	NW	16.5%	10.2%	1.6
				DAWBA		Odd's ratio
Joinson 2006 [20]	7-9	8213	DW	Separation anxiety: 11.4%	6.8%	1.8
				Attention/activity: 24.8%	13.8%	2.1
				Oppositional behaviour:10.9%	5.8%	2.0
				Conduct problems: 11.8%	6.2%	2.0
Joinson 2007 [21]	7 ½ years	8242	NW	Separation anxiety: 8.0%	6.4%	1.3
				Social anxiety: 7.0%	4.6%	1.5
				Specific phobia: 14.1%	11.5%	1.2
				Generalised anxiety: 10.5%	7.7%	1.4
				Depression: 14.2%	10.9%	1.3
				ODD: 8.8%	4.7%	1.9
				Conduct disorders: 8.5%	5.7%	1.5
				ADHD: 17.6%	11.9%	1.5

b) Urinary Incontinence (Daytime Wetting)

Daytime wetting has been neglected in epidemiological research. Only recently, the first study was published based on a cohort of 8213 children aged 7 ½ to 9 years [20]. Children with daytime wetting had significantly increased rates of psychological problems, especially separation anxiety (11.4%), attention deficit (24.8%), oppositional behaviour (10.9%) and conduct problems (11.8%). Externalising disorders predominate in daytime wetting children which, in turn, will interfere with treatment. In the same cohort, 10,000 children aged 4 to 9 years were analysed. Delayed development, difficult temperament and maternal depression / anxiety were associated with daytime wetting and soiling [25]. In another population-based study, 36.7% of children with urinary incontinence had ADHD symptoms, in comparison to 3.4% of dry children [22].

2. CLINICAL STUDIES

Clinical studies are limited by selection biases, but allow a much more detailed assessment of patients. Overall, children with nocturnal enuresis have lower rates of comorbid disorders (33.6%) than children with daytime wetting (52.6%) [26]. In another study, the rates were 29% and 46%, respectively [27]. Van Hoecke et al could also show that children with daytime wetting (or combined DW/NW) had significantly higher CBCL total problem scores than pure nocturnal enuretics or controls [28]. (**Table 5**)

a) Nocturnal Enuresis

In an early study of Berg et al [29] nearly 30% of children presented in a paediatric clinic were deemed "clinically disturbed". In another study in a paediatric setting, similar rates of 26% were found 20 years later using the CBCL [20]. These rates are almost identical to our own studies in a child psychiatric setting using the same instruments [26]. The rates of a selected group of treatment-resistant children with nocturnal enuresis undergoing Dry Bed Training were 2.2 times higher [31]. In the study of Van Hoecke et al [32], internalizing symptoms predominated in a mixed group of day and night wetting children with significantly higher scores for withdrawal, physical complaints, anxious / depressed, social problems and internalising behaviour scales compared to controls.

According to the ICCS terminology, four subgroups of nocturnal enuresis can be differentiated:

- primary monosymptomatic nocturnal enuresis
- primary non-monosymptomatic nocturnal enuresis
- secondary monosymptomatic nocturnal enuresis
- secondary non-monosymptomatic nocturnal enuresis

Regarding the subtypes of nocturnal enuresis, children with primary nocturnal enuresis showed behavioural problems less frequently (19.5%) than those with the secondary type (75.0%) [26]. The group with the lowest comorbidity – no higher than in the normative population – were those with monosymptomatic nocturnal enuresis (10.0%) without any daytime symptoms such as urgency, postponement or dysfunctional voiding. In a replication study, 29% of children with nocturnal enuresis had at least one ICD-10 diagnosis, 24% of those with monosymptomatic and 33% of those with non-monosymptomatic nocturnal enuresis [27].

Regarding the types of behavioural and emotional disorders, externalising disorders predominate [26]. The most specific comorbid disorders with enuresis

Table 5: Clinical studies: Percentage of children with clinically relevant behavioural problems in comparison to controls and their relative risk*

Study	Age (years)	N	Type of wetting	Incontinent children	Controls	Relative risk
				ICD-10 diagnoses		
von Gontard 1999 [26]	5-11	110	NW	33.6%	12.0%	2.8
von Gontard 1999 [26]	5-11	57	DW	52.6%	12.0%	4.4
Zink 2008 [27]	5-16	97	NW	29%	12.0%	2.4
	5-16	69	DW	46%	12.0%	3.8
				Rutter A questionnaire, cut off > 18 [interview)		
Berg 1981 [29]	6-13	41	NW	29.3% (26.8%)		
				CBCL Total >90th p.		
Baeyens 2001 [30]	6-12	100	NW/DW	26%	10.0%	2.6
von Gontard 1999 [26]	5-11	167	NW/DW	28.2%	10%	2.8
Hirasing 2002 [31]	6-15	91	NW	21%	10%	2.1
Van Hoecke 2004 [32]	9-12	84	NW/DW	20.4%	6.1%	3.3
Zink 2008 [27]	5-16	166	NW/DW	40%	10%	4.0

are ADHD (DSM-IV) or the Hyperkinetic Syndrome (ICD-10). In our own studies, the rates ranged from 9.3% (HKS) to 13.5% (HKS and ADHD) [26, 34]. ADHD is not associated with any specific type of nocturnal enuresis [33].

In a retrospective study of patients with ADHD, 20.9% wetted at night and 6.5% during the day. The odds-ratios were 2.7 and 4.5 times higher, respectively, which means that there is a nonspecific association of ADHD and both night and daytime wetting [35]. 25% of 140 children with ADHD were affected by nocturnal enuresis compared to 10.8% of 120 controls [36]. The highest comorbidity rates of 40% for ADHD and nocturnal enuresis were reported by Baeyens et al. [33], possibly due to selection bias: 15% had a combined, 22.5% an inattentive and only 2.5% a hyperactive type of ADHD. In a community based sample, the prevalence rate was much lower [37]. ADHD continued to be present in 72.5% of children in a two-year follow-up indicating a high stability [37]. Children with ADHD continued to wet at follow-up much more often (65%) than controls (37%) (Odds-ratio 3.17) [37]. At a 4-year follow-up, 64% still had ADHD: of these, 42% continued to wet at night (compared to 37% of the controls) [38].

In clinical practice, children with ADHD are more difficult to treat. In a retrospective study, 113 children with ADHD and nocturnal enuresis had a worse outcome on alarm treatment than controls (with nocturnal enuresis only): 43% (vs. 69%) were dry at 6 months and 19% (vs. 66%) at 12 months. There was no difference if they were treated with medication, which does not require active cooperation. Non-compliance was reported in 38% of children with ADHD, but only in 22% of the controls [39]. This means that children with both enuresis and ADHD require special attention – and both need to be treated separately.

b) Urinary Incontinence (Daytime Wetting)

Only a few studies have addressed the specific problems of children with daytime wetting. In a study of 418 children aged 5 – 17 years, day wetting children were described as being more stubborn, oppositional and secretive than nocturnal enuretic children[40]. In a subgroup of 58 children, those with and without urinary tract infections were compared: 11 % of day wetting children with urinary tract infections had a CBCL total score in the clinical range, 35 % of day wetting children without urinary tract infections and 16 % of nocturnal wetters. This indicates that children with a higher risk for behavioural problems were day wetting children without urinary tract infections [40]. In another study, 90 girls with recurrent UTI's had significantly more behavioural abnormalities than controls [41], so the issue of behavioural problems in children with and without UTI's remains to be settled.

ADHD is a common problem among day wetting children, as well. Compared to controls, children with ADHD had more symptoms of incontinence, constipation, infrequent voiding and dysuria [42]. With ADHD, treatment outcome is worse. In a retrospective analysis, 68% of day wetting children with ADHD became dry compared to 91% of controls. Non-compliance was much higher for timed voiding [39].

Daytime wetting is a heterogeneous group of disorders. According to the ICCS terminology, following subgroups can be differentiated [9]:

- Over-active bladder including urgency incontinence
- Voiding postponement
- Underactive detrusor
- Dysfunctional voiding
- Obstructive voiding
- Stress urinary incontinence
- Vaginal reflux
- Giggle incontinence
- Extraordinary daytime urinary frequency

Only some of these subgroups have been studied regarding comorbid psychological disorders.

Children with **urgency incontinence** have previously been considered to have few behavioural problems [43]. 29 % of children with urgency incontinence had an ICD-10 diagnosis and 14% had an internalizing disorder. 13.5 % had a clinical total problem score in the CBCL, again mainly internalizing problems [44, 45]. The children are distressed by their wetting and family functioning is intact [45]. In a new study, 35% of children with urgency incontinence fulfilled the criteria for an ICD-10 diagnosis [27]. Children with urgency incontinence have lower rates of comorbid disorders than those with voiding postponement (36% vs. 59%), but higher than controls (9%) [46]. Children with urgency incontinence predominantly have emotional, introversive disorders, while the most typical disorder in voiding postponement is ODD [46]. Comorbid disorders are usually a consequence of wetting in urge incontinence, while ODD seems to be the underlying disorder in voiding postponement in many children. In summary, children with urgency incontinence have only a slightly increased rate of comorbid psychiatric disorders. If they are affected, emotional, introversive symptoms predominate.

Children with **voiding postponement**, on the other hand, fall into two groups: in some it represents an acquired habit, in others, it is associated with externalising psychological disorders, especially oppositional defiant disorder (ODD). In a systematic study of children with voiding postponement in a paediatric and child psychiatric setting, 53.8 % fulfilled the criteria for at least one ICD-10 diagnosis [44]. These were mainly externalizing disorders in a third of all children such as Oppositional Defiant Disorder (ODD). Also, 37.3 % of children had a CBCL total score in the clinical range, again, with externalizing

symptoms predominating. In addition, family functioning was impaired [44,45]. In a new sample, 53% of children with voiding postponement had at least one ICD-10 diagnosis [27]. In summary, children with voiding postponement have highly increased psychiatric risks.

Systematic studies on comorbid behavioural problems in children with **underactive bladder** have not been performed, although by clinical impression the rate of associated problems is high. In the original article, the "lazy bladder syndrome" was described as an acquired behaviour: it has "developed from the habitual neglect of the patient to empty the bladder on getting the urge to micturate" [47].

Systematic investigations of psychological aspects of **dysfunctional voiding** are rare. Again, in some children it represents an acquired habit, in others severe psychological disturbances are present [48]. Dysfunctional voiding following severe sexual abuse and deprivation as well as other familial stressors such as migration has been described in case reports [49].

There have been no systematic investigations of children with **giggle incontinence**. From clinical experience, they are highly distressed by the symptom and try to avoid situations in which they might be forced to laugh. Social withdrawal, not going to parties and meeting with friends has been observed. It is not known if the rate of behavioural disorders is increased.

Regarding the **other subtypes of urinary incontinence**, not even anecdotal data is available.

IV. CLINICAL BEHAVIORAL DISORDERS IN CHILDREN WITH FAECAL INCONTINENCE

According to the Rome-III classification, two subtypes of faecal incontinence can be differentiated [11]:

• Functional constipation (with or without incontinence)

• Non-retentive faecal incontinence.

1. EPIDEMIOLOGICAL STUDIES

In the large ALSPAC study of 8242 children aged 7-8 years, children with faecal incontinence had significantly increased rates of separation anxiety, specific phobias, generalised anxiety, ADHD and ODD (**table 6**) [50]. In other words, soiling children show a completely heterogeneous pattern of both internalising and externalising disorders. Again, these will require assessment in the individual child, as they will interfere with treatment of the incontinence.

2. CLINICAL STUDIES

As many studies have used the Child Behaviour Check List (CBCL) [51], the results can be compared easily. As shown in **table 4**, 35% to 50% of all children with faecal incontinence had a total behavioural score in the clinical range in this parental questionnaire. Compared to the normative population (10%), 3.5 to 5 times more children with faecal incontinence have total behaviour scores in the clinical range. As all studies were conducted in a paediatric setting, this rate cannot be due to selection effects of mental health clinics. Children with behavioural maladjustment are less compliant than children without psychological disorders (71% vs. 38% non-compliant) – so if these behavioural problems are not addressed treatment will be less successful [52].

Children with faecal incontinence and constipation have the same rate of behavioural scores in the clinical range as children without constipation (39% vs. 44%, [52] and 37% vs. 39%, [53]). This means that the two major types of faecal incontinence cannot be differentiated according to the behavioural comorbidity. More importantly, regarding the aetiology, there is no evidence that one type (i.e. with constipation) has more somatic aetiology, while the other type (i.e. without constipation) has a more psychogenic aetiology. There is no specific psychopathology typical for faecal incontinence: all types of behavioural and emotional disorders can co-exist.

Internalising clinical behavioural scores (32%) were twice as common as externalizing ones (17%) in one study [58]. In others, single behavioural items, denoting oppositional behaviour and attentional problems predominate [53, 59]. Compared to controls, children with faecal incontinence rated significantly higher regarding anxious/depressed behaviour, attentional difficulties and disruptive behaviour on the CBCL subscales. For example, the rate of children with attentional problems in the clinical and borderline range was 6 - 7 times higher than in controls (20% vs. 3%; norms 5%) [60]. Again, the heterogeneity of behavioural symptoms is apparent.

Only few studies have assessed behavioural and emotional disorders according to standardized child psychiatric criteria. They also show a high general rate and heterogeneity of comorbid disorders. Thus, 34% of 41 children with faecal incontinence had an emotional disorder, 12% a conduct disorder and 10% a hyperkinetic syndrome according to ICD-criteria [61]. In another study of 85 highly selected child psychiatric inpatients with faecal incontinence, 83 % fulfilled the criteria for at least one ICD-10-diagnosis. 32% had a hyperkinetic syndrome, 21% an emotional disorder and 9% a conduct disorder [62]. Children with faecal incontinence and urinary incontinence have an even higher rate of behavioural and emotional disorders than children with wetting problems alone [63].

The co-occurrence of faecal incontinence and sexual abuse has been described by several authors [64]. In one study, 36% of abused boys had faecal incontinence [65], but other symptoms

*Table 6: Epidemiological and clinical studies: Percentage of children with clinically relevant behavioural problems in comparison to controls and their relative risk **

Study	Age (yrs)	N	Type of faecal incontinence	Incontinent children	Controls	Relative risk
Epidemiological studies				DAWBA		
Joinson 2006 [50]	7-8	8242	Not specified	Separation anxiety: 4.3%	0.8%	5.4
				Specific phobia: 4.3%	1.0%	4.3
				Generalised anxiety: 3.4%	0.4%	8.5
				ADHD: 9.2%	1.9%	4.8
				ODD: 11.9%	1.9%	6.3
Clinical studies				CBCL Total >90th p.		
Gabel 1986 [53]	6-11	55	Not specified	49%	10.0%	4.9
Young 1995[54]	5-17	76	Not specified	51%	10.0%	5.1
Nolan 1991 [52]	4-16	169	Not specified	43%	10.0%	4.3
Loening-Baucke 1987 [55]	6-11	38	Functional constipation	42%	10.0%	4.2
Benninga 1994 [56]	5-17	111	Functional constipation	39%	10.0%	3.9
Benninga 2004 [57]	5-17	135	Functional constipation	37%	10.0%	3.7
Benninga 1994 [56]	5-17	50	Nonretentive faecal incontinence	44%	10.0%	4.4
Van der Plas 1997 [58]	5-17	71	Nonretentive faecal incontinence	35%	10.0%	3.5
Benninga 2004 [57]	5-17	56	Nonretentive faecal incontinence	39%	10.0%	3.9

can co-exist [66,67]. However, in a retrospective analysis of 466 children having experienced sexual abuse, 429 children with externalising disorders and 641 controls, the occurrence of faecal incontinence did not differ between groups (faecal incontinence in 10.3%, 10.5% and 2%, respectively) [68].

V. SUBCLINICAL SIGNS AND SYMPTOMS OF WETTING CHILDREN

Subclinical behavioural signs and symptoms are common, understandable, adequate reactions towards the wetting problem and not disorders. Many studies have addressed the impact of wetting on children.

1. IMPACT ON CHILDREN

Most children are distressed by enuresis. For example, 35% said that they felt unhappy, 25% even very unhappy about wetting at night in one study (40 children aged 5-15 years)[69]. In a Finnish population-based study, 156 day and night wetting children (from 3375 7-year olds) showed significant differences compared to 170 controls regarding following personality traits [70]: they were more fitful (vs. peaceful), more fearful (vs. courageous), more impatient (vs. calm), more anxious (vs. does not worry) and had more inferiority feelings (vs. feels equal). In a large population-based British study of 8209 children aged 9 years, 36.7% of children consider bed-wetting to be “really difficult” – ranking 8th behind other stressful life-events [71].

In a clinical study, 70.3% of day and night wetting children aged 5 to 11 years could clearly indicate that the wetting was of disadvantage [72]. The types of disadvantages or negative consequences were: social (I can‘t sleep at friends‘ house, friends can’t stay over night – in 32.1%), affective (I feel sad, ashamed, annoyed – in 16.4%), of isolation (I feel like a baby, nobody is allowed to know about it, I feel different from other children – in 6.7%), of sensation (it feels unpleasant, cold, wet, itchy, nasty – in 32.1%) or referred to direct consequences (I have to take a shower, sleep in pampers, won’t get a bicycle – in 17.6%). Only 4.9% reported any advantages of the wetting at all (I like the wet feeling, I get more attention from mother).

One construct of special importance is that of **self-esteem**. In one study, lower self-esteem in children with enuresis disappeared upon attaining dryness [73]. In another, global self-esteem was significantly lower in children with nocturnal enuresis than in controls [74] and in yet another, the self-esteem total score was higher among enuretics than norms [75]. Therefore, it was concluded that there is no clear evidence that bedwetting leads to lower self-esteem [76] – but there can be no doubt that self-esteem can improve upon attaining dryness [75]. Self-esteem increases even if treatment of enuresis is not successful [77], showing that care and “good doctoring” for children and parents is of great help – regardless of outcome. Recently, a focus has been on **quality of life**, which is reduced in children with urinary incontinence [78].

In a population-based study of 75 boys with **faecal incontinence** were compared to 73 matched controls [79]. Specifically, encopretic boys showed higher rates of food refusal, general negativism, strong anxiety reactions, lack of self-insurance, poor tolerance to stress, both inhibited and aggressive behaviour, a strong fixation to their mother and difficulties in relationships. Also, children with faecal incontinence tended to feel less in control of positive life events and had a lower sense of self-esteem than children with other chronic conditions [80]. However, in a more recent study, self-esteem did not differ between children with faecal incontinence and controls on the Piers-Harris questionnaire [81]. Although some of these subclinical symptoms will diminish under successful treatment [57,58], it is not known which ones will persist and become chronic.

2. IMPACT ON PARENTS

Enuresis and urinary incontinence may be just as distressing for parents as for children. Generally, parents are very concerned about the welfare of their child. In a population based study, 17% worried a great deal and 46% some or a little [82]. In one study, the greatest maternal concerns were: emotional impact, social relationships, smell, extra washing and financial aspects [83]. Mothers of children with nocturnal enuresis had a reduced quality of life scores (bodily pain and emotional role) and more depressive symptoms [84].

Parents also believe that their child should be dry at a very early age, which can induce anxiety and stress: the mean anticipated age of dryness was 3.18 years in one study [85] and 2.75 years in another [86]. Also, many parents think that emotional factors are the cause of nocturnal enuresis and forget that they might be the effect of the wetting problem instead [85,86].

A minority of parents show an attitude that was described as “maternal intolerance” by Butler et al [83]. Convinced that their child is wetting on purpose, the risk for punishment is increased. The reported rates of punishment varied from 37% [89], 35.8% [85], 23% [86] to 5.6% [87]. In other cultures, punishment is even more common: 42% of Turkish children were spanked and 13% beaten [89]. Chinese parents show a high level of parenting stress associated with externalising behavioural problems or their child [90]. These parental attributions and experiences have to be taken into account in all treatment plans for enuresis, as they can decisively influence the outcome.

Parents of children with **faecal incontinence** are also stressed and worried the problem [91]. In one study, children with faecal incontinence had family environments with less expressiveness and poorer organisation than controls [81]. In another study of 104 families, nearly half (51%) had no unusual family problems; 23 had severe and widespread difficulties including sexual abuse; 11 families described moderate difficulties and 18 a single traumatic event [92]. In other words, the atmosphere was warm and supportive without major difficulties in at least half of the families.

VI. GENERAL PRINCIPLES

1. ASSESSMENT

a) Screening Questionnaires

Due to this high comorbidity of psychological symptoms as well as disturbances, every child should be screened as part of the routine assessment. The best screening instrument is still a good history and careful clinical observation, which requires some training and experience in addition to a screening questionnaire, such as the Child Behavior Check List (CBCL) [51], which contains 113 empirically derived behavioural items. These are checked on a three-point scale and are formulated in simple wording. From these items, eight specific syndrome scales and three general scales can be calculated.

Recently, even shorter screening instruments have been derived from the CBCL. Thus, Van Hoecke et al. [93] validated a short questionnaire consisting of 7 items for emotional problems, 3 for attention problems and 3 for hyperactivity/impulsivity. This is an extremely useful short questionnaire both for clinical and research uses.

In the recent ICCS document, a general screening for emotional and behavioural problems in all settings (paediatric, urologic, child psychiatric, etc.) with a validated and standardised parental behavioural questionnaire is recommended because of the high rate of comorbid disorders in 30-50% of children [8]. This can be done in two steps (short screening questionnaire such as the SSIPPE [93] first, long questionnaire next) or in one step (validated, long questionnaires such as the CBCL only). If many problem items are checked, a child psychological or psychiatric assessment should follow. If comorbid disorders are present, counselling or treatment, if necessary, is recommended (**see figure 14**).

Also, other useful questionnaires addressing specific aspects of enuresis have been developed [94]. These assess the subjective views and attributions of parents and children, such as parental intolerance. Another potentially useful questionnaire addresses aspects of everyday burden of enuresis on children and their families [95]. Other non-validated questionnaires for the assessment of children with all types of incontinence can be found in von Gontard and Neveus [9]. For children with faecal incontinence, the Virginia-Faecal incontinence-Constipation-Apperception Test (VE-CAT), a validated, picture-based questionnaire for children and parents was shown to be good at differentiating bowel-specific problems [96].

One construct of special interest in children with elimination disorders is that of self esteem. Well-known self-esteem questionnaires include the Piers-Harris Children's self – concept scale [97] as well as others [98]. Another important construct is that of health related quality of life (HQOL). This is a complex construct that tries to assess health related wellbeing in different domains of daily life. Generic HQOL questionnaires allow comparison between children with different medical disorders [99]. These range from short screening to longer, more detailed questionnaires (such as the KINDL-questionnaire)[101]. Recently, the first specific quality of life questionnaire for children with wetting problems was developed by Bower et al. [102]. This has the advantage that the specific, elimination-related effects on daily life can be assessed. For children with faecal incontinence, a health-related quality of life questionnaire with good psychometric properties was described: the Defecation Disorder List (DDL) consists of 37 items and can be used in children with all types of faecal incontinence and/or constipation [103].

b) Child Psychiatric Assessment

A child psychiatric assessment is a professional procedure with the goal of to coming to a categorical decision: to see if a diagnosis, according to the standardised classification schemes (ICD-10 or DSM-IV) is present in the child or not.

The first step is a detailed developmental, behavioural and family history in much greater detail than provided in the outline in the appendix. The next step is to observe the child as well as the parent-child-interaction, followed by an active exploration of the child. The information gained from history, observation and exploration forms the basis of the mental state examination. This is a descriptive, phenomenological assessment of mental and behavioural signs and symptoms (for example: CASCAP-D)[104].

Questionnaires are always an essential part of child psychiatric assessment. They are a time-economical way to gather information from different informants. They can contribute towards but do not provide a diagnosis. Behavioural questionnaires can again be divided into general and specific questionnaires. The best known, most widely used general parental questionnaire is the Child Behavior Check List, which has been translated into many languages (CBCL/4-18)[51]. In the meantime, Achenbach and co-workers have pro-

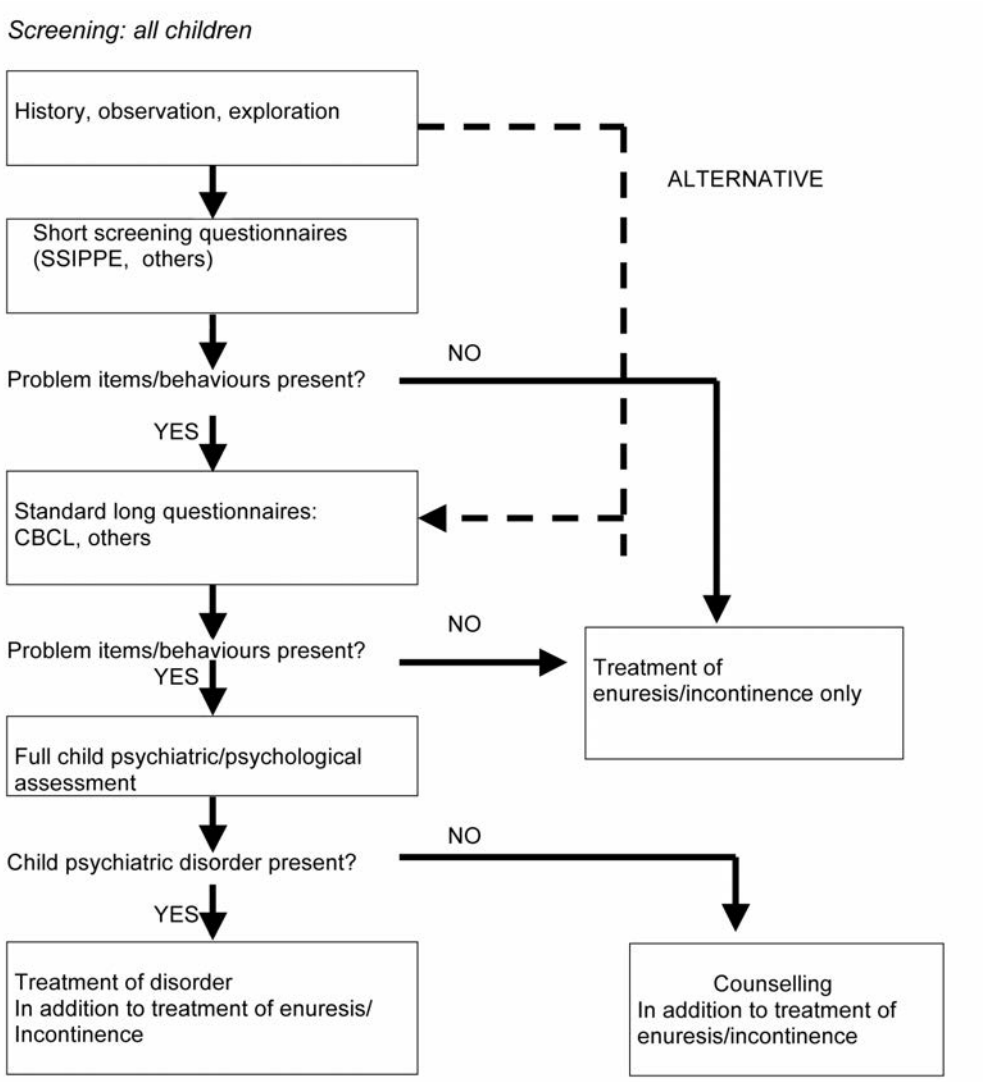


Figure 14: Flow chart for assessment of psychological symptoms (subclinical) or disorders (clinical). The specific treatment for enuresis / incontinence is the same for all children including those with symptoms requiring counselling, and those with disorders needing treatment [8]

duced a whole "family" of questionnaires for different age groups (infants, children – adolescents, young adults) and different informants (parents, teachers and for children themselves starting from age 11). In addition, other specific questionnaires address circumscribed areas such as depressive symptoms or ADHD problems.

An intelligence test is not routinely indicated in the assessment of children with elimination disorders, as the IQ is in the normal range for most children with wetting, as well as soiling problems. However, the rate of elimination disorders is clearly increased in children with general developmental disorders, including those with mental and physical handicap [105-107]. If a lower intelligence is suspected, one-dimensional tests (such as the CFT or CPM/SPM tests) or multidimensional tests such as the Kaufman or the Wechsler tests can be performed. If specific developmental disorders such as dyslexia or dyscalculia are suspected, specific tests for these circumscribed disorders are indicated. Disorders of speech or language (such as articulation, expressive and receptive speech disorders) require a detailed assessment by an audiologist and speech therapist.

Motor disorders can be assessed clinically by including soft neurological signs in the physical examination of children or by standardized tests such as the Zurich Motor Tests [108,109].

After the diagnostic process has been completed, the child's disorder is diagnosed according to standardized classification schemes. The two standard classification systems are the ICD-10 [11], which is widely used in Europe and in other parts of the world and the DSM-IV [12] employed in the United States.

In child psychiatry, a multi-axial classification is used. Six different axes denoting different domains are used, including:

1. Axis: clinical psychiatric diagnosis (such as anorexia nervosa, depressive episodes, etc.)
2. Axis: specific developmental disorders (such as dyslexia)
3. Axis: intelligence (such as dyslexia, speech and motor disorders)
4. Axis: somatic diagnosis (such as epilepsy and other paediatric diagnoses)
5. Axis: psychosocial risks occurring within the last six months (such as distorted intra-familial interaction, isolated family and other stressful life events)
6. Axis: the global severity of a disorder (ranging from mild incapacitation to disorders requiring constant supervision and guidance)

Only after the diagnostic process has been completed and discussed with parents and children, should therapeutic interventions be planned.

2. OF PSYCHOLOGICAL DISORDER

For most children with elimination disorders, a symptom-oriented approach is sufficient. If, however, another, co-occurring child psychiatric disorder is present, additional types of treatment will be necessary. In these cases, a differential indication for therapy is mandatory. The question is: which treatment is most effective for this child in this family at this moment?

For some disorders (such as ADHD), medication plays a major role. For most others, psycho-therapeutic interventions are the first-line treatment. There can be no doubt that psychotherapy in children is effective. In one of the best and largest meta-analysis of 150 studies, Weisz et al. [110] conclude that "psychotherapy with young people produces positive effects of respectable magnitude" (i.e. effect sizes in the medium to large range - 0.5 to 0.8). It has been estimated that over 500 different types of psychotherapies exist in the USA for children and adolescents alone [111]. Of those which have been evaluated, four basic schools of psychotherapy can be differentiated:

1. Depth psychology (or psycho-analysis), which addresses and works with unconscious aspects of the psyche;
2. Client-(or child-) centred-psychotherapy, which focuses on the current conscious experience of the child and the healing aspects of their therapeutic relationship;
3. Family therapy, which focuses on the interaction between family members but not the individual person;
4. Cognitive-behavioural therapy, focussing on cognitions and observable behaviour.

Before initiating any psychotherapy, a differential indication for therapy as to be made. The first basic question should be: is treatment needed at all? In many cases counselling of parents and child is all that is required. In other cases, changes in the child's environment (such as changing school) or help from social services can be more useful than psychological treatment in the narrower sense.

The modality has to be considered. Although parents are nearly always included, the focus can be on an individual, group or family therapy. The intensity and duration have to be addressed: is a short focal therapy focussed on one specific problem needed, or a longer more general treatment? The age of the patient plays an important role: while older children and adolescents can be reached verbally, younger children require play or other non-verbal media in their therapy.

Psychotherapies can be combined with other methods, such as pharmacotherapy, but also by using speech, occupational, physiotherapy, music and other types of therapies – if indicated. The decision should no longer be based on personal inclinations. Instead, empirically based "practice parameters" or "guidelines" have been developed in many countries. These interventions are usually performed on an out-patient basis. Day clinic treatment can be indicated in more severe disorders, which require a more intense approach and management. Finally, in-patient child psychiatric treatment is indicated in severe disorders, in which a more intense type of treatment is possible.

3. UROTHERAPY

A major part of therapy of incontinence in children is non-pharmacological and non-surgical. The term **urotherapy** is used in some countries. It is an umbrella term which has been defined as a "type of training which makes use of cortical control of the bladder, teaching children to recognize and employ conscious command over their lower urinary tract. Its main ingredients are information about normal lower urinary tract function and the specific dysfunction in the child, instruction about what to

do about it and support and encouragement to go through with the training program" [112].

Although not a psychotherapy in a narrow sense, it employs many psycho-therapeutical techniques borrowed especially from counselling and cognitive-behavioural therapies. As these approaches have been shown to be most effective, basic principles and findings shall be outlined.

4. NON-SPECIFIC APPROACHES

The first step in any diagnostic and therapeutical process is to **create a good** relationship with both the child and the parent. One should enquire and talk about all relevant facts, signs and symptoms openly. It is also important to ask about the subjective meanings and connotations. Next, the **provision of information** is essential, because many facts are not known. It is often forgotten that not only parents but each child needs information, as well. This should be provided in words and concepts that a child understands and in a format that is attractive. Increasing motivation and alleviation of stress and guilt feelings are also part of all patient contacts.

5. COUNSELLING

Counselling is already part of the treatment process, which has been defined as the provision of assistance and guidance in resolving personal, social, or psychological difficulties. For many children, even with psychological disorders, counselling is, in fact, sufficient. Sometimes, it can be helpful to enhance the verbal counselling by other techniques. One simple technique is that of "demonstration", e.g. actively showing how an alarm works. In "coaching", parents and children take an even more active role, e.g. they set and activate an alarm themselves. They can be observed and corrected. Other techniques might include "modelling" and "role-playing". The learning effect is much greater in these active forms of teaching than in solely verbal counselling.

6. COGNITIVE-BEHAVIOURAL THERAPY

Cognitive-behavioural therapy (CBT) is a subtype of psychotherapy that has shown to be effective for many disorders. Cognitive therapy focuses on irrational, dysfunctional conditions, thoughts and beliefs. Cognitive therapy encompasses a whole variety of techniques such as "self-monitoring" (observation and registration), "activity scheduling" (organisation of activities) and "labelling" (using positive suggestive statements). Behavioural therapy concentrates on observable behaviour, which it aims to modify with a variety of techniques. These include "classical conditioning" and "operant conditioning", which basically means learning by success, which can be achieved by different strategies using positive or negative reinforcement.

7. BASELINE AND OBSERVATION

Baseline and **observation** are effective techniques used in cognitive-behavioural therapy. Children (and parents) are advised to observe a defined symptom. Different parameters such as frequency (how often it occurs), severity (how marked it is), symptomatology (in what form it occurs) and in which situation (associated factors) can be registered, e.g. in an observation chart. The mere observation and registration actually has a therapeutic effect and many symptoms actually diminish if they are simply observed.

In nocturnal enuresis, children are asked to fill out a calendar or chart depicting the wet and the dry nights symbolically for two to four weeks [113,114]. These non-specific measures have been shown to be successful and are associated with fewer wet nights [3,115]. In one clinical trial, for example, 18% became dry after an 8-week baseline [116]. The authors of the recent Cochrane Review conclude that "simple methods could be tried as first line therapy before considering alarms or drugs, because these alternative treatments may be more demanding and may have adverse effects" [3,5].

In **urgency incontinence**, the cognitive aspects are stressed in treatment: children are asked to register feelings of urgency, refrain from using holding manoeuvres, to void and register the voiding (or any wetting) in a chart [117,118]. For children with **voiding postponement**, timed voiding 7 times a day and registration in a chart is recommended [118].

For all children with **faecal incontinence**, stool regulation is an essential part of treatment. Children are asked to sit on the toilet three times a day after meal-times in a relaxed mode for five to ten minutes [119]. This is documented in a chart and can be reinforced positively. In one study, 15 % of children were cured within six weeks by simple methods such as these [57]. If **constipation** is present and the large amount of faecal masses has accumulated, disimpaction has to be performed at the beginning of treatment. To avoid re-accumulation of faecal masses, maintenance therapy with oral laxatives, such as polyethylenglycol (PEG) is recommended for at least six, and up to twenty-four months [120]. The preferred oral laxatives are osmotic laxatives such as PEG. "These behavioural interventions when used together with laxative therapy may improve continence" according to a Cochrane review of 18 RCT's and 1168 children [6] and other reviews [121].

8. BIOFEEDBACK

Biofeedback has been shown to be effective in some elimination disorders such as **dysfunctional**

voiding [122]. It is defined as a variety of techniques, by which physiological activity is registered, enhanced and presented to the patient in real time by visual and acoustical signals [122]. In **faecal incontinence**, biofeedback is no more effective than standard behavioural techniques in faecal incontinence both with [123] and without constipation [124] and is not recommended in a systematic Cochrane Review [6].

9. ALARM TREATMENT

Alarm treatment for nocturnal enuresis is also a type of cognitive behavioural therapy. It works by positive reinforcement, as well as aversive, negative experiences and has been shown to be highly effective and was introduced by Mowrer and Mowrer [125].

It is the most effective form of treatment of nocturnal enuresis with the best long-term results (grade I level of evidence according to reviews and meta-analyses). Houts et al. [126] compiled a systematic review and meta-analysis on 78 randomised studies on nocturnal enuresis. 62% were dry at the end of treatment and 47% at follow-up. The authors conclude that "urine alarm treatments should not only be considered the treatment of choice, but the evidence from this review suggests that cure rather than management is a realistic goal for the majority of children suffering from nocturnal enuresis".

Lister-Sharp et al [115] provided a systematic review, including only RCT's on nocturnal enuresis. The likelihood for 14 consecutive dry nights was13.3 times higher than without treatment. The authors conclude that "in the long term, alarm treatment would appear to be the most clinically effective, and because the cost of drug therapy, also the most cost effective intervention". Mellon and McGrath's [127] compiled a systematic review on 70 well-controlled outcome studies. With a dryness rate of 77.9%, alarm treatment is deemed clearly efficacious. A comprehensive narrative review was written by Moffat [128] concluding that "all the current evidence suggests that conditioning gives the best long-term outcomes for bed wetters". Finally, a Cochrane review of 50 RCT's involving 3257 children concluded: "Alarm interventions are an effective treatment for nocturnal enuresis. Alarms appear more effective than Desmopressin or tricyclics because around half of the children remain dry after alarm treatment stops" [2].

Therefore, when indicated, alarm has been endorsed as a first line treatment by multidisciplinary European [129], world-wide [130], German [114] and American child psychiatric guidelines [113], as well as various individual authors [131].

The effect of alarm treatment can be enhanced by adding additional behavioural components to the treatment. Programmes that include alarm in addition to other behavioural components showed following general effects: 72% of children became dry at the end of treatment, and 56% remained so at follow-up (meta-analysis)[126], so that combinations were considered as "probably effective" [127].

These specific programmes including alarm are all essentially cognitive-behavioural techniques. **Arousal training** is a simply and easily performed [132,133]. Children are instructed to turn off the alarm within three minutes, go to the toilet and reset the alarm. This goal is reinforced positively with two tokens. If the goal is not reached, one token has to be returned. The initial success rate (89 %) and the rate of dryness after 2 ½ years (92 %) were higher than with alarm treatment alone (73 % and 72 % respectively) [132].

Dry Bed Training is a complicated program starting with an intensive night and maintenance treatment and using positive, as well as negative reinforcers [134]. Despite high success rates reported in early studies [134], recent meta analysis have shown that DBT is no more effective than alarm treatment alone [115]. The likelihood to attain 14 consecutive dry nights was 10 times higher than in controls without treatment – but not different from alarm treatment alone. Also, alarm is the most important component of DBT. DBT without alarm showed only a 2.5 times higher likelihood of attaining dryness than controls. The relapse rates were not improved by DBT compared to alarm treatment alone [115]. As it is a cumbersome treatment, it nowadays it is reserved for children and especially adolescents with therapy-resistant nocturnal enuresis, as it "may augment the effect of an alarm" and "might reduce the relapse rate" [3]. Thus, Hirasing et al. [30] could show that behavioural problems were reduced in children with persistent nocturnal enuresis treated with DBT.

Other programmes include the **Full spectrum home treatment.** This is a combination package including a written contract, full arousal, overlearning and bladder retention exercises [126]. 78.5% of children became dry in 2 studies [127], but the alarm exerts the main effect [3]. **Overlearning** is a relapse prevention programme: after attaining dryness, increasing fluids are given before sleep to stabilise the achieved effects [135]. The relapse rate could be reduced from 20-40% to 10% through this "provocation method".

Finally, alarm treatment can be combined with **pharmacotherapy**, although the evidence for combination treatment is conflicting. The combination of **desmopressin** and alarm treatment has been reported in several studies [136-139]. The combination with **anticholinergics** plays an important part in clinical practice, but has not been investigated systematically.

VII. CONCLUSION AND SUMMARY

This review summarised the most important psychological aspects in children with enuresis, urinary incontinence and faecal incontinence.

The rate of comorbid clinical behavioural disorders is increased. Children with urinary incontinence are more affected than those with nocturnal enuresis. Children with secondary and non-monosymptomatic nocturnal enuresis have especially high rates of comorbid psychological disorders. The most common single diagnosis is ADHD.

Children with daytime wetting have mainly externalising behavioural disorders. Children with urgency incontinence have a low comorbidity, those with voiding postponement are characterised by oppositional behaviour. Children with faecal incontinence have the highest rate of associated disorders – both internalising and externalising.

These disorders will not disappear upon attaining dryness. They have to be addressed, as they will interfere with the incontinence therapy due to low compliance.

Even if comorbid disorders are not present, children and parents are highly stressed by the incontinence. These subclinical symptoms will often recede upon successful treatment.

Questionnaires are useful as screening instruments in the assessment process. It is recommended that questionnaires are used as a general screening procedure for emotional and behavioural problems routinely in all settings (8]. If a psychological disorder is suspected, a full child psychiatric assessment and subsequent treatment is needed. The basic principles, including those of psychotherapy, are outlined. Psychotherapeutic techniques are used in urotherapy, especially cognitive-behavioural elements. Non-pharmacological and non-surgical techniques are most effective for most forms of incontinence based on systematic reviews. Therefore, it is important that psychological aspects are integrated into the treatment of children with incontinence problems.

REFERENCES

A. Introduction

1. Steers WD. Physiology and pharmacology of the bladder and urethra. In Walsh PC, Retol AB, Vaughan ED, Wein AJ (eds): Campbell's Urology, 7th ed. Philadelphia, WB Saunders,1997; 870-916
2. Muellner SR: Development of urinary control in children, some aspects of the cause and treatment of primary enuresis. JAMA 1960;172: 1256-61
3. Franco I: Detrusor overactivity in children. Part 1: Pathophysiology. J Urol, 2007. 178: 761-8; discussion 768
4. Ohel G, Haddad S, Samueloff A: Fetal urine production and micturition and fetal behavioral state. Am J Perinatol 1995;12:91-92
5. Goellner MH, Ziegler EE, Fomon SJ: Urination during the first 3 years of life. Nephron 1981;28:174-8
6. Yeung CK, Godley ML, Ho CKW, Ransley P, Duffy PG, Chen CN, Li AKC: Some new insights into bladder function in infancy. Br J Urol 1995;6:235-40
7. Yeung CK, Godley ML, Duffy PG, Ransley PG: Natural filling cystometry in infants and children. Br J Urol 1995;75: 531-7
8. Yeung CK, Godley ML, Dhillon HK, Duffy PG, Ransley PG: Urodynamic patterns in infants with normal lower urinary tracts or primary vesico-ureteric reflux. Br J Urol 1998; 81: 461-7
9. Bachelard M, Sillen U, Hansson S, Hermansson G, Jodal U, Jacobsson B: Urodynamic pattern in asymptomatic infants: siblings of children with vesico-ureteric reflux. J Urol. 1999; 162: 1733-7
10. Sillen U, Solsnes E, Hellstrom Al, Sandberg K: The voiding pattern of healthy preterm neonates. J Urol. 2000; 163:278-81
11. Holmdahl G, Hansson E, Hansson M, Hellstrom A-L, Hjälmås, Sillen U: Four hour voiding observation in healthy infants. J Urol. 1996; 156: 1809-12
12. Yeates WK: Bladder function in normal micturition. In Kolvin I, MacKeith RC, Meadow SR (eds): Bladder Control and Enuresis. London, W Heinemann Medical, 1973;28-365
13. Koff SA: Estimating bladder capacity in children. Urology 1983;21:248-51
14. Hjälmås K: Micturition in infants and children with normal lower urinary tract: a urodynamic study. Scand J Urol Nephrol 1976;37:9-17
15. Zerin JM, Chen E, Ritchey ML, Bloom DA: Bladder capacity as measured at voiding cystourethrography in children-relationship in toilet training and frequency of micturition. Radiology 1993;187: 803-6
16. Kaefer M, Zurakowsky D, Bauer SB, Retik AB, Peters CA, Atala A, Treves ST: Estimating normal bladder capacity in children. J Urol. 1997;158:2261-4
17. Rittig S, Kamperis K, Siggaard C, Hagstroem S, Djurhuus JC: Age Related Nocturnal Urine Volume and Maximum Voided Volume in Healthy Children: Reappraisal of International Children's Continence Society Definitions. J Urol 2010; 183:1561-67
18. Bael An M, Lax H, Hirche H, Hjälmås K†, Tamminen-Möbius T, Van Hoeck KM, Van Gool J. Reference ranges for cystographic bladder capacity in children—with special attention to vesicoureteral reflux. J Urol 2006; 176:1596-1600
19. Berk LB, Friman PC: Epidemiological aspects of toilet training. Clin Paediatrics 1990; 29:278-82
20. Hellström A.L, Hanson E, Hansson S, Hjälmås K and Jodal U: Micturition habits and incontinence in 7-year old Swedish school entrants. Eur J Paediatr 1990; 149:434-7

21. Mattsson S, Lindström S: Diuresis and voiding pattern in healthy schoolchildren. Br. J. Urol. 1995;76: 783-89

22. Wen JG, Tong EC: Cystometry in infants and children with no apparent voiding symptoms. Br. J. Urol. 1998; 81: 468-73

23. Szabo L, Fegyvernski S: Maximum and average urine flow rates in normal children- the Miskolc nomograms. Br J Urol 1995;76:16-20

24. Mattson S , Spangberg A: Urinary flow in healthy school children. Neurourol Urodyn 1994;13: 281-96

B. Evaluation in children who wet

1. Hoebeke P, Bower W, Combs A, De Jong T, Yang S. Diagnostic evaluation of children with daytime incontinence. J Urol 2010; 183: 699-703

2. Neveus T, Eggert P, Evans J, MacedoA, Rittig S, Tekgul S., et al. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol 2010; 183: 441-47

3. Van Gool JD, Hjälmås K, Tamminen-Möbius T and Olabing H. Historical clues to the complex of dysfunctional voiding, urinary tract infection and vesicoureteral reflux—the International Reflux Study in Children. J Urol 1992;148:1699-1702

4. Sureshkumar P, Craig JC, Roy LP, Knight JF. A reproducible pediatric daytime urinary incontinence questionnaire. J Urol. 2001;165:569-73

5. Benninga MA, Büller HA, Staalman CR, Gubler FM, Bossuyt PM, Plas RN van der, and Taminiau JAJM. Defecation disorders in children, colonic transit time versus the Barr-score. Eur J Pediatr 1995;154:277-84

6. Butler RJ. Establishment of working definitions in nocturnal enuresis. Arch Dis Child 1991;66:267-71

7. Achenbach TM. Manual for the child behavior checklist 4-18 and 1991 profile. Burlington, Vt: University of Vermont, 1991

8. Van Hoecke E, Baeyens D, Vanden Bossche H, Hoebeke P, Vande Walle J. Early detection of psychological problems in a population of children with enuresis: construction and validation of the Short Screening Instrument for Psychological Problems in Enuresis. J. Urol 2007; 178: 2611-2615

9. Bower WF, Wong EM, Yeung CK. Development of a validated quality of life tool specific to children with bladder dysfunction. Neurourology and Urodynamics 2006; 25: 221-7

10. Bloom D A. Sexual abuse and voiding dysfunction [editorial]. J Urol 1995;153:777

11. Martinez-Lage JF, Niguez BF, Perez-Espejo MA, Almagro MJ, Maeztu C. Midline Childs Nerv Syst. 2006;22:623-7

12. Wennergren HM, Öberg BE and Sandstedt P: The importance of leg support for relaxation of the pelvic floor muscles. A surface electromyography study in healthy girls. Scand J Urol Nephrol 1991; 25:205-13

13. Biyikli NK, Alpay H, Guran T. Hypercalciuria and recurrent urinary tract infections: incidence and symptoms in children over 5 years of age. Pediatr Nephrol. 2005;20:1435-8

14. Bower WF, Moore KH, Adams RD, Shepherd R. Frequency volume chart data from 3222 incontinent children. Br J Urol.1997; 80:658-62

15. Koff SA. Estimating bladder capacity in children. Urology 1983;21:248-51

16. Rittig S, Kamperis K, Siggaard C, Hagstroem S, Djurhuus JC. Age Related Nocturnal Urine Volume and Maximum Voided Volume in Healthy Children: Reappraisal of International Children's Continence Society Definitions. J. Urol. 2010; 183: 1561-67

17. Mattson S. Voiding frequency, volumes and intervals in healthy schoolchildren. Scand J Urol Nephrol 1994;28:1-11

18. Kirk J, Rasmussen PV, Rittig S and Djurhuus JC. Micturition habits and bladder capacity in normal children and in patients with desmopressin-resistant enuresis. In: Nørgaard JP, Djurhuus JC, Hjälmås K, Hellström A.-L and Jørgensen TM (eds.). Proceedings, Second International Workshop, International Enuresis Research Center, Aarhus. Scand J Urol Nephrol 1995;173:49-50

19. Hellström A.-L, Andersson K, Hjälmås K and Jodal U. Pad tests in children with incontinence. Scand J Urol Nephrol 1986;20:47-50

20. Imada N, Kawauchi A, Tanaka Y, Watanabe H. The objective assessment of urinary incontinence in children. Br.J Urol. 1998;81:107-8

21. Bael An M, Lax, Hirche H H, Gäbel E, Winkler P, Hellström AL, van Zon R, Jahnsen E, Güntek S, Renson C, van Gool JD (on behalf of the European Bladder Dysfunction Study EU BHM1-CT94-1006). Self-reported urinary incontinence, voiding frequency, voided volume, and pad-test results- variables in a prospective study in children. BJU Int. 2007;100:651-6

22. Akbal C, Genc Y, Burgu B, Ozden E, Tekgul S. Dysfunctional voiding and incontinence scoring system: quantitative evaluation of incontinence symptoms in pediatric population. J Urol. 2005;173:969-73

23. Farhat W, Bagli DJ, Capolicchio G, O'Reilly S, Merguerian PA, Khoury A, McLorie GA. The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. J Urol. 2000;164:1011-15

24. Afshar K, Mirbagheri A, Scott H, MacNeily AE. Development of a symptom score for dysfunctional elimination syndrome. J Urol. 2009;182:1939-43

25. Barr RG, Levine MD, Wilkinson RH and Mulvihill,D. Chronic and occult stool retention—a clinical tool for its evaluation in school-aged children. Clin Pediatr 1979;18:674-6

26. Blethyn AJ, Verrier Jones K, Newcombe R, Roberts GM and Jenkins HR. Radiological assessment of constipation. Arch Dis Child 1995;3:532-3

27. Rockney RM, McQuade WH and Days AL. The plain abdominal roentgenogram in the management of encopresis. Arch Pediatr Adolesc Med 1995;149:623-7

28. van den Bosch M, Graafmans D, Nievelstein R, Beek E. Systematic assessment of constipation on plain abdominal radiographs in children. Pediatr Radiol. 2006;36:224-6

29. Baker SS, Liptak GS, Colleti RB, Croffie JM, Di Lorenzo C, Ector W, Nurko S. Constipation in infants and childeren: evaluation and treatment. A medical position statement of the North American Society for pediatric gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 1999;29:612-26

30. Reuchlin-Vroklage LM, Bierma-Zeinstra S, Benninga MA, Berger MY. Diagnostic value of abdominal radiography in constipated children: a systematic review. Arch Pediatr Adolesc Med. 2005;159(7):671-8

31. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders:child / adolescent. Gastroenterology 2006; 130: 1527-37

32. Singh SJ, Gibbons NJ, Vincent MV, Sithole J, Nwokoma NJ, Alagarswami KV. Use of pelvic ultrasound in the diagnosis of megarectum in children with constipation. J.Pediatr.Surg. 2005;40:1941-44

33. Klijn AJ, Asselman M, Vijverberg MA, Dik P, De Jong TP. The diameter of the rectum on ultrasonography as a diagnostic tool for constipation in children with dysfunctional voiding. J Urol 2004;172:1986-88

34. Joensson IM, Siggaard C., Rittig S., Hagstroem S, Djurhuus J C. Transabdominal Ultrasound of Rectum as a Diagnostic Tool in Childhood Constipation. J Urol, 2008; 179: 1997-2002

35. van der Plas RN, Benninga MA, Buller HA, Bossuyt PM,

Akkermans LM, Redekop WK and Taminiau JA. Biofeedback training in treatment of childhood constipation: a randomised controlled study. Lancet 1996;348:776-80

36. Biggs WS, Dery WH. Evaluation and treatment of constipation in infants and children. Am Fam physician. 2006;73:469-77

37. Mattson S , Spangberg A. Urinary flow in healthy school children. Neurourol Urodyn 1994; 13: 281-96

38. Bartkowski DP, Doubrava RG. Ability of a normal dysfunctional voiding symptom score to predict uroflowmetry and external urinary sphincter electromyography patterns in children. J Urol. 2004;172:1980-85

39. Bower WF, Kwok B, Yeung CK. Variability in normative urine flow rates. J Urol. 2004;171:2657-59

40. Yang SS, Chang SJ. The effects of bladder overdise tention on voiding function in kindergartens. J Urol. 2008;180:2177-82; discussion 2182

41. Dudley NJ, Kirkland M, Lovett J, Watson AR. Clinical agreement between automated and calculated ultrasound measurements of bladder volume. Br J Radiol. 2003;76:832-4

42. Nevéus T, Von Gontard A, Hoebeke P, Hjälmås P, Bauer S, Bower W, Jørgensen TM, Rittig S, Vande Walle J, Yeung C-K, Djurhuus JC. The Standardization of Terminology of Lower Urinary Tract Function in Children and Adolescents: Report from the Standardisation Committee of the International Children's Continence Society. J Urol 2006;176:314-24

43. Hannson S, Hellström A-L, Hermansson G and Hjälmås K. Standardisation of urinary flow patterns in children. In: Nørgaard JP, Djurhuus JC, Hjälmås K, Hellström A-L and Jørgensen TM, eds. Proceedings of the Third International Children's Continence Symposium. Royal Tunbridge Wells: Wells Medical 1996;159-61

44. Kanematsu A, Johnin K, Yoshimura K, Okubo K, Aoki K, Watanabe M, Yoshino K, Tanaka S, Tanikaze S, Ogawa O. Objective patterning of uroflowmetry curves in children with daytime and nighttime wetting. J Urol. 2010;184:1674-9

45. Kuzmic AC, Brkljacic B. Color Doppler ultrasonography in the assessment of vesicoureteric reflux in children with bladder dysfunction. Pediatr Surg Int. 2002;18:135-9

46. Müller L, Bergström T, Hellström, Svensson E, Jacobsson B. Standardised ultrasound method for assessing detrusor muscle thickness in children. J Urol 2000; 164: 134-8

47. Cvitkovic-Kuzmic A, Brkljacic B, Ivankovic D, Grga A. Ultrasound assessment of detrusor muscle thickness in children with non-neuropathic bladder/sphincter dysfunction. Eur Urol. 2002;41:214-8

48. Dogan HS, Akpinar B, Gurocak S, Akata D, Bakkaloklu M, Tekgul S.Non-invasive evaluation of voiding function in asymptomatic primary school children. J Urol. 2008;179:1564-7

49. Yeung CK, Sreedhar B, Leung VT, Metreweli C. Ultrasound bladder measurements in patients with primary nocturnal enuresis: a urodynamic and treatment outcome correlation. J Urol. 2004;171:2589-94

50. Sreedhar B, Yeung CK, Leung VY, Chu CW. Ultrasound bladder measurements in children with severe primary nocturnal enuresis: pretreatment and post treatment evaluation and its correlation with treatment outcome.J Urol. 2008 Mar;179:1122-6

51. Roberts DS and Rendell B. Postmicturition residual bladder volumes in healthy babies. Arch Dis Child 1989; 64:825-8

52. Yang SS, Wang CC, Chen YT. Home uroflowmetry for the evaluation of boys with urinary incontinence. J Urol. 2003;169:1505-7

53. Lyon RP and Smith DR. Distal urethral stenosis. J Urol 1963;89:414-21

54. Saxton HM, Borzyskowski M and Robinson LB. Nonobstructive posterior urethral widening (spinning top urethra) in boys with bladder instability. Radiology 1992;182:81-5

55. Szabo L, Lombay B, Borbas E, Bajusz I. Videourodynamics in the diagnosis of urinary tract abnormalities in a single center. Pediatr Nephrol. 2004;19:326-31

56. Bauer SB. Pediatric urodynamics: lower tract. In: O'Donnell B, Koff SA, eds. Pediatric urology. Oxford: Butterworth–Heineman, 1998:125–151

57. Drzewiecki B, Bauer S. Urodynamic testing in children: indications, technique, interpretation and significance. J Urol 2011; 186: 1190-97

58. Kaufman MR, DeMarco RT, Pope JC 4th, Scarpero HM, Adams MC, Trusler LA, Brock JW 3rd. High yield of urodynamics performed for refractory nonneurogenic dysfunctional voiding in the pediatric population. J Urol. 2006;176:1835-7

59. Soygur T, Arikan N, Tokatli Z, Karaboga R. The role of video-urodynamic studies in managing nonneurogenic voiding dysfunction in children.BJU Int. 2004;93:841- 3

60. Hoebeke P, Van Laecke E, Van Camp C, Raes A, Van De Walle J. One thousand video-urodynamic studies in children with non-neurogenic bladder sphincter dysfunction. BJU Int. 2001;87:575-80

61. Chin-Peuckert L, Komlos M, Rennick JE, Jednak R, Capolicchio JP, Salle JL. What is the variability between 2 consecutive cystometries in the same child? J Urol. 2003;170:1614-7

62. Chin-Peuckert L, Rennick JE, Jednak R, Capolicchio JP, Salle JL. Should warm infusion solution be used for urodynamic studies in children? A prospective randomized study.. J Urol. 2004;172:1653-6

63. Park JM and Bloom DA. The guarding reflex revisited. Br J Urol 1997; 80:940-5

64. McGuire EJ, Woodside JR, Borden TA and Weiss RM. Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 1981;126:205-9

65. Yeung CK, Godley ML, Ho CKW, Ransley P, Duffy PG, Chen CN, Li AKC. Some new insights into bladder function in infancy. Br J Urol 1995;6:235-40

66. Yeung CK, Godley ML, Dhillon HK, Duffy PG, Ransley PG. Urodynamic patterns in infants with normal lower urinary tracts or primary vesico-ureteric reflux. Br J Urol 1998;81: 461-7

67. de Kort LM, Uiterwaal CS, Beek EJ, Jan Nievelstein RA, Klijn AJ, de Jong TP. Reliability of voiding cystourethrography to detect urethral obstruction in boys. Urology. 2004;63:967-71

68. Hoebeke P, Van Laecke E, Raes A, Van Gool JD, Vande Walle J. Anomalies of the external urethral meatus in girls with non-neurogenic bladder sphincter dysfunction. BJU Int. 1999;83:294-8

C. Nocturnal enuresis

1. Forsythe W I, Butler R J. Fifty years enuretic alarms. Archives of Disease in Childhood, 1989; 64: 879-85

2. Butler R J, Golding J, Heron J, ALSPAC Study Team. Nocturnal enuresis: a survey of parental coping strategies at 7 1/2 years. Child: Care, Health & Development, 2005; 31: 659-67

3. Crawford J. Introductory comments. J Paediat, 1989;114: 687-88

4. Verhulst F C, van der Lee J H, Akkerhuis G W et al. The prevalence of nocturnal enuresis: do DSM III criteria need to be changed? A brief research report. Journal of Child Psychology & Psychiatry & Allied Disciplines,1985; 26: 989

5. van Gool J D, Nieuwenhuis E, ten Doeschate I O et al. Subtypes in monosymptomatic nocturnal enuresis. II. Scandinavian Journal of Urology & Nephrology Supplementum, 202: 8, 1999

6. Foxman B, Valdez R B, Brook R H. Childhood enuresis:

prevalence, perceived impact, and prescribed treatments. Pediatrics, 77: 482, 1986

7. Devlin J B. Prevalence and risk factors for childhood nocturnal enuresis. Irish Medical Journal, 84: 118, 1991

8. Houts A C. Nocturnal enuresis as a biobehavioral problem. Beh Ther, 22: 133, 1991

9. Miller K. Concomitant nonpharmacologic therapy in the treatment of primary nocturnal enuresis. Clin Pediatr (Phila), Spec No: 32, 1993

10. Warzak W J. Psychosocial implications of nocturnal enuresis. Clin Pediatr (Phila), Spec No: 38, 1993

11. Liu X, Sun Z, Uchiyama M et al. Attaining nocturnal urinary control, nocturnal enuresis, and behavioral problems in Chinese children aged 6 through 16 years. Journal of the American Academy of Child & Adolescent Psychiatry, 39: 1557, 2000

12. Forsythe W I, Redmond A. Enuresis and spontaneous cure rate. Study of 1129 enuretis. Archives of Disease in Childhood, 49: 259, 1974

13. Hirasing R A. Bedwetting in adults. Paris, p. 84, 1997

14. Moilanen I, Tirkkonen T, Jarvelin M R et al. A follow-up of enuresis from childhood to adolescence. BJU, 81 Suppl 3: 94, 1998 15.

15. Bower W F, Sit F K Y, Yeung C K. Nocturnal enuresis in adolescents and adults is associated with childhood elimination symptoms. J Urol, 176: 1771, 2006

16. Yeung C K, Sihoe J D Y, Sit F K Y et al. Characteristics of primary nocturnal enuresis in adults: an epidemiological study. BJU Int, 93: 341, 2004

17. Yeung C K, Sreedhar B, Sihoe J D Y et al. Differences in characteristics of nocturnal enuresis between children and adolescents: a critical appraisal from a large epidemiological study. BJU Int, 97: 1069, 2006

18. Yeung C K, Sihoe J D Y, Sit F K Y et al. Urodynamic findings in adults with primary nocturnal enuresis. J Urol, 171: 2595, 2004

19. Wang Q W, Wen J G, Zhang R L et al. Family and segregation studies: 411 Chinese children with primary nocturnal enuresis. Pediatrics International, 49: 618, 2007

20. Bailey J N, Ornitz E M, Gehricke J G et al. Transmission of primary nocturnal enuresis and attention deficit hyperactivity disorder.[see comment]. Acta Paediatrica, 88: 1364, 1999

21. von Gontard A, Schaumburg H, Hollmann E et al. The genetics of enuresis: a review. J Urol, 166: 2438, 2001

22. von Gontard A, Hollmann E, Eiberg H et al. Clinical enuresis phenotypes in familial nocturnal enuresis. Scand J Urol Nephrol Supplementum, 183: 11, 1997

23. Bayoumi R A, Eapen V, Al-Yahyaee S et al. The genetic basis of inherited primary nocturnal enuresis: A UAE study. Journal of Psychosomatic Research, 61: 317, 2006

24. Loeys B, Hoebeke P, Raes A et al. Does monosymptomatic enuresis exist? A molecular genetic exploration of 32 families with enuresis/incontinence. BJU International, 90: 76, 2002

25. Weir K. Night and day wetting among a population of three-year-olds. Developmental Medicine & Child Neurology, 24: 479, 1982

26. Tai H-L, Chang Y-J, Chang S C-C et al. The epidemiology and factors associated with nocturnal enuresis and its severity in primary school children in Taiwan. Acta Paediatrica, 96: 242, 2007

27. Rutter M, Yule W, Graham P. Enuresis and behavioural deviance: some epidemiologial considerations. In: Bladder Control and Enuresis. Edited by I. Kolvin and R. McKeith. London: Heinemann, 1973

28. Feehan M, McGee R, Stanton W et al. A 6 year follow-up of childhood enuresis: prevalence in adolescence and consequences for mental health. Journal of Paediatrics & Child Health, 26: 75, 1990

29. Moore K, Richmond D, Parys B. Sex distribution of adult idopathic detrusor instaqbility in relation to childhood bedwetting. BJU, 68: 479, 1991

30. Fergusson D M, Horwood L J, Shannon F T. Secondary enuresis in a birth cohort of New Zealand children. Paediatric and Perinatal Epidemiology, 4: 53, 1990

31. Jarvelin M R, Moilanen I, Vikevainen-Tervonen L et al. Life changes and protective capacities in enuretic and non-enuretic children. Journal of Child Psychology & Psychiatry & Allied Disciplines, 31: 763, 1990

32. McGee R, Makinson T, Williams S et al. A longitudinal study of enuresis from five to nine years. Australian Paediatric Journal, 20: 39, 1984

33. Jarvelin M R, Moilanen I, Kangas P et al. Aetiological and precipitating factors for childhood enuresis. Acta Paediatr Scand, 80: 361, 1991

34. Weissbach A, Leiberman A, Tarasiuk A et al. Adenotonsilectomy improves enuresis in children with obstructive sleep apnea syndrome. Int J Ped Otorhinolaryngol 70: 1351, 2006

35. Basha S, Bialowas C, Ende K et al. Effectiveness of adenotonsillectomy in the resolution of nocturnal enuresis secondary to obstructive sleep apnea. Laryngoscope, 115: 1101, 2005

36. Guven A, Giramonti K, Kogan B A. The effect of obesity on treatment efficacy in children with nocturnal enuresis and voiding dysfunction. J Urol, 178: 1458, 2007

37. Slyper A H. Childhood obesity, adipose tissue distribution, and the pediatric practitioner. Pediatrics, 102: e4, 1998

38. Fielding D. The response of day and night wetting children and children who wet only at night to retention control training and the enuresis alarm. Behaviour Research & Therapy, 18: 305, 1980

39. Rittig S, Schaumburg H L, Siggaard C et al. The circadian defect in plasma vasopressin and urine output is related to desmopressin response and enuresis status in children with nocturnal enuresis. J Urol, 179: 2389, 2008

40. Norgaard J P, Jonler M, Rittig S et al. A pharmacodynamic study of desmopressin in patients with nocturnal enuresis. J Urol, 153: 1984, 1995

41. Butler R J, Holland P. The three systems: a conceptual way of understanding nocturnal enuresis. Scand J Urol Nephrol, 34: 270, 2000

42. Neveus T, Hetta J, Cnattingius S et al. Depth of sleep and sleep habits among enuretic and incontinent children. Acta Paediatrica, 88: 748, 1999

43. Hjalmas K, Arnold T, Bower W et al. Nocturnal enuresis: an international evidence based management strategy. J Urol, 171: 2545, 2004

44. Rittig S, Matthiesen T B, Hunsballe J. M et al. Age-related changes in the circadian control of urine output. Scand J Urol Nephrol Suppl, 173: 71, 1995

45. De Guchtenaere A, Vande Walle C, Van Sintjan P et al. Nocturnal polyuria is related to absent circadian rhythm of glomerular filtration rate. J Urol, 178: 2626, 2007

46. Norgaard J P, Pedersen E B, Djurhuus J C. Diurnal antidiuretic-hormone levels in enuretics. J Urol, 134: 1029, 1985

47. Rittig S, Knudsen U B, Norgaard J P et al. Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. Amer J Physiol, 256: F664, 1989

48. Devitt H, Holland P, Butler R et al. Plasma vasopressin and response to treatment in primary nocturnal enuresis. Archives of Disease in Childhood, 80: 448, 1999

49. Raes A, Dehoorne J, Hoebeke P et al. Abnormal circadian rhythm of diuresis or nocturnal polyuria in a subgroup of children with enuresis and hypercalciuria is related to increased sodium retention during daytime. J Urol, 176: 1147, 2006

50. Hansen M N, Rittig S, Siggaard C et al. Intra-individual

variability in nighttime urine production and functional bladder capacity estimated by home recordings in patients with nocturnal enuresis. J Urol, 166: 2452, 2001

51. Rittig S, Matthiesen T B, Pedersen E B et al. Sodium regulating hormones in enuresis. Scandinavian J Urol Nephrol Supplementum, 202: 45, 1999

52. Medel R, Dieguez S, Brindo M et al. Monosymptomatic primary enuresis: differences between patients responding or not responding to oral desmopressin. BJU, 81: 46, 1998

53. Neveus T, Tuvemo T, Lackgren G et al. Bladder capacity and renal concentrating ability in enuresis: pathogenic implications. J Urol, 165: 2022, 2001

54. Kruse S, Hellstrom A L, Hjalmas K. Daytime bladder dysfunction in therapy-resistant nocturnal enuresis. A pilot study in urotherapy. Scandinavian J Urol & Nephrol, 33: 49, 1999

55. Eller D A, Austin P F, Tanguay S et al. Daytime functional bladder capacity as a predictor of response to desmopressin in monosymptomatic nocturnal enuresis. European Urology, 33 Suppl 3: 25, 1998

56. Kawauchi A, Yamao Y, Nakanishi H et al. Relationship among nocturnal urinary volume, bladder capacity and nocturia with and without waterload in nonenuretic children. Urology 59: 433, 2002

57. Yeung C K, Sreedhar B, Leung V T et al. Ultrasound bladder measurements in patients with primary nocturnal enuresis: a urodynamic and treatment outcome correlation. J Urol, 171: 2589, 2004

58. Sreedhar B, Yeung C K, Leung V Y F et al. Ultrasound bladder measurements in children with severe primary nocturnal enuresis: pretreatment and posttreatment evaluation and its correlation with treatment outcome. J Urol, 179: 1568, 2008

59. Wolfish N. Sleep arousal function in enuretic males. Scandinavian Journal of Urology & Nephrology Supplementum, 202: 24, 1999

60. Bower W F, Moore K H, Shepherd R B et al. The epidemiology of childhood enuresis in Australia. BJU, 78: 602, 1996

61. Freitag C M, Rohling D, Seifen S et al. Neurophysiology of nocturnal enuresis: evoked potentials and prepulse inhibition of the startle reflex. Developmental Medicine & Child Neurology, 48: 278, 2006

62. Yeung C K, Chiu H N, Sit F K. Bladder dysfunction in children with refractory monosymptomatic primary nocturnal enuresis. J Urol, 162: 1049, 1999

63. Yeung C K, Diao M, Sreedhar B. Cortical arousal in children with severe enuresis. New England Journal of Medicine, 358: 2414, 2008

64. Baeyens D, Roeyers H, Naert S et al. The impact of maturation of brainstem inhibition on enuresis: a startle eye blink modification study with 2-year followup. J Urol, 178: 2621, 2007

65. Butler R J, Redfern E J, Holland P. Children's notions about enuresis and the implications for treatment. Scand J Urol Nephr Supplementum, 163: 39, 1994

66. Mikkelsen E J, Rapoport J L, Nee L et al. Childhood enuresis. I. Sleep patterns and psychopathology. Archives of General Psychiatry, 37: 1139, 1980

67. Norgaard J P, Djurhuus J C. The pathophysiology of enuresis in children and young adults. Clin Pediatr (Phila), Spec No: 5, 1993

68. Norgaard J P. Pathophysiology of nocturnal enuresis. Scand J Urol Nephrol Suppl, 140: 1, 1991

69. Brooks L J, Topol H I. Enuresis in children with sleep apnea. Journal of Pediatrics, 142: 515, 2003

70. Hunsballe J M. Increased delta component in computerized sleep electroencephalographic analysis suggests abnormally deep sleep in primary monosymptomatic nocturnal enuresis. Scandinavian Journal of Urology & Nephrology, 34: 294, 2000

71. Neveus T. The role of sleep and arousal in nocturnal enuresis. Acta Paediatrica, 92: 1118, 2003

72. Lottmann H. Enuresis treatment in France. Scandinavian Journal of Urology & Nephrology Supplementum, 202: 66, 1999

73. Butler R J, Robinson J C, Holland P et al. Investigating the three systems approach to complex childhood nocturnal enuresis--medical treatment interventions. Scandinavian Journal of Urology & Nephrology, 38: 117, 2004

74. Devlin J B, O'CathainC. Predicting treatment outcome in nocturnal enuresis. Archives of Disease in Childhood, 65: 1158, 1990

75. Zerin J M, Chen E, Ritchey M L et al. Bladder capacity as measured at voiding cystourethrography in children: relationship to toilet training and frequency of micturition. Radiology, 187: 803, 1993

76. Loening-Baucke V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. Pediatrics, 100: 228, 1997

77. Horowitz M, Misseri R. Diurnal and nocturnal enuresis. In: The Kelalis-King-Belman Textbook of Clinical Pediatric Urology, Fifth ed. Edited by C. D. Docimo SG, Khoury AE. London: Informa Heathcare UK Ltd, pp. 831-832, 2007

78. Longstaffe S, Moffatt M E, Whalen J C. Behavioral and self-concept changes after six months of enuresis treatment: a randomized, controlled trial. Pediatrics, 105: 935, 2000

79. Valenti G, Laera A, Gouraud S et al. Low-calcium diet in hypercalciuric enuretic children restores AQP2 excretion and improves clinical symptoms. American Journal of Physiology - Renal Physiology, 283: F895, 2002

80. Glazener C M, Evans J H. Simple behavioural and physical interventions for nocturnal enuresis in children.[update in Cochrane Database Syst Rev. 2004;(2):CD003637; PMID: 15106210]. Cochrane Database of Systematic Reviews: CD003637, 2002

81. Neveus T, Lackgren G, Tuvemo T et al. Desmopressin resistant enuresis: pathogenetic and therapeutic considerations. J Urol, 162: 2136, 1999

82. De Guchtenaere A, Van Herzeele C, Raes A, Dehoorne J, Hoebeke P, Van Laecke E, Vande Walle J. Oral lyophylizate formulation of desmopressin: superior pharmacodynamics compared to tablet due to low food interaction. J Urol. 2011;185:2308-13

83. Hunsballe J M, Hansen T K, Rittig S et al. The efficacy of DDAVP is related to the circadian rhythm of urine output in patients with persisting nocturnal enuresis. Clinical Endocrinology, 49: 793, 1998

84. Hjalmas K, Hanson E, Hellstrom A L et al. Long-term treatment with desmopressin in children with primary monosymptomatic nocturnal enuresis: an open multicentre study. Swedish Enuresis Trial (SWEET) Group. British Journal of Urology, 82: 704, 1998

85. Lackgren G, Lilja B, Neveus T et al. Desmopressin in the treatment of severe nocturnal enuresis in adolescents--a 7-year follow-up study. British Journal of Urology, 81 Suppl 3: 17, 1998

86. de la Gastine B, de la Gastine G, Mosquet B et al. [Water intoxication with desmopressin in children: report of three cases]. Therapie, 62: 65, 2007

87. Odeh M, Oliven A. Coma and seizures due to severe hyponatremia and water intoxication in an adult with intranasal desmopressin therapy for nocturnal enuresis. Journal of Clinical Pharmacology, 41: 582, 2001

88. Norgaard J P, Rittig S, Djurhuus J C. Nocturnal enuresis: an approach to treatment based on pathogenesis. Journal of Pediatrics, 114: 705, 1989

89. Kruse S, Hellstrom A L, Hanson E et al. Treatment of primary monosymptomatic nocturnal enuresis with desmopressin: predictive factors. BJU International, 88: 572, 2001

90. Glazener C M, Evans J H. Desmopressin for nocturnal enuresis in children.[update of Cochrane Database Syst Rev. 2000;(2):CD002112; PMID: 10796860]. Cochrane Database of Systematic Reviews: CD002112, 2002

91. Tullus K, Bergstrom R, Fosdal I et al. Efficacy and safety during long-term treatment of primary monosymptomatic nocturnal enuresis with desmopressin. Swedish Enuresis Trial Group. Acta Paediatrica, 88: 1274, 1999

92. Wolfish N M, Barkin J, Gorodzinsky F et al. The Canadian Enuresis Study and Evaluation--short- and long-term safety and efficacy of an oral desmopressin preparation. Scandinavian Journal of Urology & Nephrology, 37: 22, 2003

93. Robson W L, Norgaard J P, Leung A K. Hyponatremia in patients with nocturnal enuresis treated with DDAVP. [see comment]. European Journal of Pediatrics, 155: 959, 1996

94. Robson W L, Shashi V, Nagaraj S et al. Water intoxication in a patient with the Prader-Willi syndrome treated with desmopressin for nocturnal enuresis. J Urol, 157: 646, 1997

95. Apakama D C, Bleetman A. Hyponatraemic convulsion secondary to desmopressin treatment for primary enuresis. Journal of Accident & Emergency Medicine, 16: 229, 1999

96. Lebl J, Kolska M, Zavacka A et al. Cerebral oedema in enuretic children during low-dose desmopressin treatment: a preventable complication. European Journal of Pediatrics, 160: 159, 2001

97. Gairi A, Martin E, Bosch, J et al. [Incorrect dosage in the use of inhaled desmopressin associated with convulsions due to hypnatremia]. Anales Espanoles de Pediatria, 53: 385, 2000

98. Neveus T. Oxybutynin, desmopressin and enuresis. J Urol, 166: 2459, 2001

99. Kosar A, Arikan N, Dincel C. Effectiveness of oxybutynin hydrochloride in the treatment of enuresis nocturna--a clinical and urodynamic study. Scandinavian Journal of Urology & Nephrology, 33: 115, 1999

100. Nijman R J. Paediatric voiding dysfunction and enuresis. Current Opinion in Urology, 10: 365, 2000

101. Tahmaz L, Kibar Y, Yildirim I et al. Combination therapy of imipramine with oxybutynin in children with enuresis nocturna. Urologia Internationalis, 65: 135, 2000

102. Geller B, Reising D, Leonard H L et al. Critical review of tricyclic antidepressant use in children and adolescents. J Am Acad Child Adolesc Psychiatry, 38: 513, 1999

103. Glazener C M A, Evans J H C, Peto R E. Tricyclic and related drugs for nocturnal enuresis in children.[update of Cochrane Database Syst Rev. 2000;(3):CD002117; PMID: 10908525]. Cochrane Database of Systematic Reviews: CD002117, 2003

104. Gepertz S, Neveus T. Imipramine for therapy resistant enuresis: a retrospective evaluation. J Urol, 171: 2607, 2004

105. Glazener C M A, Evans J H C, Peto R E. Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics).[update of Cochrane Database Syst Rev. 2000;(3):CD002238; PMID: 10908533]. Cochrane Database of Systematic Reviews: CD002238, 2003

106. Al-Waili N S. Carbamazepine to treat primary nocturnal enuresis: double-blind study. European Journal of Medical Research, 5: 40, 2000

107. Al-Waili N S. Increased urinary nitrite excretion in primary enuresis: effects of indomethacin treatment on urinary and serum osmolality and electrolytes, urinary volumes and nitrite excretion. BJU International, 90: 294, 2002

108. Glazener C M, Evans J H, Peto R E. Alarm interventions for nocturnal enuresis in children.[update in Cochrane Database Syst Rev. 2005;(2):CD002911; PMID: 15846643][update of Cochrane Database Syst Rev. 2001;(1):CD002911; PMID: 11279776]. Cochrane Database of Systematic Reviews: CD002911, 2003

109. Houts A C, Berman J S, Abramson H. Effectiveness of psychological and pharmacological treatments for nocturnal enuresis. Journal of Consulting & Clinical Psychology, 62: 737, 1994

110. Butler R J, Robinson J C. Alarm treatment for childhood nocturnal enuresis: an investigation of within-treatment variables. Scandinavian Journal of Urology & Nephrology, 36: 268, 2002

111. Lettgen B. Differential diagnoses for nocturnal enuresis. Scandinavian Journal of Urology & Nephrology Supplementum, 183: 47, 1997

112. Evans J H. Evidence based management of nocturnal enuresis.[erratum appears in BMJ 2002 Jan 12;324(7329):98]. BMJ, 323: 1167, 2001

113. Glazener C M A, Evans J H C. Simple behavioural and physical interventions for nocturnal enuresis in children.[update of Cochrane Database Syst Rev. 2002;(2):CD003637; PMID: 12076495]. Cochrane Database of Systematic Reviews: CD003637, 2004

114. von Gontard A, Neveus T Management of disorders of bladder and bowel control in childhood. London, MacKeith Press, 2006

115. Butler RJ: Nocturnal enuresis: Psychological perspectives. Wright, Bristol, 1987

116. Butler RJ: Nocturnal enuresis - the child's experience. Oxford, Butterworth- Heinemann, 1994

117. Houts A C, Peterson J K, Whelan J P. Prevention of relapse in full- spectrum home training for primary enuresis: a component analysis. Behaviour Therapy, 17: 462, 1986

118. Woo S.-H, Park K H. Enuresis alarm treatment as a second line to pharmacotherapy in children with monosymptomatic nocturnal enuresis. J Urol, 171: 2615, 2004

119. Azrin N H, Sneed T J, Foxx R M. Dry-bed training: rapid elimination of childhood enuresis. Behaviour Research & Therapy, 12: 147, 1974

120. Glazener C M A, Evans J H C, Peto R E. Complex behavioural and educational interventions for nocturnal enuresis in children. Cochrane Database of Systematic Reviews: CD004668, 2004

121. Pennesi M, Pitter M, Bordugo A et al. Behavioral therapy for primary nocturnal enuresis.[see comment]. J Urol, 171: 408, 2004

122. Hirasing R A, Bolk-Bennink L, Reus H. Dry bed training by parents: results of a group instruction program. J Urol, 156: 2044, 1996

123. HiraSing R A, van Leerdam F J M, Bolk-Bennink L F et al. Effect of dry bed training on behavioural problems in enuretic children. Acta Paediatrica, 91: 960, 2002

124. Bollard J, Nettelbeck T. A component analysis of dry-bed training for treatment for bedwetting. Behaviour Research & Therapy, 20: 383, 1982

125. van Londen A, van Londen-Barentsen M W, van Son M J et al. Arousal training for children suffering from nocturnal enuresis: a 2 1/2 year follow-up. Behav Res Ther, 31: 613, 1993

126. Bower, W. F., Diao, M., Tang, J. L. et al.: Acupuncture for nocturnal enuresis in children: a systematic review and exploration of rationale. Neurourology & Urodynamics, 24: 267, 2005

127. Bradbury, M. G., Meadow, S. R.: Combined treatment with enuresis alarm and desmopressin for nocturnal enuresis. Acta Paediatrica, 84: 1014, 1995

128. Leebeek-Groenewegen, A., Blom, J., Sukhai, R. et al.: Efficacy of desmopressin combined with alarm therapy for monosymptomatic nocturnal enuresis. Journal of Urology, 166: 2456, 2001

129. Van Kampen, M., Bogaert, G., Feys, H. et al.: High initial efficacy of full- spectrum therapy for nocturnal enuresis in children and adolescents. BJU International, 90: 84, 2002

130. Van Kampen, M., Bogaert, G., Akinwuntan, E. A. et al.:

Long-term efficacy and predictive factors of full spectrum therapy for nocturnal enuresis. Journal of Urology, 171: 2599, 2004

131. Ng CF, Wong S, Hong Kong Childhood Enuresis Study Group. Comparing alarms, Desmopressin, and combined treatment in Chinese enuretic children. Pediatr Nephrol 20, 163-9, 2005

132. Gibb S, Nolan T, South M, Noad L, Bates G, Vidmar S. Evidence against a synergistic effect of desmopressin with conditioning in the treatment of nocturnal enuresis. J Pediatr 144: 351-357, 2004

133. Natochin, Y. V., Kuznetsova, A. A.: Nocturnal enuresis: correction of renal function by desmopressin and diclofenac. Pediatric Nephrology, 14: 42, 2000

134. Pace, G., Aceto, G., Cormio, L. et al.: Nocturnal enuresis can be caused by absorptive hypercalciuria. Scandinavian Journal of Urology & Nephrology, 33: 111, 1999

135. Kamperis, K., Hagstroem, S., Rittig, S. et al.: Combination of the enuresis alarm and desmopressin: second line treatment for nocturnal enuresis.[see comment]. Journal of Urology, 179: 1128, 2008

D. Children with both day and night time incontinence

1. Kavia, R.B., R. Dasgupta, and C.J. Fowler, Functional imaging and the central control of the bladder. J Comp Neurol, 2005. 493(1): 27-32.

2. Franco, I., Detrusor overactivity in children. Part 1: Pathophysiology. J Urol, 2007. 178(3 Pt 1): 761-8; discussion 768.

3. Baeyens, D., et al., The prevalence of ADHD in children with enuresis: comparison between a tertiary and non-tertiary care sample. Acta Paediatr, 2006. 95(3): 347-52.

4. Baeyens, D., et al., The prevalence of attention deficit-hyperactivity disorder in children with nonmonosymptomatic nocturnal enuresis: a 4-year followup study. J Urol, 2007. 178(6): 2616-20.

5. Franco I. New ideas in the cause of bladder dysfunction in children. Curr Op Urol. 2011; 21: 334-338

6. Jeffcoate, T.N. and W.J. Francis, Urgency incontinence in the female. Am J Obstet Gynecol, 1966. 94(5): 604-18.

7. Straub, L.R., H.S. Ripley, and S. Wolf, Disturbances of bladder function associated with emotional states. J Am Med Assoc, 1949. 141(16): 1139- 43.

8. Neveus, T., et al., The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol, 2006. 176(1): 314-24.

9. Hjalmas, K., P.B. Hoebeke, and H. de Paepe, Lower urinary tract dysfunction and urodynamics in children. Eur Urol, 2000. 38(5): 655-65.

10. Jarvelin, M.R., et al., Enuresis in seven-year-old children. Acta Paediatr Scand, 1988. 77(1): 148-53.

11. Bower, W.F., et al., The epidemiology of childhood enuresis in Australia. Br J Urol, 1996. 78(4): 602-6.

12. Bloom, D.A., et al., Toilet habits and continence in children: an opportunity sampling in search of normal parameters. J Urol, 1993. 149(5): 1087-90.

13. Blomfield, J.M. and J.W. Douglas, Bedwetting; prevalance among children aged 4-7 years. Lancet, 1956. 270(6927): 850-2.

14. Mattsson, S., Urinary incontinence and nocturia in healthy schoolchildren. Acta Paediatr, 1994. 83(9): 950-4.

15. Meadow, S.R., Day wetting. Pediatr Nephrol, 1990. 4(2): 178-84.

16. Vaz GT, Vasconcelos MM, Oliveira EA, Ferreira AL, Magalhães PG, Silva FM, et al. Prevalence of lower urinary tract symptoms in school-age children. Pediatr Nephrol. 2011

17. Sureshkumar, P., et al., Daytime urinary incontinence in primary school children: a population-based survey. J Pediatr, 2000. 137(6): 814-8.

18. Sureshkumar P, Jones M, Cumming R, Craig J. A population based study of 2,856 schol-age children with urinary incontinence. J Urol 2009; 181: 808-815; discussion 815-816

19. Chung JM, Lee SD, Kang DI, Kwon DD, Kim KS, Kim SY, Kim HG, Moon du G, Park KH, Park YH, Pai KS, Suh HJ, Lee JW, Cho WY, Ha TS, Han SW; Korean Enuresis Association. Prevalence and associated factors of overactive bladder in Korean children 5-13 years old: a nationwide multicenter study. Urology. 2009;73(1): 63-7; discussion 68-9

20. Hellstrom, A.L., et al., Micturition habits and incontinence in 7-year-old Swedish school entrants. Eur J Pediatr, 1990. 149(6): 434-7.

21. Himsl, K.K. and R.S. Hurwitz, Pediatric urinary incontinence. Urol Clin North Am, 1991. 18(2): 283-93.

22. Rugolotto, S., et al., Toilet training started during the first year of life: a report on elimination signals, stool toileting refusal and completion age. Minerva Pediatr, 2008. 60(1): 27-35.

23. Mota, D.M. and A.J. Barros, Toilet training: methods, parental expectations and associated dysfunctions. J Pediatr (Rio J), 2008. 84(1): 9-17.

24. Koc, I., et al., Toilet training in Turkey: the factors that affect timing and duration in different sociocultural groups. Child Care Health Dev, 2008.

25. Joinson C, Heron J, von Gontard A, Butler U, Emond A, Golding J. A prospective study of age at initiation of toilet training and subsequent daytime bladder control in school-age children. J Dev Behav Pediatr. 2009;30(5): 385-93.

26. Yang SS, Zhao LL, Chang SJ. Early initiation of toilet training for urine was associated with early urinary continence and does not appear to be associated with bladder dysfunction. Neurourol Urodyn. 2011; 30(7): 1253-7

27. Da Fonseca EM, Santana PG, Gomes FA, Bastos MD. Dysfunction elimination syndrome: Is age at toilet training a determinant? J Pediatr Urol.2011; 7(3):332- 5.

28. Swithinbank, L.V., et al., The natural history of urinary symptoms during adolescence. Br J Urol, 1998. 81 Suppl 3: 90-3.

29. Soderstrom, U., et al., Urinary and faecal incontinence: a population-based study. Acta Paediatr, 2004. 93(3): 386-9.

30. Bower WF et al: Nocturnal enuresis in adolescents and adults is associated with childhood elimination symptoms. J Urol 2006; 176(4 Pt 2):1771-5.

31. Bower, W.F., S.K. Yip, and C.K. Yeung, Dysfunctional elimination symptoms in childhood and adulthood. J Urol, 2005. 174(4 Pt 2): 1623-7; discussion 1627-8.

32. Minassian VA et al: Effect of childhood dysfunctional voidv ing on urinary incontinence in adult women. Obstetrics & Gynaecology 2006; 107(6): 1247- 51.

33. Yildirim A, Uluocak N, Atilgan D, Ozcetin M, Erdemir F, Boztepe O. Evaluation of lower urinary tract symptoms in children exposed to sexual abuse. Urol J. 2011;8(1):38-42.

34. P. Hoebeke, W. Bower, A. Combs, T. De Jong, S. Yang. Diagnostic evaluation of children with daytime incontinence. J Urol 2010; 183: 699-703.

35. Chase, J., Austin, P., Hoebeke, P., & McKenna, P. The management of dysfunctional voiding in children: a report from the Standardisation Committee of the International Children's Continence Society. J of Urol 2010; 183(4), 1296-1302.

36. von Gontard A, Baeyens D, Van Hoecke E, Warzak WJ, Bachmann C. Psychological and psychiatric issues in urinary and fecal incontinence. J Urol. 2011; 185(4):1432-6

37. Davila, G.W., et al., Bladder dysfunction in sexual abuse survivors. J Urol, 2003. 170(2 Pt 1): 476-9.

38. Pfister, C., et al., The usefulness of a minimal urodynamic evaluation and pelvic floor biofeedback in children with chronic voiding dysfunction. BJU Int, 1999. 84(9): 1054-7.

39. Parekh, D.J., et al., The use of radiography, urodynamic studies and cystoscopy in the evaluation of voiding dysfunction. J Urol, 2001. 165(1): 215-8.

40. Schewe, J., F.H. Brands, and J. Pannek, Voiding dysfunction in children: role of urodynamic studies. Urol Int, 2002. 69(4): 297-301.

41. Soygur, T., et al., The role of video-urodynamic studies in managing non- neurogenic voiding dysfunction in children. BJU Int, 2004. 93(6): 841-3.

42. Kuh, D., L. Cardozo, and R. Hardy, Urinary incontinence in middle aged women: childhood enuresis and other lifetime risk factors in a British prospective cohort. J Epidemiol Community Health, 1999. 53(8): 453-8.

43. Koff, S.A., J. Lapides, and D.H. Piazza, Association of urinary tract infection and reflux with uninhibited bladder contractions and voluntary sphincteric obstruction. J Urol, 1979. 122(3): 373-6.

44. Scholtmeijer, R.J. and D.J. Griffiths, The role of videourodynamic studies in diagnosis and treatment of vesicoureteral reflux. J Pediatr Surg, 1990. 25(6): 669- 71.

45. Soygur, T., et al., Relationship among pediatric voiding dysfunction and vesicoureteral reflux and renal scars. Urology, 1999. 54(5): 905-8.

46. Sillen, U., et al., Pronounced detrusor hypercontractility in infants with gross bilateral reflux. J Urol, 1992. 148(2 Pt 2): 598-9.

47. van Gool, J.D. and G.A. de Jonge, Urge syndrome and urge incontinence. Arch Dis Child, 1989. 64(11): 1629-34

48. Vega, P.J. and L.A. Pascual, High-pressure bladder: an underlying factor mediating renal damage in the absence of reflux? BJU Int, 2001. 87(6): 581-4.

49. Lindehall, B., et al., Effect of clean intermittent catheterisation on radiological appearance ofthe upper urinary tract in children with myelomeningocele. Br J Urol, 1991. 67(4): 415-9

50. Koff, S.A., T.T. Wagner, and V.R. Jayanthi. The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol, 1998; 160: 1019-22

51. McGrath, K.H., P.H. Caldwell, and M.P. Jones. The frequency of constipation in children with nocturnal enuresis: a comparison with parental reporting. J Paediatr Child Health, 2008; 44: 19-27

52. Bael, A.M., et al. Functional urinary and fecal incontinence in neurologically normal children: symptoms of one 'functional elimination disorder'? BJU Int, 2007; 99: 407-12

53. van Gool, J.D., M.A. Vijverberg, and T.P. de Jong. Functional daytime incontinence: clinical and urodynamic assessment. Scand J Urol Nephrol Suppl, 1992; 141: 58-69

54. Hansson, S., et al. Lower urinary tract dysfunction in girls with untreated asymptomatic or covert bacteriuria. J Urol, 1990; 143: 333-5

55. van Gool, J.D., et al. Bladder-sphincter dysfunction, urinary infection and vesico- ureteral reflux with special reference to cognitive bladder training. Contrib Nephrol, 1984; 39: 190-210

56. Bachelard, M., et al. Urodynamic pattern in infants with urinary tract infection. J Urol, 1998; 160: 522-6

57. Rushton, H.G. and M. Majd. Dimercaptosuccinic acid renal scintigraphy for the evaluation of pyelonephritis and scarring: a review of experimental and clinical studies. J Urol, 1992; 148: 1726-32

58. Wennergren, H.M., B.E. Oberg, and P. Sandstedt. The importance of leg support for relaxation of the pelvic floor muscles. A surface electromyograph study in healthy girls. Scand J Urol Nephrol, 1991; 25: 205-13

59. Varlam, D.E. and J. Dippell. Non-neurogenic bladder and chronic renal insufficiency in childhood. Pediatr Nephrol, 1995; 9: 1-5

60. van Gool, J.D., et al. Functional daytime incontinence: non-pharmacological treatment. Scand J Urol Nephrol Suppl, 1992; 141: 93-103

61. Hjalmas, K., G. Passerini-Glazel, and M.L. Chiozza. Functional daytime incontinence: pharmacological treatment. Scand J Urol Nephrol Suppl, 1992; 141: 108-14

62. Ural, Z., I. Ulman, and A. Avanoglu. Bladder dynamics and vesicoureteral reflux: factors associated with idiopathic lower urinary tract dysfunction in children. J Urol, 2008; 179: 1564-7

63. Hoebeke, P., et al. One thousand video-urodynamic studies in children with non- neurogenic bladder sphincter dysfunction. BJU Int, 2001; 87: 575-80.

64. Franco, I., Pediatric detrusor overactivity syndrome: pathophysiology and management. Paediatr Drugs, 2007; 9: 379-90

65. Hoebeke, P., et al. Pelvic floor spasms in children: an unknown condition responding well to pelvic floor therapy. Eur Urol, 2004; 46: 651-4; discussion 654.

66. Loening-Baucke, V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. Pediatrics, 1997; 100: 228-32

67. Bower, W.F., S.K. Yip, and C.K. Yeung. Dysfunctional elimination symptoms in childhood and adulthood. J Urol, 2005; 174: 1623-7

68. van Gool, J.D., et al. Historical clues to the complex of dysfunctional voiding, urinary tract infection and vesicoureteral reflux. The International Reflux Study in Children. J Urol, 1992; 148: 1699-702

69. Koff, S.A. Relationship between dysfunctional voiding and reflux. J Urol, 1992; 148: 1703-5

70. Abidari, J.M. and L.M. Shortliffe. Urinary incontinence in girls. Urol Clin North Am, 2002; 29: 661-75

71. Ellsworth, P.I., P.A. Merguerian, and M.E. Copening. Sexual abuse: another causative factor in dysfunctional voiding. J Urol, 1995; 153: 773-6

72. Cooper, C.S., et al. Do public schools teach voiding dyss function? Results of an elementary school teacher survey. J Urol, 2003; 170: 956-8

73. Hoebeke, P., et al. Anomalies of the external urethral meatus in girls with non- neurogenic bladder sphincter dysfunction. BJU Int, 1999; 83: 294-8

74. Glazier, D.B., et al. Evaluation of the utility of video-urodynamics in children with urinary tract infection and voiding dysfunction. Br J Urol, 1997; 80: 806-8

75. Vereecken, R.L. and W. Proesmans. Urethral instability as an important element of dysfunctional voiding. J Urol, 2000; 163: 585-8

76. Everaert, K., et al. Urodynamic assessment of voiding dysfunction and dysfunctional voiding in girls and women. Int Urogynecol J Pelvic Floor Dysfunct, 2000; 11: 254-64

77. Chiozza, M.L. Dysfunctional voiding. Pediatr Med Chir, 2002; 24: 137-40

78. Benoit, R.M., et al., The effect of dysfunctional voiding on the costs of treating vesicoureteral reflux: a computer model. J Urol, 2002; 168: 2173-6; discussion 2176

79. Duel, B.P., et al. A survey of voiding dysfunction in children with attention deficit- hyperactivity disorder. J Urol, 2003; 170: 1521-3; discussion 1523-4

80. Hellerstein, S. and J.S. Linebarger. Voiding dysfunction in pediatric patients. Clin Pediatr (Phila), 2003; 42: 43-9

81. Mazzola, B.L., et al. Behavioral and functional abnormalities linked with recurrent urinary tract infections in girls. J Nephrol, 2003;16: 133-8

82. Upadhyay, J., et al. Use of the dysfunctional voiding symptom score to predict resolution of vesicoureteral reflux in children with voiding dysfunction. J Urol, 2003; 169: 1842-6; discussion 1846; author reply 1846

83. Lettgen, B., et al. Urge incontinence and voiding postponement in children: somatic and psychosocial factors. Acta Paediatr, 2002; 91: 978-84

84. Maizels, M., et al. Diagnosis and treatment for children who cannot control urination. Curr Probl Pediatr, 1993; 23: 402-50

85. Arena, M.G., et al. „Enuresis risoria": evaluation and management. Funct Neurol, 1987; 2: 579-82

86. Glahn, B.E. Giggle incontinence (enuresis risoria). A study and an aetiological hypothesis. Br J Urol, 1979; 51: 363-6

87. Sher, P.K. and Y. Reinberg. Successful treatment of giggle incontinence with methylphenidate. J Urol, 1996; 156: 656-8

88. Richardson I, Palmer S. Successful treatment for giggle incontinence with biofeedback, J Urol. 2009; 182, 2062-2066

89. Berry AK, Zderic S, Carr M. Methylphenidate for giggle incontinence. J Urol. 2009;182: 2028-32

90. Elzinga-Plomp, A., et al. Treatment of enuresis risoria in children by self- administered electric and imaginary shock. Br J Urol, 1995; 76: 775-8

91. Chandra, M., et al. Giggle incontinence in children: a manifestation of detrusor instability. J Urol, 2002; 168: 2184-7

92. Mattsson, S. and G. Gladh. Urethrovaginal reflux--a common cause of daytime incontinence in girls. Pediatrics, 2003; 111: 136-9

93. Chase, J.W., et al. Functional constipation in children. J Urol, 2004; 171: 2641-3

94. Chen, J.J., et al. A multivariate analysis of dysfunctional elimination syndrome, and its relationships with gender, urinary tract infection and vesicoureteral reflux in children. J Urol, 2004; 17: 1907-10

95. Shaikh, N., et al. Dysfunctional elimination syndrome: is it related to urinary tract infection or vesicoureteral reflux diagnosed early in life? Pediatrics, 2003; 112: 1134-7

96. Mingin, G.C., et al. Children with a febrile urinary tract infection and a negative radiologic workup: factors predictive of recurrence. Urology, 2004; 63: 562-5

97. Tokgoz, H., et al. Assessment of urinary symptoms in children with dysfunctional elimination syndrome. Int Urol Nephrol, 2007; 39: 425-36

98. Erickson, B.A., et al. Polyethylene glycol 3350 for constipation in children with dysfunctional elimination. J Urol, 2003; 170: 1518-20

99. Desantis DJ, Leonard MP, Preston MA, Barrowman NJ, Guerra LA. Effectiveness of biofeedback for dysfunctional elimination syndrome in pediatrics: A systematic review. J Pediatr Urol. 2011; 7(3): 342-8

100. Cigna, R.M., et al., [Enuresis in children. Diagnostic assessment and treatment]. Minerva Pediatr, 1989; 41: 371-3

101. Hellstrom, A.L., K. Hjalmas, and U. Jodal. Rehabilitation of the dysfunctional bladder in children: method and 3-year followup. J Urol, 1987; 138: 847-9

102. Hinman, F. Urinary tract damage in children who wet. Pediatrics, 1974; 54: 143-50

103. Halliday, S., S.R. Meadow, and I. Berg. Successful management of daytime enuresis using alarm procedures: a randomly controlled trial. Arch Dis Child, 1987. 62(2): 132-7

104. Hagstroem, S., et al. Treatment outcome of day-time urinary incontinence in children. Scand J Urol Nephrol, 2008: 1-6

105. Hagstroem, S., Rittig, S., Kamperis, K., & Djurhuus, J. C. Timer watch assisted urotherapy in children: a randomized controlled trial. J Urology;184, 1482- 88

106. Vasconcelos, M., et al. Voiding dysfunction in children. Pelvic-floor exercises or biofeedback therapy: a randomized study. Pediatr Nephrol, 2006; 21: 1858-64

107. Allen, H.A., et al. Initial trial of timed voiding is warranted for all children with daytime incontinence. Urology, 2007; 69: 962-5

108. Hoebeke P, Renson C, De Schryver M, De Schrijver L, Leenaerts E, Schoenaers A, et al. Prospective evalue ation of clinical voiding reeducation or voiding school for lower urinary tract conditions in children. J Urol. 2011;186: 648-54

109. Vijverberg, M. A., Stortelder, E., de Kort, L. M., Kok, E. T., & de Jong, T. P. Long-term Follow-up of Incontinence and Urge Complaints After Intensive Urotherapy in Childhood (75 Patients Followed Up for 16.2-21.8 Years). Urology, 78: 1391-1396

110. Maizels, M., L.R. King, and C.F. Firlit. Urodynamic biofeedback: a new approach to treat vesical sphincter dyssynergia. J Urol, 1979; 122: 205-9

111. Norgaard, J.P. and J.C. Djurhuus. Treatment of detrusor-sphincter dyssynergia by bio-feedback. Urol Int, 1982; 37: 236-9

112. Vijverberg, M.A., et al. Bladder rehabilitation, the effect of a cognitive training programme on urge incontinence. Eur Urol, 1997; 31: 68-72

113. Hoebeke, P., et al. Outpatient pelvic-floor therapy in girls with daytime incontinence and dysfunctional voiding. Urology, 1996; 48: 923-7

114. McKenna, P.H., et al. Pelvic floor muscle retraining for pediatric voiding dysfunction using interactive computer games. J Urol, 1999; 162:1056-62

115. Herndon, C.D., M. Decambre, and P.H. McKenna. Interactive computer games for treatment of pelvic floor dysfunction. J Urol, 2001; 166: 1893-8

116. Senior, J. Clean intermittent self-catheterisation and children. Br J Community Nurs, 2001; 6: 381-6

117. Fishwick, J. and A. Gormley, Intermittent catheterisation in school: a collaborative agreement. Prof Nurse, 2004;19: 519-22

118. Pohl, H.G., et al. The outcome of voiding dysfunction managed with clean intermittent catheterization in neurologically and anatomically normal children. BJU Int, 2002; 89 : 923-7

119. Klingler, H.C., et al. Use of peripheral neuromodulation of the S3 region for treatment of detrusor overactivity: a urodynamic-based study. Urology, 2000; 56: 766-71

120. Primus, G., G. Kramer, and K. Pummer. Restoration of micturition in patients with acontractile and hypocontractile detrusor by transurethral electrical bladder stimulation. Neurourol Urodyn. 1996; 15: 489-97

121. Jonas, U., et al. Efficacy of sacral nerve stimulation for urinary retention: results 18 months after implantation. J Urol. 2001; 165: 15-9

122. Barroso, U., Jr., Tourinho, R., Lordelo, P., Hoebeke, P., & Chase, J. (2011). Electrical stimulation for lower urinary tract dysfunction in children: A systematic review of the literature. Neurourol Urodyn. 2011;

123. De Gennaro, M., Capitanucci, M., Mosiello, G., & Zac& cara, A. Current State of Nerve Stimulation Technique for Lower Urinary Tract Dysfunction in Children. J Urol. 2011; 185, 1571-1577

124. Barroso, U., Jr., Hoebeke, P., Van Laeke, E., De Gennaro, M., Fox, J., & Chase, J. (2011). Electrical Stimulation for Lower Urinary Tract Dysfunction. Dialogues in Pediatric Urology,2011:32(4)

125. Clarke MC, Chase JW, Gibb S et al. Decreased colonic transit time after transcutaneous interferential electrical

stimulation in children with slow transit constipation. J Pediatr Surg . 2009; 44: 408

126. Roth, T.J., et al. Sacral neuromodulation for the dysfunctional elimination syndrome: a single center experience with 20 children. J Urol. 2008; 180: 306-11

127. Van Laecke, E., et al. The daytime alarm: a useful device for the treatment of children with daytime incontinence. J Urol. 2006; 176: 325-7

128. Nijman, R.J. Role of antimuscarinics in the treatment of nonneurogenic daytime urinary incontinence in children. Urology. 2004; 63: 45-50

129. Diokno, A.C. and J. Lapides, Oxybutynin: a new drug with analgesic and anticholinergic properties. J Urol. 1972; 108: 307-9

130. Youdim, K. and B.A. Kogan, Preliminary study of the safety and efficacy of extended-release oxybutynin in children. Urology. 2002; 59: 428-32

131. Kaplinsky, R., et al. Expanded followup of intravesical oxybutynin chloride use in children with neurogenic bladder. J Urol. 1996; 156: 753-6

132. Aubert, D., P. Cencig, and M. Royer, [Treatment with oxybutynin hydrochloride of urinary incontinence and hyperactive bladder conditions in children]. Ann Pediatr (Paris), 1986; 33: 629-34.

133. Curran, M.J., et al. The detrusor overactivity in childhood: long-term results with conservative management. J Urol. 2000; 163: 574-7

134. Van Hoeck, K.J., et al. Do holding exercises or antimuscarinics increase maximum voided volume in monosymptomatic nocturnal enuresis? A randomized controlled trial in children. J Urol. 2007; 178: 2132-6

135. Todorova, A., B. Vonderheid-Guth, and W. Dimpfel, Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. J Clin Pharmacol. 2001; 41: 636-44

136. Hjalmas, K., et al. The detrusor overactivity in children: a potential future indication for tolterodine. BJU Int. 2001; 87: 569-74

137. Bolduc, S., et al. The use of tolterodine in children after oxybutynin failure. BJU Int. 2003; 91: 398-401

138. Munding, M., et al., Use of tolterodine in children with dysfunctional voiding: an initial report. J Urol, 2001. 165(3): 926-8

139. Reinberg, Y., et al. Therapeutic efficacy of extended release oxybutynin chloride, and immediate release and long acting tolterodine tartrate in children with diurnal urinary incontinence. J Urol. 2003; 169: 317-9

140. Nijman, R.J., et al. Long-term tolerability of tolterodine extended release in children 5-11 years of age: results from a 12-month, open-label study. Eur Urol. 2007; 52: 1511-6

141. Hellstrom, A.L., K. Hjalmas, and U. Jodal. Terodiline in the treatment of children with unstable bladders. Br J Urol. 1989; 63: 358-62

142. Elmer, M., et al. Terodiline in the treatment of diurnal enuresis in children. Scand J Prim Health Care. 1988; 6: 119-24

143. Lopez Pereira, P., et al., Trospium chloride for the treatment of detrusor instability in children. J Urol. 2003; 170: 1978-81

144. Marschall-Kehrel, D., et al. Treatment with Propiverine in Children Suffering from Nonneurogenic Detrusor overactivity and Urinary Incontinence: Results of a Randomized Placebo-Controlled Phase 3 Clinical Trial. Eur Urol. 2008;

145. Marschall-Kehrel D, Feustel C, Persson de Geeter C, Stehr M, Radmayr C, Sillén U, Strugala G. Treatment with propiverine in children suffering from nonneurogenic overactive bladder and urinary incontinence: results of a randomized placebo-controlled phase 3 clinical trial. Eur Urol. 2009;55:729-36

146. Hoebeke P, De Pooter J, De Caestecker K, Raes A, Dehoorne J, Van Laecke E, Vande Walle J. Solifenacin for therapy resistant overactive bladder. J Urol. 2009;182:2040-4

147. Bolduc S, Moore K, Lebel S, Lamontagne P, Hamel M. Double anticholinergic therapy for refractory overactive bladder. J Urol. 2009;182:2033-8.

148. Kuo, H.C., Botulinum A toxin urethral injection for the treatment of lower urinary tract dysfunction. J Urol. 2003; 170: 1908-12

149. Apostolidis A, Dasgupta P, Denys P, Elneil S, Fowler CJ, Giannantoni A, Karsenty G, Schulte-Baukloh H, Schurch B, Wyndaele JJ. European consensus panel. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a european consensus report. Eur urol. 2009;55:100-19

150. Hoebeke, P., et al. The effect of botulinum-A toxin in incontinent children with therapy resistant overactive detrusor. J Urol. 2006; 176: 328-30

151. Kuo, H.C. Effect of botulinum a toxin in the treatment of voiding dysfunction due to detrusor underactivity. Urology. 2003; 61: 550-4

152. Radojicic, Z.I., S.V. Perovic, and N.M. Milic. Is it reasonable to treat refractory voiding dysfunction in children with botulinum-A toxin? J Urol. 2006; 176: 332-6

153. Franco, I., et al. The use of botulinum toxin A injection for the management of external sphincter dyssynergia in neurologically normal children. J Urol. 2007; 178: 1775-9

154. Kajbafzadeh AM, Ahmadi H, Montaser-Kouhsari L, Shariu fi-Rad L, Nejat F, Bazargan-Hejazi S. Intravesical electromotive botulinum toxin type A administration--part II: Clinical application. Urology. 2011;77:439-45

155. Austin, P.F., et al. Alpha-Adrenergic blockade in children with neuropathic and nonneuropathic voiding dysfunction. J Urol. 1999; 162: 1064-7

156. Cain, M.P., et al. Alpha blocker therapy for children with dysfunctional voiding and urinary retention. J Urol. 2003; 170: 1514-5; discussion 1516-7

157. Yang, S.S., C.C. Wang, and Y.T. Chen. Effectiveness of alpha1-adrenergic blockers in boys with low urinary flow rate and urinary incontinence. J Formos Med Assoc. 2003; 102: 551-5

158. Donohoe, J.M., A.J. Combs, and K.I. Glassberg. Primary bladder neck dysfunction in children and adolescents II: results of treatment with alpha- adrenergic antagonists. J Urol. 2005; 173: 212-6

159 . Marschall-Kehrel, A.D., et al. An empirical treatment algorithm for incontinent children. J Urol. 2004; 171: 2667-71

E. Neurogenic detrusor-sphincter dysfunction

1. Bauer SB. The management of the myelodysplastic child: a paradigm shift. BJU Int. 2003; 92: 23-8

2. Retik AB, Perlmutter AD, Gross RE. Cutaneous ureteroileostomy in children. N Eng J Med 1967; 277:217-22

3. Lapides J, Diokno AC, Silber SJ, Lowe BS. Clean intermittent self-catheterization in the treatment of urinary tract disease. J Urol 1972;107:458-62

4. Bauer SB. The management of spina bifida from birth onwards. In Whitaker RH, Woodard JR (eds): Paediatric Urology. London, Butterworths, 1985, 87–112

5. Bauer SB. Early evaluation and management of children with spina bifida. In King LR [ed]: Urologic Surgery in Neonates and Young Infants. Philadelphia, WB Saunders, 1988, 252–264

6. Wilcock AR, Emery JL. Deformities of the renal tract in children with myelomeningocele and hydrocephalus, compared with those children showing no such deformities. Br J Urol 1970;42:152-9

7. Hunt GM, Whitaker RH. The pattern of congenital renal anomalies associated with neural tube defects. Dev Med and Child Neurol1987; 29:91-5

8. Pierre-Kahn A, Zerah M, Renier D, Cinalli G, Sainte-Rose C, Lellouch-Tubiana A, Brunelle F, Le Merrer M, Giudicelli Y, Pichon J, Kleinknecht B, Nataf F. Congenital lumbosacral lipomas. Childs Nerv Syst. 1997;13:298-334; discussion 335. Review.

9. Tanikaze S, Sugita Y. Cystometric examination for neurogenic bladder of neonates and infants. Hinyokika Kiyo 1991;37:1403-5

10. Zoller G, Schoner W, Ringert RH. Pre-and postoperative findings in children with tethered spinal cord syndrome. Eur Urol 1991;19:139-41

11. Ghoneim GM, Shoukry MS, Hassouna ME. Detrusor properties in myelomeningocele patients: in vitro study. J Urol 1998;159:2193-6

12. Zermann DH, Lindner H, Huschke T, Schubert J. Diagnostic value of natural fill cystometry in neurogenic bladder in children. Eur Urol 1997;32:223–8

13. Webb RJ, Griffiths CJ, Ramsden PD, Neal DE. Measurement of voiding pressures on ambulatory monitoring: comparison with conventional cystometry. Br J Urol 1990;65:152–4

14. Palmer LS, Richards I, Kaplan WE. Age related bladder capacity and bladder capacity growth in children with myelomeningocele. J. Urol. 1997; 158:1261-4

15. Agarwal SK, McLorie GA, Grewal D, Joyner BD, Bagli DJ, Khoury AE. Urodynamic correlates or resolution of reflux in meningomyelocele patients. J Urol 1997; 158:580-2

16. McGuire EJ et al. Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 1981;126:205-9

17. Sillén U, Hansson E. Hermansson G, Hjälmås, Jacobsson B, Jodal U. Development of the urodynamic pattern in infants with myelomeningocele. Br J Urol 1996;78: 596-601

18. Tarcan T, Bauer S, Olmedo E, Koshbin S, Kelly M, Darbey M. Long-term follow-up of newborns with myelodysplasia and normal urodynamic findings: Is follow-up necessary? J Urol 2001; 165:564-7

19. Kasabian NG et al. The prophylactic value of clean intermittent catheterization and anticholinergic medication in newborns and infants with myelodysplasia at risk of developing urinary tract deterioration. Am J Dis Child, 1992;146:480-7

20. Wang SC et al. Urethral dilatation in the management of urological complications of myelodysplasia. J Urol 1989; 142:1054-5

21. Lin-Dyken DC, Wolraich ML, Hawtrey CE, Doja MS. Follow-up of clean intermittent catheterization for children with neurogenic bladders. Urology 1992;40:525-9

22. Kaufman AM, Ritchey ML, Roberts AC, Rudy DC, McGuire EJ. Decreased bladder compliance in patients with myelomeningocele treated with radiological observation. J Urol 1996;156:2031-3

23. Wu HY, Baskin LS, Kogan BA. Neurogenic bladder dysfunction due to myelomeningocele: neonatal versus childhood treatment. J Urol 1997;157:2295-7

24. Kaefer M, Pabby A, Kelly M, Darbey M, Bauer SB. Improved bladder function after prophylactic treatment of the high risk neurogenic bladder in newborns with myelomeningocele. J Urol 1999;162:1068-71

25. van Gool JD, Dik P, de Jong TP. Bladder-sphincter dysfunction in myelomeningocele. Eur J Pediatr 2001; 160:414-20

26. Bauer SB. The argument for early assessment and treatment of infants with spina bifida. Dialogues in Pediatric Urology 2000;23: 11:2-3

27. Park JM. Early reduction of mechanical load of the bladder improves compliance: Experimental and clinical observations. Dialogues in Pediatric Urology 2000;23: 11:6-7

28. Lindehall B, Moller A, Hjalmas K, Jodal U. Long-term intermittent catheterization: the experience of teenagers and young adults with myelomeningocele. J Urol 1994;152:187-9

29. Joseph DB, Bauer SB, Colodny AH, et al. Clean intermittent catheterization in infants with neurogenic bladder. Pediatrics 1989;84:78-83

30. Park JM. Early reduction of mechanical load of the bladder improves compliance: Experimental and clinical observations. Dialogues in Pediatric Urology 2000;23: 11: 6-7

31. Kasabian NG, Bauer SB, Dyro FM, et al. The prophylactic value of clean intermittent catheterization and anticholinergic medication in newborns and infants with myelodysplasia at risk of developing urinary tract deterioration. Am J Dis Child 1992;146:840-4

32. Baskin LS, Kogan BA, Benard F. Treatment of infants with neurogenic bladder dysfunction using anticholinergic drugs and intermittent catheterization. Br J Urol 1990;66:532-4

33. Hopps CV, Kropp KA. Preservation of renal function in children with myelomeningocele managed with basic newborn evaluation and close followup.J Urol. 2003 Jan;169(1):305-8

34. Edelstein RA, Bauer SB, Kelly MD, Darbey MM, Peters CA, Atala A, Mandell J, Colodny AH, Retik AB. The long-term urological response of neonates with myelodysplasia treated proactively with intermittent catheterization and anticholinergic therapy. J Urol. 1995;154:1500-4

35. Geraniotis E, Koff SA, Enrile B. The prophylactic use of clean intermittent catheterization in the treatment of infants and young children with myelomeningocele and neurogenic bladder dysfunction. J Urol. 1988;139: 85-6

36. Lindehall B, Abrahamsson K, Jodal U, Olsson I, Sillen U. Complications of clean intermittent catheterization in young females with myelomeningocele: 10 to 19 years of followup. J Urol. 2007;178: 1053-5

37. Connor JP, Betrus G, Fleming P, Perlmutter AD, Reitelman C. Early cystometrograms can predict the response to intravesical instillation of oxybutynin chloride in myelomeningocele patients. J Urol 1994:151:1045-7

38. Goessl C, Knispel HH, Fiedler U, Harle B, Steffen-Wilke K, Miller K. Urodynamic effects of oral oxybutynin chloride in children with myelomeningocele and detrusor hyperreflexia. Urology 1998;51:94-8

39. Haferkamp A, Staehler G, Gerner HJ, Dorsam J. Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. Spinal Cord 2000;38:250-4

40. Ferrara P, D'Aleo CM, Tarquini E, Salvatore S, Salvaggio E. Side effects of oral or intravesical oxybutynin chloride in children with spina bifida. BJU Int 2001; 87:674-8

41. Ellsworth PI, Borgstein NG, Nijman RJ, Reddy PP. Use of tolterodine in children with neurogenic detrusor overactivity: relationship between dose and urodynamic response. J Urol. 2005 ;174:1647-51

42. Lopez Pereira P, Miguelez C, Caffarati J, Estornell F, Anguera A J. Trospium chloride for the treatment of detrusor instability in children. Urol. 2003;170:1978-81

43. Mahanta K, Medhi B, Kaur B, Narasimhan KL. Comparative efficacy and safety of extended-release and instant-release tolterodine in children with neural tube defects having cystometric abnormalities. J Pediatr Urol. 2008;4:118-23

44. Austin PF, Homsy YL, Masel JL, Cain MP, Casale AJ, Rink RC. Alpha-adrenergic blockade in children with neuropathic and non-neuropathic voiding dysfunction. J Urol 1999;162:1064-7

45. Bogaert G, Beckers G, Lombaerts R. The use and rationale of selective alpha blockade in children with non-neurogenic neurogenic bladder dysfunction. Int Braz J Urol. 2004;30:128-34.

46. Kakizaki H, Ameda K, Kobayashi S, Tanaka H, Shibata T, Koyanagi T. Urodynamic effects of alpha1-blocker tamsulosin on voiding dysfunction in patients with neurogenic bladder. Int J Urol. 2003;10:576-81.

47. Guerra LA, Moher D, Sampson M, Barrowman N, Pike J, Leonard M. Intravesical oxybutynin for children with poorly compliant neurogenic bladder: a systematic review. J Urol. 2008 ;180:1091-7.

48. Lapointe SP, Wang B, Kennedy WA, Shortliffe LM. The effects of intravesical lidocaine on bladder dynamics of children with myelomeningocele. J Urol 2001; 165:2380-2

49. Smith CP, Somogyi GT, Chancellor MB. Emerging role of botulinum toxin in the treatment of neurogenic and non-neurogenic voiding dysfunction. Curr Urol Rep. 2002; 3: 382-7

50. Leippold T, Reitz A, Schurch B. Botulinum toxin as a new therapy option for voiding disorders: current state of the art. Eur Urol. 2003 ; 44: 165-74

51. Schulte-Baukloh H, Knispel HH, Michael T. Botulinum-A toxin in the treatment of neurogenic bladder in children. Pediatrics. 2002; 110: 420-1

52. Lusuardi L, Nader A, Koen M, Schrey A, Schindler M, Riccabona M Minimally invasive, safe treatment of the neurogenic bladder with botulinum-A-toxin in children with myelomeningocele. Aktuelle Urol. 2004;35:49-53

53. Neel KF, Soliman S, Salem M, Seida M, Al-Hazmi H, Khatab A. Botulinum-A toxin: solo treatment for neuropathic noncompliant bladder. J Urol. 2007 ; 178:2593-7

54. Apostolidis A, Dasgupta P, Denys P, Elneil S, Fowler CJ, Giannantoni A, Karsenty G, Schulte-Baukloh H, Schurch B, Wyndaele JJ. Recommendations on the Use of Botulinum Toxin in the Treatment of Lower Urinary Tract Disorders and Pelvic Floor Dysfunctions: A European Consensus Report.Eur Urol. 2008

55. Hoebeke P, De Caestecker K, Vande Walle J, Dehoorne J, Raes A, Verleyen P,Van Laecke E. The effect of botulinum-A toxin in incontinent children with therapy resistant overactive detrusor. J Urol. 2006;176:328-30

56. Kajbafzadeh AM, Moosavi S, Tajik P, Arshadi H, Payabvash S, Salmasi AH, Akbari HR, Nejat F. Intravesical injection of botulinum toxin type A: management of neuropathic bladder and bowel dysfunction in children with myelomeningocele. Urology. 2006;68:1091-6

57. Akbar M, Abel R, Seyler TM, Bedke J, Haferkamp A, Gerner HJ, Möhring K. Repeated botulinum-A toxin injections in the treatment of myelodysplastic children and patients with spinal cord injuries with neurogenic bladder dysfunction. BJU Int. 2007 Sep;100(3):639-45. Erratum in: BJU Int. 2007;100:719

58. Mokhless I, Gaafar S, Fouda K, Shafik M, Assem A. Botulinum A toxin urethral sphincter injection in children with nonneurogenic neurogenic bladder. J Urol. 2006 ;176:1767-70

59. Hagerty JA, Richards I, Kaplan WE. Intravesical electrotherapy for neurogenic bladder dysfunction: a 22-year experience. J Urol. 2007;178:1680-3

60. Younoszai MK: Stooling problems in patients with myelomeningocele. South Med J 1992;85:718

61. Squire R, Kiely EM, Carr B, et al: The clinical application of the Malone ntegrade colon colonic enema. J Pediatr Surg 1993;28:1012–15

62. Whitehead WE, Wald A, Norton NJ. Treatment options for fecal incontinence. Dis Colon Rectum 2001; 44:131-42

63. Krogh K, Kvitzau B, Jorgensen TM, Laurberg S. Treatment of anal incontinence and constipation with transanal irrigation. Ugeskr Laeger 1999;161:253-6

64. Van Savege JG, Yohannes P. Laparoscopic antegrade continence enema in situ appendix procedure for refractory constipation and overflow fecal incontinence in children with spina bifida. J Urol 2000; 164:1084-7

65. Aksnes G, Diseth TH, Helseth A, Edwin B, Stange M, Aafos G, Emblem R. Appendicostomy for antegrade enemas: effects on somatic and psychosocial functioning in children with myelomeningocele. Pediatrics 2002; 109:484-9

66. Loening-Baucke V, Deach L, Wolraich M: Biofeedback training for patients with myelomeningocele and fecal incontinence. Dev Med Child Neurol 1988;30:781-6

67. Marshall DF, Boston VE Altered bladder and bowel function following cutaneous electrical field stimulation in children with spina bifida: Interim results of a randomized double-blind placebo-controlled trial. Eur J Pediatr Surg 1997;7:41–43

68. Hansson S, Caugant D, Jodal U, Svanborg-Eden C. Untreated asymptomatic bacteriuria in girls: I. Stability of urinary isolates. BMJ 1989;298:853-5

69. Hansson S, Jodal U, Lincoln K, Svanborg-Eden C. Untreated asymptomatic bacteriuria in girls: II. Effect of phenoxymethylpenicillin and erythromycin given for intercurrent infections. BMJ 1989;298:856-9

70. Hansson S, Jodal U, Noren L, Bjure J. Untreated bacteriuria in asymptomatic girls with renal scarring. Pediatrics 1989; 84:964-8

71. Johnson HW, Anderson JD, Chambers GK, Arnold WJ, Irwin WJ, Brinton JR. A short-term study of nitrofurantoin prophylaxis in children managed with clean intermittent catheterization. Pediatrics 1994;93:752-5

72. Schlager TA, Anderson S, Trudell J, Hendley JO. Nitrofurantoin prophylaxis for bacteriuria and urinary tract infection in children with neurogenic bladder on intermittent catheterization. J Pediatr 1998;132:704-8

73. Naglo AS. Continence training of children with neurogenic bladder and hyperactivity of the detrusor. Scan J Urol Nephrol 1982;16:211-17

74. Austin PF, Westney OL, Leng WW, McGuire EJ, Ritchey ML. Advantages of rectus fascial slings for urinary incontinence in children with neuropathic bladder. J Urol 2001;165: 2369-71

75. Guys JM, Fakhro A, Louis-Borrione C, Prost J, Hautier A. Endoscopic treatment of urinary incontinence: long-term evaluation of the results. J Urol 2001;165: 2389-91

76. Kassouf W, Capolicchio G, Bernardinucci G, Corcos J: Collagen injection for treatment of urinary incontinence in children. J Urol 2001;165: 1666-8

77. Kryger JV, Leverson G, Gonzalez R: Long-term results of artificial urinary sphincters in children are independent of age at implantation. J Urol 2001;165: 2377-79

F. Surgical management of urinary incontinence in children

1. Ben-Chaim J, Docimo SG, Jeffs RD, Gearhart JP. Bladder exstrophy from childhood into adult life. JR Soc Med 1996;89:39-46

2. Hollowell JG, Hill PD, Duffy PG, Ransley PG. Evaluation and treatment of incontinence after bladder neck reconstruction in exstrophy and epispadias. Br J Urol 1993;71:743-9

3. Mollard P, Mouriquand PE, Buttin X. Urinary continence after reconstruction of classical bladder exstroph6 (73 cases). Br J Urol 1994;73:298-302

4. Hollowell JG, Ransley PG. Surgical management of incontinence in bladder exstrophy. Br J Urol 1991;68:543-8

5. Canning DA. Bladder exstrophy: the case for primary bladder reconstruction. Urology 1996; 48:831-4

6. Stein R, Stockle M, Fisch M, Nakai H, Muller SC, Hohenfellner R. The fate of the adult exstrophy patient. J Urol 1994;52:1413-16

7. Hohenfellner R, Stein R. Primary urinary diversion in patients with bladder exstrophy. Urology 1996;48:828-30

8. Baird AD, Nelson CP, Gearhart JP.Modern staged repair of bladder exstrophy: A contemporary series. J Pediatr Urol. 2007 Aug;3(4):311-315.

9. Purves JT, Baird AD, Gearhart JP. The modern staged repair of bladder exstrophy in the female: a contemporary series.J Pediatr Urol. 2008 Apr;4(2):150-3.

10. Gearhart JP, Baird A, Nelson CP. Results of bladder neck reconstruction after newborn complete primary repair of exstrophy. J Urol. 2007 Oct;178(4 Pt 2):1619-22;

11. Shapiro E, Jeffs RD, Gearhart JP, Lepor H. Muscarinic cholinergic receptors in bladder exstrophy: insights into surgical management. J. Urol 1985;134:308-10

12. Lee BR, Perlman EJ, Partin AW, Jeffs RD, Gearhart JP. Evaluation of smooth muscle and collagen subtypes in normal newborns and those with bladder exstrophy. J Urol 1996;156:2034-36

13. Cervellione RM, Bianchi A, Fishwick J, Gaskell SL, Dickson AP. Salvage procedures to achieve continence after failed bladder exstrophy repair. J Urol. 2008 Jan;179(1):304-6

14. DeCambre M, Casale P, Grady R, Swartz M, Mitchell M. Modified bladder neck reconstruction in patients with incontinence after staged exstrophy/epispadias closures. J Urol. 2006 Jul;176(1):288-91.

15. Sheldon CA, Gilbert A, Lewis AG, Aiken J, Ziegler MM. Surgical implications of genitourinary tract anomalies in patients with imperforate anus. J Urol 1994;152:196-9

16. Boemers TML, Bax KMA, Rovekamp, MH, Van Gool JD. The effect of posterior sagital anoretoplasty and its variants on lower urinary tract function in children with anorectal malformations. J Urol 1995;153:1919

17. Boemers TML, Van Gool JD, de Jong TPVM, Bax KMA. Urodynamic evaluation of children with caudal regression syndrome (caudal dysplasia sequence). J Urol 1994;151:1038-42

18. Sheldon C, Cormier M, Crone K, Wacksman J. Occult neurovesical dysfunction in children with imporforate anus and its variants. J. Pediatr Surg 1991; 22:26:49-54

19. Kim YH, Horowitz M, Combs AJ, Nitti vw, Borer J, Glassberg KI. Management of posterior urethral valves on the basis of urodynamic findings. J Urol 1997;158:1011-16

20. Podesta ML, Ruarte A, Gargiulo C, Medel R, Castera R. Urodynamic findings in boys with posterior urethral valves after treatment with primary valve ablation or vesicostomy and delayed ablation. J Urol 2000;164:139-44

21. Podesta ML, Ruarte A, Gargiulo C, Medel R, Castera R. Herrera. Bladder function associated with posterior urethral valves after primary valve ablation or proximal urinary diversion in children and adolescents. J Urol 2002;1830-5

22. Ghanem MA, Wolffenbuttel KP, De Vylder A, Nijman RJM. Long-term bladder dysfunction and renal function in boys with posterior urethral valves based on urodynamic findings. J Urol 2004; 2409-12

23. Gearhar JP, Peppas DS, Jeffs RD. Complete genitourinary reconstruction in female epispadias. J Urol 1993;149:1110-13

24. Ben-chaim J, Peppas DS, Jeffs RD, Gearhart JP. Complete male epispadias: genital reconstruction and achieving continence. J Urol 1995;153:1665-7

25. Ahmed S, Morris LL, Byard RW. Ectopic ureter with complete ureteric duplication in the female child. J Ped Surg 1992;27:1455-60

26. Johnin K, Narita M, Kim CJ, Wakabayashi Y, Yoshiki T, Okada Y. Bilateral single ectopic ureters with hypoplastic bladder: How should we treat these challenging entities? J Pediatr Urol. 2007 Jun;3(3):243-6.

27. Heuser M, Zöller G, Seseke F, Zappel H, Ringert RH. Bladder dysfunction in children with bilateral single ectopic ureters. J Pediatr Surg. 2002 May;37(5):E15.

28. Podestà E, Scarsi PL, Di Rovasenda E, Ferretti S, Magillo P, Dodero P. Vesical continence in bilateral ectopic single ureters. J Urol. 2001 Jun;165(6 Pt 2):2363-5.

29. Psihramis KE, Colodny AH, Lebowitz RL, Retik AB, Bauer S. Complete duplication of the urethra. J Urol 1986;139:63-7

30. Wu HY, Baskin LS, Kogan BA. Neurogenic bladder dysfunction due to myelomeningocele: neonatal versus childhood treatment. J Urol 1997;157:2295-7

31. Kaefer M, Pabby A, Kelly M, Darbey M, Bauer SB. Improved bladder function after prophylactic treatment of the high risk neurogenic bladder in newborns with myelomeningocele. J Urol 1999;162:1068-71

32. Lendvay TS, Cowan CA, Mitchell MM, Joyner BD, Grady RW. Augmentation cystoplasty rates at children's hospitals in the United States: a pediatric health information system database study. J Urol. 2006 Oct;176(4 Pt 2):1716-20.

33. Pahernik S, Beetz R, Schede J, Stein R, Thüroff JW. Rece tosigmoid pouch (Mainz Pouch II) in children.J Urol. 2006 Jan;175(1):284-7.

34. Rösch WH, Ebert AK. [Development of treatment for extrophy-epispadias in Germany] Urologe A. 2007 Dec;46(12):1691-6.

35. D'elia, Pahernik S, Fisch M, Hohenfellner R , Thuroff JW. Mainz Pouch II technique: 10 years' experience. BJUInt 2004;93:1037-42

36. Smeulders N, Sudhakaran N, Wilcox DT, Ransley PG. Adenocarcinoma at the ureterosigmoidostomy site in a 16-year-old demonstrates the importance of screening in children. J Pediatr Urol. 2008 Jun;4(3):234-5.

37. Georgacopulo P, Tataranni G, Franchella A, Gilli P. Ureterosigmoidostomy and cancer of the colon. Report of a case.Z Kinderchir Grenzgeb. 1980 Jul;30(3):280-3.

38. Giannini O, Friedli A, Schärli AF. Sigmoid adenocarcinoA ma complicating ureterosigmoidostomy.Pediatr Surg Int. 1998 Nov;14(1-2):124-6.

39. Kliment J, Lupták J, Lofaj M, Horáková M, Beseda A. Carcinoma of the colon after ureterosigmoidostomy and trigonosigmoidostomy for exstrophy of the bladder.Int Urol Nephrol. 1993;25(4):339-43.

40. Leong CH, Ong GB. Gastrocystoplasty in dogs. Aust NZ J. Surg 1972;41:272-9

41. Nguyen DH, Mitchell ME. Gastric bladder reconstruction. Urol Clin North Am 1991;18:649-57

42. Zugor V, Schreiber M, Klein P, Schott GE. [Urinary bladder augmentation using the stomach in patients with compensate renal insufficiency] Urologe A. 2007 Jun;46(6):667-70.

43. Soylet Y, Emir H, Ilce Z, Yesildag E, Buyukunal SN, Danismend N. Quo vadis? Ureteric reimplantation or ignoring reflux during augmentation cystoplasty. BJU Int. 2004;94:379-80

44. Lopez Pereira P, Martinez Urrutia MJ, Lobato Romera R, Jaureguizar E. Should we treat vesicoureteral reflux in patients who simultaneously undergo bladder augmentation for neuropathic bladder?J Urol 2001;165:2259-61

45. Kock NG, Nilson AE, Nilsson LO, Norlen LJ, Philipson BM. Urinary diversion via a continent ileal reservoir: clinical results in 12 patients. J Urol 1982;128:469-75

46. Rowland RG, Mitchell ME, Bihrle R. The cecoileal continent urinary reservoir. World J Urol 1985;3;185-190

47. Thuroff JW, Alken,P, Engelmann U, Riedmiller H, Jacobi GH, Hohenfellner R. The MAINZ pouch (mixed augmentation ileum and zoecum) for bladder augmentation and continent urinary diversion. Eur Urol 1985;11:152-60

48. McDougal WS. Complications of urinary intestinal diversion. AUA Update series, 1992; vol XI:37

49. Rowland RG. Complications of continent cutaneous reservoirs and neobladders – series using contemporary techniques. AUA Update series,1995; Vol XIV:25

50. Medel R, Ruarte AC, Herrera M, Castera R, Podesta ML. Urinary continence outcome after augmentation ileocystoplasty as a single surgical procedure in patients with myelodysplasia. J Urol 2002 ;168:1849-52

51. Shekarriz B, Upadhyay J, Demirbilek S, Barthold JS,

Gonzalez R. Surgical complications of bladder augmentation: comparison between various enterocystoplasties in 133 patients. Urology 2000;55:123-8

52. Chadwick Plaire J, Snodgrass WT, Grady RW, Mitchell ME. Long-term follow-up of the hematuria-dysuria syndrome. J Urol 2000;164:921-3

53. Leonard MP, Dharamsi N, Williot PE Outcome of gastrocystoplasty in tertiary pediatric urology practice. J Urol 2000;164:947-50

54. Duel BP, Gonzales R, Barthold JS. Alternative techniques for augmentation cystoplasty. J Urol 1998;159:998-1005

55. Kennely MJ, Gormley MA, McGuire EJ. Early clinical experience with adult auto-augmentation. J Urol 1994;152:303-6

56. Stoher M, Kramer A, Goepel M, Lochner, Ernst D, Kruse D, Rubben H. Bladder auto-augmentation – an alternative for enterocystoplasty: preliminary results. Neurourol Urodyn 1995;14:11-23

57. Dik P, Tsachouridis GD, Klijn AJ, Uiterwaal CS, de Jong TP. Detrusorectomy for neuropathic bladder in patients with spinal dysraphism. J Urol 2003;170:1351-4

58. Usui A, Inoue K, Nakamoto T, Kadena H, Usui T. Usefulness of bladder auto- augmentation in neurogenic bladder. Nippon Nihyokika Gakkai Zasshi 1006;87:802-5

59. MacNeily AE, Afshar K, Coleman GU, Johnson HW. Auto-augmentation by detrusor myotomy: its lack of effectiveness in the management of congenital neuropathic bladder. J Urol 2003;170:1643-46

60. Marte A, Di Meglio D, Cotrufo AM, Di Iorio G, De Pasquale M. A longterm followup of autoaugmentation in myelodysplastic children. J Urol 2003;169:1602-3

61. Lindley RM, Mackinnon AE, Shipstone D, Tophill PR. Long-term outcome in bladder detrusorectomy augmentation. Eur J Pediatr Surg 2003:7-12

62. Ehrlich RM, Gershman A. Laparoscopic seromyotomy (auto-augmentation) for non-neurogenic bladder in a child: initial case report.

63. Chung SY, Meldrum K, Docimo SG. Laparoscopic assisted reconstructive surgery: a 7-year experience. J Urol 2004;171:372-5

64. McDougall EM, Clayman RV, Figenshau RS, Pearl MS. Laparoscopic retropubic augmentation of the bladder. J Urol 1995;153:123-6

65. Poppas DP, Uzzo RG, Britanisky RG, Mininberg DT. Laparoscopic laser assisted auto-augmentation of the pediatric neurogenic bladder: early experience with urodynamic follow-up. J Urol 1996;155:1057-60

66. Gonzales R. Laparoscopic laser assisted auto-augmentation of the pediatric neurogenic bladder: early experience with urodynamic follow-up. J Urol 1996; 156:1783-6

67. Koontz WW, Jr. Prout GR, Jr. Mackler MA. Bladder regeneration following serosal colocystoplasty. Invest Urol 1970;8:170-6

68. DeBadiola F, Manivel JC, Gonzalez R. Soromuscular enterocystoplasty in rats. J Urol 1991;146:559-62

69. Salle JL, Fraga JC, Luvib A, Lampertz M, Jobim G, Putten A. Seromuscular enterocystoplasty in dogs. J Urol 1990;144:454-6

70. Dewan PA, Lorenz C, Stefanek W, Byard RW. Urothelial lined colocystoplasty in a sheep model. Eur Urol 1004;26:240-6

71. Buson H, Manivel JC, Dayanc M, Long R, Gonzales R. Seromuscular colocystoplasty lined with urothelium: experimental study. Urology 1994;44:743-8

72. Garibay JT, Manivel JS, Gonzales R. Effect of seromuscular solocytoplasty lined with urothelium and partial detrusorectomy on a new canine model of reduced bladder capacity. J Urol 1996;154:903-6

73. Denes ED, Vates TS, Freedman AL, Gonzales R. Seromuscular colocystoplasty lined with urothelium protects dogs from acidosis during ammonium chloride loading. J Urol 1997;158:1075-80

74. Frey P, Lutz N, Leuba AL. Augmentation cystoplasty using pediicled and de-epithelialized gastric patches in the mini-pig model. J Urol 1996;156:608-13

75. Gonzales R, Buson H, Reid C, Reinberg Y. Seromuscular colocystoplasty lined with urothelium: experience with 16 patients. Urology 1995;45:124-9

76. Lima SV, Araujo LA, Vilar FO, Kummer CL, Lima EC. Nonsecretory sigmoid cystoplasty: experimental and clinical results. J Urol 153:1651-1654, 1995.

77. Lima SV, Araujo LA, Vilar FO. Nonsecretory intestinocystoplasty : a 10 year experience. J Urol 2004;165:2636-40

78. Gonzalez R, Jednak R, Franc-Guimond J, Schimke CM. Treating neuropathic incontinence in children with seromuscular colocystoplasty and an artificial urinary sphincter. BJU Int 2002;90:909-11

79. Oge O, Tekgul S, Ergen A, Kendi S. Urothelium-preserving augmentation cystoplasty covered with peritoneal flap. BJU Int 2000;85:802-5

80. Arikan N, Turkolmez K, Budak M, Gogus O. Outcome of augmentation sigmoidocystoplasty in children neurogenic bladder. Urol Int 2000;64:82-5

81. Jednak R, Schimke CM, Barroso U JR, Barthold JS, Gonzalez R. Further experience with seromuscular colocystoplasty lined with urothelium.J Urol 2000;164:2045-9

82. De Badiola F, Ruiz E, Puigdevall J, Lobos P, Moldes J, Lopez Raffo M, Gallo A. Sigmoid cystoplasty with argon beam without mucosa. J Urol 2001;165:2253-5

83. Churchill BM, Aliabadi H, Landau EH, McLorie GA, Steckler RE, McKenna, PH, Khoury AE. Ureteral bladder augmentation. J Urol 1993;150:716-20

84. Dewan PA, Nicholls EA, Goh DW. Ureterocystoplasty: an extraperitoneal, urothelial bladder autmentation technique. Eur Urol 1994;26:85-9

85. Gosalbez R, Jr, Kim CO, Jr. Ureterocystoplasty with preservation of ipsilateral renal function. J Ped surg 1996;31:970-5

86. Ben-Chaim,J, Partin AW, Jeffs RD. Ureteral bladder augmentation using the lower pole ureter of a duplicated system. Urology 1996;47:135-7

87. Denes FT, Nahas WC, Borrelli M, Rocha FT, Mitre AI, Gianini PTR, Apexatto M, Arap S. Urererocistoplastia J Bras Urol 1997;23 (supl Espec):170-90

88. Husmann DA, Snodgrass WT, Koyle MA, Furness PD 3rd, Kropp BP, Cheng EY, Kaplan WE, Kramer SA. Ureterocystoplasty: indications for a successful augmentation. J Urol. 2004;171:376-80

89. Ahmed S, De Castro R, Farhoud RA, El Traifi A. Augmentation ureterocystoplasty in bladder exstrophy: 5-year follow-up in two cases. Eur Urol 2002 ;42:631-4

90. Perovic SV, Vukadinovic VM, Djordjevic ML. Augmentation ureterocystoplasty could be performed more frequently. J Urol 2000;164:924-7

91. Tekgul S, Oge O, Bal K, Erkan I, Bakkaloglu M. Ureterocystoplasty: an alternative reconstructive procedure to enterocystoplasty in suitable cases. J Pediatr Surg 2000;35:577-9

92. Carneiro PM, Binyamini J, Sofer M, Ben-Chaim J. Augmentation ureterocystoplasty: is it the preferred choice? East Afr Med J. 2005 May;82(5):247-9.

93. Youssif M, Badawy H, Saad A, Hanno A, Mokhless I. Augmentation ureterocystoplasty in boys with valve bladder syndrome.J Pediatr Urol. 2007 Dec;3(6):433-7.

94. Johal NS, Hamid R, Aslam Z, Carr B, Cuckow PM, Duffy PG.Ureterocystoplasty: long-term functional results. J Urol. 2008 Jun;179(6):2373-5; discussion 2376.

95. Nahas WC, Lucon M, Mazzucchi E, Antonopoulos IM, Pi-

ovesan AC, Neto ED, Ianhez LE, Arap S. Clinical and urodynamic evaluation after ureterocystoplasty and kidney transplantation. J Urol 2004;171:1428-31

96. Talic RF. Augmentation ureterocystoplasty with ipsilateral renal preservation in the management of patients with compromised renal secondary to dysfunctional voiding. Int Urol Nephrol 1999;31:463-70

97. Taghizadeh A, Mahdavi R, Mirsadraee S, Ghorbani HR, Patel HR. Ureterocystoplasty is safe and effective in patients awaiting renal transplantation. Urology. 2007 Nov;70(5):861-3.

98. Atala A, Vacanti JP, Peters CA, Mandell J, Retik AB, Freeman MR. Formation of urothelial structures in vivo from dissociated cells attached to biodegradable polymer scaffolds in vitro. J Urol 1992;148:658-62

99. Hutton KA, Trejdosiewicz LK, Thomas DF, Southgate J. Urothelial tissue culture for bladder reconstruction: an experimental study. J Urol 1993;150:721-5

100. Atala A, Freeman MR, Vacanti JP, Shepard J, Retik AB. Implantation in vivo and retrieval of artificial structures consistingof rabbit and human urothelium and human bladder muscle. J Urol 1993;150:608-12

101. Hakim S, Merguerian PA, Chavez D. Use of biodegradable mesh as a transport for a cultured uroepithelial graft: an improved method using collagen gel. Urology 1994;44:139-42

102. Scriven SD, Booth C, Thomas DF, Trejdosiewicz LK, Southgate J. Reconstruction of human urothelium from monolayers culture. J Urol 1997;158:1147-52

103. Magnan M, Berthod F, Champigny MF, Soucy F, Bolduc S. In vitro reconstruction of a tissue-engineered endothelialized bladder from a single porcine biopsy.J Pediatr Urol. 2006 Aug;2(4):261-70.

104. Moriya K, Kakizaki H, Murakumo M, Watanabe S, Chen Q, Nonomura K, Koyanagi T. Creation of luminal tissue covered with urothelium by implantation of cultured urothelial cells into the peritoneal cavity. J Urol. 2003 Dec;170(6 Pt 1):2480-5.

105. Zhang Y, Lin HK, Frimberger D, Epstein RB, Kropp BP. Growth of bone marrow stromal cells on small intestinal submucosa: an alternative cell source for tissue engineered bladder.BJU Int. 2005 Nov;96(7):1120-5.

106. Nakanishi Y, Chen G, Komuro H, Ushida T, Kaneko S, Tateishi T, Kaneko M. Tissue-engineered urinary bladder wall using PLGA mesh-collagen hybrid scaffolds:a comparison study of collagen sponge and gel as a scaffold.J Pediatr Surg. 2003 Dec;38(12):1781-4.

107. Hafez AT, Afshar K, Bägli DJ, Bahoric A, Aitken K, Smith CR, Khoury AE. Aerosol transfer of bladder urothelial and smooth muscle cells onto demucosalized colonic segments for porcine bladder augmentation in vivo: a 6-week experimental study.J Urol. 2005 Oct;174(4 Pt 2):1663-7; discussion 1667-8.

108. Zhang Y, Kropp BP, Moore P, Cowan R, Furness PD 3rd, Kolligian ME, Frey P, Cheng EY. Coculture of bladder urothelial and smooth muscle cells on small intestinalsubmucosa: potential applications for tissue engineering technology.J Urol. 2000 Sep;164(3 Pt 2):928-34; discussion 934-5.

109. Drewa T, Sir J, Czajkowski R, Wozniak A. Scaffold seeded with cells is essential in urothelium regeneration and tissue remodeling in vivo after bladder augmentation using in vitro engineered graft. Transplant Proc. 2006 Jan-Feb;38(1):133-5.

110. Atala A, Bauer SB, Soker S, Yoo JJ, Retik AB. Tissue-engineered autologous bladders for patients needing cystoplasty.Lancet. 2006 Apr 15;367(9518):1241-6.

111. Vorstman B, Lockhart J, Kaufman MR, Politano V. Polytetrafluoroethylene injection for urinary incontinence in children. J Urol 1985;133:248-50

112. Malizia AA, Jr, Reiman HM, Myers RP, Sande JR, Bahrman SS, Benson RC, Jr, Dewanjee MK, Utz WJ. Migration and granulomatous reaction after periurethral injection of polytef (Teflon). JAMA 1984;251:3277-81

113. Bomalski MD, Bloom DA, McGuire EJ, Panzi A. Glutaraldhyde cross-linked collagen in the treatment of urinary incontinence in children. J Urol 1996;155:699-702

114. Chernoff A, Horowitz M, Combs A, Libretti D, Nitti V, Glassberg KL. Periurethral collagen injection for the treatment of urinary incontinence in children. J Urol 1997;157:2303-5

115. Capozza N, Caione P, DeGennaro M, Nappo S, Patricola M. Endoscopic treatment of vesicoureteral reflux and urinary incontinence. Technical problems in the pediatric patient. Br J Urol 1995;75:538-42

116. Sundaram CP, Reinberg Y, Aliabadi HA. Failure to obtain durable results with collagen implantation in children with urinary incontinence. J Urol 1997;157:2306-7

117. Block CA, Cooper CS, Hawtrey CE. Long-term efficacy of periurethral collagen injection for the treatment of urinary incontinence secondary to myelomeningocele. J Urol 2003:169;327-9

118. Caione P, Capozza N. Endoscopic treatment of urinary incontinence in pediatric patients: a 2-year experience with dextranomer / hyaluronic acid copolymer. J Urol 2002;168:1868-71

119. Lottmann HB, Margaryan M, Bernuy M, Rouffet MJ, Bau MO, El-Ghoneimi A, Aigrain Y, Stenberg A, Lackgren G. The effect of endoscopic injections of dextranomer based implants on continence and bladder capacity: a prospective study of 31 patients. J Urol 2002;168:1863-7

120. Lottmann HB, Margaryan M, Lortat-Jacob S, Bernuy M, Läckgren G. Long-term effects of dextranomer endoscopic injections for the treatment of urinary incontinence: an update of a prospective study of 61 patients.J Urol. 2006 Oct;176(4 Pt 2):1762-6.

121. Guys JM, Simeoni-Alias J, Fakhro A, Delarue A. Use of polydimethylsiloxane for endoscopic treatment of urinary incontinence in children. J Urol 1999;162:2133-5

122. Guys JM, Fakhro A, Louis-Borrione C, Prost J, Hautier A. Endoscopic treatment of urinary incontinence: long-term evaluation of the results. J Urol 2001;165: 2389-91

123. Halachmi S, Farhat W, Metcalfe P, Bagli DJ, McLorie GA, Khoury AE. Efficacy of polydimethylsiloxane injection to the bladder neck and leaking diverting stoma for urinary continence. J Urol 2004;171:1287-90

124. Guys JM, Breaud J, Hery G, Camerlo A, Le Hors H, De Lagausie P. Endoscopic injection with polydimethylsiloxane for the treatment of pediatric urinary incontinence in the neurogenic bladder: long-term results. J Urol. 2006 Mar;175(3 Pt 1):1106-10.

125. Dyer L, Franco I, Firlit CF, Reda EF, Levitt SB, Palmer LS. Endoscopic injection of bulking agents in children with incontinence: dextranomer/hyaluronic acid copolymer versus polytetrafluoroethylene. J Urol. 2007 Oct;178(4 Pt 2):1628-31.

126. Kitchens DM, Minevich E, DeFoor WR, Reddy PP, Wacksman J, Koyle MA, Sheldon CA. Incontinence following bladder neck reconstruction--is there a role for endoscopic management? J Urol. 2007 Jan;177(1):302-5; discussion 305-6.

127. Dean GE, Kirsch AJ, Packer MG, Scherz HC, Zaontz MR. Antegrade and retrograde endoscopic dextranomer/hyaluronic Acid bladder neck bulking for pediatric incontinence.J Urol. 2007 Aug;178(2):652-5.

128. Misseri R, Casale AJ, Cain MP, Rink RC. Alternative uses of dextranomer/hyaluronic acid copolymer: the efficacy of bladder neck injection for urinary incontinence.J Urol. 2005 Oct;174(4 Pt 2):1691-3; discussion 1693-4.

129. Lund L, Yeung CK. Periurethral injection therapy for urinary incontinence using a laparoscopic port. J Endourol 2003;17:253-4

130. Scott FB, Bradley W W, Timm GW. Treatment of urinary incontinence by implantable prosthetic sphincter. Urology 1973;1:252-9

131. Diokno AC, Sonda P. Compatibility of genitourinary prosthesis and intermittent self catheterization. J Urol 1981;125:659-60

132. Gonzalez R, Nguyen DH, Koilelat N, Sidi AA. Compatibity of enterocystoplasty and the artificial urinary sphincter. J Urol 1989;142:502-4

133. Strawbridge LR, Kramer SA, Castillo OA, Barrett DM. Augmentation cystoplasty and the artificial genitourinary sphincter. J Urol 1989;142:297-301

134. Holmes NM, Kogan BA, Baskin LS. Placement of artificial urinary sphincter in children and simultaneous gastrocystoplasty. J Urol 2001;165:2366-8

135. Gonzalez R, Merino FG, Vaughn M. Long term results of the artificial urinary sphincter in male patients with neurogenic bladder. J Urol 1995;154:769-70

136. Levesque PE, Bauer SB, Atala A, Zurakowski D, Colodny A, Peters C, Retik AB. Ten year experience with the artificial sphincter in children. J Urol 1996;156:625-8

137. Singh G, Thomas DG. Artificial urinary sphincter in patients with neurogenic bladder dysfunction. Br J Urol 1996;77:252-5

138. Simeoni J. Artificial urinary sphincter for neurogenic bladder: A multi-institutional study in 107 children. Br J Urol 1996;78:287-93

139. Castera R, Podesta ML, Ruarte A, Herrera M, Medel R. 10-Year experience with artificial urinary sphincter in children and adolescents. J Urol 2001;165:2373-76

140. Kryger JV, Leverson G, Gonzalez R. Long-term results of artificial urinary sphincters in children are independent of age at implantation. J Urol 2001;165:2377-9

141. Nurse DE, Mundy AR. One hundred artificial sphincters. Br J Urol 1988;61:318-25

142. Barrett DM, Parulkar BG, Kramer SA. Experience with AS800 artificial sphincter in pediatric and young adult patients. J Urol 1993;42:431-6

143. Hafez AT, McLorie G, Bagli D, Khoury A. A single-centre long-term outcome analysis of artificial urinary sphincter placement in children. BJU Int 2002;89:82-5

144. Albouy B, Grise P, Sambuis C, Pfister C, Mitrofanoff P, Liard A. Pediatric urinary incontinence: evaluation of bladder wall wraparound sling procedure. J Urol. 2007 Feb;177(2):716-9.

145. Lopez Pereira P, Somoza Ariba I, MartÃnez Urrutia MJ, Lobato Romero R, Jaureguizar Monroe E. Artificial urinary sphincter: 11-year experience in adolescents with congenital neuropathic bladder.Eur Urol. 2006 Nov;50(5):1096-101; discussion 1101.

146. Rodó JS, Cáceres FA, Lerena JR, Rossy E. Bladder augmentation and artificial sphincter implantation: urodynamic behavior and effects on continence. J Pediatr Urol. 2008 Feb;4(1):8-13.

147. Herndon CD, Rink RC, Shaw MB, Simmons GR, Cain MP, Kaefer M, Casale AJ. The Indiana experience with artificial urinary sphincters in children and young adults. J Urol 2003;169:650-4

148. Herndon CD, Rink RC, Shaw MB, Cain MP, Casale AJ. Experience with non-cycled artificial urinary sphincters. BJU Int 2004;93:1049-52

149. Spiess PE, Capolicchio JP, Kiruluta G, Salle JP, Berardinucci G, Corcos J. Is an artificial sphincter the best choice for incontinent boys with Spina Bifida? Review of our long term experience with the AS-800 artificial sphincter. Can J Urol 2002;9:1486-91

150. Aliabadi H, Gonzalez R. Success of the artificial sphincter after failed surgery for incontinence. J Urol 1996;143:987-91

151. Woodside JR, BordenTA. Pubovaginal sling procedure or the management of urinary incontinence in a myelodysplastic girl. J Urol 1986;78:808-9

152. Gormley EA, Bloom DA, McGuire EJ, Ritchey ML. Pubovaginal slings for the management of urinary incontinence in female adolescents. J Urol 1994;152:822-5

153. Kakizaki H, Shibata T, Kobayashi S, Matsumara K, Koyanagi T. Fascial sling for the management of incontinence due to sphincter incompetence. J Urol 1995;153:644-7

154. Elder JS. Periurethral and puboprostatic sling repair for incontinence in patients with myelodysplasia. J Urol 1990;144:434-7

155. Decter RM. Use of fascial sling for neurogenic incontinece: Lessons learned. J Urol 1993;150:683-6

156. Raz S, Ehrlich RM, Zeidman EJ, Alarcon A, McLaughlin S. Surgical treatment of the incontinent female patient with myelomeningocele. J Urol 1988;139:524-6

157. Bauer SB, Peters CA, Colodny AH, Mandell J, Retik AB. The use of rectus fascia to manage urinary incontinence. J Urol 1989;142:516-9

158. Perez LM, Smith EA, Broecker BH, Massad CA, Parrott TS, Woodard JR. Outcome of sling cystourethropexy in the pediatric population: A critical review. J Urol 1996;156:642-6

159. Dik P, Klijn AJ, van Gool JD, de Jong TP. Transvaginal sling suspension of bladder neck in female patients with neurogenic sphincter incontinence. J Urol 2003;170:580-1

160. Colvert JR 3rd, Kropp BP, Cheng EY, Pope JC 4th, Brock JW 3rd, Adams MC, Austin P, Furness PD 3rd, Koyle MA. The use of small intestinal submucosa as an off-the-shelf urethral sling material for pediatric urinary incontinence. J Urol 2002 ;168:1872-5

161. Bugg CE Jr, Joseph DB. Bladder neck cinch for pediatric neurogenic outlet deficiency. J Urol 2003;170:1501-3

162. Misseri R, Cain MP, Casale AJ, Kaefer M, Meldrum KK, Rink RC. Small intestinal submucosa bladder neck slings for incontinence associated with neuropathic bladder.J Urol. 2005 Oct;174(4 Pt 2):1680-2; discussion 1682.

163. Godbole P, Mackinnon AE. Expanded PTFE bladder neck slings for incontinence in children: the long-term outcome. BJU Int. 2004;93:139-41

164. Dave S, Pippi Salle JL, Lorenzo AJ, Braga LH, Peralta-Del Valle MH, Bägli D, Khoury AE. Is long-term bladder deterioration inevitable following successful isolated bladder outlet procedures in children with neuropathic bladder dysfunction?J Urol. 2008 May;179(5):1991-6; discussion 1996.

165. Nguyen HT, Baskin LS. The outcome of bladder neck closure in children with severe urinary incontinence. J Urol 2003:169; 1114-16

166. Hoebeke P, De Kuyper P, Goeminne H, Van Laecke E, Everaert K. Bladder neck closure for treating pediatric incontinence. Eur Urol 2000;38:453-6

167. Young HH. An operation for incontinence associated with epispadias. J Urol 1922;7:1-32

168. Dees J. Congenital epispadias with incontinence. J Urol 1949;62:513-22

169. Leadbetter GW. Surgical correction of total urinary incontinence. J Urol 1964;91:261-6

170. Mollard P. Bladder reconstruction in exstrophy. J. Urol 1980;124 :525-9

171. Jones JA, Mitchell ME, Rink RC. Improved results using a modification of the Young-Dees-Leadbetter bladder neck repair. Br J Urol 1993;71:555-61

172. Salle JL. Urethral lengthening with anterior bladder wall flap (Pippi Salle procedure): modifications and extended indications of the technique. J Urol 1997;158:586-90

173. Hendren WH. Congenital female epispadias with incontinence. J Urol 1981;125:558-64

174. Lepor H and Jeffs RD. Primary bladder closure and bladder neck reconstruction in classical bladder exstrophy. J Urol 1083;123:1142-5

175. Kropp KA and Angwafo FF. Urethral lengthening and ree

implantation for neurogenic incontinence in children. J. Urol 1986;135:533-6

176. Snodgrass W. A simplified Kropp procedure for incontinence. J Urol 1997;158:1049-52

177. Surer I, Baker LA, Jeffs RD, Gearhart JP. Modified Young-Dees-Leadbetter bladder neck reconstruction in patients with successful primary bladder closure elsewhere: a single institution experience. J Urol 2001;165:2438-40.

178. Mitrofanoff P. Cystostomie continente trans-appendiculaire dans le traitement de vessies neurologique. Chirugae Paediatrica 1980;621:297-305

179. Duckett JW, Snyder HM. Continent urinary diversion: variations on the Mitrofanoff principle. J Urol 1986;136:58-62

180. Woodhouse CRJ, MacNeilly AE. The Mitrofanoff principle: expanding on a versatile theme. Br J Urol 1994;74:447-53

181. Leibovitch I, Avigad I, Nativ O, Goldwasser B. The frequency of histopathological abnormalities in incidental appendectomy in urological patients: the implications for incorporation of the appendix in urinary tract reconstructions. J Urol 1992;148:41-3

182. Yang WH. Yang needle tunneling technique in creating antireflux and continence mechanisms. J Urol 1993;150:830-4

183. Monti PR, Lara RC, Dutra MA, Rezende de Carvalho R. New techniques for construction of efferent conduits based on the Mitrofanoff principle. Urology 1997;49:112-5

184. Gerharz EW, Tassadaq T, Pickard RS, Shah PJR, Woodhouse CRJ. Transverse retubularised ileum: early clinical experience with a new second line Mitrofanoff tube. J Urol 1998;159:525-8

185. Liard A, Seguier-Lipszyc E, Mathiot A, Mitrofanoff P. The Mitrofanoff procedure: 20 years later. J Urol 2001;165:2394-8.

186. Malone PR, d'Cruz VT, Worth PHL, Woodhouse CRJ. Why are continent diversions continent? J Urol 1989;141:303-6

187. Riedmiller H, Burger R, Muller SC, Thuroff J, Hohenfellner R. Continent appendix stoma: a modification of the Mainz pouch technique. J Urol 1990;143:1115-7

188. Woodhouse CRJ. The Mitrofanoff principle for continent urinary diversion. World J Urology 1996;14:99-104

189. Duckett JW, Lofti A-H. Appendicovesicostomy (and variations) in bladder reconstruction. J Urol 1993;149:567-9

190. Fishwick J, Gough DCS, O'Flynn KJ. The Mitrofanoff: does it last? British Journal of Urology International 2000;85:496-7

191. Cain MP, Casale AJ, King SJ, Rink RC. Appendicovesicostomy and newer alternatives for the Mitrofanoff procedure: results in the last 100 patients at Riley Children's Hospital. J Urol. 1999;162:1749-52

192. Piaggio L, Myers S, Figueroa TE, Barthold JS, González R. Influence of type of conduit and site of implantation on the outcome of continent catheterizable channels. J Pediatr Urol. 2007 Jun;3(3):230-4.

193. Hitchcock RJ, Sadiq MJ. Button vesicostomy: A continent urinary stoma. J Pediatr Urol. 2007 Apr;3(2):104-8.

194. Gilchrist RK, Merricks JW, Hamlin HH, Rieger IT. Construction of substitute bladder and urethra. Surgery, Gynecology and Obstetrics 1950;90:752-60

195. Harper JGM, Berman MH, Herzberg AD, Lerman F, Brendler H. Observations on the use of cecum as a substitute bladder. J Urol 1954;71:600-2

196. Rowland RG, Mitchell ME, Bihrle R, Kahnoski PJ, Piser JE. Indiana continent urinary reservoir. J Urol 1987;137:1136-9

197. Rowland RG. Webster G, Goldwasser B, editors. Urinary diversion. 1 ed. Oxford: Isis Medical Media; 1995; 22, Right colon reservoir using plicated tapered ileal outlet. p. 229-35

198. Thuroff J, Alken P, Reidmiller H, Jakobi GH, Hohenfellner R. 100 cases of Mainz pouch: continuing experience and evolution. J Urol 1988;140:283-8

199. Robertson GN, King L. Bladder substitution in children. Urol Clin North America 1986;13:333-44

200. Skinner EC, Lieskovsky G, Boyd JD, et al. Hendry WF, editors. Recent advances in urology/andrology. 5 ed. Edinburgh: Churchill Livingstone; 1991; 9, Continent cutaneous diversion and total bladder replacement using the Kock principles. p. 135-48

201. Engelmann UH, Felderman TP, Scott FB. The use of the AMS AS800 artificial sphincter for continent urinary diversion 1. investigations including pressure flow studies using rabbit intestinal loops. J Urol 1985;134-83

202. Light KK. Long term clinical results using the artificial sphincter around bowel. Br J Urol 1989;64:56-60

203. Mor Y, Quinn FMJ, Carr B, Mouriquand PD, Duffy PG, Ransley PG. Combined Mitrofanoff and antegrade continence enema procedures for urinary and fecal incontinence. J Urol 1997;158:192-5

204. Herschorn S, Hewitt RJ. Patient perspective of long term outcome of augmentation cystoplasty for neurogenic bladder. Urology 1998;52:672-8

205. Leng WW, Balock HJ, Fredricksson WH, English SF, McGuire EG. Enterocystoplasty or detrusor myomectomy: comparison of indications and outcomes for bladder augmentation. J Urol 1999;161:758-63

206. Metcalfe PD, Cain MP, Kaefer M, Gilley DA, Meldrum KK, Misseri R, King SJ,Casale AJ, Rink RC. What is the need for additional bladder surgery after bladder augmentation in childhood? J Urol. 2006 Oct;176(4 Pt 2):1801-5; discussion 1805.

207. Dayanc M, Kilciler M, Tan O, Gokalp A, Goktas S, Peker AF. A new approach to bladder augmentation in children: seromuscular enterocystoplasty. BJU Int 1999;84:103-7

208. Landau EH, Jayanthi VR, Mclorie GA, Churchill BM, Khoury AE. Renal transplantation in children following augmentation ureterocystoplasty. Urology 1997;50:260-2

209. N'Dow J, Robson CN, Matthews JNS, Neal DE, Pearson JP. reducing mucus production after urinary reconstruction: prospective randomized trial. J Urol 2001;165:1433-40

210. Mansson W, Bakke A, Bergman B. Perforation of continent urinary reservoirs. Scandinavian Journal of Urology and Nephrology 1997;31:529-32

211. Rink RC, Hollensbe DW, Adams MC, Keating MA. Is sigmoid enterocystoplasty at greatest risk or perforation? Observations and etiology in 23 bladder perforations in 264 patients. Scandinavian Journal of Urology and Nephrology 1992;142(Supplement):179-83

212. DeFoor W, Tackett L, Minevich E, Wacksman J, Sheldon C. Risk factors for spontaneous bladder perforation after augmentation cystoplasty. Urology 2003;62:737-41

213. Metcalfe PD, Casale AJ, Kaefer MA, Misseri R, Dussinger AM, Meldrum KK, Cain MP, Rink RC. Spontaneous bladder perforations: a report of 500 augmentations in children and analysis of risk.J Urol. 2006 Apr;175(4):1466-70; discussion 1470-1.

214. Nurse DE, Mundy AR. Metabolic complications of cystoplasty. BrJ Urol 1989;63:165-70

215. Wagstaff KE, Woodhouse CRJ, Rose GA, Duffy PG, Ransley PG. Blood and urine analysis in patients with intestinal bladders. Br J Urol 1991;68:311-6

216. Ditonno P, Battaglia M, Ricapito V, Saracino GA, Selvaggi FP. Metabolic acidosis and urinary tract infections in ileocolic orthotopic reservoirs with an afferent ileal loop. Scandinavian Journal of Urology and Nephrology 1992;142:134-5

217. Poulsen AL, Thode J, Steven K. Acid base metabolism following urinary diversion with the ileal Kock reservoir. Scandinavian Journal of Urology and Nephrology 1992;142(Supplement):135-6

218. Mitchell ME, Piser JA. Intestinocystoplasty and total bladder replacement in children and young adults: follow up in 129 cases. J Urol 1987;138:579-84

219. Mingin GC, Nguyen HT, Mathias RS, Shepherd JA, Glidden D, Baskin LS. Growth and metabolic consequences of bladder augmentation in children with myelomeningocele and bladder exstrophy. Pediatrics 2002;110:1193-8

220. Kalloo NB, Jeffs RD, Gearhart JP. Long term nutritional consequences of bowel segment use for lower urinary tract reconstruction in pediatric patients. Urology 1997;50:967-71

221. Racioppi M, D'Addessi A, Fanasca E. Vitamin B12 and folic acid plasma levels after ileocaecal and ileal neobladder reconstruction. Urology 1997;50:888-92

222. Rosenbaum DH, Cain MP, Kaefer M, Meldrum KK, King SJ, Misseri R, Rink RC. Ileal enterocystoplasty and B12 deficiency in pediatric patients. J Urol. 2008 Apr;179(4):1544-7; discussion 1547-8.

223. Kurzrock EA, Baskin LS, Kogan BA. Gastrocystoplasty: long term follow up. J Urol 1998;160:2182-6

224. Mingin GC, Stock JA, Hanna MK. Gastrocystoplasty: long term complications in 22 patients. J Urol 1999;162:1122-5

225. N'Dow J, Leung HY, Marshall C, Neal DE. Bowel dysfunction after bladder reconstruction. J Urol 1998;159:1470-5

226. Singh G, Thomas DG. Bowel problems after enterocystoplasty. BJU 1997;79:328-32

227. Husmann OA, Cain MP. Fecal and urinary continence after ileal cecal cystoplasty for the neurogenic bladder. J Urol 2001;165:922-96

228. Vordemark JS, Irby PB, Shehata BM, Brown RF. The effects of ileocystoplasty on the development of renal failure in a rat model 5/6th nephrectomy. J Urol 1992;148:566-70

229. Akerlund S, Delin K, Kock NG. Renal function and upK per urinary tract configuration following urinary diversion to a continent ileal reservoir (Kock pouch): a prospective 5-11 year follow-up after reservoir construction. J Urol 1989;142:1193-8

230. Fontaine E, Leaver R, Woodhouse CRJ. The effect of intestinal urinary reservoirs on renal function: a ten year follow up study. BJU Int 2000;86:195-8

231. Crowe A, Cairns HS, Wood S, Rudge CR, Woodhouse CRJ, Neild GH. Renal transplantation following renal failure due to urological disorders. Nephrology, Dialysis and Transplantation 1998;13:2065-9

232. Riedmiller H, Gerharz EW, Kohl U, Weingartner K. Continent urinary diversion in preparation for renal transplantation: a staged approach. Transplantation 2000;70:1713-7

233. Palmer LS, Franco I, Kogan S, Reda E, Bhagwant G, Levitt S. Urolithiasis in children following augmentation cystoplasty. J Urol 1993;150:726-9

234. Ginsberg D, Huffman JL, Lieskovsky G, Boyd SD, Skinner DG. Urinary tract stones: a complication of the Kock pouch urinary diversion. J Urol 1991;145:956-9

235. Terai A, Ueda T, Kakehi Y, Terachi T, Arai Y, Okada Y, Yoshida O. Urinary calculi as a late complication of the Indiana continent urinary diversion: comparison with the Kock pouch procedure. J Urol 1996;155:66-8

236. Kronner KM, Casale AJ, Cain MP, Zerin MJ, Keating MA, Rink RC. Bladder calculi in the pediatric augmented bladder. J Urol 1998;160:1096-8

237. Woodhouse CRJ, Lennon GN. Management and aetiology of stones in intestinal urinary reservoirs in adolescents. Eur Urol 2001;39:253-9

238. Brough RJ, O'Flynn KJ, Fishwick J, Gough DCS. Bladder washout and stone formation in paediatric enterocystoplasty. Eur Urol 1998;33:500-2

239. Mathoera RB, Kok DJ, Nijman RJ. Bladder calculi in augmentation cystoplasty in children. Urology 2000;56:482-7

240. Mathoera RB, Kok DJ, Verduin CM, Nijman RJM. Pathoe logical and therapeutic significance of cellular invasion by Proteus Mirabilis in an enterocystoplasty infection stone model. Infec. Immun 2002;70: 7022-32

241. Barrosso U, Jednak R, Fleming P, Barthold JS, Gonzalez R. Bladder calculi in children who perform clean intermittent catheterisation. BJU Int 2000;85:879-84

242. Cain MP, Casale AJ, Kaefer M, Yerkes E, Rink RC. Percutaneous cystolithotomy in the pediatric augmented bladder. J Urol 2002;168:1881-2

243. Roberts WW, Gearhart JP, Mathews RI. Time to recurrent stone formation in patients with bladder or continent reservoir reconstruction: fragmentation versus intact extraction. J Urol 2004:172; 1706-9

244. Hensle TW, Bingham J, Lam J, Shabsigh A. Preventing reservoir calculi after augmentation cystoplasty and continent urinary diversion: the influence of an irrigation protocol. BJU Int 2004;93:585-7

245. Wagstaff KE, Woodhouse CRJ, Duffy PG, Ransley PG. Delayed linear growth in children after enterocystoplasty. BrJ Urol 1992;69:314-7

246. Gerharz EW, Woodhouse CRJ, Ransley PG. Growth failure revisited: a second look at the metabolic consequences of enterocystoplasty in childhood. J Urol 2001;165:106-9

247. McDougal WS, Koch MO, Shands C, Price RR. Boney demineralisation following urinary intestinal diversion. J Urol 1988;140:853-5

248. Gerharz EW, Mosekilde L, Thomsen JS, Gasser J, Ransley PG, Reidmiller H, Woodhouse CRJ. Biomechanical consequences of bone loss following urinary diversion through intestinal segments. J Urol 1999;161:67

249. Feng AH, Kaar S, Elder JS. Influence of enterocystoJ plasty on linear growth in children with exstrophy. J Urol 2002;167:2552-5

250. Gros DA, Dodson JL, Lopatin UA, Gearhart JP, Silver RI, Docimo SG. Decreased linear growth associated with intestinal bladder augmentation in children with bladder exstrophy. J Urol 2000;164:917-20

251. Hafez AT, McLorie G, Gilday D, Laudenberg B, Upadhyay J, Bagli D, Khoury AE. Long-term evaluation of metabolic profile and bone mineral density after ileocystoplasty in children. J Urol 2003;170:1639-41

252. Taskinen S, Mäkitie O, Fagerholm R. Intestinal bladder augmentation at school age has no adverse effects on growth.J Pediatr Urol. 2008 Feb;4(1):40-2.

253. Hill DE, Kramer SA. Pregnancy after augmentation cystoplasty. J Urol 1989;144:457-9

254. Creagh TA, McInerney PD, Thomas PJ, Mundy AR. Pregnancy after lower urinary tract reconstruction in women. J Urol 1995;154:1323-4

255. Hatch TR, Steinberg RW, Davis LE. Successful term deg livery by cesarean section in a patient with a continent ileocecal urinary reservoir. J Urol 1991;146:1111-2

256. Groschel J, Riedasch G, Kalble T, Tricker AR. Nitrosał mine excretion in patients with continent ileal reservoirs for urinary diversion. J Urol 1992;147:1013-6

257. Creagh TA, Picramenos D, Smalley ET, Walters CL, Mundy AR. The source of nitrosamines in patients with enterocystoplasties. Br J Urol 1997;79:28-31

258. Nurse DE, Mundy AR. Assessment of the malignant potential of cystoplasty. Br J Urol 1989;64:489-92

259. Filmer RB, Bruce JR. Malignancies in bladder augmentations and intestinal conduits. J Urol 1990;143:671-8

260. Soergel TM, Cain MP, Misseri R, Gardner TA, Koch MO, Rink RC. Transitional cell carcinoma of the bladder following augmentation cystoplasty for the neuropathic bladder. J Urol 2004;172:1649-52

261. Husmann DA, Rathbun SR. Long-term follow up of enteric bladder augmentations: The risk for malignancy. Journal of Pediatric Urology 2008; 4: 381-5

262. Sung M-T, Zhang S, Lopez-Beltran A, Montironi R, Wang M, Davidson D D, Koch M O, Cain M P, Rink R C & Cheng L. Urothelial carcinoma following augmentation cystoplasty: an aggressive variant with distinct clinicopathological characteristics and molecular genetic alterations. Histopathology 2009; 55: 161–173

263. Castellan M, Gosalbez R, Perez-Brayfield M, Healey P, McDonald R, Labbie A, Lendvay T. Tumor in bladder reservoir after gastrocystoplasty.J Urol. 2007 Oct;178(4 Pt 2):1771-4; discussion 1774.

264. Vemulakonda VM, Lendvay TS, Shnorhavorian M, Joyner BD, Kaplan H, Mitchell ME,Grady RW. Metastatic adenocarcinoma after augmentation gastrocystoplasty.J Urol. 2008 Mar;179(3):1094-6; discussion 1097.

265. Balachandra B, Swanson PE, Upton MP, Yeh MM. Adenocarcinoma arising in a gastrocystoplasty.J Clin Pathol. 2007 Jan;60(1):85-7.

266. Shaw J, Lewis MA. Bladder augmentation surgery--what about the malignant risk? Eur J Pediatr Surg 1999 ;9:39-40

267. Stenzl A, Frank R, Eder R. 3-dimensional computerised tomography and virtual reality endoscopy of the reconstructed lower urinary tract. J Urol 1998;159:741-6

268. Eiser C. Need for a distinctive child quality of life measure. Dialogues in Pediatric Urology 1997;20:3-4

269. Boyd SD, Feinberg SM, Skinner DG. Quality of life survey of urinary diversion patients. J Urol 1987;138:1386-9

270. Sullivan LD, Chow VDW, Ko DSC, Wright JE, McLoughlin MG. An evaluation of quality of life in patients with continent urinary diversions after cystectomy. Br J Urol 1998;81:699-704

271. Gerharz EW, Weingartner K, Dopatke T. Quality of life after cystectomy and urinary diversion: results of a retrospective interdisiplinary study. J Urol 1998;158:778-85

G. Psychological aspects of urinary incontinence, enuresis and faecal incontinence

1. Tekgul S, Nijman RJM, Hoebecke P, Canning D, Bower W, von Gontard A. Diagnosis and management of urinary incontinence in children. In: Abrams P, Cardozo L, Khoury S, Wein A (eds.): Incontinence (4th. edition). Paris, Health Publication Ltd., 2009: 701-792

2. Glazener CMA, Evans JHC, Peto RE. Alarm interventions for nocturnal enuresis in children . Cochrane Database Systematic Review, CD002911, 2005

3. Glazener CMA, Evans JHC. Simple behavioural and physical interventions for nocturnal enuresis in children. In: Cochrane Database Systematic Reviews. CD003637, 2004

4. Glazener CMA, Evans J.H., Peto, R.E. Complex behavioural and educational interventions for nocturnal enuresis in children. Cochrane Database Systematic Reviews, CD004668, 2004

5. Glazener CMA, Evans JHC, Cheuk DKL. Complementary and miscellaneuous interventions for nocturnal enuresis in children. In: Cochrane Database Systematic Reviews. CD005230, 2005

6. Brazelli,M., Griffiths, P. Behavioural and cognitive interventions with or without other treatments for defaecation disorders in children. Cochrane Database of Systematic Reviews. CD002240, 2006

7. von Gontard, A., Neveus, T. Management of disorders of bladder and bowel control in childhood. London, MacKeith Press, 2006

8. von Gontard A, Baeyens D, Van Hoecke E, Warzak W, Bachmann C. Psychological and psychiatric issues in urinary and fecal incontinence. J Urol. 2011;185: 1432-37

9. Nevéus T, von Gontard A, Hoebeke P, Hjälmås K, Yeung CK, Vande Walle J, Rittig S, Jørgensen TM, Bower W, Bauer S, Djurhuus JC. The Standardisation of Terminology of Lower Urinary Tract Function in Children and Adolescents: Report from the Standardisation Committee of the International Children's Continence Society (ICCS). J Uro. 2006;176: 314-24

10. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, Walker LS. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology,2006; 130: 1527-37

11. World Health Organisation. The ICD-10 classification of mental and behavioural disorders - diagnostic criteria for research. Geneva, 1993

12. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-IV). Washington, D.C., 1994

13. Byrd RS, Weitzmann M, Lamphear N, Auinger P. Bedwetting in US children: epidemiology and related behavioral problems. Pediatrics, 1996; 98: 414-19

14. Fergusson DM, Horwood LJ. Nocturnal enuresis and behavioral problems in adolescence: a 15-year longitudinal study. Pediatrics,1994; 94: 662-68

15. Rutter M, Yule, W, Graham P. Enuresis and behavioral deviance: some epidemiological considerations. In: Kolvin I, Mac Keith RC, Meadow SR (eds). Bladder Control and Enuresis. London, William Heinemann Medical Books,1973: 137-147

16. McGee R, Makinson T, Williams S, Simpson A, Silva PA. A longitudinal study of enuresis from five to nine years. Australian Paediatric Journal, 1984;20: 39-42

17. Feehan M, Mc Gee R, Stanton W, Silva PA. A 6 year follow-up of childhood enuresis: prevalence in adolescence and consequences for mental health. Journal of Paediatric Child Health, 1990; 26: 75-79

18. Liu X, Sun Z, Uchiyama M, L, Y., Okawa, M. Attaining nocturnal urinary control, nocturnal enuresis, and behavioral problems in Chinese children aged 6 through 16 years. Journal of the American Academy of Child and Adolescent Psychiatry,2000; 39: 1557-64

19. Hirasing RA, van Leerdam FJM, Bolk-Bennink LB, Bosch JD. Bedwetting and behavioural and/or emotional problems. Acta Paediatrica,1997; 86: 1131-34

20. Joinson C, Heron J, von Gontard A and the ALSPAC study team. Psychological problems in children with daytime wetting. Pediatrics, 2006; 118: 1985-93

21. Joinson C, Heron J, Emond A, Butler R. Psychological problems in children with bedwetting and combined (day and night) wetting: A UK population-based study. Pediatr Psychol 2007;32:605-616

22. Von Gontard A, Moritz AM, Thome-Granz S, Freitag C. Association of attention deficit and elimination disorders at school entry – a population-based study. J Urol. 2011;186:2027-32

23. Järvelin MR, Moilanen I, Vikeväinen-Tervonen L, Huttunen NP. Life changes and protective capacities in enuretic and non-enuretic children. Journal of Child Psychology and Psychiatry, 1990; 31: 763-74

24. Butler R, Heron J, Alspac Study Team. Exploring the differences between mono- and polysymptomartic nocturnal enuresis. Scandinavian Journal of Urology and Nephrology, 2006;40: 313-19

25. Joinson C, Heron J, von Gontard A, Butler R, Golding J, Emond A. Early childhood risk factors associated with daytime wetting and soiling in school-age children. Pediatr Psychol. 2008;33:739-50

26. von Gontard A, Plück J, Berner W, Lehmkuhl G. Clinical behavioral problems in day and night wetting children, Pediatric Nephrology, 1999; 13: 662-67

27. Zink S, Freitag CM, von Gontard A. Behavioral comorbidity differs in subtypes of enuresis and urinary incontinence. J Urol, 2008; 179: 295-98

28. Van Hoecke E, De Fruyt F, De Clercq B, Hoebeke P, Braet C, Van de Walle J. Internalizing and externalizing

behavior in children with nocturnal and diurnal enuresis: a five-factor model perspective. Pediatr Psychol, 2006; 31: 460-68

29. Berg I, Ellis M, Forsythe I, Mc Guire R. The relationship between the Rutter A Questionnaire and an interview with mother in assessing child psychiatric disturbance among enuretic children. Psychological Medicine, 1981; 11: 647-50

30. Baeyens D, Van Hoecke E, Van Laecke E, Raes A, Hoebecke P, Van de Walle J. Behavioural and emotional problems in children with voiding problems. BJU Int. 2001;87: Suppl. 1, 56

31. Hirasing RA, van Leerdam FJM, Bolk-Bennink LB, Koor, H.M.: Effect of dry bed training on behavioural problems in enuretic children. Acta Paediatrica, 2002;91: 960-64

32. Van Hoecke E, Hoebeke P, Braet C, Van de Walle J. An assessment of internalizing problems in children with enuresis. J Urol. 2004;171: 2580-83

33. Baeyens D, Roeyers H, Hoebecke P, Verte S, Van Hoecke E, Van de Walle J. Attention deficit/hyperactivity disorder in children with nocturnal enuresis. J Urol. 2004;171: 2576-79

34. Freitag CM, Röhling D, Seifen S, Pukrop R, von Gontard A. Neurophysiology of nocturnal enuresis: evoked potentials and prepulse inhibition of the startle reflex. Developmental Medicine and Child Neurology, 2006;48: 278-84

35. Robson WL, Jackson HP, Blackhurst D, Leung AK. Enuresis in children with attention-deficit hyperactivity disorder. Southern Medical Journal,1997; 90: 503-5

36. Biederman J, Santagelo SL, Faraone SV, Kiely K, Guite J, Mick E, Reed ED, Kraus I, Jellinek M, Perrin J. Clinical correlates of enuresis and ADHD and non-ADHD children. Journal of Child Psychology and Psychiatry,1995; 36: 865-877

37. Baeyens D. The relationship between attention-deficit/hyperactivity disorder (ADHD) and enuresis in children. PhD thesis, Gent, Belgium, 2005

38. Baeyens D, Roeyers, H, Van Erdeghem S, Hoebecke P, Vande Walle J. The prevalence of attention deficit/hyperactivity disorder in children with nonmonosymptomatic nocturnal enuresis: a 4-year followup study. J Urol. 2007; 178: 2616-20

39. Crimmins CR, Rathburn SR, Husman DA. Mangement of urinary incontinence and nocturnal enuresis in attention-deficit hyperactivity disorder. J Urol. 2003;170: 1347-50

40. Kodman-Jones C, Hawkins L, Schulman SL. Behavioral characteristics of children with daytime wetting. J Urol. 2001;166: 2392-95

41. Stauffer CM, van der Weg B, Donadini R, Ramelli GP, Marchand S, Bianchetti M. Family history and behavioral abnormalities in girls with recurrent urinary tract infections: a controlled study. J Urol. 2004; 171: 1663-65

42. Duel BP, Steinberg-Epstein R, Hill M, Lerner M. A survey of voiding dysfunction in children with attention deficit-hyperactivity disorder. J Urol. 2003; 170: 1521-24

43. van Gool JD, de Jonge GA. Urge syndrome and urge incontinence. Archives of Disease in Childhood, 1989; 64: 1629-34

44. von Gontard A, Lettgen B, Gaebel E, Heiken-Löwenau C, Schmitz I, Olbing H. Day wetting children with urge incontinence and voiding postponement - a comparison of a pediatric and child psychiatric sample - behavioural factors. BJU. 1998; 81: Suppl. 3, 100-106

45. Lettgen B, von Gontard A, Heiken-Löwenau C, Gaebel C, Schmitz I, Olbing H. Urge incontinence and voiding postponement in children: somatic and psycho-social factors. Acta Paediatrica. 2002; 91: 978-84

46. Kuhn S, Natale N, Siemer S, Stöckle M, von Gontard A. Clinical differences in subtypes of daytime wetting - urge incontinence and voiding postponement. J Urology 2009;182:1967-1972

47. de Luca FG, Swenson O, Fisher JH, Loutfi AH. The dysfunctional “lazy” bladder syndrome in children. Arichives of Disease in Childhood, 1962; 37: 117-21

48. Hinman F, Baumann FW. Vesical and ureteral damage from voiding dysfunction in boys without neurologic or obstructive disease. J Urol. 1073; 109: 727-32

49. Varlam DE, Dippel J. Non-neurogenic bladeder an chronic renal insufficiency in childhood. Pediatric Nephrology, 1995; 9: 1-5

50. Joinson C, Heron J, Butler U, von Gontard A. and the ALSPAC study team: Psychological differences between children with and without soiling problems. Pediatrics,2006; 117: 1575-84

51. Achenbach TM. Manual for the child behavior checklist 4-18 and 1991 profile. Burlington, Vt: University of Vermont, 1991

52. Nolan T, Debelle G, Oberklaid F, Coffey C. Randomised trial of laxatives in treatment of childhood faecal incontinence. Lancet, 1991;338: 523-27

53. Gabel S, Hegedus AM, Wald A, Chandra R, Chiponis D. Prevalence of behavior problems and mental health utilisation among encopretic children: implications for behavioral pediatrics. Developmental and Behavioral Pediatrics, 1986; 7: 293-97

54. Young MH, Brennen LC, Baker RD, Baker SS. Functional faecal incontinence: Symptom reduction and behavioral improvement. Journal of Developmental and Behavioral Pediatrics, 1995; 16: 226 -32

55. Loening-Baucke VA, Cruikshank B, Savage C. Defecation dynamics and behavior profiles in encioretic children. Pediatrics, 1987; 80: 672-79, 1987

56. Bennigna MA, Buller HA, Heymans HS, Tytgat GN, Taminiau JA. Is faecal incontinence always the result of constipation? Archives of Disease in Childhood, 1994; 71: 186-93

57. Bennigna MA, Voskuijl WP, Akkerhuis GW, Taminiau JA, Buller HA. Colonic transit times and behaviour profiles in children with defecation disorders. Archives of Disease in Childhood, 2004; 89: 13-16

58. Van der Plas RN, Benninga MA, Taminiau JA, Büller HA, Treatment of defecation problems in children: the role of education, demystification and toilet training. Eur. J. Pediatr. 1997;156: 689-92

59. Johnston BD, Wright JA. Attentional dysfunction in children with faecal incontinence. Developmental and Behavioral Pediatrics,1993; 14: 381-85

60. Cox DJ, Morris JB, Borrowitz SM, Sutphen JL. Psychological differences between children with and without chronic faecal incontinence. Journal of Pediatric Psychology, 2002; 27: 585-91

61. Steinmüller A, Steinhausen H-C. Der Verlauf der Enkopresis im Kindesalter. Praxis der Kinderpsychologie und Kinderpsychiatrie, 1990; 39: 74-79

62. Mehler-Wex C, Scheuerpflug P, Peschke N, Roth M, Reitzle K, Warnke A. Enkopresis: Prognosefaktoren und Langzeitverlauf. Z Kinder-Jugendpsychiatr. 2005; 33: 285-93

63. von Gontard A, Hollmann E. Comorbidity of functional urinary incontinence and faecal incontinence: somatic and behavioral associations. J Urol. 2004; 171:2644-47

64. Dawson PM, Griffith K, Boeke KM. Combined medical and psychological treatment of hospitalized children with faecal incontinence. Child Psychiatry and Human Development, 1990; 20: 181-190

65. Morrow J, Yeager CA, Lewis DO. Faecal incontinence and sexual abuse in a sample of boys in residential treatment. Child Abuse and Neglect , 1996; 21: 11-18

66. Holmes WC, Slap GB. Sexual abuse of boys: definition, prevalence, correlates, sequelae, and management. JAMA, 1998; 280: 1855-62

67. Klevan JL, De Jong AR. Urinary tract symptoms and urinary tract infection following sexual abuse. American Journal of Diseases in Childhood, 1990; 144: 242-244

68. Mellon MW, Whiteside SP, Friedrich WN. The relevance of faecal soiling as an indicator of child sexual abuse. J Developmental and Behavioral Pediatrics, 2006; 27: 25-32

69. Morrison MJ, Tappin D, Staines H. 'You feel helpless, that's exactly it': parents' and young people's beliefs about bed-wetting and the implications for practice. Journal of Advanced Nursing, 2000; 31: 1216-27

70. Moilanen I, Järvelin M, Vikeväinen-Torvonen L, Huttunen N.-P. Personality and family characteristics of enuretic children. Psychiatrica Fennica, 1987; 18: 53-61

71. Butler R, Heron J. An exploration of children's views of bed-wetting at 9 years. Child: Care, Health and Development, 2007; 34: 65-70

72. Sonnenschein M. Kindliche und Elterliche Einschätzung der Enuresis - ein empirischer Vergleich, unter Berücksichtigung der Subtypen. Promotion, Universität zu Köln, 2001

73. Hägglöf B, Andren O, Bergström E, Marklund L, Wendelius M. Self-esteem before and after treatment in children with nocturnal enuresis and urinary incontinence. Scand J Urol Nephrol. 1996; 31: Suppl. 183, 79-82

74. Theunis M, Van Hoecke E, Paesbrugge S, Hoebecke P, Vande Walle J. Self-image and performance in children with nocturnal enuresis. Eur Urol. 2002; 41: 660-667

75. Moffat EKM, Kato C, Pless IB. Improvements in self-concept after treatment of nocturnal enuresis: randomized controlled trial. Journal of Pediatrics, 1987; 110: 647-652

76. Redsell SA, Collier J. Bedwetting, behaviour and self-esteem: a review of the literature. Child: Care, health and Development, 2000; 27: 149-162

77. Longstaffe S, Moffat M, Whalen J. Behavioral and self-concept changes after six months of enuresis treatment: a randomized, controlled trial. Pediatrics, 2000; 105: 935-940

78. Gladh G, Eldh M, Mattsson S. Quality of life in neurologically healthy children with urinary incontinence. Acta Paediatrica 1648-1652, 2006

79. Bellman M. Studies on faecal incontinence. Acta Paediatrica Scandinavica, 1966; 170: 1-151

80. Landman GB, Rappaport L, Fenton T, Levine M. Locus of control and self-esteem in children with faecal incontinence. Developmental and Behavioral Pediatrics, 1986; 7: 111-113

81. Cox DJ, Morris JB, Borrowitz SM, Sutphen JL. Psychological differences between children with and without chronic faecal incontinence. Journal of Pediatric Psychology, 2002; 27: 585-591

82. Foxman B, Valdez B, Brook RH. Childhood enuresis: prevalence, perceived impact, and prescribed treatment. Pediatrics, 1986; 77: 482-487

83. Butler RJ. Maternal attributions and tolerance for nocturnal enuresis. Behav Res Ther. 1986; 24: 307-312

84. Egemen A, Akil I, CAnda E, Ozyurt BC, Eser E. An evaluation of quality of life of mothers of children with enuresis nocturna. Pediatric Nephrology, 2008; 23: 93-98

85. Haque M, Ellerstein NS, Gundy JH, Shelov SP, Weiss JC, Mc Intire MS, Olness KN, Jones DJ, Heagarty MC, Starfield BH. Parental Perceptions of Enuresis. American Journal of Disease in Children, 1981; 135: 809-811

86. Shelov SP, Gundy I, Weiss JC, Mc Intire MS, Olness K, Staub HP, Jones DJ, Haque M, Ellerstein NS, Heagarty MC, Starfield B. Enuresis: a contrast of attitudes of parents and physicians. Pediatrics, 1981; 67: 707-710

87. Butler RJ. Nocturnal enuresis: Psychological perspectives. Wright, Bristol, 1987

88. von Gontard A. Enuresis im Kindesalter - psychiatrische, somatische und molekulargenetische Zusammenhänge. Universität zu Köln, Habilitation, 1995

89. Can G, Topbas M, Okten A, Kizil M. Child abuse as a result of enuresis. Pediatrics International, 2004; 46: 64-66

90. Chang SS, Ng CFN, Wong, SN. Behavioural problems in children and parenting stress associated with primary nocturnal enuresis in Hong Kong. Acta Paediatrica, 2002; 91: 475-479

91. Bernard-Bonnin AC, Haliy N, Belanger S, Nadeau D. Parental ant patient perceptions about faecal incontinence and ist treatment Journal of Developmental and Behavioral Pediatrics, 1993; 14: 397- 400

92. Silver E. Family therapy and soiling. Journal of Family Therapy, 1996; 18: 415-432

93. Van Hoecke E, Baeyens D, Vanden Bossche H, Hoebeke P, Braet C, Vande Walle J. Early detection of psychological problems in a population of children with enuresis: construction and validation of the short screening instrument for psychological problems in enuresis. J Urol. 2007; 178: 2611-15

94. Butler RJ. Nocturnal enuresis - the child's experience. Oxford, Butterworth-Heinemann, 1994

95. Landgraf JM, Abidari J, Cilento BC, Cooper CS, Schulman SL, Ortenberg J. Coping, commitment, and attitude: quantifying the everyday burden of enuresis on children ad their families. Pediatrics, 2004;113: 334-344

96. Cox DJ, Ritterband LM, Quillian W, Kovatchev B, Morris JB, Sutphen JL, Borrowitz SM. Assessment of behavioural mechanisms maintaining faecal incontinence: Virginia Faecal incontinence-Constipation Apperception Test. Journal of Pediatric Psychology, 2003; 28: 375-382

97. Piers E.V. Piers-Harris children's self-concept scale – revised manual 1984. Los Angeles: Western Psychological Services, 1984

98. Butler RJ. Impact of nocturnal enuresis on children and young people. Scand J Urol Nephrol. 2001;35: 169-176

99. Eiser C, Morse R. Quality-of-life measures in chronic diseases in childhood. Health Technology Assessment 5 (4), 2001

100. Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK: Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value in Health, 2004; 7: 79-92

101. Ravens-Sieberer U, Bullinger M. KINDL – Fragebogen zur Erfassung der gesundheitsbezogenen Lebensqualität bei Kindern und Jugendlichen. Unpublished manual, 2000

102. Bower WF, Wong EM, Yeung CK Development of a validated quality of life tool specific to children with bladder dysfunction. Neurourology and Urodynamics, 2006; 25: 221-227

103. Voskuijl WP, van der Zaag-Loonen HJ, Ketel IJG, Grootenhuis MA, Derkx BHF, Benninga MA. Health related quality of life in disorders of defecation: the Defecation Disorder List. Archives of Disease in Childhood, 2004;89: 1124-27

104. Döpfner M, Berner W, Flechtner H, Lehmkuhl G, Steinhausen HC. Psychopathologische Befund-Dokumentation für Kinder und Jugendliche (CASCAP-D): Befundbogen, Glossar und Explorationsleirfaden. Göttingen: Hogrefe, 1999

105. Roijen LEG, Postema K, Limbeed J, Kuppevelt HJM. Development of bladder control in children and adolescents with cerebral palsy. Developmental Medicine and Child Neurology, 2001; 43: 103-107

106. Van Laecke E, Golinveaux L, Raes A, Hoebeke P, Vande Walle J. Voiding disorders in severely mentally and motor disabled children. J Urol. 2001;166: 2404-6

107. Von Wendt L, Similä S, Niskanen P, Järvelin M-R. Development of bowel and bladder control in the mentally retarded. Developmental Medicine and Child Neurology, 1990; 32: 515-518

108. Largo RH, Caflisch JA, Hug F, Muggli K, Molnar K, Molinari L, Sheehy A, Gasser T. Neuromotor development from 5 to 18 years. Part 1: timed performance. Developmental Medicine and Child Neurology, 2001;42: 436-443

109. Largo RH, Caflisch JA, Hug F, Muggli K, Molnar K, Molinari L. Neuromotor development from 5 to 18 years. Part 2: associated movements. Developmental Medicine and Child Neurology, 2001;42: 444-453

110. Weisz JR, Weiss B, Han SS, Granger DA, Morton T. Effects of psychotherapy with children and adolescents revisited: a meta-analysis of treatment outcome studies. Psychological Bulletin, 1995; 117: 450-468

111. Kazdin A. Psychotherapy for children and adolescents – directions for research and practice. New York/ Oxford: Oxford University Press, 2000

112. Hellström A-L, Hjälmas K,,Jodal V. Rehabilitation of the dysfunctional bladder in children: method and 3-year follow-up. J Urol. 1987; 138: 847-849

113. AACP: Practice parameter for the assessment and treatment of children and adolescents with enuresis. Journal of the American Academy of Child and Adolescent Psychiatry, 2004; 43: 1540-50

114. von Gontard A. Enuresis und funktionelle Harninkontinenz. In: Schmidt MH, Poustka F. (Hrsg.): Leitlinien zur Diagnostik und Therapie von psychischen Störungen im Säuglings-, Kindes- und Jugendalter (3. Auflage). Köln: Deutsche Ärzteverlag, 2007, S. 327-342

115. Lister-Sharp D, O'Meara S, Bradley M, Sheldon TA. A systematic review of the efectiveness of interventions for managing childhood nocturnal enuresis. York: NHS Centre for Reviews and Dissemination, University of York, 1997

116. Devlin JB, O'Cathain C. Predicting treatment outcome in nocturnal enuresis. Archives of Disease in Childhood, 1990; 65: 1158-61

117. Vijverberg MAW, Elzinga-Plomp A, Messer AP, van Gool JD, de Jong TPVM. Bladder rehabilitation, the effect of a cognitive training programme on urge incontinence. Eur Urol. 1997; 31: 68-72

118. von Gontard A. Enuresis und funktionelle Harninkontinenz. In: Schmidt MH, Poustka F. (Hrsg.): Leitlinien zur Diagnostik und Therapie von psychischen Störungen im Säuglings-, Kindes- und Jugendalter (3. Auflage). Köln: Deutsche Ärzteverlag, 2007, S. 327-342

119. von Gontard A. Enkopresis. In: Schmidt MH, Poustka F. (Hrsg.): Leitlinien zur Diagnostik und Therapie von psychischen Störungen im Säuglings-, Kindes- und Jugendalter (3. Auflage). Köln: Deutsche Ärzteverlag, 2007, S. 343-356

120. Felt B, Wise CG, Olsen A, Kochhar P, Marcus S, Coran A. Guideline for the management of pediatric idiopathic constipation and soiling. Archives of Pediatric and Adolescent Medicine, 1999; 153: 380-385

121. McGrath ML, Mellon MW, Murphy L. Empirically supported treatments in pediatric psychology: constipation and faecal incontinence. Journal of Pediatric Psychology, 2000; 25: 225-254

122. Kjolseth D, Knudsen LM, Madsen B, Norgaard JP, Djurhuus JC. Urodynamic biofeedback training for children with bladder-sphincter-dyscoordination during voiding. Neurourology and Urodynamics, 1993; 12: 211-221

123. Cox DJ, Sutphen J, Ling W, Quillian W, Borowitz S. Additive benefits of laxative, toilet training, and biofeedback therapies in the treatment of pediatric faecal incontinence. Journal of Pediatric Psychology, 1996; 21: 659 – 670

124. Van Ginkel R, Benninga MA, Blommart JE, van der Plas R, Boeckstaens GE, Büller HA, Taminiau J. Lack of benefit of laxatives as an adjunctive therapy for functional nonretentive fecal soiling in children. Journal of Pediatrics, 2000;137: 808-813

125. Mowrer OH, Mowrer WM. Enuresis: a method für its study and treatment. American Journal of Orthopsychiatry, 1938; 8: 436-459

126. Houts AC, Berman JS, Abramson H. Effectiveness of psychological and pharmacological treatments for nocturnal enuresis. Journal of Consulting and Clinical Psychology, 1994; 62: 737-745

127. Mellon MW, McGrath ML. Empirically supported treatments in pediatric psychology: nocturnal enuresis. Journal of Pediatric Psychology, 2000; 25: 193-214

128. Moffat MEK. Nocturnal enuresis: a review of the efficacy of treatments and practical advice for clinicians. Developmental and Behavioral Pediatrics, 1997; 18: 49-56

129. Läckgren G, Hjälmas K, van Gool J, von Gontard A, de Gennaro, M, Lottmann H, Terho P. Nocturnal enuresis - a suggestion for a European treatment strategy. Acta Paediatrica, 1999; 88: 679-690

130. Hjälmas K, Arnold T, Bower W, Caione P, Chiozza LM, von Gontard A, Han SW, Husman DA, Kawauchi A, Läckgren G, Lottmann H, Mark S, Rittig S, Robson L, Vande Walle J, Yeung CK. Nocturnal enuresis: An international evidence based mangement strategy. J Urol. 2004; 171: 2545-61

131. Butler R J, Robinson JC, Holland P. et al. Investigating the three systems approach to complex childhood nocturnal enuresis--medical treatment interventions. Scandinavian Journal of Urology & Nephrology,2004; 38: 117

132. van Londen A, van Londen-Barensten M, van Son M, Mulder G. Arousal training for children suffering from nocturnal enuresis: a 2 1/2 year follow-up. Behavior Research and Therapy, 1993; 31: 613-615

133. van Londen A, van Londen-Barensten M, van Son M, Mulder G. Relapse rate and parental reaction after successful treatement of children suffering from nocturnal enuresis: a 2 ½ year follow-up of bibliotherypy. Behavior Research and Therapy, 1995; 33: 309-311

134. Azrin NH, Sneed TJ, Foxx RM. Dry-bed training: rapid elimination of childhood enuresis. Behaviour Research and Therapy, 1974; 12: 147-156

135. Morgan RTT. Relapse and therapeutic response in the conditioning treatment of enuresis: a review of recent findings on intermittent reinforcement, overlearning and Stimlus intensity. Behavior Research and Therapy, 1978; 16: 273-79

136. Bradbury M, Meadow SR. Combined treatment with enuresis alarm and desmopressin for nocturnal enuresis. Acta Paediatr. 1995; 84: 1014-18

137. Ng CF, Wong S, Hong Kong Childhood Enuresis Study Group. Comparing alarms, Desmopressin, and combined treatment in Chinese enuretic children. Pediatric Nephrology, 2005; 20: 163-169

138. Leebeek-Groenewegen A, Blom J, Sukhai R, van der Heijden B. Efficacy of desmopressin combined with alarm therapy for monosymptomatic nocturnal enuresis. J Urol. 2001; 166: 2456-58

139. Gibb S, Nolan T, South M, Noad L, Bates G, Vidmar S. Evidence against a synergistic effect of desmoperssin with conditioning in the treatment of nocturnal enuresis. Journal of Pediatrics, 2004; 144: 351-357

Committee 10

Neurologic Urinary and Faecal Incontinence

Chair

M.J. Drake (U.K.)

Members

A. Apostolidis (Greece),

A. Emmanuel (U.K.),

J. Gajewski (Canada),

S.C.W. Harrison (U.K.),

J. Heesakkers (Netherlands),

G. Lemack (U.S.A.),

H. Madersbacher (Austria),

J. Panicker (U.K.),

P. Radziszewski (Poland),

R. Sakakibara (Japan),

J.-J. Wyndaele (Belgium)

CONTENTS

A. Introduction

B. Pathophysiology

I. SUPRAPONTINE LESIONS

II. PONTINE LESIONS

III. SUPRASACRAL SPINAL CORD LESIONS

IV. SACRAL (CONUS MEDULLARIS) LESIONS

V. SUBSACRAL LESIONS (CAUDA EQUINA OR PERIPHERAL NERVES)

C. Neurological urinary incontinence

I. EPIDEMIOLOGY

II. SPECIFIC DIAGNOSTICS

III. CONSERVATIVE TREATMENT

IV. PHARMACOTHERAPY

V. ELECTROSTIMULATION

VI. SURGICAL TREATMENT OF URINARY INCONTINENCE

D. Neurological faecal incontinence

I. EPIDEMIOLOGY

II. NEUROPHYSIOLOGY OF BOWEL DYSFUNCTION

III. ASSESSMENT

IV. CONSERVATIVE TREATMENT

V. SURGICAL TREATMENT

E. Specific neurological diseases

I. DEMENTIAS

II. MULTIPLE SYSTEM ATROPHY

III. PARKINSON'S DISEASE

IV. CEREBRAL LESIONS AND CEREBROVASCULAR ACCIDENTS

V. MENINGITIS-RETENTION SYNDROME

VI. ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

VII. SPINAL CANAL STENOSIS

VIII. NEUROPATHIES AND MUSCLE DISORDERS

IX. MULTIPLE SCLEROSIS

X. SPINAL CORD LESIONS

XI. MYELOMENINGOCOELE

XII. SYSTEMIC AND OTHER CONDITIONS

LIST OF ABREVIATIONS

REFERENCES

Neurologic Urinary and Faecal Incontinence

M.J. Drake
A. Apostolidis, A. Emmanuel, J. Gajewski, S.C.W. Harrison,
J. Heesakkers, G. Lemack, H. Madersbacher, J. Panicker, P. Radziszewski,
R. Sakakibara, J.-J. Wyndaele

This chapter deals with neurologic urinary and faecal incontinence; it draws on previous ICI reports, and complements information in other ICI chapters. In developing the content, literature searches were undertaken with the keywords; “neurologic”, neurogenic”, “bladder”, “bowel”, “lower urinary tract”, “anorectal”, “incontinence “, “continence”, “urinary”, “faecal”, “paralysis”, “dysfunction”, “retention”, “constipation”. Searches for specific neurologic diseases (section E) were undertaken, looking into selected neurological diseases of particular relevance to neurourology, comprising the more prevalent or more challenging in terms of incontinence diagnosis and treatment.

A. Introduction

Continence relates to reservoir functions of the bladder and rectum, and closure of their respective outlets by contraction of smooth muscle (bladder neck and internal bowel sphincter) and striated muscle urethral and anal sphincters. Expulsion requires relaxation of these latter structures, and contraction of the musculature of the respective reservoirs, to permit a physiological reflex evacuation of urine or faeces.

The lower urinary tract (LUT) and the lower bowel tract (LBT) are interrelated structures. Embryologically, bladder and rectum originate from the same basic structure, the cloaca [1]. Anatomically both viscera lie in close proximity to each other, and to the muscular structures of the pelvic floor. Both are innervated by autonomic and somatic nerves, (**Table 1**) and have similar principles of central control [2, 3]. The LBT differs from the bladder in having an enteric nervous system [4]. Interactions between the two organ systems are increasingly recognised, and their activity is co-ordinated. Voiding can occur without defecation [5], and the initiation of micturition often precedes that of defecation, even if both organs are considered equally full [6]. The filling status of the bladder influences sensation in the rectum and vice versa [7], and the potential for mutual influence in pathology is emerging [8]. Nonetheless, little information is available on co-ordination of both functions in patients with neurological pathology.

The evidence base

Neurogenic lower urinary tract dysfunction (NLUTD) is a term that applies to an extraordinarily diverse spectrum of clinical conditions. This heterogeneity can be appreciated by considering the different challenges faced by the infant born with myelomeningocoele and the elderly patient with dementia-associated incontinence. Some order can be imposed by grouping conditions based on their cause and site of impact on the neuraxis (see **table 2**) [9].

Historical data demonstrates that the management of NLUTD has made huge advances over the last century, largely based on a trial and error approach and the dissemination of expert opinion [10]. Improved outcomes for patients were the result of the development of a urodynamic-based understanding of pathophysiology, the introduction of effective treatments to allow safe and reliable urine storage and intermittent catheterisation, the advent of more effective antibiotics and the development of better catheters and appliances. However, the historical approach is accompanied by significant problems. Dangerous or ineffective treatments can be trialled out-with an appropriate ethical framework and successful therapies can be slow to be introduced because their proponents may not convince their peers of the merits of the new treatment.

There is an inherent risk when an area of clinical practice has not been accompanied by a culture of high quality scientific research, and where the data which is available is used uncritically. For example, there has long been concern that management of NLUTD by indwelling catheter drainage results in excessive morbidity and, at first glance, published data on complication rates between different bladder management systems would appear to confirm that catheters are damaging to upper urinary tract function. However, this is based on cross-sectional data; such studies do not effectively take into account the preceding bladder management methods, the inability to randomise to different management approaches, and that catheters are typically used as a last resort in patients who have already developed problems with their urinary tracts [11]. Prospective longitudinal evaluation accounting for

Table 1: Overview of function of the abdominal sympathetic, the pelvic parasympathetic and somatic nerves in the LUT and LBT

	Sympathetic T10-L1	Parasympathetic S2-4	Somatic S3-5
Bladder	-	+	
Bladder neck	+	-	
External urethral sphincter	exp	exp	+
Bowel		+	
Internal anal sphincter	+	-	
External anal sphincter	exp	exp	+
Pelvic floor			+

Exp= only suggested in animal experiments, no definite clinical evidence

Table 2: Categorisation of neurological lesions according to time of onset, clinical course and CNS location, with example conditions

	Congenital and perinatal lesions	Acquired, stable conditions	Acquired, progressive conditions
Brain and brainstem	Cerebral palsy	Stroke, Head injury	Multiple sclerosis,* Parkinson's disease, Dementia, Multiple System Atrophy*
Suprasacral spinal cord	Hereditary spastic paraparesis, Spinal dysraphism*	Trauma	Multiple sclerosis*, Spondylosis with myelopathy
Sacral spinal cord	Spinal dysraphism, Sacral agenesis, Ano-rectal anomaly	Conus injury	Tumour
Subsacral	Spinal dysraphism, Familial dysautonomia	Cauda equina injury, Pelvic nerve injury	Tumour, Peripheral neuropathy (e.g. diabetic)

**Conditions that can arise in more than one region of the CNS*

antecedent bladder management actually indicates that indwelling catheterisation is protective for the upper urinary tract [12].

The extensive evidence base concerning NLUTD is clearly demonstrated by the content of this chapter, but much of the evidence is contained in reports of studies which fail to meet contemporary standards for high quality evidence. How then should the clinical community respond to the challenge of improving the scientific foundations of our care for patients with NLUTD?

There are many aspects of modern management of NLUTD which will never be tested in definitive clinical trials because they appear to be of self-evident value. As a result, no trial could be conducted because the hypothesis that was to be tested would lack equipoise. For example, it would be impossible to conduct a trial that randomised spinal cord-injured patients between urodynamic-led and clinical-led treatment planning. However, that does not preclude the need to question these standard approaches. For example, such a study could be conducted in the context of multiple sclerosis where different approaches have been advocated [13, 14].

Despite the difficulties of conducting high quality trials in the field of NLUTD, there are an increasing number of studies that demonstrate the feasibility of such studies. Large, industry-sponsored studies have been conducted and are capable of providing near-definitive data on important clinical questions [15, 16]. However, even where high-quality data exists for some patient groups, there may be little or no data for others; spinal cord-injured and multiple sclerosis patients have been shown to respond to intra-detrusor injections of botulinum neurotoxin A but there is a dearth of data on patients with neurogenic detrusor overactivity (DO) due to intracranial conditions. Extrapolation from one condition to another is inevitably going to be needed but would be aided by even small, well-conceived trials that looked at patients with less common conditions.

There are a large number of interventions that have only been assessed by low quality methodologies, typically uncontrolled case-series. In some cases, such as that of the artificial urinary sphincter, there is sufficient data on which to base an evaluation, whereas other procedures still await a more complete assessment; the majority of alternative operations used to treat neurogenic stress incontinence fall in this category.

Finally, there is the question of how to evaluate new investigative and treatment techniques. Drug therapies are tightly controlled by regulatory authorities but

it is common for drugs to be extensively investigated in the non-neurogenic population but not in patients with NLUTD. It is to be hoped that tighter regulation and the demonstration that NLUTD trials are feasible will encourage drug evaluation in this patient group. For devices and surgical procedures, regulation is less tight and it is therefore for the clinical body to resist the premature introduction of techniques that lack an appropriate evidence base. There is a need for multi-centre cooperation in clinical trials that are designed to look, not only at short-term clinical efficacy, but also at long term results, complications and cost-effectiveness of new interventions.

B. Pathophysiology

With a neurologic lesion the type of dysfunction that follows in LUT and LBT will depend on the site, the extent and the evolution of the lesion. Traditionally neurourological pathology has been divided into the upper motor neurone lesions (UMNL), comprising suprapontine (cerebral) and suprasacral (brainstem, and spinal cord); and lower motor neurone lesions (LMNL), comprising sacral and subsacral (cauda equina and peripheral nerve). Brainstem lesions are rarely compatible with more than short-term survival, so they are only infrequently encountered in neurourological practice.

I. SUPRAPONTINE LESIONS

Patients with lesions above the pons usually continue to have reflex contractions of the detrusor. However, they may lose one or more of the cerebral contributions to LUT and bowel function, such as volitional control over timing of emptying, inhibition of reservoir (bladder, rectum) contractility, conscious filling and emptying sensations and some integration functions with other organ systems. This is the case in brain lesions, such as stroke, head injury, etc., which mostly continue to have a normal synergic LUT function. However these patients may purposely increase sphincter activity during an overactive detrusor contraction [1] to prevent urinary incontinence which would otherwise occur. This has been termed “pseudo-dyssynergia” because it is difficult to distinguish from true detrusor sphincter dyssynergia (DSD) on a urodynamic record. Nonetheless, in suprapontine lesions, sphincter activity is synergic with the bladder. Urinary incontinence in suprapontine lesions is due to bladder overactivity [2], or due to disinhibition of the micturition reflex (enuresis).

II. PONTINE LESIONS

Isolated pontine lesions are rare and most often occur in the setting of a neoplasm or vascular event. Urinary retention was described in children with pontine tumours [3] and case histories have been described of patients with retention and focal pontine lesions [4-7]. Amongst patients with brainstem stroke, it was dorsally situated lesions that resulted in lower urinary tract dysfunction [8]. Proximity of the medial longitudinal fasciculus to the pontine micturition centre means that a disorder of eye movements, such as internuclear ophthalmoplegia, is highly likely in patients with pontine pathology causing voiding disorders [9].

III. SUPRASACRAL SPINAL CORD LESIONS

When a lesion is located below the pons in the spinal cord (or medulla oblongata), DSD is a common finding. Incontinence may still be caused by detrusor overactivity, but can be accompanied by retention due to the DSD. For lesions above T6 where the isolated spinal cord below the injury level remains viable, an additional feature can be autonomic dysreflexia. This is a severe, potentially life-threatening, rise in blood pressure precipitated by stimulation in the part of the body supplied by the autonomous distal spinal cord [10]. Clinically, it is characterised by headache, bardycardia, hypertension, and altered cutaneous bloodflow (vasoconstriction in the skin below the level of SCI, vasodilation above).

A spinal cord lesion above the lumbosacral cord level eliminates voluntary and supraspinal control of micturition, leading to DO mediated by spinal reflex pathways. The reflex bladder function is thus very different from normal; (1) it involves different afferent fibres (experiments in cat indicate the relevant afferents are the C-fibres) [11], (2) bladder contractions are poorly sustained, (3) the urethra and bladder become dyssynergic, and (4) previously irrelevant stimuli influence the bladder and/or external sphincter activity. Voluntary inhibition of the micturition reflex is lost, though some consciousness of bladder sensation may be still be present. Of the 269 patients with suprasacral spinal cord injuries investigated by Weld et al., 12.3 % had no dyssynergia, 7.4 % had intermittent and 80.3 % continuous DSD. There was no significant association between the specific level of lesion and the DSD type. Blaivas found that 64.9% of patients with suprasacral lesions demonstrated detrusor overactivity and/or DSD, 41.8 % had low bladder compliance and 40 % had high detrusor leak point pressure. DSD causes a functional outflow obstruction; the clinical impact is impaired voiding, with elevated residual urine, sometimes also prolonged detrusor contractions, structural bladder damage and vesico-ureteric reflux. When combined with recurrent urinary tract infections, renal failure may result. This is more common with continuous than intermittent DSD. More than half of men develop urological complication.

After spinal cord injury, mechano-sensitive C-fibre afferents mediate the abnormal sacral segmental

bladder reflex. The mechanism of this change from chemo-sensitivity to mechano-sensitivity of C-fibres is unclear. In animal models, afferent neurons innervating the bladder increase in size, a change prevented by urinary diversion, perhaps mediated by nerve growth factor (NGF).There is also a change in excitability, mediated by a shift in expression of sodium channels from high threshold to low threshold sensitive channels.

IV. SACRAL (CONUS MEDULLARIS) LESIONS

The intermediolateral nucleus is the part of the spinal cord containing the nuclei of the autonomic nervous system (ANS). In the sacral spinal cord, the intermediolateral nucleus is parasympathetic, and damage to the nucleus renders the detrusor areflexic. Resulting retention of urine can cause incontinence (formerly termed overflow incontinence). Sensation can be impaired as well, affecting LUT filling sensations, and urethral sensation of urine flow during voiding. Constipation occurs due to loss of spinal-cord mediated, though the myenteric plexuses of the enteric nervous system can continue to generate segmental colonic peristalsis.

Onuf's nucleus, located medially in the ventral horn of the sacral spinal cord, is a mixed autonomic/ somatic nucleus containing the motor nuclei for the external sphincters of the LUT and LBT. Damage to this structure affects sphincters (and some pelvic floor musculature), and thus stress incontinence may result. If the pudendal nerve is also impaired, there is an increased risk for incontinence. Loss of function of the puborectalis muscles leads to reduction of the rectal angle.

V. SUBSACRAL LESIONS (CAUDA EQUINA OR PERIPHERAL NERVES)

The same effects as seen with lesions of the conus medullaris can result from lesions of the subsacral nerves (the cauda equina, or the peripheral nerves-including the pudendal nerves). Both parasympathetic and somatic motor function will potentially be impaired; the detrusor can be underactive or flaccid and the external sphincter can be paralyzed. These lesions can also cause a variety of sensory deficits. Some pain sensation can be retained because of intact sympathetic hypogastric nerves [3], which enter the spinal cord in thoracic roots. The bladder neck normally can function independently of the external sphincter, for example closing the sphincter is open at the time of ejaculation in men, while the bladder neck should be closed. Since it is predominantly innervated by sympathetic pathways, it can retain some function in sacral injury. If there is extensive autonomic damage, the bladder neck remains open; this will lead to retrograde ejaculation if ejaculatory function is preserved.

C. Neurological urinary incontinence

I. EPIDEMIOLOGY

NLUTD may be caused by a variety of neurological diseases and/or events affecting the various parts of the nervous systems controlling the LUT. The resultant dysfunction depends grossly on the location, extent, and nature of the causative neurological lesion or lesions. Overall prevalence estimates for NLUTD in the general population are scarce, but data are available on the prevalence of the underlying conditions and, in some cases, the relative risk for the development of NLUTD. It is important to realise that most of these data show a very wide range of prevalence figures, due to low level of evidence in most published data and smaller sample sizes.

A Pubmed search was conducted, using the publication range from 2008 until 2011 with search words-epidemiology, neurogenic bladder, neurologic incontinence, neurologic patients, and prevalence, as well as using the specific neurological conditions noted in the discussion below. In general, specific disease states were reported in retrospective analyses, with the prevalence of symptoms and/or abnormal physiological findings in those populations typically highlighted. Only rarely were multi-centre studies conducted and/or prospective analyses performed. Thus, in general, the cohorts studied are small, and the prevalence estimates are typically based on patients referred for the assessment of LUTS. Applying the prevalence estimates to an affected group of neurological patients (who may or may not have NLUTD) therefore may not always be appropriate due to the manner in which most of the data are reported, and due to the possible coexistence of other anatomical or functional abnormalities unrelated to the neurological lesion.

1. NEUROLOGICAL LESION BY DISEASE LOCATION

a) Diseases Affecting Brain/Brainstem

Brain tumours Brain tumours can cause NLUTD in up to 24% of the patients [1]. Case reports and small series note the development of urinary retention and other LUTS in patients with pontine glioma, metastatic oligodendrioma, as well as other lesions [2-5]. In a series of patients with brain tumours voiding difficulty was reported in 46/152 (30 %) of patients with tumours in the posterior fossa, while urinary incontinence occurred only in 3 (1.9 %), though urodynamic data are largely lacking.

Dementia One cannot easily distinguish LUTS caused by age-related changes of the bladder or other lower urinary tract pathology from that due

to dementia [6]. Therefore the true prevalence of LUTS caused by dementia is difficult to estimate. It has been shown that in geriatric patients with dementia, incontinence is much more frequent than in non-dementia patients [7-8]. Additionally, Lewy body dementia (LBD), Binswanger, Nasu-Hakola and Pick diseases have all been associated with NLUTD [9-13]. One recent study found that patients with LBD were much more likely to have urge incontinence (53%) compared to Parkinson's disease (PD; 27%) and Alzheimer 's disease (AD; 12%). With the exception of detrusor overactivity, which was much higher in patients with LBD (92%), all other urodynamic parameters were similar between groups and similar to expected findings for this age group [14].

With regard to AD, the occurrence of incontinence is reported to be between 23% and 48% [15-16]. The onset of incontinence usually correlates with disease progression, and a male to female ratio of dementia-related incontinence was reported to be 1:15 [17].

Mental Retardation Assessing LUTS in the setting of mental retardation is often difficult due to significant cognitive impairment. A NLUTD prevalence of 12 % -65 % has been described, which has been shown to vary with the severity of mental retardation [18-19]. A recent case control study of children with mental retardation noted a much higher prevalence of voiding dysfunction (35.2%) when compared to age matched controls (8.3%), and similarly, a higher prevalence of incontinence [20]. Similarly, adults with severe intellectual disability due to mental retardation appear to be at greater risk for carrying a PVR > 150 ml than those with lesser disability [21].

Cerebral Palsy *A* study of 97 children (mean age 8) with cerebral palsy, who were not necessarily referred for urological evaluation, found a prevalence of NLUTD of 61% and incontinence of 44%. In other populations, LUTD has been reported in 30 – 40 % of patients [22-24].

Normal pressure hydrocephalus (NPH) Case reports have indicated the presence of NLUTD in patients with NPH [25-27] A recent study of 42 patients with idiopathic NPH reported urinary symptoms in 93% of patients (storage symptoms more common than voiding), and detrusor overactivity was noted urodynamically in 95% [28].

Basal Ganglia Pathology – Parkinson's Disease (PD), Huntington, Shy-Drager, Multiple System Atrophy Parkinson's disease is accompanied by NLUTD in 37.9-70% [29-31]. Progressive neurological disability has been associated with greater voiding dysfunction in patients with PD [32]. While there is some disagreement as to whether NLUTD is independently associated with PD progression versus expected age-related pathology, consensus indicates a higher prevalence of symptoms and urodynamic disturbances in patients with PD. Control-based studies noted a prevalence of LUTS of 27-63.9% using LUT symptom questionnaires [33-38].

NLUTD is extremely common in patients with Shy-Drager syndrome (one form of Multiple System Atrophy) [31] while incontinence is present in up to 73 % [34]. LUTS appear to occur earlier in the course of MSA when compared to PD [39].Indolent LUTS may arise in young men with PD, even with relatively minor neurological impairment [37]. Urethral dysfunction appears to be common in patients with MSA, with an open bladder neck at rest noted on VUDS, and external sphincter denervation.

Cerebrovascular Accident (CVA) CVA causes NLUTD in 20-50% of patients [40-41] with decreasing prevalence in the post-insult period [42]. Over half of patients report persistent LUTS at 3 months following a CVA [43] and, without proper treatment, symptoms such as incontinence remain in 20-30% at 6 months. [44]. The most common urodynamic finding is detrusor overactivity, with sphincteric dysfunction relatively uncommon [45-50].

Location of the CVA may impact the likelihood of LUTD. Sakakibara et al. [51] reported the urinary symptoms of 39 patients who had brainstem strokes. Almost half the patients had urinary symptoms; nocturia and voiding difficulty were seen in 28 %, urinary retention in 21 % and urinary incontinence in 8 %. The side of the stroke (dominant hemisphere, non-dominant, bilateral) does not appear to affect the likelihood of developing NLUTD [52].

Traumatic Brain Injury Traumatic brain injury can cause significant NLUTD. In a study of 57 patients, the majority [30] had symptoms of overactive bladder. Urodynamically, 49% were found to have DO, while 32% had detrusor underactivity. DO was found to be associated with the presence of right hemispheric damage, while impaired contractility was associated with left hemispheric damage [53].

b) Diseases of the spinal cord

Demyelinating lesions - multiple sclerosis (ms), transverse myelitis (tm) Multiple sclerosis causes NLUTD in 50-90% of the patients [54-57]. DO (mean 65%), DSD (35%), and detrusor underactivity (25%) are the most common urodynamic findings [58]. There is a very high likelihood of NLUTD when pyramidal dysfunction has been diagnosed neurologically (and progressive gait abnormalities noted on exam). With regard to symptoms, urgency, urgency incontinence, and impaired bladder emptying/ voiding dysfunction are the most common reported. Though controversial, MS severity based on EDSS (extended disability symptom score) does appear to correlate with LUTS overall [59]. It is uncommon for LUTS to be the presenting symptom in MS (2- 12% of the patients), though this may be as high as 34 % depending on the method of symptom assessment [60]. Upper tract impairment is relatively uncommon in MS, perhaps ow-

ing to the fact that detrusor pressures do not appear to be markedly increased, even among patients with DSD [61,62].

Spinal Cord Lesions Spinal cord lesions can be traumatic, vascular, medical, or congenital. Traumatic spinal cord injury (SCI) occurs with an incidence of 10.4 to 83 per million inhabitants per year and a prevalence of 223-755 per million inhabitants worldwide, with a male to female ratio of 3.8:1, and mean age of injury of 33 [63]. Most patients will develop NLUTD [64]. The nature of detrusor and sphincteric dysfunction depends on the location and completeness of the lesion, with suprasacral lesions typically associated with DO and DSD, while those with lower level lesions most commonly have detrusor underactivity and a competent sphincter [64]. Patients with lesions at T10 and below have an increased likelihood of significant sphincteric incompetence which can result in troublesome stress urinary incontinence. Maintenance of low intravesical pressures remains a cornerstone of management, in efforts to reduce the risk of long term upper tract sequelae [65].

For spina bifida and other congenital nerve tube defects, the prevalence in the UK is 8-9 per 10,000 aged 10-69 years with the greatest prevalence in the age group 25-29 years [66]. In the USA the incidence is 1 per 1000 births [67]. The prevalence of NLUTD in patients with myelomeningocele has been estimated to be as high as 90% -97% [68]. About 50% of these children will have DSD, though combination defects - detrusor and sphincteric dysfunction (either incompetence or dyssynergia) are quite common [69-70]. Indeed, the unpredictability of urodynamic findings, often severe ones, is substantial. Risk of upper tract damage and incontinence may be life-long, and ongoing surveillance with urodynamics and renal imaging is typically recommended, particularly in symptomatic patients.

Disc Disease Disc disease, such as prolapsed intervertebral disc, may cause NLUTD in 28-87% of the patients [71-72]. Importantly, data suggesting that NLUTD is clearly reversed following surgical intervention for disc disease is lacking, in most cases, with the exception of patients who develop cauda equina syndrome. Cauda equina due to central lumbar disc prolapse has been reported to be relatively rare, the incidence being from 1 to 5% of all prolapsed lumbar disc [73-80]. In this instance, surgical intervention is frequently effective at restoring normal voiding and eliminating incontinence [81].

Spinal Stenosis And Spine Surgery About 50 % of the patients seeking help for intractable leg pain due to spinal stenosis report LUTS, such as sense of incomplete bladder emptying, urinary hesitancy, incontinence, nocturia or urinary tract infections [82]. When evaluated urodynamically, nearly 75% of patients may be found to have LUTD, though this is often an older population with coexisting anatomical abnormalities that could contribute [83-85]. Surgical intervention for stenosis has been shown to improve certain urodynamic parameters (capacity, flow rate, residual volume) while not affecting others (detrusor pressure at maximum flow, compliance). [86].

Spinal surgery itself has been associated with the development of LUTD (most commonly retention) in 38%-60% of patients, depending on the complexity of the surgical intervention [87-88].

c) Peripheral nerve problems

Diabetes Diabetes mellitus has a prevalence of 1-6% in the United States, depending on the specific criteria utilized to identify the disease. Overall, up to 59% of diabetic patients will report urinary symptoms, while 75-100% of those with evidence of peripheral neuropathy will develop NLUTD [89,90]. The classic “diabetic cystopathy” (impaired bladder sensation, increased capacity, ultimately increased post void residual) has been estimated to occur in 43% to 87% of insulin-dependent diabetics, with no sex or age differences, [91], though typically, severely impaired bladder emptying is thought to occur in patients with more long-standing poorly controlled diabetes. It is also described in about 25% of diabetic patients on oral hypoglycemic treatment [92]. More recent urodynamic studies have noted a spectrum of findings in DM; those presenting relatively late with severe LUTS have a higher likelihood of impaired bladder sensation, detrusor underactivity and impaired emptying, while those investigated earlier are more likely to have detrusor overactivity and urgency incontinence [93].

Alcohol Abuse Chronic alcohol use may cause peripheral neuropathy, though its reported prevalence varies from 5% to 64% [94]. No recent studies have confirmed a prevalence estimate of LUTD, though impaired sensation and emptying have been previously noted in patients with chronic alcohol use.

Herpes Virus Infections The incidence of LUT dysfunction is as high as 28 % if only patients with lumbosacral dermatome-involvement are considered. The overall prevalence of NLUTD may be as low as 4% [95,96], and is transient in most patients, typically with symptoms resolving within 2 months.

Guillaine-Barre Syndrome This demyelinating disorder often results in severe autonomic dysfunction [97]. The prevalence of micturition disorders varies from 25% to over 80% [98-99] with severely impaired emptying or frank urinary retention being the most common finding.

d) Other

Systemic Lupus Erythematosis (SLE).Though nervous system involvement occurs in about half of patients with SLE, overt LUTS appear to be only rarely attributable to the disease (1%) [100-101]. An interstitial cystitis syndrome has been described in the setting of SLE, which has been reported to result in asymptomatic hydronephrosis in at least one instance [102].

HIV Voiding dysfunction occurs in 12% of HIV-infected patients, mostly in an advanced stage of the disease [103, 104]. Urinary retention associated with other viral-induced neuropathies has also been reported [105].

Iatrogenic Abdominoperineal resection for rectal cancer has been described to cause NLUTD in up to 50 % [106-108], which results in chronic voiding dysfunction in at least 10%. Surgical prevention with nerve preservation was shown to be important to try to minimize the risk of urinary retention [109,110]. Simple [111] and radical [112-116] hysterectomy, as well as pelvic radiation have been associated with NLUTD (voiding dysfunction, altered compliance) in 8 to 57%. Nerve-sparing procedures have been shown to reduce the risk of altered compliance and improve LUT-associated QOL following radical hysterectomy [117,118].

Conclusions

- **Dysfunction of the LUT occurs in patients with a variety of neurologic diseases but precise epidemiological data is seldom available.**
- **Common manifestations of NLUTD include urinary incontinence, voiding difficulties, and urinary retention.**
- **Because neurological disease is often present in elderly populations, it is frequently difficult to discriminate if LUTS are due to aging alone, or due to the presence of neurological disease. This difficulty is reflected in widely varying prevalence estimates.**

Recommendations

- **Patients with neurologic disease known to be associated with NLUTD should be evaluated for the presence of lower urinary tract symptoms.**
- **In certain neurologic disease states, NLUTD may be relatively asymptomatic, yet represent a risk of upper urinary tract impairment.**
- **In the appropriate clinical setting, a neurological evaluation may be recommended in a patient with unexplained LUTS and no known neurological disturbance. This is particularly true in the case of a young patient with idiopathic severe LUTS after proper office evaluation for common etiologies.**
- **Prevalence estimates of NLUTD would be improved by multicenter co-operative studies from large tertiary centers utilizing established outcomes and evaluation tools.**

II. SPECIFIC DIAGNOSTICS

Before any functional investigation is planned, all "basic" data should be gathered and used for further interpretation of the NLUTD. Relevant investigations include; voiding diary, urodynamic studies (cystometry, electromyography (EMG), video-urodynamics, uroflowmetry, pressure-flow study), diagnostic imaging with voiding cystourethrography and ultrasonography. In this chapter are highlighted some data specially related to NLUTD. Some tests developed for the diagnosis of neurologic dysfunction are considered specifically; the bethanechol supersensitivity test, and the ice water or bladder cooling test. Neurophysiologic studies are discussed in the chapter "Clinical Neurophysiological testing", and only some data for NLUTD is given here.

1. HISTORY

The general history aims at gathering information on the neurological and congenital abnormalities, previous urinary complications or treatments. The use of medication with known or possible effects on the LUT, menstrual, sexual and bowel function, and obstetric history are also important. Hereditary or familial risk factors, metabolic diseases and other must be known. Lifestyle factors such as smoking, alcohol, or addictive drug use should be assessed as well as an evaluation of Quality of Life. Patients with a spinal cord lesion above Th6 may develop autonomic dysreflexia, so a history of severe headaches should be explored.

The signs and symptoms that bring the patient to consultation must be documented. Symptoms related to storage and voiding, continence and /or retention, as well as onset and nature of the NLUTD (acute or insidious) should be determined. If appropriate this information should be compared with the patient's condition before the NLUTD developed. Bladder sensation and mode and type of voiding (catheterization) should be considered. Warning signs and symptoms that warrant early further investigation include; fever, pain, hematuria, catheterization problems, clinical infections and signs of autonomic dysreflexia. Individuals with NLUTD may not be accurate at determining whether they have a UTI based on their symptoms [3]. UTI management is not standardised and clinical practice suffers from a weak evidence base [4].

A urinary diary can be used to capture information on the number of voids (frequency and nocturia), the sensation at each void, volumes voided, incontinence, and volume/ time of fluid intake. Little information is available on optimal diary duration in NLUTD, considering information captured balanced against

inconvenience to the patient [5]. Nonetheless, such diaries deliver useful assessment for evaluating treatment outcomes [6].

2. PHYSICAL EXAMINATION

A general impression of patient's physical and mental possibilities is relevant to the choice of investigations and treatment. Severely impaired mobility, extreme spasticity, severe mental disorder or general weakness are all important in this respect. The physical examination evaluates the lower abdomen, external genital organs and perineal skin. Palpation per vagina or per rectum is done in search of pelvic organ descent, or cervix-uterus/ prostate disease. The strength of the pelvic floor muscles should be assessed. Cardiovascular function should be considered. Patients with very high neurological lesions may suffer from a significant drop in blood pressure when changing position.

Specific examination of the lumbo-sacral innervation includes: sensation of fine touch and pin-prick in the different perineal dermatomes (**figure 1 and 2**), evaluation of bulbocavernosus/ anal/ cremaster reflexes, tone of anal sphincter and voluntary contraction of the anal sphincter / pelvic floor muscles. Clinical neurological findings correlate well with NLUTD in some types of neuropathy such as single level traumatic spinal cord lesions [7] but less in other types like meningomyelocoele or combined traumatic spinal cord lesions [8,9]. Urinary symptoms and pathological urodynamic findings increase along with the degree of motor function impairment in infantile cerebral palsy [10].

3. URODYNAMIC TESTS

Urodynamic techniques evaluate multiple functional parameters in NLUTD [11]. The International Urodynamic Basic Spinal Cord Injury (SCI) Data Set sets out data to be included in the urodynamic evaluation of patients with spinal cord injury. Variables included are; bladder sensation during filling cystometry, detrusor function and compliance during filling cystometry, detrusor function during voiding, detrusor leak point pressure, maximum detrusor pressure, cystometric bladder capacity and post-void residual [12].

Often, the nature of NLUTD is impossible to anticipate from clinical assessment alone, exemplified by CNS tumours in children [13]. Likewise, severity of NLUTD does not necessarily correspond with severity of neurological lesion.

a) Electromyography (EMG) during cystogram

The basis of EMG has long been a question of debate [13a]. Sundin and Petersen [14] used cystometry (EMG) investigation in NLUTD for patients with an active detrusor contraction associated with

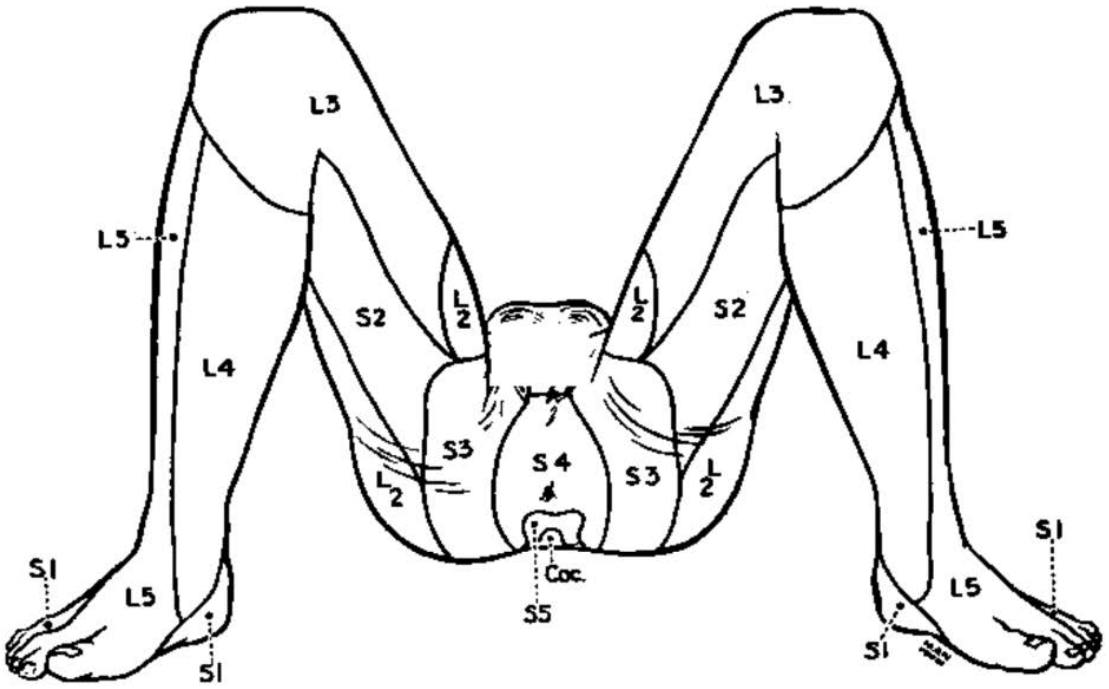


Figure 1: Dermatomes of spinal cord levels L2-S4

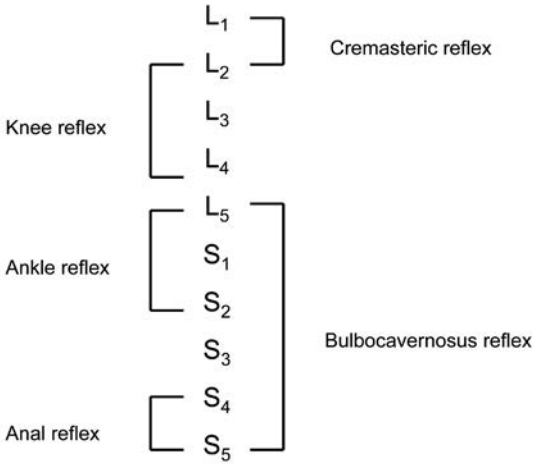


Figure 2: Urogenital and other reflexes in lower spinal cord

impaired bladder emptying. A voluntary control of external urethral sphincter relaxation was found in most of the healthy volunteers, and cystometry-EMG gave reliable information on DSD in patients. Perkash [15] found rhythmic detrusor contractions on cystomanometry with associated marked increase in EMG activity on attempted voiding to be relevant characteristics of patients with DSD. Rodriquez et al. [16] used EMG-gas cystometrogram to select SCI patients for removal of a Foley catheter. Important factors governing success were the amplitude of the detrusor contraction, the presence of detrusor-sphincter synergy and the presence of a flaccid sphincter. Mayo and Kiviat [17] used multichannel urodynamic studies in patients with incomplete bladder emptying secondary to suprasacral spinal cord lesions. They found that bladder pressure and sphincter EMG measurement during voiding, combined with fluoroscopy, are ideal methods to identify the factors responsible for incomplete emptying in problem cases. Perlow and Diokno [18] and Koyanagi et al. [19] found cystometry-EMG informative in SCI patients.

Blaivas et al. [20] described three types of dyssynergia. Type 1 had a crescendo increase in EMG activity that reached a maximum at the peak of the detrusor contraction, type 2 had clonic sphincter contractions interspersed throughout the detrusor contraction and type 3 was characterized by a sustained sphincter contraction that coincided with the detrusor contraction. There was no correlation between the clinical neurologic level and the type of dyssynergia. In DSD, Rudy et al. observed clinically that increases in EMG activity and external urethral sphincter pressure were associated clearly with a positive slope of the intravesical pressure trace, whereas decreases in both parameters were associated with a negative slope [21].

Simultaneous recording of intravesical pressure, sphincter electromyography and uroflowmetry was compared by Aoki et al. [22] with cystometry EMG. They found some influence of the catheter in the urethra. Micturition pressure and opening pressure were larger with cystometry EMG, and incidence of DSD was greater. The authors also found that the Credé manoeuvre exaggerated the DSD. Urodynamics with EMG permitted Kirby [23] to differentiate between patients with pelvic nerve injury, distal autonomic neuropathy, progressive autonomic failure - multiple system atrophy, and idiopathic Parkinson's disease. This influenced the selection of patients for transurethral surgery. Pavlakis et al. [24] studied cystometry concomitant with perineal floor and rectus abdominis EMG and were able to improve the recognition of intravesical pressure elevation owing to voluntary contraction of the abdominal musculature. EAS motor unit potential (MUP) analysis and EMG cystometry were used to differentiate multiple system atrophy (MSA) from Parkinson's disease in the first five years after disease onset. It showed that involvement of Onuf's nucleus in MSA is time-dependent; before the fifth year of illness, the prevalence of neurogenic change does not seem to be high, so a negative result cannot exclude the diagnosis of MSA [25]. Rapidi et al. used combined urodynamic and electrophysiological study of diabetic cystopathy [26].

b) Filling parameters

The importance of detrusor pressure has been acknowledged for many years. Filling rate is important in NLUTD, and slow filling is recommended by the International Continence Society to minimise artefactually affecting compliance [27].

Bruschini et al. [28] undertook clinical, urodynamic and imaging evaluation of the upper and lower urinary tract in inadequately managed myelomeningocele patients. The urodynamic data correlated with the status of the upper urinary tract (UUT). The cystometry showed detrusor overactivity (DO), poor compliance, increased bladder capacity and normal cystometry in 48, 49, 2 and 1% of the patients, respectively. Detrusor leak point pressure (DLPP) over 40 cm H2O was associated with UUT damage. Patients with decrease of functional bladder capacity (FBC) had more renal scars than their counterparts. Incomplete SCI patients with neurogenic DO should be evaluated with the same caution as complete SCI patients, as there can be little difference in cystometric capacity and leak point pressure between complete and incomplete spinal cord injury patients [29].

The importance of urodynamic tests for diagnosis and follow up was demonstrated in the study by Abrahamsson et al. [30] on urodynamic changes with untethering in myelomeningocoele children. After untethering, 35% experienced improved bladder function and 5% deteriorated. All of the patients who deteriorated before untethering improved afterward,

and 90% of those who were stable preoperatively continued to be stable postoperatively. Regular evaluation of bladder function in children with myelomeningocele is recommended. Kang et al. [31] used urodynamic tests to determine prognostic factors affecting urological outcome after untethering surgery for lumbosacral lipoma.

Perkash and Friedland [32] found simultaneous transrectal ultrasonography helpful. They recommended not to irritate the bladder when introducing the urodynamic catheter, and to examine the entire curve of the CMG, not simply the initial rise [33].

c) Filling technique

In SCI patients with neurogenic LUT dysfunction, Ko et al. [34] determined whether cystometry performed by filling using diuretics (FMCG) reveals different findings compared with conventional CMG. Significant differences between the two techniques were found in pressures and compliance in neurogenic DO, but not in hyporeflexic or areflexic bladders. Natural filling by the production of urine can change the results of cystometry considerably, and should be considered when performing urodynamic investigations and interpreting the results.

De Gennaro et al. [35] performed continuous urodynamic monitoring over six hours in children and compared this with standard urodynamics. They found continuous monitoring feasible, permitting a better diagnosis than standard cystometry in some cases. Zermann et al. [36] investigated the diagnostic value of natural fill cystometry (NFC) in children with neurologic bladder in comparison to conventional videocystometry. In 45%, NFC detected additional findings. The extra value of ambulatory urodynamics as compared to conventional urodynamics in spinal cord injury patients was investigated by Martens et al. They concluded that ambulatory urodynamics do not seem necessary for diagnosis and risk assessment in SCI patients suspected for DO when conventional urodynamics are done properly [37].

d) The outlet during voiding

Pressure-flow study can demonstrate an obstructive pattern (high pressure voiding) in neurologic patients due to urethral relaxation failure [38,39]. Videourodynamics (VUDS) offers visualisation of bladder neck and urethral sphincter activity during filling and voiding [40,41]. Accordingly, VUDS is a test that can determine the site of obstruction. Zerin et al. [42] found that the urographic position of the bladder neck in relation to the pubic symphysis was correlated with lower motor neuron (LMN) denervation of the urethral sphincter as detected with electromyography in infants and children with myelodysplasia. They concluded that, although not as precise as urodynamic testing, significant descent of the bladder neck is a reliable urographic finding of complete LMN denervation of the external urethral sphincter in infants and children with myelodysplasia. In men with SCI, some cystometric variables and detrusor overactivity may remain consistent over sequential studies [43].

e) Bladder sensation

In a large cohort study it was shown that impaired perception of bladder filling during CMG is a sign of neuropathy [44]. Nonetheless, despite spinal abnormality, patients can experience bladder filling sensation, signifying the presence of afferent pathways joining the spinal cord at higher levels. In 52 SCI patients, 26 % of those with a supposed complete lesion had sensation of bladder filling during cystometry [45]. In 41 patients with myelodysplasia the perception of bladder filling was present in a majority [46]. In a study of 26 SCI patients, bladder sensation was reported by 73% of patients in daily life. However, only 41% of patients had analyzable bladder sensation concomitant with detrusor overactivity during ambulatory Urodynamics [47].

Ersoz and Akyuz [48] investigated bladder filling sensation in 73 SCI patients with complete lesions above T11 and below T10 and with incomplete lesions. Bladder filling sensation was present to some degree in all incomplete SCI patients, in 82.4% of the patients with complete lesions below T10, and in 38.9% of the patients with complete lesions above T11. Bladder-filling sensation investigations were reproducible in terms of bladder filling sensation category in 36 SCI patients who had a second CMG. The authors concluded that presence of bladder-filling sensation in many SCI patients reveal the potential for sensation-dependent bladder emptying, especially in the ones with complete lesions below T10 and the ones with incomplete lesions. The safe use of sensation-dependent bladder emptying was shown to be dependent on the urodynamic situation [49].

The amplitude of the first overactive contraction and the maximal detrusor contraction were found to be statistically greater in female patients with multiple sclerosis and neurogenic detrusor overactivity compared to women with idiopathic overactivity. The threshold volume for detrusor overactivity was greater, likely secondary to the elevated post void residual urine volume in the MS patients. In this study using a cut off value of 30 cm H2O for amplitude of the first overactive contraction achieved a positive predictive value of 88% for identifying multiple sclerosis [50].

f) Complications of urodynamic testing

Complications of cystometry include hematuria due to the urethral catheter, the development of oedema in the urinary bladder wall and urinary bladder spasm as a result of catheter irritation. One case report of twist and knot formation in the double lumen urethral catheter after cystometry of a patient with a hypocompliant bladder has been published [51]. Another case report describes bladder rupture during filling cystometry many years after bladder augmentation in a girl with meningomyelocoele [52].

Symptomatic urinary tract infections after cystometry are not infrequent and antibiotic prophylaxis has been advocated [53]. Randomised controlled trials (RCTs) comparing effectiveness of prophylactic antibiotics with placebo or nothing in reducing bacteriologically proven UTI after invasive cystometry for all patients, including NLUTD [54]. The use of prophylactic antibiotics in urodynamics reduced the risk of significant bacteriuria.

Conclusions

- **Findings of Urodynamic tests can be difficult to anticipate from clinical assessment alone in NLUTD (LOE 2).**
- **A combination with EMG and /or imaging adds to the diagnostic possibilities (LOE 2).**
- **Filling rate can influence the outcome of several urodynamic parameters (LOE 2).**
- **Pressure development in the bladder is one of the important parameters to be studied and high leak point pressure is a risk factor for renal deterioration (LOE 2).**
- **Sensation of filling may be preserved despite spinal abnormality (LOE 2).**
- **Complications of urodynamic testing are rare, but antibiotic prophylaxis can be advocated (LOE 2).**

Recommendations

- **Urodynamic tests should selectively be employed to supplement clinical assessment in determining management in NLUTD.**
- **Methods of Urodynamic testing in NLUTD should follow International Continence Society recommendations.**

4. SPECIAL TESTS

a) Bladder-cooling reflex; the ice water test (IWT)

The ice water test (IWT) is a C-fiber mediated reflex, first described as a way to differentiate upper from lower motor neuron lesions. It is based on the principle that mucosal temperature receptors can elicit a spinal reflex contraction of the detrusor, a reflex that is normally inhibited by supraspinal centers. An upper motor neuron lesion interrupts these inhibitory pathways, resulting in manifestation of the reflex, whereas a lower motor neuron lesion does not. A positive test should therefore theoretically occur in patients with upper motor neuron lesions, whereas those with lower motor neuron lesions and neurologically normal patients should have a negative test. Simultaneous measurement of intravesical pressure with cold fluid instillation enables evaluation of the response. Patients without neurogenic disease have a greater perception of cold during the IWT than neurogenic patients; this must be considered when evaluating test results [55]. The bladder cooling reflex was blocked in 16 out of 17 neurogenic patients when 30 mg intravesical oxybutinin was instilled [56].

There is a significant correlation between a positive IWT with abnormal sensation of bladder filling and inability to inhibit micturition voluntarily. A negative IWT also corresponded with the occurrence of phasic detrusor contractions during cystometry. The IWT may be useful for functional subdivision of overactive bladders. In patients with voiding dysfunction in the absence of LUT inflammation, a positive test is an indicator of a silent or overt neurological disorder. Geirsson [57] reported positive or a false negative IWT in a large cohort study. Geirsson and Fall [58] used the IWT in patients suspected of DSD (cystometry and needle EMG). A positive test with a high detrusor pressure was stated to indicate DSD, whereas the contrary applies to the negative test. All patients who responded to cold stimulation with detrusor contraction but without fluid leakage (called positive non-leakage IWT), manifested DSD on EMG. The authors concluded that the simpler IWT could substitute for a needle EMG study.

Ishigooka et al. [53] evaluated urinary bladder sensation to ice water instillation in patients with diabetes mellitus. There was no apparent relationship between prevalence of peripheral neuropathy and that of negative sensation of IWT. Impairment of ice water perception was less frequent than that of mechanoreceptor sensation in patients with diabetic cystopathy.

Ronzoni et al. [60] studied the IWT in 148 patients with neurologic bladder dysfunction resulting from a traumatic lesion and in 130 patients with neurologic bladder dysfunction and multiple pathogenic disorders. IWT was positive in 95% of patients affected by complete and in 86% of patients with incomplete medullary lesions. The IWT in patients with lower motor neuron medullary lesions was always negative. The test was used diagnostically in patients with lower motor neuron lesions. In those with upper motor lesions it was used as a rehabilitation method during the medullary-shock phase to accelerate the appearance of the micturition reflex. In 9% of patients it was used to induce micturition during cystography. The authors consider IWT as a useful complement to urodynamic examinations in patients with neurological bladder disease.

Chancellor et al. [61] determined the clinical utility of IWT during urodynamic evaluation in SCI patients and found that it did not contribute to their management because of the insensitivity and non specificity. Autonomic dysreflexia can occur during evaluation.

Repeating the IWT has been shown to increase its positivity [62]. Combining the IWT and electrical perception threshold (EPT) testing will reinforce the results of both tests and can indicate more clearly the possibility of an unsuspected neurologic pathologic

finding in patients with idiopathic DO. In multiple sclerosis it may have pathophysiological value, indicating a spinal rather than cerebral mechanism of overactive bladder, and diagnostic value, indicating multifocal demyelination [63].

Conclusions:

- **The literature results from IWT show value in the diagnosis of NLUTD and in the differentiation between reflexic and areflexic neurologic bladder (LOE 2).**

Recommendation:

- **The ice water test is an optional test which should be interpreted in the context of all data from the diagnostic evaluation (B).**

b) Bethanechol supersensitivity test (BST)

Bethanechol is a muscarinic agonist which may improve bladder emptying in some non neurologic patients, and correspondingly increase bladder sensitivity [64]. The BST was developed by Lapides et al. in 1962 [65] to try to distinguish between a neurologic and a myogenic etiology in an acontractile bladder. It is based on the observation that after an organ is deprived of its nerve supply, it develops hypersensitivity to the normal excitatory neurotransmitters. A neurologically intact bladder should have a pressure increase of less than 15 cm H2O above the control value, whereas a denervated bladder shows a response greater than 15 cm H2O. The clinical utility has not been studied in detail recently.

The test is considered unreliable by some [66]. Penders [67] considered the test reliable when the indications are good (large capacity, hypotonic bladder, clinical suspicion of lower neuron lesion) and when the interpretation is based on a right understanding of its mechanism. Pavlakis et al. [68] suggest that the BST is more sensitive and more specific than perineal floor electromyography in corroborating bladder neuropathy. Sidi et al. [69] studied patients with neurologic or non-neurologic detrusor areflexia with the BST, EMG of the urethral rhabdosphincter and bulbocavernosus reflex latency and found the sensitivity of these tests in detecting neurologic mechanisms to be 90, 87.5 and 78.1%, and the specificity 96, 76 and 80%, respectively. When all three tests were performed together, the combined accuracy approached 100 %. They conclude that these combined tests are useful in the diagnosis of patients with equivocal bladder neurologic conditions and in those with subtle neurological lesions. Denervation supersensitivity to bethanechol was demonstrated in acute idiopathic autonomic neuropathy [70].

Wheeler et al. [71] found the positive BST not diagnostic of neurologic detrusor areflexia because of the many variables that can influence the test. In a later study, the same group [72] suggested that flow rate, surface electromyography, and bethanechol supersensitivity test cannot help differentiate neurologic from non-neurologic detrusor failure. Although no test can accurately differentiate neurologic from non-neurologic female urinary retention, careful neurourologic evaluation will help guide to more appropriate management.

Conclusion:

- **The literature on the value of the bethanechol test for the diagnosis of neurologic pathology is contradictory. The test may contribute to overall evaluation of neurologic LUT dysfunction. (LOE 2)**

Recommendation:

- **The bethanechol supersensitivity test has limitations, and result should be interpreted in conjunction with established diagnostic results. (B)**

c) Electrodiagnostic tests

1. EMG of the Urethral Sphincter

EMG of the urethral sphincter has been used for decades in the diagnosis of NLUTD; its value in practice remains uncertain. Use of needle or surface electrodes is debated. Urethral concentric needle electrodes were found to be superior to surface patch electrodes for evaluating relaxation of the muscle during voiding in neurologically intact women [73]. Nordling and Meyhoff [74] used cystometry in combination with urethral and anal sphincter EMG in patients with suspected NLUTD and found anal sphincter EMG to be highly unreliable. Koyanagi et al. [75] also found discordant activities between the anal and the external urethral sphincters in 39 % of male patients with SCI. The degree of bladder dysfunction was related more to the degree of dyssynergia of the urethral than the anal sphincter. Nevertheless, Podnar states that anal sphincter EMG is the most useful diagnostic test, particularly for focal sacral lesions, and atypical Parkinsonism [76]. Fowler et al. [77] introduced a technique of recording EMG activity of striated muscle in the urethral sphincter by using a concentric needle electrode and an oscilloscope with a delay line and trigger. Individual motor units were isolated and measured. Vodusek also studied individual motor units [78]. Both conclude that quantitative EMG may be a helpful technique in the investigation of patients with disorders of micturition.

Ziemann and Reimers [79] found the sphincter EMG the most sensitive technique in the diagnosis of chronic pudendal lesions. However, pure afferent lesions cannot be detected by the sphincter EMG. In this case, the BCR, using unilateral stimulation of the dorsal nerves of the penis, provides the opportunity to distinguish between afferent and efferent lesions of the sacral innervation. Fowler [80] concluded that sphincter electromyography (EMG) has is valuable for identifying patients with Parkinsonism who have multiple system atrophy.

Tests which examine aspects of nerve conduction velocity have proved to be of lesser value both because such investigations test conduction of nerve fibres rather than levels of innervation. Furthermore, they examine large myelinated fibre conduction, rather than the unmyelinated fibres which comprise the autonomic innervation. Sphincter EMG is a diagnostic test of Fowler's syndrome in young women with urinary retention [81]. Sphincter EMG can be used in gauging timing of stimulation for suppressing DO [82].

De E J et al. [83] found a significant disagreement between needle EMG and voiding cystourethrogram (VCUG) for diagnosis of DSD. A combination of EMG and VCUG may identify more cases of DSD than either modality alone and underscores the need for more strict criteria when defining this entity from a urodynamic standpoint.

Anal sphincter EMG as well as external urethral sphincter EMG can be used to detect the onset of detrusor contractions in patients with both neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD) opening a door for the use of triggered devices to inhibit unwanted contractions through continuous electrical stimulation of sensory nerves [84, 85]. Light et al. [86] found in patients with detrusor areflexia and a high spinal cord lesion, EMG of the pelvic floor muscles is the neurophysiological test which best predicts detrusor contractility.

EMG of the urethral sphincter has been used to investigate retention in multiple-system atrophy [87], LUT function in Machado-Joseph disease [88], the impact of pregnancy and delivery on vesico-urethral disorders in patients with multiple sclerosis [89] and children with cerebral palsy [90].

2. EMG of Detrusor Muscle

Detrusor EMG has not been widely studied in neurologic patients. La Joie et al. [91] recorded simultaneous EMG recordings from the bladder detrusor muscle and the inferior rectus abdominis muscle in 6 normal subjects, in 4 patients with LMN bladder disease and in 2 patients with an UMN type of bladder lesion. The bladder electrodes did not appear to record muscle activity remote from the abdominal muscles so that any increased detrusor electrical activity with abdominal contraction must have some other explanation. Kaplan and Nanninga [92] analysed detrusor EMG in upper motor neuron type NLUTD. Kinder et al. did not advocate detrusor EMG [93]. Recent data are lacking and so the technique cannot be considered a standard diagnostic test.

Conclusion

- **Sphincter EMG can be valuable in the diagnosis of patients with neurologic bladder dysfunction (LOE 2).**
- **Detrusor EMG is not established as a diagnostic test.**

Recommendation:

- **EMG of the urethral sphincter can be considered as a diagnostic method in patients with neurologic LUT dysfunction and neurologic urinary incontinence (B B).**

3. Dynamic Bulbocavernosus Reflex (BCR).

Walter et al. [94] studied dynamic BCR during micturition induced by using periodic dorsal penile nerve stimulation; the evoked reflex response was recorded with an anal sphincter pressure sensing balloon. Results indicate that an enhanced BCR is a factor contributing to increased urethral resistance during micturition.

Kaiho et al. [95] recorded the evoked potential of the BCR (BCR-EP) with a concentric needle electrode at the periurethral striated muscle. They found was BCR-EP suppressed during voluntary voiding in normal subjects, but it was insufficiently suppressed in the patients with NLUTD. It was suggested that the measurement of BCR-EP could distinguish involuntary voiding caused by pathological urethral sphincter relaxation from voluntary voiding. The same group [96] investigated the change of sacral reflex activity of the striated urethral sphincter in the urine storage phase with BCR-EP in normal male subjects and male patients with NLUTD due to suprasacral spinal cord injury. Sacral reflex activity was accelerated by bladder filling in both the normal subjects and SCI patients, particularly in the latter. In addition to the conventional evaluation of the integrity of sacral reflex arc by BCR examination, the observation of changes of BCR affected by bladder filling may provide information on the continuity of sacral segment and supraspinal micturition center. Niu et al. showed that in 8% of patients with SCI and in 70% of patients with peripheral nerve lesions the BCR was abnormal [97].

4. Motor Evoked Potentials

Motor evoked potentials (MEP) has been used to assess neurogenic lesions affecting the urethral compressive musculature with simultaneous recording of evoked pressure curves [98]. MEP recording is an accurate and easily applicable test for the diagnosis of lumbosacral spinal cord lesions [99].

5. Nerve Conduction Studies

In patients with diabetes mellitus, conduction velocities are decreased [100]. Vereecken et al. [101] found urethral and anal responses produced by electrical stimulation of penis, bladder neck and anus were delayed and the duration reduced. Carbone et al. [102] assessed the effect of urinary bladder filling on the excitability of somatic spinal motor neurones in patients affected by neurogenic and non-neurogenic DO and proposed that H-reflex modulation may be considered a tool in the differential diagnosis of voiding dysfunctions.

6. Somatosensory Evoked Potentials

In the committee's literature search, no recent publications were found on somatosensory evoked potentials (SSEP). Badr et al. [103] described techniques of recording evoked potentials in humans in response to stimulation of the urinary bladder. Galloway et al. [104] described a method of sacral evoked response to measure the integrity and function of the lower sacral segments by stimulation at the urethral and anal sphincters.

Mochida et al. [105] studied evoked spinal cord potentials (ESCP) in surgical patients with cervical myelopathy. The presence of NLUTD was closely correlated with severe limb symptoms and relatively slow ESCP velocity. However, for 47% of the patients with urinary complaints, findings of urodynamic examinations were negative; these patients may have had pathologic or psychosomatic factors other than neurogenic bladder due to cervical myelopathy.

Curt et al. [106] studied the significance of SSEP recordings in predicting the recovery of bladder function in acute, traumatic spinal cord injury (SCI). They found a good correlation with the recovery of the external urethral sphincter function, but not with the urodynamic impairment. SSEP in response to stimulation of the tibial nerve have been studied in patients with hyperactive urinary bladder to clarify their role in prognosis of tibial neuromodulation efficacy [107].

7. Afferent Nerve Recording on Sacral Roots

Afferent nerve activity from the sacral dermatome, bladder and rectum can be recorded using cuff electrodes placed on the extradural S3 sacral root in humans, but improvements in recording quality and sophisticated signal processing methods are needed for chronic application. The applicability in clinical practice is very limited [108,109].

Conclusions:

- **Detrusor EMG, BCR-EP and MEP are techniques of experimental interest, but with insufficient basis for use as standard clinical diagnostic tests.**
- **There are some arguments that nerve conduction studies can be useful in the further differentiation of the nerve deficits in cases of neurologic pathology of the bladder (C).**
- **Direct measurement of sacral afferent nerve activity is still experimental**.

Recommendation:

- **Somatosensory evoked potentials can be of use in the further diagnosis of nervous deficits related to LUT dysfunction (C).**

8) Electrosensation in the LUT

Measurement of the sensory threshold of the LUT towards electrical stimulation was attempted as early as 1899 [110]. After re-introduction of the technique by Markland et al. [111] several authors have studied its value in neurologic bladder dysfunction. Kieswetter [112], and Powell and Feneley [113] demonstrated abnormal electrosensation in patients with NLUTD. Frimodt- Möller [114] described pathological electrosensation in patients with Parkinson's disease, multiple sclerosis and meningomyelocoele. He also found abnormal electrosensation in half of patients with diabetes and generalized sensory neuropathy, but only in 10% of the diabetic patients with a neurologic bladder. Electro sensation was present in many meningomyelocoele patients with absent skin sensation and absent reflexes, and in many patients with suspected complete spinal cord injury on clinical evaluation [44, 46].

Wyndaele [115] determined the threshold of sensitivity to electrical stimulation in several parts of the LUT in 436 consecutive patients. In the groups with different patterns of disturbed sensation a higher incidence of neuropathy was found than in the group with a normal sensation. Further neurological investigation revealed abnormal innervation in 29% of patients who lacked electrosensitivity in one or more parts of the LUT but who had no previous evidence of neuropathy.

Standardization is necessary to develop the technique and achieve reproducible results [116]. While it is a constructive concept to be able to determine threshold of different fibre types selectively [117], so far no such fibre selectivity has been demonstrated in the bladder [118]. In the committee's literature search, no recent publications were found.

Conclusion:

- **To determine the electrosensation in the LUT might be valuable to evaluate the afferent innervation in cases of neurologic bladder.**
- **Absent electrosensitivity might guide further neurologic tests in patients with LUT dysfunction (LOE 2).**
- **Further development and standardisation is needed for the use of electrosensation test to become established as a clinical test.**

9. Sympathetic Skin Response

Schurch et al. [119] assessed the descending sympathetic spinal tract and correlated these findings with bladder neck function in SCI patients. Evidence was presented that the integrity of the descending sympathetic spinal tract is necessary for a synergic function of the vesicourethral complex and that sympathetic skin responses (SSR) are of value in the diagnosis of bladder neck dyssynergia. SSR's

are absent in case of bladder neck dyssynergia. For lesions below the T12 level, other investigative methods to exclude bladder neck dyssynergia are necessary. Rodic et al. [120] found that recording the perineal SSR in addition to that of the hand and foot represents a sensitive diagnostic tool for assessing sympathetic nerve function within the thoracolumbar spinal cord, representing a reliable and accurate diagnostic tool for assessing bladder neck competence and incompetence.

SSR recordings above a spinal lesion level after urethral electrostimulation might provide a useful and technically simple objective diagnostic tool to assess integrity of autonomic (visceral) afferent nerves from the LUT. Somatosensory deficits are not always paralleled by viscerosensory loss and vice versa. SSR may be superior to visceral sensory evoked potentials, which are more difficult to record. The clinical utility needs to be further studied.

Conclusion

- **Sympathetic skin responses may help evaluate the integrity of LUT-related sympathetic function, including bladder neck competence and synergia (LOE 2)**

III. CONSERVATIVE TREATMENT

Therapeutic principles in different patterns of NLUTD depend on the underlying processes: dysfunction of the detrusor, dysfunction of the sphincter or a combination of both. Neurogenic detrusor overactivity leads to reflex-incontinence, detrusor areflexia to incontinence with retention (overflow incontinence). An areflexic (incompetent) sphincter causes neurogenic stress-incontinence, a hyperreflexic (spastic) sphincter overflow-incontinence. Quite often detrusor and sphincter are affected simultaneously by the neurogenic lesions. In most patients the storage problem, leading to incontinence, is associated with an emptying problem; therefore both aspects have to be considered at the same time. Therapy of neurogenic incontinence is primarily a conservative one. Timed bladder emptying, by whatever means, controlled fluid-intake and avoidance of urinary tract infections are the prerequisites for successful treatment.

If incontinence persists, and if operative procedures are not indicated or possible, containment products will be needed. The indwelling catheter remains an option for conservative therapy, and can offer acceptable quality of life outcomes [1] and long-term protection of the upper urinary tract [2, 3]. Most experts regard indwelling catheterisation as being associated with significant problems [4]. While suprapubic catheters are generally preferred over urethral, there is little evidence on which to base practice [5]. Urethral leakage can persist despite continuous drainage with a SPC, so additional steps such as bladder neck closure may need to be considered [6].

1. OVERVIEW ACCORDING TO TYPE OF LESION

a) Supraspinal lesions

In supraspinal lesions, neurogenic DO is mostly combined with normal sphincter function; overactivity incontinence is the main symptom and antimuscarinic therapy together with behavioural treatment is the method of choice, especially in patients with cognitive impairment.

b) Suprasacral lesions

Spinal lesions mostly cause simultaneous dysfunction of the detrusor and the sphincter. In suprasacral lesions, the spinal reflex bladder manifests the combination of DO with an overactive/ dyssynergic sphincter. For these patients, spontaneous reflex voiding may be possible. However, detrusor contractions may inadequate, and detrusor striated sphincter dyssynergia is present, both potentially leading to inefficient voiding. Triggered reflex voiding is recommended only if it is urodynamically safe and reflex incontinence is manageable; accordingly, careful support is needed to achieve adequate symptom control [7] and long-term renal safety [3]. Treatment to lower tone and spasticity of the urethral sphincter can be used to aid emptying, such as sphincterotomy [8], stenting [9] or botulinum toxin injections into the sphincter [10]. Any unit managing patients with SCI should be appropriately set up to manage acute autonomic dysreflexia. Sphincterotomy may help in reducing episodes of autonomic dysreflexia [11a].

The mainstay of treatment in current practice is intermittent catheterization (IC) [12], undertaken by the patient or carer. However, to achieve low pressure LUT urine storage and continence between catheterisations, additional pharmacotherapy may be necessary. If bladder relaxing agents fail or are not tolerable, electrotherapy is an alternative in incomplete lesions: ano-genital electrostimulation (penile, clitoral, vaginal and anal) can inhibit neurogenic detrusor overactivity by stimulating pudendal nerve afferents.

c) Lower motor neuron lesions

For complete conus lesions, areflexia of the detrusor with areflexia of the sphincter is characteristic. Sphincter incompetence causes neurogenic urinary stress incontinence and may be combined with dribbling incontinence if adequate emptying is not achieved. Conservative treatment to achieve continence is often unsuccessful. Bladder expression is potentially dangerous, and pharmacotherapy is not helpful in this situation. Accordingly, appliances and condom catheters are often necessary, and consideration of suitability of surgery may be needed [10].

Areflexia of the detrusor combined with overactivity of the sphincter may occur in epiconal lesions. This pattern may also result from decompensation of a neurogenic overactive bladder after chronic urinary retention. With this combination, overflow incontinence can be controlled by intermittent catheterization- mostly without adjunctive additional pharmacotherapy. If intermittent catheterization is not possible, an indwelling catheter, preferable suprapubic, may be needed. If overactivity of the detrusor is combined with areflexia of the sphincter, reflex incontinence is combined with neurogenic stress incontinence. This pattern is sometimes found in epiconal lesions, especially in myelomeningoceles. Bladder relaxant agents may diminish neurogenic detrusor overactivity. In incomplete lesions, electrical stimulation of the pelvic floor musculature may improve sphincter function. However, with this type of neurogenic LUT dysfunction, conservative treatment alone is generally unable to restore continence; therefore either appliances or operative treatment must be considered.

Cauda equina and peripheral nerve lesions are often incomplete. Hypoactivity or areflexia of the detrusor may be combined with a normally functioning external striated sphincter, a combination which can be seen after intrapelvic surgery, when the pudendal nerves remain intact. Conversely, pudendal nerve lesions in which the pelvic plexus remains intact, a combination of a normally functioning detrusor with a hypo- or areflexic external sphincter may be present. If there is DO, pharmacotherapy is the first choice treatment. For some lesions, intravesical electrotherapy has been reported to increase detrusor contractility [13]. Injection of botulinum toxin in the striated sphincter has created a potential new treatment option, but more research is needed.

2. SPECIFIC INTERVENTIONS

During the acute period of spinal or cerebral shock, bladder management comprises proper bladder drainage. For the post shock period, or for non-acute neurogenic dysfunctions, several conservative treatments are in use [14, 15]:

a) Behavioral therapy

1. Triggered Reflex Voiding

"Automatic" or "reflex" bladder behavior can occur following recovery from spinal shock in spinal cord lesions not involving the conus or cauda equina. This can be used as a means to empty the bladder, using voluntary approaches to provoking a bladder contraction by stimulation of the sacral and lumbar dermatomes. The most commonly used manoeuvres are suprapubic "tapping", thigh scratching and anal/rectal manipulation. A quadriplegic patient who is unable to perform ISC may choose this option because it gives more independence. If the efferent branches of the pelvic nerve are impaired, reflex emptying is much less complete, and considerable voluntary straining is additionally required to empty the bladder to a satisfactory degree. Integrity of the sacral reflexes predicts the potential to use this approach. The aims of regular triggered reflex voiding are to achieve "balanced voiding", decreasing incontinence but ensuring safe (low pressure) urodynamic function. The possibility of collecting the urine in a socially acceptable way and a reasonable time period for bladder emptying are needed. Frequency of emptying has to be specified for each patient. Whether bladder outlet obstruction is present also has to be considered; this is not often considered in published literature. To improve emptying, control autonomic dysreflexia related to bladder filling and contraction, and avoid upper tract damage, alpha-blockers or botulinum toxin sphincteric injections should be tried; sphincterotomy and/or bladder neck incision may sometimes be needed. Regular follow-up is essential, though the frequency of check-up appointments is not validated.

Triggered voiding should not be recommended as first line management; in current practice, IC is the accepted standard for continence, upper urinary tract protection and improvement of quality of life.

Conclusions

- **Reflex voiding is based on an unphysiological sacral reflex. It is potentially dangerous and has a limited role in managing the reflex bladder (LOE3).**
- **Costs of appliances and of adjuvant therapies (pharmacotherapy, surgery, urethral prosthesis etc) have to be evaluated (LOE 2).**
- **Treatment of co-existing sphincteric spasticity/ bladder neck obstruction and co-morbidity should be taken into consideration (LOE 1 and 2)**

Recommendations

- **Triggered voiding could be recommended only for patients whose situation has proven to be urodynamically safe and stable, and who can manage reflex incontinence.**
- **Triggered voiding can be considered for patients after sphincterotomy and/or bladder neck incision and/or alpha-blockers and/or intrasphincteric botulinum toxin injections, in order to improve spontaneous reflex voiding (C).**
- **Reflex voiding can be recommended only if an adequate follow-up is guaranteed (C)**
- **Any unit managing patients with SCI should be appropriately set up to manage acute autonomic dysreflexia.**

2. Bladder Expression (Crédé and Valsalva)

Bladder expression comprises various techniques aimed at increasing intravesical pressure in order

to facilitate bladder emptying. The most commonly used are the Valsalva (abdominal straining) and the Crédé (manual compression of the lower abdomen). It has been recommended for a long time for patients with a combination of an areflexic detrusor with an areflexic sphincter or with an incompetent urethral closure mechanism of other origin (e.g. after sphincterotomy). Difficulties in emptying the bladder by expression may be due to an inability to open the bladder neck. However, especially in men, these techniques may induce a functional obstruction at the level of the striated external sphincter despite complete paralysis of the musculature of the pelvic floor. Over time, a high proportion of patients manifest problems such as reflux into the prostate and seminal vesicles, or epididymo-orchitis. Moreover, the high pressures could cause reflux into the upper urinary tract. The stress to the pelvic floor with these techniques several times a day also can make incontinence worse, and causes additional genital-rectal prolapse and haemorrhoids.

Adjunctive therapy to decrease outflow assistance includes alpha-blockers, sphincterotomy or botulinum toxin injections. If effective, they usually cause or increase neurogenic urinary stress incontinence. Expression of the bladder for voiding by Crédé and Valsalva can be effective. To empty the bladder, the pressures measured may be high and potentially dangerous for the upper urinary tract. Bladder expression is often not safe. Sphincter-hyperreflexia and detrusor-sphincter dyssynergia are contra-indications for bladder expression.

Conclusions

- **Bladder expression by Valsalva or Credé is potentially hazardous for the urinary tract due to functional obstruction at the level of the pelvic floor (LOE 3).**
- **It is contraindicated if it creates a high intravesical pressure, particularly in association with reflux into the ureters or seminal vesicles. Hernias, pelvic organ prolapse, haemorrhoids and urethral pathology (strictures) are relative contraindications (LOE 3).**
- **Bladder expression may adversely affect a flaccid pelvic floor, potentially exacerbating incontinence (LOE 3).**
- **Alpha-blockers, sphincterotomy or botulinum toxin may reduce the outflow resistance, but may also induce or increase urinary stress incontinence (LOE 3).**

Recommendations

- **Before recommending bladder expression by Valsalva or Credé, it must be proven that the LUT is urodynamically safe. (B)**
- **Exclude contraindications, such as vesicoureteric reflux, pelvic organ prolapse, hernias, urethral pathology and symptomatic UTIs before recommending this type of bladder emptying. (B)**
- **In general, bladder expression should be replaced by CIC in most patients with neurogenic bladder-sphincter dysfunction. (B)**
- **Adjunctive therapy of outflow obstruction can be considered. (B).**

3. Toileting Assistance: Timed Voiding, Habit Retraining, Prompted Voiding.

See also the chapters on adult conservative treatment and frail elderly.

Adaptation of the drinking and voiding regimen requires education and can be implemented by the patient and/or caregivers. The aim of the behavioural process in adults is to re-establish the control of urinary continence. The goals include correcting faulty habit patterns of frequent urination, improving ability to control bladder urgency, prolonging voiding intervals, increasing bladder capacity, reducing incontinent episodes, and building a patient's confidence in controlling his/her bladder. In dependent patients all these techniques can be proposed and tried, provided that caregivers (physiotherapist, nurse, family members, etc.) are supportive.

Timed voiding is characterized by a fixed interval between toileting. It is a passive toileting assistance program, initiated and maintained by caregivers. It is considered appropriate for patients who cannot participate in independent toileting. It has been used where incontinence is associated with cognitive and/or motor deficits. Its aim is more to avoid incontinence than to restore a normal bladder function. For neurologic patients it has also been considered as an adjunct to tapping and/or Crédé manoeuvre and/or intermittent catheterisation. Timed voiding can be recommended in management of patients with excessive bladder volumes, exemplified by diabetic patients with impaired bladder filling sensation.

Habit retraining and prompted voiding have to be initiated and maintained by caregivers. They are more suited to patients with brain diseases than spinal cord diseases, and for patients with cognitive and/or motor deficits. The aim of habit retraining is to help patients to avoid incontinence by decreasing voiding intervals. Such program has to be adapted to each patient and needs a specific analysis of voiding patterns to select a good individual schedule for voiding. Such a program is very useful for institutionalised patients. Prompted voiding is used to teach people to initiate their own toileting through requests for help and positive reinforcement from caregivers. There are no specific evaluations on neurologic patients in the literature.

Conclusions

- **Behavioural techniques should be used in conjunction with other therapies (pharmacological treatment, catheterisation) (LOE 2).**
- **When appropriate, toileting assistance should be used to improve continence of neurologic impaired patients (LOE 3).**
- **Prompted voiding may be able to decrease incontinence episodes. Patients likely to benefit from the technique are those with less cognitive impairment and higher dependency (LOE 2/3).**

Recommendations

- **Behavioural techniques are a suitable component of the rehabilitation program for each individual. (C)**
- **There are no guidelines or consensus on suitable intervals for bladder emptying. They should ideally be derived from the voiding diary and other related factors (bladder volume, fluid intake, post-void residual urine volume, urodynamic parameters). (C)**
- **The mental status of a patient must be taken into consideration, and a rehabilitation program realistically tailored to the patient's possibilities. (B/C).**

b) Catheters and appliances

1. Intermittent Catheterization

Intermittent catheterization (IC), including intermittent self-catheterization (ISC), aims to resume normal bladder storage and regularly complete urine evacuation. They avoid some of the complications of indwelling catheterization (IDC). IC can improve incontinence, or make patients with neurogenic bladder continent, if; bladder capacity is sufficient, bladder pressure is kept low, urethral resistance is adequate, and fluid intake is balanced with frequency of catheterization. In children with SCI, IC used with anticholinergic drugs appears to minimise upper urinary tract deterioration, improve continence and decrease infections; safe increase in capacity appears to increase with growth [16, 17]. Post-void residual signifying the need to institute IC remains to be clarified. However, Dromerick et al. [18] (LOE 2) demonstrated in a series of stroke patients that a post-void residual greater than 150ml is an independent risk factor for development of UTI.

Most appropriate technique and catheter depend on individual anatomic, social and economic possibilities [19] (LOE 1). Two main techniques have been adopted, sterile IC (SIC) and clean IC (CIC). The sterile non-touch technique involves the use of sterile materials handled with sterile gloves and forceps. In an intensive care unit, some advocate wearing a mask and a sterile gown as well [20]. De Ridder et al. [21] compared SpeediCath hydrophilic-coated catheters versus uncoated polyvinyl chloride (PVC) catheters, in SCI patients. This 1-year, prospective, open, parallel, comparative, randomised, multi centre study included 123 male patients injured within the preceding 6 months. Primary endpoints were occurrence of symptomatic UTI and hematuria. Secondary endpoints were development of urethral strictures and convenience of use. The results indicate a beneficial effect regarding UTI when using hydrophilic-coated catheters. Bjerklund-Johansen et al. evaluated patient willingness to change and satisfaction with catheters for IC in neurogenic bladder dysfunction. They also compared patient response to conventional catheters and a packaged hydrophilic catheter: LoFric Primo [22]. 409 neurogenic patients were recruited and 378 (283 males, 95 females; mean age 43.5 years) completed a short-term trial. Patient satisfaction was expressed on a Visual Analogue Scale for seven topics covering use and general satisfaction. Differences regarding satisfaction, handling, time spent, and ability to cope with daily life were reported. Kovindah and Madersbacher investigated whether a silicone catheter reused over years for clean IC was safe for men with SCI [23]. Reused silicone catheter appeared to function as well as disposable. However, to reuse urinary catheters, one should consider the increased risk of infection. The authors suggest that for SCI patients in developing countries, CIC with a reusable silicone catheter may be a suitable and safe choice if one cleans and applies it. In the same way, Getliffe performed a systematic Cochrane review summarizing current evidence on the relationship between sterile single-use catheters or clean reused catheters and the incidence of UTIs [24]. 13 trials met the inclusion criteria. There was considerable variation in length of follow-up, definitions of UTI, and numbers of subjects. Attrition was a problem for several studies, and all were underpowered. Several studies were more than 10 years old, and outcome measures were imprecise, making it difficult to draw conclusions on the benefit of one catheterization method over another. They concluded that there are no definitive studies illustrating that incidence of UTIs is affected by sterile single-use or coated catheters compared to clean reused catheters. However the current research base is weak and design issues are significant. Based on the current data, it is not possible to state that one catheter method is better than another and further research is needed (LOE1). Research to evaluate clean vs. sterile PVC catheter use, and hydrophilic vs PVC use (both sterile and reused), is needed.

Frequency of catheterization depends on many factors, e.g. bladder volume, fluid intake, post void residual, and urodynamic parameters (compliance, detrusor pressure). Usually it is recommended to catheterize 4 – 6 times a day during the early stage after spinal cord lesion. Some will need to keep this frequency if IC is the only way of bladder emptying. Others will

catheterize 1 – 3 times a day to check and evacuate residual urine after voiding. To overcome high detrusor pressure, adjunctive therapy with antimuscarinic drugs or other bladder relaxants can be indicated. For those who develop a low compliance bladder, upper tract deterioration or severe incontinence, injection of Botulinum toxin in the bladder wall or surgery, such as bladder augmentation, may be necessary.

If catheterization is begun by patients with recurrent or chronic UTI and urinary retention, the incidence of infection usually decreases. If symptomatic infections occur, improper CIC or misuse should be considered. Chronic infection persists if the cause of the chronicity remains. Treatment of UTI is necessary if the infection becomes symptomatic. Lindehall et al. evaluated the rate of complications associated with catheterization and the risk of urethral lesions in myelomeningocele treated with clean IC for a minimum of 10 years. They found that there were remarkably few problems [25]. The incidence of major urethral lesions did not increase during puberty. Larger catheters seemed to be protective against major lesions [26] (LOE3). In contrast, Chen et al. found that the incidence of urethral strictures increases with a longer follow-up, and bladder stone formation is associated with long-term use of CIC in SCI patients [27] (LOE3).

Oh et al. evaluated health-related quality of life (HRQOL) with IC in neurogenic bladder. They conducted a prospective trial involving 132 patients (81 men and 51 women, mean age 41.8 years, range 18 to 80 years) with SCI [28]. Patients using IC have a reduced quality of life in all health domains, as assessed by the SF-36 (LOE2) [29].

Conclusions

- **IC in the neurogenic bladder is effective and safe in short- and long- term use. (LOE 1)**
- **Complications such as UTI are regularly seen and seem to be related to both the catheterization itself and the pre-existing LUT condition (LOE 2).**
- **Urethral and bladder complications seem to increase in the long- term (LOE 3).**
- **In order to reduce and prevent complications, appropriate materials and correct techniques should be taught and performed (LOE 3).**
- **Adequate frequency of CIC, a non-traumatizing technique and suitable materials are the key factors for a successful outcome (LOE 2).**

Recommendations

- **IC is the first choice treatment for those with inability to empty the bladder adequately and safely in neurogenic voiding dysfunction. It is a valuable tool for achieving continence. (A)**
- **Proper education and teaching are necessary to achieve a good outcome. (B)**
- **To prevent and reduce complications, a non-traumatizing technique (external lubricant or lubricant coated catheters) with adequate frequency of catheterization and complete emptying should be achieved. (B)**
- **Annual follow-up is needed. (B/C)**
- **It is not currently possible to state whether any IC method is advantageous (Grade D) and further research on the topic is strongly recommended.**

2. Indwelling Catheter (IDC)

The Foley catheter was developed in the early 20th century. After the World War I, most SCI and other neurologic patients were treated with indwelling urethral catheterization (IDUC) or suprapubic catheterization (SPC) due to difficulty in voiding or urinary incontinence. While IC is nowadays recommended for neurologic patients, many still choose IDC due to difficulty in performing IC, or persistent leakage between catheterizations. In developing countries, IDC can still be the method of choice for those with urinary retention or incontinence.

IDUC placement requires meticulous technique. More frequent catheter changes may be needed in patients with recurrent UTIs. IDUC can cause various complications, such as; urethral trauma and bleeding, urethritis, bladder stones, cystitis, acute and chronic UTI, bladder neck incompetence, meatus and urethral sphincter erosion, and bladder carcinoma. Fistulas can result from pressure effects, caused by improper catheter size and inadequate securing technique, particularly with long-term use. Therefore many experts advocate removal of an IDUC as soon as possible, and usage of other methods such as IC or SPC. Nowadays the complications of IDC seem less, presumed due to better materials, judicious size selection and a proper technique of securing the catheter. For CIC wet patients, overnight IDUC self-placement seems to decrease risk of febrile episode due to UTI, as compared to CIC alone [30]. In the morning, the catheter was removed, washed with tap water and stored in disinfectant (LOE3).

The study by Pannek (LOE 3) reported an incidence 0.11% for bladder cancer in catheterised SCI individuals (48 out of 43,561 patients), similar to that observed in the general population [31]. However, more than 60% of the patients with SCI initially presented with muscle-infiltrating bladder cancer. Hypothetically, the expression of inducible nitric oxide synthase with IDC [32] might predispose to formation of potentially carcinogenic nitrosamines in the bladder. Hamid et al. [33] did not find bladder cancer on bladder biopsies in patients with SC I and a mean IDC use of 12.1 years.

Routine antibiotic prophylaxis for patients with IDC is not recommended. Attempts at eliminating bacteriuria associated with indwelling or intermittent catheters are generally unsuccessful [34, 35] (LOE 4). For prevention of UTI, general cleanliness and local hygiene should be encouraged. In symptomatic UTI, it is important to consider catheter blockage and problems such as urinary stones. Symptomatic UTIs have to be treated with the most specific, narrowest spectrum antibiotics available for the shortest possible time. Guidelines for selecting antimicrobial agents in SCI patients are similar to guidelines for the treatment of complicated UTIs in the general population. Characteristics of the quinolones make them well suited for treating UTI in SCI patients [36] (LOE 4). Recommendations of the local microbiology department should be sought.

The benefit and risks of SPC are similar to IDUC, including the risk for UTI, stone formation and maintenance cost of catheter and bag. Advantages include: minimized risk of urethral trauma and pain- in neurologically impaired women with even relatively short-term IDUC, urethral destruction is a significant risk. The key disadvantage is that SPC placement requires a minor 'surgical' produce to insert the suprapubic catheter, with potential to injure nearby organs [37]. While most centres favour SPC use, complications are well-recognised and literature is limited. Most publications are old, there are no prospective studies and no RCTs on SPC.

Conclusions:

- **Long-term IDUC use in neurologic patients can predispose to complications. (LOE 2)**
- **Catheters should have as large a lumen as possible to maximise time to blockage by encrustation, and 5-10 ml self-retaining balloons to minimise the pressure effect on the bladder neck. (LOE 4)**
- **Closed drainage systems are associated with lower infection risk. (LOE 1)**
- **Frequency of change largely depends on time to blockage, which is influenced by catheter materials and lumen, patient factors and infection. (LOE 3)**
- **SPC is a reasonable alternative to IDUC, but IC is the first line intervention (LOE 3).**
- **SPC is a safe and effective short-term management of urinary retention. (LOE 3)**

Recommendations:

- **Silicone or hydrogel-coated catheters are preferable. (A/B)**
- **Use sterile materials and aseptic technique, and routine catheter care in the context of a closed drainage system. (C/D)**
- **Catheters should be changed regularly, to try to pre-empt obstruction or infection. (C/D)**
- **Bladder irrigation and antibiotic prophylaxis are not recommended as a routine infection-control measure. Symptomatic UTI should be treated with narrowest spectrum antibiotic possible, according to local microbiology practice. (B)**
- **Patient education on daily cleanliness and hygiene care are mandatory. (C)**
- **Short-term IDC during the acute phase of neurological injury is a safe management for neurologic patients. (B)**
- **Long-term IDC may be safe only if a careful check-up of urodynamic, renal function, and upper and lower tract imaging are performed. (B)**
- **Bladder screening for bladder cancer is strongly recommended, especially those with IDC more than 5-10 years. (C)**
- **Annual cystoscopy and biopsy may be necessary for those with gross hematuria, or chronic symptomatic UTI refractory to therapy. (C)**
- **Consider the use of antimuscarinic drugs in individuals with suprasacral lesions using chronic indwelling catheters. (C)**
- **Patient comfort, convenience, sexuality and quality of life need to be considered. (C)**

3. Condom Catheters and External Appliances

Male patients with neurogenic bladder and chronic urinary incontinence can be candidates for a condom catheter connected to a collection bag. However, some men have difficulty in applying condom catheters, e.g. due to obesity, penile atrophy or retraction.

Conclusions

- **Condom catheters facilitate urinary containment in neurologic male patients (LOE 3).**
- **Long-term use does not increase the risk of UTI when compared to other methods of bladder management. (LOE 3)**
- **Complications may be less if technique, hygiene, replacement and maintenance of low bladder pressures are optimised. (LOE 3)**

Recommendations

- **Size selection should consider control of leakage, and prevention of penile compressive effects. (B)**
- **Regular bladder emptying with low bladder pressures and low post void residual should be confirmed (B).**

IV. PHARMACOTHERAPY

This chapter deals only with specific issues of continence pharmacotherapy in neurologic patients. For a fuller description of the drugs in use, see chapter 8. The principal causes of urinary incontinence in this subpopulation are neurogenic DO and/or incompetence of urethral closing function. Accordingly, treatment aims to decrease storage-phase detrusor activity, increase bladder capacity and/or increase bladder outlet resistance. This picture is blurred by the occurrence of DSD, which can be present concomitantly with DO. Pharmacologic therapy is particularly helpful in relatively mild degrees of neurogenic bladder dysfunction. Patients with more profound neurogenic bladder disturbances may require pharmacologic treatment to improve results of other forms of management, such as IC.

The two most commonly used classes of agents are antimuscarinics and alpha-adrenergic antagonists. However most drugs have not been evaluated specifically in neurogenic bladder dysfunction.

1. DRUGS FOR NEUROGENIC STORAGE DYSFUNCTION

a) Bladder relaxants

General indications of pharmacological treatment in neurogenic DO are to improve reflex incontinence, ameliorate high intravesical pressure and support other interventions e.g. IC and IDC. Antimuscarinic therapy is a symptomatic treatment. In neurogenic DO, antimuscarinics may increase post void residual urine.

The evidence base for the use of antimuscarinics in patients with a neurogenic bladder is limited. In fact, in a recent Cochrane review performed on all current literature regarding anticholinergic therapy for MS-related incontinence, only five usable studies were found, and no conclusion supporting benefit could be drawn from the analysis [1].

1. Oxybutynin

Oxybutynin hydrochloride is a moderately potent antimuscarinic agent with a pronounced muscle relaxant activity and local anesthetic activity as well-the clinical relevance of the latter is debatable. In a prospective, 12-week dose titration trial of controlled release oxybutynin (OXY-XL), Bennett et al. [2] evaluated the efficacy and tolerability of higher dose oxybutynin chloride in patients with neurogenic bladder and multiple sclerosis, spinal cord injury or Parkinson's disease. A 7-day washout period was used before initiation of the starting dose of 10 mg OXY-XL. Doses of OXY-XL were increased by 5 mg at weekly intervals to a maximum dose of 30 mg per day guided by patient perception of efficacy versus side effect. At the end of the study statistically significant decreases in the number of voids in 24 hours, episodes of nocturia and incontinence episodes were observed. Residual urine remained unchanged. No patient experienced serious adverse events (LOE2). In a prospective, open label trial of 3 formulations of oxybutynin (tablets, syrup and extended release tablets), Franco et al. [3] evaluated the efficacy and safety of oxybutynin in children with neurogenic DO. The effect of treatment on average urine volume per catheterization and on secondary urodynamic outcomes was evaluated. Maximal cystometric capacities increased, and mean detrusor and intravesical pressures were significantly decreased at week 24. Improvements in bladder function were consistent across all oxybutynin formulations (LOE 2). Gajewski et al. demonstrated in a prospective randomized study that oxybutynin was more effective than propantheline in the treatment of DO in patients with multiple sclerosis (LOE 1) [4].

2. Propiverine

In a randomized, double-blind, prospective multicenter clinical study, Stöhrer et al. [5] compared the efficacy and tolerability of propiverine and oxybutynin in patients with neurogenic detrusor overactivity. Propiverine and oxybutynin were equally effective in increasing bladder capacity and lowering bladder pressure. The trend for better tolerability of propiverine compared to oxybutynin achieved significance for dryness of the mouth (LOE1). Propiverine hydrochloride has also been shown to be effective in neurogenic detrusor overactivity in children and adolescents, even in some of those cases unresponsive to other anticholinergics [6, 7]. The low incidence rate of adverse events evidenced a favourable risk-benefit profile of propiverine hydrochloride (LOE3).

3. Trospium

Trospium is a quaternary ammonium derivative with mainly antimuscarinic actions. Trospium has been shown to significantly reduce the number of urinations, increase cystometric capacity and mean effective volume of the bladder, and reduce the incidence of urgent voids in neurogenic patients [8, 9] (LOE1).

4. Tolterodine

Tolterodine is a competitive muscarinic receptor antagonist. Tolterodine has a high selectivity in vitro and exhibits selectivity for the urinary bladder over the salivary glands in vivo. Several phase II studies have demonstrated the efficacy and safety of tolterodine in patients with overactive bladder [10]. Ethans conducted a prospective, randomized, double-blind, crossover trial plus open-label comparative stage, aiming at comparing tolterodine with oxybutynin and placebo in people with neurogenic DO. Tolterodine, when used at self-selected doses (SSDs) was comparable with oxybutynin at SSDs in enhancing bladder volume and improving continence, but with less dry mouth. It seems that larger

doses of tolterodine are needed to achieve best effect on neurogenic bladder [11, 12] (LOE3).

5. Solifenacin succinate

Solifenacin has been extensively studied in OAB [13, 14] (LOE1). In a prospective, open-label study of solifenacin for the treatment of OAB in MS patients, van Rey et al. demonstrated a significant improvement in number of micturitions, number of pads used per day and severity of urgency compared to baseline following eight weeks of treatment [15] (LOE 2).

6. Darifenacin

Dariferacin has a higher relative selectivity for the M3 receptor compared with other anticholinergics. Dariferacin has been extensively studied in OAB, but not in neurogenic bladder dysfunction.

7. Fesoterodine

Fesoterodine acts functionally as a prodrug, hydrolysed by nonspecific esterases to 5-hydroxymethyl tolterodine (5-HMT). This active metabolite, responsible for the antimuscarinic activity of fesoterodine is also an active metabolite of tolterodine. Phase 3 trials have evaluated fesoterodine in OAB, but there is no current data on the effect of fesoterodine in neurogenic LUT dysfunction.

8. Dual therapy with antimuscarinics

Dual therapy (between combinations of oxybutynin, tolterodine and trospium) has been shown to be effective and well tolerated in a few patients with neurogenic bladder dysfunction [16] (LOE 2).

9. Antimuscarinics in neurological patients with cognitive impairment

In the cognitively impaired, antimuscarinics should be prescribed with a warning about possible deterioration in memory or the onset of confusion. It would appear sensible to recommend the use of antimuscarinics that are likely to have less impact on cognition, either by lower propensity to cross the blood–brain barrier (e.g. trospium chloride) or by relative selectivity for the M3 receptor (e.g. darifenacin) which is not known to be involved in cognition; evidence affirming these considerations is limited. No studies have specifically evaluated patients with neurological disease. In a randomised, double-blind, parallel group, multicentre study of 3 weeks treatment with darifenacin in the healthy elderly, no significant effects on memory compared to placebo was observed, in comparison to oxybutynin ER which caused significant memory deterioration [17] (LOE 1). In a single-centre, non-comparative, pre-post dose intervention phase IV study of healthy elderly that was primarily designed to evaluate CSF trospium levels after orally dosed trospium , no decline in performance on tests of learning and memory was observed following ten days [18] (LOE 2).

Recommendations

• The evidence demonstrating the efficacy of antimuscarinics in the management of overactive bladder symptoms in patients with a neurogenic bladder is limited. Randomised control studies are needed to evaluate this further.

b) Intravesical bladder relaxants

1. Antimuscarinics.

Since the first use of the intravesical application by Brendler et al. 1989 [19], there have been several articles reporting successes of intravesical oxybutynin to treat OAB and neurogenic DO. The main findings were, at least at short term follow up; improved LUTS, fewer incontinence episodes, an increase of maximum bladder capacity and decreased DO. George et al. 2007 compared the therapeutic response of intravesical oxybutynin, propantheline, and capsaicin in the treatment of neurogenic DO [20]. Oxybutynin 5 mg in solution or propantheline 15 mg in solution and capsaicin were instilled intravesically in each patient. Urodynamic studies were done before and after the intravesical instillation of each drug. There was a significant difference in therapeutic response between intravesical oxybutynin, propantheline, and capsaicin in the treatment of detrusor overactivity for leak volume (LV) and leak frequency at 2nd week. When comparing responses of oxybutynin and propantheline, more subjects demonstrated improvement with intravesical propantheline than oxybutynin for reflex volume, detrusor leak point pressure, clean intermittent catheterization volume, and LV (LOE3). However, there is no standard instillation protocol concerning the use of intravesical oxybutynin; doses used range between 5-30 mg, diluted in 30-40 ml saline [20, 21]. Also the instillation frequency is not standardized and varies between 1 to 3 times /d. Small case series report on long-term success of intravesical oxybutynin (up to 3 years in adults, up to one year in children with NDO (LOE4) [22, 23]. Despite favourable results on urodynamic parameters, there is also a low level of evidence for the use of intravesical oxybutinin in low-compliance neurogenic bladders [24]. Modulation of the ice-water test and suppression of the electrical perception threshold by oxybutynin has been studied [25]. An animal experiment suggested that early administration of oxybutynin might have a protective effect on structural bladder alterations, at least in obstructed animals [26].

Fader et al. 2007 [27] tested the efficacy and side effect profiles of intravesical atropine compared to oxybutynin immediate release (IR) in MS. They performed a study to determine the most effective dose of atropine. Eight participants used increasing doses of intravesical atropine (2 to 6 mg in 20 ml saline) during a 12-day period. Bladder diary data

showed that the instillation of 6 mg atropine 4 times daily was most effective for increasing bladder capacity (voided/catheter volumes). Afterwards they performed a randomized, double-blind crossover trial. Participants received 14 days of treatment with oral oxybutynin IR 5 mg twice daily (range 2.5 twice to 5 mg 4 times daily) or with intravesical atropine, followed by 14 days of alternative treatment. Participants recorded a bladder diary and rated side effects and quality of life. The primary outcome variable was bladder capacity. 57 participants with MS completed the study. Average change in bladder capacity was higher in the atropine arm. Changes in incontinence events and voiding frequency were not statistically different between the arms. Changes in total side effect and dry mouth scores were significantly better in the atropine treatment arm. These findings suggest that intravesical atropine is as effective as oxybutynin IR for increasing bladder capacity and has less antimuscarinic side effects (LOE2). However, no further results of clinical trials with intravesical atropine have been published since.

2. Nociceptin/Orphanin FQ (N/OFQ)

Nociceptin is a peptide that exerts several physiologic actions at both the central and the peripheral level by activating a specific G-protein-coupled receptor named nociceptin orphan peptide (NOP) receptor. Animal studies have demonstrated that N/OFQ inhibits the micturition reflex in the rat [28]. Lazzeri et al. recently studied the feasibility, safety and efficacy of daily intravesical instillation of 1 mg of the endogenous peptide N/OFQ in a selected group of patients who performed CIC for neurogenic DO [29]. A total of 18 patients were randomized to receive 1 mg nociceptin/orphanin FQ in 10 ml saline or placebo (saline) at the first catheterization for 10 days. Mean daily urine leakage episodes significantly decreased from 2.18 at baseline to 0.94 during nociceptin/orphanin FQ treatment, while no significant changes were reported in the placebo group. The bladder capacity significantly increased in patients receiving nociceptin/orphanin FQ. The urodynamic parameters showed an increase in cystometric capacity and a decrease in maximum bladder pressure. Although these findings supported the use of nociceptin/orphanin FQ peptide receptor agonist as an alternative approach for controlling NDO incontinence (LOE2), no further study results have been published in five years.

3. Compounds Acting Via the Transient Receptor Potential (TRP) Channels

The vanilloids, capsaicin (CAP) and resiniferatoxin (RTX), desensitize afferent nerves by binding TRPV1 receptors. CAP has been the subject of small, short-lasting placebo-controlled trials in patients with SCI or MS [30] (LOE1-2). Thus, the use of CAP is still largely experimental and limited by the fact of prolonged and painful excitation of the sensory c-fibers. The alcoholic solvent may be a major factor in the poor tolerability of alcoholic CAP instillation, as suggested by the result of one placebo controlled study showing that side effects appeared to be the same after intravesical instillation of CAP diluted in 30% ethanol as after instillation of ethanol alone (LOE2).

RTX acts without the potent neuronal excitatory effect of capsaicin, and therefore elicits less discomfort. The difference in tolerability of the 2 vanilloids (CAP vs. RTX) was usually attributed to the differential pungency of the 2 agents. Nevertheless, because we know the role of the solvent in the irritative effect on bladder mucosa, it is reasonable to assume that differential effects could be related to the use of different vectors. From a technical point of view the choice of the solvent is limited because of the poor hydrosolubility of CAP, imposing the use of an alcoholic, lipidic or glucidic vector. The safety of the lipidic solution could be imperfect because of difficulty of achieving complete elimination of lipidic solution from the bladder. On the contrary, a glucidic solution may represent a safe and valuable alternative to the alcoholic vector. De Seze et al. [31] compared the efficacy and tolerance of intravesical instillations of CAP and RTX using a glucidic solvent for CAP and the 10% ethanol solvent for RTX in a controlled randomized, double blind study in patients with severe urinary incontinence due to spinal cord injury. On day 30, improvement was found clinically and urodynamically in 78% and 83% respectively of patients treated with CAP vs. 80% and 60% treated with RTX. No significant difference between the 2 groups was observed. The benefit remained in two-thirds of the 2 groups on day 90. There were no differences in regard to incidence, nature or duration of side effects in CAP vs. RTX treated patients. These results once more strongly argue for the importance of accounting the role of vanilloid solute when interpreting efficacy and tolerance of vesical vanilloid instillation in neurogenic DO cases. They suggest that a glucidic solution is a valuable solvent for CAP instillation (LOE2).

RTX seems to have a beneficial effect on neurogenic DO (LOE 2). However, good randomized controlled studies are needed to determine its place in the treatment of NDO. Also the optimum doses (concentration) as well as the inter treatment intervals need to be determined. Moreover, the long-term safety of vanilloid agents, particularly concerning mutagenic and carcinogenic effects on the bladder wall is not perfectly known. RTX belongs to the family of tumor promoting phorbol esters, strengthening the need to ensure the safety of RTX before extending its therapeutic applications.

Initial interest in RTX has declined following the introduction of intradetrusor Botulinum toxin injections in the treatment of intractable neurogenic DO. In a randomized trial comparing onabotulinumtoxinA injection to resiniferatoxin intravesical instillation in 25 patients with spinal neurogenic DO [32] there was

a significant decrease in catheterization and incontinence episodes for both treatments at 6, 12, and 18-months of follow-up. However, onabotulinumA injections provided superior clinical and urodynamic benefits as compared to intravesical resiniferatoxin, although RTX did not necessitate subsequent intermittent catheterisation (LOE1-2).

Transient receptor potential channels are being increasingly investigated as targets for the treatment of detrusor overactivity. Piperine, a novel vanilloid compound, was found to have both acute and prolonged in vitro effects [33]. In an animal model of chronic spinal NDO, systemic administration of GRC-6211, a novel TRPV1 antagonist, could abolish DO [34]. An antagonist of another TRP channel, the ankyrin-repeat transient receptor potential 1 channel (TRPA1), could decrease the number and amplitude of non-voiding bladder contractions in SCI rats [35]. Finally, nitro-oleic acid, an electrophilic fatty acid nitroalkene derivative which modulates gene transcription and protein function via post-translational protein modification demonstrated TRP-agonist actions affecting both the TRPV1 and the TRPA1 receptors in rat bladders [36].

4. Botulinum Neurotoxin Type A

Efficacy: The past decade saw the emergence of the most successful intravesical treatment for refractory neurogenic DO to date, namely Botulinum neurotoxin (BoNT) intradetrusor injections. Following several publications from increasing numbers of centres worldwide and multicentre registration studies, BoNT type A (BoNT/A) in the OnabotulinumtoxinA (BOTOX™) format has become the newest approved treatment for urinary incontinence in adult neurological patients with inadequate response to (or reduced tolerance of) an anticholinergic medication (U.S. Food and Drug Administration approval). Similar approval has been granted or is awaited in a number of European countries. Several systematic reviews [37-40], a number of randomized, placebo-controlled trials (LOE1, four fully published studies [41-44], one active comparator-controlled trial (LOE1-2) [32], three LOE2 studies [45-47], and several LOE3 studies have confirmed the efficacy of BoNT/A in the treatment of refractory neurogenic DO incontinence. Clinical improvement is accompanied by significant ameliorations in bladder function, as urodynamic parameters that matter in the management of NDO, namely maximum cystometric capacity, maximum detrusor pressure and reflex volume, appear to gain substantial benefits in most published patient series [37-39]. Almost all studies have published on two BoNT/A preparations, onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport) [39]. The two formats are not interchangeable and there are no direct comparisons for dose, efficacy and safety, at least in urological indications. Although both products appear to be efficacious in NDO, onabotulinumtoxinA has been more comprehensively studied than abobotulinumtoxinA [39]. An LOE1 study has been published reporting abobotulinumtoxinA [46]. An LOE3 study suggests that onabotulinumtoxinA may be more efficacious than a novel BoNT/A preparation, Prosigne, in the treatment of refractory NDO [48].

The mean duration of efficacy of a single injection is 6-16 months for onabotulinumtoxinA and 5-12 months for abobotulinumtoxinA [39]. The FDA regulatory trials (275 and 416 patients, respectively) demonstrated a mean duration of effect of [37-42 weeks for onabotulinumtoxinA compared to 13 weeks for placebo [43, 49]. Complete continence was achieved in 36-38% and 40-41% respectively with the 200U and 300U doses of onabotulinumtoxinA as opposed to 7.6-10% with placebo. Interestingly, significantly higher post-treatment continence rates have been reported in single-centre studies with both preparations (a mean 71% with onabotulinumtoxinA and 65% with abobotulinumtoxinA) [39]. The concomitant use of anticholinergics did not appear to provide additional benefit, although this needs to be confirmed in specifically-designed studies. Several retrospective studies now attest to the sustained efficacy of repeat treatment sessions with either of the two formulations [50-58].

Reported failure rates range was 5-25% for onabotulinumtoxinA and 10-32% for abobotulinumtoxinA [39]. Clinical predictors of success/failure in NDO have not been studied. A study of patients with MS proposed that longer duration of MS may be a predicting factor for treatment failure [59] (LOE3). To date there is no robust evidence to link treatment failure with the formation of neutralizing BoNT/A antibodies, but a wide range of antibody formation rates following treatment has been reported (0-35%) [60-63] and its clinical significance needs further investigation. A small, controlled study in children (LOE1-2) found no association between antibody formation and treatment failure, but reported an increased rate of antibody formation in those receiving repeat versus single injections (71% versus 38%) [64] in the mid-term (up to 4 months post treatment). In the long-term, antibody titers returned to control levels.

Patient populations: The majority of the studies involved participants with neurogenic bladder due to SCI or MS, often mixed, while only small case series investigated efficacy in patients with Parkinson's disease, multiple system atrophy or cerebrovascular accident (CVA) [65-68]. Comparisons of efficacy between neurological subpopulations are generally lacking, although a small LOE3 study suggested better continence outcomes and more significant improvements in maximum detrusor pressures in SCI patients compared to those with CVA [68]. The largest RCTs which involved MS and SCI patients conclude that the toxin is highly efficacious in both subpopulations [43, 49]. A lower placebo effect

in the SCI subpopulation could be noted, although the studies were not designed for head-to-head comparisons. The same studies demonstrated a similar efficacy and adverse event profile for the 200U and 300U onabotulinumtoxinA (BOTOX) doses, suggesting a plateau in the efficacy of the toxin. Similar conclusions had been drawn by the results of an earlier study in the IDO population (plateau dose 150U onabotulinumtoxinA) [69]. Providing the best benefit/risk ratio, the 200U onabotulinumtoxinA dose was recommended for the treatment of refractory NDO incontinence [43, 49]. A LOE2 study suggested a trend towards better clinical and urodynamic improvements with 750U as opposed to 500U abobotulinumtoxinA [46]. Other, non-randomised and inadequately powered studies (LOE3) [45, 56, 70] could not identify a clear dose-response for higher doses of abobotulinumtoxinA, although 1000U abobotulinumtoxinA might produce a beneficial effect of greater duration than that with 500U [45].

Little data exists on lower doses. A pilot LOE3-4 study suggests that 100U onabotulinumtoxinA could be effective in MS patients and minimize unfavourable side-effects, particularly the need for IC [71], while a LOE1 dose-response study still in abstract format confirms a more significant clinical benefit of the 200U dose as opposed to the 50U and 100U doses of onabotulinumtoxinA in patients with SCI [72].

Effect on quality of life (QOL): Both preparations have been shown to improve patients' QOL in RCTs. A single injection of 500 units abobotulinumtoxinA, diluted in 25 ml saline and injected into 25 injection sites, was compared to placebo in 31 patients with NDO-associated incontinence. At 26 weeks follow-up, patients in the abobotulinumtoxinA group had a more significant change in clinical QOL and urodynamic parameters, and anticholinergic use [42]. Similarly, 200U and 300U onabotulinumtoxinA administered into 30 injection sites improved QOL scores significantly more than placebo in all LOE1 studies [43, 44, 49, 73]. The I-QOL questionnaire has been used in the majority of LOE1 studies.

Administration technique: A large variance in the number and volume of injections has been described. However, in the majority of studies onabotulinumtoxinA was given at 30 injection sites (range 10–40) at a dilution of 10U/1ml per injection site (total volume of 30 ml, range 3–30 ml), as described in the original publication by Schurch et al. [74]. The same dilution and number of injection sites was used when administering either 300U or 200U onabotulinumA in the regulatory trials. Administration of abobotulinumtoxinA is less standardized (10–30 injection sites, total volume of 5–30 ml), but a total 30 ml given at 30 injection sites appears to be the most common again [39]. The effect of these variables on outcomes has little been studied. In a LOE3 study, Karsenty et al. compared 10 versus 30 injection sites (300 U Botox) [75]. They reported no significant difference in efficacy measured by number of incontinence episodes or cystometric capacity, but a significant reduction in post-procedure pain was noted in the 10 injection-sites group.

The majority of studies reported injections into the detrusor muscle sparing the trigone, as in the original technique [74]. There is, however, LOE2 evidence to suggest that trigonal injections may produce better continence rates than detrusor injections alone; urodynamic parameters were affected to a lesser extent, as only reflex volume was improved more significantly in patients who received trigonal injections [47].

Alternative delivery techniques are being investigated in preclinical studies and include intravesical instillation of BoNT/A encapsulated in liposomes [76] or via electromotive drug administration (EMDA) [77]. The latter method has also been tested in a pilot LOE3-4 study in children with myelomeningocele and significant improvements were reported in maximum cystometric capacity, detrusor pressure, urinary incontinence, vesicoureteric reflux and even fecal incontinence [78], but these conclusions need to be confirmed in controlled trials.

Safety: The treatment appears to be overall safe in currently used doses and techniques. The most common adverse event is the significant increase in postvoid residual in patients not using CIC prior to treatment. In onabotulinumA placebo-controlled trials, 12-22%, 30-47%, and 42-49% of patients in the placebo, 200U, and 300U groups, respectively, initiated CIC post-treatment. Although earlier studies had reported a reduced incidence of UTIs in NDO patients treated with BoNT/A [55, 79, 80], recent large RCTs suggest a higher incidence of UTIs in those treated with onabotulinumtoxinA as opposed to placebo-treated patients [43, 49]. This might be associated with the increased rate of de novo CIC in the Botox-treated population. Prospective, long-term trials are needed to clarify this apparent discrepancy.

Haematuria, constipation and flu-like symptoms have also been described [39, 43, 49], while inclusion of trigonal injections does not appear to produce vesicoureteral reflux (LOE2-3) [47, 81, 82]. A study in SCI male patients found a post-treatment decrease in the volume of ejaculate accompanied by improvements in semen quality, sperm mobility and vitality, as well as semen culture [83]. Further research is needed to confirm these results and explore whether they are due to a local re-organisation of autonomic function which also affects the reproductive system.

The most serious adverse event is generalised paraparesis/ fatigue, which has been described in 0.005% of patients receiving onabotulinumtoxinA and in 0.026% of patients receiving abobotulinumtoxinA [39]. The effect resolves spontaneously after 4-6 weeks and appears to be dose-related, with

most cases reported in those patients injected with 750-1000U abobotulinumtoxinA or 300U onabotulinumtoxinA [49, 53, 84].

As BoNT/A studies in skeletal muscles have identified autonomic, histological and other secondary effects [85, 86], further investigation is needed on safety issues, especially after repeat injections [38]. A single study to-date prospectively examined distant effects post-BoNT/A bladder injection using single-fibre EMG; one-third of the patients had findings of neuromuscular jitter post-treatment, but there was no placebo arm or pre-treatment data for comparison [87] (LOE3). Other studies produced histological evidence of reduced or no additional fibrosis after one or multiple injections, including in children [88-90].

Future research should highlight the gaps in our knowledge of long-term treatment, overall safety and different techniques of application.

5. Potential Intravesical Treatments with Cannabinoid Modulators

While orally administered cannabinoid modulators appear to improve neurogenic OAB symptoms, particularly in MS patients [91], the identification of functional cannabinoid receptors (CBs) in the human bladder urothelium [92, 93] has intensified research in intravesical cannabinoid agonists for bladder dysfunctions. To date, only preclinical studies exist, and in non-neurogenic bladder models. Cannabinor, a selective CB2 receptor agonist, was found to affect bladder function in both normal rats as well as rats with bladder outlet obstruction, by increasing intervals between bladder contractions as well as flow pressures [94, 95]. In rats, but not humans, a Cannabis sativa extract enriched in cannabidiol drug substance reduced cholinergic-mediated bladder contractility in vitro [96]. Intravesical application of a non-selective cannabinoid agonist suppressed afferent activity via activation of CB1 receptors [97]. Finally, intravesical administration of the fatty acid amide hydrolase, the enzyme responsible for the degradation of the endocannabinoid anandamide, altered afferent-related urodynamic parameters in normal rats [98]. In a single study using a spinal cord injury model, systemic administration of a CB2-selective agonist could improve spontaneous voiding, possibly via a positive effect on inflammatory responses in the spinal cord [99].

c) Drugs for sphincter deficiency

Several drugs, including alpha-adrenergic agonists, estrogens, beta-adrenergic agonists and tricyclic antidepressants, and duloxetine have been used in an effort to increase outlet resistance. No adequately designed controlled studies of any of these drugs for treating neurogenic sphincter deficiency have been published.

2. DRUGS FOR TREATING VOIDING DYSFUNCTION

a) Alpha-adrenergic antagonists

Alpha-adrenoceptors are present in the bladder base, posterior urethra and prostate. Alpha-blockers have been already reported to be useful in neurogenic bladder by decreasing urethral resistance during voiding. Tamsulosin has been shown to improve bladder storage and emptying in MS and SCI [100]. Abrams et al. [101] evaluated the efficacy and safety of tamsulosin in patients with neurogenic lower urinary tract dysfunction secondary to suprasacral spinal cord lesions in a 4-week randomized controlled trial (RCT) followed by a 1-year, open label, long-term study. A total of 263 patients were randomized to 4-week double-blind therapy with placebo, or 0.4 or 0.8 mg tamsulosin once daily. The primary efficacy parameter was maximum urethral pressure (MUP). In the long-term study, but not in the RCT trial, there was a statistically significant mean decrease in MUP from baseline to end point. In the long-term study tamsulosin also improved several cystometry parameters related to bladder storage and emptying, e.g. decreased maximum urethral closure pressure. It also increased mean voided volume based on the micturition diary. There was statistically significant improvement for the International Prostate Symptom Score Quality of Life. Both doses were effective and well tolerated. (LOE1).

b) Botulinum toxin

Sphincter injections were historically the first application of BoNT/A in the lower urinary tract [102], but there is still inadequate evidence to support its use. The most commonly injected volume is 4ml of either the onabotulinumtoxinA or the abobotulinumtoxinA preparations. Usually 100U onabotulinumtoxinA or 150U abobotulinumtoxinA have been delivered transperineally or transurethrally [103, 104]. There exists no direct comparison of injection techniques; there is LOE4 to suggest the two delivery approaches are equally effective [105].

In a LOE1 study, the effects on DSD of botulinum toxin versus placebo was studied in 86 multiple sclerosis (MS) patients [106]. The study employed a single transperineal injection of onabotulinumtoxinA, 100 U in 4 ml normal saline, or placebo, into the striated sphincter with EMG guidance. The primary endpoint was post void residual volume at 30 days. The secondary endpoints included voiding and urodynamic variables. OnabotulinumtoxinA failed to decrease post-void residual volume in this group of MS patients, although it increased voided volume and reduced pre-voiding and maximum detrusor pressures. These findings differ from those in patients with spinal cord injury and may be due to lower detrusor pressures in MS patients. A small LOE1 study showed a superior effect of onabotulinumtoxinA over lidocaine 0.5% injected in the urethral sphincter in MS patients [104]. In MS patients

there is also LOE3 to suggest that a combination of detrusor and sphincter injections may facilitate bladder emptying [105]. In children with NDO and DSD due to myelomeningocele there is LOE1-2 to suggest that sphincter injections additional to the detrusor injections accomplish significant improvements in post-void residuals, as well as more significant benefits in urinary incontinence, constipation, vesicoureteral reflux and creatinine levels [107].

c) Cholinomimetics

In general, bethanechol chloride seems to be of limited benefit for detrusor areflexia and for elevated residual urine volume. Elevated residual volume is often due to sphincter dyssynergia. It would be inappropriate potentially to increase detrusor pressure when concurrent DSD exists.

Conclusions

- **Antimuscarinic drugs improve storage function (LOE 1).**
- **Antimuscarinic drugs have a high incidence of side effects (dry mouth, constipation, urinary retention, etc.). Tolterodine, propiverine, trospium and controlled-release oxybutynin have significantly less side effects compared to immediate-release oxybutynin (LOE 1).**
- **High doses of oxybutynin have been used to treat patients with neurogenic bladder dysfunction (LOE 3).**
- **Intravesical instillation of oxybutynin may be an alternative route of administration (LOE 4).**
- **Intravesical instillation of capsaicin/resiniferatoxin has been reported to improve spinal reflex incontinence. Resiniferatoxin is preferable (LOE 3). Recent results supporting their use are lacking.**
- **Botulinum neurotoxin A (BoNT/A) injection into the detrusor muscle improves clinical and urodynamic parameters (LOE1), and has been approved as second-line treatment for urinary incontinence associated with neurogenic detrusor overactivity in patients with inadequate response to or intolerance of an anticholinergic.**
- **Repeat intradetrusor injections of BoNT/A provide sustained clinical benefits (LOE3)**
- **Treatment with intradetrusor BoNT/A is considered overall safe, with increased post-void residual and need for post-treatment CIC being the most common adverse event (LOE1).**
- **Long-term alpha adrenergic antagonists are effective and well tolerated in patients with MS and suprasacral spinal cord lesion with neurogenic lower urinary tract dysfunction (LOE1).**
- **BoNT/A is probably safe and effective for the treatment of DSD in spinal cord injury patients (LOE2). However, on the basis of one LOE1 study, BoNT/A does not provide significant benefit for the treatment of DSD in MS patients.**
- **There is no adequately designed controlled study of any drug for neurogenic sphincter deficiency.**

Recommendations

- **Antimuscarinic drugs should be recommended for the treatment of neurogenic detrusor overactivity (A). Titration of the dosage of these drugs individually should be done to optimal balance of therapeutic and adverse effects. If one drug is not tolerated, another drug should be tried (C/D).**
- **BoNT/A should be offered as a treatment option for incontinence associated with neurogenic detrusor overactivity (A).**
- **Further research is needed on long-term outcomes and safety, administration techniques, the bio-equivalence of the various preparations, the concomitant use of anticholinergic drugs, mechanisms of action, and wider effects (A).**
- **Vanilloid intravesical therapy still remains experimental and therefore is not recommended except within clinical trials (C/D).**
- **For decreasing outlet resistance in neurogenic bladder a-adrenergic antagonists may be used (B/C).**
- **BoNT/A may be considered for DSD in spinal cord injury patients (B).**
- **For neurogenic sphincter deficiency, no effective drugs are available up to now; further research is needed (D).**
- **For detrusor areflexia no effective drugs are available up to now; further research is needed .**

V. ELECTROSTIMULATION

1. ELECTRICAL NEUROMODULATION

In the last decade, sacral nerve neuromodulation (discussed in the Surgical Treatment section of this chapter) has been established as a treatment option for patients with OAB. The success with sacral neuromodulation has increased the interest in other neuromodulation techniques. Additional methods include; (a) anogenital stimulation (b) pudendal nerve stimulation, (c) dorsal genital nerve stimulation (d) percutaneous tibial nerve stimulation, (e) magnetic stimulation and (f) deep brain stimulation. It is not really known how neuromodulation works, but there is evidence that sites of action are spinal and supraspinal [1]. Firstly the non-surgical ways of neuromodulation will be presented, followed by the surgical techniques.

a) Anogenital Stimulation

This has been applied in children with OAB complaints. Gladh et al. found a response for anogenital stimulation in 53% of the children [2]. Trsinar and Kralj used an endoanal electrode and reported a complete or partial response to the treatment in 75% of the patients [3]. In a control group of patients who had the endoanal electrode introduced but not activated, no patient had the symptoms resolved completely. No recent publications could be found.

b) Pudendal Nerve Stimulation

Pudendal nerve stimulation and electrode positioning can be carried out under neurophysiological monitoring (using a St. Mark's electrode) in order to guide the electrode in Alcock's Canal as close as possible to the pudendal nerve [4]. Electrode implantation can also be carried out by a rear approach under local anesthesia according to the method described by the same team [5, 6]. On the other hand, an anatomical study demonstrated that the technique for implanting electrodes at the pudendal level may carry some risk [7].

Direct pudendal nerve stimulation has beneficial effects on numerous pelvic floor function impairments such as urinary and/or fecal incontinence, retention, and constipation. In preceding literature the implant technique required a fairly complex and invasive procedure, although recent advances with percutaneous placement of the lead through an introducer have made the procedure much less invasive. Electrical stimulation of pudendal nerve afferents can inhibit bladder contractions in patients with SCI, and bladder capacity can be increased [8] (LOE3). Implants such as the InterStim system have made this treatment modality commercially available (see sacral nerve stimulation). Common to these implantable systems is that they use continuous stimulation. Detrusor inhibition is in principal only necessary during an involuntary contraction and, thus, stimulation could be turned off between contractions (i.e. conditional stimulation) [9]. Such a stimulation scheme could have a number of advantages. Power consumption may be decreased and, thus, extend battery lifetime. Furthermore, continuous stimulation of a reflex may lead to habituation, which would be minimized or prevented by conditional stimulation. Hansen et al. [10] examined the effect of the automatic, event driven electrical stimulation of pudendal nerve afferents on bladder capacity in patients with SCI. The study included two women and 14 men older than 18 years with NDO, bladder capacity below 500 ml and complete or incomplete suprasacral SCI. Detrusor pressure (Pdet) was recorded during natural bladder filling. In a similar subsequent recording Pdet was used to trigger electrical stimulation when pressure exceeded 10 cm H2O. Of the 16 patients enrolled in this study, 13 had increased bladder capacity and reduced storage pressure decrease achieved by event-driven electrical stimulation. During stimulated filling, Pdet never exceeded 55 cm H2O. An average bladder capacity increase of 53% was achieved (LOE 3). Ohlson et al. treated eight patients with NDO in whom vaginal/rectal stimulation failed, with acute pudendal nerve stimulation. Five achieved a decrease in urinary frequency and four had an increase in cystometric capacity [11].

Spinelli et al. [5] performed a staged procedure similar to that of sacral neuromodulation (SNM) to place a tined lead near the pudendal nerve, using neurophysiological guidance. They named this approach chronic pudendal nerve stimulation (CPNS). Fifteen neurogenic patients (eight male, seven female) with urgency incontinence underwent CPNS. All patients had complete neurophysiological and urodynamic evaluation at baseline and follow-up and were asked to complete a voiding and bowel diary for 7 days. During screening, the average number of incontinent episodes per day decreased from 7+/-3.3 to 2.6+/-3.3 ($P<0.02$, paired t-test). Eight patients became continent, two improved by more than 88% (from 9 to 1 daily incontinence episodes) and two patients reduced the number of incontinence episodes by 50%. The implantable pulse generator (IPG) was subsequently implanted in those 12 patients. Three patients without improvement did not continue to second stage. In implanted patients with 6 months follow-up, urodynamic evaluation showed an objective improvement in the maximum cystometric capacity which increased from 153.3+/-49.9 to 331.4+/-110.7 ml ($P<0.01$, paired t-test). The maximum pressure decreased from 66+/-24.3 to 36.8+/-35.9 cmH2O ($P=0.059$, paired t-test). Eight patients reported significant improvement in bowel function (LOE3).

c) Dorsal Genital Nerve (DGN) stimulation

DGN stimulation can be continuous or conditional. Goldman et al. used continuous stimulation for one week [12]. They found a 55% increase in cystometric capacity. In 47% there was >50% reduction in incontinence episodes, and in 81% there was >50% reduction in number of urgency events. Increases in cystometric capacity vary significantly between studies using continuous stimulation (range 11-177%) and also conditional stimulation (range 37-144%). Horvath et al. and Oppisso et al. showed that DO was suppressed conditionally, with a subsequent increase in bladder volume and postponement of incontinence [13, 14]. Martens et al. found with conditional stimulation that increase in stimulation current results in a more pronounced detrusor inhibition [15]. Besides DO suppression, increases of the pressure at the bladder neck and the urethral sphincter contribute to continence [16]. In general, patients tolerate conditional stimulation well and they adapt to the sensation in long-term use [17]. Stimulation effectively suppresses urgency and decreases urgency episodes. Suppression of urgency

during stimulation might contribute to tolerance of stimulation. This might enable stimulation at higher current to increase effectiveness when stimulation is applied conditionally.

d) Posterior tibial nerve stimulation

Percutaneous posterior tibial nerve stimulation (PTNS) was described 20 years ago as a minimally invasive treatment for urge incontinence due to neurogenic detrusor overactivity (NDO) in spinal cord injury (SCI) patients. Interestingly, the location where the tibial nerve is stimulated is in the same area as the Sanyinjiao (SP6) point used in Chinese acupuncture to treat pelvic floor organ dysfunctions. The PTN is derived from the L4-S3 nerve roots and therefore shares common roots with those serving bladder functions. SCI and Parkinson patients with neurogenic DO have been treated with PTNS. PTN seems to increase cystometric bladder capacity and bladder volume at which DO and associated leakage occurs [18, 19] (LOE3). Gobbit et al. looked at the effect in 21 MS patients. Eighty-nine percent of patients reported a treatment satisfaction of 70%. Significant improvement in QoL was seen in most domains of the King's Health QoL questionnaire [20]. Kabay et al. looked at the clinical and urodynamic effects in MS and Parkinson's disease [21, 22]. They found significant clinical and urodynamic improvements, although it was impossible to completely suppress DO. De Seze et al. looked at transcutaneous PTNS in 70 MS patients [23]. With daily stimulation sessions, they showed clinical improvement in urgency and frequency in more than 80% of patients at three months. They also observed an initial acute cystometric response in > 50% of the patients without correlation with clinical efficiency. There still is debate about the possibilities to really influence voiding behavior via the posterior tibial nerve [24]. PTNS is a stimulation technique that allows for sham comparison. It should therefore be tested in this fashion.

e) Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex induces a long-lasting modulation of spinal cord excitability [25]. Thus, it represents a potentially useful tool for the treatment of neurogenic urinary disturbances. Centonze et al. [26] investigated the effects of high frequency (5 Hz) excitatory rTMS over the motor cortex on LUT dysfunction in a population of 10 MS patients complaining of urinary symptoms. All but one of the patients reported an improvement of voiding phase LUT symptoms and a significant reduction of post void residual volume. In patients with pure detrusor underactivity, there was increase of PdetQmax and Qmax. In patients with DSD, on the other hand, rTMS produced negligible effects, although the observation of a reduction of PdetQmax in this context seems to suggest a better relaxation of the urethral sphincter (LOE3). Brusa et al. also observed positive effects lasting 2 weeks after rTMS in 8 patients [27].

f) Deep brain stimulation

1. Subthalamic Nucleus Deep Brain Stimulation (ST-MN-DBS)

A large proportion of patients suffering from Parkinson's disease present with urinary dysfunction including urgency, increased frequency or incontinence [28]. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been established as a surgical treatment of motor symptoms in Parkinson's disease patients [29]. However, data from experimental urodynamic measures in men [30] and animal models [31] have also demonstrated a significant influence of STN-DBS on urinary bladder function. In these studies, the main effect of STN-DBS appeared to be a normalization of urodynamic parameters in the storage phase with a delayed first desire to void and an increased bladder capacity. Herzog et al. investigated the effect of STN-DBS on the neural mechanisms underlying cerebral bladder control. Using PET to measure changes in regional cerebral blood flow (rCBF), 11 patients with bilateral STN-DBS were studied during urodynamic bladder filling in STN-DBS ON and OFF condition. A filled bladder led to a significant increase of rCBF in the anterior cingulate cortex, which was further enhanced during STN-DBS OFF. A significant interaction between bladder state and STN-DBS was observed in lateral frontal cortex with increased rCBF when the bladder was filled during STN-DBS OFF [32, 33] (LOE3).

2. Thalamic Deep Brain Stimulation

The precise mechanisms underlying cerebral regulation of lower urinary tract function are still poorly understood. Essential tremor (ET) is not known to induce lower urinary tract symptoms (LUTS) or neuropathological changes in the thalamus. Consequently, DBS in patients with ET offers the unique opportunity to investigate the role of the thalamic ventral intermediate nucleus (VIM) nucleus in lower urinary tract function. Kessler at al. [34] evaluated the effect of thalamic DBS on urodynamic parameters in patients with ET. Seven patients were examined (two females, five males) with ET 15–85 months after implantation of DBS leads into the VIM. They compared urodynamic parameters during thalamic DBS (ON state) and 30 min after turning the stimulator off (OFF state). In the ON compared with the OFF state, there was a significant decrease in bladder volume at first desire to void (median, 218 ml vs. 365 ml, $p = 0.031$), at strong desire to void (median, 305 ml vs. 435 ml, $p = 0.031$), and at maximum cystometric capacity (median, 345 ml vs. 460 ml, $p = 0.016$). No significant differences between the ON and OFF state were detected for changes in detrusor pressure during filling cystometry, bladder compliance, maximum detrusor pressure, detrusor pressure at maximum flow rate, maximum flow rate, voided volume, and postvoid residual (LOE3).

Conclusions

- **Electrical neuromodulation is not first line treatment for neurogenic DO. There are some limited reports showing that it may be beneficial (LOE 3).**
- **Automatic, event-driven electrical stimulation in the treatment of neurogenic DO is feasible (LOE 3).**
- **Chronic pudendal nerve stimulation is feasible. Neurophysiological guidance seems to be mandatory to place the lead near the pudendal nerve (LOE3).**
- **Percutaneous Tibial Nerve Stimulation gives improved clinical and urodynamic parameters. (LOE3), but its role is not established.**
- **Enhancing corticospinal tract excitability by rTMS might be useful to ameliorate detrusor contraction and/or urethral sphincter relaxation in MS patients with bladder dysfunction (LOE3).**
- **Thalamic deep brain stimulation resulted in an earlier desire to void and decreased bladder capacity, suggesting a regulatory role of the thalamus in lower urinary tract function (LOE3).**
- **STN-DBS appeared to tend to normalization of urodynamic parameters in the storage phase, with a delayed first desire to void and an increased bladder capacity (LOE3).**

Recommendations

- **If pharmacotherapy fails to relax the hyperreflexic detrusor, electrical neuromodulation may be optional in patients with neurogenic DO (C/D).**
- **Although the setup for conditional, event-driven electrical stimulation is not suitable in a clinical setting, the treatment modality is promising and it warrants further investigation (D).**
- **Further studies on chronic pudendal nerve stimulation must be carried out to identify the best stimulation parameters and to verify the long term results (D).**
- **The thalamus may be a promising target for the development of new therapies for lower urinary tract dysfunction. Further investigation on this matter is needed before its potential role can be elaborated.**

2. ELECTRICAL STIMULATION OF THE PELVIC FLOOR MUSCULATURE

The aim of electrical stimulation in patients with neurogenic urinary stress incontinence is to improve key functions, namely the strength and/or timing of the pelvic floor muscle contraction. Electrical stimulation is provided nowadays mostly by portable battery powered stimulation, offering a wide combination of wave forms, frequencies, intensities, electrode placements etc.

In patients with incomplete denervation of the pelvic floor muscle and of the striated sphincter, electrical stimulation via anal or vaginal plugs performed over months, may improve pelvic floor function, and may thus improve incontinence. The incompleteness of the lesion should be as such that the patient is able to contract voluntary the pelvic floor to some extent, even if such contraction is weak.

Conclusions

- **There is no study published which deals with electrical stimulation via anal or vaginal plugs could be able to improve the strength of pelvic floor musculature (LOE 4).**

Recommendations

- **In patients with incomplete denervation and some voluntary contraction of the pelvic floor muscle and the striated sphincter, electrical stimulation may be an option to improve pelvic floor function, thus improve incontinence (C/D).**

3. INTRAVESICAL ELECTRICAL STIMULATION (IVES)

The technique involves a catheter with a stimulation electrode, introduced into the bladder and connected to the stimulator. Saline (0.9 %) is used as the current leading medium within the bladder. The neutral electrode is attached to the skin in an area with preserved sensation, usually in the lower upper abdomen. The afferent stimuli induced by IVES travel along afferent pathways from the LUT to the corresponding CNS structures. This “vegetative afferention” results in sensation of bladder filling/urge to void, with subsequent enhancement of active contractions, and possibly also in voluntary control over the detrusor. Feedback training is mediated by enabling the patient to observe the change of the detrusor pressure on a water manometer, which enables the patient to notice when a detrusor contraction takes place. This also facilitates voluntary control.

Intravesical electrical stimulation of the bladder (IVES) is still not established as a therapy for patients with neurogenic detrusor dysfunction. IVES may help to verify function of afferent pathways, proper indication is crucial and this type of therapy should only be applied in those with afferent fibers between the bladder and the cortex, proved by the evaluation of viscerosensory cortical evoked potentials. Intravesical electrotherapy may be able to improve neurogenic bladder dysfunction. Studies about IVES were reviewed in previous consultations [35].

Conclusions

- **Basic research during the last decade supports the underlying working concept of IVES (LOE 3).**

- **The results reported in the literature are controversial, mainly because of varied inclusion and exclusion criteria (LOE 3).**
- **In the only sham-controlled study the treatment period was short and the inclusion and exclusion criteria were not fully defined (LOE 3).**

Recommendations

- **Intravesical electrotherapy may improve neurogenic bladder dysfunction, inducing bladder sensation and the urge to void (B/C).**
- **IVES is the only available option to induce/ improve bladder sensation and to enhance the micturition reflex in patients with incomplete central or peripheral nerve damage, but corroborating controlled evidence is needed (B).**
- **Selection of patients is crucial and IVES should be applied only if afferent fibers between the bladder and the cortex are still intact and if the detrusor muscle is still able to contract (B).**
- **The ideal indication is the neurogenic hyposensitive and hypocontractile detrusor (C).**

VI. SURGICAL TREATMENT OF URINARY INCONTINENCE

1. SACRAL NEUROMODULATION

Two indications for neuromodulation are clearly valid in urology: overactivity/ urgency urinary incontinence and chronic urinary retention (aside from vesicosphincteric dyssynergia) [1], as discussed elsewhere in the consultation. This section focuses on the possible application of sacral neuromodulation in patients with neurological bladder dysfunction. The literature survey was undertaken with the key words: neurogenic bladder; spinal cord injury; spina bifida; meningomyelocoele; multiple sclerosis, sacral neuromodulation.

a) Hypotheses on the modes of action of neuromodulation

The first effects of electricity on the bladder were reported during electro stimulation treatment of pelvic floor muscles (with the aid of electrodes situated in the anus, the vagina, on the penis...) during urinary incontinence reeducation [2-5]. Inhibition of bladder contractions by electrostimulation was seen. Tanagho and Schmidt, the pioneers of neuromodulation, attributed the benefits of neuromodulation in urinary incontinence to a hypertrophy of the pelvic muscles, allowing better control [6]. Voluntary contractions of the pelvic floor muscles can cause reflex relaxation of the bladder. However, the most widely held hypothesis currently is that neuromodulation allows a restoration of normal vesical reflexes [7-9] (LOE4). This hypothesis explains that the stimulation can inhibit the guarding reflex pathway and restore normal urination or turn off supraspinally mediated overactivity by blocking ascending sensory pathways. The role of cortico-subcortical structures was recently emphasized in studies of patients with incontinence [10, 11] (LOE4) or retention [12] (LOE4). Somatic afferents as the vectors for neuromodulation mechanism of action is supported by the observation that visceral nerve fibers are not activated by the parameters normally used [13] (LOE4). Despite data obtained in animals [14] (LOE4), it seems that neuromodulation cannot be effective in patients with a non functional peripheral nerve circuit.

b) Treatment of neurogenic detrusor overactivity incontinence

There is little in the literature concerning sacral neuromodulation (SNM) in this specific indication. Many studies recorded results for incontinence and for retention at the same time, without always separating the results. Since the technique's first stages, Vodusek [5, 6] (LOE4) reported that non-muscular electrical stimulation of the sacral somatic afferents can induce bladder inhibition in patients who present with DO secondary to a medullary lesion, be it due to trauma or to multiple sclerosis (MS).

Two points must be kept in mind when treating patients with neurological bladder:

- The disappearance of wettings between catheterizations can be considered a success by itself in patients using IC. In contrast, in able-bodied patients, treating retention with IC is most often considered a failure.
- On the other hand (contrasting, for example with botulinum toxin injections), neuromodulation does not systematically require the use of IC. Furthermore, reversibility of neuromodulation is a strong point that must be considered when devising a therapeutic plan.

The main published series are summarized in T**able 3**. Author definitions for neurological pathology differed widely: some authors considered a history of pelvic surgery as a possible etiology while others included only patients with medullary neurological lesions. Despite this, several points considering the neurological etiology of the bladder dysfunction can be discussed;

- MS is not a contra-indication for neuromodulation [10, 15, 16] (LOE3-4). However, it seems important to propose this treatment only in patients who present with a stabilized form of multiple sclerosis. In addition, patients must be clearly informed that the results of neuromodulation may be altered by the evolution of their underlying illness.
- Patients with incomplete medullary lesions, whether of traumatic or other origins, may benefit from neuromodulation [10, 17-22] (LOE3-4). On the other hand, all authors agree on excluding

Table 3: Results of sacral neuromodulation (test and implantation) in neurogenic patients.

Author	LOE	Year	n (neurogenic bladder)	Follow-up (months)	Neurological Pathology	Type of dysfunction	Number of patients tested	Test success Criteria	Number of implanta-tions	Success criteria after the implantation	Number or percentage of success after the implantation at the end of the study
Bosch et al. 1996 [16] #80}	4	1996	5(5)	6	MS 5	Incontinence	NA	>50%	5	>50%	4/5
Bosch et al. 1998 [17]	4	1998	6(6)	24	MS 5 Incomplete SCI 1	Incontinence	NA	>50%	6	>50%	5/6
Chartier-Kastler et al. 2000 [10]	4	2000	9(9)	43,6	MS 5 Myelitis 1 Vascular myelitis 1 SCI 2	Incontinence	23	>50%	9/26	>75%	7/9
Spinelli et al. 2001 [18]	4	2001	196(10)	12	Discal hernia 5 MS 1 Incomplete SCI 2 Cerebral lesion 1	Incontinence Retention	NA	>50%	196(10)	>50%	Retention: 66% Incontinence: 50%
Hohenfellner et al. 2001 [19]	3	2001	27(27)	54	SCI 9 Myelitis 5 Cerebral lesions 2 Discal hernia 7 Pelvic surgery 4	Incontinence Retention	27	>50%	12	>50%	1/12
Scheepens et al. 2002 [22]	4	2002	211(24)	NA	Incomplete SCI 9 Caudal syndrome 5 Stroke 3 MS 6 Spina 1	Incontinence	211	>50%	NA	NA	NA
Bross et al. 2003 [21]	3	2003	24	NA	Pelvic surgery 5 Ependymoma A Cerebral tumours 7 Discal hernia 5 Polyradiculoneuritis 6 Spina bifida 1	Retention	24	>50%	8/24	NP	NP
Guys et al. 2004 [25]	2	2004	21	12	Spina bifida 13 Partial sacral agenesis 2 SCI 2 Tumour 2 Various 2	Incontinence	NA	NA	21	NP	NP
Spinelli et al. 2005 [22]	3	2005	15(15)	6	SCI incomplete 7 Various Medullar lesions 8	Incontinence	15	>50%	12/15	NP	NP
Wallace et al. 2007 [15]	3	2007	33(33)	12,4	MS 16 Parkinson 6 Spina bifida 2 Stroke 2 Other 6	Incontinence Retention	33	>50%	28/33	>50%	NP (3 neuromodulators removed)
Chaabane et al. [27]	3	2011	62	51	MS 13 Incomplete SCI 13 Peripheral neuropathy 8 Parkinson 4 Myelitis 4 Stroke 4 Other 16	Incontinence Retention	62	>50%	41/62	>50.2%	76%

NP: Not precisely stated, NA: Not applicable; LOE: Level of evidence MS: Multiple sclerosis

patients with complete medullary lesions. Clinical data, especially from the Hohenfellner series [19] (LOE3), support among others those reported by Schurch et al. in 2003 [23] (LOE4). These authors published a study in which they recorded external anal sphincter (EAS) electromyographic activity caused by stimulation of the S3 sacral root during a percutaneous needle evaluation (PNE) test in three patients who presented with neurogenic DO and DSD secondary to a complete traumatic medullary lesion. They describe a reflex response with early and late latency in the three patients. They also demonstrated that the EAS contraction observed during the PNE represented an indirect motor response mediated by the afferent nerves towards the spinal cord. Despite the recording of an EAS motor response in the three patients, they did not obtain any urodynamic or clinical benefit. This suggests the participation of supraspinal neuronal centers— presumptively a spino-bulbar spinal pathway—in the SNM mode of action. However, these data are contradicted by an experimental study using bilateral neuromodulation in the cat [24] (LOE4).

- Guys et al. [25] demonstrated significant but limited urodynamic differences in children (LOE3). However, the clinical translation of these modifications has not been reported. It must be emphasized that, in the absence of electrodes adapted to paediatric sizes, the study was carried out without the usual percutaneous evaluation phase.

- Encouraging short term results in neurological bladder dysfunction do not necessarily translate into long-term efficacy [19] (LOE2). Despite a positive test in about half of the patients tested, long term (54 months) results were poor in almost all patients (1/12 had neuromodulation efficacy).

- Sievert et al. [26] performed acute bilateral sacral S3 nerve stimulation in 10 patients with complete spinal cord lesions (SCLs) during the spinal shock phase, with six patients as controls. After a mean follow-up of 26 months, the cystometric capacity increased and IDC were abolished in the stimulation group. Further studies should look into this technique and question the ideas about the working mechanism in sacral nerve stimulation since afferent stimulation effects are unlikely in complete SCI.

- One of the largest and latest series is from Chaabane et al. [27]. They looked at the results of PNE testing and SNM implants with a mean follow-up of 4.3 years in 62 patients (34 with DO, 28 with chronic urinary retention). DSD was present in nine cases. 41 patients (66.1%) had more than 50% improvement on urodynamic evaluation and bladder diary with PNE, and 37 were implanted. At follow-up results remained similar to the evaluation phase in 28 cases (75.7%). In six cases (16.2%), clinical response had been lost; in these six cases, neuromodulation failed on average 12.0 months after implantation.

Scheepens et al. [20] reported two prognostic factors for poor response (the study population was six incomplete medullary injuries, five patients with cauda equina syndrome, six with multiple sclerosis, and one with myelomeningocele) (LOE3): duration of the symptoms (more than seven months in this study) and the existence of a neurological cause for bladder dysfunction. Neurological patients with a very localized and incomplete nervous condition were the most successful. Patients with herniated disc surgery had a greater chance of good response. Patients with complete medullary or large sacral lesions were poor neuromodulation candidates.

Clinical results of neuromodulation do not necessarily correlate to urodynamic results. Bosch indicated in his series [17] that almost half of the patients considered to have had a good outcome clinically in reality retained some overactivity. One publication reported correspondence between urodynamic test data and clinical data [10] (LOE4). In 2001 Chartier-Kastler [28] et al. published the results of a prospective study concerning the evolution of urodynamic parameters during the acute phase of the PNE test in 14 patients with neurogenic DO. The authors concluded that the acute phase of PNE was accompanied by a significant change in urodynamic parameters in more than 2/3 of the patients, and that this should be a possible means for selecting patients.

c) Sacral neuromodulation for urinary retention in neurological bladder dysfunction

The only study which reported specific results for neurogenic urinary retention is from Hohenfellner et al. [19] (LOE3), reporting on 11 patients. Of these patients, three were implanted and there were temporarily satisfactory results in only two. Thus, it seems that neuromodulation has a marginal place in retention patients with neurological bladder. Patients need to be clearly informed of the high risk of failure. In this respect the bladder contractility test can be helpful in order to predict a successful outcome of sacral nerve stimulation in acontractile neurogenic bladders [29]. It is also necessary to be especially prudent in patients with cauda equina problems, who may have the illusion of recovering urination, but actually may be enhancing abdominal straining to evacuate their bladder. In reflex incontinence, patients with complete spinal cord or cauda equina lesions are poor candidates (LOE4). While a few studies have reported on SNM in specific contexts [30-33], patients should be informed that IC is the first-line therapeutic option for neurogenic urinary retention.

Recommendations

- **Sacral neuromodulation can have an inhibitory effect on neurogenic DO (C).**

- **While sacral neuromodulation has a place in the care of neurological urinary incontinence or neurological urinary retention, the proportion of patients whose condition is improved is much less than in non-neurological pathologies (B).**
- **Indications for sacral neuromodulation in the care of DSD in neurological urinary dysfunction are still not established (D).**

2. DENERVATION PROCEDURES FOR TREATING REFLEX URINARY INCONTINENCE DUE TO DETRUSOR OVERACTIVITY

a) Peripheral bladder denervation

Various techniques of peripheral bladder denervation, such as prolonged hydrodistension or bladder trans-section, are no longer used. Some authors have reported transient improvement in certain patients after prolonged hydrodistension, but DO recurs rapidly and the procedure is not straightforward. There are no reports for patients presenting specifically with neurogenic DO [34]. Bladder transsection was briefly popular at the end of the 70s [35-37]. It involved complete section of the bladder wall from one ureteric orifice to the other. The technique was indicated for urgency incontinence. However, a lack of anatomical and physiological information to support the mechanisms of efficacy of the procedure, and a lack of reproducible results from the initial series, explains why it is no longer used.

Another bladder denervation technique was developed by Ingelman-Sundberg [38, 39], by resection of the inferior hypogastric plexus in contact with the bladder through an inverted U-shaped vaginal incision, dissecting the bladder laterally and posteriorly, as widely as possible. In the most recent paper [39], the authors report up to 54% recovery over a mean follow-up of about three years. Each published series is from the same group, is retrospective and reports only a small sample size (LOE4). It has only occasionally been used in neurogenic DO.

b) Isolated rhizotomy of ventral and/or dorsal sacral roots

Historically, attempts at sacral root surgery first focused on cutting the motor (ventral) sacral roots. It was soon clear that this method failed within six months. With a different objective, Brindley [40] developed a technique involving stimulation of ventral sacral roots to obtain controlled and complete bladder voiding in cases of SCI. He realised that patients only acquired continence if the stimuli causing reflex bladder contraction could be blocked [41]. Early techniques consisted in selective destruction of the dorsal sacral roots that evoke detrusor contractions. These selective rhizotomies did not, however, give the best results. Only after complete de-afferentation of the sacral micturition centre by intradural rhizotomy were better results obtained [42-45] (LOE2-3).

The technique of “selective” dorsal sacral rhizotomy has been studied more extensively. It involves making an extra-dural approach to the sacral roots (S2-5), isolating and stimulating the dorsal (sensory) contingent whilst monitoring changes in urodynamic pressure within the bladder in order to cut only those fibres responsible for overactivity. To retain reflex erection, S2 must be preserved, at least on one side. This treatment may be proposed for patients with neurogenic DO, and also those with urgency incontinence. The literature records only case series without control groups. Preliminary results were promising but were based on a small number of cases with short follow-up times [46-49] (LOE4). The outcome seems to deteriorate over time. Opsomer et al. [50] reported deterioration after one year for all treated patients (n=8)(LOE4). Torrens, one of the first to use the technique, was led to re-evaluate his long-term results [51]. The most recent article by Lucas et al. [52] concerning 22 patients (LOE3), also reported a significant, but less marked, deterioration at four years. At the mean follow-up of 4 years, 39% of patients retained a urodynamically stable bladder with satisfactory clinical response. The authors ascribe these improved results to a more extensive rhizotomy. However, it should be noted that there was a marked heterogeneity of patients in this series, three out of the eight, considered to be “successes”, were IDC patients with leakage due to DO.

Mertens et al. [53] applied a technique previously used for limb spasticity, namely microsurgical DREZotomy, the aim of which is to destroy the dorsal root entry zone (DREZ). This zone, first defined in 1972 by Sindou [54], is a functional anatomical entity that groups together the proximal portion of the dorsal root, the medial portion of the dorso-lateral tract and the superficial layers of the dorsal horn. The technique involves making a micro-surgical lesion (by micro-coagulation) on the ventro-lateral portion of the entry zone, near the apex of the dorsal zone. The effect of DREZotomy is to selectively block nociceptive afferents, and their relays, and myotatic afferents. The benefit of the limited lesion is to avoid complete abolition of tactile and proprioceptive sensitivity and to prevent the development of deafferentation phenomena. To treat neurogenic DO, the lesion must be made on both sides from S2 to S3, or even S4. The results from the first series concerned 38 patients treated for incapacitating lower limb spasticity, treated by extended DREZotomy from L2 to S1. 58% of these patients were permanently catheterized. At six months, DO had disappeared in 82%, with 63% having significantly improved bladder capacity. At 18 months post-surgery, leakage had disappeared in 89% of cases. In the last 8 years, no publications on DREZotomy for neurogenic LUT disorders were found.

Hohenfellner [55] following Brindley’s experience,

proposed “neurogenic bladder augmentation”. This involved completely destroying the ventral and dorsal sacral roots, possibly followed by continent cystotomy and simplified urinary catheterization. The author reported his experience with eight patients retrospectively (LOE3). After surgery in all patients, bladder capacity increased from about 177 ml to 670 ml, with complete disappearance of detrusor overactivity. No updates have been published since 2001 on this technique.

Percutaneous sacral root block

Sacral root block is an old technique, since Dogliotti [56] proposed it as early as 1931 to relieve vertebral cancer pain by chemically sectioning several dorsal roots. An injection of alcohol causes denervation due to the fragmentation of myelin in the endoneurium. In the 1950s, Bors [57] applied the technique to the bladder, standardized the procedure and described preliminary results. Later authors reported on a few series (LOE3) [58, 59], but always with the same result; the benefit disappeared after a few months. Phenol, considered to be “selective” for C fibers was then tried but the results were no better [60-62]. Chemical destruction of the sacral nerve roots has proved ineffective and is accompanied by a high rate of minor complications (pain), resulting in significant discomfort and prolonged hospitalization (LOE3) [58, 59]. Mulcahy et al. [63] proposed sacral rhizotomy by percutaneous radiofrequency for neurogenic bladder (LOE4). A recent study was published by Ferreire et al. [64]. In 8 SCI patients they performed a bilateral block of S3 with bupivacaine. These 8 responders had an increased bladder capacity and for 3 out of 4 patients autonomic dysreflexia (AD) improved.

c) Rhizotomy of posterior sacral roots and stimulation of the anterior sacral roots

Electrostimulation to improve micturition in patients with spinal cord injury has been extensively researched since 1954. Direct stimulation of the detrusor, the spinal cone, the splanchnic and sacral nerves have not produced reliable results. Since 1969, G.S. Brindley has developed a set of electrodes for stimulating the spinal roots in the cauda equina. The technique, first tested in baboons, led to the development of an implanted stimulator to induce micturition in paraplegic patients. Sacral rhizotomy performed during implant surgery makes it possible to control bladder hyperactivity and ensure continence. The energy source and the microprocessor for adjusting the stimulation parameters are not implanted. The transmitter transforms the electric current from the energy source into electromagnetic waves, which are picked up by the implanted receptor and re-transformed into an electric current that circulates to the electrodes in contact with the nerve. Depending on the surgeon’s decision, the implant is placed within the membranes of the dura mater or outside them, so as to stimulate the sacral roots from S2 to S4. At the same time, it is essential to perform posterior rhizotomy from S2 to S4 to remove any detrusor overactivity, though this is difficult to perform [65] (LOE4). This technique can only be performed in those with spinal damage who are para- or tetraplegic. The sacral reflex arc must be preserved.

Micturition is not continuous: the detrusor cannot be stimulated without also stimulating the sphincter. The parasympathetic fibers and the fibers destined for striated muscles are stimulated together. The response of detrusor smooth muscle fibers causes a gradual increase in pressure, which continues after stimulation has ceased. The “on-off” response to stimulation of striated muscle fibers is different. When stimulation stops, the striated sphincter immediately relaxes, whilst the detrusor continues to contract. A new wave of stimulation increases and maintains sufficient detrusor pressure to cause micturition after stimulation stops. The careful selection of stimulation and stopping times results in a discontinuous, but satisfactory, micturition. Sphincter fatigue due to electrical stimulations, blocking of pudendal nerve motor fibers [66] (LOE4) or use of specific detrusor stimulation by performing an anodal block [67] (LOE 4) have been reported, together with poor efficacy.

Stimulation can also help defecation and erection, but it should be remembered that the principal object of sacral nerve stimulation combined with posterior rhizotomy is to achieve urine continence and bladder voiding. Induced erection is a secondary benefit but not an indication for the procedure, and men should be warned that they would lose reflex erection after posterior rhizotomy.

The results of the intervention are summarized in **Table 4**. Briefly, the outcome with regard to continence and bladder voiding are good (LOE 2-3). Failures result from incomplete rhizotomy, where bladder hyperactivity persists, or from sphincter insufficiency which may be treated by additional placement of an artificial sphincter [44, 45] (LOE3). Incomplete rhizotomy can be surgically completed [44, 45, 68] (LOE 2-3). In all reported series, mean bladder capacity increased significantly (LOE 2-3). Micturition was obtained by electrostimulation with a post-voiding residue (PVR) of ≤ 50 ml in 69 to 100% of patients. All series reported decreased incidence of urinary infection, but the defining criteria were too varied to allow conclusions to be drawn. Posterior sacral rhizotomy probably protects the upper urinary tract from detrusor overactivity. It can resolve the problem of pre-operative reflux [68, 69] (LOE4). However, posterior sacral rhizotomy should be complete. Indeed, in a series of 500 patients, Brindley [68] (LOE3) reported twelve cases of upper urinary tract impairment, ranging from grade I reflux to upper urinary tract dilation.

Table 4: Results of series on Sacral anterior root stimulation technique + Sacral deafferentation

	Patient numbers	Sex ratio (M/F)	LOE	Mean follow-up (extremes)	Pre-op. conti-nence (%)	Pre-op. Post-op. Continence (%)	Pre-op. bladder capacity (ml)	Post-op. bladder capacity (ml)	% complete micturition (PVR < 50ml)	Pre-op. dysreflexia (%)	Post-op. dysreflexia (%)	Pre-op. UTIs (%)	Post-op. UTIs (%)
Brindley et al. (1994) [68]	500	271/229	3	4 years	-	-	-	-	82	-	-	-	-
Barat et al. (1992) [71]	40	26/14	3	2 ½ years	2,5	90	210 (50-500)	463 (200-600)	82	-	-	100	30
Van Kerrebroeck et al. (1996) [72]	52	29/23	3	3.5 years		81	285	592	87	14	4	4.2/year	1.4/year
Schurch et al. (1997) [71]	10	3/7	3	3.4 years	0	80	160	>500ml	100	60	60	80	30
Egon et al. (1998) [44]	96	68/28	3	5.5 years (0.5-14)	1	88	200 (40-600)	565 (300-600)	89	22	0	100	32
Van der Aa et al. (1999) [69]	37	33/4	3	(0.4-12)	-	84	75% < 400 ml	95% > 400 ml	91	-	-	-	-
Creasey et al. (2001) [74]	23	16/7	3	> 1 year	65	87	243 (30-450)	> 400 ml	69	35	7	82	78
Bauchet et al. (2001) [43]	20	6/14	3	4.5 years (1-8.5)	0	90	190 (40-600)	460 (350-800)	90	15	0	100	-
Vignes et al. (2001) [75]	32	-	3	8 years (4-11)	0	90	220 (50-600)	550 (350-600)	80	18	2	100	30
Kutzenberger (2005) [45]	464	244/220	2	6.6 (6-17)	-	83	173	470	81	-	-	6.3/yr	1.2/yr
Martens (2011) [70]	46	36/10	3	13(1-19)	-	52	-	-	-	-	-	-	50 (>1 yr)

Martens et al. looked at patients in the Netherlands who underwent a Finetech-Brindley procedure [70]. They investigated the effects on quality of life in a group of 46 patients that still used the implant. They also looked at the presumed beneficial effects of the rhizotomy only, comparing with a group of 70 matched controlled patients that had optimised standard care. The patients had a significant better Specific Impact of Urinary Problems score, general QoL index (Qualiveen), and continence rate, and less urinary tract infections compared to the Control Group. If the stimulator was not used anymore, patients still benefited from the rhizotomy with regard to QoL and continence rate. The subscales of the SF-36 had better scores for the patients who used their stimulator as compared to those who did not use the stimulator and compared to the Control Group. The conclusion was that the active group had a better QoL than the rhizotomy group, and both groups had advantages over optimized standard care.

Schurch [71] focused on the specific problem of dysreflexia and recorded its persistence during stimulation in all patients who had suffered prior to surgery, but with marked improvement in symptoms.

Conclusion

- **Bladder denervation is mainly reserved for those suffering complete spinal cord injuries.**

Recommendations

- **No peripheral bladder denervation technique has passed the test of time (D).**
- **Injections of neurolytic products to treat detrusor overactivity should be abandoned, since they are ineffective in the medium and long term and expose patients to morbidity (A).**
- **Sacral dorsal rhizotomies need to be quite extensive to treat successfully neurogenic DO. So they may be performed only in patients with lower limb neurological impairment (B).**
- **In certain situations, dorsal rhizotomies can be undertaken in association with ventral root stimulators (Brindley's technique) or even with continent cystostomy (B).**
- **Electrostimulation of the anterior sacral roots is a valid option for managing neurogenic bladder in patients with spinal lesion, with long-term follow-up (B).**
- **It must be combined with destruction of all or part of the posterior sacral nerves, and cannot therefore be performed in patients with conserved lower limb motility (B).**
- **The reflex arc must be intact(B).**
- **Posterior rhizotomy exposes men to loss of reflex erection and women to a loss in reflex vaginal lubrication(B).**
- **It is vital to assess the patient carefully before implantation so as to determine whether he/she will be able to mount a toilet or grasp a urinal handrail (B).**

3. SURGERY FOR INCONTINENCE ASSOCIATED WITH POOR BLADDER EMPTYING DUE TO DETRUSOR UNDERACTIVITY

Incontinence in neurological patients can be aggravated by deficient bladder emptying and retention. Two mechanisms can be involved: detrusor sphincter dyssynergia (DSD) or bladder hypocontractility. A literature search was undertaken for the terms: neurogenic bladder; spinal cord injury; spina bifida; myelomeningocele; multiple sclerosis; sphincterotomy; stent.

a) Surgical treatment of detrusor external sphincter dyssynergia

DSD is a characteristic feature of suprasacral and infrapontine lesions. The aim of sphincterotomy is to produce reflex micturition into a condom catheter, thus protecting the upper urinary tract. For the last thirty years, endoscopic sphincterotomy has been the technique of choice for patients who cannot or do not want to do IC. It is invasive, irreversible and the patient has no adaptation period [76, 77] (LOE3). Prosthetic sphincterotomy using a urethral endoprosthesis (or stent) is an alternative.

Sphincterotomy recommendation supposes a diagnosis of a neurological cause of DSD that is complicated by hydronephrosis, vesicoureteral reflux, autonomic dysreflexia or repeated urinary infections secondary to poor bladder voiding. Patients should have failed or refused IC. Main contra-indications are [78, 79]:

- Impossibility to retain a condom catheter. All sphincterotomy techniques, including stenting, are contra-indicated for men who cannot retain a condom catheter (hence also for women). A semi-rigid penile prosthesis can be placed to help retain the condom catheter [80] (LOE3). However, patients must be informed that there is a 20% to 30% risk of erosion and infection of the penile prosthesis for those with SCI, as opposed to only 2.7% in the general population [81, 82] (LOE3).
- Detrusor acontractility or hypocontractility. Patients with spinal cord injury and no reflex detrusor contraction during urodynamic tests are poor candidates for the various techniques of sphincterotomy.
- Patients who wish to father children and are candidates for vibro/electro-ejaculation and an artificial insemination program.

1. Endoscopic Sphincterotomy

Emmett [83] first described endoscopic sphincterotomy in 1948. He performed cervico-prostatic incisions

in patients with SCI, but later realized that the problem lay in the striated sphincter. External sphincterotomy was performed in 1958 by Ross et al. [84]. They carried out cold-blade surgery and placed a catheter (Ch 22-26) for tamponade, since nearly all patients required transfusion (one of the ten patients in the series died after surgery). A few attempts at surgical sphincterotomy via the perineal and subpubic myotomy routes were tried later. Complexity and frequent serious complications explains why these approaches were abandoned [85, 86]. Sphincterotomy with electrocoagulation was finally found to be the best technique.

Endoscopic sphincterotomy morbidity includes hematuria, which can be abundant and sometimes difficult to control, requiring transfusion in 2-13% of patients (LOE2-3). Incision at the twelve o' clock position seems to offer the lowest risk of hemorrhage, with three and nine o' clock sphincterotomies entailing the highest risk [87] (LOE4).

Post-operative impotence is also a common complication. Rates of up to 56% were reported in early series [88-91] (LOE3). More recent series (**table 5**, LOE 2-3), most using a median, or slightly deviated incision, have not affected sexual function. However, it should be noted that the population concerned may have many other reasons (neurological, psychological, etc.) for suffering from erectile dysfunction. When sphincterotomy is accompanied by complete incontinence there are obvious reasons for psychological difficulties during intercourse. This issue must be discussed with the patient before surgery. The fear of this sequel sometimes causes the patient to decide against surgery; use of an incontinent prosthesis as first-line therapy can enable the patient to gain insight into this potential consequence of endoscopic sphincterotomy.

If striated sphincter section fails, the possibility of bladder neck stenosis should be investigated. This is seen in from 2 to 21% of patients (LOE 2-3). Section of the bladder neck may then improve voiding, but will result in permanent incontinence. Before surgery, the surgeon must make sure that the patient accepts this situation and can use a condom catheter.

Results of endoscopic sphincterotomy are summarized in **Table 5** (LOE2-3). Any analysis is made difficult by the absence of unequivocal criteria of success. Some patients are improved by sphincterotomy, even with a 200 ml residue. Most authors use indirect urodynamic criteria to evaluate success (decrease in bladder pressure during micturition, decrease in PVR). The most obvious result is the improvement in autonomic dysreflexia observed in tetraplegic patients. It also appears that the intervention reduces the rate of symptomatic UTIs. However, chronic bacteriuria is not improved [92]. The reported results concerning resolution of hydronephrosis and vesicorenal reflux differ, and in each series, there are very few patients. Another essential point, well known in practice but rarely reported, is the recurrence of neurogenic DSD in many patients [77, 93, 94] (LOE3). Riccotone et al. (LOE3) [94] reported 82% recurrence of symptoms after ten years of follow-up. Juma et al. [77] (LOE3) report similar results after eleven years, with patients undergoing an average of 1.7 sphincterotomies. Pan et al. reported a mean duration of benefit of almost seven years, which could be sustained with a repeat procedure [95]. A single study has tried to address predictive factors for a successful sphincterotomy. In this retrospective study, although detrusor leak point pressure and retrograde perfusion pressure were found to be superior to residual urine volume in predicting sphincterotomy success, results were not statistically significant [96]. 30-68% of patients eventually develop some impairment of the upper urinary tract [77, 95]. Patients who have undergone this surgery must therefore be regularly monitored to detect any distension of their upper urinary tract.

2. Prosthetic sphincterotomy

In 1990, Shaw et al. proposed using a wire mesh stent (Urolume) to treat patients with spinal injury presenting with DSD [97] (LOE3). Since then, various stents have been used. **Table 6** lists the types of stent used for DSD, according to classification criteria [98, 99]. They can be placed in various sections of the urinary tract: prostatic urethra, through the striated sphincter or more distal in the subsphincteric urethra. Our review is limited to placement through the striated sphincter.

• *Temporary prosthetic sphincterotomy*

Temporary stents make it possible to carry out a therapeutic test to check the feasibility of condom catheter use, check that placing a foreign body in the urethra does not induce autonomic dysreflexia and ensure the patient accepts the mode of micturition. Moreover, during this trial period, it is possible to study how the bladder empties in the seated position, and assess the necessity of additional treatment for smooth muscle sphincter dyssynergia at the level of the bladder neck. Moreover, as this treatment is simple and reversible, it is possible to propose it very early to the patients, rendering the patient autonomous with regard to carer-assisted catheterization, if this were the prior mode of micturition and leaving the possibility to discuss any fertility and sexual issues, and considering the possibilities of preserving sperm. For patients with SCI, early temporary stent placement (within six months of trauma) theoretically has the added advantage of waiting for recovery of upper limb motility to enable IC, decrease the risk of nosocomial infection during rehabilitation by reducing carer-assisted catheterization, and relieve nursing load during rehabilitation. The last two points, though logical, are yet to be proved by relevant studies. After using a temporary stent, the patient may choose his mode of micturition; i.e. return

Table 5: Results of endoscopic sphincterotomy

	Number patients	LOE	Mean Follow-up (months)	Success criteria
Chancellor *et al.* 1999 [92]	26	2	24	- PVR decrease - Hydronephrosis, VR reflux decrease (100%, 100%) - Improved micturition comfort (80%) - Improved autonomous hyperreflexia (100%)
Catz *et al.* 1997 [132]	32	3	NP	- Significant decrease in PVR - Decrease in infections (74%) - Decrease in hydronephrosis, reflux (66%, 40%) - Improved autonomous hyperreflexia (100%)
Perkash *et al.* 1998 [121]	37	2	9	NK
Fontaine *et al.* 1996 [133]	92	2	20.6	- Decrease in hydronephrosis, reflux (100%, 90%) - Significant decrease in PVR, micturition pressure - Decrease in infections (74%) - Improved micturition comfort (73%) - Improved autonomous hyperreflexia (93%)
Noll *et al.* (1995) [76]	105	3	59	No statistical study, but: - Improved autonomous hyperreflexia (42 to 17%) - Decrease in mean PVR (180 to 70 ml) - Decrease in micturition pressure (from 97 to 37 cm H2O) - Decrease in frequency of symptomatic urinary infections (8.1 to 3.6 per year)
Rivas *et al.* 1995 [120]	22	2	12	- Improved autonomous hyperreflexia (44%) - Significant decrease in PVR, micturition pressure - Decrease in hydronephrosis (40%)
Juma *et al.* 1995 [77]	63	3	132	- Renal function (creatinine): normal in 97% of patients - on X-ray, 30% of patients showed upper urinary tract impairment. - 2/3 patients had more than one sphincterotomy
Vapnek *et al.* 1994 [93]	16	3	39	- 31% required repeated sphincterotomy - 50% failure rate (sub-pubic catheter placed)
Namiki 1984 [134]	9	4	3	- PVR < 50 (100%)
Ruutu *et al.* 1982 [135]	11	4	NS	- Subjective improvement in micturition comfort (56%) - Improved autonomous hyperreflexia (100%)
Carrion *et al.* 1979 [136]	60	3	12	- Reflux disappeared (86%) - Significant decrease in reflux: 75%

LOE: Level of evidence; NK: Not known; PVR: Post-Void Residue

Table 6: Urethral stents used in neurogenic DSD

Temporary stents					
Stent	Expansion method	Size		Material	Maximal duration (months)
		Caliber (F)	Length (mm)		
Not specific to the striated sphincter First-generation					
Urospiral [137]	Non expandable	21	40-80	Stainless steel	<12
IUC [138]	Non expandable	16-18	25-80	Polyurethane	<6
Second-generation					
Memokath [139]	Heat	22/34	30-70	Nitinol	<36
Specific to the striated sphincter					
Diabolo [100]	Self-expansion	18	38	Medical steel	>12
Permanent stents					
Stent	Expansion method	Size		Material	
		Caliber (F)	Length (mm)		
Urolume Wallstent [140]	Self-expansion	42	20-40	Steel alloy	
Titan [141]	Balloon	43	19-58	Titanium	
Memotherm [142]	Heat	42	20-80	Nitinol	
Ultraflex [144]	Self-expansion	42	20-50	Nitinol	

to his former state, change to another temporary stent, replace it by a permanent stent, or choose surgical sphincterotomy.

By definition, temporary stents should be self-retaining, easy to remove and must not epithelialize. Only the temporary stent Diabolo [100] is specific for the external urethral sphincter. The results of two types of temporary stenting (test) for incontinence have been published in the same series [101] (LOE3). In a retrospective study of 147 patients, the authors demonstrated a significant effect on incontinence throughout the mean ten month test period, with very low morbidity (15%). The temporary stents were removed easily from all patients without sequelae. After this period, 62.6% of patients chose permanent sphincterotomy, usually by means of a permanent stent. During the study, the authors abandoned the first used stent (Nissenkorn), replacing it with Diabolo.

Memokath is another device that has been studied in neurological patients [102-107] (LOE3-4). Several authors report complications (32-100%) using this stent, which seems to induce a lot of bladder stones and to be quite difficult to remove, especially if it is left longer than 18 months. When used as second-line treatment following failed sphincterotomy, Memokath successfully reduced post-void residuals, but failed to improve urodynamic parameters including bladder capacity, detrusor leak point pressure, bladder compliance, and maximum detrusor pressure [102].

• *Permanent prosthetic sphincterotomy*

Permanent stents are designed to integrate with the urethral wall [108]. They resist the striated sphincter and prevent its closing during reflex contraction. They can be removed if necessary, or at the patient's request, with recovery of striated sphincter contraction [109, 110]. Permanent stents are made of biocompatible materials such as nitinol (a nickel and titanium alloy) and titanium. They usually consist of a mesh comprising a single thread (e.g. Urolume) or several threads (e.g. Ultraflex). None of the stents are specifically adapted for the urethral striated sphincter. Three have been reported for treating neurological patients with DSD: Urolume, Memotherm and Ultraflex. All can be placed under local anesthesia. **Table 7** summarizes the principal series published on these devices. Only Urolume was studied according to strict prospective criteria [92] (LOE1-2). Using stringent clinical and statistical methods, they classified the stent as LOE 1 for effectiveness and morbidity in DSD with a 5-year follow-up. 160 patients with SCI (mean age 36.3 years) in 15 North American centres, were treated prospectively with Urolume for DSD. Urodynamic parameters for micturition pressure, PVR and functional bladder capacity were measured before treatment and then annually up to 5 years afterwards. Mean micturition pressure, the primary criterion, was significantly lower 5 years after stenting. PVR decreased significantly and was maintained after 5 years. Mean bladder capacity remained constant. Hydronephrosis, suffered by 28 patients before surgery, disappeared in 22 (78.6%) and was improved in the others. Autonomic dysreflexia resolved in 70% of cases. The indwelling catheters of 63 of the 86 (84.9%) patients catheterized before surgery could be removed. The percentage of positive urine cultures remained unchanged after stenting. No case of peri- or post-operative bleeding, soft tissue erosion or bladder lithiasis were observed during the study. One case of prosthetic encrustation occurred during the first year; three during the second year; three during the third year; two during the fourth year and five in the fifth year. Urothelial reaction was reported in 44.4% of cases, but 93.3% of these were mild and none required treatment. No erectile dysfunction was reported. Stents had to be removed from 24 patients (15%), four of whom received new implants. 80% of the patients considered their situation improved by stenting, and 84% of physicians considered the treatment effective. 47 patients required supplementary treatment on the bladder neck (endoscopic section in 20 cases). In the mid-term, prosthetic sphincterotomy using a Urolume stent appears to be satisfactory. However, the situation is not so clear over the longer-term. It is not always easy to remove the stent, especially from patients who have not been monitored regularly. Some teams report highly complex surgery for stent removal, especially in the event of associated urethral stenosis [111-114] (LOE3). A small study (n=12) following patients up to twenty years after insertion, suggests a high rate of complications, as 5/6 patients who completed the 20-year follow-up developed bladder neck dyssynergia requiring incision, 2 patients developed obstructive encrustations within the first year of insertion and another patient developed bladder cancer [115]. However, in those patients who completed the 20-year follow-up, sustained significant improvements in maximum detrusor pressure and duration of detrusor contraction were recorded.

Whether patients should be offered prosthetic or endoscopic sphincterotomy is not yet agreed. Endoscopic sphincterotomy is the preferred standard treatment for DSD, where IC cannot be performed. Two prospective studies carried out in the US in 1994 indicated that prosthetic sphincterotomy was at least as effective as standard sphincterotomy in patients with SCI, and offered advantages in terms of morbidity, duration of hospitalization and cost [116, 117]. The two studies were not randomized. Follow-up was short (mean 15 months), with a potential risk of bias, since the conclusion that external sphincter balloon dilatation is as effective as endoscopic and prosthetic sphincterotomy is not borne out by long-term outcomes [118].

Table 7: Results of the main series on sphincterotomy using urethral stents

	Stent	Year	LOE	n	Efficacy (%)	Mean follow-up (Months)	Migration (%)	Complications
Pannek et al. 2011 [102]	Memokath	2011	3	22	78	10	18	32
Mehta et al. [105]	Memokath	2006	3	29	89	21	23	42
Hamid [146]	Memokath	2003	3	25	89	20	28	48
Vaidyanathan et al. 2002 [107]	Memokath	2002	4	10	90	20	10	100
Low et al. 1998 [104]	Memokath	1998	3	24	54	16	33	38
Shah et al. 1997 [147]	Memokath	1997	3	14	78	24	NA	NA
Game et al. 2007 [101]	Nissenkorn/Diabolo	2007	3	147	NR	10	29	30
Denys et al. 2004 [144]	Memokath	2004	3	47	81	19	22	15
Juan Garcia et al. 1999 [142]	Memokath	1999	3	24	100	15	16	17
Rivas et al. 1994 [117]	Urolume/vs sphincterotomy	1994	2	46	79	16	15	0
Chancellor et al. 1999 [92]	Urolume	1999	2	160	84	60	28	20
Chancellor et al. 1999 [119]	Urolume/vs sphincterotomy	1999	1	54	81	24	9	0
Hamid et al. 2003 [103]	Urolume	2003	3	12	77	144	NR	16
Abdul-Rahman et al. 2010 [115]	Urolume	2010	3	12	80	144	0	80

A prospective, multicenter, randomized study comparing endoscopic sphincterotomy with prosthetic sphincterotomy was published in 1999 by Chancellor and Rivas, using the Urolume stent [119]. Fifty-seven patients in three specialist spinal cord injury centers were included. The study concluded that prosthetic sphincterotomy was as effective as endoscopic sphincterotomy and required shorter hospitalization. These findings are relevant only for the short and medium-term. The long-term outcome of prosthetic sphincterotomy for incontinence remains unreported. At present, it is vital that stented patients be monitored carefully at least once a year during the years following implant surgery.

3. Other sphincterotomy techniques

Two authors reported using Nd-YAG lasers for sphincterotomy [120, 121]. Although no randomized study has been conducted, comparison with results from the literature (with very short follow-up), suggests that these techniques are not as good as standard endoscopic sphincterotomy. However, the reported morbidity (particularly hemorrhage) was reduced (LOE2). External sphincter balloon dilatation was recommended by Chancellor et al. [122], with short-term results similar to those of surgical sphincterotomy. However, the technique has been abandoned by its sponsors and the device has not been distributed, probably indicating poor efficacy in the medium and long-term, compared with other mini-invasive methods such as stenting.

b) Bladder neck incision (BNI) for detrusor-bladder neck dyssynergia (DBND)

The rationale to use BNI was that sympathetic overactivity might inhibit detrusor contraction and transurethral incision of bladder neck might interrupt the inhibitory reflex arc and result in restoration of detrusor contractility. In a single retrospective study BNI was performed in 22 patients with high-level SCI and DBND demonstrated upon video-urodynamics, who were previously managed by either IC or indwelling catheter [123]. Voiding symptoms were complicated by autonomic dysreflexia in 17/22 patients. Deep incisions were carried out at the 5 and 7 o'clock positions, sparing the external urethral sphincter. A satisfactory surgical outcome, defined as greater or equal to 2-point reduction in the AUA/IPSS quality of life index was recorded in 86.4% of the patients 3 months post-op (LOE3). Presentation of urodynamic results is not, however, clear. Significant reductions were reported in those patients with preoperative Pdet >15cm H2O and significant increases in those with preoperative Pdet <15cm H2O, but it was not clarified whether detrusor pressures refer to filling or voiding Pdet. Post-void residual improved significantly in both patient subgroups. While all patients additionally suffered from DSD preoperatively, an open urethral sphincter during voiding was reported in 86.4% of them following BNI, and autonomic dysreflexia became less severe or resolved in 88.2% of sufferers. The authors hypothesized the presence of a urethra-to-bladder neck reflex pathway to explain additional improvements in DSD, but this theory as well as the clinical results need to be verified in further studies.

BNI, however has been used as supplementary treatment in patients who were originally managed with a urethral stent. It is not clear whether in those cases BDND was an overlooked primary dysfunction or developed secondary to the use of the stent. It is recognized in a large percentage of patients with a permanent stent [92, 115, 124], and is reported to be treatable with BNI although detailed results are missing (LOE 3-4).

Recommendations

- **Where clean intermittent catheterization is not possible, the long-term use of indwelling catheters should be avoided (B).**
- **Whatever type of sphincterotomy is chosen (surgical or prosthetic):**
  - **Patients must think carefully about the different modes of micturition possible for them (A).**
  - **The few studies reporting long-term results of sphincterotomy demonstrate the vital importance of regular patient monitoring for the recurrence of DSD or blockage (B).**
  - **This mode of micturition is contraindicated in women, and in men with difficulty in maintaining a condom catheter (B).**
  - **Men who wish to have children should be warned of the risk of ejaculatory duct obstruction (B).**
- **For patients who have chosen surgical sphincterotomy:**
  - **The reference technique involves an elective 11, 12 or 1 o'clock incision of the urethral sphincter (B).**
  - **Although surgical sphincterotomy is the accepted reference treatment for neurogenic DSD, analysis of the literature highlights the lack of reliable efficacy and reproducibility criteria for the technique (B).**
- **For patients who have chosen prosthetic sphincterotomy:**
  - **Different types of stent are used, depending on whether sphincterotomy is temporary or permanent. Stents are complementary, and different designs can be used for different situations (B).**

- **o Surgical complications depend as much on the surgeon's competence as on the material and may be reduced by experience (C).**
- **o Clinical studies have demonstrated that neurogenic patients prefer prosthetic sphincterotomy because it is reversible, even when permanent stents are placed (C).**
- **o Careful follow-up, using yearly cystourethroscopy is mandatory when leaving a permanent urethral stent (B).**
- **o Published data is inadequate to support a recommendation on the use of bladder neck incision in patients with inadequate bladder emptying due to detrusor-bladder neck dyssynergia, either as a first-line procedure or as a complementary approach to DBND recognised following permanent urethral stenting. Further studies are needed.**

4. SURGERY TO INCREASE DETRUSOR STRENGTH

For some patients, the cause of bladder hypocontractility lies in the bladder wall. In this case, the control circuit functions but the bladder muscle is too weak. At present there is no medical treatment for this situation. The general objective is to reduce peripheral resistances as much as possible and where this fails, to propose IC. However, some teams have suggested placing rolled strips of muscle around the bladder. Some authors have also suggested a strip of rectus abdominis muscle. This is easier to perform and may be used essentially for reconstructive surgery, such as in bladder exstrophy [125-127] (LOE4). The only team to have published results on bladder hypocontractility in man is that of Ninkovic et al. [128] (LOE2). They reported interesting results from twenty patients suffering from neurogenic detrusor underactivity and requiring self-catheterization. They reported a technique that they had designed in animal experiments [129, 130] (LOE4) and which consisted of transferring a free strip of latissimus dorsi muscle, which was anastomosed to the epigastric vessels and the lowest branch of the intercostal nerve. Out of twenty patients, with a mean follow-up of 44 months, 60% no longer required IC, with PVR below 100 ml. After complementary surgery on the bladder neck, there was a 90% success rate that was stable over time. The authors reported no heavy morbidity, particularly with regard to the donor site. These promising results were largely confirmed in a multicentre trial involving 24 patients with a median follow-up time of 46 months [131]. Complete spontaneous voiding (mean PVR 25ml) was restored in 71% of the patients, while frequency of CIC was reduced in another 13%. Recurrent UTIs ceased in 91% of patients. A critical increase in bladder contractility index may be required to achieve complete bladder emptying, but the number of patients was too small for safe conclusions. Future development could use tissue-engineering techniques to construct vascularized and contractile strips implanted around the bladder with the same procedure. Reduction cystoplasty, previously used in Prune Belly syndrome has not been reported in neurogenic LUT dysfunction.

Recommendations:

- **Latissimus dorsi myoplasty on the bladder is a promising technique that needs to be validated further (C).**

5. STRESS URINARY INCONTINENCE (SUI) DUE TO SPHINCTERIC INCOMPETENCE

Some patients with neurogenic lower urinary tract dysfunction will suffer from incontinence due to sphincter weakness. In general, patients with lesions affecting the brain or suprasacral spinal cord will not suffer from this problem, as the sacral sphincter guarding reflexes will be intact. However, patients with lesions of the conus medullaris, the cauda equina or peripheral sacral nerves are at risk of developing neurogenic stress incontinence. Patients with neurological disease may also suffer from stress incontinence due to direct sphincter injury from urethral catheter trauma or as a result of previous interventions such as sphincterotomy or dorsal rhizotomy. In women, SUI may be present for non-neurogenic reasons such as urethral hypermobility due to previous pregnancy and childbirth.

People with neurogenic lower urinary tract dysfunction and SUI may also have impaired bladder storage function. If this is the case, a surgical procedure that treats the stress incontinence in isolation might put the patient at risk of upper urinary tract deterioration (as the upper tracts become exposed to the full force of the bladder dysfunction, having lost the "safety valve" effect of a weak sphincter) or of persisting incontinence. Pre-operative urodynamic evaluation of bladder function is therefore mandatory before undertaking surgery for neurogenic SUI.

The question as to when it is safe to treat neurogenic SUI while leaving bladder dysfunction uncorrected has been studied most intensively in the paediatric age group. Most series relate to children with spinal dysraphism/myelomeningocoele and, typically, authors report the necessity to proceed to bladder augmentation in at least a third of patients. Even with a thorough urodynamic and radiologic preoperative evaluation, some patients will have late bladder compliance deterioration [148-165]. However, the issue continues to generate debate and studies have not reached total consensus; for example, Snodgrass et al. [166] (LOE3) published a retrospective analysis of 30 children (mean age: 8.6 years) who had a bladder neck sling procedure and appendico-vesicostomy without augmentation. At 22 month of mean follow-up, only one patient had

had to undergo a bladder augmentation. In a subset of 16 patients who had urodynamics at 24 months, 13/16 had an increase of their maximum bladder capacity. However, 67% of the patients required anticholinergic therapy. In contrast, Dave et al. [167] (LOE3) strongly advocate the case for simultaneous bladder augmentation. The authors report a series of 15 children followed for at least five years after an isolated bladder outlet procedure (5 Pippi-Salle, 5 slings and 5 artificial urinary sphincter). At a mean follow-up of 11.25 years, all the patients underwent surgery to increase bladder capacity, either for recurrent incontinence or for upper urinary tract deterioration. At present, no definitive conclusions can be drawn as to advisability of routine prophylactic bladder augmentation, but many authors recommend a concomitant bladder augmentation when performing a bladder outlet procedure [168] (LOE4). The option of using detrusor injections of botulinum toxin in children offers a further therapeutic approach in circumstances where there is uncertainty.

A further important consideration when contemplating neurogenic SUI surgery is the means of bladder emptying following treatment of the sphincter weakness. In particular, patients who are emptying their bladders using an element of straining will not be able to empty in this way post-operatively. Patients will therefore need to consider how they will empty their bladder once continence is achieved. The options available to patients will include: IC (either via the urethra or a continent catheterisable abdominal conduit) or the use of a suprapubic catheter (either on free drainage or with a catheter valve). There will be some patients, who have only limited neurological damage, who will continue to be able to empty their bladder using voluntary voiding post-operatively but, even in this group, it is necessary to warn patients of the possible need for post-operative IC and to make sure that they are capable of using the technique before embarking on treatment.

a) Bulking agents

There have been some studies reporting on the use of bulking agents in neuropathic patients (**table 8** and 20-27). Most of the published series relate to the use of periurethral injections in children. Various agents have been used. Polytetrafluoroethylen (TEFLON) was one of the first [169, 170]. It was once popular for treating vesico-ureteric reflux, but it has been progressively abandoned after several authors reported possible particle migration and granulomatous reaction to this product [171, 172] (LOE2). Collagen has also been used, although collagen lysis can lead to the loss of the bulking affect over time [170, 173-180]. Other synthetic products that have been used include polymethylsiloxane (MACROPLASTIQUE) and dextranomer hyaluronic acid copolymer (ZUIDEX) [169, 181-187]. Zuidex is no longer used in SUI, but is in use for vesico-ureteric reflux. Henly et al. [188] demonstrated that distant migration of particulate silicone was observed in animals after periurethral injection with polymethylsiloxane (LOE4). This was not demonstrated with dextranomer acid copolymer injections [189] (LOE4).

One of the main advantages of periurethral injections of bulking agents is that they are minimally invasive and can even be carried out as an outpatient procedure. The product is usually injected in the region of the bladder neck using a retrograde endoscopic approach. The bulking agent is injected at up to four sites with the aim of achieving urethral coaptation. Dean et al. [187] have suggested using an antegrade approach whereby the bladder neck is accessed using a percutaneous puncture into the bladder.

The results of periurethral injection surgery are summarized in **Table 8.** There are difficulties in comparing results from different series, because patient populations and definitions of treatment success differ. In particular, the criteria for defining “improvement” and “social continence” vary. Therefore, it seems appropriate to consider the proportion of “dry patients” as defining clear-cut success (even if some authors add to this result a notion of “dryness for some hours” between voiding or catheterization). Using this definition, 0 to 36% of the patients are considered to be cured using bulking agents (LOE2-3). Moreover, these results are observed after a mean follow up that rarely exceeds 2 years (LOE2-3), although one series has reported long-term improvement up to 7 years after the last injection [190].

There are other important considerations to be made when interpreting the results of periurethral bulking agents. The first is that the studies in children generally contain patients with two types of problems: congenital urinary tract malformations (epispadias, bladder exstrophy) and neurogenic lower urinary tract dysfunction (mainly myelomeningocoele). This is of importance because there is some indication that, in children, bulking agents work slightly better in patients with malformations than in those with neurological problems [169, 176, 184, 190]. The global results of the series are therefore probably more optimistic than the results that might be observed in a population of only neurological patients. A second point is that these children have frequently already undergone various surgical procedures, which could modify the results of the injection procedure. Although a high proportion of the patients in these studies use IC, some have satisfactory outcomes while continuing to void spontaneously.

Although the use of bulking agents does not appear to cause any severe complications, there is the suggestion that the presence of deposits of inert material might lead to greater difficulty in performing future bladder neck surgery [184, 197, 190]. It is also important to acknowledge that the failure to correct

Table 8: Results of bulking agent injection in patients with neurological bladder dysfunction

	n	LOE	Neurogenic bladder number of patients	Bulking agent	Age (years)	Male/ female	Follow up (years)	Dry (%)	Improved (%)
Leonard et al. [178]	18	3	10/18	Collagen	10.5	12/6	1.3	36	28
Perez et al. [177]	32	3	25/32	Collagen	9	23/9	0.9	20	28
Bomalaski et al. [176]	40	2	25/40	Collagen	12.1	28/12	2.1	22	54
Caione et al. [185]	16	2	3/16	DHAC	10.1	9/7	1	18.7	56.3
Sundaram et al. [174]	20	3	12/20	Collagen	9.5	12/8	1.3	5	25
Kassouf et al. [180]	20	3	20/20	Collagen	13.3	15/5	4.2	5	15
Chernoff et al. [179]	11	3	8/11	Collagen	10.6	6/5	1.2	36	18
Block et al. [175]	25	3	25/25	Collagen	11.7-21.9	15/10	2.9-4.7	4	44
Hamid et al. [183]	14	3	14/14	PDS	41	14/0	2.9	36	21
Godbole et al. [170]	15	3	14/15	PTFE, collagen, PDS	10.2	10/5	2.33	20	53
Halachmi et al. [181]	28	3	10/28	PDS	12.5	22/6	1	0	42
Misseri et al. [186]	16	3	12/16	DHAC	4 to 18	6/10	0.8	19	31
Lottmann et al. [190]	61	2	27/61	DHAC	10.3	41/20	3	26	26
Guys et al. [184]	49	3	49/49	PDS	10.5	21/28	6.1	33	14
Dean et al. [187]	34	3	28/34	DHAC	11.7	18/16	0.3	NS	71
Dyer et al. [169]	34	3	12/34	PTFE, DHAC	2.7 (PTFE)/ 14 (DHAC)	NS	NS	6	12
DeVocht et al. [226]	89	3	27/27	DHAC, PDS	Children	14/13	14/13	7	17

DHAC (Dextranomer Hyaluronic Acid Copolymer) PDS (polydimethylsiloxane), PTFE (Polytetrafluoroethylene), NS (Not stated), LOE (Level of evidence)

incontinence is in itself a complication of the operation [168]. Most authors agree that no more than two injections should be undertaken since further injections are unlikely to produce a long term improvement. Gender and previous bladder/sphincter surgery do not seem to be reliable prognostic factor regarding the success of the injections.

b) Autologous Sling Procedures:

In women with neurogenic lower urinary tract dysfunction, the use of an autologous fascial sling to support the urethra (usually close to the bladder neck) has been widely used to treat stress incontinence. A sling can either be used in isolation or in conjunction with other procedures such as bladder augmentation. **Table 9** summarises the results of published case series. Complete continence is observed in 83 to 89% of the patients (LOE3). Once again it should be emphasised that many patients will be dependent on bladder emptying using IC or an SPC, because the patient's neurological dysfunction may preclude voluntary voiding and because the sling may have to be inserted under tension in order to provide sufficient outflow resistance in the face of neurogenic intrinsic sphincter deficiency. All of the series report a low morbidity rate from the procedure. In particular, the risk of urethral erosion is very low when fascial slings are used. Synthetic sling materials have generally not been advocated when significant sling tension is

Table 9: Results of bladder neck sling procedures in patients with neurological bladder dysfunction

	n	LOE	Neurogenic bladder number of patients	Age (years)	Male/ female	Bladder augment. surgery (%)	Follow up (years)	Continence rate (%)
Snodgrass et al, 2007 [166]	30	3	30/30	8.6		0	1.9	57
Karsenty et al, 2007 [191]	11	3	11/11	42	0/11	100	3.6	72
Albouy et al, 2007 [193]	14	2	14/14	14	7/7	100	5	79
Castellan et al, 2005 [192]	58	3	58/58	11.4	15/43	100	4.2	88
Austin et al, 2001 [148]	18	3	18/18	14	8/10	33	1.8	87
Barthold et al, 1999 [149]	27	3	26/27	NP	7/20	81	2,1/3,6	28(sling)/50 (wrap)
Gosalbez et al, 1998 [150]	30	3	28/30	10	6/24	97	3.1	93
Kakizaki et al, 1995 [151]	13	3	11/13	13	10/3	69	3	76
Gormley et al, 1994 [227]	15	3	15/15	NS	0/15	13	NK (0.5-8.5)	85
Elder et al, 1990 [228]	14	3	14/14	12.6	4/10	7	1	86

(LOE: level of evidence, NS not stated)

required because of the risk of secondary urethral erosion [170, 197-199] (LOE3). However, there is a lack of studies that compare the use of autologous tissue and synthetic material. Bladder neck slings appear to be capable of providing good results in children. Some series suggest that girls have better outcomes [166, 191-193].

c) Suburethral tapes

Midurethral tape operations, such as the tension-free vaginal tape procedure, have taken a major role in the management of stress incontinence in the non-neuropathic population but have not been adopted for the treatment of neurogenic stress incontinence; concerns about the risk of urethral erosion have been discussed already. Furthermore, intrinsic sphincter deficiency represents the usual pathophysiology in neurogenic SUI, contrasting with urethral hypermobility in non-neuropathic women.

There is very little published data available on the efficacy of midurethral tension-free tape operations in adult women with neurogenic LUTD. In a retrospective series of 12 women treated by TVT [200] with a mean follow up of 10 years, 9 patients were available for assessment of which 7 were dry and 2 were improved. The authors did not report any urethral erosions on follow up.

For male patients with post-prostatectomy incontinence, the use of synthetic tapes is increasing but, there is very little data for patients with a neurological cause to their incontinence, other than case reports. The use of this type of device in patients with underlying neurological illness should clearly be very cautious until further data emerges from clinical trials (LOE4).

d) Artificial urinary sphincter (AUS)

Since it was introduced in clinical practice [201], the AUS is recognized as one of the most effective treatments for urinary incontinence. It has the inherent advantage that it provides an adequate urethral closure pressure during the urine storage phase of the micturition cycle but then allows voiding to take place in the face of a low bladder outlet resistance. In patients with SUI, it is able to deliver either complete or “social” continence in 75 to 87% with satisfaction rates ranging between 85 and 95%. These rates are provided by published case series that contain a majority of patients with post-prostatectomy stress incontinence (PPI), along with some neuropathic patients. However, outcomes are probably similar for patients with neuropathic stress incontinence and a low-pressure bladder reservoir (LOE4) [202]. It should be noted that most of the published data on the use of the AUS in neurogenic SUI relates to men, although the device is also used in female patients with neurological disease.

Before using the AUS in neurogenic SUI, several factors must be considered:

• Firstly, the risk of implant infection and erosion is probably higher than in the PPI population. It is generally recommended that patients undergo

pre-operative urine culture and sterilisation of the urine before surgery [203] (LOE4).

• Manual dexterity must be sufficient to allow the patient to use the AUS pump- either to open the cuff to urinate, or to allow IC [202]. They must also accept the need for IC should the bladder have reduced contractility. However, some studies seem to indicate that the cycling activation of the pump could be avoided in patients performing IC (LOE3) [204, 205]. Bersch et al. [204] have described a modified technique.

• The cuff implantation site in adult patients with a neurologic bladder dysfunction is debated. The cuff can be implanted via a retropubic approach at the level of the bladder neck or around the prostatic apex. Alternatively the cuff can be implanted around the bulbar urethra using a perineal incision. Proponents of the retropubic approach argue that perineal incisions may cause cicatrisation problems for patients in wheelchairs. Moreover, traumatic catheterization is a well-known risk factor of urethral erosion in the non-neurological population undergoing an AUS [160] (1 to 5.5% in contemporary series) and, although it is recognized that IC is possible in AUS implanted patients [206], the risk of traumatic catheterization and subsequent cuff erosion might be higher when the bulbar urethral site is used. On the other hand, inserting an AUS cuff around the bladder neck is technically more difficult in adults in comparison with peri-bulbar implantation (LOE4). Some investigators are now exploring the possibility of using a laparoscopic technique for sphincter implantation [207].

• It is necessary to know the ejaculatory status of males in order to discuss the possible impact of the device on ejaculatory function. Cuff implantation around the bladder neck may allow patients to achieve antegrade ejaculation [208, 209] (LOE4).

As previously stated, a thorough urodynamic evaluation of the bladder is mandatory in order to evaluate the potential impact of bladder compliance following AUS implantation. This has been reported in several retrospective series (LOE3) [152-165]. The reasons for this change in bladder behaviour are not known, and it has been observed particularly in populations of patients with myelomeningocoele [157, 159, 161,162, 164]. In the event of any doubt about the quality of the bladder reservoir, bladder augmentation should be performed. The main results of published series are summarized in **table 10**. The continence rate is high, especially when a bladder augmentation has been performed (59 to 100% of the patients). The older series include some patients with the previous version of the AMS 800 (AMS 792). Therefore, it is possible that the long-term outcomes for patients being implanted today may be better than those seen in the past as a result of technical modifications of the device. Device infection, cuff erosion into the urethra and loss of fluid from the implant are the main causes of loss of an AUS. Infection and erosion typically occur in the early months after implant but late erosions are seen [156] (LOE3). The average "survival" for AUS is ten years. This particular point has to be explained to the patient, especially when they are very young. However, it is important to stress that sphincter replacement is usually possible so that continence can be restored. The majority of the authors consider AUS to be the "gold standard" procedure to treat neurogenic sphincter deficiency in men.

e) Surgery of the bladder neck

Three main procedures have been described. Historically, the technique of Young [210], later modified by Dees [211] and Leadbetter [212] came into use, essentially for reconstruction in cases of exstrophy and epispadias. The principle was to mobilise the trigone (after ureteric reimplantation) in order to resect bladder neck tissue, so as to reconstruct the trigone around a small catheter. Although some authors [213, 214] described its use in neurogenic patients, the procedure has rarely been used in this patient group. However, a recent paper describes an interesting hybrid procedure whereby a bladder neck reconstruction was combined with implantation of a fascial sling in neuropathic children with a post-operative continence rate of 82% [77]. Tanagho [215] (LOE3) described a variation of this technique which can be used in difficult situations in incontinent adult patients, when the implantation of an AUS is not possible [216].

The Kropp procedure [217] involves the use of a tubularised flap of the anterior bladder wall, which is used to extend the bladder neck and create an intravesical conduit. The tube is secured to the posterior bladder wall between the ureteric orifices. In the initial technique, the tube was tunnelled submucosally, but this manoeuvre was thought to increase the risk of tube stenosis [218, 219] (LOE3).

A third technique is that described by Pippi-Salle [220]. It is considered to be a variant of the Kropp procedure (also called a Kropp-onlay), with an anterior bladder wall flap that is not tubularised. Initial descriptions involved routine ureteric reimplantation but this was abandoned in later patients as long as there was an absence of reflux [221, 222] (LOE3). In a systematic review, Kryger et al. [168] (LOE4) stated that only data on 83 patients for the Kropp technique and 25 with the Pippi-Salle procedure have been published. Since that review there has been a lack of further significant data concerning the outcomes of these procedures. The continence results are good (50-69% for the Pippi-Salle procedure, 78-81% for the Kropp procedure) [218, 219]. However, several problems exist with the two techniques. Firstly, the techniques do not allow easy endoscopic access to the bladder. This is a major problem because it prevents or limits future endoscopic

Table 10: Results of artificial urinary sphincter in patients with neurological bladder dysfunction

	n	LOE	Neurogenic bladder number of patients	Age (years)	Male/ female	Bladder augment. surgery (%)	Follow up (years)	Continence rate (%)	Cuff Implantation Site	Complication/revision rate (%)
Bersh et al. 2009 [153]	51	3	51/51	38.7	37/14	19.6 (sacral root surgery)	8	70.6% (total) /90.2% (social continence)	Bladder neck	7.8/35.3
Lai et al. [160]	218	3	11/218	46.3	215/3	NP	2.4	69	Peri-bulbar	18.2/36.4
Lopez Pereira et al. [162]	35	3	35/35	14.4	22/13	20/35	5.5	91.4	Bladder neck	11.4/20
Patki et al. [163]	9	4	9/9	38.2	9/0	NP	5,9	77	Peri-bulbar	22/43
Murphy et al. [229]	30	3	13/30	54	29/1	NP	NP	23	Peri-bulbar	33/70
Herndon et al. [158]	134	3	107/134	10	94/41	85/134	7.5	86%	Bladder neck (122), peri-bulbar (12)	16/41
Castera et al. [154]	49	3	38/49	14	39/10	9/49	7.5	67	Bladder neck (37), peri-bulbar (12)	20/12
Shankar et al. [230]	45	4	NP	11	45/0	NP	7	89	Bladder neck	4.4/6.7
Kryger et al. [159]**	32	3	28/32	6.7/14.5	25/7	9/32	15.4	100/	Bladderneck	41/95
Elliott et al. [155]	323	3	10/323	Global: 60.4	313/10	NP	5.7	NP	Bladder neck/ peri bulbar	Global: 26.2/28.6
Fulford et al. [156]	61	3	34/61	26	43/18	7/34	10 to 15	88	Bladder neck (female)/peri bulbar (male)	29.4/91.2
Levesque et al. [161]	54	3	49/54	10/12	34/20	23/54	NS (>10)	59.3	Bladder neck	24/67
Singh et al. [165]	90	3	90/90	26	75/15		4	92	Bladder neck/ peri-bulbar	16.7/28
Simeoni et al. [164]	107	3	107/107	13.7	74/33	22/107	5	76.6	Bladder neck(98)/ peri-bulbar(9)	22.3/19.6
Gonzales et al. [157]	19	3	19/19	8.4	19/0	7/19	8	84.2	Bladder neck	5/100
Belloli et al. [152]	37	3	37/37	10-19	35/2	2/37	4.5	59	Bladder neck(33)/ peri-bulbar(4)	10.8/38

** AUS modified**AUS modified and two groups of patients depending of their age at AUS implantation*

procedures (especially ureteroscopy, botulinum toxin injections and litholopaxy). Secondly, 28-45% of patients (especially male) report catheterisation difficulties following a Kropp procedure. For the Pippi-Salle procedure, continence rates are lower than for the Kropp procedure, but fewer cases of catheterisation difficulty have been reported [168]. However, a revision procedure is necessary in significant numbers, and it has rarely been used in male patients.

f) Complete bladder neck or urethral closure

Closure of the bladder outlet may be required if alternative approaches to managing stress incontinence are inappropriate or have failed. In women, closure can be achieved either via a vaginal or an abdominal approach while in men, either the bladder neck or the bulbar urethra can be the site of closure. Bladder drainage is maintained using a continent catheterisable abdominal conduit (e.g. using the Mitrofanoff principle), an SPC or (rarely) an ileo-vesicostomy. Bladder neck or urethral closure can be technically difficult and a secondary operation to close a persistent fistula may be needed in some cases [224]. Interposing vascularised tissue between the bladder neck suture line and the urethral or vaginal closure is a well-described aid to the avoidance of closure failure; a flap of rectus abdominis can be used for this purpose. Bladder neck closure has also been used in children where other means of correcting SUI have failed or are felt to have a limited chance of success. The published series of cases provided some reassurance that children with closed bladder necks do not suffer from excessive complications in the form of renal deterioration, bladder rupture or stone formation.

As a general principle, urethral closure should not be undertaken in cases where it is possible to maintain urethral patency using alternative approaches to treat SUI. For example, patients with neurogenic lower urinary tract dysfunction are at high risk of stone formation in the bladder or upper tracts and it is desirable to maintain easy endoscopic access to the bladder in order to allow potential endoscopic treatment. Finally, preserving the natural urethra may constitute a safety measure if high bladder storage pressures are present or in the event of any complication with bladder access via a continent catheterisable abdominal conduit or suprapubic catheter [225].

Recommendations:

- **Patients with stress incontinence in association with neurogenic lower urinary tract dysfunction require careful assessment in order to plan appropriate management. Video-urodynamic study must be used to evaluate both bladder and sphincter function (C).**
- **The clinical assessment must also evaluate the degree of patient handicap in order to determine whether they can perform self-catheterization, or whether an alternative means of emptying the bladder will be required. (D).**
- **Patients require careful preoperative counselling with respect to the benefits and risks of different operative approaches**
- **Autologous slings can be used to treat neurogenic stress incontinence. (B). The use of synthetic slings and tapes is not supported by an adequate evidence base at present. (C).**
- **Artificial urinary sphincter can be used to treat neurogenic stress incontinence (A).**
- **Bladder neck reconstruction can be used to treat neurogenic stress incontinence (D).**
- **Bulking agents can be used to treat neurogenic stress incontinence when there is a demand for a minimally invasive treatment (D). The patient should be aware that the technique has a low success rate.**
- **Bladder neck closure should be offered to patients who have persistent neurogenic stress incontinence where alternative treatments have either failed or are likely to fail (B).**

6. SURGICAL ALTERNATIVES EXCLUDING DENERVATION PROCEDURES TO TREAT REFLEX INCONTINENCE DUE TO NEUROGENIC DETRUSOR OVERACTIVITY

Keywords; neurogenic bladder; spinal cord injury; spina bifida; myelomeningocele; multiple sclerosis; bladder augmentation; enterocystoplasty; gastrocystoplasty; sigmoidocystoplasty; colocystoplasty; ureterocystoplasty; autoaugmentation; detrusorectomy

a) Bladder augmentation using intestinal segments

The aim of bladder augmentation is to provide long-term protection to the upper urinary tract by reducing the risk of impairment due to high bladder pressure, as well as to improve storage function [231]. First performed in man by Von Mickulicz [232] who used a segment of small intestine, the technique has regained popularity since the 1970s after the introduction of IC [233]. Unlike complete bladder replacement, enterocystoplasty preserves the integrity of the trigone of the bladder with the urethra and ureters, and reimplantation is not necessary. A segment of the gastrointestinal tract is taken out of continuity from the rest of the gut, and sutured onto the bladder. Various augmentation techniques using different segments of the gastrointestinal tract (caecum, colon, and ileum) have been described. Bladder augmentation is indicated wherever bladder capacity and compliance is reduced, or in the event of detrusor overactivity, when all conservative treatments (medical treatments, detrusor injections

of botulinum toxin and/or neuromodulation of the posterior sacral roots) have failed [231, 234].

Before performing bladder augmentation, it is essential to ensure that:

- There is no malignant disease or lithiasis in the bladder.
- Renal function is normal and the upper urinary tract is unimpaired (screen particularly for lithiasis).
- There is no gastrointestinal tract disease (Crohn's disease, hemorrhagic rectocolitis, short gut syndrome, etc.).
- The patient is willing and capable of self-catheterization. This can be combined with continent cystostomy.

Technical principles:

There are two stages to the surgical procedure: first bladder preparation and then augmentation. Usually open surgery is performed, but recently laparoscopy has been reported [235, 236] (LOE3). At present, except for technical articles on laparoscopy, there are no publications comparing this technique with open surgery.

The bladder can be prepared either by clam cystoplasty or by supratrigonal cystectomy. The preferred preparation depends on the quality of the detrusor, and more particularly on whether the bladder has retained its visco-elastic properties. Where the detrusor is very fibrous and thick, supratrigonal cystectomy should be envisaged, since otherwise exclusion of the ileal patch may occur.

1. Clam Cystoplasty

Clam cystoplasty involves freeing the anterior/ posterior surfaces and dome of the bladder. The bladder can be opened either in the transverse plane or sagittal plane, the incision starting and ending about 2 cm above the bladder neck. If the lateral surfaces are not mobilised, the vesical arteries can be preserved to maintain vascularization of the bladder dome. Robot-assisted laparoscopic augmentation cystoplasty has been recently introduced. Preliminary results have been reported in children with spina bifida [237].

2. Supratrigonal Cystectomy

Supratrigonal cystectomy involves resection of the body of the bladder, but retaining the trigone. The bladder is freed under the peritoneum and the superior vesical arteries ligated and sectioned. The bladder pedicles are ligated and sectioned laterally up to the trigone, which is preserved. The body of the bladder is excised 1-2 above the trigone. During the bladder dissection, care must be taken to spare the ureteric vascularization.

3. Ureteric Reimplantation

Ureteric reimplantation must be carefully discussed in the event of vesicoureteric reflux (VUR). Several authors have reported that improved bladder compliance precludes the need for reimplantation (LOE 3) [238-241]. They have reported a resolution rate of about 85% for VUR, classified below grade IV. For grade V reflux, improvement was observed in 2/3 of patients. Except for the work of Simforoosh [238], these results were obtained in small heterogeneous series of children (neurogenic bladders and congenital anomalies), and after relatively short mean follow-up times (1 to 5 years).

Hayashi et al. [242] reported on 22 patients treated by ureteric reimplantation during bladder augmentation (LOE 3). Their work was original in that it gave detailed account of renal function after long-term follow-up (mean 12 years). Ureteric reimplantation during bladder augmentation did not result in greater morbidity and 97% of patients recovered. Renal function was preserved and satisfactory. The case for ureteric reimplantation during augmentation cystoplasty was supported by a small non-randomised study (LOE2-3), where Wang et al. demonstrated that lack of ureteric reimplantation during cystoplasty in children with neurogenic bladder was a risk factor for residual high-grade reflux, which, in turn, was a risk factor for febrile UTIs [243]. A larger non-comparative non-randomised study (LOE3-4) reported equal success rates for the two methods, but ureteric reimplantation had been mostly reserved for the higher grade reflux cases [244]. These results were presented as part of a literature review which was inconclusive as to the superiority of the results of either method [244]. Accordingly, the need for ureteral reimplantation during bladder augmentation should still be considered, especially for cases of grade V reflux. However, improved bladder compliance will reduce some VUR.

4. Intestinal Segments

The choice of intestinal segment depends on patient's history and the local conditions. All segments of the gastrointestinal tract may be used, except the jejunum because of the risk of water-electrolyte disorders. The most frequently used segment in adults is the ileum, because it is easy to remove, is close to the bladder and may be shaped easily into a reservoir. Colon segments are used more often in children. The removed intestinal segment must always be detubularized to reduce peristalsis to a minimum and to obtain a reservoir with low pressure. The segment is then placed and sutured onto the bladder in the form of a patch. For supratrigonal cystectomy, the intestinal segment needs to be longer and fashioned into a neo-bladder [234].

Technical variations aim to reduce mucus secretion and reduce the reabsorption of urine by the intestinal mucosa that leads to metabolic acidosis. A number of variant techniques have been proposed but not developed extensively. Seromuscular colocystoplasty lined with urothelium involves removing the detrusor,

leaving the bladder mucosa intact, and then covering it with a demucosalized sigmoid patch [245]. Seromuscular enterocystoplasty necessitates removing the mucosal membrane of the intestinal segment surgically, or destroying it argon beam [246], before placing it onto the prepared bladder [247].

A third technique uses an appendicular-based cecal flap, aiming for a less invasive form of augmentation cystoplasty [248]. The technique involves isolation of a 10-12 x 3 to 5-cm cecal flap on the base of the appendicular pedicle, by which the bladder was augmented and the appendix was brought out through the abdominal wall for catheterization. Without any bowel anastomosis, the cecal anterior wall was repaired.

An experimental technique tested only pre-clinically is the reversed seromuscular ileocystoplasty, where the seromuscular layer of the ileal loop from its antimesenteric aspect was sutured to the bladder mucosa of the previously bivalved bladder. Complete epithelialization of the ileum's serosal surface with transitional epithelium was confirmed 4 weeks postoperatively [249].

5. Results of Enterocystoplasty

The main published series for patients undergoing surgery for neurogenic bladder are summarized in **Table 11.** Peri-operative mortality is estimated between 0 and 3.2% (LOE 2-3). The most frequently reported early morbidity (LOE 2-3) is prolonged post-operative ileus in up to 11.7% [250-253]. A nasogastric catheter is no more justified in neurological patients than in the general population (LOE3) [254]. Other common complications include episodes of febrile UTI (4.8-9%), urinary fistula (0.4-4%), that usually resolve, and thrombo-embolic complications (1-3%). When the pelvis has been irradiated, the patient must be warned of the increased risk of entero- or colovesical fistula. Stoma revisions (up to 50% in a small series) and wound infections have also been reported [253].

Chronic bacteriuria always occurs with IC and should not be considered a complication [203] (LOE4). Cases of late urosepsis have, however, been reported [255]. The risk of calculus in the enlarged reservoir ranges from 10-50% [255-9] (LOE 2-3). There may be a higher risk of developing upper urinary tract lithiasis than in the general population [260-2] (LOE3).

After bladder augmentation, intestinal transit disorders are frequent and probably underestimated (0- 30% [263-5]). Several explanations have been proposed (ileocecal valve not preserved, biliary salt malabsorption, etc.). Somani et al. conducted a cohort study (LOE2) focusing on this particular problem [266]. They report a high rate of intestinal transit disorders, affecting almost 50% of patients treated for neurogenic bladder. These complications distressed patients and nearly 10% regretted having undergone surgery. Although transit disorders cannot be attributed to surgery alone (patients with neurogenic bladder may have intestinal transit disorders unrelated to surgery), patients should be informed of this risk.

Since the gastrointestinal tract mucosa resorbs urine, water-electrolyte disorders may occur. Hyperchloremic acidosis is reported in up to 15% of cases (LOE 2-3). These water-electrolyte disorders may be accompanied by anomalies of calcium metabolism that do not appear to have any significant long-term effect, for example on growth in childhood, but the subject is still under debate (LOE 3) [267-270]. However, care must be taken when treating patients with a marked decrease in creatinine clearance, since metabolic acidosis is no longer compensated [234] (LOE4).

In theory, diversions performed using the ileocaecal junction and the end segment of the ileum would expose patients to a risk of vitamin B12 deficiency (with possible onset of megaloblastic anemia). The fact that the intestinal segments measure less than 50 cm would explain why few patients suffer clinically overt vitamin B12 deficiency.

The risk of cancer development of the newly formed reservoir is particularly important, since neuro-urological surgery is often indicated in patients with long life expectancy, many being children. The general consensus today is that patients with a bladder reservoir are at higher risk of developing a tumour than are the general population, but this risk has not as yet been clearly defined. The figures usually given for the risk of tumour development range from 1 to 4.6% [271-274] (LOE 3-4). Most of the published cases concern adenocarcinoma at the junction of the intestinal mucosa with the urothelium. These usually developed long after the initial surgery (over 10 years in most cases). Some patients developed urothelial tumours with the typical risk factors. Two facts should be emphasised with regard to neurogenic bladder (augmented or not):

- The sensitivity and specificity of the routine bladder tumour diagnostic and monitoring tools (urinary cytology, BTA test, simple cystoscopy, etc.) may be reduced. Patient monitoring can only be envisaged by regular cystoscopy with biopsy of suspect areas.
- Monitoring is essential, since many patients develop tumours without symptoms and may not be diagnosed until late.

Monitoring frequency needs further investigation. A review of a series of cystoplasties performed in patients with congenital abnormalities including neurogenic bladder found comparable risk of bladder cancer, compared to control patients managed only by IC (4.6% vs 2.6%, p=0.54) [274]. In addition, a projected

Table 11: Gastro-intestinal bladder augmentation in neurological patients with bladder dysfunction

Authors	LOE	Total number of patients (neurological patients)	Type of bladder augmentation	Max BC pre-op	Max BC post-op	DP pre-op	DP post-op	Mean Follow-up (months)	Increased compliance (% patients)	Post-op continence status	Results for quality of life
Gurung et al. [255]	3	19	Ileum	TBC	TBC	TBC	TBC	176.4	NP	92% ???	92% satisfied
Gundeti et al [237]	3	6	Ileum	TBC	250-450	NP	NP	18	NP	100%	NP
Chen et al. [333]	3	40 (34)	ileum	115	513	NP	NP	93.6	NP	90%	NP
Shakeri et al. [248]	3	10	Cecum	171.4	263.7	62.2	13	23.8	100	90%	
Blaivas et al. [282]	3	76 (41)	Ileum, cecum	166	572	53	14	108	NP	Cured 70%/ Improved: 18%	NP
Mor et al. [283]	3	11(11)	Ileum	NP	NP	NP	NP	115	NP	Cured/improved: 82%	NP
Quek et al. [334]	3	26(26)	Ileum	201	615	81	20	96	92	Cured: 69%/Improved: 27%	NP
De Foor et al [276, 287]	3	105 (47)	Stomach, ileum, colon	NP	NP	NP	NP	88,8	NP	Cured/improved: 92%	NP
Medel et al. [335]	3	26(26)	Stomach, ileum, colon	NA	NA	NA	NA	45.6	100	Cured: 84.6% Improved: 5.4%	NP
Nomura et al. [336]	3	21(21)	Ileum	149	396	>60	NP	66	100	Cured/improved: 95%	NP
Shekarriz et al. [250]	3	133(100)	Ileum, sigmoid, autoaugmentation	NP	NP	NP	NP	64	NP	Cured/improved: 95%	NP
Arikan et al. [337]	3	18(18)	Sigmoid	86	370	NP	NP	40	NP	Cured/improved: 95%	NP
Chartier-Kastler et al. [251]	2	17	Ileum	174.1	508	65.5	18.3	75.6	100	Cured/improved: 88.5%	NP
Venn et al. [338]	3	267 (152)	Ileum	NP	NP	NP	NP	36	NP	Cured/improved: 86.6%	NP

(Max BC: Maximal Bladder capacity, DP: Detrusor pressure at the maximal bladder capacity)

Table 11: Gastro-intestinal bladder augmentation in neurological patients with bladder dysfunction (continued)

Authors	LOE	Total number of patients (neurological patients)	Type of bladder augmentation	Max BC pre-op	Max BC post-op	DP pre-op	DP post-op	Mean Follow-up (months)	Increased compliance (% patients)	Post-op continence status	Results for quality of life
Herschorn et al. [281]	2	59(59)	Ileum, cecum, sigmoid	220	531	48.9	15.8	72.6	100	Cured: 67% Improved: 28.8%	Excellent: 69.5% Good: 20.3%
Flood et al. [278]	2	122 (59)	Ileum, sigmoid	NP	NP	NP	NP	37	95	Cured: 75% Improved: 20%	NP
Hasan et al. [252]	2	48 (13)	Ileum	307	588	NP	NP	38	69	Cured/improved: 92%	Good: 83% Moderate:15%
Mast et al. [339]	3	28(24)	Ileum	235	511	72	46	30	95	Cured/improved: 95%	NP
McInerney et al.[280]	3	100(50)	Ileum	196	867	NP	NP	24	92	NA	NP
Singh & Thomas [279]	3	78	Ileum, cecum, sigmoid	NP	NP	NP	NP	100	NP	Cured/improved: 93.6%	NP
Khoury et al. [340]	3	100	Ileum, cecum, sigmoid	NP	NP	NP	NP	37	NP	Cured/improved: 91.7%	NP
Luangkhot et al. [341]	3	21(21)	Ileum, cecum	185	595	53	16	37	100	Cured/improved: 95%	NP
Nasrallah et al. [214]	3	14(14)	Sigmoid	101	383	61	NP	25	NP	Cured/improved: 86%	NP
Robertson et al.[342]	3	25(19)	Ileum, cecum	122	659	23	7	14		Cured/improved: 40%	NP
Hendren et al. [343]	3	129	Ileum, stomach, sigmoid	NP	NP	NP	NP	NP	NP	Cured/improved: 94%	NP
Sidi et al. [344]	3	12(12)	Cecum, sigmoid	134	562	NP	<30	1.3	NP	Cured/improved: 100%	NP
Lockhart et al. [345]	3	15(15)	Ileum, cecum, sigmoid	<150	330-480	>40	18-38	NP	NP	Cured/improved: 86%	NP

(Max BC: Maximal Bladder capacity, DP: Detrusor pressure at the maximal bladder capacity)

cost-analysis based on post-augmentation malignancy and cost estimates from published reports or US government sources concludes that annual screening with cytology and cystoscopy of children with spina bifida subjected to augmentation cystoplasty is unlikely to be cost effective at commonly accepted willingness-to-pay thresholds, but would be justified if the annual rate of cancer development were more than 0.26% (12.8% lifetime risk) or there were a greater than 50% increase in screening effectiveness and cancer risk after augmentation [275].

The most serious and possibly life-threatening complication is cystoplasty perforation (LOE3). This can happen whichever gastrointestinal segment is used, but occurs more often after ileocystoplasty [276] (LOE3). It is estimated to occur in 5-13% of cases [250] (LOE3). Perforation usually occurs on the graft or at the junction of the bladder with the enterocystoplasty, and often results from high pressure within the enterocystoplasty, or more rarely from traumatic catheterization or urodynamic investigations [277] (LOE4).

6. Functional Outcome

The functional outcome of bladder augmentation by enterocystoplasty is given in **Table 11.** Only series of patients undergoing bladder augmentation for neurogenic bladder were retained in our analysis. Given the wide range of indications, surgical techniques and enteric segments used, and retrospective nature of studies, it is difficult to draw any clear conclusions. Nonetheless, all authors reported an improvement in bladder capacity and compliance (LOE2-3). More than 90% of patients achieved nocturnal continence, and 91-100% achieved diurnal continence (LOE2-3).

Two quality-of-life studies (LOE2) reported improvement rates exceeding 90% [252, 281]. A 92% satisfaction rate was reported by a long-term follow-up study (mean 14.7 years) and patients would recommend the treatment to a friend [255]. However, a potential bias might arise due to the heterogeneous population analysed in some of these studies, including a mixture of patients with neurogenic and idiopathic DO.

If the bladder compliance defect persists, exclusion or ischemia of the intestinal patch must be investigated [272, 280]. Sometimes urinary leakage is related to sphincter deficiency and may be treated by an AUS [283] or other means of urethral pressure reinforcement [272, 282]. However, most authors consider that this type of adjunctive treatment should not be performed routinely since most patients have a good functional outcome after bladder augmentation, and only those with marked sphincter deficiency prior to surgery require these measures.

7. Possible Alternatives to Enterocystoplasty

• Gastrocystoplasty and ureterocystoplasty

The use of a pedicled segment of stomach (gastrocystoplasty) or ureter (ureterocystoplasty) as an alternative to enterocystoplasty has been reported mainly for children with a neurogenic bladder. In theory, its advantage lies in the absence of metabolic acidosis, but in adults this is very theoretical. Moreover, both these intestinal segments secrete less mucus than the small and large intestines [284-288]. Abdel-Azim et al. [286] reported gastrocystoplasty in adults (LOE3). In the light of their experience with children, they decided to use this technique in a set of young adults (mean age: 23 years, range: 4-32 years). Their paper records that the short-term results (3 years mean follow-up) of gastrocystoplasty were satisfactory, with increased functional bladder capacity and no impairment of the upper urinary tract (LOE3). However, two disadvantages are reported. First, a hematuria-dysuria syndrome requiring occasional use of antacids sometimes accompanied gastrocystoplasty. Second, the maximum bladder capacity was lower than that observed with enterocystoplasty. This may have a benefit for easier bladder voiding, but if the bladder were to lose some capacity, further surgery would potentially be required. The outcome in the very long-term for patients who have undergone this procedure remains unknown.

8. Kidney Transplantation and Augmentation Cystoplasty

The general notion is that augmentation cystoplasty should be beneficial in patients with chronic renal failure and performed prior to transplantation, as a low-pressure reservoir might delay the native kidney's death and optimize graft survival rates. However, published studies suggest otherwise. In a small series (n=11) of neurogenic bladder patients, augmentation cystoplasty did not affect progression to end-stage renal disease (LOE2-3) [289]. More strikingly, prior cystoplasty was found to be associated with higher risk of graft rejection compared to non-cystoplasty transplants, up to 7 years postoperatively (LOE2-3). Although the authors suggest this may be due to higher rates of febrile UTIs and chronic rejection, it might also be due to a more severe underlying pathophysiology which resulted in the necessity of a cystoplasty in those children [291]. The same group of authors conclude that the timing of augmentation cystoplasty in relation to the transplant surgery (before or after) has no significant effect on the outcome of the transplantation, with respect to graft acute rejection, graft survival (up to 7 years) and incidence of febrile UTIs (LOE2-3) [292]. In terms of serious complications, patients with augmented bladders and a history of renal transplant on chronic immunosuppression were found to have a significantly higher incidence of bladder cancer compared to patients who were not immunosuppressed (15% vs 2.8%) [274] (LOE3).

b) Autoaugmentation by detrusor myotomy

Bladder autoaugmentation without any associated gastrointestinal tract surgery as an alternative to enterocystoplasty was proposed as early as 1972

by Mahony and Laferte [293] who performed detrusorotomies (detrusor incision without resection) to increase bladder capacity and reduce incontinence. With Cartwright and Snow [294], the technique then evolved to detrusorectomy (myectomy). This involves excising a thick segment of muscle from the dome of the bladder, leaving only the mucosal membrane in place. Bladder pressure gradually dilates the "demuscularized" area resulting in bladder augmentation. The intervention, initially described by extra-peritoneal laparotomy, can be performed by video-assisted surgery [295, 296] or by robot-assisted surgery [297] (LOE4). The detrusor can be dissected by laser [298] (LOE3). The area around the detrusorectomy can be protected using the omentum [299] or a striated muscle [300] (rectus abdominis muscle) to prevent perforation and retraction(LOE4).

Techniques using free-graft or pedicled de-epithelialized gastric patches [301, 302] require gastrointestinal tract surgery and were therefore not included in the present work. Furthermore, most of the previously published studies concerned children. All the studies are retrospective and with few patients. For children, most authors [299, 304-7] report poor results after surgery, both symptomatic and urodynamic, together with a risk of upper urinary tract impairment (LOE4). Two authors recently reported better results with certain technical adjustments, namely an extensive detrusorectomy [308] (LOE4) and rectus muscle hitch and backing [300] (LOE4). The last technique supposes a large dissection of the rectus muscle. Urothelium is then sutured to this muscle in the theoretical objective to prevent its retraction and shrinkage.

Only three retrospective series are available for adults. The first, published by Stöhrer et al. in 1997 [309] (LOE3), reports interesting results for efficacy, with increased functional bladder capacity. However, the authors did not report mean follow-up and described a mixed population with 39 patients with neurogenic bladder and 11 patients without. The two other published series concerning adults [303, 304] did not confirm these findings but did confirm the marked superiority of enterocystoplasty with respect to both urinary symptoms and upper urinary tract impairment (LOE3). Detrusor myectomy achieves better results for idiopathic DO; nearly all patients (5 of 6) with neurogenic DO were not improved, with a mean follow-up of 79 months [303] (LOE3).

There is little information on specific complications, but detrusorectomy is simpler and seems to present less risk than enterocystoplasty. A comparative retrospective study (LOE4) reported 20% complications for enterocystoplasty (infectious, digestive and parietal complications) against only 3% for detrusorectomy [304]. The rate of secondary rupture and/or perforation is poorly documented. An experimental animal study concluded that the bladder rupture pressure was slightly lower after detrusorectomy than after enterocystoplasty, thus potentially exposing the patient to an increased risk of rupture [310] (LOE4).

c) Bladder augmentation using biomaterials

Research interest in the role of tissue engineering in bladder reconstruction is growing. This research appears to evolve along three axes [311]:

a. use of acellular natural or synthetic biomaterials: an acellular biomaterial graft is used as a tissue implant which becomes incorporated through the ingrowth of cells of the native host bladder

b. use of biomaterial scaffolds which have been preincubated with autologous cultured human urothelial and smooth muscle cells

c. composite cystoplasty, which combines the use of autologous cultured urothelial cells with a host pedicled and de-epitheliased smooth muscle segment.

Most publications concern preclinical studies [312-326] (LOE4). Several biomaterials have been used which can be grouped in 3 categories: (a) decellularized natural matrices produced from a variety of tissues; (b) matrices produced from natural extracted polymers (e.g., collagen, alginate, chitosan and hyaluronan); and (c) synthetic polymers including polyglycolic acid (PGA) and poly-caprolactone (PCL) (see reviews [311, 327]). These biomaterials can only be used after performing clam cystotomy since the area to be colonized should not be too large. It also appears that the use of biomaterials is associated with higher incidence of bladder lithiasis. The best studied natural materials are porcine intestinal submucosa (SIS, Cook) and bladder-derived acellular matrix [318, 328-33].

Results from only two pilot human studies have been fully published to-date [331, 332].The former reported on neurological patients, the latter on non-neurogenic OAB patients. In a small prospective study of 7 young myelomeningocele patients (LOE 2-3), Atala [332] describes his technique, which consists of seeding patient's urothelial and muscle cells on a biodegradable scaffold. After 7 weeks, this engineered artificial bladder could be implanted in patients. Although the small number of patients doesn't allow definitive conclusions, a trend towards an improved bladder capacity and compliance was observed. It was also implied that patients who received cell-seeded collagen-coated PGA scaffolds wrapped in omentum as a vascular bed had the best outcomes. Encouraging results were also reported in 12 women with intractable non-neurogenic OAB who were submitted to bladder augmentation using an acellular matrix of porcine dermal collagen and elastin fibres (Pelvicol, Bard) [331] (LOE4). Significantly improved or cured incontinence was achieved in 67% of them at a 12-month follow-up. Finally, a recent review article [327] claims results in short report form from two small Phase II trials on patients with neurogenic bladders due to either spina

bifida (paediatric patients) or SCI (adults). Success rates of 60% and 67% are reported for up to 2-year follow-ups, depicting patients with preoperative 'normal bladder cycles' as the best candidates for bladder augmentation with a tissue-engineered scaffold. Further studies, including larger trials are necessary to evaluate routine use of biomaterials.

Recommendations

- **Any segment of the gastrointestinal tract may be used for bladder augmentation, but the ileum seems to give the best results in terms of ease of use, risk of complications and efficacy (B). Few data are available concerning gastrocystoplasty and ureterocystoplasty in adults (D)**
- **When the bladder suffers a significant compliance defect, supratrigonal cystectomy and reconstruction is preferable to clam cystoplasty (B).**
- **Bladder augmentation may solve low-grade vesicoureteric reflux. In the event of grade IV or V reflux, ureteric reimplantation may be necessary (C).**
- **Patients should be informed that the most frequent and serious complications are bladder calculi and perforation at the bladder/bowel junction, usually caused by over-pressure (B).**
- **Bladder augmentation may have sequelae such as intestinal transit disorder, and patients should be informed of this before surgery (C).**
- **The body of evidence concerning detrusor myomectomy in neurological patients is controversial. Therefore, detrusor myomectomy should not be recommended in these patients with impaired bladder function (D).**
- **Bladder augmentation using biomaterials or tissue engineering is promising, but the preliminary results need to be confirmed by larger studies (D).**
- **Due to risk of complications, regular follow up is needed (B).**

d) Cutaneous continent urinary diversion

For certain patients, urethral catheterization can be or become, unacceptable or even impossible. The following list is not exhaustive, but describes the more frequent reasons:

- Functional limitations of the upper limbs (tetraplegia [346] unilateral or bilateral plexus problems, musculoskeletal trauma problems).
- Cognitive disorders (forgetfulness, lack of comprehension, refusal).
- Difficulties in terms of mobility and/or undressing (spasticity, upper SCI resulting in difficulty in maintaining the equilibrium of the trunk and or limited control of the upper limbs, obesity).
- Failure to reach the urethra independently (more common in women, compounded by the tilted pelvis and all other factors that cause mobility difficulties.)
- Urethral injuries (stenosis, fistulas, hyperesthesia), urethral pain.

In these situations, management requires careful consideration; in some, a continent cystostomy may be an option. The general principle is to permit the emptying of a full bladder, independently and easily, by IC through an efferent tube attached to the wall of the lower half of the abdomen. The absence of any leakage from the cystostomy is controlled by its own watertight system, associated with the return process of a capacitive and compliant reservoir. This will require careful selection of patient candidates, especially when there is any function impairment of the upper limbs (trauma to the spinal cord) [347-9] (LOE3).

Assessment is essential, and must include the motivation of the patient, capabilities for dressing and undressing, capability of catheterization in the planned stomal area, and tolerance for the time and potential discomfort involved. In the case of cognitive difficulties that are too significant, if a severe upper limb dysfunction exists [346], or if compliance of the patient remains an impossible obstacle, continent diversion is not indicated. Impaired renal function can also be a contraindication [350].

In neuro-urology, techniques for heterotopic continent neo-reservoir (e.g. Koch pouch, Benchekroun, Mainz, Miami pouches) are seldom used initially. They can be offered to patients with VUR, with incontinence through the native urethra despite bladder enlargement, or when closure of the bladder neck will be needed (e.g. uretero-vaginal fistula).

1. Results of the Different Types of Cystostomy:

The series are mainly retrospective (LOE 3) and frequently combine several techniques. This makes the analysis of the results difficult, but some major facts can be gleaned from them. The catheterizable tube must be able to penetrate the intact or enlarged bladder and it must be able to reach the abdominal wall through a direct pathway with easy access for the patient that has already been predetermined by pre-operative research. The pathway of the tube must be direct in order to facilitate self-catheterization. Techniques can be grouped in two major categories : simple tubes implanted with an anti-reflux system and intestinal loop invaginations.

Simple tubes

Virtually any anatomical structure that is tubular or that can be tubularized and that is vascularized can be used to make a continent catheterizable tube

[350] (LOE4). The two structures that are the simplest to use are:

- The appendix: Trans-appendicular cystostomy according to Mitrofanoff's procedure [351] has long been the most used technique (LOE3). Different modifications have been proposed, especially to gain more length by removing a cecal cuff.
- A short, remodeled intestinal segment (small intestine, less frequently the sigmoid or right colon). Yang and Monti simple [352] (LOE3) or double technique and the Yang-Monti technique modified according to Casale in order to gain length by avoiding a double tube [353] (LOE3).

Other structures have been used in a more anecdotal manner, primarily in children: cecum and appendix monobloc [354] (LOE4), bladder [355] (LOE4), stomach [356] (LOE4), distal ureter [357] (LOE4), Meckel's diverticulum [347, 358] (LOE4), or the preputial or clitoral skin [359] (LOE4).

For most authors, continence of the tube was achieved by implantation in the native bladder or in the augmentation via a submucosal path similar to that used in ureteral reimplantation for VUR. (LOE4). The submucosal path length must be at least 2cm, and is adapted to the bore of the tube (two to three times the diameter) [349] (LOE4). A posterior or posterolateral bladder flap (kept in case of a supratrigonal cystectomy) should allow a more solid implantation of the tube in the bladder [360] (LOE2). Direct implantation into the cystoplasty has also been reported. The cutaneous anastomosis is made in the lower half of the abdomen, at the umbilicus, or in the right or left iliac fossa. It seems essential that the site of the stoma would be determined preoperatively in patients with functional limitations of the upper limbs. The site is chosen based on the patient's capabilities and the position during self-catheterization (seated in a chair, supine, other). The surgical technique used in this particular case must allow access to any point on the lower half of the abdominal wall [361-3]. Most authors recommend the interposition of a skin flap in the distal end of the tube in order to minimise stenosis of the circular orifice scars. Several techniques have been proposed: flap in V, VQZ [364] (LOE3), and VR [365] (LOE3). However, at present, the results published do not confirm that the risk of stenosis is avoided by any of the techniques.

Table 12 summarizes the results in terms of stoma continence and complications, specifically pertaining to the continent stoma. The necessity of reservoir augmentation (80% of published cases) and techniques allowing reinforcement of ureteral continence are addressed elsewhere. Continent stomas are obtained overall in 75 to 100% of cases (LOE3). Seven studies indicate significant improvement in quality of life after the procedure related to improved autonomy in bladder evacuation, to continence, and to improved sex life [348, 360, 362, 363, 366-368] (LOE2-3).

The rate of stoma complications (16-60%) is dominated by the risk of stenosis, which is most often treatable by a simple dilation [369] (LOE3). Many authors emphasize the fact that this complication occurs most often in the year following surgery. However, Liard et al. [370] (LOE3) reported an elevated (65%) intervention rate at 20 years of monitoring. For most authors the rate of complications related to the tube continence was lower when the segment used was the appendix or intestines remodeled according to Yang-Monti (LOE3). However, these two plasties seem to have equivalent complication rates. Only Narayanaswamy et al. [371] (LOE3) reported higher rates for catheterization difficulty and reintervention with the Yang-Monti tube in comparison to the appendix. The Monti tubes in this study were double tubes in 68% (17/25) of cases, and the majority of the complications were related to the junction area for the two hemi-tubes and not to stoma stenosis. Therefore it seems that this lengthening method should be used with caution. If there is a problem with tube length, the method proposed by Casale [353] (LOE4) has the theoretical advantage of avoiding an anastomosis on the tube or a bent pathway at the junction of the two tubes.

The umbilical anastomosis site for the stoma may be related to an increased frequency of stoma stenosis [355, 372] (LOE3). The poorer vascularization of the umbilicus has been proposed as an explanation [372]. However, results on this point are contradictory with more recent studies [360].

Other types of continent urinary stoma:

Techniques are extremely varied. Two technical approaches can be broadly outlined here:

- Invaginated valves (Koch pocket, Benchekroun, Mainz), in which the continence mechanism is tied to the flattening of the invaginated valve by urine accumulated in the neo-reservoir;
- Ileal-caecal reservoirs, in which a portion of the ileum and the ileal-caecal valve are used as a continence mechanism (Indiana pouch, Charleston pouch, Miami pouch).
- A new technique using a pedicled cutaneous flap which is surgically elevated from a hairless area on the abdomen, tubularized and passed through the anterior abdominal wall directly into the bladder (The Daoud technique) [373].

Data in the literature do not allow a determination to be made as to the superiority of one type of stoma over the others. However, the catheterization difficulties seem to be lower with stomas that use the appendix, and the risk of lithiasis seems to be higher with the stomas constructed using metal staples [374] (LOE4). Several authors have also specifically

Table 12: Results for continent reconstructive surgery

Team	Year	LOE	n (neurogenic bladder)	Mean follow-up (months)	Technique	Functional continent cystostomy (%)	Stoma complication (%)	New procedure on the stoma
Wille et al. [383]	2011	3	? 11	20 (median)	Mitrofanoff (robot assisted)	100 (initial 91)	27	3
Spahn et al. [382]	2010	3	6 (out of 17)	68	Mitrofanoff 8 Ileal intussusception valve 9	100 (initial 82)	23	7
Nguyen et al. [302]	2009	4	? out of 10	14.2 (median)	Mitrofanoff (9 robot-assisted)	100 (initial 70)	30	2
Vian et al. [384]	2009	3	32	21.6	Mitrofanoff 17	86	33	11
Welk et al. [385]	2008	3	67 (?)	28	Mitrofanoff 54 Ileovesicostomy 13	94	26	13
Mhiri et al. [386]	2007	3	20(28)	53	Mitrofanoff	100	13	3
Karsenty et al. [360]	2007	2	13(13)	44	Mitrofanoff 7 Yang-Monti 6	100	0	0
Touma et al. [368]	2007	3	12(12)	33	Casale	100	17	0
Franc-Guimond et al. [365]	2006	3	12(12)	18	Mitrofanoff	100	8	8
Thomas et al. [369]	2006	3	78 (62)	28,4	Mitrofanoff:33 Yang-Monti: 30 Bladder: 16	98	23	8
Castellan et al. [358]	2005	3	135 (100)	38	Mitrofanoff 74 Yang-Monti 45 Gastric tube 8 Bladder tube 2 Meckel tube 1	NP	23,5	8

Table 12: Results for continent reconstructive surgery (continued)

Team	Year	LOE	n (neurogenic bladder)	Mean follow-up (months)	Technique	Functional continent cystostomy (%)	Stoma complication (%)	New procedure on the stoma
Blaivas et al. [377]	2005	3	98(15)	108	NP	87	42	16
Chulamorkodt et al. [387]	2004	3	54 (48)	30	Mitrofanoff 47 Yang-Monti 7	95	16	NP
Barqawi et al. [388]	2004	3	109 (60)	46	Mitrofanoff 114 Yang-Monti ileac 21 Ureter 11 Others 5	92	36	NP
Lemelle et al. [389]	2004	3	46(32)	64	Mitrofanoff 23 Yang-Monti 18	96	46	NP
Walsh et al. [362]	2004	4	6(6)	44	Mitrofanoff 3 Hemi Kock 2	NP		NP
Zommick et al. [348]	2003	3	21(21)	59	Mitrofanoff 7 Hemi Kock 2 Kock 6 Indiana 2	70	11	NP
De Ganck et al. [372]	2002	3	53(45)	32	Mitrofanoff 45 Yang-Monti 8	90	36	NP
Cain et al. [355]	2002	3	31 (15)	41	Bladder	100	45	NP
Tekant et al. [366]	2001	4	46(11)	28	Mitrofanoff 38 Yang Monti 6	86	19,5	NP
Kochakarn et al. [390]	2001	4	12(12)	12	Mitrofanoff 10 Yang Monti 2	100	NP	NP
Narayanaswamy et al. [371]	2001	4	92 (21)	30	Mitrofanoff 69 Yang Monti 25 (17 double, 8 simple)	NP	Appendix 26 Yang Monti 60	NP

Table 12: Results for continent reconstructive surgery (continued)

Team	Year	LOE	n (neurogenic bladder)	Mean follow-up (months)	Technique	Functional continent cystostomy (%)	Stoma complication (%)	New procedure on the stoma
Liard et al. [370]	2001	4	23(22)	240	Mitrofanoff 20 Bladder flap 2 Ureter 1	75	39	65
Harris et al. [391]	2000	4	31/50	51	Mitrofanoff	96	16	16
Cain et al. [392]	1999	4	69/100	48	Mitrofanoff 57 Yang Monti 22 Bladder tube 21	98	20	Appendix 21 Yang Monti 10 Bladder tube 29
Mollard et al. [347]	1997	4	56(46)	120	Mitrofanoff 48 Distal ureter 8	92	16	NP
Sylora et al. [361]	1997	4	7(7)	NP	Mitrofanoff 5 Yang-Monti Ileac 2	86	14	NP

reported results in neurological patients [363, 373, 375-380] (LOE3). Continence rates for the stoma vary between 63 and 100%. Complication rates for the stoma are between 10 and 23%.

Bladder outlet management; although prospective studies are missing, evidence from retrospective analyses (LOE2-3) suggest that continent diversion combined with bladder neck closure is superior in terms of functional outcomes to continent diversion with an open bladder neck, whilst having similar morbidity [381]. Another series reports primary continence rate following bladder neck closure and continent vesicostomy of 82% [382]. Both series report however on a mixed patient population.

Recommendations:

- **Indication for cystostomy presumes a multidisciplinary evaluation involving the urologist and a neurologist or a reeducation doctor, as well as stomatherapy nurses or occupational therapists for estimating patient catheterization capabilities (A)**
- **Use of the appendix to carry out continent cystostomy is the standard method in children, but few long term data are available in adults (C). The appendix may have a short mesentery, so a reconfigured ileal segment is often needed.**
- **If the patient has undergone an appendicectomy, the use of a segment of the small intestine can be proposed, with slightly poorer short term results (C).**
- **Long term follow up of after continent cystostomy is needed to have a better idea of the long term results of the various procedures (C).**

e) Non-continent cutaneous urinary diversion

Non-continent cutaneous diversion refers to all methods used to divert urine, and where incontinence remains or where a system of extra-physiological continence is created, i.e. urine flow is continuous and requires a means of collecting urine attached to the skin. In the context of neurogenic bladder, these diversions make it possible to obtain low bladder pressure and to preserve the upper urinary tract. This type of surgery is a last resort for the many complications related to neurogenic bladder (and congenital anomalies of the lower urinary tract), in patients for whom other therapies have failed to help. Urinary diversion techniques, however, have been largely replaced by augmentation cystoplasty in the treatment of refractory neurogenic bladder, at least in some groups of neurological patients. The analysis of the US national database of patients with spina bifida between 1998-2005 demonstrated that 3,403 patients were submitted to augmentation cystoplasty as opposed to 772 treated with urinary diversion. Moreover, patients undergoing urinary diversion required more healthcare

resources, with significantly longer hospital stays, higher total charges and more use of home health care after discharge home [393].

Four techniques are described for non-continent urinary diversions for patients with neurological vesico-sphincter disorders. In order of frequency these are: ileal conduit urinary diversion, ileovesicostomy, cystostomy and cutaneous ureterostomy.

1. Ileal Conduit Urinary Diversion

Ileal conduit urinary diversion is the type of diversion most frequently performed on neurological patients with bladder dysfunction. Pre-operative location of the intended stoma site is crucial and must be adapted to the patient's main position (wheelchair or bed); the stoma site must be easy to access for management. The ileal segment must be as short as possible to prevent stasis [394] (LOE3). There is a variant to this technique whereby a segment of jejunal loop is removed and a stoma made on the left hemi-abdomen. This technique can be proposed after irradiation of the pelvis minor, if the ileum has been impaired and a short loop must be used (about 10 cm) to avoid metabolic disorder (jejunal conduit syndrome: hyperkalaemia, hyponatraemia, hypochloraemia, acidosis) [395] (LOE3).

In neurological patients, ileal conduit urinary diversion by laparoscopy and by robot-assisted laparoscopy have been described [396-400] (LOE4). Patients seem to benefit from the procedure, though this remains to be confirmed in the medium and long-term [401] (LOE 2). Uretero-ureterostomy on conduit diversion has also been described in neurological transplant recipients in whom the donor ureter is too short to achieve a tension-free ureteroileal anastomosis [402]. Graft survival rates at mean 5.3 years follow-up was 83%.

Some series of neurological patients were evaluated to determine the onset of early and late complications [401, 403-408] (LOE2-3). The first study to use the recently introduced Clavien system reported on a series of multiple sclerosis patients (n-53), of whom 43% developed minor complications (Clavien grades I-II) and 11% major complications (Grades III-IV) [409]. Early series of children can be evaluated to determine the morphology of the upper urinary tract and renal function after urinary diversion over a long period (up to 20 years) [410-415] (LOE3). Despite complications, significant improvements in patients' quality of life were recorded, in both retrospective [410] and prospective studies [401]. The latter, however, noted that only aspects of QOL associated with the limitations and constraints induced by urinary problems were improved, not the overall QOL.

Mortality is estimated between 0 and 3.4% (LOE2-3). The commonest early complication is intestinal occlusion (4 to 12.6%), usually reversible after prolonged intestinal drainage [401, 403, 404, 406-408] (LOE2-3). The risk of gastrointestinal fistula should also be taken into account (0 to 3.3%). As for enterocystoplasty, the current trend is to try to reduce nasogastric tube drainage time to a few hours [416] (LOE3). The most frequent medical complications encountered (3 to 8%) are febrile urinary infections and thrombo-embolism (2 to 3%; LOE2-3). Other major complications include: urinary fistula in 0.3 to 3.4% of patients which may be prevented by placing a ureteric catheter for about ten days (LOE3). This complication could be a risk factor for later ureteroileal anastomosis stricture (LOE4).

The risk of long-term intestinal occlusion ranges between 5 and 7% (LOE3). Even when a short intestinal segment is used, some patients can experiment transient constipation or diarrhoea, which could adversely affect their quality of life [417] (LOE2).

Complications affecting the bladder left in situ. For the particular indication of neurological patients with bladder dysfunction, several authors have proposed not carrying out cystectomy so as to avoid potentially morbid surgery. At present, this is debatable for several reasons:

- There is a risk of pyocystis formation in the unused bladder (21-50%) [403, 404, 408, 418] (LOE3). Even where conservative treatments have been attempted (combining vesicular irrigation with antibiotherapy) [419] (LOE3), secondary cystectomy is then necessary in a high proportion [404, 410, 412]. For women, a surgical alternative is vaginovesicostomy, which appears to be effective [405, 412] (LOE4).

- The unused bladder frequently becomes infected and may become an "irritative thorn", especially in patients with spinal injury or multiple sclerosis (LOE 4) [404, 420].

- The risk of bladder neoplasia is higher in neurogenic patients, the principal risk factors being long-term indwelling catheterization (more than 8 years), bladder calculi and smoking [421-423] (LOE3). Moreover, screening by cystoscopy-biopsy is not effective [424, 425] (LOE3).

- Improvement of the cystectomy technique (noticeably laparoscopic cystectomy) has considerably reduced related morbidity [401, 426] (LOE2-3). Supratrigonal cystectomy can be performed in men, preserving the prostate and preventing any genital and sexual sequelae.

Upper urinary tract complications. Stenosis of the uretero-ileal anastomosis may occur in the medium and long term. This is very damaging to the upper urinary tract and requires regular monitoring. In contemporary series, it occurs in 2 to 7.8% of cases within 10 years [403-408] (LOE3). For cases followed for more than 10 years, the finding of 16.5 to 50% stenosis is essentially that of early paediatric series

[410-415] (LOE3). Impairment of the upper urinary tract and renal function seems to be correlated mainly with stenosis of the uretero-ileal anastomosis, but also with a long ileal graft and stomal stenosis leading to poor voiding and pyelonephritis [411] (LOE4). In the event of poor functioning of the uretero-ileal anastomosis, some authors suggest endoscopic dilation before further surgical repair of the anastomosis (LOE3) [407, [407, 427-429]. Surgery however remains the reference treatment [427] (LOE3).

The risk of upper urinary tract lithiasis (3 to 31%) is always present in these patients (even without stenosis of the uretero-ileal anastomosis) [403, 404, 407, 408] (LOE3). Patient monitoring should include regular screening of the upper urinary tract to detect any lithiasis and to implement timely treatment (LOE 4). Chronic bacteriuria is frequent but should not be treated if asymptomatic. Both patients and attending physicians must be informed so as to avoid the administration of unnecessary antibiotics. However, the risk of febrile infection persists over the long term and may be predisposed by uretero-ileal stenosis (12 to 34%) [403, 404, 407, 408].

Stoma complications. These are relatively frequent (18.6 to 30%) and varied [404, 407, 408]. The risk of peristomal herniation is the most frequently reported (between 7.7 and 10%). Stomal stenosis may also occur. Stoma complications appear to occur more often in obese patients (LOE3) [430].

Some patients, usually adults who underwent surgery as children and who subsequently to recover a continent system, or who have had complications with their non-continent urinary diversion could ask for undiversion [431-435] (LOE3-4).

2. Ileovesicostomy

This technique was first described by Cordonnier in 1957 for treatment of three children suffering from myelomeningocele [436, 437](LOE4). Its theoretical advantages are relative simplicity, the absence of dissection and suture of the ureter, thus preventing ureteral complications and the potential of restoring the integrity of the bladder (only one case described) [438] (LOE4). The surgery consists in removing a 10 cm ileal segment from about 15 to 20 cm above the ileocecal valve. One side of the segment is anastomosed to the dome of the bladder and the other to the skin halfway between the iliac spine and the umbilicus. A partial cystectomy is performed to reduce reservoir volume and possible urine stagnation. Surgical variants have been described with simple partial detubularization of the ileum before vesico-ileal suture [439], or the creation of a modified Boari flap on the bladder associated with partial detubularization of the ileum [438, 441-444] (LOE3). These improve drainage by reducing the ileal segment. Laparoscopic ileovesicostomy seems to be feasible [440, 445] (LOE4), and robotic ileovesicostomy has been described. A small, retrospective comparative study (LOE3) reported similar results in terms of continence and complications with the open surgery group, although a trend for less blood loss and shorter hospital stays was noted in the robotic group [446, 447].

One of the problems with ileovesicostomy, particularly in women, is the need for further surgery to prevent residual urinary leakage. All authors agree that this significantly prolongs surgery time. This further surgery may consist in closing the bladder neck or placing a suburethral tape [436, 438,443, 448, 449] (LOE3). Some authors propose performing this surgery later, where necessary [439] (LOE3).

Early complications are related to the underlying condition of these patients, which is often poor. No case of post-operative mortality has been reported in the published series [436, 438, 439, 441-444, 446-451] (LOE3). Other early complications were related to poor results of the surgery performed to render patients continent (**Table 12**). Patients with this type of problem are the most likely to resort to cystectomy with ileal diversion (3 to 6%) [438, 448] (LOE3).

Late complications are summarized in **Table 13**. Only one series to date has more than five years of follow-up [451]. It should be noted that, despite reduction in complication rates, particularly those related to chronic upper tract infections and stone formation, none of the patients in this series remained complication-free [450]. The largest series to-date also report high complication rates (up to 74%), albeit reduced in comparison with preoperative rates [448].The most frequent new adverse events appear to be poor emptying related to stenosis of the stoma or the ileovesical anastomosis. Only one group of authors specifically mention problems related to stoma equipment that occur in about 38% of patients [448] (LOE3). The incidence of renal or vesicular lithiasis can be as high as 25% in some series, and several authors report that affected patients had a history of lithiasis [450].

Renal function appears to be preserved with this procedure at least with a mean follow-up of five years (LOE 3) [438, 439, 441-444, 448, 449, 452]. No case of impaired renal function, or even post-operative uretero-hydronephrosis was reported. Two patients in a series with long-term follow-up developed a bladder tumour [444] (LOE4).

3. Vesicostomy

Vesicostomy was described by Blocksom in 1957 [453] and detailed subsequently by Lapides [454, 455]. The technique consists in constructing a bladder tube anastomosed to the skin by making a transverse suprapubic incision to reach the space of Retzius. The stoma is located half way between the umbilicus and the incision. The principal benefits simplicity and reversibility, particularly in children [456-462], making it possible to envisage temporary surgery to treat an acute urological problem. In

Table 13: results for contemporary series of ileovesicostomy

	LOE	n	Mean follow-up (months)	Re operation following primary surgery (%)	Stomal problems (%)	Kidney lithiasis (%)	Bladder lithiasis (%)	Continent (%)	Post op hydronephrosis (%)	Symptomatic urinary infection (%)
Zimmerman et al. 2011 [451]	4	7	26	40	0	0	0	60	0	16
Hellenthal, 2009 [450]	3	12	66	42	17	17	25	92	0	67
Tan et al., 2008 [448]	3	50	26,3	54	38	2	6	72	0	10
Gauthier & Winters, 2003 [449]	4	7	37,4	NP	14	14	0	NP	0/7	1/7
Atan et al., 1999 [441]	3	15	23,2	NP	16	33	20	67	0	20
Gudziak et al., 1999 [443]	3	13	23	23	8	8	0	92	0	8
Leng et al., 1999 [444[	3	38	52	NP	13	10	5	NP	3	3
Mutchnik et al., 1997 [439]	4	6	12	1/6	1/6	0	0	6/6	0/6	0
Rivas et al., 1995 [442]	3	11	24	NP	NP	NP	NP	100	0	0
Schwartz et al., 1994 [438]	3	23	45	NP	21	0	0	NP	0	NP

pediatric series, an improvement in the symptoms of infection was reported, with 6 to 20% of patients suffering bladder calculi and 6 to 18% stomal stenosis. Hydronephrosis improved or stabilized in most cases. The rate of end-stage renal failure varied between 6 and 18% for mean follow-ups of 6-7 years.

Nowadays, it is rare to conserve a vesicostomy long term. The long-term results of Lapides [455] (LOE3) are therefore all the more interesting. At two years of follow-up, there was no urinary infection, 16% poor drainage, 12% calculi, and renal function was preserved. At 10 years, however, end-stage renal failure, mainly due to calculi and repeated infection of the upper urinary tract, and mortality were reported [455, 463] (LOE3). Follow up at intervals ranging up to 20 years, showed the rate of chronic renal failure is around 16.6% [453-464] (LOE3).

Recently, percutaneous button vesicostomy placement under endoscopic control was proposed as a temporary continent alternative to Mitrofanoff in a series of 10 children with neurogenic bladders. The authors only discuss the feasibility of the procedure, not its efficacy [465].

4. Cutaneous ureterostomy

Cutaneous ureterostomy was first performed in the 1960s, to treat children with spina bifida and severe upper urinary tract impairment [466, 467]. The technique was also developed to treat malformative uropathies (exstrophy of the bladder and the posterior urethral valves) [467-470]. During this procedure, the ureters are anastomosed direct to the skin without using intervening gastrointestinal tract tissue. It is only feasible in the context of significant ureteric dilatation, and even then chronic stenting is often needed. The absence of gastrointestinal resection/ anastomosis avoids a major source of morbidity and mortality, but successfully achieving urine containment with appliances can cause considerable problems. In the absence of cystectomy, two short lateral incisions are made in the iliac fossa, at approximately 3-4 cm from the anterosuperior iliac spine. Direct retroperitoneal access is made and the two ureters located on the internal border of the psoas muscle or above the iliac vessels. It is important that the peri-ureteral region be spared and the ureter sectioned as low as possible. The ureter is then catheterized and raised to the skin. The stoma is formed by attaching the ureter to the skin, or by spatulating the sutured ureter on a V-shaped cutaneous incision (separate sutures with fine resorbable thread). Variants are described so as to obtain only one stoma: Y-transuretero-ureterostomy, implantation of both ureters in a single stoma, and implantation of a single ureter (ureter of the less functional kidney ligated, or even nephrectomy). The use of cutaneous plasties may remove the need for ureteral catheterization [471].

The main inconveniences are: cutaneous stenosis if the stoma is left unstented, upper urinary tract infections, and calcification around catheters. Moreover, it is frequently necessary to construct a double stoma. It is used in adults, usually in the context of palliative urinary diversion for those with obstructive pelvic cancer (bladder, uterus, rectum), and rarely in neurological patients [467-472]. Long-term results with a mean follow-up of 8 years are given hereafter: rates of stenosis between 8.7 to 11%, infections from 6.6 to 10% and calculi from 10 to 15.5%) [470, 472] (LOE3). Renal function was preserved for short follow-up times, but fatal end-stage renal failure occurred in up to 26.6% of children during long-term follow-up [469] (LOE3).

This technique is almost never used for neurological patients with bladder dysfunction anymore because conservative treatments (intermittent catheterization, urological endoscopy) have improved and the number of children suffering from spina bifida or presenting with complex malformation of the lower urinary tract has gradually lowered. Moreover, new urinary diversion techniques have been developed.

Recommendations:

- **Non-continent urinary diversion is the last resort for patients with neurogenic bladder (A).**
- **Bladder should be removed during the procedure because of the risk of later complications at this site (B).**
- **It may be indicated for urological dysfunction or in the event of a motor handicap that prevents other modes of micturition (C).**
- **Ileal conduit urinary diversion has the best long-term results for non-continent diversion, if the following pre- and peri-operative precautions are taken (B):**
  - **o Pre-operative identification of optimal location for the stoma site, with wheelchair test, if necessary.**
  - **o Utilization of a short intestinal segment (10 cm maximum).**
  - **o Minimal dissection of the ureters.**
- **There are several reports of good results for ileovesicostomy, but the medium-term results need to be confirmed in the long term. Quality-of-life studies should also be performed (C).**
- **Vesicostomy may be a useful temporary solution, particularly for children (D).**
- **Cutaneous ureterostomy shouldn't be used for non continent urinary diversion in adult patients because of the rate of long term complications (B).**

D. Neurological faecal incontinence

I. EPIDEMIOLOGY

Disorders of the central nervous system (CNS) are common, with worldwide estimates of the prevalence of spinal cord injury (SCI) at over 2.5 million, multiple sclerosis (MS) considerably greater than 1.5 million and Parkinson's disease (PD) approximately 3 million [1-3]. Whilst mobility, pain and bladder dysfunction has been relatively well studied, the bowel and pelvic floor dysfunction has been neglected by comparison. This is doubly unfortunate, as a large proportion of patients with CNS dysfunction experience frequent bowel symptoms, and these symptoms are amongst the most physically, socially and emotionally disabling [4-6]. Most of the literature deals primarily with the bowel dysfunction associated with three common CNS diseases – SCI, MS and Parkinson's disease. The literature on the most common of all CNS diseases – stroke – is more patchy and often directed towards acute post-stroke problems, as opposed to chronic neurogenic bowel dysfunction. With rapid advances in rehabilitation medicine resulting in increased survival of patients, these individuals are experiencing bowel symptoms for ever-longer periods.

Spinal cord injuries are common, with an estimated 50 people per million sustaining a traumatic spinal injury every year in the Western world [7]. Non-traumatic injury (vascular, infection, tumour) is more common, and cancer alone is estimated to cause more SCI than trauma [8]. Traumatic injury mostly affects young men, and advances in rehabilitation medicine mean that the longevity of paraplegics is similar to the general population while that of tetraplegics is 10 years shorter [9]. Bowel dysfunction affects almost all patients with a chronic SCI – up to 95% report constipation, faecal incontinence is experienced at least once per year by 75% and daily by 5%, with 33% experiencing regular abdominal pain [4, 10, 11]. Inevitably, given the nature and chronicity of the bowel symptoms, they represent a significant contributor to reduced quality of life in SCI individuals [4]. Patients with SCI reported bowel dysfunction as more problematic than bladder dysfunction, sexual dysfunction, pain, fatigue and body image [4].

Bowel dysfunction is less studied, but almost as prevalent in other neurological conditions. The prevalence of MS is approximately 1 per 1 000 [2]. About one-third of MS patients suffer from constipation and one-quarter are incontinent at least once per week [5, 12]. In patients with Parkinson's disease, constipation, in particular difficulty with defaecation, occurs in 37% [13]. One quarter of stroke survivors experience constipation, and 15% suffer with faecal incontinence [14].

II. NEUROPHYSIOLOGY OF BOWEL DYSFUNCTION

The pathophysiology of pelvic floor and colorectal dysfunction is broadly similar in patients with both SCI and MS. The extent of injury is the most important factor in determining bowel symptoms in both SCI and MS. However, in chronic SCI patients the lesion is usually sharply defined and unchanging, while in patients with MS the lesions typically occur at multiple levels and tend to vary with time.

Gastrointestinal transit is under the complex regulatory interplay of the enteric nervous system and extrinsic autonomic innervation. Parasympathetic innervation accelerates transit, proximally provided by the vagus and distally by the lower sacral roots (S2-S4). The vagus provides parasympathetic input up to the distal transverse colon, so in spinally injured patients, the dysfunctional gut segment is the distal colon. The sympathetic innervation (T9-L2) retards intestinal transit. Standard clinical classification of SCI relates to this, in that lesions are classified as supraconal (above the conus medullaris, where inhibitory input is lost), within the conus or being located in the cauda equina (where excitatory sacral parasympathetic supply is lost).

In supraconal SCI, an "upper motor neurone" type injury of the bowel results; there is slowed whole gut transit [1, 2] and hypertonia and hyperreflexia of the hindgut (i.e. distal to the splenic flexure) [3, 4]. The slowing of transit is autonomic-mediated, but also contributed to by reduced mobility and attenuation of the gastro-colic response [5]. The rectal hypertonia results in reduced rectal compliance and predisposes to reflex defaecation and incontinence. In cauda equina lesions the efferent limb of the reflex arc to the hindgut is interrupted, resulting in a "lower motor neurone" type bowel dysfunction with hypotonia and hyporeflexia [6]. Complete SCI has been shown to result in the most severe degree of bowel dysfunction [7]. However, in incomplete injuries, the relationship is more variable. The ASIA classification of severity of the lesion has not been convincingly shown to relate to magnitude of bowel symptoms, which may relate to the influence of the enteric nervous system in moderating gut-function post-injury.

Anal continence rests on an interplay between rectal musculo-sensory function and the internal and external anal sphincters. The internal anal sphincter is a condensation of the circular smooth muscle of the colon. As such, it is not subject to voluntary control but receives an autonomic (excitatory sympathetic and inhibitory parasympathetic input) [8]. Nevertheless, supraconal injury tends not to alter anal tone, whilst the reduced tone of cauda equina lesions may relate to faecal bolus impaction as much as loss of sympathetic input. The striated external anal sphincter is under voluntary control from Onuf´s nucleus in the ventral horn of the sacral

spinal cord via the pudendal nerves. Thus, in complete SCI the voluntary control of the external anal sphincter is lost [9].

Faecal incontinence relates not only to motor factors affecting the sphincter, but also to anorectal sensation. The anal mucosa has a dense network of sensory receptors, and loss of sensation can result in anal incontinence. Rectal hyposensation occurs in both supraconal and cauda equina lesions, and predisposes to faecal impaction (especially in the flaccid rectum of patients with cauda equina lesions) [9].

The pathophysiology of bowel dysfunction in patients with Parkinson´s disease (PD) is quite different from that of SCI or MS. Dystonia of the striated muscles of the pelvic floor and external anal sphincter explains the defecatory dysfunction [10]; this aetiological factor is supported by the observation that pelvic floor dysfunction is alleviated with L-Dopa [11]. In addition to the pelvic dysfunction, colonic transit time is usually prolonged in patients with idiopathic PD [10]. Two important pathophysiological factors contribute to this: firstly, the number of dopamine producing cells in the colonic wall is reduced in idiopathic PD [12] and secondly Lewy bodies, typical of PD, form in the enteric ganglia [13]. Recent observations have identified that men with a bowel opening frequency less than every 24 hours have an almost threefold risk of developing PD in later life compared to men with a daily or more often bowel frequency [14], suggesting that PD is not just a degenerative disorder of the CNS but also of the enteric nervous system.

III. ASSESSMENT

Patients with PD, where bowel dysfunction can long pre-date neurological diagnosis, often report decades of bowel symptoms. Current bowel symptomatology is next assessed, regarding bowel frequency, stool consistency, faecal incontinence and manoeuvres needed to achieve bowel management. This information is usually gathered from standard patient and carer history, but scoring systems exist which may supplement this. There are standard instruments (Cleveland Constipation score, St Mark's incontinence score [1, 2], and recently a condition specific score has been developed for neurologic patients [3]. This Neurogenic Bowel Dysfunction (NBD) Score is validated in SCI, but not PD; it is currently being assessed in patients with MS.

Digital rectal examination is an essential component, allowing assessment of rectal filling, resting anal tone, ability to generate a voluntary contraction and it also gives a crude assessment of anal sensitivity. The place of more interventional physiological or radiological transit investigations is not established, but may be appropriate if there is any co-morbidity (prior anal surgery, obstetric history, pelvic organ prolapse). Plainly, patients with alarm symptoms should have necessary colonic imaging performed. Alarm symptoms in this patient group are more difficult to recognise, but any worsening of established bowel dysfunction, weight or blood loss warrants investigation.

IV. CONSERVATIVE TREATMENT

The primary aims of bowel care are twofold: to achieve bowel evacuation in a timely manner and to avoid fecal incontinence. The first step of this bowel care consists of optimizing stool consistency with adequate fluid and fiber intake, and stimulating evacuation of stool on a regularly scheduled basis with digital rectal stimulation. A range of other non-invasive interventions may supplement this: Valsalva or manually-generated external pressure, oral medications – stool softeners, stimulant laxatives and prokinetic agents; diet modification; biofeedback; electrical stimulation and functional magnetic stimulations. The key to successful bowel management is intensive patient education and training. If conservative bowel management fails, surgical management may be necessary.

Search strategy; in updating previous consultations [1, 2], Pubmed items from 2007-2011 were searched with the key words: faecal incontinence, neurogenic, neuropathic, neurologic, neurogenic bowel, bowel management, bowel care, conservative treatment, practice guideline, incontinence, constipation, cisapride, colonic, dietary fibre, laxative, suppositories. From such searches, resulted a number of papers of various levels of evidence described below.

1. BOWEL PROGRAM /BOWEL CARE

Krassioukov et al. [3] in a large literature review found 57 studies on bowel care in SCI. They concluded that multi-faceted programs are the first approach to neurogenic bowel and are supported by lower levels of evidence (LE). There is level 4 evidence (from three pre-post studies) that multifaceted bowel management programs reduce gastrointestinal transit time, incidences of difficult evacuations and duration of time required for bowel management. Coggrave et al. described bowel management in community-dwelling SCI individuals [4]. In 1334 SCI individuals, median 52 years old and with duration of injury of 18 years, the most common intervention was digital evacuation (56%). Less than 30 minutes was spent on each bowel care episode by 58% of respondents, the others needed more time. Reported problems included constipation (39%), haemorrhoids (36%) and abdominal distension (31%). Reduced satisfaction with bowel function was associated with longer duration of each bowel care episode, fecal incontinence, greater number of interventions used and more problems reported. Impact of bowel dysfunction on the

respondent's life was rated as significantly greater than other aspects of SCI. Emmanuel has summarized the evidence base [5]. Initial management for all subjects is medication review (especially bladder drugs such as antimuscarinics, baclofen, ditropan, codeine analgesia, non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics) and addressing any unusual dietary habits.

In general, scheduled defecation should be attempted once a day or on alternate days. However, knowledge of bowel frequency prior to injury is important in deciding on the bowel program. The bowel regime approach used at the UK's National Hospital for Neurology and Neurosurgery [5] includes

- For patients with an upper motor neuron type bowel lesion and normal or minimally impaired anorectal sensation: aiming to have a stool consistency soft enough to be passed after rectal stimulation, but not so loose as to risk incontinence in between bowel actions; stool softened by regular use of gentle osmotic laxatives and stool softeners titrated in dose to obtain a stool of the desired consistency; stimulant laxatives are best used on an as-and-when basis rather than regularly; rectal stimulation is achieved by the simplest means possible (from digital stimulation to suppositories to enemas).

- For patients with an upper motor neuron type bowel lesion and absent or grossly impaired anorectal sensation: aiming as above, but there is less room for adjusting stool consistency, since loose stools will always result in incontinence; fiber-based laxatives are occasionally recommended alongside osmotic ones, although use should be cautious to avoid worsening abdominal distension and flatulence; rectal stimulation is performed as above.

- For patients with a lower motor neuron type bowel lesion: aiming to have a formed stool which is manually removed or irrigated from the rectum; bulking agents can be helpful in this situation, along with softening agents or gentle osmotic laxative use to get the correct consistency of a formed stool. Stimulants are not helpful; manual extraction, enemas or rectal irrigation are required to remove the stool. On rare occasions tiny doses of loperamide syrup may be given after bowel care to minimize the risk of subsequent soiling. The emphasis is on avoiding becoming constipated.

2. SPECIFIC TECHNIQUES

a) Diet

Patients with an upper motor neuron type bowel will tend to have slow whole-gut transit, and a high-fiber diet will tend to cause bloating and flatulence. In general reducing the fiber intake – especially of insoluble (i.e. cereal) fiber – is helpful in improving these symptoms. Patients with lower motor neuron type bowel may find that a higher fiber diet helps improve stool consistency and therefore prevent fecal soiling. The most important aspect of diet is to get into a pattern of regular eating, which helps optimize bowel motility. Excessive quantities of caffeine, alcohol and foodstuffs containing the sweetener sorbitol can cause the stools to become looser and hence more difficult to manage [5].

b) Toileting

Patients need to have a sense of privacy and comfort to achieve a successful bowel regime. Bowel contractions are maximal on waking up and after a meal or warm drink (the gastro-colic response), therefore many patients should optimize this with scheduled defecation after a warm drink and breakfast. Where possible, it is best to exploit gravity to evacuate the bowel, so sitting on a toilet or commode chair is preferred. When this is not practicable, toileting has to be done on the bed. There are previous case reports on positive effects of using a standing table or a washing toilet seat with visual feedback [3]. Valsalva maneuver (breathing hard against a closed glottis) may help, but should be avoided in patients with significant autonomic or cardiorespiratory problems [5].

c) Digital rectal stimulation

Digital rectal stimulation (DRS), involves circular motion of a finger in the anal canal with the intention of causing a reflex contraction of the colon and rectum, and hence a bowel action. A lubricated, gloved finger is gently inserted into the anus and rotated for 20–30 seconds before being withdrawn. If there is no result within 5 minutes the procedure can be repeated at that point. This process also serves as a useful check to see if there is any stool present in the rectum [5]. It was demonstrated that DRS contributes to bowel evacuation in individuals with SCI in part by increasing left-side colonic motility. Mechanical stimulation must be done with caution as it may cause local trauma and induce autonomic dysreflexia (AD) in SCI individuals [2].

d) Manual stool extraction

Manual extraction of stool differs from DRS, attempting physical removal of the stool from the rectum with a gloved finger hooking stools out. This technique is only possible when the stools are formed. Manual extraction can be combined with a Valsalva maneuver to improve effectiveness [5]. In a randomized, controlled trial, systematic use of less invasive interventions could not reduce the need for oral laxatives and manual evacuation in individuals with chronic SCI [6]. It provided evidence of acceptability of the technique.

3. CHEMICAL STIMULANTS

Suppositories and enemas may supplement the above by causing a reflex contraction of the rectum. Implicitly, there is little point in using these agents when the rectum is empty on digital checking [5].

Stimulants range in potency, from glycerine suppositories, through micro-enemas, to larger volume stimulant enemas. Ideally, these agents should be retained for at least 10 minutes.

Krassioukov et al. gave an extensive overview of publications on medications. There is LoE 1 evidence to support polyethylene glycol-based suppositories for bowel management. Cisapride did significantly reduce colonic transit time for chronic constipation but did not seem to have clinically useful effects in people with SCI. It has now been withdrawn because of cardiac side effects. Psyllium did not alter colonic transit time but was associated with increased stool frequency in people with Parkinson's disease. Prucalopride increases stool frequency, improves stool consistency and decreases gastrointestinal transit time in chronic constipation, and has shown some benefit in this patient group [7]. The time schedules for administration of rectal medication may influence bowel responses. The clinical significance of any of these results was difficult to interpret because of the limited number of papers and the quality of the research. During the last three years there has been no research study on the effectiveness of such medications in patients with neurogenic bowel dysfunction.

4. ASSISTIVE TECHNIQUES FOR DEFECATION

a) Abdominal massage

Abdominal massage with the heel of the palm, in a circular motion from right to left may help increase bowel transit and movement of content towards the rectum [5]. In small controlled trials, positive effects were seen in patients with multiple sclerosis [8] and with spinal cord injury [9].

b) Anal stimulation with water streams

Pulsed water irrigation consists of supplying intermittent, rapid pulses of warm water into the rectum to break up stool impactions and to stimulate peristalsis. Pulsed irrigation evacuation would be a safe and effective method for individuals with SCI who develop impactions, or do not have an effective bowel routine [3].

c) Transanal / Transrectal irrigation (TAI)

Several studies have been published comparatively recently on this technique. Christensen et al. [2009] described how 163 of 348 patients (47 percent) had a successful outcome from treatment with TAI after a mean follow-up of 21 months. Success rates varied between patients with different underlying pathology: for neurogenic bowel dysfunction, the success rate of 67 of 107 (63 percent) was higher than in patients with anal insufficiency, sequela to anorectal surgery, idiopathic constipation, and miscellaneous [10]. Amongst factors correlating with positive outcome were neurogenic bowel, low rectal volume at urge to defecate, low maximal rectal capacity, and low anal squeeze pressure increment. Two non-fatal bowel perforations were found in approximately 110,000 irrigation procedures.

Faaborg et al. studied long-term application of TAI and found a drop-off in effect, with successful outcome in 46% of neurologic patients after a mean follow-up of 19 months. The rate of success was 35% after 3 years and remained almost unchanged thereafter. TAI was relatively safe, with a perforation rate of about 1 in 100,000 [11]. Whether this perforation rate is cumulative or seen only at the initiation of treatment remains to be determined in long-term studies.

Ausili et al. treated 60 children with myelomeningocele with TAI for three months. Sixty percent (36/60) reported relief from constipation and 75% (12/16) for fecal incontinence. Wheelchair-bound and walking patients showed similar improvements of bowel habit. There was a clear improvement in quality of life. They observed a reduction of urinary tract infections during the course of treatment and few complications [12].

Neel prospectively evaluated the efficacy and durability of combined intradetrusor botulinum-A toxin, endoscopic treatment for vesicoureteral reflux, with anal irrigation in a small group of young (5.3 +/- 2.5 years), incontinent, treatment-refractory myelomeningocele children. Ten of 13 patients achieved stool dryness with anal irrigation 1 to 2 times weekly. Three patients who were stool continent on standard enemas did not require this irrigation system [13].

TAI using a self-administered system results in a lower total cost to society than conservative bowel management [14]. Building on the positive data reported for patients with SCI, continued evaluation in the clinical trial setting is required to further define the utility of TAI in other populations with NBD [15].

5. APPLIANCE/ASSISTIVE TECHNIQUES FOR FAECAL INCONTINENCE

a) Anal plug

Previous studies employing anal plugs have yielded conflicting results [3]. Bond et al. undertook a randomized controlled trial with the Conveen anal plug (Coloplast Limited) used for 12 months in patients, including a number with neurologic bowel. The anal plug proved of benefit to the majority of patients. It did not suit all eligible patients, with in situ plug retention being a problem for some [16].

b) Neuromodulation /Electrostimulation/Magnetic stimulation

Tsai et al. state that functional magnetic stimulation, featuring broad-spectrum application, can be incorporated successfully into other therapies as an optimal adjuvant treatment for neurogenic bowel dysfunction resulting from SCI- both with supraconal and conal/caudal lesion [17]. Kajbafzadeh et al. applied transcutaneous interferential (IF) electrical

stimulation for constipation symptoms in children with myelomeningocele (MMC). They found sphincter pressure and rectoanal inhibitory reflex significantly improved compared with sham stimulation and pretreatment measures. In 73% of patients, the characteristics of constipation decreased immediately after IF therapy, while in 53% patients, they persisted for 6 months. Frequency of defecation increased statistically significant [18].

In a small pilot study Fu et al. explored the efficacy of neuromodulation. One patient with permanent sacral electrode and neurostimulator implantation was overall successful. Four out of 8 with dorsal penile/clitoral nerve neuromodulation had decrease in Wexner constipation score. Patients also showed a significant improvement in their symptoms and quality of life during follow up. If confirmed, sacral neuromodulation and dorsal penile/clitoral nerve neuromodulation may be effective for some neurogenic constipation. However, there are no predictive tests to anticipate the candidates with the best chance of benefit with the procedure [19].

In the previous literature [4], one good quality RCT, with only a few study subjects, showed that external electrical stimulation of the abdominal wall muscles can improve bowel management for individuals with tetraplegia. In a prospective controlled trial, 25 minutes of electrical stimulation of the abdominal muscles per day, five days a week, for eight weeks, resulted in accelerated colonic transit times when compared to the placebo control group. In a case study, posterior tibial nerve stimulation improved bowel management in incomplete SCI. Functional magnetic stimulation on the thorax and lumbosacral nerves (simulation placed at T9 and L3 spinal processes) reduced colonic transit times and self-reported symptoms of constipation [4].

c) Quality of life

No specific new study has been published, but in several studies mentioned above an improvement of QoL was shown.

Conclusions

- **In reflex bowel, digital rectal stimulation relaxes the external anal sphincter and increases peristaltic contractions by facilitating an excitatory anorectal (ano-colonic) reflex, and enhances bowel movement and evacuation (LOE 3).**
- **Abdominal massage has beneficial effects on neurogenic bowel dysfunction, including defecation function and fecal incontinence (LOE 3).**
- **Transanal irrigation is a safe method to improve constipation and faecal incontinence in individuals with neurogenic bowel dysfunction (LOE 2).**
- **An anal plug can help control fecal incontinence in selected neurological patients (LOE 3).**
- **Different forms of electrical stimulation seem promising for fecal incontinence and defecation management in neurologic patients (LOE 3).**
- **To increase adherence rate with bowel care program/clinical practice guideline, implementation strategies should be addressed to care providers (LOE 3).**

Recommendations

- **Multi-faceted programs are the first approach to neurogenic bowel management and are supported by lower levels of evidence (B). They may consist of toileting, rectal stimulation (digital or with water stream), manual feces extraction, transanal irrigation and other assistive techniques (B).**
- **Diet can help but multi fibre is not necessarily indicated in patients with upper motor neuron lesion (B).**
- **Autonomic dysreflexia when using mechanical stimulation and assistive techniques can occur in neurologic patients with a high spinal cord lesion (B/C).**

Recommendations for research

- **Development of sensitive and valid instruments to quantify bowel dysfunction in neurogenic conditions other than spinal cord injury.**
- **Well-designed controlled trials with adequate numbers and clinically relevant outcome measures of bowel management are needed, including for administration of stimulants.**
- **Larger and good quality randomized crossover trials are needed to confirm the effects of neuromodulation and other forms of electrical therapy for controlling fecal incontinence and reducing constipation in neurologic patients.**
- **Transanal irrigation needs to be studied in patients with causes of neurologic bowel different from spinal cord lesion and meningomyelocoele. Long-term follow up of TAI populations is important to determine the safety, and factors predicting poor outcome.**
- **Given the prevalence of bowel dysfunction in Parkinson's disease (which is increasing in prevalence), specific studies in this population are required.**

V. SURGICAL TREATMENT

Using MEDLINE we identified English-language journal articles and reviews published from 2000 to December 2011, looking for the keywords; neurogenic constipation and faecal incontinence, surgery,

sacral nerve stimulation, antegrade continent enema procedure, dynamic graciloplasty, artificial anal sphincter and colostomy.

The mainstay of current treatment in neurogenic fecal incontinence is adopting a conservative approach towards reversing the systemic effects and optimizing the mechanics of defecation through the use of laxatives and irrigation approaches. Surgery should be normally reserved for patients who have failed conservative therapy. This section focuses on specific aspects of faecal incontinence surgery in neurogenic patients. Although traumatic lesion of the external anal sphincter in neurologically intact patients is treated by reconstruction, functional impairment of anal sphincter without mechanical defect of the sphincter in neurogenic patients can not be treated by this simple surgical approach. Thus, options for surgical treatment of neurogenic bowel dysfunction are limited. They consist of; 1) sacral nerve stimulation, 2) antegrade continent enema procedure, 3) dynamic graciloplasty, 4) artificial anal sphincter, 5) elective colostomy, 6) postanal repair.

1. SACRAL NERVE STIMULATION

Electrical stimulation of sacral nerve roots has been reported to restore continence in patients with intact muscle structure. The procedure includes a test phase: acute percutaneous testing, today mostly using tined lead electrodes as part of a two stage operative procedure, or temporary percutaneous nerve evaluation, prior to permanent electrostimulation with an implanted neurostimulation device. An electrode inserted into the S3 sacral foramen provides low grade stimulation. If patients respond to acute or temporary percutaneous sacral nerve stimulation tested for 2 to 3 weeks, permanent stimulation can be considered. Thus is achieved with a chronic stimulator implanted under the anterior abdominal wall or subcutaneously in the gluteal region. The first case report with this technique was published by Matzel et al. [1] in 1995 who described a successful outcome in three patients with faecal incontinence. Since then, ten articles have been published [2-11] (**Table 14**). Matzel et al. [2] reported a multicentre, prospective trial with chronic sacral nerve stimulation in a series of 34 patients at a median follow-up of 23.9 months. At least 83 % of patients had a 50 % or greater improvement in total number of incontinent episodes per week and at least 71 % of patients a 50 % or greater improvement in total number of days per week with continence during the course of follow-up. Continence was fully restored in at least 12 (37 %) patients. Quality of life improved in all four ASCRS (American Society of Colon and Rectal Surgeons) scales ($p<0.0001$) and in seven of eight SF-36 scales, though only social functioning was significantly improved ($p=0.0002$). Although 12 patients had 19 device-related adverse events including pain (ten episodes in 9 patients), lead breakage in one patient, recurrent infection needing device removal in one patient and deterioration of bowel symptoms in three patients, resolution rate was 63.2 % and 100 % for all and severe complications, respectively. However, this study excluded patients with neurological diseases.

Similar success rates (73-100%) with this technique have been reported from other centres [3-5, 7-11]. Among these reports, only one case-series by Rosen et al. [12] mainly evaluated faecal incontinence in patients with neurological lesions. In that study, 20 patients (15 neurogenic, 5 idiopathic) with severe faecal incontinence were initially treated by temporary external stimulation over a period of 10-14 days. Sixteen patients (11 with neurogenic causes, including SCI, spinal cord surgery, myelomeningocele and MS) who had shown a positive response to the temporary stimulation subsequently underwent permanent implantation. The median follow-up was 15 months (range, 3-26 months). All patients who had received a permanent implant revealed a marked reduction in their incontinent episodes, as well as an increase in retention time. In the neurogenic subpopulation, the median numbers of incontinence episodes decreased significantly ($p<0.01$) from 7 (4-15) to 2 (0-5), and a median retention time significantly ($p< 0.01$) increased from 2 minutes (0-5) to 7 minutes (2-15) after chronic stimulation. Assessment of QOL scales using ASCS questionnaires after 6 months treatment showed significant improvement on all scales. Three patients (2 neurogenic and 1 idiopathic) had severe infections needing explantation of the device and wound drainage 0-3 months after implantation. Another one patient had dislocation of the permanent electrode. No complications were observed in the remaining 12 patients (60 % of total series). All of those patients with functioning systems showed improved incontinence during the follow-up period. Although the mechanism of SNS in improving faecal incontinence is uncertain, rises in anal resting and squeezing pressures and changes in rectal sensitivity and motility have been proposed. Particularly in neurogenic patients, neuromodulation of sacral reflexes and regulation of rectal sensitivity appear to be the major reasons for the functional improvement [7]. Where the diagnostic stage is performed as a staged implant, a tined lead is employed with four active electrodes (compared with a single electrode used in PNE) and has self-retaining flanges, which reduce risk of lead migration. Usage of the tined lead has the benefit of minimizing false-negative results.

Jarrett [2005] [14] reported on experience with sacral nerve stimulation for faecal incontinence in patients with previous partial spinal injury including disc prolapse: the spinal insults were disc prolapse (six), trauma (four), spinal stenosis (one) or occurred during neurosurgery (two). Temporary SNS was performed in thirteen patients (median age 58,5, range 39-73 years). Twelve patients had successful temporary stimulation and proceeded

Table 14: Published data on sacral nerve stimulation for fecal incontinence

Authors, year	No. of patients (neurogenic patients) with chronic stimulation	No. of patients underwent test stimulation	Median follow up (months) (range)	Improvement rate (fully continent rate)	Complications
Lombardi et al., 2010 [16]	32(32)	39	38	25%, all others improved by at least 50%	
Holzer et al., 2007 [15]	29(29)	36	35 (3-71)	28 patients marked improvements, see text	
Jarrett, 2005 [14]	12(12)	13	12(6-24)	incontinence episodes decreased from 9.33 to 2.39 per week	
Matzel et al., 2003 [2]	34 (0)	37	23.9	83% (37%)	
Ripetti et al., 2002 [3]	4 (0)	21	15(6-24)	100%	
Ramussen et al., 2002 [4]	10	14	4.5	90%	
Kenefick et al., 2002 [5]	14 (0)	ND	24 (3-60)	100% (73%)	
Matzel et al., 2001 [6]	6 (1)	ND	36(5-66)	100%	removal 2 for pain
Rosen et al., 2001 [7]	16 (11)	20	15(3-26)	75%	
Ganio et al., 2001 [8]	16 (2)	ND	15.5(3-45)	100%	
Leroi et al., 2001 [9]	6 (0)	9	6	50%	
Ganio et al., 2001 [10]	5	23	19.2(5-37)	100%	
Malouf et al., 2000 [11]	5	ND	16	100%	
Rosen et al., 2001 [12]	20 (15)	20	15 (3-26)	100 %	

to permanent implantation. The median follow-up time was 12 (range 6-24) months, the mean number of episodes of incontinence decreased from 9.33 (7.64 per week at baseline 2.39 [3.39] at last follow-up (p = 0.012). The number of days per week with incontinence and staining decreased significantly (p = < 0.001). The ability to defer defecation improved from a median of "not able to defer" (range 0-1 min.) to being able to defer 5-15 min (range 0->15) mean (p = 0.022). The authors conclude that SNS can benefit patients with faecal incontinence following partial SCI. Holzer et al. [2007] [15] reported on 36 patients included in a trial of SNS, of whom 29 subsequently had a permanent implant. After a medium follow-up of 35 (range 3-71) months, 28 patients showed a marked improvement: incontinence to solid or liquid stool decreased from a median of 7 (range 4-15) to 2 (range 0-5) episodes in 21 days (p = 0.002). Saline retention time increased from a median of 2 (range 0-5) to 7 (range 2-15) min. (p = 0.002). The quality of life on all scales among patients who received the permanent implant increased at 12 and 24 months after operation.

Based on a retrospective, non-blinded study without controls comprising 39 patients, Lombardi et al. [16] evaluated the clinical outcome of SNS in incomplete SCI with neurogenic bowel dysfunction: Twenty-three patients were submitted to definitive SNS, maintaining their clinical benefits after permanent implantation with a median follow-up of 38 months. The length of time since neurological diagnosis to SNS therapy represented the only factor significantly related to the success of the implantation. In subjects with constipation [12] the median number of evacuations shifted from 1.65 to 4.98 per week, whereas the Wexner score changed from 19.91 to 6.82 in the final checkup with P<0.05. In subjects with fecal incontinence [11], the median number of episodes per week in the final follow-up was 1.32 compared to 4.55 pre-SNS. General and mental health showed statistically significant improvement. Anorectal manometry showed no important variation compared with baseline. There were no major complications. The authors consider SNS an option for the treatment of neurogenic bowel symptoms for selected patients with *incomplete SCI* when conservative treatments have failed.

The overview of the studies shows that electrical nerve stimulation is effective in partial spinal cord injury. There are no reports for complete spinal cord lesions.

Conclusions

- **SNS is a minimally invasive procedure, and seems to be an option for faecal incontinence and constipation due to functional deficit of the anal sphincter without structural defect in incomplete neurogenic lesions (LoE3/4).**

Recommendations

- **Studies on larges series with long term follow-up are needed to determine the role of SNS in the treatment of faecal incontinence associated with neurological lesions (D) and identify those patients most likely to benefit.**

2. ANTEGRADE CONTINENCE ENEMA (ACE)

The original procedure was developed by Malone et al. [17]. The principles of antegrade colonic washout and the Mitrofanoff non-refluxing catheterisable channel were combined to produce a continent catheterisable colonic stoma. The intention was that antegrade washouts delivered by this route would produce complete colonic emptying and thereby prevent soiling. Malone et al. reported successful results in five children with intractable faecal incontinence. This procedure has been applied mainly to the paediatric population with neuropathic bowel dysfunction and anorectal anomaly, and successful outcome was achieved in 70-100 % [18-38] (**Table 15**). Several modifications have been reported including laparoscopic technique, left colonic continence stoma, etc. This procedure was also applied to adult neurogenic patients with faecal incontinence, and similar success rates (83-100 %) were reported. Overall, stoma stenosis is the most common complication, affecting 10-41 %. In a study of 62 children with median follow-up of 5.4 (3.25 to 8.25) years, 84% were completely continent or had soiling less than once a month [20]. There was a significant correlation between the level of continence and satisfaction with the procedure. Improvement of self-esteem and psychosocial function after the ACE procedure in children with myelomeningocele has been reported [22].

Casale et al. [39] compared total continence reconstruction to staged-reconstruction of neuropathic bowel and bladder. In this retrospective chart review of all patients with myelomeningocele who underwent reconstruction with a cutaneous catheterisable urinary channel or Malone ACE stoma, the authors were unable to find any differences in the continence rate or stoma complications between total continence reconstruction and/ or staged reconstruction. However, because of shared pathology the authors believe that most patients are likely to require intervention for both gastrointestinal and genitourinary problems. Therefore, a major advantage of total continence reconstruction is avoidance of the morbidity of requiring major surgical procedures on separate occasions for the two organ systems (LOE 3).

Herndon et al. 2004 [40] reported on ACE stoma in 127 patients (76 females and 51 males, average t age at the time of surgery 9.6 years), reflecting a 6-year experience. Diagnoses included myelomeningocele in 116 cases, lipomeningocele in 6, SCI in 2, sacral agenesis in 1 and functional constipation

Table 15: Antegrade continence enema stoma

Table: Summary of reported data on antegrade continent enema for faecal incontinence							
Authors reference no., year	Level of evidence	No. of patients	Mean age (range)	Median follow up (range)	Success rate	Overall complication rate	Stomal stenosis
Bar-Yosef et al., 2011 [41]	Level 3	21	10.4(6-22)	4,7 years (066-11.7)	90%	25%	14%
Malone et al., 1990 [17]	Level 4	5	(8-18)	(2-8 mos.)	100%	40%	
Herndon et al., 2004 [40]	Level 3	127	9.6	26.9 mos.	91 %	10 %	8 %
Teichman et al., 2003 [18]	Level 4	7	34	4,5 yrs. (all>4 yrs.)	83%	67%	
Dey et al., 2003 [19]	Level 4	62	11,5 (3,8-17,6)	5,4 yrs. (3,25-8,25)	84%	66%	42%
Liard et al., 2002 [20]	Level 4	24	15	3,7 yrs.	100%		
Aksnes et al., 2002 [21]	Level 4	20	10,9 (6,8-17)	16 (9,5-23)mos.	80%	30%	20%
Liloku et al., 2002 [22]	Level 4	7	8-21	(1,5-18 mos.)	71%	29%	14%
Tackett et al., 2002 [23]	Level 4	45	10,5 (3,8-25,8)	25,3 (4-65) mos.	87%	22%	18%
Perez et al., 2001 [24]	Level 4	12	14 (7-20)	15 mos.	92%		58%
Kajbafzadeh et al., 2001 [25]	Level 4	40	9,5 (4-22)	22 (8-48) mos.	100%	2,5%	
Van Savage et al., 2000 [26]	Level 4	16	12 (4-21)	1,5 yrs	100%	50%	6,3%
Bruce et al., 1999 [27]	Level 4	7	33,6 (23-54)	22,4 (3-34) mos.	100%		14%
Robertson et al., 1999 [28]	Level 4	30	9,5 (5-16)	>1yr. (3mos.-3,5yrs.)	90%	33%	27%
Teichmann et al., 1998 [29]	Level 4	7	32	11 mos.	100%	57%	28%
Meier et al., 1998 [30]	Level 4	20	10 (4-18)	24 (9-45) mos.	90%	10%	5%
Driver et al., 1998 [31]	Level 4	29	10 (5-16)	28 (7-71) mos.	79%		38%
Hensle et al., 1998 [32]	Level 4	27	16 (10-31)	(9-30 mos.)	70%	37%	18,5%
Levitt et al.,1997 [33]	Level 4	20	(3-27)	(1-29 mos.)	95%	25%	10%
Goepel et al., 1997 [34]	Level 4	10	13,2 (6-26)	18,5 (8,5-36) mos.	100%	20%	
Dick et al., 1996 [35]	Level 4	13	8 (6-14)	32 (24-60) mos.	85%	46%	38%
Ellsworth et al.,1996 [36]	Level 4	18	12 (5-31)	6,6 (2-24) mos.	96%	22%	17%
Koyle et al., 1995 [37]	Level 4	22	13 (5-26)	>4 mos.	77%	36%	9%
Squire et al., 1993 [38]	Level 4	25	(3-18)	13 (2-61) mos.	88%	24%	20%

in 1. The mean follow-up was 26.9 months. Faecal continence was reported by 91% of the patients, while 13 stoma revisions were required in 11 patients (for stenosis in 10, prolapse in 2 and leakage in 1). Major complications included a caecal volvulus requiring a right hemicolectomy in one patient, small bowel obstruction in two and a shunt infection and/ or malfunction in two. The authors conclude that the in situ ACE procedure has reliable long-term results for treating faecal incontinence associated with neuropathic bowel.

Bar-Yosef et al. [41] performed a retrospective chart review from 1997 to 2007 in a total of 21 patients with myelomeningocele who underwent total continence reconstruction for urinary and feacal incontinence using the artificial urinary sphincter (AUS) and a Malone ACE stoma (using the appendix in 19 patients and cecal-based flaps in 2). There were 19 patients (90%) who reported fecal continence, with two reporting soiling 1 to 2 times a week. ACE stoma stenosis occurred in 3 patients and 2 required revisions. Sixteen patients (76%) achieved complete continence of stool and urine. Therefore ACE stoma and AUS in conjunction provide urinary and fecal continence in a single total continence reconstruction procedure, for patients.

Conclusion and Recommendation

- **Antegrade continence enema stomas are effective for controlling faecal incontinence and constipation associated with neurogenic bowel dysfunction especially in neuropathic children (LoE 3; Grade B). Patients should be properly selected to determine appropriate motivation.**

3. DYNAMIC GRACILOPLASTY

This procedure consists of transposition of the gracilis muscle around the anal canal and subsequent implantation of a pulse generator to stimulate and entrain the gracilis muscle. Before continuous stimulation is applied, the muscle is trained for 4 to 8 weeks according to a protocol. During a stimulation program the fatiguable type 2 skeletal fibres may be replaced by slow type 1 fibres, which are able to sustain a longer-lasting contraction- though formal documentation of such transition is not evident. Satisfactory continence has been reported in 56% to 81% of patients [42-53] (**Table 16)**. However, all studies presently available include small numbers of neurogenic patients, or there is no subgroup information on the outcome in neurogenic patients.

A prospective study of 200 consecutive patients with a follow-up of at least two years showed a 72% overall success rate. Complication rates are high (42%-92%)- especially infectious complications, which occur in about one quarter of the patients. Impaired rectal emptying occurs in 16% to 29%. A prospective controlled comparative study of a single stage operation with the conventional two-stage procedure showed no significant difference in infection rates, continence rates, morbidity or quality of life between the two groups after a mean 521-day follow up. Chapman et al. [53] reported a systematic review article of this procedure, where they searched articles published until November 1999, and found 40 articles met the inclusion criteria. Mortality rates were around 2% for both graciloplasty and colostomy. However, morbidity rates reported for graciloplasty appear to be higher than those for colostomy. Rongen et al. [42] reported an 80% success rate with this procedure in 16 patients with neurogenic faecal incontinence.

A prospective controlled study comparing dynamic graciloplasty with artificial anal sphincter in 16 patients (8 in each group) showed that both of the two procedures had a high incidence of technical failures and complication requiring re-operation [52], with a median observation time of 44/39 months. In this study, Ortiz et al. [52] came to the following conclusion: the artificial anal sphincter is a more convenient technique than dynamic graciloplasty for institutions treating a small number of patients. However, technical failures and complications during follow-up that require reoperation are very high in both types of treatment.

Conclusions and Recommendations

- **Dynamic graciloplasty seems to be associated with high complication rates, and outcome appears to correlate to surgeon's experience.**
- **Graciloplasty should be carried out in specialist centres with a reasonably large number of patients, and should be reserved for carefully selected patients with intractable faecal incontinence, where other methods have failed (C).**
- **Further studies are needed to determine its role in the neurogenic subpopulation.**

4. ARTIFICIAL ANAL SPHINCTER

Implantation of an artificial anal sphincter (AAS), also referred to as artificial bowel sphincter (ABS) was first reported in 1987 [54]. The sphincter used was originally designed for treatment of urinary incontinence, but subsequently the device was modified. The system consists of an inflatable cuff placed around the upper anal canal, a pressure-regulating balloon to maintain closure of the cuff, placed in the subperitoneal space lateral to the bladder, and a control pump accessible to the patient to empty the cuff for defaecation placed in the scrotum or labium. The system is left deactivated for 4 to 6 weeks after placement. The reported success rates obtaining acceptable continence range from 41 to 90% [55-70] (**Table 17**). A multicentre prospective, non-randomized trial in 112 patients with one year follow-up showed 73 revision operations were required in 51 (46%), and the infection rate necessitating surgical revision was 25%. Forty-one patients (37%) have

Table 16: Summary of reported data on graciloplasty for neurologic faecal incontinence

Authors [Reference no], year	Level of evidence	No. of patients	No. of neurogenic patients	Median follow up (range)	Success rate (success rate in neurogenic pts.)	Complication rate	Infection rate	Explantation rate	Emptying problem
Ortiz et al.; 2003 [52]	Level 3	8 (neuropathy 2)		39	No change in the CCS application	50%		50%	
Rongen et al', 2003 [42]	Level 3	200	16	>2 yrs.	72% (80%)	69%	12%	12%	16%
Wexner et al., 2002 [43]	Level 3	129		2 yrs.	56%				
Bresler et al., 2002 [44]	Level 4	24			79%	92%	25%		
								4%	
Matzel et al., 2001 [45]	Level 3	121	0	1.5 yrs.		77%	37%		27%
Baeten et al., 2000 [46]	Level 3	123	0	1 yr.(1-52 mos.)	74%	74%			
Madoff et al., 1999 [47]	Level 3	128		2 yrs.	66%		11%		
Sielenzneff et al., 1999 [48]	Level 4	16	1	20 (6-37) mos.	81%	50%	44%		31%
Christiansen et al., 1998 [49]	Level 4	13	0	(7- 27mos.)	77%		8%		23%
Geerdes et al., 1996 [50]	Level 4	67	0	2.7 yrs.(14w ks.- 8.7yrs.)	78%	79%	16%		
Baeten et al., 1995 [51]	Level 3	52	2	2.1yrs.(12wks.- 7.4yrs.)	73% (50%)		13%		

Table 17: Summary of reported data on artificial anal sphincter for faecal incontinence

						Complication rates			
Authors reference no., year	Level of evidence	No. of patients (neurogenic)	Mean age (range)	Median follow up (months) (range)	Success rate (in neurogenic)	Explantation	Infection	Revision	Emptying problem
Parker et al., 2003 [56]	Level 4	45(2)	44(15-72)		51% (50%)	40%	34%	21/13pts	11%
Michot et al., 2003 [57]	Level 4	37(16)	51(22-73)		79%	30%			37%
Devesa et al., 2002 [58]	Level 4	53(9)	46(16-76)	26,5(7-55)	65%	19%	13%	26%	22%
Wong et al., 2002 [55]	Level 3	112(ND)	49(18-81)		53%	37%	25%	46%	
Ortiz et al., 2002 [59]	Level 4	22(ND)	47(17-72)	26(6-48)	63%	44%			9%
Altomare et al., 2001 [60]	Level 4	28(4)	58(35-79)	19(7-41)	75%	32%	11%		57%
O´Brien et al., 2000 [61]	Level 4	13(1)	44(16-71)		77%	23%			
Lehur et al., 2000 [62]	Level 4	24(4)	44(14-80)	20(6-35)	75%	29%	12%	17%	45%
Christiansen et al., 1999 [63]	Level 4	17(10)	46(32-65)	7(5-10)years	47%	41%	18%	63%	13%
Vaizey et al.,1998 [64]	Level 4	6		10(5-13)	83%	16%			
Lehur et al., 1998 [65]	Level 4	13		30(5-76)	85%				
Lehur et al., 1996 [66]	Level 4	13(2)		20(4-60)	90% (69%)	23%	15%	15%	
Wong et al., 1996 [67]	Level 4	12(3)		58	50% (75%)	33%	25%	42%	
Christiansen et al., 1987 [54]	Level 4	1		3	100%				

had their devices completely explanted [55]. Explantation rates in the reported series were 20-40%. Technical complications like rupture of the cuff, which occurred frequently with the earlier versions of the device, are now rare. Emptying problems in the absence of anatomical stenosis, as described for dynamic graciloplasty, have also occurred frequently (13 to 45%) in most series and have necessitated explantation in some patients. Other complications leading to explantation have been erosion of the cuff through the skin, or into the anal canal.

As shown in the Table, most studies have a small number of neurogenic patients or do not indicate the number of neurogenic patients included. In the study reported by Christiansen et al. [63], 10 (59 %) out of 17 patients had neurological disorders, and the overall success rate was 47%, which seems to be lower than the others. The authors mentioned that the result in neurogenic subgroup was clearly poorer than that in non-neurogenic subgroup.

In a prospective, randomized controlled clinical trial of placement of the artificial bowel sphincter for the control of faecal incontinence O'Brien et al. [2000] [61] compared its effects to a program of supportive care and patients were followed for six months from operation or entry into the study. The principal outcome measure was the level of continence, measured with the Cleveland Continence Score, categorising from perfect control through to total incontinence. Secondary outcome measures were peri-operative and late complications in the artificial bowel sphincter group and the changes in quality of life in both groups. In the control group (N = 7) the Cleveland Continence Score was not significantly altered. The artificial bowel sphincter group (N = 7) showed a significant improvement. One patient in the artificial bowel sphincter group had failure of healing and implantation of the device. There were major improvements in the quality of life for all measures in the artificial bowel sphincter group. The authors conclude that the placement of an artificial bowel sphincter is safe and effective when compared with supportive care alone. Perioperative and late problems are likely to continue to occur and between 15% and 30% of patients may require permanent explantation. The authors conclude the device is easy and discrete to use, effective in achieving continence, and able to generate an improvement in quality of life (LoE 3).

In an article on "The artificial bowel sphincter in the treatment of severe fecal incontinence in adults", Lehur and Meurette [68] concentrated on the most recent and significant published data. They state that several centers in Europe, the United States, and Australia have adopted the ABS to treat severe fecal incontinence not amendable to local repair. Reports with larger numbers of cases and longer follow-up have recently appeared, providing a better assessment of the technique and its present place in the treatment strategy of incontinent patients. Contraindications include excessive perineal descent and severe constipation. In cases of neurogenic fecal incontinence it is essential to take into account possible associated bowel emptying problems and excessive perineal descent. The ABS creates an obstacle to rectal evacuation, which can sometimes cause considerable evacuation difficulties. Continence restoration should not be achieved to the detriment of evacuation capacities. However, an objective assessment of the state of pre-operative transit is not always easy.

Michot et al. [69] described an implantation procedure of artificial sphincter for anal incontinence using a transvaginal approach. Between 2003 and 2005, the Acticon Neosphincter was implanted via a transvaginal approach in nine patients (average age 43 (range 25-73) yrs). Successful outcome was achieved in eight of nine patients (89 %), with a mean follow-up of 21.5 (range 8-38) months; incontinence scores decreased from 19 (range 18-20) before the procedure to 8.6 (range 2-14) at the last follow-up. Although it is not stated whether patients with neurogenic faecal incontinence are included, a transvaginal approach could be considered with destroyed or scarred perineum.

Conclusions and Recommendations

- **Implantation of the artificial anal sphincter may be undertaken in neurogenic faecal incontinence, except in patients with previous perianal infections or with a thin and scarred perineum, in whom muscle transposition is preferable.**
- **Due to the relatively high risk of treatment failure and of complications requiring re-operation, patient selection and counselling should be very strict (C).**

5. COLOSTOMY

Several retrospective studies on the effect of colostomy formation in SCI patients showed a significant decrease in the average time spent on bowel care per week and improvement of QoL [70-78]. The early and long-term complication rates reported are 6 to 15%, and 15 to 37.5%, respectively. The commonest long-term complication is mucus discharge per rectum. One of the more frequent, persistent, problematic complications is diversion colitis [81, 82]. Symptoms include hemorrhagic purulent rectal discharge, abdominal pain and tenesmus. This condition is thought to result from a deficiency of luminal short-chain fatty acids [83]. Steroid enemas, 5-aminosalicylic acid enemas or suppositories, or short-chain fatty acid enemas have been reported as helpful [84].

Hocevar and Gray [85] published a systemic review from January 1960 to November 2007 including prospective and retrospective studies that directly compared clinical, functional, QoL outcomes or satisfaction among patients with intestinal diversions with

patients managed by conservative means. Creation of an ostomy in selected patients provides equivocal or superior QoL outcomes when compared to conservative bowel management strategies. Both colostomy and ileostomy surgery significantly reduce the amount of time required for bowel management. Patients who undergo ostomy surgery tend to be satisfied with their surgery, and a significant portion report a desire to be counselled about this option earlier. There are no clear advantages when functional, clinical, or QoL outcomes associated with colostomy are compared to those seen in SCI patients undergoing ileostomy.

Conclusion

- **Elective colostomy may be an option for some SCI patients with severe uncontrolled faecal incontinence (C).**

6. POSTANAL REPAIR

Mackey et al. [86] published the long-term results of postanal repair carried out in patients whose incontinence was thought to be because of neurogenic sphincter weakness. Anorectal physiology studies were carried out in 89% of the cases, and the clinical diagnosis of neurogenic incontinence was confirmed by prolonged unilateral or bilateral pudendal nerve terminal motor latency (PNTML) (>2.2 m/s) or increased threshold of anal mucosal electrosensitivity (or both). Patients were selected for surgery only after failure of medical and conservative therapies, including dietary manipulation, loperamide, or biofeedback where appropriate. A total of 111 patients underwent a postanal repair, 57 remained eligible, for whom full data were available. The mean duration of follow-up was 9.1 years (2.2-18.7 years). Mean CCS (Cleveland Continence Score) was 11.7; 26% scored none or minimal incontinence, 26% moderate and 48% severe incontinence. 97% (n = 45) were satisfied with the outcome. A low CCS significantly correlated with good patient satisfaction and was influenced by high QoL score (P < 0.0001). A favourable CCS was associated with a shorter duration of follow-up. Although a deterioration in continence with passage of time was observed, satisfaction amongst the patients was high. Only a quarter of patients showed a very good continence after a mean time of 9 years. Patients undergoing postanal repair are counselled appropriately and have realistic goals regarding their bowel functions in both the short and long term.

The procedure is inexpensive in comparison with graciloplasty and sacral nerve stimulation, and has low morbidity. Additionally, this procedure be useful in the elderly or those with significant co-morbidities. Although long-term continence has been found to deteriorate, the procedure can result in a satisfactory outcome in the long-term in a proportion of patients.

Conclusions and Recommendations

- **Postanal repair results in satisfactory outcome in the long-term in patients with neurogenic sphincter weakness. However, this is a single centre experience, which needs further confirmation (C).**

E. Specific neurological diseases

I. DEMENTIAS

1. DEMENTIA AND URINARY INCONTINENCE

Methods Using MEDLINE we identified English-language journal articles and reviews published from May 2008 to January 2012, which were added to literature obtained for previous Consultations, looking for the keywords Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, urinary incontinence, bladder dysfunction, management.

The dementias can be categorized according to clinical presentation, neuropathology and/or etiology into four major dementia groupings, (I) the Alzheimer's group (Alzheimer's disease, AD); (II) the vascular group (including large and small vessel disease, particularly white matter disease); (III) the Parkinson's group (including Parkinson's disease dementia complex (PDD, being regarded as identical to DLB), and dementia with Lewy bodies (DLB), both being connoted as Lewy Body diseases); (IV) the frontotemporal group (including Pick's disease and Semantic dementia) [1]. Normal pressure hydrocephalus (NPH) is a less common pathology, but nonetheless important.

2. ALZHEIMER'S DISEASE

a) Epidemiology and prevalence

Alzheimer's disease (AD) is the most common type of dementia in clinical and autopsy surveys. AD affects mostly elderly people. The symptoms include worsening of the memory, impairment of language and other cognitive functions (analytical thinking, abstract reasoning). Ultimately, there is loss of self-hygiene, eating, dressing and ambulatory abilities, incontinence and motor dysfunction. The onset of incontinence usually correlates with the disease progression (LOE 3)[2]. In other words, urinary incontinence inevitably occurs in the advanced stage of disease, while urinary incontinence is not common in the early stage of AD. This is in contrast with early occurrence of urinary urgency and incontinence in vascular dementia and dementia with Lewy bodies. The prevalence of incontinence in AD is reported to be between 23 % and 48 % (LOE 3) [3, 4]. However, most previous studies did not mention the type of dementia concerning 'frequency of

urinary incontinence in dementia'. The prevalence of incontinence in dementia ranges from 10% (of out-patients) to more than 90% (of advanced, institutionalized individuals) (LOE 3) [5].

b) Pathology and disease-specific urinary tract problems

AD at the outset was identified by its unique pathology, the amyloid plaques and neurofibrillary tangles containing phosphorylated tau that Alzheimer referred to as "a clotting of fibrils…. in addition an extraordinary number of peculiar patches disseminated throughout the entire cortex." Amyloid and tau can now be measured in vivo by positron emission tomography and/or examination of the cerebrospinal fluid (CSF). There is a familial occurrence of AD [3]. In such cases, mutations in the genes encoding amyloid precursor protein (APP); presenilin 1 (PSEN1), or presenilin 2 (PSEN2) are reported.

The clinical hallmark of AD is memory impairment. A sense of memory failure, detected by the patient or a close relative, is usually the presenting symptom. Motor and sensory symptoms are absent until late in the course of the disease. However, other cognitive domains, such as language, praxis and recognition skills, are affected even early in the presentation. AD has a gradual and progressive course, typically 10 years from diagnosis to death. The advent of central cholinesterase inhibitors and glutamate receptor antagonists has had a positive effect on the memory symptoms of AD [6-8].

In early stages of AD the prevalence of urgency incontinence is lower than in dementia with Lewy bodies [9, 10]. During stage III (advanced) AD, urinary and fecal incontinence occur due to loss of sphincter control [10]. In a study by Del Ser et al. (LOE 3) urinary incontinence was associated with severe cognitive decline in pure AD but usually preceded severe mental failure in patients with dementia due to diffuse Lewy body disease [10]. Nobili et al. (LOE 3) performed quantitative EEG in AD patients, finding that incontinence was predicted by alpha power in the right side [11]. In another study by Nobili et al. (LOE 3) the value of regional cerebral blood flow from a posterior temporal-inferior parietal area in each hemisphere predicted development of incontinence [12]. A brain computer tomography study done by Sugiyama et al. (LOE 3) in AD patients showed that the degree of brain atrophy was more severe in those with detrusor overactivity (DO) than those without it [13]. DO was found in 40-61 % of their patients [13] (LOE 3). The incidence of DO in AD patients is low as compared with vascular dementia and dementia with Lewy bodies [9]. Haddad et al. (LOE 3) described two patients with vesicoureteral reflux, one of them showing buccosalivary, gastroesophageal, vesicoureteral, urethroprostatic and urethrovesicular reflux as a consequence of the neurologic dysfunction [14].

c) Diagnosis and treatment

Franssen et al. (LOE 2) examined the occurrence of the following developmental reflexes: the tactile suck reflex, the palmar and plantar grasp reflexes, and the plantar extensor reflex in healthy elderly, cognitively and functionally mildly impaired patients, and patients with AD [15]. Prevalence of all five reflexes was more than 6 times higher for those categories that comprised permanently doubly incontinent patients as compared to those categories that comprised continent individuals. It is interesting that the frequency of developmental reflexes rose sharply with the onset of progressive incontinence, suggesting its cortical origin. As demonstrated above, the development of incontinence in AD patients is associated with cognitive impairment and brain degeneration, suggesting its CNS origin. Therefore behavioural therapy, toilet training and prompted voiding would be most useful treatment modalities for this type of incontinence.

Hutchinson et al. (LOE 3) suggested that caregivers of patients with AD should study the toileting behaviours. This would permit them to provide physical and cognitive assistance while attempting to avoid accidents and catastrophic events [6]. Tariot (LOE 4) stressed the necessity for taking into account different factors (like mobility, cognitive functions, general medical conditions), when planning treatment (also for incontinence) in AD patients [7]. Lancioni et al. reported three AD patients who could learn to use urine alarms [16] (LOE 4). Again the general guidelines should apply for choosing the best management of incontinence in AD patients. The treatment should be tailored to individual patient needs and disease status.

There is still some controversy that the central acethylcholinesterase (AChE)- inhibitors given by the neurologist might exacerbate urinary incontinence in those patients. Donepezil hydrochloride is a selective central AChE inhibitor, which decreases degradation of acetylcholine in the brain, then increasing the concentration of acetylcholine in the synaptic cleft [17]. This drug is widely used to ameliorate cognitive decline in patients with AD [18, 19] which is thought to be due to a decrease in cholinergic innervation of the cerebral cortex and the basal forebrain [20]. Since the bladder is innervated by the parasympathetic cholinergic nerves, neurogenic lower urinary tract (LUT) dysfunction occurs in a subset of patients with AD [5, 13].

Although donepezil may facilitate cholinergic neurotransmission mostly in the CNS, common adverse effects of donepezil, such as nausea and abdominal discomfort, have been attributed to the peripheral nervous system (PNS) [18]. Therefore, the increased bladder contraction is reasonably attributed to the PNS effects as seen with other cholinergic drugs. However, according to Sakakibara et al. [2005] the patients with AD showed a slight increase in

the bladder capacity, which cannot be explained by the PNS effects alone [21] (LOE 3). Although it is unknown to what extent central cholinergic circuit may participate in the regulation of micturition, recent experimental studies showed that lesions in the nucleus basalis Mynert in the basal forebrain (central cholinergic nucleus projecting fibres to the frontoparietal cortex) give rise to decreased bladder capacity) [22]. In addition, improved cognitive status and alertness may well lead to proper initiative to hold urine. Central AChE inhibitors including donepezil hydrochloride, therefore, may have complex effects on the LUT function. Although the number of the patients was small, it seems possible that donepezil could ameliorate cognitive function without serious adverse effects on the LUT function in patients with AD. This should be true also for other selective central AChE inhibitors.

Many elderly patients and their caregivers seek medical care for dementia and overactive bladder (OAB) together. In order to answer this, recent clinical trials of a combination therapy of central AChE inhibitors and peripheral anti-cholinergics for ameliorating both cognition and incontinence are available. In 26 older individuals who had both cognitive problems and overactive bladder (AD in 8, vascular dementia in 5, a combination of AD and multiple cerebral infarction in 8, and others), Sakakibara et al. reported that addition of 20 mg/day propiverine, an anticholinergic agent, to 5 mg/day donepezil improved OAB without any cognitive change [23] (LOE 3). Sink and colleagues retrospectively studied 3536 nursing home residents who were taking central AChE inhibitors, in whom 10.6% were prescribed anticholinergics together [24]. They found no differences in cognitive function between groups of AChE inhibitors alone and AChE inhibitors with anticholinergics (LOE 3). The combined use of a 'central' AChE inhibitor and a 'peripheral' muscarinic receptor antagonist remains a matter of controversy and needs forther clarification, whereas there is a study indicating that this combination would be pharmacologically sound as a site-directed therapy [25].

d) Guidance for further research

There is still no cure for AD, which is progressive and a type of dementia-associated disease. We are still lacking studies evaluating LUT disorders in AD. No systematic review has been performed regarding the possibilities of medical management (both pharmacological and behavioural) of incontinence. An open issue also remains the question of aggressive surgery for LUT problems in these patients. Whether we should we offer surgical therapy for incontinence in female patients with stress incontinence and progressive AD is so far unanswered.

Conclusions

- **Detrusor overactivity seems to be the most common cause of incontinence in Alzheimer's disease (AD) patients (LOE 3), while the incidence is low as compared with vascular dementia and dementia with Lewy bodies.**
- **The degree of functional incontinence is associated with cognitive impairment and brain degeneration (LOE 3).**
- **EEG studies, occurrence of developmental reflexes and regional blood flow studies can predict the development of incontinence in AD patients (LOE 3).**
- **Selective central AChE inhibitors ameliorate cognitive function without serious adverse effects on LUT functions in patients with AD (LOE 3).**
- **A combination therapy of central AChE inhibitors and peripheral anticholinergics for ameliorating both cognition and incontinence awaits further studies (LOE 3).**

Recommendations

- **The extensive and aggressive therapy of incontinence in AD patients should be reserved for those with good general status and ambulation (C).**
- **In the case of ambulatory patients, prompted voiding, behavioural therapy and oral anticholinergics seem to be the treatment of choice (C).**

3. VASCULAR DEMENTIA

a) Epidemiology and prevalence

Vascular dementia is the second most common form of dementia after Alzheimer's disease (AD) among the elderly. Pooled prevalence from eight European countries was 1.6% for vascular dementia in subjects older than 65, compared to a prevalence of 4.4% for AD (LOE 3) [26]. A meta-analysis of the European studies on the incidence of dementia showed vascular dementia constituted 17.6% of all incident dementia (LOE 3) [27].

In contrast, recent population-based MRI studies suggest that moderate white matter disease (WMD, a major cause of vascular dementia) affects around 10% (7.6–24%) of the general population of persons over 55 years of age [28], comparable to type 2 diabetes. WMD develops into three different geriatric syndromes; 1) vascular dementia (usually mild in the Mini-Mental State Examination and other general cognitive function), 2) vascular parkinsonism, and 3) so-called vascular incontinence, i.e. urinary frequency/ urgency with or without incontinence [29]. Among these three syndromes, urinary and gait disorders are more prominent than dementia, and usually precede dementia. Comorbidity of Alzheimer's disease (a degenerative disease) and WMD (a vascular disease) is not uncommon.

b) Diagnosis

Vascular dementia may be the result of a single strategic infarct, particularly involving the thalamus

and left angular gyrus, or multiple cortical or subcortical infarcts that produce WMD. There is an elevated risk for subsequent dementia in patients who have had a stroke in comparison to controls without any evidence of a stroke (LOE 2) [30]. Diabetes and hypertension are stronger risk factors for vascular dementia than for Alzheimer's disease (LOE 3) [31]. The apolipoprotein e4 genotype is a risk factor for vascular dementia as well as AD (LOE 3) [32]. The incidence of WMD significantly increases with gene polymorphism of aldosterone synthase, angiotensin II type 1 receptor, nitric oxide synthase, etc., which are all relevant to atherosclerosis (LOE 3).

c) Pathology and disease-specific urinary tract problems

In patients with WMD, diffuse abnormalities are seen in the small deep perforating vessels of the hemispheric white matter, basal ganglia and brain stem. Pathological changes range from lipohyalinosis to fibrinoid necrosis and disintegration of small vessels. Disruption of the blood brain barrier is likely to precipitate or worsen progression of WMD [33] (LOE 3). Positron emission tomography imaging with 18F-fluoromisonidazole showed higher susceptibility to ischemia of white matter than gray matter in stroke cases [34]. Cortical WMD in MRI looks diffuse. However, within the brain, detailed pathology studies confirmed that the frontal lobe is most severely affected [35]. This is in line with documented frontal lobe atrophy on MRI volumetry, where glucose metabolism was also most severely reduced [36] (LOE 3). Corresponding to this, brain perfusion is most reduced in the frontal lobe of subjects with WMD [37] (LOE 3), a finding that remains to be fully explained.

The frontal cortex is now recognized as an important higher center for micturition: damage to the prefrontal cortex, medial superior/middle frontal gyri, anterior cingulate cortex, supplemental motor area and insula result in marked lower urinary tract dysfunction in humans [38] (LOE 3). These clinical observation have been corroborated by functional neuroimaging in humans [39, 40] (LOE 3). Altered spinobulbospinal micturition reflex micturition control may contribute to DO emergence in brain lesions [41] (LOE 3). Functional neuroimaging studies showed that the prefrontal cortex was deactivated in elderly subjects with urinary frequency/ urgency as compared with controls [42] (LOE 3). Jirovec et al. (LOE 3) found that cognitive ability and mobility differ significantly between continent and incontinent patients [43]. When the variables were examined together, mobility emerged as the best predictor of the patient's urine control, followed by cognitive impairment.

The prevalence of DO in WMD cases is reported as 70-91% of patients. In Sakakibara's study, urodynamic studies in 33 subjects found DO more commonly in grade 1-4 white-matter lesions (82%) than grade 0 white-matter lesions (9%) ($p<0.05$). Yoshimura et al. (LOE 3) found a 47 % prevalence of DO which correlated with the presence of dementia [44].

d) Disease specific diagnosis and treatment

No specific diagnostic tests to evaluate dementia-related incontinence have been described. Since patients with dementia and incontinence usually have one or more concomitant diseases, the evaluation of the LUT functions should follow standard principle, bearing in mind that this is a population of frail elderly people. The treatment should start with modification of behaviour, and general rehabilitation targeted at making the patient more ambulatory. No other specific treatment in dementia has been described, however certain issues like prompted voiding, anticholinergic drugs and intermittent catheterization have been studied.

In a review of trials where prompted voiding was implemented, Eustice et al. (LOE 1) found that prompting increased self-initiated voiding and decreased incontinence episodes in the short-term [45]. A single small trial suggested that adding oxybutinin, reduced the number of incontinent episodes in the short-term. In a study by Suzuki et al. (LOE 3) the best results were obtained with ambulatory patients with the use of a portable chamber pot and induced urination, while no improvement was seen in bedridden patients treated with anticholinergics [46]. Sugiyama et al. (LOE 3) studied the effects of anticholinergic therapy in patients aged 65 years or older, with and without dementia. The patients received anticholinergic agents for more than two weeks [47]. Urodynamic studies demonstrated significant increase of maximum bladder capacity in the dementia group and the non-dementia group. There was no significant difference in rate of objective improvement between both groups. On the other hand, rate of subjective improvement was significantly higher in the non-dementia group (40 %) than in the dementia group (15 %). Improvement of functional bladder parameters was not associated however with improvement of subjective symptoms in the dementia patients.

In case of voiding failure, intermittent catheterization (IC) is a treatment of choice. Lieu et al. (LOE 3) found that carer-assisted clean IC is an effective and safe treatment option for persistent urinary retention in elderly female patients with cognitive impairment and other disabilities [26]. With this method of treatment, 54% of the patients were able to void spontaneously and were continent after a median period of 6 weeks with a range of 1 to 40 weeks. 27% had significant improvement in the symptoms of urinary incontinence and the residual urine volumes became progressively smaller. However, 19% failed this treatment modality. The recovery of spontaneous voiding was found to be significantly influenced by the age of the patient, the carer performing the IC and the development of catheter-related UTI. 25% of the study patients developed symptomatic UTI, which was associated with a delay in the recovery of spontaneous

voiding. Its development was also found to be significantly associated with the presence of pre-existing diabetes mellitus, the person doing the catheterization, the presence of dementia and with more predisposing common medical conditions.

Another interesting issue is the surgical treatment in patients with dementia. Two major groups of surgical procedures could be contemplated: prostate surgery and incontinence surgery. Yonou et al. (LOE 3) studied a group of 13 patients with dementia who underwent TURP procedure [48]. Six patients reported good urination, 3 reported some improvement in urination after surgery although requiring IC, and 1 developed incontinence. No specific study addressing the issue of incontinence surgery in woman with dementia has been reported. However, it seems that incontinence surgery in patients with dementia should be reserved only for the cases with good ambulation and without concomitant functional disorders of micturition (overactive bladder, hypocontractile detrusor).

e) Recommendations for further research

Since dementia is not a homogeneous disease, a population study targeted specifically at disorders of micturition is needed. Also, a study evaluating different treatment modalities in patients with dementia (especially anticholinergic treatment for overactive bladder and surgical treatment for stress incontinence) is lacking.

Conclusions

- **Dementia-associated incontinence occurs in 30-100 % of patients with dementia (LOE 3).**
- **The degree of incontinence is strongly associated with the patient's general status and ambulation (LOE 3).**
- **There is no one major cause for incontinence in these patients; however overactive bladder is responsible for a significant proportion of incontinence (LOE 3).**

Recommendations

- **Interventional therapy of incontinence in dementia patients should be reserved for patients with good general status and ambulation (C).**
- **In case of ambulatory patients, prompted voiding, rehabilitation and oral anticholinergics can be employed (C).**
- **Where there is a significant post-void residual, intermittent catheterization is the treatment of choice (B).**

4. DEMENTIA WITH LEWY BODIES

a) Epidemiology and prevalence

Dementia with Lewy bodies (DLB) is thought to be the third most common type of dementia in the elderly, accounting for 10 – 15% of cases at autopsy. In population-based studies of subjects aged 65 and older, the prevalence of DLB was found to be 0.7%, which is consistent with its rate of 10 – 15% of hospital-based cases at autopsy [49]. The epidemiology of DLB is sparse; age and gender distribution, and potential risk factors have yet to be defined.

b) Pathology and disease-specific urinary tract problems

DLB primarily affects both the basal ganglia (as in Parkinson's disease) and the cerebral cortex. Lewy bodies and Lewy neuritis are pathologic aggregations of alpha-synuclein (SNCA), a ubiquitously-expressed synaptic protein that has been implicated in vesicle production [50]. Lewy bodies also contain chaperone proteins and elements of the ubiquitin-proteasome system. Immunohistochemical staining for alpha-synuclein has been shown to be the most sensitive and specific method for detecting Lewy bodies and can be used in a semiquantitative grading of severity of Lewy-related pathology [51]. Alpha-synuclein can now be measured in vivo by positron emission tomography and/or the cerebrospinal fluid.

Many patients with DLB also have Alzheimer's disease pathology, which alters the clinical presentation. DLB patients who also have numerous neurofibrillary tangles display more core clinical features of AD [52]. Conversely, Lewy bodies also occur in more than half of all patients with sporadic and early-onset AD [53]. The essential feature for a diagnosis of possible or probable DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Fluctuations (waxing and waning of cognition, functional abilities and arousal, from almost normal to markedly confused or hypersomnolent) are a core feature of dementia with Lewy bodies. In DLB, autonomic dysfunctions occur and are included as a supportive feature for clinical diagnosis [54].

Horimoto et al. (LOE 3) found 97 % incidence of urinary incontinence amongst patients with DLB. From the urological point of view, patients with DLB tend to develop urgency and urgency incontinence more often than do patients with Parkinson's disease (PD) or AD. Similar bladder capacity, detrusor pressure at maximum voiding, maximum urine flow, mean voided volume and post-void residual volume were found in each of these diseases; however, DO, the major cause of urgency and urge incontinence, was more prevalent in DLB than in PD and in AD [9]. Urinary symptoms are seen in one third of patients with DLB. Detrusor overactivity, the major cause of urge and urge incontinence was more prevalent in DLB and AD. No detrusor-sphincter-dyssynergia was observed. DLB patients with detrusor overactivity had significantly higher Hoehn and Yahr scores than did those without detrusor overactivity. Since the prevalence of frequency, urgency, urge

incontinence and detrusor overactivity is markedly lower in AD than in DLB, LUTS may contribute to the differential diagnosis of these two entities.

c) Disease specific diagnosis and treatment

Since patients with Lewy Body disease and incontinence usually have one or more concomitant diseases, the evaluation of the LUT functions should follow the general rules, bearing in mind that this is most often a population of frail elderly people (LOE3).

5. FRONTOTEMPORAL DEMENTIA (FTD)

a) Epidemiology and prevalence

Prevalence studies of FTD are inconsistent (LOE 3), giving ranges of 3.6-15.0 per 100,000 [55]. There is a high familial occurrence of FTD [56]. In such cases, a combination with parkinsonism, and rarely amyotrophic lateral sclerosis, also occurs. The distribution of FTD is equal between men and women. The mean duration of illness from onset to death is 4-6 years, with a range of 2-20 years.

b) Pathology and disease-specific urinary tract problems

Frontotemporal dementia (FTD), also known as Pick's disease, encompasses a diverse group of clinical and pathological disorders. There are several distinct clinical presentations, most commonly behavioral changes, but a language disorder, usually in the form of a progressive non-fluent aphasia, can be the main presenting sign. The most common clinical presentation of FTD is characterized by profound changes in personality and social conduct, including a decline in manners and social skills that are incongruent with the patient's premorbid behaviour. Affected patients lack emotional warmth, empathy and sympathy and are indifferent to others.

MRI of patients with FTD often shows atrophy in the frontal and temporal lobes (LOE 2), which may be asymmetric [57]. At autopsy, markedly gross atrophy of the frontal and temporal lobes is seen in FTD. On histologic examination the salient features include neuronal loss, micro-vacuolization and astrocytes gliosis centred on cortical layer II. Up to now, molecular pathology of FTD has identified four subtypes. First, classical Pick's disease (Pick body with accumulation of 3-repeat tau); second, mutations in the MAPT (microtubule-associated protein tau) gene; third, accumulation of TDP-43 (TAR DNA binding protein-43) with mutations in the PGRN (progranulin) gene; and fourth, accumulation of FUS (fused in sarcoma) protein.

There a no data on LUTS in patients with FTD, however it is obvious that due to the cognitive state these patients have incontinence, either because they forget to take down clothes when they go into the toilet, or they have difficulty finding the toilet, or they may urinate in inappropriate places and pass urine more often than usual. Moreover, they may be affected by constipation, diarrhoea or faecal incontinence.

c) Diagnosis and treatment

No specific diagnostic tests to evaluate dementia-related incontinence were described. There are no studies which show the significance of LUTS in fronto-temporal dementia. Such studies would be of value in future research projects.

Conclusions

- **There are no studies available which show the significance of LUTS in patients with fronto-temporal dementia.**
- **Since the underlying pathology is gross atrophy of frontal and temporal lobes, autonomic dysfunction including LUTS can be anticipated, but further research is needed.**

Recommendations

- **The recommendations do not differ from those for other types of dementia.**

6. CONSTIPATION AND FECAL INCONTINENCE IN DEMENTIA

Only one paper was retrieved related to the influence of dementia on the prevalence of urinary and faecal incontinence in an age group of 85-year-old men and women [58]. This reported the influence of dementia on the prevalence of urinary and faecal incontinence in 85 year-old men and women in a random sample n= 485 of the total population of 85-year-olds from the city of Gothenburg, Sweden. The prevalence of urinary and faecal incontinence and dementia were 38%, 17% and 29% respectively. Demented men (50%) and women (60%) were more often incontinent than non-demented men (18%) and women (36%). Also, faecal incontinence was more prevalent in demented (34,8%) than non-demented subjects (6,7%): both urinary and faecal incontinence were more prevalent in demented women (43% and 20% respectively) than in men (27% and 11% respectively). The prevalence of urinary and faecal incontinence and dementia were higher in residents of a nursing home or hospital (74%, 51% and 92% respectively) than in subjects living at home (32%, 9% and 18% respectively): of the demented residents in an institution 78% were incontinent compared with 37% living at home.

No specific paper was found on the management of faecal incontinence in demented people. Demented patients may benefit from a bowel habit training programme, which also includes management of constipation with non-pharmacologic (such as exercise and fibre) and pharmacologic measures.

Conclusions

- **Although faecal incontinence is prevalent in people with dementia, no paper was found**

dealing with the disease-specific management of faecal incontinence (LOE3).

Recommendations

- **Studies should be undertaken to ascertain management strategies for constipation and faecal incontinence in dementia.**

7. NORMAL PRESSURE HYDROCEPHALUS

a) Epidemiology and prevalence

Normal-pressure hydrocephalus (NPH) is characterized by a clinical presentation of gait disturbance, memory deficit, and urinary incontinence, combined with dilated cerebral ventricles and normal cerebrospinal fluid (CSF) pressure [59] (LOE 3). The clinical triad of this disorder is very much akin to those of vascular dementia or white matter disease (WMD). Therefore, before performing brain imaging, we have to think about NPH as well as WMD. The syndrome was first described by Hakim and Adams in 1965 [60] . After five decades of investigation, the effectiveness of the diversion of CSF flow by shunt operation in treating this syndrome is well documented [59] (LOE 2). Recent population-based MRI studies also suggest that the incidence of NPH, or asymptomatic ventriculomegaly with features of idiopathic normal pressure hydrocephalus on MRI (AVIM), to be around 1% (0.51-2.9%) in the general population of persons over 65 years of age [61], being estimated as one-tenth of WMD (LOE 3).

b) Pathology and disease-specific urinary tract problems

Lower urinary tract symptoms in NPH are basically urinary urgency and frequency (overactive bladder, OAB). Sakakibara et al. found urinary symptoms in 93% of 42 idiopathic NPH patients [62] (LOE 3). These symptoms included storage symptoms in 93% of patients (nocturnal urinary frequency, 64%; urinary urgency, 64%; urgency urinary incontinence, 57%; diurnal urinary frequency, 36%) and voiding/ post micturition symptoms in 71% (hesitancy 50%; prolongation /poor flow, 50%; sensation of post-void residual, 29%; straining, 21%; intermittency, 14%). Particularly, in some patients urinary urgency /frequency preceded urinary incontinence. Among the clinical triad of NPH, urinary incontinence has been regarded a late symptom. However, as in cases of WMD, gait disturbance and OAB can be the early manifestation of NPH.

Urodynamic findings of 42 NPH patients by Sakakibara et al. included low Qmax (<10 cm/s) in 40%; increased post-void residual (>30 ml) in 43% (average PVR volume 42.1 ml); low volume at first sensation (< 100 ml) in 33%; decreased bladder capacity (< 200 ml) in 57%; and DO in 95% of patients [62] (LOE 3). Although the number of cases included in other reports has been small (4-12 cases), DO is also most common (63-100%) [63] [64] (LOE 4). The high prevalence of DO suggests altered brain autonomic control in NPH [65].

c) Diagnosis and treatment

Diagnosis of NPH may comprise:

a) Possible features; gait, cognitive and urinary disorders with typical ventricular dilatation in brain imaging.

b) Probable features; improved clinical symptoms by 30 ml withdrawal of the cerebrospinal fluid by a lumbar tap (the Tap test).

c) Definite; improved clinical symptoms by ventriculoperitoneal shunt surgery etc.

Functional neuroimaging in normal volunteers has shown that the anterior cingulate, prefrontal cortex and insula are activated in response to bladder filling as compared with an empty bladder [41]. Although NPH is a diffuse brain disease with dilated ventricles, hypoperfusion in the frontal lobe has been documented in NPH patients using PET [66], single-photon emission computed tomography (SPECT) [67] , and perfusion-weighted MRI [68] (LOE 3). Therefore, the frontal lobe is thought to be the anatomical substrate for urinary urgency and incontinence in NPH. According to the study by Sakakibara et al, using 97 NPH patients and [123I]-iodoamphetamine (IMP)-SPECT statistical mapping, there was a significant decrease in tracer activity in the right-side-dominant bilateral frontal cortex and the left inferior temporal gyrus in the severe urinary dysfunction group ($p<0.05$) [69]. The findings indicate that there is a link between the right frontal hypoperfusion and urinary dysfunction in NPH. Importantly, bladder dysfunction and frontal lobe hypoperfusion in NPH can be reversed after shunt surgery. Recovery rate of OAB and urinary incontinence in NPH ranges from 20-80% [59] (LOE 4). Among them, cerebral perfusion in the prefrontal cortex and mid-cingulate gyrus tended to return normal particularly in patients with good OAB/ incontinence recovery.

Since there is a surgical shunt therapy for NPH, early diagnosis of NPH in patients with OAB is important. In addition to OAB with/without urinary incontinence, patients with NPH commonly have gait disorder (parkinsonian and wide-based gait) and dementia that is milder than Alzheimer's disease. Differential diagnosis should include vascular dementia or white matter disease. If the shunt surgery failed, or was not applied to individuals with particular reasons such as dementia etc., medical management (pharmacological and behavioural) of incontinence starts. However, no systematic review has been performed regarding the medical management of urinary incontinence in NPH.

Conclusions

- **Clinical manifestations in NPH mimic those of vascular dementia or white matter disease (LOE 3).**
- **Urinary urgency and frequency may precede urinary incontinence in NPH (LOE 3).**
- **Detrusor overactivity seems to be the most common cause of incontinence in NPH patients (LOE 3).**
- **Shunt surgery ameliorates urinary incontinence in NPH but the degree varies significantly (20-80%) (LOE 4).**

Recommendations

- **Typical gait, cognitive and urinary disorders with ventricular dilatation in brain imaging favours the diagnosis of NPH; then a Tap test and a shunt surgery may follow (B).**
- **However, no systematic review has been performed regarding the medical management of urinary incontinence in NPH if the shunt surgery failed or is not applied to individuals (C).**

II. MULTIPLE SYSTEM ATROPHY

1. EPIDEMIOLOGY AND PREVALENCE

Multiple system atrophy (MSA) is a rare, adult-onset degenerative disease of the nervous system of unknown origin. Autonomic failure (postural hypotension and urinary dysfunction) is fundamental to the diagnosis of MSA: it is diagnosed when the criteria of either postural hypotension (systolic blood pressure fall > 30 mmHg or diastolic > 15 mmHg) or urinary dysfunction (persistent, urinary incontinence/ incomplete bladder emptying) or both are fulfilled, along with poorly levodopa-responsive parkinsonism, or cerebellar dysfunction [70]. Based on the major motor deficits, MSA can be classified as MSA-P (Parkinsonism-predominant) or MSA-C (cerebellar-predominant) [70]. The discovery in 1989 of glial cytoplasmic inclusions in the brains of patients with MSA [71] provided a pathological marker for the disorder (akin to Lewy bodies in idiopathic Parkinson's disease), which combined three disorders previously called striatonigral degeneration, sporadic livopontocerebellar atrophy, and Shy-Drager syndrome.

Urinary symptoms of incontinence are caused by neurogenic DO and external sphincter weakness [3] (LOE 2). Sphincter electromyography (EMG) abnormalities were found in 91% of the patients with MSA [72] (LOE 2). Approximately 60% of patients with MSA develop urinary symptoms, either prior to or at the time of presentation with the motor disorder [73] (LOE2). This indicates that many of these patients seek urological advice early in the course of their disease. Although postural hypotension was thought to be a marker for autonomic failure in MSA, Wenning et al. [74] (LOE2) noted urinary incontinence in 71%, urinary retention in 27%; postural faintness in 53%, and syncope in 15% of 100 patients with MSA. Sakakibara et al. [1999] [73] (LOE2) found that urinary symptoms (96%) were more common than orthostatic symptoms (43%) ($p < 0.01$) among 121 patients with MSA. Kirchhof et al [75] (LOE2), found that bladder symptoms preceded symptoms of orthostatic hypotension in 76% of their 71 male patients. Sakakibara et al. [73] (LOE2) also found that among 53 patients with both urinary and orthostatic symptoms, those who had urinary symptoms first (48%) were more common than those who had orthostatic symptoms first (29%), and some patients developed both symptoms simultaneously (23%).

2. PATHOLOGY AND DISEASE-SPECIFIC URINARY TRACT PROBLEMS

Sakakibara et al. [1993] [76] (LOE2) performed an extensive study of the urological symptoms in MSA patients. They found the following prevalence of different symptoms: difficulty of voiding in 79%, nocturia in 74%, sensation of urgency in 63%, urgency incontinence in 63%, diurnal urinary frequency in 45%, enuresis in 19% and urinary retention in 8% of the patients. All of the MSA patients presented with some kind of LUT symptoms; many of them had both storage and voiding urinary symptoms.

In 245 cases of MSA, Ito et al [77] (LOE2), found that average volume of post-void residuals was 71ml at the first year, which increased significantly to 170ml at the 5th year ($p<0.01$) after onset of the disease. Patients were not always aware of their post-void residuals. The frequency of weak detrusor ascertained by a pressure-flow analysis was 20% at the first year, which increased to 53% at the 5th year ($p<0.05$). The frequency of detrusor-external sphincter dyssynergia (DSD) was 12% at the first year, which increased to 39% at the 5th year ($p<0.05$). Therefore, detrusor underactivity seemed to contribute to voiding dysfunction in MSA more than DSD did. The responsible sites of lesion (micturition-facilitating area) for voiding difficulty and retention in MSA seem to be the locus coeruleus (pontine micturition center). The work of Bennaroch demonstrated, that in MSA there is severe depletion of catecholaminergic neurons of the Cl and Al areas in the ventrolateral medulla, and this may contribute to orthostatic hypotension and endocrine disturbances in this disorder, respectively. Loss of corticotrophin-releasing factor (CRF) neurons in the pontine micturition area may contribute to neurologic bladder dysfunction [78] (LOE 2). In addition, the sacral intermediolateral cell columns, where preganglionic neurons innervating the bladder are located, are affected in post-mortem MSA cases.

The prevalence of detrusor overactivity was 61% at the first year, which increased to 75% at the 5th year

(p<0.05) [77] (LOE2). The frequency of neurogenic pattern in the sphincter EMG was 52% at the first year, which increased to 83% at the 5th year (p<0.05) [79] (LOE2). Abnormalities in the videourodynamic study included open bladder neck at the start of filling in 53% of MSA patients [80] (LOE2). Similar results were reported by others [81]. The responsible sites of lesion (storage-facilitating area) for urinary urgency and incontinence in MSA seem to be the basal ganglia, cerebellum [82], lumbar intermediolateral cell columns where preganglionic neurons innervating the bladder neck are located, and sacral Onuf's nucleus innervating the external sphincter, all of which are affected in post-mortem MSA cases, causing urinary stress incontinence.

Repeated urodynamic studies in MSA patients showed that the cystometrogram changed from DO to low-compliance or acontractile detrusor, and from negative to positive bethanechol supersensitivity [83] (LOE2). In fact, as the disease progresses, symptoms may change from urinary urgency and frequency to those due to incomplete bladder emptying. These findings suggest that the responsible sites of the bladder cholinergic disorder may change from the center to the periphery. The cystometrograms of patients with MSA often show neurogenic DO with impaired contractile function (DHIC), mostly accounting for urinary urgency / frequency and large post-void residuals, respectively. This condition presumably reflects lesions in both storage and voiding-facilitating areas in this disorder [84].

Beside bladder disorders, patients with MSA may have nocturnal polyuria, which results in nocturia and morning hypotension. In normal children over 7 years and adults, the circadian release of arginine vasopressin from the posterior pituitary gland into plasma peaks at night. This leads to a nocturnal decrease in urine formation. The ratio of night-time to daytime urine production is usually <1:2, which can be estimated by a bladder diary. A post-mortem study of the brains of patients with MSA revealed the degeneration of arginine vasopressin neurons in the suprachiasmatic nucleus [85] (LOE 2), leading to impairment of the circadian rhythm of the plasma arginine vasopressin concentration in MSA [86] (LOE 2).

3. DIAGNOSIS AND TREATMENT

Since LUT functional disturbances often precede orthostatic hypotension and other autonomic nervous system symptoms in MSA patients, the full assessment of underlying mechanisms of LUT symptoms is of paramount importance.

External sphincter EMG is the most sensitive test. Sphincter motor unit potential analysis showed neurologic motor unit potentials in 93% of those with MSA, suggestive of external sphincter denervation. Palace et al. [87] (LOE 2) demonstrated abnormal sphincter EMG in 93% of MSA patients, which can differentiate this disorder from idiopathic Parkinson's disease. Oertel et al. [88] (LOE2) suggested that reduced genital sensation in females could be pathognomonic for MSA (with equal importance as erectile dysfunction in males). A total of 47% of the MSA patients and 4% of the control group had reduced genital sensation. Moreover, the appearance of reduced genital sensitivity in female MSA patients showed a close temporal relation to the onset of the disease. Hahn and Ebersbach [89] (LOE 2) investigated the value of sonography of the bladder to evaluate post-void residual urine (PVR) for the differential diagnosis between idiopathic Parkinson's disease and Multiple System Atrophy. The positive predictive value of increased residual urine for MSA was 91.6 % in the study, while the negative predictive value was only 67.8 %. They state that bladder sonography is an objective, simple and safe tool that allows one to screen for urinary retention which is highly suggestive, but incompletely sensitive for MSA. Because sonography is easily accessible and rapidly performed, it is feasible for routine assessment of atypical Parkinson syndromes. The overall average volume of PVR was 140 cc in their patients, increasing from 71 cc in the first year, to 129 cc in the second year, and 270 cc in the 5th year.

Aggressive surgical therapy is not recommended in MSA patients. Chandiramani et al. [90] (LOE2) found that all MSA patients who underwent transurethral resection of the prostate (TURP) due to voiding problems were incontinent postoperatively, most probably due to pre-existing sphincter weakness. The same observations were made by Beck et al. [72] (LOE2), who evaluated the results of TURP and stress incontinence surgery in MSA patients. They concluded that the results of surgery were unfavourable. Patients benefited from IC, anticholinergic medication and desmopressin spray [91] (LOE 3), which improved continence in 82%.

As nearly half of the MSA patients suffer from voiding difficulties, its management by means other than IC would be very attractive. Sakakibara et al. [92] (LOE 3) compared different non-selective and alpha-IA selective alpha blocking agents (prazosin and moxisylite) in the treatment of LUT dysfunctions in MSA patients. The respective means for reductions in residual urine volume for the prazosin and moxisylite groups were 38.1% and 35.2%, and there was lessening of urinary symptoms. Side effects due to orthostatic hypotension were seen in 23.8% of the prazosin group and 10.7% of the moxisylite group. A more recent study showed that the effects of alpha blocking agents, as well as those of TUR-bladder neck, for lessening post-void residuals lasted for up to 2 years in MSA, although during that period patients benefited from the therapies [77] (LOE2). On the contrary, administration of amezinium, an adrenergic drug for ameliorating postural hypotension, may increase the risk of retention and post-void residual volume compared to that before treatment [93] (LOE2). Amezinium most probably

stimulates the alpha receptors, both in the vascular wall (alpha1B receptors) and the proximal urethra (alpha1A/D-adrenergic receptors).

Both postural hypotension and bladder dysfunction are common clinical features in MSA. Pyridostigmine, an acetylcholinesterase inhibitor, might be effective in lessening post-void residual volumes, since it stimulates muscarinic acetylcholine receptors on the bladder (M2/3-muscarinic receptors) that are innervated by parasympathetic cholinergic neurons. Pyridostigmine also lessens postural hypotension, presumably by enhancing nicotinic acetylcholine receptor transmission in the sympathetic ganglia [94] (LOE3).

Guidance for further research

MSA is a slowly progressive disease without any cure. More research is needed to evaluate the effects of long term LUT treatment and to evaluate the effects of different drug treatment modalities.

Conclusions

- **LUT symptoms often precede the clinical manifestation of multiple system atrophy (LOE2).**
- **The most common LIJT disturbances are detrusor overactivity, detrusor-external sphincter dyssynergia, sphincter and detrusor weakness (LOE2).**
- **Significant post void residual is observed in about half of the multiple system atrophy patients (LOE2).**

Recommendations

- **The most sensitive test to detect multiple system atrophy associated LUT abnormalities is sphincter EMG (A), and post-voiding residual volume , especially when differentiating from Idiopathic Parkinson's disease.**
- **Due to the complex dysfunction and progressive nature of the disease, aggressive treatment and LUT surgery (e.g. TURP) are not recommended (A).**
- **Treatment of choice in case of increased post void residual are alpha blocking agents and IC (B).**

4. FAECAL INCONTINENCE

Lower gastrointestinal tract (LGIT) dysfunction is also common in patients with MSA. Sakakibara et al [95] (LOE2) performed a bowel questionnaire in 15 patients with MSA and in 10 age-matched healthy control subjects. The MSA group showed decreased bowel frequency (< 3 times a week) in 9, difficulty in expulsion in 11, and faecal incontinence in 3; the control group showed decreased bowel frequency in only 2, mild difficulty in expulsion in 2, fecal incontinence in none. Therefore, constipation is the major bowel dysfunction in this disorder, although in advanced stages faecal incontinence is not uncommon.

Studies on the mechanism of bowel problems in this disorder are scarce. Stocchi et al. [96] (LOE2) performed anorectal manometry in 16 patients with MSA; 13 patients showed paradoxical anal sphincter contraction on fictive straining. Bardoux et al. [29] (LOE3-4) reported a case of a fecally incontinent patient due to MSA, who showed inability of anal squeezing. Sakakibara et al. [97] (LOE2) performed colonic transit time, sphincter electromyography (EMG) and rectoanal videomanometry in 15 patients with MSA and 10 age-matched healthy control subjects. Compared with the control subjects, MSA patients had significantly prolonged colonic transit time in the rectosigmoid segment ($p<0.05$) and total colon ($p<0.05$). Sphincter EMG showed neurogenic motor unit potentials in none of control subjects but in 93% of MSA ($p<0.01$). In the resting state, MSA patients showed a lower anal squeeze pressure (external sphincter weakness) ($p<0.01$) and a smaller increase in abdominal pressure on coughing ($p<0.01$). During rectal filling, MSA patients showed smaller amplitude in phasic rectal contraction ($p<0.01$), which was accompanied by an increase in anal pressure that normally decreased, together with leaking in 3 patients. During defecation, most MSA patients could not defecate completely, with larger post-defecation residuals ($p<0.05$). MSA patients had weak abdominal straining, smaller rectal contraction on defecation and larger anal contraction on defecation (paradoxical sphincter contraction on defecation, or anismus), though these differences were not statistically significant.

Constipation in MSA most probably results from slow colonic transit, decreased phasic rectal contraction and weak abdominal straining, whereas fecal incontinence results from weak anal sphincter due to denervation. The responsible sites for these dysfunctions are still not known. However, as described in idiopathic Parkinson's disease, they most probably reflect lesions of both central and peripheral nervous systems that regulate the LGIT.

LGIT functional disturbance is often preceded by LUT dysfunction in MSA patients. Abnormalities in colonic transit time and rectoanal videomanometry in MSA were mostly similar to those in idiopathic Parkinson's disease, except for the sphincter denervation and resultant fecal incontinence in MSA.

When treatment of the bowel disorder in MSA is planned, use of objective parameters is recommended in order to clarify the action of drugs. A few such studies are available: Eichhorn and Oertel [98] (LOE3) gave polyethylene glycol 3350, an osmotic agent with high water binding capacity, in 2 patients with MSA, and found an improvement in stool frequency and difficult defecation in both

patients. Similarly, Sakakibara et al. [99] (LOE2) measured colonic transit time in 4 patients with MSA. After administration of calcium polycarbophil, an osmotic and highly bulking agent, colonic transit time of total and the right segment shortened significantly. Liu et al. [100] (LOE2) performed colonic transit time and rectoanal videomanometry in 7 patients with MSA. After administration of mosapride citrate, a novel selective 5-HT4 receptor agonist, the patients showed a shortened total and recto-sigmoid segment colonic transit time, lessened first sensation and an augmented amplitude in phasic rectal contraction. During defecation, mosapride augmented the amplitude in rectal contraction and lessened the volume of post-defecation residuals significantly. Similar results were obtained in a study by Sakakibara et al. [101] (LOE2), in which dietary herb extract Dai-Kenchu-To, one active component of which is hydroxy-beta-sanshool (5-HT3 receptor agonistic action), was prescribed.

MSA is a slowly progressive disease currently without cure. More research is needed to evaluate the pathophysiology of LGIT dysfunction, and to evaluate the effects of different drug treatment modalities.

Conclusions

- **Patients with multiple system atrophy have often abnormal bowel function (LOE2) .**
- **The most common bowel disturbances are slow colonic transit, decreased phasic rectal contraction and weak abdominal straining; faecal incontinence results from weak anal sphincter, due to denervation (LOE2).**
- **Bowel dysfunction, such as constipation, is common and has significant impact on quality of life of patients with multiple system atrophy (LOE3).**

Recommendations

- **More studies on neurologic bowel dysfunction and management in patients with multiple system atrophy are needed before giving any recommendation.**

III. PARKINSON'S DISEASE

1. URINARY INCONTINENCE

Parkinson's disease (PD) is a movement disorder due to degeneration of dopaminergic neurons in the substantia nigra and a loss of dopamine-containing nerve terminals in the basal ganglia. Degeneration of the nigrostriatal pathway is accompanied by decreases in corresponding biochemical markers, including dopamine, tyrosine hydroxylase, dopamine metabolites, and dopamine transporter. These central nervous system changes also have influence on autonomic function; the most common problems are gastrointestinal (constipation), perspiratory (hypohidrosis) and urinary systems [102].

LUT dysfunction in PD was estimated to occur in 37-71% in uncontrolled studies. Among these, in a study of Hattori et al. [103] (LOE3) 60% of PD patients had urinary symptoms, which could be divided in the following categories: storage LUTS in 28%, voiding in 11%, and both types in 21%. The prevalence of urinary symptoms correlated with severity of the disease, but not with the duration of illness. Gray et al. [104] (LOE3) reported that LUT functional disturbances in PD are not disease-specific and only correlated with age. In the more recent, control-based studies [106-109] (LOE2) the prevalence of LUT symptoms (LUTS) was found to be 27-64% using validated questionnaires [105-107], or 53% in men and 63% in women using a non-validated questionnaire that includes a urinary incontinence category [7], with all of these values being significantly higher than healthy controls. The majority of patients had onset of the bladder dysfunction after the appearance of motor disorder. In one study, urinary incontinence in PD frequently occurred in conjunction with fecal incontinence, whereas no significant relation was observed between bladder and sexual dysfunction. Bladder dysfunction substantially affects the quality of life in patients with PD [108] (LOE2). Bladder dysfunction in PD correlates with neurological disability [105] (LOE2), and stage of disease [108] (LOE2), both suggesting a relationship between dopaminergic degeneration and LUTS. LUTS was more common in a group of PD patients with older age, as in healthy populations. Among LUTS, nocturia (night-time urinary frequency) is the most prevalent symptom (>60%) [105-108] (LOE2). Patients also complain of urinary urgency (33-54%), daytime frequency (16-36%), and urinary incontinence in 26% of males and 28% of females. These figures are almost the same in untreated, early PD patients [109]. Although less common than storage symptoms, PD patients also report voiding symptoms. In the study by Sakakibara et al. [110] (LOE2), PD patients had significantly higher rates of delay in initiating urination (44% of men), prolongation/poor stream (70% of men), and straining (28% of women) compared with the control group. However, despite the voiding symptoms, PD patients have low post-void residuals.

a) Pathology and disease-specific urinary tract problems

The net effect of the basal ganglia on micturition is thought to be inhibitory [111]; in PD, the bladder becomes overactive. Functional neuroimaging during bladder filling resulted in activation in the globus pallidus of normal volunteers and in the putamen in PD patients with detrusor overactivity [112] (LOE2). In contrast, dopamine transporter imaging (indicating brain dopamine neurons) was decreased in PD patients with urinary dysfunction than in those

without it [13] (LOE2). The micturition reflex is under the influences of nigrostriatal dopamine (both inhibitory in D1 and facilitatory in D2) and GABA (inhibitory). Deep brain stimulation in the subthalamic nucleus results in amelioration of motor disorder as well as increased bladder capacity and decreased post-void residuals [114] (LOE2). Therefore, urinary dysfunction in PD could reflect degeneration of the nigrostriatal dopaminergic cells associated with specific motor disorders. In addition to the nigrostriatal dopaminergic projection, the ventral tegmental area (VTA, the A10 cell group)-limbic cortex and the hypothalamic (the A11 cell group)-spinal cord dopaminergic projections are presumably involved in urinary dysfunction in PD.

In a study of PD and multiple system atrophy (MSA) patients, Sakakibara et al. [116] (LOE2) found urinary symptoms in 72% of PD patients. They were mostly attributed to DO (81%) and external sphincter relaxation problems (33%). Failure of sphincter relaxation may reflect bradykinesia, rather than true DSD. During micturition, PD patients did not demonstrate DSD, but impaired detrusor contractility was observed in 66% of women and 40% of men. In addition, patients with PD had partial bladder outlet obstruction, e.g. mean bladder outlet obstruction index was 43 in men (equivalent parameters gave a value of 40 in women). Nevertheless, average volume of post-void residuals in PD was only 18 ml. Similar observations were reported by Defreitas et al. [117] (LOE2). These urodynamic findings are almost the same in untreated early PD patients [110].

b) Specific diagnosis and treatment

In the differential diagnosis of PD and parkinsonian-type MSA, large post-void residuals, open bladder neck, and neurogenic change in sphincter motor unit potentials are common in MSA [115, 118] (LOE2), whereas they are rarely seen in clinically typical PD [119]. However, recent evidence suggests that PD with dementia, or dementia with Lewy bodies, may have large post-void residuals and neurogenic change in the sphincter motor unit potentials [120], thereby mimicking MSA (LOE3). Bladder dysfunction in PD parallels other autonomic dysfunctions [121], cardiac denervation [122], and falls [123] (LOE3).

Levodopa and other antiparkinson medication may affect bladder function in PD. To date the results are not consistent and the responses are not straightfoward. Some reports have shown storage-facilitating effects of dopaminergic drugs; a questionnaire study reported that voiding symptoms (intermittency and sensation of residual urine) were more common in those taking levodopa and bromocriptine (D2-selective agonist) than in those taking levodopa alone [111a] (LOE2). In contrast, Kuno et al. [124] (LOE3) showed that change of bromocriptine to pergolide (D1<2 agonist) brought lessening of nocturia, and Yamamoto [125] (LOE3) described improvement of DO by pergolide. Others have shown voiding-facilitating effects. In early PD [126] (LOE2) and advanced PD with the on-off phenomenon [127] (LOE2), a single-dose of levodopa exacerbates DO in the filling phase, but also improves bladder emptying through increased detrusor contractility. We still do not know the reasons for the discrepancy between different studies.

There are several factors underlying the complex bladder behaviour in PD. Post-synaptic dopamine D1 (excitatory) and D2 (inhibitory) receptors have a millimolar affinity to dopamine, whereas dendritic D2 (inhibitory) autoreceptors have a picomolar affinity to dopamine. Therefore, when levodopa is administered externally, it may first stimulate dendritic D2 autoreceptors, which might suppress the nigral cells and facilitate the micturition reflex. In cases of PD under long-term treatment with levodopa, dopamine receptors are down-regulated. Bladder overactivity might also involve an activation of D2 receptors in the spinal cord [128] (LOE2). In addition, in experimental animals, single doses of apomorphine showed a biphasic effect [129] (LOE2).

There are no specific studies on systematic anticholinergic drugs to treat neurologic DO in PD patients. A systematic review of anticholinergic use (centrally acting) to treat PD was done by Katzenschlager et al. [130] (LOE I). Cognitive adverse events of anticholinergics are a concern, particularly in elderly PD patients. This was first described in 1997 by Donnellan et al. in PD patients with overactive bladder [131] (LOE 3). They gave oxybutynin in four patients, who subsequently developed dementia, which reversed after discontinuation of oxybutynin. Factors underlying the cognitive effects of these medications include: 1) central muscarinic receptor affinity, e.g. high M1-receptor selectivity; and 2) easy penetration of the blood-brain barrier (BBB), e.g. high lipid solubility (water versus oil partition coefficient [LogP]<3; number of hydrogen bonds<8); a neutral charge or low degree of ionization (polar surface area<90A); and a less bulky (number of rotatable bonds<5) and smaller molecular size (<450Da) [132] (LOE 2). Most anticholinergics are non-selective muscarinic blockers, but darifenacin is an M3-selective antagonist. Regarding BBB penetration, most anticholinergics have a molecular size between 300-400Da. Oxybutynin can readily penetrate the CNS. Trospium, a quaternary amine, has a high polarity that may limit BBB penetration.

Deep brain stimulation (DBS) is a treatment option in advanced PD. The subthalamic nucleus (STN) is regarded as the key area in the indirect pathway, which is dominant in the parkinsonian state. DBS inhibits many cells within the STN, probably due to depolarization block and release of GABA from activation of inhibitory afferent terminals. In the STN, neuronal firings related to the micturition cycle have been observed in cats [133] (LOE2). DBS increased

bladder capacity, facilitated bladder afferent pathways, and augmented activity of the prefrontal cortex in the brain of PD patients [134] (LOE2). DBS can cause urinary retention [135] (LOE3). Intravesical botulinum toxin injection seems to be a promising method to treat intractable DO in patients with PD [136, 137] (LOE3). For voiding failure, the treatment of choice is IC; however, PD patients rarely have post-void residual volume > 100ml.

As in MSA, a very important issue in PD affected patients is the indication for pelvic surgery. Myers et al. [138] (LOE2) found that women with PD and LUT complaints have a lower maximum cystometric capacity and a higher rate of DO at lower bladder volumes in comparison with non-neurologic controls. Therefore surgery for stress incontinence in women with PD should be performed only when no significant DO is present, since this type of surgery can evoke or aggravate DO and subsequent urgency incontinence. A secure diagnosis of BOO is needed before considering transurethral prostate resection in PD, and the neurological diagnosis of PD likewise needs to be secure, since MSA inevitably develops urinary retention in the course of neurologic illness. In true PD, prostate surgery is not contraindicated, whereas it is in MSA.

Conclusions

- **In Parkinson's disease, LUT symptoms are associated with degeneration of dopaminergic neurotransmission (LOE2).**
- **The most common LUT disturbances are detrusor overactivity, and detrusor hypocontractility (LOE2).**
- **The effect of levodopa on LUTS in PD patients remains to be fully elucidated (LOE3).**

Recommendations

- **Detrusor overactivity in PD patients can be treated with antimuscarinic drugs (B).**
- **For voiding failure with significant post void residual, the treatment of choice is intermittent catheterization (B).**
- **LUT surgery for patients with Parkinson's symptoms is an option, but MSA should be excluded. However stress incontinence surgery should not be offered to patients with significant detrusor overactivity (C).**

2. CONSTIPATION AND FAECAL INCONTINENCE

Lower gastrointestinal tract (LGIT) dysfunction is common in Parkinson's disease (PD). In recent, control-based studies, the incidence of decreased stool frequency (< 3 times a week) in PD patients ranges from 20% to 81%, difficulty in stool expulsion 57-67%, and diarrhea 21% [139, 140] (LOE2). All of these values are significantly higher than in the normal population (range, decreased stool frequency, 0-33%; difficulty in stool expulsion, 26-28%; diarrhea, 10%). Fecal incontinence affects 10-24% in PD [139, 141] (LOE2). Therefore, constipation is the most prominent LGIT symptom in patients with PD. Indeed, PD is a risk factor for elderly nursing home residents to have constipation. Bowel dysfunction affects the quality of life in patients with PD. The rate of dissatisfaction for bowel dysfunction (59%) is significantly higher than for urinary (28%) or sexual dysfunction (29%), although the prevalence rate of all three dysfunctions is almost the same (more than 60%). The rate of dissatisfaction for the bowel dysfunction in PD is also significantly higher than in healthy controls (16%) [141] (LOE2).

Difficulty in expulsion, and diarrhea are more common in the higher grade of Hoehn and Yahr staging, suggesting a relationship between dopaminergic degeneration and LGIT symptoms. Fecal incontinence in PD occurs commonly with urinary incontinence, whereas no significant relation has been seen between bowel and sexual dysfunction. Constipation in PD is often associated with a low coefficient of variation in electrocardiographic R to R intervals [142] (LOE3). The findings indicate that parasympathetic dysfunction might underlie these abnormalities.

Intestinal pseudo-obstruction (IPO), also called paralytic ileus, is the most severe presentation of constipation in patients with PD and constitutes a medical emergency. The incidence of IPO/ volvulus is 2.4-7.1% [143, 144] (LOE3). The clinical features are mean age 78.5 years with illness duration 5.3 years, with no gender bias; constipation was seen in all and urinary dysfunction in most. Although rare, emergency IPO needs hospitalization and may lead to a poor outcome. Therefore, preventative treatment of constipation, including consideration of prokinetic drugs is necessary, particularly in elderly PD patients.

There seems to be an association between the frequency of bowel movements and the future risk of developing PD [145] (LOE1). This observation is in line with the pathological staging of PD by Braak et al. [146] (LOE1), in which disease process in the central nervous system starts earlier in the dorsal motor vagal nucleus than in the substantia nigra in PD. From a clinical perspective, it is of particular relevance that patients may see gastroenterologists or physicians first because of their bowel dysfunction, prior to a correct diagnosis of PD being made. Therefore, constipation as the initial presentation of PD is akin to urinary dysfunction as the initial presentation of multiple system atrophy.

a) Pathology and disease-specific problems

The enteric nervous system generates the peristalsis responsible for bowel content transit [147] (LOE2). The components of peristalsis are contraction on the oral side of the bolus, and relaxation on

the caudal side. Cholinergic receptors have a major role in the contraction proximally. The strength of cholinergic transmission is regulated by opposing receptors; serotonin 5-HT4 receptor-mediating excitation and dopamine D2 receptor-mediating inhibition [38]. Post-mortem studies of bowel in PD have shown decrease in dopaminergic myenteric neurons and the appearance of Lewy bodies along the proximal-distal axis, being most frequent in the lower esophagus, but scarce in the rectum [148-150] (LOE2). Thus PD affects not only central, but also peripheral (enteric) nervous system.

LGIT function primarily consists of [1] colonic transport of the bowel content to the anorectum, [2] transient storage in the anorectum, and [3] defecation. In PD, constipation results primarily from decreased transport and/or disturbed anorectal evacuation. Fecal incontinence may result from disturbed anorectal reservoir function, or overflow secondary to constipation. Previous reports have shown that total colonic transit time (CTT) is increased beyond the normal threshold in 80% of PD patients, which translates into an increased average CTT ranging from 44 hours to 130 hours [139, 141, 151] (LOE2), and 89 hours in de novo PD patients [48] (LOE2), all of which are significantly longer than the CTT in controls (range, 20-39 hours). Prolonged CTT has also been documented in PD patients without subjective constipation. Slow colonic transit is the major cause of decreased stool frequency. The slow colonic transit is likely to reflect a decrease in slow waves and spike activities of the colon [147].

In resting anal manometry, the anal pressure of PD patients is low or normal [139, 141, 151] (LOE2). The resting anal pressure may reflect sympathetic innervation in the internal anal sphincter, since lesions or anaesthetic blocks at T12-L3 (where the sympathetic preganglionic neurons are located) substantially lessen the anal pressure. Similarly, most PD patients have normal anal pressure increase on squeezing. This finding corresponds to a lack of neurogenic changes in the external sphincter EMG. Nevertheless, latent anal sphincter dysfunction may explain the fecal incontinence that occurs in most advanced cases. In slow-filling rectoanal videomanometry, PD patients had the same rectal volume at first sensation and a maximum desire to defecate, and the same rectal compliance as control subjects [141, 152] (LOE2). In contrast to the bladder, the normal rectum shows spontaneous phasic contraction. However, the amplitude of the spontaneous phasic rectal contraction in PD patients is significantly less than that in control subjects. The decreased spontaneous phasic rectal contraction may share the same aetiology with the decrease in CTT.

During defecation, healthy subjects utilize the final wave of spontaneous phasic rectal contractions. However, rectal contraction on defecation in PD patients is smaller than that in controls [141] (LOE2). In addition, in PD patients abdominal straining is smaller. In PD patients, paradoxical anal sphincter contraction on defecation (PSCD), or anismus, is observed in studies using sphincter EMG, radiography, and anal pressure measurement. The mechanism of the impaired straining in PD may include rigidity and reduced contractility of the axial muscles, and a failure of coordinated glottis closure. However, neuronal degeneration in the brain of PD patients relevant to straining is yet to be clarified. Mathers et al. [153] consider PSCD a focal dystonia. Dysfunction in the suprasacral descending pathway to the external sphincter may be a contributing factor. Apomorphine was shown to lessen PSCD [153] (LOE2). This effect was not antagonized by domperidone, which does not penetrate the BBB, suggesting that CNS pathology may contribute to PSCD.

b) Disease-specific diagnosis and treatment

Insoluble dietary fibers produced an improvement in stool consistency and an increase in stool frequency in PD, which paralleled an improvement in levodopa absorption [154] (LOE3). Dietary fibers such as psyllium[155] (LOE2) and polyethylene glycol 3350 [156] (LOE2), or bulking and highly hydrophilic agent polycarbophil [157] (LOE2), improve constipation in neurodegenerative disorders, including PD. Although psyllium does not alter CTT or anorectal parameters in PD patients, polycarbophil shortens the total CTT, particularly in the proximal bowel segments.

It is possible that levodopa and other antiparkinson medication may affect bowel function in PD. Endogenous dopamine is thought to inhibit intestinal motility via D2 receptors. Tateno and Sakakibara performed the quantitative lower-gastrointestinal autonomic test (QL-GAT, a combination of colonic transit and manometry) in 19 early, untreated PD patients before and after administration of 200 mg/day of levodopa [158]. Levodopa augmented rectal contraction, lessened paradoxical anal sphincter contraction on defecation (PSCD, anismus), and thereby ameliorated anorectal constipation, without apparent adverse effects. This might be brought about by both peripheral and central dopaminergic stimulation.

Since levodopa is absorbed from the small intestine, bowel dysfunction in PD may interfere with levodopa absorption, worsen the motor disorder, or even lead to malignant syndrome [140, 159] (LOE3/4). Domperidone, a peripheral D2 receptor antagonist that does not cross the blood-brain barrier, causes a mean 12% increase in peak plasma levodopa concentrations that occurs a mean of 10 min earlier than when levodopa is given alone [160] (LOE3).

The selective 5-HT 4 receptor agonist cisapride [161], though no longer licensed, and newer agents such as mosapride [162] (LOE2) and tegaserod [163] significantly reduce CTT and ameliorate constipation in PD. Mosapride shortened total CTT

(particularly the caudal segment), and augmented the amplitude in rectal contraction during defecation in patients with PD [162]. Notably, improvement of parkinsonism is more significant with pergolide-mosapride than with pergolide-domperidone, presumably reflecting better levodopa absorption. Similar results were obtained in PD by dietary herb extract Dai-Kenchu-To, one active component of which is hydroxy-beta-sanshool (5-HT3 receptor agonistic action) [164] (LOE2). A series has shown a role for Botulinum toxin A injections into the puborectalis muscle [165] (LOE3).

Conclusions

- **Patients with PD often have abnormal anorectal function (LOE2).**
- **The most common bowel disturbances in PD are slow colonic transit, decreased phasic rectal contraction, weak abdominal straining, and paradoxical sphincter contraction on defecation (anismus) (LOE2).**
- **Bowel dysfunction such as constipation is common and has significant impact on quality of life of PD patients (LOE2).**

Recommendations

- **More studies on management of neurologic bowel dysfunction in PD are needed.**

IV. CEREBRAL LESIONS AND CEREBROVASCULAR ACCIDENTS

Listing of terminology used for the searches: cerebrovascular accident, cerebral lesions, bladder dysfunction, urinary incontinence, faecal incontinence.

1. URINARY INCONTINENCE

Cerebro-vascular accident (CVA) is the third most frequent cause of death in industrialised countries, after myocardial infarction and malignancies. Based on age-dependence of CVA and the increasing age of the population, the importance of CVA is increasing: currently one out of 200 people will suffer from a CVA, 80 to 90% of them above the age of 65. The 5-year-survival rate is 56% in men and 64 % in women.

At the time of maximal impairment following a CVA, 41.1% of 4499 patients (46.0% of females and 37.3% of males studied) had urinary incontinence [167]. An analysis of the symptoms of 532 patients seen within 7 days of their stroke found that the presence of urinary incontinence appeared to be a more powerful prognostic indicator for poor survival and eventual functional dependence than a depressed level of consciousness [168, 169]. It was suggested either that incontinence was the result of a severe general rather than specific loss of function or that those who were incontinent were less motivated to recover from both continence and more general function impairment. Outcome was so much better in those who remained or became dry that it seems possible that recovery of continence may promote morale and self-esteem, which might hasten overall recovery. Urinary incontinence with impaired awareness of bladder sensation seem to be associated with poorer outcome than urgency urinary incontinence with preserved bladder perception [170]. 20-30% of patients still suffer from urinary incontinence six months after the CVA if no proper treatment has been instigated [171]. Six months after stroke, 16% of patients experience urine loss, and that urinary loss was perceived as urinary incontinence when it occurred at least monthly [172].

a) Pathology and disease specific LUT problems

Prior to the findings of functional brain imaging studies, all that was known about the cortical control of the bladder was based on clinical studies of patients with brain lesions. The most influential study was that by Andrew and Nathan, 1964 [173]. The typical clinical picture of frontal lobe incontinence they described was of a patient with severe urgency and frequency of micturition and urgency incontinence, without dementia, the patient being socially aware and embarrassed by the incontinence. Micturition was normally co-ordinated, indicating that the disturbance was in the higher control of these processes. The authors made the comment: “this paper was written because people did not believe that there was such a thing as cerebral disturbance of the bladder“.

There have been a number of urodynamic studies of patients who have developed urinary symptoms after CVA, disparate cortical lesions. In general, voiding is normally co-ordinated, as patients do not show DSD, and the commonest cystometric finding is DO [174-176].

At 3 months, 53% of stroke patients have significant urinary complaints [177]. The commonest LUTS were nocturia in 36%, urgency incontinence in 29% and voiding difficulty in 25%. Urinary retention was seen in the acute phase of illness in 6 %. A significant positive correlation was found between the occurrence of a urinary disturbance and hemiparesis. Brain imaging techniques confirmed a more anterior location of brain lesions in these groups. Urodynamic studies on 22 symptomatic patients showed DO in 68% and uninhibited sphincter relaxation in 36%. DSD was reported in 14%, which should not occur in suprapontine lesions; whether DSD was appropriately diagnosed, rather than representing a hold-on manoeuvre to prevent urinary leakage, could not be clarified from the paper. There was some indication that lesion size was related to the occurrence of urinary symptoms. In contrast to the findings of Maurice-Williams [178] and Kuroiwa et al. [176], who found a correlation of urinary incontinence with lesions of the right brain hemisphere, Sakakibara

et al. [177] could not find a preponderance of right sided lesions for incontinence. Their findings suggest that the damage to the antero-medial frontal lobe, its descending pathway and to the basal ganglia is mainly responsible for micturition dysfunction in stroke patients. An epidemiological study showed an association of hemispatial neglect due to right hemisphere and urinary incontinence [180]. In the latter study, no urodynamic tests were done, and urinary incontinence might have been secondary to general neglect syndrome.

Urinary incontinence in stroke patients is usually interpreted as the loss of central inhibition. However, loss of bladder perception as a concomitant factor may also be relevant. Deficit of bladder sensation seems to be associated with poorer general outcome. Such patients have more parietal lobe but less frontal lobe impairment than patients with urge urinary incontinence and preserved bladder sensation [177]. Patients with frontal lobe lesions (tumours) and damage to the right superior bifrontal region have temporary incontinence, whereas permanent incontinence was associated with bilateral damage [180].

Urinary retention has also been described in patients with brain lesions. Three case histories of elderly females with various forms of right frontal lobe pathology were described as urinary retention. In two, one with an abscess and the other with a haematoma, successful treatment brought recovery of bladder function [181, 182]

An experimental model for studying the effect of forebrain lesions and voiding dysfunction was developed in the rat by occluding the middle cerebral artery under pentobarbital or halothane anaesthesia. At thirty minutes after recovery from anaesthesia bladder capacity in animals with cerebral infarct was markedly decreased. The decreasing bladder capacity continued as long as four months after artery occlusion. Based on the effects of two different types of receptor antagonists on OAB induced by left middle cerebral artery occlusion, the authors [183] concluded that the NMDA receptor (N-methyl-D-aspartate) has a role in the development of OAB after CVA. A glutamate receptor antagonist thus might be beneficial for OAB caused by cerebrovascular disease, as the induced potentiation of bladder reflexes seems to depend on NMDA glutamate transmission (LOE 4).

Brainstem lesions give a different profile from hemispheric lesions. In 1926 Holman [184] noted that voiding difficulty could be a sign of tumours in the posterior fossa. In a series of patients with brain tumours, Ueki et al. [185] reported voiding difficulty to occur in 46/152 (30 %) of patients with tumours in the posterior fossa, while urinary incontinence occurred only in 3 (1.9 %). Renier and Gabreels [186] found urinary retention in 12/17 children with pontine glioma. There are a number of case histories published presenting difficulties with micturition in various brain stem pathologies [187-190].

Sakakibara et al. [189] reported the urinary symptoms of 39 patients who had brainstem strokes. Almost half the patients had urinary symptoms, nocturia and voiding difficulty in 28 %, urinary retention in 21 % and urinary incontinence in 8 %. The problems were more common following haemorrhage, probably because the damage was usually bilateral. Urinary symptoms did not occur in those with lesions of the midbrain, but they did in 35 % of those with pontine lesions and in 18 % of those with medullary stroke. Urodynamic studies in 11 symptomatic patients showed DO in 8/11, low compliance in 1/11. Detrusor acontractility occurred in 3 of the 11 at three months, six months and 3 years after the occurrence. A non-relaxing sphincter on voiding was found in 5/11 and uninhibited sphincter relaxation in 3/11 (LOE 3).

b) Disease-specific diagnosis and management

Basic diagnosis comprises a targeted history and clinical investigation, urine analysis, postvoid residual urine and a bladder diary. In patients with significant residual urine of over 100 cc or more than 50 % of bladder capacity, a urodynamic investigation may help to differentiate between detrusor weakness, and functional or morphological outflow obstruction.

Urinary incontinence within seven days of acute stroke has a highly predictive prognostic value for long term outcome [168, 191] (LOE3). Large lesions involving the frontal lobe, which is relevant to bladder control, might also affect the motor function. Immediately after the CVA, an indwelling transurethral or suprapubic catheter allows control of the urinary output in the Stroke Unit. Diuresis should be monitored. Once the stroke situation is stabilised and diuresis is normalised the catheter should be removed and the patient put on intermittent catheterisation if voiding is inefficient. In the early stage after the stroke, urinary incontinence can be managed by a condom catheter or by pads. Further treatment comprises behavioural therapy (initially toileting, later on micturition training) and anticholinergic therapy, if the voided volumes are below 250 cc. The patient's ability to squeeze the anal sphincter voluntarily is a good prognostic sign for subsequent return of continence. In the early phase, especially during catheter drainage, special care must be taken to avoid urinary tract infections with secondary complications. In diabetic patients low dose infection prophylaxis is recommended (LOE 4).

Behavioural intervention has a good outcome for urinary incontinence after stroke [192-194] (LOE 4). When urinary urgency and incontinence persist after stroke, anticholinergics are generally used, but no systematic survey of anticholinergic use in post stroke patients is available. One trial has reported suburothelial injection of botulinum A toxin

for neurogenic DO, including patients post CVA. Results are not as good as for SCI [195].

Regarding further research, there is a need for further epidemiologic studies of the true incidence of LUT symptoms including incontinence after CVA in the longer term. Evidence is lacking concerning efficacy and safety of currently used therapeutic interventions. Controlled studies comparing behavioural therapy and anticholinergic medication alone and in combination would be useful.

Conclusions

- **Incontinence after CVA is a prognostic indicator for survival and eventual functional dependence. (LOE 2).**
- **The commonest urological problems after stroke are nocturia (36 %), urgency incontinence (29 %) and difficulty in voiding (25 %). (LOE 2/3)**
- **There is a positive correlation between the occurrence of urinary dysfunction and hemiparesis. (LOE 2/3)**
- **Urodynamic studies revealed detrusor overactivity in 68%, and sphincter relaxation problems in 36%. (LOE 4)**
- **Damage to the antero-medial frontal lobe and its descending pathways, and the basal ganglia are mainly responsible for voiding dysfunction in stroke patients. (LOE 3)**
- **With brainstem pathology, symptoms of impaired voiding (urinary retention) predominate. (LOE 3)**

Recommendations

- **As the urological symptoms, especially incontinence are very distressing, urological care is mandatory for these patients (B).**
- **Prevention of early urinary tract infection, especially during the acute phase of indwelling catheterisation, is needed. Thereafter, behavioural training and anticholinergic therapy are the mainstays of treatment (C).**
- **Intermittent catheterisation is occasionally necessary, due to inefficient voiding. This may be in men with pre-existing infravesical obstruction, who can consider standard management of bladder outlet obstruction if they achieve satisfactory general recovery (C).**

V. MENINGITIS-RETENTION SYNDROME

Urinary retention in childhood, young adults, and in women is very uncommon, and may reflect a neurologic disorder [196]. Spina bifida occulta/ tethered cord syndrome is one such disorder known to lead to urinary retention without marked neurological abnormalities, except for saddle anesthesia [197]. Fowler's syndrome is another disorder that causes urinary retention, particularly in neurologically-intact young women, and isolated urethral sphincter hypertonicity underlies this condition [198]. Benign inflammatory nervous diseases also cause acute urinary retention, in which patients lack apparent urethral outlet obstruction, but exhibit only minor neurological as well as cerebrospinal fluid (CSF) abnormalities. Based on the mechanism of urinary retention, these disorders can be divided into two subgroups: disorder of the peripheral nervous system (PNS) (e.g. sacral herpes, with unilateral sacral pain, sensory signs and often skin rashes in the same area [199]); and disorder of the central nervous system (CNS) (e.g. meningitis-retention syndrome (MRS), with fever, headache, stiff neck, and minor pyramidal signs). Previously the latter condition has been only occasionally reported, but now it is recognized as a specific category [200, 201], which is considered to be a very mild form of acute disseminated encephalomyelopathy (ADEM) (LOE3). Since it is rare, true prevalence of MRS has not been fully investigated.

In its typical form, ADEM appears after vaccination or after exanthematous infections, and serological and pathological studies have suggested that ADEM is of parainfectious/ autoimmune origin [202]. Antecedent/ comorbid infections are diverse, e.g. human herpes virus 6 [203]. A combination of signs of encephalitis (e.g., disturbance of consciousness, epilepsy, and hemiparesis), signs of myelitis (e.g., sensory disturbance below the level of the lesion, spastic paraplegia, whereby flaccid parapalegia may occur in the initial shock stage), and lower urinary tract (LUT) / bowel dysfunction typically occur in patients with ADEM. Lesions observed in brain MRI are usually confined to the white matter. Lesions in the spinal cord involving the conus are also seen [201]. CSF pleocytosis, increased protein, mildly decreased glucose content, increased myelin basic protein (MBP)/oligoclonal bands, and a lack of increased viral titres, are all features of this disease. Patients with ADEM commonly exhibit LUT dysfunction [204, 205], which varies from urinary retention to urgency incontinence. LUT dysfunction appears to be related to pyramidal tract involvement, and most probably reflects the severity of the spinal cord lesion. Urodynamic findings have included detrusor overactivity in the storage phase, brisk bulbocavernosus reflex, and DSD (reflective of a suprasacral spinal cord lesion); detrusor areflexia in the voiding phase (reflective of either acute spinal shock or conus lesion); and neurogenic sphincter EMG in one of four patients studied (reflective of a conus lesion) [204, 205]. The responsible lesion sites in cases of LUT dysfunction have appeared to be the

cervico-thoracic spinal cord, and, to a lesser extent, the conus [206] (and possibly the spinal nerve roots [207]) in patients with ADEM. In addition, cases of ADEM presented with LUT dysfunction as the only remaining consequence of the disease, thus suggesting that LUT innervation was selectively vulnerable in these cases. Recently, it is also reported that cases of ADEM/ parainfectious myelitis initially presented with urinary retention [208, 209] or leaves urinary retention as the sole sequel [210]. In some cases, abnormal F-waves were recorded, suggesting conus or radicular lesion [201].

Although aseptic meningitis is a common neurological disorder, a combination of aseptic meningitis and acute urinary retention (MRS) has not been previously well recognized. The clinical manifestations of Sakakibara's three cases [200] are mostly the same as those of the six reported cases in the literature (including cases written in Japanese) [211]. The clinical manifestations of MRS cases differ markedly from those of ADEM, because other than presenting with aseptic meningitis, MRS cases lack the following: apparent encephalitic signs such as disturbance of consciousness, epilepsy or aphasia; and myelitic signs such as gait abnormalities, or sensory-level abnormalities. Only one patient reported by Fukagai et al. showed drowsiness without meningeal irritation. Whereas brain and spinal cord lesions typically appear in ADEM, such change is not observed in MRS. However, a reversible splenial lesion was noted in the brain MRI of a patient with MRS [212].

The CSF examination showed a mononuclear pleocytosis of 38-370 /mm3, normal to increased protein content (up to 260 mg/dl), and normal to mildly decreased glucose content (up to 33% of that in the serum). All viral titres studied in the CSF and the serum of such cases were negative. Nevertheless, it appears likely that the urinary retention in such patients is of neurologic aetiology, since none of the patients appear to exhibit urologic abnormalities such as prostatic hyperplasia, and also because a strong chronological association is observed between the onset of urinary retention with, or just after, the occurrence of the aseptic meningitis. As it is observed in ADEM, antecedent/ comorbid infections or conditions with MRS include angiostrongylus cantonensis [213, 214], Epstein Barr virus [215], and herbal medicine use [216], whereas such antecedent infections are not apparent in the remaining cases [217, 218].

Urodynamic study results have shown that all patients examined had detrusor areflexia, which results in an inability to contract the bladder on voiding, and some patients had an unrelaxing sphincter. Detrusor areflexia originates from various lesion sites along the neural axis; most commonly, PNS lesions are observed. However, CNS lesions that affect the spinal cord or the brain can also cause detrusor areflexia, which is particularly seen in the acute shock phase of patients with transverse myelitis (often immune-mediated) or ADEM. A case report described repeated urodynamic studies in one patient, in which an initially areflexic detrusor became overactive after a 4-month period, suggesting an upper motor neuron bladder dysfunction [219]. As described above, encephalitic features are absent in patients with MRS. However, three MRS patients (including Sakakibara's cases 1 and 3) showed the brisk lower extremity reflexes suggestive of mild myelitis. In one of Sakakibara's cases, MBP was increased, which is suggestive of CNS demyelination. Therefore, it appears possible that MRS is a very mild variant of ADEM, which selectively affects LUT innervation.

Arriving at a diagnosis is easy when a combination of aseptic meningitis and acute urinary retention is confirmed, although such a diagnosis should be made both urologically and neurologically, in order to exclude sacral herpes, a benign variant of Guillain-Barre syndrome (inflammatory radiculitis), typical ADEM, myelitis with leg weakness [220], herpetic brainstem encephalitis, chemical meningitis, focal subarachnoid bleeding, and other common causes of neurogenic urinary retention (e.g., diabetic neuropathy, lumbar spondylosis, etc.). For the differential diagnosis, detailed history, brain/spinal MRI and nerve conduction study are necessary.

The term "Elsberg syndrome" has been occasionally used, which is rather vaguely assigned to sacral myeloradiculitis of undetermined etiology, sacral herpes, sacral vasculitic neuropathy, possible MRS, possible ADEM, or conus infarction. However, in contrast to the majority of "Elsberg syndrome" cases, Kennedy, Elsberg, and Lambert [1913] [221] reported five cases of pathology-demonstrated cauda equina radiculitis. Clinical pictures of these cases were characterized by rare CSF abnormalities (only one of the four cases described showed an increased cell count as well as increased protein levels); no clinical meningitis; subacute/chronic course (in one case the course of disease was subacute: 3 months, but in the remaining four cases, the course of disease was chronic: 4.5-36 months); the patients presented with typical cauda equina motor-sensory-autonomic syndrome (in particular, four of the patients had apparent muscle atrophy/ weakness in the lumbosacral segment); Wallerian degeneration of the spinal afferent tracts; and mild upper motor neuron signs. The authors assumed that the etiology of these cases was either inflammatory or toxic. The exact cause of these five cases remains uncertain, although clinical pictures of these cases resemble, at least in part, those of paraneoplastic [222] or autoimmune lumbosacral radiculoplexus neuropathy [223]. Clinical features of sacral herpes or MRS differ markedly from those of Kennedy's cases.

Since MRS has a benign and self-remitting course (i.e., a duration of 2-10 weeks), the effectiveness

of immune treatments (e.g., steroid pulse therapy) remains unclear, although such treatments may shorten the duration of the disease. Management of the acute urinary retention is necessary to avoid bladder injury due to overdistension (LOE4).

Since MRS is rare, true prevalence has not been fully investigated and evaluation of this is warranted in future research. Similarly, in order to shorten the urinary retention period, the effectiveness of immune treatments (e.g. steroid pulse therapy) in MRS remains unclear, and future research is desirable.

Conclusions

- **Meningitis-retention syndrome, with fever, headache, stiff neck, and minor pyramidal signs, is thought to be a very mild form of acute disseminated encephalomyelopathy (ADEM).**
- **Both urologists and neurologists may encounter this disorder.**
- **Initially the bladder is areflexic, but soon becomes normal or overactive during the course of the disorder.**

Recommendations

- **Management of the acute urinary retention is necessary to avoid bladder injury due to overdistension in patients with MRS.**

VI. ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

Acute disseminated encephalomyelitis (ADEM), also known as post-infectious encephalomyelitis, is a demyelinating central nervous system (CNS) disorder that usually follows infection, or more rarely vaccination [224]. ADEM can be confused for MS; indeed, the early symptoms of ADEM are similar to an acute relapse of MS. Presence of constitutional symptoms such as fever and headache, and the simultaneous involvement of various parts of the CNS may help differentiate this condition from MS. However, it can be difficult to distinguish the two, and the only sure way is follow up and the observation of any relapses over time.

ADEM is a disease that is characterized by an inflammatory reaction and demyelination in the brain and spinal cord. In contrast to MS, there is a tendency for perivenous localization of pathological changes [225]. Bladder dysfunction is common in ADEM. In a consecutive series of sixty one patients with ADEM, 20 (33%) had evidence of LUTD [205] (LOE 3/ 4). Lesions in the cerebral and spinal cord white matter result in LUTD. Both voiding and storage symptoms are reported in ADEM, however the pattern of bladder dysfunction depends upon the time point at which they are assessed. In the acute stage, Panicker et al. reported that voiding dysfunction is more common; in their series of 20 patients, 16 were in urinary retention [205] (LOE 3/ 4). Urodynamics demonstrated detrusor overactivity in four patients and underactivity in four patients. Incontinence was reported more often in patients with frontoparietal white matter changes in MR imaging [205] (LOE 3/ 4). In the series of Sakakibara et al., patients were followed up for 3 to 38 months, and seven of nine patients with retention were able to pass urine once again, five had difficulty in voiding and four developed urinary frequency or urgency incontinence. Motor unit analysis of the external sphincter revealed polyphasic neurogenic changes in only one of four patients. They also observed that bladder disturbances in ADEM seemed to be as common and severe as in MS [204] (LOE 3/ 4). LUTD is common especially in patients with lower limb pyramidal involvement [205].

Management of LUTS is essentially supportive. Patients complaining of LUTS should have their post-void residual checked regularly during the progressive phase of ADEM. If retaining urine, an indwelling catheter may be preferable during the acute phase. The need for catheterisation should be reviewed regularly as voiding dysfunction often recovers [202, 205]. If suitable, IC could be considered. Patients with overactive bladder symptoms are likely to benefit from an antimuscarinic medication, once it is confirmed they are not retaining urine.

For future research, there are currently only limited studies evaluating the natural history of LUTD in ADEM and patients should be followed up to assess lower and upper urinary tract changes with time. There is a dearth of information about the role of botulinum toxin or sacral neuromodulation in this condition.

Conclusions

- **In the acute phase of ADEM, LUTS may be seen in a third of patients (LOE3/4).**
- **Both voiding and storage dysfunction are observed in ADEM (LOE3/4).**
- **Recovery of LUT functions occurs, along with the recovery of motor weakness (LOE3/4).**

Recommendations

- **Patients with ADEM and bladder symptoms should be managed according to their symptoms, and the findings on urodynamic tests, particularly post-void residual (C).**
- **LUTS can change as the disease stabilises; re-evaluation during follow-up is therefore recommended (C).**
- **Patients with overactive bladder symptoms are likely to benefit from antimuscarinic pharmacotherapy, once they are shown not to be retaining urine.**

VII. SPINAL CANAL STENOSIS

About half of the patients with intractable leg pain in spinal canal stenosis also have bladder symptoms – urinary difficulty with high post-void residual (PVR) and reduced flow rate and/or incontinence indicating effects on the cauda equina. Such symptoms, including urinary incontinence usually improve after surgical decompression.

Schkrohowsky et al [2007] [226] reported that one third of patients with achondroplasia developed SCS, especially at the lumbar level, and 77% of these had urinary incontinence. According to Johnsson and Sass [2004] [227], in the County of South Jutland, Denmark during a 5-year period [1996-2000], the annual incidence of SCS was 272 per million inhabitants. Of 340 cases diagnosed with SCS during that period, only one patient presented with acute cauda equina syndrome. This was a 74-year-old woman with SCS from L2 to L4, who presented with urinary retention and fecal incontinence (FI) for the preceding 24 hours; after urgent surgery she recovered from her anal sphincter paresis within 5 days and from her bladder paresis within 5 weeks.

Goh et al [2004 [228] carried out a comprehensive retrospective review of the clinical features, radiological changes and outcome of 75 patients with radiologically diagnosed lumbar SCS; imaging of the lumbar spine showed that moderate to severe central spinal stenosis correlated with complaints of weakness and abnormal motor power on clinical examination. The commonest symptom was numbness or tingling of the legs. According to the study of Inui et al [2004] [229], 58.8% of the 34 patients were diagnosed with neuropathic bladder; however there was no difference in the cross-sectional area of dural sac between those with and without neurogenic bladder dysfunction in patients with lumbar SCS. Nonetheless, the anteroposterior diameter of the dura was shorter in those with bladder dysfunction, and a critical size for the dural sac of patients was reported as 8 mm.

Usually signs and symptoms of compressive neuropathy of multiple lumbar and sacral roots is an indication for surgical intervention, but relatively unknown as a post-operative complication [230]. Four years after diagnosis, 65% had undergone surgical decompression; a third of patients felt that their symptoms had improved while a quarter felt that they had worsened. Imran and Halim [2005] [231] reported a 63-year-old man who developed acute cauda equina syndrome due to fat graft compression after decompressive laminectomy, posterior instrumented fusion with pedicle screw fixation for spinal stenosis of L5 and S1 vertebral levels, and free fat grafting to cover the exposed dura; three days postoperatively, gradual neurological deficit started with sensory loss and weakness of the affected dermatomes and myotomes, followed by FI on the 12th postoperative day; and immediate removal of the fat graft resulted in recovery from cauda equina syndrome. Another case was reported by Tubbs et al [2005] [232]; a Caucasian girl who had idiopathic growth hormone deficiency and Klippel-Feil and Duane's syndromes with symptomatic stenosis of the first cervical vertebrae presented with episodes of loss of tone with subsequent falling, facial cyanosis, UI, hand weakness, and difficulties with swallowing; following suboccipital craniectomy and the removal of the posterior arch of the atlas, her symptoms were resolved and UI improved.

To demonstrate narrowing of the lumbar canal with compression of the cauda equina, CT or MRI is often recommended, to reveal either bony or soft tissue compression [233]. Miyata et al [1998] [234] studied the relationship between bladder function and roentgenographic changes in the spinal canals of ossification of posterior longitudinal ligament (OPLL) patients. CO2-filling cystometry, uroflowmetry and PVR were measured and the vertical extent of OPLL and the degree of SCS was estimated by X-ray films and CT. The occurrence of abnormal detrusor activity had no relationship to the degree of canal stenosis, while the occurrence of an areflexic or underactive detrusor correlated with the vertical extent of OPLL [10]. Yamanishi et al [1998] [235] found DO in 14 lumbar canal stenosis patients (29%) and most of them had voiding symptoms and had storage symptoms which seemed to be caused by the irritation of sacral roots. Of 10 patients followed up after surgical decompression, DO disappeared in 5 patients, improved in 1 patient and remained unchanged in 4 patients [235]. Lee et al [1997] [236] did an expansive cervical laminoplasty in patients with non-traumatic cervical spondylosis with myelopathy and found that age greater than 60 years at the time of presentation, duration of symptoms more than 18 months prior to surgery, preoperative bowel or bladder dysfunction, and lower-extremity dysfunction were associated with poorer surgical outcome.

Conclusions

- **Patients with spinal stenosis, especially at lumbar levels, may present with bladder and bowel involvement – urinary retention/ incontinence and faecal incontinence (LOE 3/4).**
- **Lumbar canal stenosis may cause either detrusor underactivity/ acontractility or overactivity (LOE 3).**
- **Imaging helps diagnose spinal stenosis, while urodynamic study categorises neurogenic bladder dysfunction (LOE 3/4).**
- **Acute symptoms of incontinence or urinary retention may recover after decompression of spinal stenosis (LOE 3/4).**

Table 18. Causes for a cauda equina syndrome

Compressive	*Noncompressive*
Central prolapsed intervertebral disc* Trauma- vertebral fracture* Tumour- primary, metastatic Spinal canal stenosis Pott's disease- tuberculosis Abscess	Ischemia- spinal AV malformation causing steal Iatrogenic- spinal surgery* Following spinal anaesthesia- rare* Inflammation

**Can present acutely*

Recommendations:

- **Surgical decompression is recommended in patients with spinal stenosis having acute symptoms of urinary retention/incontinence and faecal incontinence (A).**

1. CAUDA EQUINA SYNDROME

The nerve roots of L2 to S4 that occupy the spinal canal below the termination of the spinal cord, at the lower border of the L1 vertebra, form a tightly-packed bundle giving the appearance of a horse's tail- hence they are referred to as the "cauda equina". Damage to these nerve roots produces a characteristic pattern of symptoms called the cauda equina syndrome where bladder, bowel, sexual dysfunction and sensory loss of the perineum are the predominant complaints. **Table 18** lists the common causes for a cauda equina syndrome.

2. LUMBAR DISC PROLAPSE

Medline/ Pubmed [1966-2012] searched for keywords: Disc prolapse (or disc hernia), bladder dysfunction, neurogenic bladder, sphincter dysfunction, bowel dysfunction, fecal incontinence, and constipation.

Central lumbar disc prolapse compresses sacral nerve fibers to and from the bladder, the large bowel, the anal and urethral sphincters, and the pelvic floor. Cauda equina syndrome due to central lumbar disc prolapse has been reported to be relatively rare, the incidence being from 1 to 5% of all prolapsed lumbar disc [237-244]. Clinical features of the cauda equina syndrome include low-back pain, bilateral sciatica, saddle anesthesia, and urinary retention, loss of urethral sensation as well as constipation and erectile dysfunction [240, 243, 245, 246]. Those patients with cauda equina syndrome usually have some sensory disturbance in the sacral dermatomes. A retrospective cohort study with prospective clinical follow-up showed that bowel dysfunction at presentation was associated with sexual problems at follow-up [247].

The most common urinary symptom associated with lumbar disc prolapse is acute urinary retention [248, 249]. At the onset, acontractile detrusor with impaired bladder sensation is a typical urodynamic finding [240, 246, 248-250]. Severe denervation of pelvic floor [248] and external urethral sphincter [10] is also frequently demonstrated. Detrusor overactivity may occur [250-252]. Urinary disorders usually follow or accompany more obvious neurologic symptoms, such as lumbar pain and perineal sensory disturbances, that prompt the appropriate diagnosis. However, sometimes voiding disturbances may be the only or the first symptom of this condition, which makes it more difficult to diagnose [240, 246]. Nevertheless, urgent MRI assessment is recommended in all patients who present with new onset urinary symptoms concomitantly with lumbar back pain or sciatica because it is impossible in a significant proportion of patients to exclude the diagnosis of prolapsed intervertebral disc in the context of referral with suspected cauda equina syndrome.

Emergency surgical decompression has been reported to increase the chance of satisfactory neurological recovery in patients with cauda equina syndrome due to central lumbar disc prolapse [240, 254, 255]. In a meta-analysis of surgical outcomes, Ahn et al. [2000] [243] reported that a significant improvement in sensory and motor deficits as well as urinary and rectal function occurred in patients who underwent the surgery within 48 hours, compared with those who had the surgery more than 48 hours after the onset of the cauda equina syndrome. Although there is still a controversy [247], most of other reports support the concept that decompression performed within 48 hours of onset of this syndrome resulted in improved functional outcomes [239, 244, 256]. However, acontractile detrusor is usually irreversible, even after immediate decompression [246, 257, 258], although many patients can empty their bladder postoperatively, this may achieved only by straining or changing voiding postures [246, 258]. In contrast to bladder dysfunction, urethral function shows a better recovery after surgery [246, 249].

For future research, good epidemiological studies on the occurrence of lower urinary tract/ bowel dysfunction are needed. This is increasingly relevant with the advent of new, minimally invasive treatment options for disc prolapse.

Conclusions:

- **Cauda equina syndrome is a relatively rare complication of lumbar disc prolapse (LOE 3).**
- **Bladder and bowel manifestations of lumbar disc prolapse include: urinary retention, loss of sensory functions, decreased sexual functions (LOE 3).**

Recommendations

- **Emergency surgical decompression is the treatment of choice, the optimum timing is considered to be within 48 hours (Grade B/C).**
- **Full recovery of lower urinary tract functions, including bladder contractility, is unreliable (Grade C).**

VIII. NEUROPATHIES AND MUSCLE DISORDERS

1. GUILLAIN BARRE SYNDROME

Since the eradication of poliomyelitis, Guillain-Barré syndrome (GBS) has become the most common cause for acute, flaccid paralytic disease in many parts of the world [1]. It presents as a rapidly progressing ascending areflexic motor paralysis, with or without sensory and autonomic dysfunction. Following an initial acute progressive phase, which by definition reaches a nadir within four weeks, there is a plateau phase and finally a recovery phase. Symmetrical limb weakness is the common presentation, however there may be in addition cranial nerve and respiratory muscle weakness. The disorder affects children and adults of all ages and both sexes. GBS is amenable to treatment with intravenous immunoglobulin or plasma exchange. However despite this, 4% to 15% of patients die from this syndrome, most often due to cardiovascular autonomic disturbances, respiratory compromise or aspiration. Nearly 20% have persistent disability [2].

Autonomic dysfunction is a frequently-overlooked complication. Cardiovascular autonomic dysfunction is recognized in up to 60% of GBS patients [3]. However, bladder and bowel dysfunction occurs much less often. Indeed, the presence of bladder or bowel symptoms at the onset of disease, or their persistence, casts doubt on the diagnosis [3A] and other conditions such as spinal cord disease needs to be excluded. During the acute phase, it is often difficult to assess LUTD specifically due to neurological dysfunction. Patients are often catheterized as part of their general nursing care to monitor water balance or maintain hygiene [2]. Furthermore, patients may be on medications such as opiates and tricyclic antidepressants, which in themselves can affect bladder and bowel functions. In the largest study to date, Sakakibara et al. [4] studied 65 patients with definite GBS (meeting clinical and neurophysiological criteria) and LUTD was observed in 27.7% (LOE3/4). This figure is almost is similar to that quoted by Guillain and others in the early papers about this condition [5, 6].

The condition is characteristically a symmetrical radiculo-neuropathy most often predominantly due to demyelination (Acute Inflammatory Demyelinating Polyradiculoneuropathy, AIDP), but also there are subtypes where axonal damage prevails (Acute Motor Axonal Neuropathy, AMAN). There is a dearth of systematic studies evaluating LUTD in GBS. In a few reports [10-12], detrusor areflexia and disturbed bladder sensation were the common findings, and a non-relaxing urethral sphincter was also seen (LOE3/4). In the study by Sakakibara et al. [4], patients most commonly reported voiding symptoms in 24.6%, including urinary retention in 9.2%. Storage symptoms were noted in 7.7%, urinary urgency in 7.7%. None of the patients in this study became incontinent. Urinary dysfunction was more common in AIDP (39%) than AMAN (19%), although the prevalence of urinary retention was almost the same (AIDP, 7%; AMAN, 11%, respectively). Factors that were associated with bladder symptoms included age, severity of motor weakness (Hughes motor grade) and concurrent bowel dysfunction. When patients were followed up, improvment in bladder symptoms paralleled improvement in motor weakness. Interestingly, there was no correlation between the presence of cardiovascular autonomic dysfunction and bladder dysfunction. Urodynamic studies performed within eight weeks of disease (n=9) showed variable results, demonstrating detrusor underactivity (n=2), DO (n=3), both DO and underactivity (n=5) and non relaxing urethral sphincter (n=2). Three patients had an elevated post void residual and one patient had reduced bladder sensations [4] (LOE3/4). Their results were similar to the urodynamic findings from Gabavac et al. [12] (LOE3/4).

a) Urinary dysfunction

Urinary dysfunction in patients with GBS tends to appear after the onset of motor weakness in all cases [4]; however, in two patients with axonal GBS, it was reported that voiding difficulty and motor weakness appeared almost simultaneously [7, 8] (LOE3/4). A close relationship between severity of GBS and bladder dysfunction has been reported [8A] (LOE3/4). Lichtenfeld [9] (LOE3/4) has reported urinary retention in one-third of patients requiring ventilator assistance. Even though up to 11% of GBS patients may develop urinary retention at the peak of motor weakness, it will most often improve along with other neurological signs after supportive patient management, with or without immunomodulation. However bladder dysfunction can persist, and it is reported that urinary retention failed to recover for 10 months, even after a patient (with axonal GBS) regained the ability to walk [8] (LOE3/4).

GBS primarily affects the large myelinated fibers, but pathological studies have demonstrated moderate to severe loss of small myelinated fibers and inflammatory cell infiltration in the lumbosacral spinal roots, sympathetic chain, and spinal cord [1,13]. It has been postulated that LUTD in GBS may be arising from inflammatory or immunologically mediated damage of of the autonomic fibres of the lumbosacral nerves [1,13, 13A] (LOE3/4). Contrast magnetic resonance imaging (MRI) has demonstrated enhancement of the nerve roots of the cauda equina in GBS [14] (LOE3/4). The possible mechanism for DO might be abnormal spontaneous depolarisations in demyelinated nerve fibres, and impairment of inhibitory spinal cord interneurons, both of which can result in lumbosacral autonomic hyperactivity [13A, 15, 16] (LOE3/4).

Management of LUTS is essentially supportive. Patients complaining of LUTS should have their post-void residual checked regularly during the progressive phase of the disease. If retaining urine, an indwelling catheter may be preferable during the acute phase. The need for catheterisation should be reviewed regularly as voiding dysfunction can recover in parallel to recovery of motor weakness, but in some cases this might be delayed. If suitable, IC should be considered. Wosnitzer et al. reported a successful case of sacral neuromodulation for urinary retention that persisted 18 months after GBS [16A] (LOE3/4). Patients with overactive bladder symptoms are likely to benefit from an antimuscarinic medication once it is shown they are not retaining urine. Of specific consideration to GBS is the side effect of tachycardia, as many patients may have concomitant cardiovascular autonomic dysfunction.

There are only limited studies evaluating the natural history of LUTD in GBS and long-term follow-up studies of patients are required. Studies evaluating the correlation between LUTD and other evidence for autonomic dysfunction (such as cardiovascular autonomic dysfunction) should be specifically evaluated.

Conclusions

- **In the acute phase of GBS, about 25% of patients demonstrate LUT functional problems (LOE3/4).**
- **Both voiding and storage dysfunction are observed in GBS (LOE3/4).**
- **Recovery of LUT function occurs along with the recovery of motor weakness. However, in rare cases it might take months (LOE3/4).**

Recommendations

- **Recovery of LUT functions is expected in GBS; supportive care, including an indwelling catheter or IC, is the treatment of choice for urinary retention (C).**
- **Patients with overactive bladder symptoms are likely to benefit from an antimuscarinic, once they are shown not to be retaining urine.**
- **A systematic evaluation of LUTD during the acute phase and recovery following GBS is required to optimize therapy (C).**

b) Bowel dysfunction

Bowel dysfunction occurs less commonly in GBS, in up to 15% of patients [17, 18]. In a study by Burns et al. [17] (LOE3/4) adynamic ileus was noted in 17 out of 114 GBS patients. However, cardiovascular symptoms coincided with ileus in only 5 patients, suggesting a different pathophysiology for these two manifestations of autonomic dysfunction. Indeed in 4 patients, mechanical ventilation and immobilization was implicated. In 8 patients, pre-existing conditions such as prior abdominal surgery or incremental doses of opiates could also be linked to ileus. However, three case reports by Gazulla Abio et al. (LOE3/4) [19], Sawai et al. (LOE3/4) [20] and Noew et al. (LOE3/4) [21] have also shown that paralytic ileus can be the initial presenting symptom in GBS.

There is a lack of good systematic studies on bowel disorders in GBS during the acute and chronic phase of GBS. However, there are some reports suggesting an involvement of bowel autonomic fibers in GBS. Sawai et al. (LOE3/4) [21] performed a detailed bowel function test in a 47-old man with acute motor axonal neuropathy (AMAN) type of GBS who presented with ileus (also called intestinal pseudo-obstruction) by an abdominal X-ray. Sitzmarks showed prolonged total colonic transit time (86.4 hours; normal 16.0-48.0), suggesting slow transit constipation. Pathological studies of GBS have revealed moderate to severe loss of small myelinated fibers and inflammatory cell infiltration in the lumbosacral spinal roots, sympathetic chain, and spinal cord. Therefore, involvement of bowel autonomic fibers might also occur in GBS [21], as shown in an autopsy case of autoimmune gastroparesis [18].

Adynamic ileus or intestinal pseudo-obstruction occurs in up to 15% of patients during a course of GBS, particularly in those with severe motor dysfunction or those under mechanical ventilation [17] (LOE3/4). Recovery of bowel function usually occurs along with the recovery of motor weakness in GBS, after an intensive immune therapy including intravenous immunoglobulin.

There is still a lack of a detailed functional evaluation of the bowel in GBS patients. Such studies are needed in order to optimize the therapy in the future.

Conclusions

- **About 15% of patients demonstrate bowel functional problems particularly in the acute**

phase, but they can also be presenting symptoms (LOE3/4).

- **Constipation and intestinal pseudo-obstruction are observed in GBS (LOE3/4).**
- **Recovery of bowel function usually occurs, along with the recovery of motor weakness.**

Recommendations

- **Supportive care, including laxatives or enemas, is the treatment of choice (C).**

2. FAMILIAL AMYLOID POLYNEUROPATHY

Familial Amyloid Polyneuropathy (FAP) is a rare autosomal dominant neuropathy affecting predominanatly the peripheral autonomic nerves. Neuropathy starts insidiously in the lower limbs and is characterised by lancinating pains, numbness and impaired temperature sensations.

Autonomic manifestations are common and may be the intial manifestation in nearly 25% of patients [22] (LOE3/4). These include erectile dysfunction, orthostatic hypotension, bladder dysfunction, distal anhydrosis and abnormal pupils. LUTS generally appear early on and are present in 50% of patients within the first three years of the disease. Patients most often present with voiding dysfunction and incontinence (LOE3/4). Often, however, bladder dysfunction may be asymptomatic and uncovered only during investigations. Urodynamic studies have demonstrated reduced bladder sensations, underactive detrusor, poor urinary flow and an open bladder neck. There may be failure of relaxation of the smooth and striated sphincters as well. Ultrasound scans of the bladder may show bladder wall thickening, a finding which becomes more prominent as the disease progresses, and may represent either amyloid deposition in the bladder wall or detrusor hypertrophy secondary to functional obstruction (LOE3/4). 10% of patients with FAP type I may proceed to end stage renal disease [23] and bladder diaries may demonstrate global polyuria. Bladder dysfunction is likely to be due to small nerve fibre damage and deposition of amyloid substance in the detrusor muscle.

Patients should be followed up regularly, as overdistention is likely to contribute to bladder dysfunction. In the early stage of disease, post-void residual urine will often be less than 100 ml and bladder scheduling and double voiding is often sufficient. However when bladder emptying deteriorates, intermittent catheterization is required.

Lower gastrointestinal dysfunction results in alternating constipation and diarrhea. This occurs concomitantly with other manifestations such as episodic nausea, vomiting, and malnutrition. Anorectal physiology studies have demonstrated prolonged colonic transit time, low anal pressure at rest and loss of spontaneous phasic rectal contractions during squeeze, suggesting an enteric neuropathy [24] (LOE3/4).

Liver transplantation remains the only potentially curative treatment and gastrointestinal symptoms improve in about half of cases [22]. Studies suggest that bladder dysfunction does not improve following transplantation [25] (LOE3/4). Interestingly, the occurence of urinary incontinence preoperatively has been shown to predict higher postoperative mortality [25].

3. FAMILIAL DYSAUTONOMIA

Familial dysautonomia (FD) or Riley-Day syndrome is the best known of the hereditary sensory and autonomic neuropathies (HSAN). This autosomal recessive condition is characterised by autonomic and small fibre sensory dysfunction. LUTD is known to occur in this condition and patients most often present with incontinence- stress incontinece but also overactive bladder symptoms. The limitation of using antimuscarinics is that it can exacerbate an already dry mouth from the underlying autonomic neuropathy. Less often, patients may have voiding dysfunction manifesting with hesitancy for micturition and high post-void residual volumes, and may be predisposed to recurrent urinary tract infections [26] (LOE3/4).

4. CHARCOT-MARIE-TOOTH DISEASE

Lower urinary tract dysfunction is only occasionally described in Charcot-Marie-Tooth disease. It has been reported in a family with proximal lower limb weakness where it manifested as loss of bladder sensations and urinary retention with detrusor underactivity demonstrated in urodynamics [27].

5. AUTONOMIC NEUROPATHIES

a) Acute Idiopathic Autonomic Neuropathy.

Bladder dysfunction is well recognized in acute idiopathic autonomic neuropathy (acute pandysautonomia). Acute onset autonomic dysfunction is the hallmark, and is thought to be due to lesions of the pre- and postganglionic sympathetic and parasympathetic fibres. Urinary retention and voiding difficulty are common and cystometry demonstrates detrusor areflexia. Bladder dysfunction tends to resolve earlier than other features of autonomic dysfunction, such as orthostatic hypotension. Constipation is common [28] (LOE3/4).

b) Autoimmune Autonomic Ganglionopathy.

Presentation is with rapid onset of severe autonomic failure: orthostatic hypotension, gastrointestinal dysmotility, anhidrosis, bladder dysfunction, erectile dysfunction and sicca symptoms. They have circulating ganglionic acetylcholine receptor (AChR) antibodies. Bladder dysfunction generally manifests with voiding difficulty and incomplete

emptying. Severity and distribution of autonomic dysfunction appear to depend upon the level of antibody titers [29] (LOE3/4).

c) Pure Autonomic Failure.

PAF is a degenerative postganglionic autonomic disorder. Nocturia and voiding dysfunction are common and bladder emptying is often affected. Bladder diaries may demonstrate nocturnal polyuria. Urodynamics may however demonstrate detrusor overactivity in some patients [30]. Bladder dysfunction in PAF appears to be as common as, but less severe than, MSA and this could possibly reflect slower progression of the disease [30] (LOE3/4). Constipation is common.

6. DISORDERS OF THE NEUROMUSCULAR JUNCTION

Widespread autonomic dysfunction is a hallmark of Lambert-Eaton myaesthenic syndrome (LEMS). This is associated with antibodies to voltage-gated calcium channel (VGCC) of the P/Q-type and patients can present with erectile dysfunction, constipation and bladder dysfunction [31].

In the more common disorder of the neuromuscular junction, myasthenia gravis, LUTS is rare. This is presumably because the auto-antibodies are directed against the nicotinic acetylcholine receptors, rather than the muscarinic. However voiding difficulties have been reported and urodynamic studies have revealed detrusor underactivity in these patients. In fact, voiding dysfunction may herald a new diagnosis of myasthenia or an exacerbation of the disease process [32] (LOE3/4). The proposed mechanism is involvement of acetylcholine receptors in the detrusor muscle or pelvic ganglia [33]. Ganglionic acetylcholine receptor antibodies may be present in some patients [34]. Urinary incontinence is a listed side effect of anticholinesterase medications which are used in treating myaesthenia gravis [British National Formulary (online), 2009 March, cited 8 Sept 2009], though in clinical practice this is rarely observed. Intestinal pseudo-obstruction has been reported in patients of myasthenia gravis with subacute autonomic failure.

7. MUSCLE DISORDERS

a) Muscular Dystrophies

Case series in boys with Duchenne Muscular Dystrophy (DMD) have reported the occurence of overactive bladder symptoms, and DO has been demonstrated in urodynamics. Symptoms improve with antimuscarinic medications [35] (LOE3/4). The exact mechanism for DO is uncertain, though it is likely to be due to a disturbance of neural control rather than myopathy of the detrusor or external sphincter. Patients may have severe scoliosis as a consequence of their muscle disorder and this, as well as spinal fusion surgery for correcting scoliosis, can contribute to LUTS because of spinal cord compression [36].

Myotonic dystrophy (MD) is an autosomal dominant disorder caused by unstable trinucleotide repeat expansions. The commonest bowel complaint is constipation, however most disabling is fecal incontinence. EMG has demonstrated myotonia and myopathic changes in the external anal sphincter. Bowel incontinence is often refractory to treatment [37] and procainamide (300 mg twice a day) has been proposed as a treatment option [38]. Constipation is usually treated with prokinetics, laxatives and enemas. Bladder dysfunction is variable and less often reported with detrusor overactivity or atonia being documented in urodynamics [39] (LOE3/4).

b) Mitochondrial cytopathy

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disorder characterized by gastrointestinal, extraocular, peripheral nerve and cerebral white matter involvement. The gastrointestinal disease manifests with intermittent diarrhea and pseudo-obstruction. Mitochondrial DNA abnormalities and/or thymidine phosphorylase mutations in the proper clinical setting are diagnostic [40]. Bowel dysmotility has also been reported in Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, acronym DIDMOAD) [41]. Lower urinary tract dysfunction has been described in both conditions, and the latter may be associated with urinary retention and dilated upper urinary tracts [41] (LOE3/4).

Conclusions

- **Lower urinary tract and bowel dysfunction can occur in a variety of neuromuscular disorders (LOE3/4).**
- **Both voiding and storage dysfunction are observed in these conditions (LOE3/4).**

Recommendations

- **Patients with neuromuscular disorders with bladder symptoms should be managed according to their symptoms and the findings of urodynamic tests (C).**

LUT and bowel dysfunction can change as these diseases progress and therefore follow-up is recommended (C).

8. PERIPHERAL NEUROPATHY DUE TO IATROGENIC LESIONS (FOCAL NEUROPATHY)

LUT dysfunctions can occur from damage to the nerves innervating the pelvic organs, anywhere in the course of these nerves through the cauda equina, the spinal nerve roots, the sacral plexus, or to the various individual nerves that arise from the plexus. Most injuries to these nerves are iatrogenic. Extensive pelvic surgery, such as abdomino-perineal resection for

rectal cancer, radical hysterectomy, and aorto-iliac surgery are all likely to damage the pelvic parasympathetic nerves to the bladder and genitalia. Of course this listing is not complete and almost any surgery in the pelvis could damage some nerves e.g. adenomectomy, radical prostatectomy, prolapse surgery. Additionally, pelvic irradiation, apart from directly affecting the irradiated tissue, could cause damage to the adjacent nerve fibers, resulting in altered functions. A variety of types of voiding, erectile and fecal dysfunctions can result.

a) Hysterectomy (simple and radical).

It is difficult to attribute certain dysfunctions to neuronal damage alone, since hysterectomy directly affects static and dynamic functions of the pelvic structures. Parys et al. [42] (LOE 3) studied 126 women after simple hysterectomy. The results show that 47.0% had DO, 36.7% had urethral obstruction and 24.8% stress incontinence. Sekido et al. [43] (LOE 3) described 9 women treated with radical hysterectomy more than 10 years before the study. Obstructive voiding symptoms and/or urinary incontinence were observed in 7 patients. Cystometry revealed impaired bladder sensation, detrusor acontractility, straining on voiding, and impaired relaxation of the sphincter in all assessable patients. In addition, decreased bladder compliance was observed in 5 patients. Axelsen [44] (LOE 2) studied 100 women after radical hysterectomy and found that those women who reported incontinence had lower urethral pressure. In a prospective study of over 1000 women Jackson et al. found hysterectomy to be an independent risk factor of incontinence [45] (LOE 2). Plotti et al. analysed literature between 1952 and 2010 and found that in studies with follow up longer than 12 months, 34% of patients demonstrated DO and lowered compliance [46] (LOE 2).

The introduction of nerve sparing hysterectomy appeared to reduce urinary and sexual dysfunctions in comparison with the standard radical hysterectomy. It was found that autonomic nerve preservation significantly improved morbidity 6 months after treatment [3-5] (LOE 3). There is however significant lack of long term observations of patients after radical hysterectomy in terms of lower urinary tract neurogenic dysfunctions.

b) Abdominoperineal resection and total mesorectal excision

Retrospective analysis of 52 patients after abdominoperineal resection was performed by Eickenberg et al. [47] (LOE 3). Neurologic bladder dysfunction of various degrees was found in 50% but represented a long-term problem in only 10%. Baumgarner et al. [48], (LOE 3) studied 86 consecutive cases of abdominoperineal resection and described 11 cases of various functional problems of micturition. These reports lack specific tests of LUT functions and are not prospective. At 1 year follow up, dysuria incidence is higher after abdominoperineal resection than after anterior resection [48] (LOE 3).

Curative total mesorectal excision with autonomic nerve preservation can be done with high rates of preservation of such function. Pocard et al. [49] (LOE 3) investigated 20 patients (13 men, 7 women) following curative total mesorectal excision with autonomic nerve preservation for rectal cancer. There was no difference in preoperative and postoperative LUT function, International Prostate Symptom Score or urodynamic results, nor in the results of the quality of urinary function questionnaire. Sexual function and potency were also unchanged in these men. The authors conclude that autonomic nerve preservation is possible and does not impair urinary and sexual function. Also Kim et al. [50] (LOE 3) showed relative safety in preserving sexual and voiding dysfunction with total mesorectal excision with pelvic autonomic nerve preservation. Evaluation was based on uroflowmetry, voided volumes and residual volume, while symptoms were evaluated with the IPSS. There were significant differences in maximum urinary flow rate and voided volume, but no differences in residual volume before and after surgery. The IPPS increased after surgery from 6.2 +/- 5.8 to 9.8 +/- 5.9 ($p < 0.05$).

Similar results were reported by Turaldo et al. [51] (LOE 3) evaluating incidence and pathogenesis of LUT dysfunction after surgical treatment of rectal cancer in a series of 219 patients with normal urinary function preoperatively. In the immediate follow-up, only 17 patients with dysfunction were observed, 14 stage II, 2 at stage III and 1 at stage IV according to Astler-Koller classification; six months later only 8 patients reported urinary dysfunction and 1 required catheterisation. However no urodynamic studies were performed. There was no correlation of LUT dysfunction with staging, radiotherapy, size of tumour, or surgical technique. However, worse functional results were observed in patients who underwent abdomino-perineal resection.

Lim et al. found that not only surgery but also preoperative irradiation could cause lower urinary tract and anorectal dysfunctions. The maximum resting anal pressures were unchanged after chemoradiation, but the maximum squeeze anal pressures were reduced after chemoradiation. They concluded that preoperative chemoradiation for rectal cancer carries a significant risk of pudendal neuropathy, which might contribute to the incidence of fecal incontinence after restorative proctectomy for rectal cancer [52] (LOE 3). However Lange et al. found that it is mostly the surgery, not the preoperative radiotherapy which is causing urinary dysfunction [53] (LOE 3).

Focal injury to peripheral innervation of the bladder and/or sphincter results in decentralization or denervation of the above mentioned organs. Therefore detrusor hypocontractility (acontractility) and/or sphincteric deficiency will be the result of such

damage. This in turn will result in impaired bladder emptying and/or stress incontinence. No prospective studies referring specifically to the problem of functional disturbances of the LUT in focal iatrogenic neuronal injury in patients after hysterectomy or colorectal surgery have been performed.

Iatrogenic faecal incontinence can be caused by sphincter damage caused during childbirth, and surgery for anorectal problems, trauma, fistulae and abscesses. Vaginal delivery can cause not only sphincteric, but also neuronal damage to the innervation of the anal sphincter [54] (LOE 3). There is a significant paucity of epidemiological data regarding fecal incontinence after pelvic surgery.

Anorectal reflexes and anorectal manometry may predict recovery of function [55, 56] (LOE 3). An interesting test in this specific patient population was described by Nordling et al. [57] (LOE 3). In patients after radical hysterectomy, those who had a completely denervated bladder had a greater rise in maximum urethral pressure during noradrenaline infusion (exceeding 20 cm H2O) than normal subjects (1 to 15 cm H2O). The authors concluded that urethral supersensitivity to noradrenaline may be signify damage of the sympathetic nervous innervation of the LUT.

Detailed knowledge of pelvic neuroanatomy and meticulous preparation of the structures adjacent to nerves potentially at risk is essential [58-61] (LOE 3). Nerve sparing surgery seems to have favourable effect on bladder functions and continence in patients after radical hysterectomy [61-65] (LOE3). Thus it seems that it is the nerve function, rather than the biomechanics of the urethrovesical complex, which are responsible for incontinence. A method of intraoperative identification of the vesical branches of the pelvic nerves during radical hysterectomy was described by Kuwabara et al. [66] (LOE 3). Postoperative compliance of the detrusor in cases where this method was implemented demonstrated less decrement from preoperative values than in cases with conventional approaches. These patients required significantly fewer days to achieve residual urine volumes less than 50 ml after surgery.

Nerve sparing technique and intraoperative identification of parasympathetic nerves seem also to play a role in rectal cancer surgery. Kneist and Junginger studied 62 patients undergoing mesorectal excision. Pelvic autonomic nerve preservation (PANP) was assessed macroscopically and with the aid of intraoperative electrical stimulation of pelvic autonomic nerves. In 46 patients, preservation of parasympathetic nerves was confirmed and these patients remained unchanged in early and long-term urinary function, contrasting with patients in whom preservation of the nerves was not confirmed [67] (LOE 3).

Should injury to the nerves innervating the bladder/urethra complex occur, the treatment should be based on standard principles and on the results of functional examination of the LUT. Zanolla et al. [68] (LOE 2) suggested that early implementation of rehabilitative treatment (prompted voiding) allows satisfactory functional recovery of the bladder activity in 91% of the symptomatic patients after radical hysterectomy. Another interesting issue is the feasibility of the use of the artificial urinary sphincter to treat stress incontinence in patients with outlet denervation after colorectal surgery, hysterectomy and/ or radiotherapy. Only one study on this subject was identified [69] (LOE 3), describing a series of patients after radical prostatectomy and amongst them a patient after abdominoperineal resection with adjuvant radiation. Authors concluded that this method of incontinence therapy should be the method of choice, however there is a significantly greater risk of revision (38% versus 22% in the literature for low risk groups). Bulking agents may be considered after radical hysterectomy, if no other treatment options are possible [10]. If not resulting from sphincter damage, fecal incontinence after colorectal surgery might be considered for sacral neuromodulation [70] (LOE 3).

Future research priorities include good epidemiological research, particularly prospective studies of the true incidence of peripheral injury related functional disorders of micturition. Descriptive studies of diagnostic testing and therapy are needed. A registry database of urinary and fecal incontinence after different types of pelvic surgery would be a considerable benefit for insight into prevalence and preparation of guidelines on treatment/prophylaxis

Conclusions:

- **Injury to the bladder/sphincter innervation occurs in 30-50% of patients after extensive pelvic surgery (LOE 3).**
- **Pelvic irradiation could cause nerve damage affecting bladder/bowel functions (LOE 2).**
- **Fecal incontinence due to iatrogenic innervation damage could occur after complicated labor, anorectal surgery and pelvic irradiation (LOE 3).**
- **Focal injury results in impaired detrusor contractions and/or external urethral sphincter deficiency or detrusor/sphincter dyssynergia (LOE 3-4)**
- **The key means to avoid these complications are nerve sparing techniques and intraoperative nerve identification (LOE 3).**

Recommendations:

- **.Patients after extensive pelvic surgery demonstrating functional disorders of micturition should be properly evaluated due to the varied potential underlying mechanisms (C)**

- **Early rehabilitation of the LUT and of the anal sphincter might improve voiding in a majority of patients (C).**
- **Treatment of choice for acontractile bladder in this group remains intermittent catheterization (B).**
- **Autonomic nerve preservation should be considered when performing surgery for rectal cancer. Targeted voiding history before and after surgery and post-operative post-void residual urine measurements are mandatory to minimise risk of secondary detrusor damage through chronic urinary retention (B).**

IX. MULTIPLE SCLEROSIS

1. EPIDEMIOLOGY

Even though there are few studies today to confirm it, the impact on the quality of life for patients with vesicosphincteric disorders (VST) due to multiple sclerosis (MS) is probably significant. Moreover, in a recent cross-sectional study (LOE4), Notvedt et al [1] demonstrated that those patients with VST had distinctly lower quality of life scores on the SF36 scale in comparison with the population of MS patients that is asymptomatic. The tools for evaluating quality of life that take into account VST in MS have been validated so that variations in it over the course of the illness can be measured [2-5].

VST is extremely polymorphic, and it appears in the great majority of cases within the first 6 to 10 years of the progression of the illness [6-11]. Once VST has started (2 to 10% of cases as primary symptom [7, 12-14]), they will present a more elevated risk of developing severe follow-on urological problems (LOE4) [15]).

The prevalence of VST in the global population of patients who are suffering from MS is in the order of 30 to 96% [6-8, 10, 11, 13, 14, 16-32] (LOE 2b-4). The size of this interval manifests the differences linked to the type of MS, to the duration of the illness, and to the degree of handicap, as well as to a probable under-evaluation by certain practitioners of the urological problems that develop progressively and slowly.

2. URINARY DYSFUNCTION IN MS

Urinary symptomatology in MS is polymorphic and, like its incidence, probably subject to change over time. The most frequent urinary symptoms are indisputably overactive bladder (OAB) symptoms: urinary frequency (32 to 99%), urgency (32 to 85%), and urge incontinence (19 to 80 %) (LOE2b-4) [7-11, 13-15, 18-22, 24-34].

Obstructive urinary symptoms also exist to a lesser degree: difficulty of voiding and chronic or acute urinary retention. Dysuria was found in 6 to 79% of the patients, and acute episodes of urine retention were reported in 8 to 73% of the patients (LOE2b-4) [8-11, 13, 14, 18-22, 24-35].

All of these studies were carried out most frequently in a retrospective fashion or on a population of patients coming for a consultation for another reason, which can upwardly bias the estimated frequency of the disorders. There was a cross-sectional study from Marrie et al [5] (LOE4) of 16,858 patients. Of those patients, 9688 (57.5%) had responded to the two questionnaires that were posted (Bowel Control Scale (BWCS) and Urogenital Distress Inventory-6 (UDI-6)). The figures confirm the frequency of urinary disorders in the MS population: urinary frequency (28%), urgency (17%), urge incontinence (14%), and difficulty with bladder emptying (12.5%). Independent of the non-response rate, there are several elements that cause us to think that these figures are in actuality higher. Indeed, 65% of the patients complain of having at least 1 episode of urinary tract infection, and the majority of patients have not been treated or had a specific checkup. One can think of this very elevated rate of episodes, labeled “UTI”, as manifesting the underlying vesicosphincteric disequilibrium in numerous patients. Problems with emptying the bladder are particularly poorly evaluated by patients, with a large number of patients having a significant post-void residual amount without an evident clinical manifestation. In a cross-sectional study (LOE4) carried out in 2004, Kragt et al had also found a proportion of 16% of patients who had a post-void residual (PVR) greater than 100 ml but without any symptoms that were detected by the questionnaires that are normally used in evaluations of MS (EDSS, Guys Neurological disability Scale (GNDS)).

The estimation of the global incidence of these disorders in the body of patients with MS underlines the frequency of VST in this population. In practice, it is therefore important that the tools that are used to evaluate these problems are the most appropriate ones possible, because, all of the authors agree that the fact that VST is often ignored by the doctors who take care of these patients is due to the fact that the patients under-report their symptoms (LOE5). What is more, a certain number of the patients will suffer from uronephrological complications secondary to VST. It is therefore important to be able to isolate the groups of patients that are at risk so that complex examinations that are seen as risky are not imposed upon the entire population of patients who are suffering from MS [8, 29, 35].

In a systematic review of the literature, De Sèze et al [17] found that the duration of the progression of MS was one of the principal factors that influenced the frequency of VST (LOE 2b-4). Thus, the majority of the studies that were carried out in patients who had a duration of the progression of MS of more than

13 years found a more homogenous frequency for the different symptoms that was in the high range in comparison with the other figures cited up until the present: urinary frequency (38.5 to 99%), urgency (44 to 85%), and urge incontinence (63 to 72%) (LOE2b-4). The frequency of obstructive disorders is likewise markedly more elevated [36-79.5%) [7-10, 14, 18, 20, 25, 28]. A second important factor that is associated with the frequency of VST is the degree of the patient's physical handicap as estimated by the EDSS (LOE2b-4)(Expanded Disability Status Scale) [1, 8, 20, 29, 36-40]. It is difficult to confirm from these studies whether this factor has a role in itself, however, on the other hand, clinical practice indicates this common sense observation. A person who can compensate for the urgency by going to the toilet beforehand will see the appearance of urge incontinence following the appearance of a new motor or visual handicap (LOE5). The appropriate management of this problem can allow the improvement of urinary disorders without any specific action on the bladder or the sphincter. As in those patients who have medullar injuries, the clinical examination does not always allow the discovery of the specific neurological insults that are associated with VST. Certain authors have found an association between the pyramidal syndrome and irritable VST [8, 14, 20, 29]. No neurological presentation has been found that is associated in a manifest fashion with bladder voiding disorders [10, 41, 42]. No correlation between radiological insults on the central nervous system (localization and intensity) and clinical VST has actually been found [36, 43-45]. The analysis of a series of autopsies that were done on patients who had a sacral and lumbar insult (autopsy series) did not find any correlation with clinical VST [46] (LOE5).

Other associations have been indicated, but they have all been controversial. The type of progression for the MS (progressive or by crisis), the age at which MS started, and the sex, the age, the geographical location where the patient lives, and the like do not thus appear to be associated with a more elevated frequency of VST [14, 20, 29, 36, 38-40, 47]. The age of the patient does not have impact anymore. On the other hand, older patients will have the same problems as the general population (benign prostate hyperplasia in men and stress urinary incontinence in women), and those problems will of course often be more difficult to treat than they are in the general population.

It is difficult to precisely establish mortality from uronephrological complications. In a recent study of the causes of death in MS patients in the U.S. that was carried out using death certificates (LOE4), a symptomatic urinary tract infection was considered as a contributing cause to the death in 8.4% of the cases, which made it one of the principal causes that were associated with mortality [48]. In that study, terminal renal insufficiency was not found to be a notable cause of mortality.

a) Infectious complications

The reported frequency of lower urinary tract infections is elevated in the literature, ranging from 13 to 80% [17] [7, 9, 10, 18, 21, 25, 29, 30, 38, 49-52] after at least 10 years of progression of the illness. In the study by Marrie et al, 64.6% of the patients indicated at least one annual episode of urinary tract infection. The diagnoses of symptomatic urinary tract infection is therefore very difficult in those patients who have a neurogenic bladder. Indeed, in close to half of these cases the symptoms that are related to neurogenic detrusor overactivity will be complicated by a lower urinary tract infection, as has been well demonstrated by Lisenmeyer et al (LOE 3c) in spinal cord injury patients (SCI) [53]. There is also an incompressible rate of asymptomatic bacteriuria in many neurological patients [54] (LOE4). The occurrence of febrile urinary tract infection (pyelonephritis, orchitis, or prostatitis) is estimated to be between 2 and 23% (9% on average). In addition to the risk of mortality from certain of these infections that has already been underlined, several retrospective studies (LOE5) report an aggravation of MS following an episode of this type [1, 55, 56]. Neurogenic detrusor overactivity is probably a significant factor in the occurrence of upper urinary tract infections. Game et al [57] have also reported a prospective open study in which the injection of botulinum toxin in the detrusor in patients with MS had allowed a significant reduction of symptomatic urinary tract infections to be observed (LOE3c).

b) Alterations of the bladder

Morphological alterations of the trabeculation, thickening of the bladder wall, and diverticula were found in 4 to 75% of cases according to the series (30% on average) [9, 10, 14, 19, 21, 25, 27-31, 34, 38, 49, 50, 52, 58, 59]. These alterations did not have pathological consequences that were different from those that are found in the general population (primarily increased risk of symptomatic urinary tract infections). The exact proportion of vesical calculus is difficult to estimate, because the majority of studies do not indicate the precise site of calculi events. It can be estimated to be in the neighborhood of 5%. Several factors are associated with the discovery of morphological alterations of the lower tract: post void residual greater than 100 ml and a progression of MS of more than 10 years in duration [19, 60]. There is no correlation between VST and the morphological anomalies that were found [14].

c) Bladder cancer

The data on the more elevated risk of a vesical tumor in patients with MS are controversial. Indeed, it known that those patients who have a neurogenic bladder have had a more elevated risk of developing a particular bladder tumor: epidermoid carcinoma (LOE2b-4) [61-64]. There are other factors that increase this risk in theory, such as tobacco use, indwelling urinary catheters, untreated vesical calculi,

and chronic urinary tract infection. In patients with MS, the use of treatment by cyclophosphamide can be an additional risk. The risk is even further elevated in those patients who have an indwelling urinary catheter or who have been exposed to tobacco. The risk of bladder cancer appears to be slightly increased in those patients who suffer from MS, as a result of risk factors related to their neurogenic bladder as well as from medullar trauma: indwelling urinary catheter, vesicular calculi, and chronic infections. There are other factors that increase this risk in theory, such as tobacco use and treatment with cyclophosphamide. The several studies that have specifically analyzed the risk of vesical tumor in patients with MS (LOE4-5) allow its incidence to be estimated at around 0.29%, which is two to three times higher than the incidence in the general population [23, 65-67]. The diagnoses of these cancers is particularly difficult in neurological patients, especially if they have been catheterized, because the usual diagnostic tools (cystoscopy, cytology, and BTA test) may not be as accurate as usual because of the inflammatory change of the bladder [63].

d) Complications of the upper urinary tract

Renal calculi were found in 2-10% of the cases, hydronephrosis was found in 1 to 16% of the cases, and vesicoureteral reflux was found in 2 to 15% of the cases (LOE 2b-4) [9, 10, 14, 18, 21, 25, 27-31, 34, 38, 49, 50, 52, 59]. Contrary to the case in medullar traumatization and in spina bifida, the incidence of terminal renal insufficiency is rare in patients with MS, and does not appear to be greater than what it is in the general population [68]. On the other hand, a certain degree of renal insufficiency is indicated in certain articles, and may be as high as 2 to 3% in those patients whose illness has progressed for more than 10 years [19, 25, 27].

e) Risk factors in urological complications

As we have specified previously, the great heterogeneity of the clinical signs of VST in MS leads to delayed diagnosis of urological complications. Simple clinical surveillance therefore exposes one to the risk of overlooking a complication that could significantly increase the risk of urinary tract infection, such as post micturition residue (LOE4) [42]. De Sèze et al [17] looked at data based on the literature in an attempt to discern the principal risk factors for urological complications. Those results must be considered with prudence, because the majority of the studies that were used in that analysis were retrospective (LOE4). The duration of the progress of MS is the principal risk factor, with an increase in the frequency of disorders appearing after 6 to 8 years of progression of the illness. These data are consistent with two cross-sectional studies (LOE4) that report a duration of the progress of MS that is significantly more elevated in those patients who have alterations of the upper urinary tract [9, 49].

The second significant risk factor (especially infectious) is the method of urinary drainage. The indwelling catheter (LOE2b-4) [9, 25] has been associated with a number of known infectious complications [69]. The utilization of suprapubic catheters was associated with a reduced risk (LOE3c) [70, 71], however, the series that was published was mid-term [5 to 6 years) and not long term follow up. If one relies on the data that is available for the treatment of patients with SCI, then the best urinary drainage methods are intermittent catheterizations and voluntary voiding (when it can be done without residue) (LOE2) [72].

The third classic risk factor, independent of diagnosis with MS, is the occurrence of post void residual, which is associated with a more elevated risk of urinary tract infection, of vesicular calculus, and, over time, of the distention of the upper urinary tract.

The other risk factors, suggested by many authors, are more rarely reported and do not allow for a group analysis. The urodynamic risk factors will be addressed in the following chapter. The progression of MS and the patient's sex are not associated with particular alterations of the upper urinary tract. Men were more disposed to have febrile urinary tract infections (LOE4) [8, 9, 25, 35]. Older patients were more susceptible to presentation with urological complications, due on the one hand to the occurrence of urological pathologies at their age, but also probably due to the longer progression since the start of MS [17]. The same factor could explain the data of certain authors who report more frequent urological complications in those patients who have a more severe handicap (LOE4) [9, 14, 15, 51].

f) The role of urodynamics in multiple sclerosis

The clinical manifestation of vesicosphincteric disorder in MS is heterogeneous, and urodynamic examination is indicated in two situations. The first is in cases in which the patient requests treatment for urinary symptoms that bother him or her. The purpose of the examination is to understand the vesicosphincteric disorder that is causing the clinical symptom and to propose an appropriate treatment. The second situation is one in which the patient is considered at risk and for whom a search for additional urodynamic risk factors is to be carried out.

With urodynamic examination before the treatment of urinary symptoms, the most frequently found anomaly is detrusor overactivity, which is found in 34 to 99% of cases. It is defined by the presence of detrusor contractions outside of the bladder filling phase. The second anomaly was detrusor underactivity, which was found in 5 to 37% of the cases [6, 9-11, 18, 20, 22, 24-26, 28-30, 32-36, 38, 50, 52, 59, 73, 74]. In those patients who have urinary symptoms, a normal cystomanometry was found in at the most 30% of the cases [21, 25, 33].

Regarding the sphincter, vesicosphincteric dyssynergia (VSD) was found in 6 to 82% of the cases (35% on average). It is defined by the absence of relaxation or by the reinforcement of the electrical activity of the external sphincter during vesicular contraction for micturition, and is the object of needle electromyography of the anal sphincter [58, 75]. VSD is associated indifferently with detrusor overactivity or detrusor underactivity, although the association of detrusor overactivity with VSD (43 to 80% of cases [7, 18, 34, 50, 51]) is more frequent than that of detrusor underactivity with VSD (less than 10% [9, 73]). OAB syndrome seems to more often be the result of DO, especially urgency incontinence [20, 52] (one of the incontinence risk factors that was found was the female sex and the existence of low closure pressure [25]). Obstructive VST was as often associated with DO as it was with detrusor underactivity, and there is also often an associated VSD [10, 20]. VSD does not appear to correlate to the type of urinary symptom [20].

The urodynamic presentations progress through time in a manner that cannot be predicted, especially from the detrusor component. However, VSD, when it is demonstrated in a patient, most often persists without change [26, 59, 73, 76].

The role of the urodynamic examination (UDE) in a patient who is considered at risk for urological complications is much more debated. Certainly, UDE is indicated because of the association of certain UDE anomalies with the possible occurrence of urological complications. The purpose of UDE is therefore the exclusion of an area of risk for the occurrence of complications. Even though this approach is today the most agreed upon, it is useful here to remember that, at least in the case of MS, it has never been evaluated in a strict fashion as part of a prospective protocol. This is explained in part by the fact that sometimes many years will pass before the urological complications occur, which makes the task of evaluation very difficult. The adversaries of proceeding in this fashion propose a more pragmatic approach, with regular surveillance of simple criteria (post micturition residue, renal echography) and they propose a therapeutic approach only in those patients who present with a complication. This approach has the advantage of simplicity for the patient and for the doctor. The theoretical risk is that of the late diagnoses of a future complication (indeed, close to 50% of asymptomatic patients have urodynamic anomalies (LOE4)) [21] and of having to therefore propose a therapy to the patient that is more intensive than what could have been proposed had an earlier diagnosis been made.

The three elements of UDE that were strongly associated with urological complications were detrusor overactivity, bladder compliance failure, and VSD [9, 77]. The relationship between DO, bladder compliance failure, and the alteration of the upper urinary tract are classic in neurogenic bladders. The advent of the use of intradetrusor botulinum toxin reinforced the notion of causality between an elevated intravesical pressure regime and the risk of alteration of the upper urinary tract, because certain authors indicated a disappearance of vesicorenal reflux after injection of botulinum toxin, at which time the intravesical pressure regime normalized [57]. The relationship between urological complications and VSD is more debated [15, 29, 35]. The practical difficulties of researching this anomaly, the invasive nature of the electromyogram that is necessary for confirmation, and the absence of targeted therapeutic efficacy for VSD restrict this systematic search.

3. COLORECTAL DYSFUNCTION IN MS

a) Epidemiology

Digestive disorders are very frequent in patients who have MS, and, like the urinary disorders that are to blame, when they are significant they have a significant impact on patients' quality of life (LOE4) [1, 5, 78]. What is more, the patients seem to tend to be ashamed of these problems and seldom report them. Clinicians have few tools at their disposal for evaluating this impairment. Consequently, digestive disorders are often undetected (LOE3-4) [27, 34].

Taking into account the great diversity of definitions in the several studies that are concerned with this problem, one is obliged to regroup the digestive symptoms into two large groups: those symptoms that can be defined as "retentive", including abdominal pain, flatulence, and constipation on the one hand, and those symptoms that can be defined as "irritant", including false urges to defecate, diarrhea, and/or incontinence of stool and/or gas on the other hand. Digestive disorders of both types were found in 45 to 68% of the cases (LOE 4) [27, 78-82]. The frequency of the "retentive" symptoms was clearly the more elevated, ranging from 31% to 54% [27, 78-82]. The frequency of the irritant symptoms ranged from 6 to 20% [27, 78-82]. The authors who had sought to flush out the more exceptional episodes of incontinence found a frequency of at least one episode of that type in the months that preceded the interview in 29 to 30% of the cases [27, 79]. Finally, a proportion of about 20% of the symptomatic patients had a combination of irritant and retentive disorders [27, 78-82]. The figures were clearly more significant than in the general population, where the "retentive" disorders have a frequency that is estimated to be around 2 to 20% and the "irritant" disorders have a frequency of 2% [83].

Risk factors for digestive disorders in MS have not been identified, to enable [27, 78-82]. Similarly, the duration of the progress of MS does not appear to be a factor that influences the frequency of digestive disorders. The factor that seems to be the most important is the estimated degree of disability (LOE3c-4) [82, 84]. Thus, Munteis et al. [84] found in

a case control study (LOE 3c) a frequency of digestive disorders that exceeded 21.2% if the patients had an EDSS between 0 and 1. This frequency exceeded 78% in those patients who had an EDSS that was greater than 4.5. Other risk factors were suggested (LOE4), but they seemed to have an influence that was less clear, such as female gender, the existence of related urinary disorders, age, and taking anticholinergic treatments [27, 78-82, 84].

b) Pathophysiology of MS-related digestive disorders

Few studies have been carried out specifically in patients who have multiple sclerosis. One of the difficulties is the frequent existence of related treatments that can themselves bring about the specific symptoms. The colic transit times can be extended or shortened in those patients who present with digestive disorders [85-87]. Several anorectal manometry anomalies were in evidence: reduced tone and compliance, a reduced sensation of filling and incoordination of the external anal sphincter during expulsion, with an onset of the phenomenon known as paradoxical anal sphincter contraction. In patients with faecal incontinence, a decrease in anal canal pressures and hyper-reactivity of the rectal wall have been shown manometrically. In the most recent of these studies, Munteis et al [84] has found that the anomalies that are found the most often are those of maximal sphincter pressure, of anal inhibitory reflex (which occurred later than in the control population), and the presence of paradoxical contraction of the puborectal musculature during straining. These anomalies might be able to allow the proposal of biofeedback re-education in affected patients. However, at present the benefit of this approach has not yet been proven.

X. SPINAL CORD LESIONS

1. URINARY INCONTINENCE

a) Epidemiology and prevalence

Spinal cord injury (SCI) including cauda equina injury usually causes impairments of urinary functions such as urinary incontinence (UI) and/or difficulty in urination. Studies on prevalence of bladder management in chronic SCI persons [1-3] (see **Table 19**) and one study in patients with chronic cauda equina lesions [4]. About 8%-11% of chronic SCI persons had normal voiding [1,2], not different from the time after initial rehabilitation [2]; and more normal voiding in tetraplegics then paraplegics [2].

According to the study from Denmark [2], at discharge from the initial rehabilitation period of 233 traumatic SCI patients, bladder-emptying methods were as follows: 12% normal voiding, 57% suprapubic tapping, 19% abdominal pressure, 5% Crédé manoeuvre, 11% CIC, 2% SIC, 8% urethral indwelling catheter (IDC), 0.4% suprapubic catheter (SPC), 0.4% sacral-anterior-root-stimulation (SARS), and 5% use of condom-catheter or diaper. When dividing the patients by years of injury (before 1981 and after 1980), there was a decreasing trend of using suprapubic tapping (drop from over 60% to 45%), abdominal pressure (from over 20% to 15%) and Crédé manoeuvre (drop from over 12% to 1%) but there was an increasing trend of using CIC (rise from 0% to 26%). Over times, 37.5% to 46% of SCI persons changed their bladder-emptying management [2,3]; 28% found their bladder-emptying methods to be a problem; of these 58% were tetraplegic [2]; and the biggest bother bladder management to the subjects was in the compression or straining group (over 50% of the subjects) [1].

There was a statistically significant difference in the frequency of urinary tract infection (UTI) between the bladder management (P< 0.001) [1]; the frequency of UTI was high (about 70%) in the mixed group (65% used CIC with other methods) and the CIC group and less (less than 50%) in the groups with catheter free [1]. According to the study financed by Medicon Valley Academy and Coloplast A/S and done in Denmark, of those using CIC, 92% reported using hydrophilic-coated catheters [2] but there was no report about frequency of UTI. However there was a report of reused silicone catheter for CIC in 28 SCI men done in Thailand [5] with the average time of usage of each catheter of 3 years, 36% reported fever with cloudy urine and 64% of foul smell urine; however, where the frequency of CIC is higher, the abnormality of the urethra was lower (P, 0.05) [5].

In a large prospective cohort study, Drake et al. [4] reported the changes in bladder management method with advancing time after SCI, finding that 29% of patients with SCI for at least 20 years changed method over the 6 year period. Podnar et al [5] studied 55 patients with chronic cauda equina or conus medullaris injury: 76% of the patients reported LUT dysfunction, 70% had urinary incontinence (UI) (56% of men and 71% of women); and a post void residual (>100 ml) was found in 40% of men and 17% of women. Perianal sensation was abnormal in 96%, electromyography (EMG) of the external anal sphincter (EAS) muscle in 88%, and sacral reflex in 84% of patients; using multiple linear regression analysis, perianal sensory loss (P=0.0001) and female gender (P<0.02) had a significant positive effect on urinary incontinence score [5].

b) Pathology and disease-specific LUT problems

Pontari et al. [6] analyzed 7 bladder specimens from 6 cervical SCI patients and 1 L1 congenital myelomeningocele (MMC) and compared them with bladder specimens obtained from 8 organ transplant donors to determine whether the muscarinic receptor subtype mediating contraction alters, and found that whereas normal detrusor contrac-

Table 19: Studies reporting prevalence of specific bladder management methods in chronic SCI

Study (year)	Subjects	Methods of bladder management
Dahlberg et al (2004)[1]	129 traumatic SCI in Finland; mean time since injury 18 years (SD 13)	Normal voiding: 11% Controlled voiding (assisted voiding or incontinence: 12% CIC: 12%; mixed (CIC with other methods):23% Suprapubic tapping 24% Compression or straining (usually with condom catheter): 12% Catheter or conduit: 5%
Hansen et al (2004)[2]	233 SCI in Denmark (82% males, 47% tetraplegics, mean age at the time of follow-up of 50.5 years and mean time since injury of 24.1 years)	46% changed bladder emptying method Normal voiding: from 12% to 8% CIC: from 11% to 36% SPC: from 0.4% to 6% Suprapubic tapping: from 57 to 31% Crede manoeuvre: from 5 to 19%
Patki et al (2006)[3]	64 traumatic pediatric onset, ambulate SCI; mean follow-up 7 years; mean age 46 years	Spontaneous voiding: initial 62.5%; 47.5% of them deteriorated CSIC: initial 31.2%; 25% of them improved SPC: initial 6.3% 37.5% required a change in urological management 68.7% had abnormal urodynamics at the last follow-up

tions are mediated by the M3 receptor subtype, in patients with NBD, contractions can be mediated by the M2 muscarinic receptor subtype [6]. Haferkamp et al [2006] [7] evaluated the role of neuropeptide Y in 31 patients with NDO and 7 patients with stress urinary incontinence (SUI) and concluded that the reduction of neuropeptide Y-containing nerves, inhibiting the contractile response of the detrusor, may play a role in the development and persistence of NDO in SCI patients. Oner-Iyidoğan et al [2004] [8] found that urine 8-iso PGF2alpha concentrations were significantly increased in SCI with hyperreflexic group (median value 0.89 pg/mg creatinine) compared to both normal control (0.52 pg/mg creatinine) and SCI with areflexic groups ($P < 0.001$); and the lowest concentrations of urinary 8-iso PGF2alpha were observed in the areflexic group (0.22 pg/mg creatinine) [8].

According to the study of viscerosensory pathway of the lower urinary tract (LUT) by Schmid et al [2004][9], after electrical stimulation (ES) of the posterior urethral mucosa (single square pulses of 0.2 ms, 2 to 3-fold sensory threshold, 60 mA in complete SCI patients), evoked skin sympathetic responses (SSRs) of the hand could be recorded in 14 of 15 sensory incomplete SCI patients with disturbed urethral sensation but not in 13 sensory complete SCI patients with loss of any urethral sensation. Electrically evoked urethral sensations resembled the subjective desire to void at full bladder reported by controls and patients [9].

Schmid et al [10] did a comparative study of motor evoked potentials (MEP) and evoked pressure curves (EPC) from the urethral compressive musculature (UCM) in 9 healthy persons and 33 patients with neurogenic UI (15 SCL, 14 cauda equina lesion, and 4 multiple sclerosis). In healthy subjects the central latency was 19.0 msec, the peripheral latency was 4.25 msec, and the ratio between central and peripheral latencies was 4.4. In patients with incomplete SCL, the central latency was significantly delayed (22.7 msec), whereas the peripheral responses were normal; and the ratio (5.5) was increased. Those with a complete SCL showed no UCM reaction after transcranial stimulation, whereas peripheral responses were normal. The increased ratio of 6.0 indicated a SCL. Ten patients with incomplete cauda equina lesions and UI had normal central latencies but prolonged peripheral latencies of 6.7 msec; the ratio of 3.4 indicated a lesion of the sacral caudal roots. In patients with complete cauda equina injury neither central nor peripheral responses could be evoked [10].

According to Dai and Xiao [2005] [11], the thresholds of stimulation on ventral root were 0.02 ms duration, 0.2-0.4 mA, (mean 0.3 mA+/-0.07 mA), compared with 0.2-0.4 ms duration, 1.5-3 mA (mean 2.3 mA+/-0.5 mA) for dorsal root ($P<0.01$) to cause evoked potentials and EMG. The continuous stimulation for about 3-5 seconds on S2 or S3 ventral root (0.02 ms, 20 Hz, and 0.4 mA) could resulted in bladder detrusor contraction, but the strongest bladder contraction

over 50 cm H2O was usually caused by stimulation on S3 ventral root in 7 of the 10 patients [11].

1. Urodynamic Studies

Ockrim et al [2005] [12] found that in men with SCI, cystometric variables and detrusor overactivity (DO) remained consistent over sequential studies while in those with LUT symptom of urge, a significant decrease in the number and pressure of involuntary detrusor contractions (IDCs) in consecutive cystometries resulted in a reduction of observed DO from 72% to 63% and 48%, in the three studies. Chou et al [2006] [13] did a retrospective study on urodynamic studies to provide reference ranges for "normal" variability in urodynamic parameters that can be considered as "no real change" from one study to the next. Fifty consecutive individuals with SCI had 2 trials (trial 1 and trial 2) of urodynamic studies done 5 minutes apart, and the following data were collected: maximum cystometric capacity, opening pressure, maximum detrusor pressure, volume voided, and postvoid residual (see **Table 20**).

Generao et al [2004] [14] did a retrospective review of SCI cases with 1-year minimum follow up to determine the effect of SCI on the developing bladder and kidneys using video-urodynamics, sonograms. In 42 children (average age at injury of 5.3 years and mean follow up of 5.5 years), 40 used CIC and 37 took antispasmodics. No patient had reflux, hydronephrosis or renal scarring. Safe bladder capacity, the pressure specific volume at 40 cm water or less, was less than the expected capacity in 80%, 58% and 50% of cervical, thoracic and lumbar injured patients but 100%, 76% and 67% of the respectively groups undergoing multiple urodynamics had increasing capacity with time.

Ersoz and Akyuz [2004] [15] investigated bladder-filling sensation in 73 consecutive traumatic SCI patients to determine to examine the quality of the preserved sensation and to determine the potential for sensation-dependent bladder emptying in this patient group. Bladder-filling sensation was present to some degree in all incomplete SCI patients, in 82.4% of the patients with complete lesions below T10, and 38.9% of the patients with complete lesions above T11. There were statistically significant differences between three groups with respect to bladder sensation category (P<0.001). About 86% of the patients with incomplete lesions, 53% of the patients with complete lesions below T10 and 22% of those with lesions above T11 had bladder-filling sensation before Pves reached 25 cmH2O and simultaneous bladder capacity of more than 150 ml was present in 61.2, 41.2 and 22.2% of the patients in the groups, respectively. Bladder-filling sensation investigations were reliable in terms of bladder filling sensation category in 36 SCI patients who had second cystometric examination.

To quantitatively measure bladder mucosal sensory function, Ukimura et al [2004] [16] used neuroselective Current Perception Threshold (CPT) tests in 8 healthy volunteers and 38 patients with NBD. Standardized neuroselective CPT measures were obtained from the left index finger and the mucosa of the posterior bladder wall. The CPT values in the bladder could be determined using the neuroselective measures in all patients but three who had no sensory response (absence of sensation) caused by complete SCI. In the 8 patients with NDO due to incomplete supra-sacral SCI, the bladder CPT value (4.0+/-1.9) at 5Hz was significantly lower (p<0.01) than that in the controls (26.2+/-17.7). In the NBD determined to be underactive (n=11, including post pelvic surgery, post infra-sacral level SCI and diabetes patients), the higher CPT values of bladder mucosal sensory functions were found at 5Hz (p<0.05), 250Hz (p=0.07), and 2000Hz (p<0.05) compared to the controls. As described in the section diagnosis of neurogenic urinary incontinence, no fibre specificity has so far been found depending on frequency of current used or current type.

Table 20: Variability in urodynamic parameters for 50 SCI individuals (adapted from Chou et al. [13])

Urodynamic parameters		Maximum 5th to 95th percentile		Maximum 10th to 90th percentile		Maximum 25th to 75th percentile	
	Mean	Increase	Decrease	Increase	Decrease	Increase	Decrease
Cystometric capacity (mL)	234.63	+213.50	-158.05	+126.40	-74.60	+72.00	-27.00
Opening pressure (cmH2O)	54.56	+30	18.00	+13.70	-12.00	+4.00	-9.50
Maximum detrusor pressure (cmH2O)	60.82	+17.35	-27.80	+10.00	-20.00	+4.00	-10.00
Volume voided (mL)	122.20	+177.25	-176.00	+105.60	-82.00	+50.00	-30.00
Postvoid residual (mL)	176.06	+197.25	-118.00	+131.00	-86.00	+50.00	-30.00

2. Detrusor (external) Sphincter Dyssynergy

Schurch et al [2005] [17] assessed types of DSD in 105 chronic SCI males and evaluated the change in the DSD pattern over time. Results showed that those with an incomplete sensory and motor SCL presented with DSD type 1 whereas those with complete sensory and motor SCI lesion had DSD type 2 to type 3. A correlation was also found between the AIS and the DSD type but not between the DSD type and the level of lesion; and at medium to long-term follow-up, a significant change was found in the DSD type [17]. Generally, presence of DSD was determined by increased wire needle EMG activity and/or by dilated bladder neck and proximal urethra during detrusor contraction, in the absence of valsalva or attempt to inhibit voiding. De et al [2005] [18] did a comparative study to explore the diagnostic congruence for DSD between needle EMG and voiding cystourethrogram (VCUG) in the neurogenic population. They found 60% agreement and 40% disagreement between EMG and VCUG for diagnosis of DSD. Binomial testing demonstrated significant disagreement ($P < 0.000$) in observed proportions [18]. By retrospectively analyzing clinical data consisting bladder and EAS EMG from 41 SCI individuals with NDO, Wenzel et al [2006] [19] found that the onset of bladder contractions was detected within 1 sec of the start of the EAS contraction for both synergic and dyssynergic human subjects; and they concluded that this detection could be used as a control signal to deliver inhibitory ES to arrest nascent bladder contractions and maintain continence [19].

3. Complications Related to Urethral Indwelling Catheterization (IDC)

During 2004-2006, at least three papers reporting urinary complications related to prolonged urethral IDC such as follows: the catheter balloon of a Foley catheter inserted only half-way was inflated in the urethra distal to the stricture and a long-term IDC caused urethral erosion and a severe degree of hypospadias (Vaidyanathan et al, 2004) [20]; contracted bladder followed by autonomic dysreflexia (AD), gross hematuria and extravasation of contrast media due to improper technique of voiding cystourethrography (Kovindha et al, 2005) [21]; and continuously incontinent despite a catheter and low bladder compliance leading to a urinary diversion to achieve continence (Stoffel and McGuire, 2006) [22]. In chronic SCI, IDC was associated with higher mean levels of C-reactive protein (CRP) while intermittent catheterization was associated with lower levels of CRP when compared with other methods of bladder management [Frost et al, 2005] [23].

4. Vesicoureteral Reflux (VUR)

VUR seems common among SCI patients with upper motor neuron (UMN) neurogenic bladder. According to the study of Linsenmeyer et al [2004[[24], there was an association of posterior position of ureteral orifices and reflux ($p = 0.004$) but no differences were found with regard to bladder capacity, bladder wall compliance, or voiding pressures between the reflux group and nonreflux group.

5. Stone Formation

Linsenmeyer and Linsenmeyer [2004] [25] found that the majority of bladder stones were calcium phosphate (46.8%) or struvite (26.7%). According to the retrospective study in 32 patients with NBD, Matlaga et al [2006] [26] found renal stones were infectious in etiology in 37.5% (12 struvite/carbonate apatite) and metabolic in 62.5%. All with struvite calculi were infected with urea-splitting bacteria.

Stone formation is usually related to IDC. In 2006, there were five papers reporting on such. Ke et al. [27] found bladder calculi with a nidus of hair that could have been introduced into the bladder accidentally during the cystostomy catheter replacement. According to the retrospective study of Ku et al [28], over the 17 years 28% and 15% of 140 men were diagnosed with bladder and renal stones for a total of 59 and 25 episodes, respectively; bladder stone was more common in patients injured when aged > or = 24 years than in those injured when aged <24 years (OR 2.5; 95% CI 1.1-5.7; $P = 0.03$); patients with complete injury had a greater risk of renal stone formation than those with incomplete injury (OR 4.1, 95% CI 1.3-12.9; $P = 0.016$); renal stone was more common for patients with urethral catheterization than for those voiding spontaneously (OR 5.7, 95% CI 1.3-24.6, $P = 0.021$) and for patients with bladder stone than for those without (OR 4.7, 1.5-15.1; $P = 0.01$). According to the review by Ost and Lee [29], recurrent UTI, IDC, VUR, and immobilization hypercalcuria were major risk factors for the development of urolithiasis.

According to the retrospective study of Ozawa et al [2005] [30], the incidence of bladder stone in urethral IDC was 1.11 times/100 months, cystostomy was 1.05, contemporary urethral IDC at night time only was 0.96, CIC-wet was 0.61, and CIC-dry was 0.21; and the urethral IDC group had significantly higher incidence of bladder stone than CIC-dry ($p<0.05$).

Linsenmeyer and Linsenmeyer [2006] [31] did a prospective cohort study by examination of IDC for encrustation at the time of removal for cystoscopy and found that 35% of 49 SCI individuals had bladder stones. Catheter encrustation was noted in 13 patients and 11 of them also had bladder stones i.e., a positive result for catheter encrustation had a positive result for bladder stones 85% of the time. Thirty-six individuals had no catheter encrustation; of these, 16% were found to have bladder stones.

6. Bacteriuria

In a retrospective study, Jayawardena and Midha [2004] [32] suggested that healthy asymptomatic

SCI patients who came for annual evaluations should not have routine urine cultures if they are at low risk for UTIs; that is, <6 WBC/HPF in the urine and/or nitrite negative [32]. Svensson et al [2004] [33] studied the occurrence of bacteriuria in SCI patients with NBD who used CIC. Of 344 cultured samples, there were 285 isolates: coagulase-negative Staphylococci (27%), Enterococci (25%), Klebsiella spp (19%), and Escherichia coli (12%); and bacteria grew at concentrations of 105-108 cfu/L, but only a few at 104 cfu/L. Levendoglu et al [2004] [34] prospectively studied in 27 SCI patients who applied CIC during the initial rehabilitation and 40 controls. E. coli was predominantly isolated from the urine and the urethral cultures of both female and male patients; there was concordance between urethra and urine cultures concerning the growth of E. coli (P=0.82); and Pseudomonas was colonized more in male patients [34]. Waites et al [2004] [35] found that among 77.1% of men with bacteriuria, uropathogens were shown in the perineum in 57.4% and in the urethra in 85.2%; differences in the occurrence of uropathogens in men with and without bacteriuria were statistically significant, and organisms were present in higher numbers in men with bacteriuria.

7. Epididymo-Orchitis and Other Complications

Over the 17-year follow-up study of Ku et al [2006] [36], of 140 male patients (24.3% complete, the average age at onset of 24.8 years old, the average time since SCI of 16.9 years), 27.9% were diagnosed with epididymo-orchitis; and in multivariate analysis, patients on CIC had a 7.0-fold higher risk (OR, 6.96; 95%CI, 1.26-38.53; P=0.026); however, a history of urethral stricture lost statistical significance (P=0.074). Nambiar et al [2005] [37] reported a C4 tetraplegia man presenting with a necrotic ulceration on the ventral aspect of the penis and scrotum of 2 days duration and diagnosed with fulminant Fournier gangrene. Vaidyanathan et al [2004] [38] reported cases of a perirenal haematoma due to warfarin and a tumour like of necrotic slough and debris in the bladder.

8. Quality of Life (QoL)

Oh et al [2005] [39] conducted a prospective trial involving 132 SCI patients and 150 controls matched to age and sex to determine the psychological and social status of patients using CIC. According to health-related quality of life (HRQOL), the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) scores did not reveal any significant differences between the men and women in the patient group. When patients and controls were divided into two groups according to sex and age, the SF-36 scores of the patients were significantly lower than the controls across both sex and all age groups, other than the energy and vitality scale, the differences for which were not statistically significant in women and those younger than 50 years. Later Oh et al [2006] [40] used the Beck Depression Inventory (BDI) with SCI patients on CIC and control group and found that, the average total BDI scores were 20.3+/-1.0 in the patient group and 11.4+/-0.5 in the control group, respectively (P<0.001); 69.6% of 102 the patients reported severe depression; female patients had a 3.8-fold higher risk (OR 13.83; 95%CI 1.42-10.31; P=0.008) of depression than male patients; and those who were unable to perform catheterization independently had a 4.6-fold higher risk (OR 4.62; 95% CI 1.67-12.81, P=0.003) of depression than those who were able to perform self-catheterization.

c) Disease specific management

1. Urological Follow-up Practice

According to cohort studies [4, 5, 41], there was evolution of bladder management by time, outcomes and complications in both pediatric onset and adult onset SCI; treatment was modified in a substantial proportion of patients over the observation periods. Regular urodynamic follow-up is warranted for protection of the upper urinary tract (UUT) and maintenance of continence, however, urological follow-up practice varied: in Bochum, Germany, follow-up included urodynamic evaluation, sonography of the UUT and LUT, urine examination, and evaluation of renal function and treatment modifications were based on the urodynamic findings [42]; in the Spinal Injuries Units of U.K., all units performed routine upper tract screening, ranging from annually to every 3 years [43].

According to the retrospective chart review of Sepahpanah et al. [44], the 24-hour creatinine clearance (CCr) was highly variable from one evaluation to the next and the within-subject standard deviation (SD) for CCr was 25.9mL/min; for all comparisons of repeatability, variability, and reliability, serum creatinine was superior to CCr; and renal ultrasound results and post-void residuals were the major factors in changing medical management with regard to renal function preservation. To determine the accuracy of bladder stone detection by abdominal x-rays of individuals with SCI, 13/62 (20.97%) of stones found during cystoscopy were detected by the x-ray; the detection by x-ray was 33% for stones 1.0 cm to 1.49 cm, 33% for stones 1.5 cm to 1.9 cm, and 54% for stones > or = 2.0 cm; and 57% for volumes > or = 1.0 cm3 [25]. In addition, long-term SCI individual with aged 50 to 60 or more should be screened for prostate and bladder cancer [45, 46]; however, PSA cannot be used in patients with IDC and diagnosis should be based on prostatic biopsies [45].

2. Intermittent Catheterization (IC)

IC is recommended as the safest method of bladder emptying for SCI persons with NBD [47], especially for those who have sufficient hand skills or a willing caregiver to perform the catheterization [48]. Mizuno et al [2004] [49] reported a paraplegic

woman using CSIC for 27 years who had no complications and absence of UI due to underactive and normal capacity bladder. However SCI men on CIC, according to the retrospective comparative study of patients on CIC had a 7.0-fold higher risk of epididymo-orchitis [28].

3. Techniques

Previously, recommended bladder training with CIC was time-dependent, however, some experienced bladder over-distention, especially in those with polyuria that made an IC programme unmanageable [50]. Polliack et al [2005] [51] compared volume-dependent IC (VDIC) following bladder volume measurement by a portable ultrasound device in SCL patients with time-dependent IC (TDIC). After 12-30 days follow-up, the number of IC per patient per day, the time required to perform volume measurements and IC, and their total cost, were approximately 44, 49, and 46% lower in the VDIC group than in the TDIC group. UTI was found in three patients in the TDIC group and in none in the VDIC group.

4. Type of Catheter

In developed countries, there is a variety of urethral catheters available for SCI individuals.

However, in reviewing all controlled trials comparing methods of using catheters in people with neurogenic bladder dysfunction, Jamison et al [2004] [52] could not draw any conclusions regarding the use of different types of catheter. According to the multicentre RCT of De Ridder et al [2005] [53], 57 SCI male patients completed the 12-month study; 64% of those using the SpeediCath hydrophilic-coated catheter experienced 1 or more UTIs compared to 82% of those using the uncoated polyvinyl chloride (PVC) catheter ($p = 0.02$); and twice as many patients in the SpeediCath group were free of UTI. According to another multi-centre study of Bjerklund Johansen et al [2007] [54], of 378 SCL (the mean duration of IC was 4.6 yr) who completed a 12-d trial of the novel hydrophilic catheter: LoFric Primo, 55.2% of the patients were happy to continue with the novel device, which was 74% of patients using standard PVC catheters and 36% of those using prelubricated PVC ($p=0.04$).

In a developing country, such as Thailand, Japanese reusable silicone catheters were reused and median duration of usage for each catheter was 2 years. Electron microscopic findings of the reused catheters for 2 years revealed encrustation but no obstruction in the lumens and 20% increase in stiffness. Demographic data, urinary management and complications did not have significant relation to the abnormality of the urethrogram or UTI [21].

Ozawa et al [2005] [30] applied a contemporary (reusable) balloon catheter at night time only. After a mean follow up of 41 months, the incidence of febrile episode was as follows: CIC-wet 3.36 times/100 months, IDC 2.96, cystostomy 1.26, the contemporary catheter 0.57, and CIC-dry 0.42. The incidence of febrile episode in CIC-wet and IDC were significantly higher than in CIC-dry ($p<0.05$). The incidence of bladder stone was as follows: IDC 1.11 times/100 months, cystostomy 1.05, the contemporary catheter 0.96, CIC-wet 0.61, and CIC-dry 0.21.

5. Bladder Relaxants

Many SCI individuals with NDO experienced high detrusor pressure with incontinence and post-voiding residual, bladder relaxants – antimuscarinic drugs, usually are prescribed for those applying CIC as well as IDC. Tolterodine, 2 mg twice daily [55], controlled release oxybutynin (OXY-XL) [56], doubled dosage of tolterodine ER or Trospium [57] and self-selected dosages (SSD) of tolterodine and oxybutynin [55] showed reduction in degree of UI and increase in IC volumes, and cystometric capacity; but the side effect of dry mouth was differed significantly when comparing tolterodine SSD with oxybutynin SSD ($P < 0.05$) [55].

6. Intravesical Vanilloid Instillation

According to a review article [58], intravesical treatment options may either act on the afferent arc of the reflex such as local anaesthetics or vanilloids or on the efferent cholinergic transmission to the detrusor muscle such as intravesical oxybutynin or botulinum toxin. Clinical trials and case series done in SCI with NDO proved the efficacy of intravesical instillations of various concentrations of resiniferatoxin (RTX) by cystometric/ urodynamic parameters and degree of UI [59-64]; intravesical capsaicin (CAP) also improved in symptoms and urodynamic parameters [57,61], without a significant difference between the CAP and the RTX groups [61]. When compared RTX with injection of 300 units botulinum A-toxin diluted in 30 ml normal saline, both treatments provided significant reduction in mean catheterization and episodes of incontinence, and a significant increase in mean first involuntary detrusor contraction and in mean maximum bladder capacity at 6, 12 and 24 months after therapy; while botulinum-A toxin significantly reduced also the maximum pressure of uninhibited detrusor contractions more than RTX at all follow-up time points [59].

7. Treatment of DSD

In those using reflex voiding to empty bladder, it is recommended to attempt use of non-surgical methods – for example alpha-blocker and botulinum toxin injection into the urethral sphincter [48]. According to the study of Reitz et al [2004] [65], 12 male SCI patients with NDO and DSD received 10 mg of isosorbide dinitrate sublingually and found that nitric oxide significantly reduced external urethral sphincter pressures at rest ($p < 0.05$) and during dyssynergic contraction ($p < 0.05$); and the mean post triggering residual volume was significantly reduced ($p < 0.05$).

8. Prevention of UTI

According to 2 double-blinded, placebo-controlled RCTs [66, 67] studying the effectiveness of cranberry supplement (400-mg cranberry 3 times a day for 4 weeks [66] and 2 g per day for 6 months [67]), at preventing UTIs in SCI individuals with NBD, bacterial count, white blood cell (WBC) count, bacterial counts in urine, urinary pH or episodes of symptomatic UTI did not differ between the placebo and cranberry groups. According to another RCT to determine the effectiveness of methenamine hippurate (MH) (1 g twice-daily) and of cranberry (800 mg twice-daily), MH as well as cranberry did not have a significantly longer UTI-free period compared to placebo Lee et al [2007] [68]. In addition, when taking phosphorus supplementation, there was no significant change in urine pH during the 2-week period compared to when the patient was off supplementation Schlager et al [2005] [69].

9. Antibiotic Prophylaxis

Some advocated antibiotic prophylaxis for recurrent UTI [43]. To determine the safety and efficacy of a weekly oral cyclic antibiotic (WOCA) regimen consisting of the alternate administration of an antibiotic once per week over a period of at least 2 years to prevent UTI in SCI adult patients, symptomatic UTI dropped from 9.4 to 1.8 per patient-year; and no severe adverse events and no new cases of colonization with multiple drug resistant bacteria were reported [Salomon et al, 2006] [70].

10. Bladder Irrigation

Waites et al [2006] [71] conducted a randomized, double-blind comparison of twice daily bladder irrigation using 1 of 3 different solutions for 8 weeks with 30 mL of (a) sterile saline, (b) acetic acid, or (c) neomycin-polymyxin solution in community-residing persons with NBD who used IDC. Results showed that the 3 irrigants had no detectable effect on the degree of bacteriuria or pyuria; no significant development of resistance to oral antimicrobials beyond what was observed at baseline; but all groups had a significant increase in urinary pH.

11. Treatment of UTI

Bycroft et al [2004] [43] found few routinely treating asymptomatic UTI in SCI individuals using catheters; and the range of recommended duration of treatment for symptomatic UTI was 3-14 days (mean 6.3).

12. Electrical Stimulation

Lavano et al [2004] [72] reported improvement in bladder emptying and continence in 6 neuropathic patients treated with sacral nerve stimulation (SNS) and results were unchanged during the follow-up (maximum 26 months) in all except 1 patient. Kutzenberger et al [2005] [73] reported a 17-year experience with sacral deafferentation (SDAF) and implantation of sacral anterior root stimulator (SARS). Of 464 paraplegics receiving a SDAF-SARS, complete deafferentation was successful in 94.1% and continence was achieved in 83%. With a mean follow-up of 6.6 years, 420 out of 440 paraplegics used the SARS for voiding (frequency 4.7 per day) and 401 used it for defecation (frequency 4.9 per week); UTI declined from 6.3 per year preoperatively to 1.2 per year postoperatively and kidney function presented stable. Hansen et al [2005] [74] applied automatic event driven ES of the dorsal penile/clitoral nerve triggered by Pdet exceed 10 cmH2O and reported during stimulated filling Pdet never exceeded 55 cm H2O and an average bladder capacity increase of 53% was achieved in suprasacral SCI patients.

d) Guidance for further research:

Most of the papers relating to epidemiology and pathology of urinary incontinence in spinal cord lesion patients were case series; and few papers were clinical trials or RCTs relating to pharmacological treatments. As UTI is a common complication among SCI individuals, further RCT to prove whether a weekly oral cyclic antibiotic for UTI prophylaxis as well as optimal dosage, effectiveness and safety of bladder relaxants including drugs for blocking nerves innervating bladder is beneficial in SCI with NBD should be done. Regarding types of catheter, RCT should be conducted to prove whether to reuse catheters is safe. In addition, to make an automatic, event driven electrical stimulation for the treatment of NDO suitable in a clinical setting further investigations are needed.

Conclusions:

- **The profile of muscarinic receptors in the bladder may be altered in patients with neurological disease (LOE 3).**
- **Skin sympathetic responses and motor evoked potentials may help assess autonomic and somatomotor pathways of the lower urinary tract. (LOE 3).**
- **In patients with neurological disease, individuals often change their method of bladder management, influenced by a range of factors including renal function. (LOE 2)**
- **Long-term urethral indwelling catheterization leads to bladder and urethral complications (LOE 3).**
- **Encrustation of a catheter is predictive of bladder stones; abdominal x-ray is not an adequate method to detect bladder stones (LOE 3).**
- **Volume-dependent intermittent catheterization may offer advantages compared with time-dependent intermittent catheterization. (LOE 3)**
- **Combined clean intermittent catheterization during the day time with indwelling contemporary balloon catheter at night time showed less**

urinary infection than clean intermittent catheterization with incontinence and permanent urethral indwelling catheterization. (LOE 3)

- **Increased dosage of Tolterodine or Trospium gave a better effect to control neurogenic detrusor overactivity with incontinence. (LOE 2)**
- **Urethral flora may be a bacterial source for the development of urinary infection. (LOE 3)**
- **Low bacterial concentrations in the urine (<105cfu/L) of patients on intermittent catheterization might be due to contamination. (LOE 3)**
- **Cranberry extract, methenamine hippurate or phosphorus supplements were not found to be effective in acidifying urine or preventing urinary tract infection. (LOE 2)**
- **A weekly oral cyclic antibiotic seemed efficacious in preventing UTI. (LOE 3)**
- **Bladder irrigation was not effective in reducing bacteriuria in persons with neurogenic bladder using indwelling catheterization. (LOE 2)**

Recommendations:

- **Regular urological monitoring, at least annually, is appropriate to early detect complications and to adjust bladder management in patients with neurogenic bladder dysfunction. (A/B)**
- **Recommend urine culture only there is high risk of urinary tract infection. (C)**
- **Routinely inspect catheters for encrustation, as an early indicator of risk of bladder stone formation. (C)**
- **Cystoscopy is necessary if bladder stones are suspected. (C)**
- **Adjust urinary tract management according to results of urological evaluation and emergence of complications. (B)**
- **Clear diagnosis of DSD requires VCUG facilitated by EMG. (C)**
- **Clear instructions on catheter management can help to reduce risk of complications. (B)**
- **Dosages of bladder relaxant drugs in excess of the licensed doses have been used in attempting to control neurogenic detrusor overactivity and incontinence; if side-effects cannot be tolerated, intravesical botulinum toxin injection are effective. (B)**

2. FAECAL INCONTINENCE

a) Epidemiology and prevalence

[According to Dvorak et al, 2006] [75], in patients with central cord syndrome, bowel and bladder continence was reported by 81% in those with American Spinal Injury Association (ASIA) motor score improvement from a mean of 58.7 at injury to a mean of 92.3 at follow-up. However, neurogenic bowel dysfunction (NBoD) is common among spinal cord injury (SCI) patients (**Table 21**). From 2004 to 2007, there were 6 studies reporting epidemiology of NBoD in chronic spinal cord injured (SCI), from various countries [76-80] (more details see section D1 in this chapter). Apart from SCI [2-6], there were other spinal cord lesions (SCL) that causes NBoD such tumors (e.g. a conus medullaris ependymoma and filum terminale lipoma [81]; a clear cell meningioma along the thoracic and lumbar levels [82], neuroblastoma [83]); venous congestive myelopathy, mostly at thoracolumbar and/or conus medullaris levels [84]; transverse myelitis [85]; and iatrogenic [86, 87]. Tanaka et al [2006] [85] 77% of 22 transverse myelitis (average age at onset 8.8 years, mean follow-up 7.1 years) had NBoD.

Table 21. Prevalence of neurogenic bowel dysfunctions reported in spinal cord injury patients

Study (year)	Countries	Subjects	Prevalence		
			Faecal incontinence	Constipation	Others
Liem et al (2004) [76]	Canada	352 SCI (> 20 years)	41.8% (including diarrhea)	47.9%	
Ng et al (2005) [77]	Australia	110 SCI (duration from injury, median 17 years)	41%	46% (including laxative use)	Abdominal pain 33% Abdominal bloating 22%;
Tongprasert & Kovindha (2006) [78]	Thailand	100 SCI (duration from onset, mean 6 years)	35% (normal subjects: 1.8%, p = 0.0013)	86% (including uses of laxative, enema, etc)	Haemorrhoid 16% (normal subjects, 20%, p =0.338)
Vallès et al (2006) [79]	Spain	54 motor complete SCI (mean duration from onset 6 years)	85%	67%	
Vallès et al (2006) [79]	Spain	109 patients 83% had spinal sacral reflexes (SSR)	31%	27% more in tetra A,B,C	
Pagliacci et al (2007) [80]	Italy	403 SCI (duration from discharge to follow-up, mean 3 years)	2.7% (20.1% partial)		

b) Pathology and disease specific lower gastrointestinal (LGIT) problems

According to electromyography (EMG) of external anal sphincter (EAS), 18 and 22 of 64 patients with cauda equina or conus medullaris lesions had bilateral and unilateral EMG abnormalities [88]. Using anorectal manometry, the maximum anal resting pressure of a 26-lumbosacral SCI patients group with mixed symptoms of constipation and/or FI was slightly lower than that of a 13-normal volunteers control group [89]. During defecation , 88.5% of the patients but 7.7% of the control group significantly showed pelvic floor dysfunction (PFD). Rectoanal inhibitory reflex (RAIR) was identified in both groups. The rectal volume for sustained relaxation of the anal sphincter tone in lumbosacral SCI patients group was significantly higher than the control group. The mean rectal volume to generate the first sensation was significantly higher in SCI patients than in the control group. Regarding constipation, its association with level of injury was supported by many studies, i.e. upper motor neuron vs lower motor neuron NBoD. Decreased colonic pressure activity was found during sleep in SCI individuals and may contribute to delayed colon transit time after SCI [90].

Furlan and Fehlings [2006] [91] examined the characteristics of the top 100 most frequently cited articles (so-called “citation classics”) on traumatic SCI that were published between 1986 and 2003, and compared this selected professional literature with the consumers’ perspective on the key issues in SCI research. From a SCI consumers’ perspective, the areas of greatest interest included motor function, bowel and bladder control, sexual function, and pain. Motor function was the leading topic in the matching list between professional literature and consumers’ perspective. According to Anderson’s quality of life (QOL) survey of the SCI population [2004] [92], regaining arm and hand function was most important to quadriplegics, whereas regaining sexual function was the highest priority for paraplegics; and improving bladder and bowel function was of shared importance to both injury groups. Later, according to a web-based survey of 286 SCI population aged 18 years or older completed the survey, results showed that bladder and bowel concerns during sexual activity were not strong enough to deter the majority of the population from engaging in sexual activity [93]; however, bladder and/or bowel incontinence during sexual activity was a highly significant concern in women with SCI. In addition, the occurrence of autonomic dysreflexia (AD) during typical bladder or bowel care was a significant variable predicting the occurrence and distress of AD during sexual activity [94].

FI had 10 times more impact on QOL than those with no FI and NBoD had significant impact on their QOL [95]. They had significantly lower Gastrointestinal QOL score as compared with the normal persons [96]. There were no statistically significant differences in satisfaction or QOL between those with colostomies and those with traditional bowel care programs; however, 55.7% of those with colostomies and 41.7% of those without colostomies were very unsatisfied with their bowel care program [97].

c) Conservative bowel management

According to the “Neurogenic Bowel Management in Adults with Spinal Cord Injury” Clinical Practice Guideline published by the Consortium for Spinal Cord Medicine [98], rectal stimulations help assist elimination of the stool: mechanical stimulations – digital rectal stimulation (DRS) and manual evacuation; and chemical stimulations – suppository and mini-enema (liquid suppository). Korsten et al. [99] used a manometric catheter to assess colonic motility at baseline, during DRS, and after DRS and evacuation of barium oatmeal paste in six subjects with SCI; and results showed that manometric changes in response to DRS were accompanied by expulsion of barium oatmeal paste in every subject by the fifth DRS. In patients with cervical SCI, a significant increase in systolic blood pressure (BP) was induced by insertion of rectal medications and persisted during additional DRS, and the manual removal of stool induced AD were reported; however, systolic BP recovered to pre-program values within 5 min after defecation[100].

Uchikawa et al. [101] reported a successful bowel movement in 75% of 20 SCI patients by using a modified washing toilet seat equipped with a camera monitor and an electronic bidet to facilitate precise hitting of the anal area with water streams to stimulate bowel movement for a maximum of 30 minutes. Regarding transanal irrigation, it showed improvement in constipation, FI and symptom-related QOL in SCI individuals [102].

Push up, abdominal massage and a forward-leaning position may aid evacuation by increasing abdominal pressure [98]. Ayaş et al. [103] studied in patients with SCI and showed that abdominal message gave positive effects – increase in frequency of defecation per week, decrease in total colonic transit time and lesser FI. As contraction of the abdominal wall musculature plays a role in normal defecation, Korsten et al. [104] assessed whether an abdominal belt with implanted electrodes would improve difficulty with evacuation in SCI individuals and demonstrated that neuromuscular stimulation of the abdominal wall improved defecation function, including time to first stool and total bowel care time.

Oral medications to enhance bowel movement have been used, but evidence of efficacy is lacking. Cisapride does not seem to have clinically useful effects in people with SCI [104]. Korsten et al. [105] did a randomized, blinded design, to test the efficacy of neostigmine in SCI persons with defecation difficulty by infusing one of three intravenous infusates (normal saline, 2 mg neostigmine, or 2 mg

neostigmine + 0.4 mg glycopyrrolate – to prevent neostigmine's muscarinic effects) on separate days and determining on bowel evacuation of the barium paste, heart rate and airway resistance; and results indicated that both neostigmine and neostigmine + glycopyrrolate resulted in prompt bowel evacuation. Studies have shown that neostigmine + glycopyrrolate intravenous administration is safe and well tolerated in persons with chronic SCI [105, 106] and studies have been under way to assess the efficacy of neostigmine by other routes [106].

d) Guidance for further research

Most of the studies reported were case series and used different definitions of faecal incontinence and constipation. Therefore further researches should base on internationally acceptable definitions so that they can be compared. In addition, RCTs on rectal or anal stimulations both mechanical and chemical as well as medications promoting bowel movement are needed.

Conclusions:

- **Constipation is more common than faecal incontinence among people with established SCI (LOE 3).**
- **Constipation is more common in those with preserved sacral reflexes, whereas faecal incontinence is more common in those without sacral reflexes. (LOE 3)**
- **Faecal incontinence has impact on the QOL of SCI individual and is a substantial concern for women with SCI during sexual activity. (LOE 3)**
- **Digital rectal stimulations aid bowel evacuation in individuals with SCI, in part by increasing left-side colonic motility. (LOE 3)**
- **Transanal irrigation with water improves constipation and quality of life in individuals with SCI. (LOE 2)**
- **Abdominal massage may be effective in enhancing bowel movement and defecation. (LOE 3)**
- **Anal stimulation by water stream may be effective in stimulating bowel movement and shortening bowel care time. (LOE)**

Recommendations:

- **Encourage adherence to the clinical practice guidelines on neurogenic bowel management in adults with spinal cord injury (A).**
- **Apply mechanical stimulation e.g. digital rectal stimulation, to aid bowel evacuation- especially in those with preserved sacral reflexes (B).**
- **Use chemical stimulants when mechanical stimulation fails (C).**
- **Beware of autonomic dysreflexia during bowel care, especially in those with a high SCI lesion (C).**
- **Consider transanal irrigation with water for those with severe chronic constipation and faecal impaction (B).**

XI. MYELOMENINGOCOELE

The following text describes the literature relating to adult patients.

1. URINARY INCONTINENCE

Myelomeningocele (spina bifida) is one of the most common birth defects of the spine and brain. It occurs in 1-2 births per 1000, potentially involving all levels of the spinal column (lumbar 26%, lumbosacral 47%, sacral 20%, thoracic 5% and cervical spine 2%). Associated Arnold- Chiari malformation is seen in 85% of children, often requiring ventriculoperitoneal shunting of cerebrospinal fluid. Ingestion of folic acid prior to conception and during the first trimester of pregnancy has significantly reduced the incidence of this problem and other associated neural tube defects. The neurologic defect produced is quite variable and cannot be totally predicted by the vertebral level of the lesion. Additionally the fibrosis associated with myomeningocele closure, may tether the cord. Subsequent growth of the infant or child will produce further neurologic problems, manifesting as changes in bladder, bowel and lower extremity function.

The incidence of urethrovesical dysfunction in myelomeningocele is not absolutely known, but most studies suggest it is very high (>90%). Similarly, anorectal dysfuction is very common, but its exact incidence has not been reported. Congenital neurologic bladder dysfunction with spina bifida and sacral dysgenesis that manifested itself only at middle age in a 48-year-old male is reported by Kaneoya et al. (LOE4) [1]. Yamamura et al. reviewed the literature of tethered cord of adult onset and found 56 cases published.(LOE 3) [2].

The two major consequences of the vesicourethral dysfunction are urinary incontinence and hydroureteronephrosis which can occur early or later in life. There are many studies documenting the urodynamic characteristics of the vesicourethral unit in myelomeningocele patients but almost all in children. Almodhen and colleagues examined myelomenigocele patients in postpubertal age and correlated these findings with upper urinary tract changes [3] (LOE 3). Of the 26 patients with urinary incontinence before puberty, 12 achieved continence following puberty. Hydronephrosis remained stable in 4 patients, improved in 3 and was new onset in 3 , whilst vesicoureteral reflux persisted in 1 patient, resolved in 4 and was new onset in 1. Regarding the urodynamic findings in patients

achieving urinary continence following puberty, total cystometric bladder capacity increased significantly and maximum detrusor pressure and detrusor leak point pressure showed insignificant changes. Conservative treatment is thus a viable option for some myelomeningocoele patients, and with current treatment modalities including IC, significant upper tract deterioration is rare after puberty.

In the past, much attention has been directed at the significance of dyssynergia between the external sphincter and the bladder, and the associated deterioration of the upper renal tracts in these patients. With the increasing use of IC, more emphasis has been placed on the pressure the bladder is able to generate prior to leaking as a prognostic factor in predicting upper tract deterioration.

Urodynamics is the cornerstone in the diagnosis of vesicourethral dysfunction in myelomeningocele. Urodynamic findings may predict the patients at risk of upper tract deterioration. Controversy continues as when to initiate these studies, either as soon as possible after back closure, at the first sign of upper tract changes, or before considering management of incontinence. Studies supporting each position have been reported, although the preponderence of evidence suggests earlier diagnosis of potentially unfavourable factors is advisable.Taskinen et al. [4] examined 30 patients with anorectal anomalies. All patients underwent spinal magnetic resonance imaging and urodynamic investigation. Major lumbosacral abnormalities were detected in 57% of patients, including 13, 4 and 3 with a tethered cord, syringomyelia and caudal regression, respectively. Significant dysfunction of the LUT in 57% of the cases involved DO in 11, DSD in 4, distended bladder in 4 and lazy bladder in 1. When the spinal cord was normal, 54% of the patients had abnormal urodynamic findings but when the spinal cord was abnormal, 59% had abnormal urodynamics. When the bony spine was normal, 33% of the patients had an abnormal spinal cord but when the bony spine was abnormal, 69% had an abnormal spinal cord (LOE3).

As hydronephrosis and vesico-ureteric reflux are a consequence of detrusor dysfunction, synchronous fluoroscopic evaluation of the urinary tract is advisable at the time of urodynamics. Similarly, renal ultrasound has become an invaluable routine serial evaluation in these patients, assessing renal growth, development of scarring and, most importantly, hydroureteronephrosis. Repeat urodynamics and ultrasound may have a role in this patient population, however recommendations for timing and frequency of these studies still need to be elucidated. Although renal scans are routinely used, especially in the myelomeningocele patient with hydronephrosis, the exact role of this study in these patients is not clear.

Urologic treatment depends on the age of the patient and the nature of the vesico urethral dysfunction as characterized by urodynamics. In a retrospective study, urinary sepsis accounted for the majority of admissions (62%), while 38 of 62 patients required 60 surgical procedures [5]. Targeting the primary urological abnormality (the dysfunctional and usually poorly compliant bladder) allowed implementation of effective treatments, including regular IC (52%) in order to preserve upper renal tract function. Associated postural abnormalities complicated both conservative and interventional therapies.

The mainstay of treatment is IC and antimuscarinic medication. As continence is not at issue in the neonate and infant, treatment may be postponed, unless upper tract changes are present. Some evidence exists pointing to the fact that early initiation of treatment may prevent subsequent deleterious bladder changes. Recently botulinum toxin was suggested as a possibility to avoid invasive surgery in these patients [6].

In adult patients who in childhood underwent bladder augmentation surgery, it is thought that there is an increased risk of a developement of bladder malignacies. This assumption is made on case reports only. However a detailed analysis comparing control group with patients after ileal/colonic cystoplasty revealed that there was no difference ($p=0.54$) in the incidence of bladder cancer in patients with augmentation cystoplasty vs controls [1] (LOE 2). Screening for bladder malignacies in a myelomeningocele group of patients with augmented bladder was not shown to be cost effective [2] (LOE2). Bruschini et al. evaluated 104 patients who were not managed and followed-up adequately during their childhood [7] (LOE 3). Reflux and urinary tract damage were found in 30 patients, and 6 patients presented signs of upper tract damage without reflux. The cystometry showed DO in 48% of patients, poor compliance in 49% of patients, increased bladder capacity in 2% and normal cystometry in 1%. Detrusor leak point pressure over 40 cm H_2O was associated with upper urinary tract damage. Patients with a decrease of functional bladder capacity over 33% had more renal scars than their counterparts. Overall, 26 % of urological untreated myelomeningocele patients had kidney damage.

On the other hand, work by Olsson and colleagues, evaluated 175 Swedish myelomeningocele patients in adult age [8] (LOE 3). IC for bladder emptying was used by 85%, and 59% used enemas on a regular basis because of the neurogenic bowel dysfunction. Renal dysfunction was than seen only in 1.7% of the adolescents.

Lumbar to sacral nerve re-routing was suggested to be a viable alternative to restore voiding and bowel movement in spina bifida patients. Recently a study from North America demonstrated a 78 % sucess rate of this novel treatment modality [3] (LOE3). Another interesting treatment option is fetal surgery. However recent data from an observational study of

28 patients who underwent in utero surgical myelomeningocele clossure between 1997 and 2002 demonstrated that at a mean age of 9.6 years 23 used IC to manage the bladder, 24 required a bowel regimen to manage constipation and 6 underwent lower urinary tract reconstruction with enterocystoplasty and a catheterizable bladder channel. Videourodynamics performed in 14 patients at a mean age of 7.4 years revealed decreased bladder capacity in 71%, DO in 35% and increased detrusor pressure in 25% [4]. Management of incontinence and/or upper tract deterioration mirrors the treatment of neurologic bladder dysfunction. Variations in this algorithm include the use of vesicostomy in the younger child who has failed conservative measures and has evidence of deteriorating upper tracts. External sphincterotomy has no routine place in the management of these patients and the use of the appendico vesicostomy in continent LUT reconstruction (Mitrofanoff) has become very popular. Most studies on surgical management of the myelomeningocele bladder are descriptive (LOE 4) at best.

Data from adult and paediatric surveys show renal damage to be the single most prevalent cause of morbidity and mortality; even in children, 30-40% exhibit evidence of renal damage. Additional factors such as chronic infection and stone formation will then render the kidney more vulnerable to progressive loss of renal mass and subsequent chronic renal failure. Renal transplantation is now considered the optimal treatment for end-stage renal disease in all age groups. Although more prone to complications, recent data on patients with meningomyelocele or severely abnormal LUTs demonstrate good patient and graft outcomes [9](LOE 3).

Guidance for further research

Further clarification of the role of fetal surgery to repair the neural tube defect is required, especially in term of prevention of damage to the lower urinary tract. Similarly the role of early intervention, conservative or surgical, is required. The timing of surgical intervention needs further study as well as better quality of life assessments and risk/ benefit analyses of LUT reconstructive procedures. The development of a tissue-engineered substitute for cystoplasy and nerve re-routing is being studied. Finally, the fate of the adult myelomeningocele patient, especially those who have undergone reconstruction needs to be documented.

Conclusions:

- **Myelomenigocele is one of the commonest birth defects (LOE 1).**
- **Incidence is decreased by appropriately-timed folate ingestion during pregnancy (LOE 2).**
- **Most patients have bladder dysfunction which can lead to incontinence and / or upper tract deterioration (LOE 3).**
- **The majority will derive significant benefit from conservative measures (LOE 3).**

Recommendations

- **Regular surveillance with urodynamics and renal ultrasound is mandatory from infancy. However the exact timing is not defined. One must observe the general rules for neurogenic bladder (B).**
- **Early initiation of conservative measures (clean intermittent catheterization, antimuscarinic medication) generally provides protection of the upper urinary tract (B).**
- **The role of new treatment options, for example biotechnology and nerve surgery, needs to be evaluated (C).**
- **Extensive surgery is reserved for failed conservative treatment (B).**

2. BOWEL PROBLEMS

Using MEDLINE we identified English-language journal articles and reviews published from 2000 to April 2012, looking for the keywords myelomeningocele, fecal incontinence, management.

Voluntary control of defecation requires rectal sensation, peristalsis and adequate anorectal sphincter function. Neurological defects in patients with spinal lesions may affect one or more of these components resulting in different types of defecation disorders: fecal incontinence, chronic constipation or both. Incontinence is one of the major stigmas affecting patients born with myelomeningocele [10]. Bowel dysfunction occurs in most children with spinal cord impairment from disease or injury.

Although many different regimens have been used to manage this problem, none has had universal success. Behavioural modification and laxatives failed to achieve an acceptable result because of the persistence of soiling. A small dose of laxatives alone accomplished nothing while administering a large dose to an incontinent patient only resulted in profound embarrassment [11]. Biofeedback was introduced for use in children with intact rectal sensation, but recent trials have reported less encouraging results. “Digital disimpaction” is unpleasant to perform and only succeeds in emptying the distal rectal ampulla.

Bearing in mind that none of these patients can resist the push of peristalsis, the most effective therapy is complete emptying of the colon, since it takes at least 24–48 h to refill again. This can be achieved nowadays by two ways, (A) retrograde colonic enema (RCE) using a special ballon catheter or (B) an operative procedure which allows an antegrade continence enema (ACE). In neurological fecal incontinence, standard enemas are difficult if not impossible to administer, because there is inability to retain

the enema- which flows out involuntarily through the weak anus during its instillation. Therefore a catheter-based RCE system has been developed by industry, the application of which can easily be applied either by the parents or even by children over the age of 7–8 years. Not all children tolerate this procedure, as colonic peristalsis creates pains in some of them. However the reported results are good according to Eire et al. [12]. Shandling et al. [13] reported 100% success in using the enema continence catheter in the management of his patients with spina bifida. These authors regard the RCE as one of the best conservative methods of treatment for relieving fecal incontinence originating from myelomeningocele and other neurological problems.

The impact of ACE surgery in the management of patients with myelomeningocele was analysed by Lemelle et al. [10]. 47 patients were treated with ACE, of whom 41 still used the method at a mean time of 4.1± 1.9 years after the ACE operation. With ACE, faecal incontinence was significantly improved compared with conventional management and neither retrograde rectal enema nor digital extraction were required. In most cases, ACE was performed using the appendix or the caecum. Six patients (12.8%) stopped using the ACE for various reasons, from conduit problems due to stomal stenosis or catheterization difficulties, lack of motivation or "too long time to empty the enema". ACE stoma surgery was applied before, concomitantly or after urinary incontinence surgery in 5, 27 and 10 cases respectively. Enemas were performed at most three times a week, and tap water was used in the majority of patients. Mean volume for ACE was 1.2 L (range 0,25–3,0 L). Mean enema time for colonic washout with ACE was 50 ± 19 min (range 15–90 min), however mean washout duration for ACE tended to be shorter with implantation of the conduit on the left-segment of the colon.

Casale et al. [18] were unable to find any differences in the continence rate or stomal complications between total reconstruction (ACE and continent urine stoma) or staged reconstruction. However, because of shared pathology the authors believe that most patients benefit from intervention in the gastrointestal and the genitourinary tract. Therefore, a major advantage of total continence reconstruction is avoidance of the morbidity of a second major surgical procedure (LOE 3). Nevertheless, conventional treatment should be tested first, and the efficacy of RCE may be a predictor of the efficacy of ACE on bowel management. Moreover, percutaneous endoscopic insertion is fully reversible and does not present drawbacks potentially encountered with the catheterizable conduit [10]. Nevertheless, experience with the Malone procedure has proved that a suitable continent and catheterizable conduit can be obtained with an appropriate technique. In selected and motivated patients, and with the help of a specialist nurse providing close support in the postoperative period, surgical ACE procedure might be preferred according to the surgeon´s experience.

As no absolute indication has been defined for ACE, other criteria should be used to evaluate clinical outcome of bowel management, including health – related quality of life (HRQoL). The development of a disease-specific HRQoL measure for use with myelomeningocele has been proposed by Parkin et al. [20]. HRQoL assessment should be performed prospectively when ACE produce is planned and performed during pre and post-operative periods. According to Eire et al. [1998] ACE procedure and RCE can be the best options for achieving the best social integration. For wheelchair users and other selected patients, the ACE (being faster and easier) is better than the RCE, which needs some help in its use [12, 15].

Sacral neuromodulation has been described also in the therapy of these patients, but the persistence of continence control and tolerance of the patient need to be evaluated for a prolonged period of time. Sacral neuromodulation may only be successful in a small selected number of patients, in whom preserved anatomy of the sacral nerves permits placement of the electrodes on the sacral nerves [19].

Conclusions (LOE 3)

- **Neurologic bowel dysfunction and bowel problems, including fecal incontinence and constipation, are prevalent among myelomeningocele patients.**
- **Fecal incontinence and methods of bowel care affect the QoL and social activities of myelomeningocele patients.**
- **The main goal is to empty the colon as much as possible, to achieve continence during the subsequent 24–48 hours. This can be achieved by retrograde colonic enema using a special ballon catheter, or by an operative procedure which allows an antegrade continence enema (ACE).**

Recommendations B/C:

- **colorectal problems deserve more attention in the treatment of myelomeningocele patients**
- **Appropriate bowel programme / management should be properly designed for each person, after adequate counselling.**

XII. SYSTEMIC AND OTHER CONDITIONS

1. SYSTEMIC LUPUS ERYTHEMATOSIS

a) Urinary incontinence

Nervous system involvement occurs in about half of patients with systemic lupus erythematosis (SLE).

Neurological manifestations of systemic lupus erythematosis are subacute encephalo-myelopathy, subacute myelopathy (rarely) and chronic encephalomyelopathy. Seizures and psychiatric disorders are the most common manifestations; spinal cord lesions are uncommon. Symptoms of LUT dysfunction can occur, however data on prevalence are not available.

Sakakibara et al. (LOE 4) [1] published the findings of 6 women and 2 men, mean age 23 years, suffering from SLE for 2-25 years under immunosuppressant therapy. All 8 patients had urodynamic abnormalities: 5 had decreased urinary flow, 3 increased post-void residual urine, 2 increased maximum urethral closure pressure, 5 detrusor overactivity, and 5 impaired detrusor contractility. Detrusor-sphincter dyssynergia was found in 4 patients and abnormal motor behaviour of the external sphincter during EMG. They found DO more common in patients with brisk deep tendon reflexes (80%) than in those without (33%). Repeated studies during a follow-up period of between 2 months and 8 years showed deterioration in 3 patients including loss of bladder sensation, development of a low compliance bladder and decreased bladder capacity (LOE 4). A study by Duran-Barragan et al. demonstrated similar findings in their series of ten patients and they postulated that LUTD was predisposing the patients to recurrent UTIs [3] (LOE 4).

Yu et al. studied 152 women with SLE and found a significant relationship between central nervous system involvement and the adapted AUA index score. The most common urodynamic finding was a small cystometric bladder capacity (<150 ml; n = 7 patients), followed by a weak urinary flow rate (<12 ml/second; n = 6 patients). In 3 of 7 patients with small cystometric bladder capacities, imaging studies documented a contracted bladder with marked hydroureteronephrosis [2] (LOE 3)

Conclusions

- **Half of the patients with systemic lupus erythematosis show nervous system involvement. In 30%, subacute and chronic encephalomyelopathy may cause LUT dysfunction with variable patterns, including; reduced bladder capacity, detrusor overactivity, impaired detrusor contractility, pathologic voiding pattern and increased post-void residual urine (LOE 4).**

Recommendations

- **The dysfunction pattern may change over time, therefore urological follow-up is recommended (C).**
- **Urodynamic tests are necessary to define the underlying pathophysiology of the urinary symptoms (C).**
- **Patients with SLE and voiding dysfunctions should be managed expectantly, according to the urodynamic results (C).**

2. HERPES ZOSTER

Herpes zoster (shingles) results from reactivation of the dormant varicella-zoster virus (VZV) resulting in vesicular eruptions of the skin or mucous membranes. Two distinct syndromes due to genital varicella zoster infection, cystitis and urinary retention, have been described. Cystitis classically presents with dysuria, frequency and hematuria and cystoscopic verification of local inflammatory changes on the bladder mucosa should be performed for the diagnosis of herpetic cystitis [4] (LOE 3).

The overall incidence of LUT dysfunction is 4% [5], however involvement is reported as high as 28 % if cases of lumbosacral involvement are considered. According to Chen et al., voiding dysfunction following herpes zoster can be; 1. Cystitis-associated, whereby direct involvement of the bladder wall results in herpetic cystitis, 2. Neuritis-associated, due to retrograde spread of infection by the VZV from the dorsal root ganglia of the sacral segments, or 3. Myelitis-associated, caused by herpetic myelitis. Occasionally, patients with skin rash in the lumbar or even lower thoracic dermatomes may develop bladder dysfunction and this is thought to be due to spread of VZV to the sacral segments (LOE 3).

Two case reports describe urodynamics findings in herpes-zoster patients. Usually patients develop complete urinary retention, with or without overflow incontinence due to detrusor acontractility and lack of bladder sensation. Repeat urodynamic studies at week 10 after the onset of the disease demonstrated a return of the detrusor contraction, normalising after 14 weeks [6, 7] (LOE 4).

Herpes zoster-associated voiding dysfunction is a transient phenomenon and is not uncommon in patients with lumbosacral dermatome involvement. Treatment with IC or indwelling catheter placement is recommended in order to avoid secondary damage to the LUT due to chronic urinary retention or UTIs. The disease usually is of a benign clinical course, with recovery of bladder functions.

Conclusions

- **28 % of patients with Herpes zoster in the lumbosacral dermatomes show LUT dysfunction, with impaired voiding as the most common symptom (LOE 4).**
- **The most common symptom is overflow incontinence due to detrusor acontractility and lack of bladder sensation (LOE 4).**
- **Voiding dysfunction has a transient course and almost every patient will regain normal voiding within 3-4 months, or at the least achieve balanced bladder function (LOE 3).**

Recommendations

- **Till functional recovery takes place, urinary tract management with intermittent catheterisation or indwelling catheter is recommended ©.**

3. HIV

a) Urinary incontinence

HIV virus belongs to the family of retroviruses. This family of viruses is known for latency, persistent viremia, infection of the nervous system, and weak host immune responses. HIV has high affinity for CD4 T-lymphocytes and monocytes. HIV binds to CD4 cells and becomes internalized. The virus replicates itself by generating a DNA copy by reverse transcriptase. Viral DNA becomes incorporated into the host DNA, enabling further replication. HIV enters the nervous system early, at the time of initial infection, and may immediately cause symptoms, or it may cause delayed-onset symptoms, potentially at any time during the person's lifetime. All parts of the nervous system may be involved. Neurological disorders could be HIV-related, or due to secondary infections, malignancies, metabolic or nutritional problems and to therapy.

It is estimated that up to 80% of patients are symptomatic in terms of nervous system and for 30%, neurological symptoms are the initial clinical problem, in the absence of anti-retroviral treatment. Neurological syndromes may be the sole clinical problem or cause of death. The following brain symptoms have been described: meningitis, dementia, stroke, seizures, and degenerative disorders. For the spinal cord, transverse myelitis and progressive myelopathy have been observed.

Due to nervous system involvement in HIV infection, consequent effects on LUT function can be anticipated [8]. Shin et al. (LOE3) described a higher prevalence of incontinence in HIV-positive patients as compared to HIV-negative in nursing homes [9]. Whether this represents a true trend, or or an observation related to the terminal stage of the disease and associated comorbidities, remains to be elucidated. Gyrtrup et al. (LOE 3) found voiding problems in 12% of HIV-infected patients, mostly in advanced stages of the disease [10].

Virtually all parts of the body could by involved in AIDS patients, either as the primary location of HIV infection or secondary to HIV-related complications. Among the different manifestations, particular attention should be paid to the primary locations as they develop early in the stage of the disease. HIV can affect all areas of the central and peripheral nervous system- for example, HIV-associated dementia, vacuolar myelopathy, distal sensory peripheral neuropathy and myopathy. Pelvic organ dysfunction has, however, been little studied. Patients may develop voiding dysfunction and chronic retention due to lumbosacral polyradiculopathy. Prior to the introduction of the newer anti retroviral therapies in the 1990s, infection with cytomegalovirus was the most common cause [11] and other causes include lymphomatous infiltration, syphilis or a herpetic radiculopathy due to herpes varicella zoster or simplex. Mahieux et al. (LOE 3) described a case of acute myeloradiculitis due to cytomegalovirus as the initial manifestation of terminal stage HIV [12]. Matsumoto et al. (LOE 3) [13] reported a case of lumbosacral polyradiculopathy where voiding difficulties and lower limb paresis were the primary manifestation of HIV infection. Another pattern of LUT dysfunction is urgency incontinence and DSD [14] in the context of vacuolar myelopathy.

Begara et al. (LOE 3) performed urodynamic studies in 10 patients with AIDS and voiding disorders and found that the most common symptom was urgency incontinence and the most common urodynamic finding was DSD [15]. In 3 patients they found demonstrable functional disorders of the LUT (2 patients had DO: one of them had a history of encephalopathy from HIV and the other patient had polyneuritis; the third patient had myelitis and a urodynamically-diagnosed sympathetic decentralization. Detrusor areflexia was described in 2 HIV-positive patients by Menendez et al. [16] (LOE 3). One of them had an ascending myelitis of probable herpetic origin, the other had a cerebral abscess caused by Toxoplasma gondii.

Since during the course of the disease all parts of the nervous system can be involved, either as the primary location or secondary to AIDS-related complications, no disease specific diagnosis or treatment can be proposed. It is important to observe that sometimes functional disorders of the LUT can be the first manifestation of the HIV infection. When managing the patient with HIV infection one must bear in mind that both storage and voiding problems can occur and that both should be treated according to the results of urodynamic studies.

Future research needs to be supported by a stronger evidence base. All reports of HIV and voiding problems are rather anecdotal and no good prospective studies exist. The need for such studies is particularly important, when realizing that it takes up to 20-30 years from HIV infection to AIDS full manifestation, and that new antiviral treatment modalities could prolong the life of a patient with HIV significantly. Particular attention should be paid to primary nervous system involvement by HIV and the voiding dysfunctions that could be the side effects of HIV drug therapy.

b) Faecal incontinence

As diarrhoea is common in HIV infected patients, faecal incontinence can also occur, mostly due to anal sphincter weakness. The true incidence of HIV neuropathy-related faecal incontinence is not known and further studies are needed [17] (LOE 4). Many of the limitations of knowledge seen with urinary incontinence apply to faecal incontinence.

Conclusions:

- **HIV can influence the nervous system and LUT function in two ways: as a result of primary**

infection, or secondary to AIDS-related complications (LOE2/3).

- **Nervous system manifestation of HIV infection can by the only sign of infection, and it is therefore important to take the possibility of HIV infection into consideration when facing unusual signs and symptoms from the LUT without any other obvious cause (LOE 3).**
- **HIV/AIDS is a progressive disease and dynamic changes to the LUT functions can occur during the evolution of the disease (LOE 2).**
- **Faecal incontinence in HIV/AIDS patients is usually associated with diarrhoea, however the true incidence is not known (LOE 4).**

Recommendations:

- **Patients with HIV and nervous system pathological signs and symptoms should be evaluated for functional LUT problems (B).**
- **Due to the variety of LUT functional damage in HIV patients, dynamic evaluation of LUT function is essential for tailoring of therapy (C).**
- **No HIV-specific therapy of LUT problems and faecal incontinence is currently available. Due to the variety of functional damage, therapy should be individually tailored, according to the results of functional/ imaging studies (C).**

4. NEUROSYPHILIS

Neurosyphilis results from longstanding infection with Treponema pallidum. Bladder dysfunction is common, though most classically in tabes dorsalis. The predominant neurological manifestations are sensory ataxia and spontaneous lancinating pains. Voiding dysfunction occurs due to involvement of sacral posterior roots and the dorsal column of the spinal cord, resulting in loss of bladder sensation and significantly elevated post-void residual urine. The bladder is atonic, though there may be some myogenic damage from chronic over distention. Some patients may demonstrate detrusor overactivity and DSD [18, 19]. The condition is rare and there is no contemporaneous epidemiological data.

5. DIABETES MELLITUS

a) Urinary incontinence

Diabetes is one of the commonest causes of polyneuropathy. Amongst different types of polyneuropathies in diabetic patients “diabetic cystopathy” occurs in 43% to 87% of insulin-dependent diabetics, with no sex or age differences. It is also described in about 25% of diabetic patients on oral hypoglycemic treatment. A Scandinavian study showed that in patients who have had diabetes for 10 years, the prevalence of diabetic cystopathy in those who were insulin-dependent was 2 to 4 per 1000 and in those on oral hypoglycemic agents was 1 to 3 per 1000. The correlation between diabetic cystopathy and peripheral neuropathy ranged from 75% to 100%. Nephropathy was seen in 30% to 40% of cases [20] (LOE 3)

Diabetes duration, treatment type, peripheral neuropathy, and retinopathy were significantly associated with severe incontinence in multiple regression models adjusted for age, education, and history of UTI [21] (LOE 3). Lewis et al. in a cross-sectional studies of 50-90 year old women found that insulin dependent diabetes was strongly associated with urinary incontinence, while non insulin dependent diabetes was not [22] (LOE 2).

Van Poppel et al. [23] reported neuropathological examination of bladder biopsies from 14 patients with severe insulin-dependent adult-onset diabetes, compared with acetylcholinesterase and S100 staining of 38 control specimens. A decrease in acetylcholinesterase activity, due to axonal degeneration was found in all cases. An increase in S100 positivity was found in the majority and is due to Schwann cell proliferation as a regeneration attempt after demyelination or axonal degeneration. When acetylcholinesterase activity decreases and an S100 density increase is found in a patient with diabetes, this combination is highly suggestive of diabetic cystopathy amenable to early symptomatic treatment (LOE 2). Because of the uncontrolled hyperglycemia, patients with DM develop altered NGF activity, which may be a mechanistic factor in the development of diabetic bladder dysfunction [24, 25].

Since the peripheral nerves are involved, the clinical manifestations of diabetic cystopathy might be very different. Usually there is reduced sensation of bladder fullness, and decreased frequency of voiding. This is followed by slowing of the urinary stream and difficulty in voiding due to impaired detrusor contraction. Post-voiding dribbling may also occur. The impaired bladder emptying and urinary retention predispose to urinary tract infections. No prospective studies referring specifically to the problem of functional disturbances of the LUT in diabetic patients have been reported. It has been shown that urine output does not contribute significantly to diabetic cystopathy [26].

Yamaguchi et al. studied 84 diabetic cystopathy patients [27]. In addition to large post-void residual and decreased sensation, urinary urgency, DO, and increased bladder sensation were seen in 55%, 42% and 14%, respectively. The prevalence of DO in patients with increased bladder sensation was 58%. DO increased with age, but not with the duration of diabetes. A brain MRI was performed in 32 cases. The prevalence of multiple cerebral infarction in patients with DO was 76.5%. The authors concluded that urinary urgency is not uncommon in diabetic cystopathy. Both central and peripheral mechanisms are involved [28] (LOE 3).

Ishigooka et al. [29] (LOE 3) described the results of the ice-water test in diabetic patients with and without

cystopathy. 12.5% of patients without cystopathy and 25% of patients with cystopathy did not feel the ice water sensation. Ueda et al. [30] (LOE 2) performed studies evaluating sympathetic skin response in correlation with cystometry. They found that patients without sympathetic skin responses had increased residual urine and decreased detrusor contraction pressure, while patients with a lower amplitude of sympathetic skin response and more prolonged latency than controls had a significant decrease in detrusor contraction pressure. The changes within the bladder function were observed as early as within one year from the diagnosis of diabetes.

Beylot et al. [31], (LOE 2) found that the presence of residual urine in diabetic patients, after exclusion of co morbidities, was strongly associated with peripheral neuropathy. Ho et al. showed increased bladder sensation, followed by DO in 94 female diabetic patients undergoing urodynamic studies [32]. Those patients with OAB are more likely to have impaired voiding function.

No specific treatment has been described in regards to the population of patients with diabetic cystopathy. Therefore general rules as for the other bladder conditions with impaired (absent) detrusor contractions should be followed. Sacral Neuromodulation has been used to treat LUTD in DM, with similar long term results as in non DM patients [33].

Future research should endeavour to give epidemiological information on the incidence of diabetes-related functional disorders of micturition, and specific results of therapeutic interventions.

Conclusions:

- **Diabetic cystopathy occurs in up to 80% of insulin dependent diabetes mellitus (LOE3).**
- **Urinary incontinence is strongly associated with insulin dependent diabetes, but not with insulin independent diabetes (LOE 2).**
- **Overactive bladder is not uncommon in diabetes, presumably reflecting both central and peripheral mechanisms (LOE 3).**
- **Patients with diabetic cystopathy generally can have OAB and/ or impaired detrusor contractions with increased post-void residual (LOE 3,4).**
- **Recurrent urinary tract infections might be a long term problem (LOE 3,4).**
- **There is a lack of specific treatment for diabetic cystopathy.**

Recommendations:

- **Post void residual measurement and urine dipstick (optional culture) for patients with insulin dependent diabetes mellitus should be performed yearly (C).**
- **In case of increased post-void residual, prompted voiding might be useful (C/D).**
- **Treatment of choice for acontractile bladder in this group remains intermittent catheterization (B/C).**

b) Faecal Incontinence

Caruana et al. [34] (LOE 3) found that diabetic patients with faecal incontinence showed increased thresholds of phasic external sphincter contraction ($P<0.05$) and had reduced resting/ maximal voluntary anal sphincter pressures compared with controls ($P< 0.05$). Increased thresholds of conscious rectal sensation in some incontinent patients with diabetes may contribute to faecal incontinence by impairing the recognition of impending defecation. Nakayama et al. [35] (LOE 3) found that age and diabetes have an independent negative influence on faecal incontinence after stroke. Abnormal internal-anal-sphincter function could be contributory in diabetic patients with faecal incontinence [36] (LOE 3). Russo found that acute hyperglycaemia inhibits external anal sphincter function and decreases rectal compliance, which could explain the aetiopathogenesis of faecal incontinence [37] (LOE 3).

Talley [38] (LOE 3) studied gastro-intestinal symptoms, frequent abdominal pain, bowel-related abdominal pain, reflux, dyspepsia, constipation, diarrhea and fecal incontinence in diabetic patients. There was a clinically significant decrease in QoL scores in diabetics compared with population norms across all subscales. The impact on QoL in diabetes was predominantly observed in type 2 diabetics. For all the Short Form-36 subscales, GI symptom groups were significantly (all $p < 0.0001$) associated with poorer QoL in diabetes, independent of age, gender, smoking, alcohol use, and type of diabetes.

Conclusions

- **Faecal incontinence in diabetes patients may be due to impaired anorectal sensation and/or decreased anal closing pressure after hyperglycemic episodes (LOE 3).**
- **Gastro-intestinal symptoms impact negatively on health-related QoL in diabetes mellitus (LOE 3).**

Recommendations:

- **Patients with diabetes and fecal incontinence should have anorectal manometry performed before introducing therapy for fecal incontinence (C/D).**
- **More studies on neurologic bowel dysfunction and management in diabetes are needed before giving further recommendation (B).**

LIST OF ABBREVIATIONS

Most abbreviations used in the text are given here. Others may be given within the front of the section in which they are used

ACh	acetylcholine
AChE	acethylcholinesterase
AD	autonomic dysreflexia
ADL	activities of daily living
ALD	Alzheimer's disease
AS	anal sphincter
AUS	artificial urethral sphincter
BBB	Blood-brain barrier
BCR	bulbocavernosus reflex
BST:	bethanechol supersensitivity test
CC	cystometric capacity
CIC	clean intermittent catheterization
CMG	cystometrogram
CPG	clinical practice guideline
CPT	current perception threshold
CT	computer tomography
CTT	colonic transit time
CUM	continuous urodynamic monitoring
CVA	cerebro-vascular accident
CVC	conventional cystometry
DI	double incontinence
DLB	dementia with Lewy bodies
DOA	detrusor overactivity
DRS	digital rectal stimulation
DSD	detrusor sphincter dyssynergia
ES	electrical stimulation
EAS	external anal sphincter
EMG	electromyography
EPT	electric perception threshold
FI	faecal incontinence
FTD	fronto-temporal dementia
GBS	Guillain-Barre Syndrome
ID	indwelling catheter
IC	intermittent catheterization
IVES	intravesical electrical stimulation
IWT	ice water test
LGIT	lower gastrointestinal tract
LMNL	lower motor neuron lesion
LOE	level of evidence
LS	lumbosacral
LUT	lower urinary tract
LUTD	lower urinary tract dysfunction
LUTS	lower urinary tract symptoms
Pdet max	maximum detrusor pressure
MMC	meningomyelocoele
MUP	motor unit potential
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSA	multiple system atrophy
NBo	neurogenic bowel
NBoD	neurogenic bowel dysfunction
NDO	neurogenic detrusor overactivity
NLUTD	neurological lower urinary tract dysfunction
NUI	neurogenic urinary incontinence
NFC	natural fill cystometry
OR	odds ratio
PD	Parkinson's disease
PF	pelvic floor
PFD	pelvic floor dysfunction
PSP	progressive supranuclear palsy
Psym	parasympathetic
PVR	post void residual
QoL	quality of life
RCT	randomised controlled trial
SARS	sacral anterior root stimulation
SCI	spinal cord injury
SCL	spinal cord lesion
SDAF	sacral deafferentation
SIC	sterile intermittent catheterization
SLE	systemic lupus erythematosis
SNS	sacral nerve stimulation
SOM	somatic
SPC	suprapubic catheter
SSEP	somatosensory evoked potentials
SSR	sympathetic skin response
SUI	stress urinary incontinence
Sym	sympathetic
TBI	traumatic brain injury
TRI	transrectal irrigation
TURS	transurethral sphincterotomy
UFM	uroflowmetry
UI	urinary incontinence
UMN	upper motor neuron
US	urethral sphincter
U/S	ultrasound
UTI	urinary tract infection
UUT	upper urinary tract
VCUG	voiding cystourethrogram
VSD	vesicosphincteric disorders
VUR	vesicoureteric reflux
WBC	white blood cells

REFERENCES

A. Introduction

1. Nievelstein RA, van der Werff JF, Verbeek FJ, Valk J, Vermeij-Keers C. Normal and abnormal embryonic development of the anorectum in human embryos. Teratology. 1998 Feb: 57:70-8
2. Birder L, de Groat W, Mills I, Morrison J, Thor K, Drake M. Neural control of the lower urinary tract: peripheral and spinal mechanisms. Neurourol Urodyn. 2010: 29:128-39
3. Drake MJ, Fowler CJ, Griffiths D, Mayer E, Paton JF, Birder L. Neural control of the lower urinary and gastrointestinal tracts: supraspinal CNS mechanisms. Neurourol Urodyn. 2010: 29:119-27
4. Furness JB. The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol. 2012 Mar 6:
5. Shafik A. The effect of vesical filling and voiding on the anorectal function with evidence of a 'vesico-anorectal reflex'. Neurogastroenterol Motil. 1999 Apr: 11:119-24
6. De Wachter S, de Jong A, Van Dyck J, Wyndaele JJ. Interaction of filling related sensation between anorectum and lower urinary tract and its impact on the sequence of their evacuation. A study in healthy volunteers. Neurourol Urodyn. 2007: 26:481-5
7. De Wachter S, Wyndaele JJ. Impact of rectal distention on the results of evaluations of lower urinary tract sensation. J Urol. 2003 Apr: 169:1392-4
8. Malykhina AP. Neural mechanisms of pelvic organ cross-sensitization. Neuroscience. 2007 Nov 9: 149:660-72
9. NICE. Guideline on Management of incontinence in neurological disease: Introduction (in press). To be available 2012 at http://wwwniceorguk. 2012:
10. Donovan WH. Donald Munro Lecture. Spinal cord injury--past, present, and future. J Spinal Cord Med. 2007: 30:85-100
11. Drake MJ. Re: Influences on renal function in chronic spinal cord injured patients. J Urol. 2001 Jun: 165:2006
12. Drake MJ, Cortina-Borja M, Savic G, Charlifue SW, Gardner BP. Prospective evaluation of urological effects of aging in chronic spinal cord injury by method of bladder management. Neurourol Urodyn. 2005: 24:111-6
13. Fowler CJ, Panicker JN, Drake M, et al. A UK consensus on the management of the bladder in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2009 May: 80:470-7
14. Stohrer M, Blok B, Castro-Diaz D, et al. EAU guidelines on neurogenic lower urinary tract dysfunction. Eur Urol. 2009 Jul: 56:81-8
15. Abrams P, Amarenco G, Bakke A, et al. Tamsulosin: efficacy and safety in patients with neurogenic lower urinary tract dysfunction due to suprasacral spinal cord injury. J Urol. 2003 Oct: 170:1242-51
16. Cruz F, Herschorn S, Heesakkers J, et al. Efficacy and safety of onabotulinumtoxin A in patients with urinary incontinence due to neurogenic detrusor overactivity. Eur Urol Suppl. 2011: 10(2):190 (abstract 579)

B. Pathophysiology

1. Siroky MB, Krane RJ. Neurologic aspects of detrusor-sphincter dyssynergia, with reference to the guarding reflex. J Urol. 1982; 127: 953-7
2. Brocklehurst JC, Andrews K, Richards B, Laycock PJ. Incidence and correlates of incontinence in stroke patients. J Am Geriatr Soc. 1985; 33:540-2
3. Renier WO, Gabreels FJ. Evaluation of diagnosis and non-surgical therapy in 24 children with a pontine tumour. Neuropediatrics 1980; 11: 262-73.
4. Yaguchi H, Soma H, Miyazaki Y, Tashiro J, Yabe I, Kikuchi S, et al. A case of acute urinary retention caused by periaqueductal grey lesion. J Neurol Neurosurg Psychiatry 2004; 75(8):1202-3.
5. Manente G, Melchionda D, Uncini A. Urinary retention in bilateral pontine tumour: evidence for a pontine micturition centre in humans. J Neurol Neurosurg Psychiatry 1996; 61(5):528-9.
6. Komiyama A, Kubota A, Hidai H. Urinary retention associated with a unilateral lesion in the dorsolateral tegmentum of the rostral pons. J Neurol Neurosurg Psychiatry 1998; 65(6):953-4.
7. Sakakibara R, Hattori T, Fukutake T, Mori M, Yamanishi T, Yasuda K. Micturitional disturbance in herpetic brainstem encephalitis; contribution of the pontine micturition centre. J Neurol Neurosurg Psychiatry 1998; 64(2):269-72.
8. Sakakibara R, Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance and the pontine tegmental lesion: urodynamic and MRI analyses of vascular cases. J Neurol Sci 1996; 141(1-2):105-10.
9. Sakakibara R, Fowler C, Hattori T. Cortical and Subcortical Disorders. In: Fowler CJ, Panicker JN, Emmanuel A, editors. Pelvic Organ Dysfunction in Neurological Disease. Cambridge: Cambridge University Press, 2010:167-8.
10. Khastgir J, Drake MJ, Abrams P. Recognition and effective management of autonomic dysreflexia in spinal cord injuries. Expert Opin Pharmacother. 2007 May: **8**:945-56.
11. Habler HJ, Janig W, Koltzenburg M. Activation of unmyelinated afferent fibres by mechanical stimuli and inflammation of the urinary bladder in the cat. J Physiol. 1990; 425: 545-62.

C. Neurological urinary incontinence

CI. Epidemiology

1. Andrew J, Nathan PW. Lesions of the anterior frontal lobes and disturbances of micturition and defecation. Brain 1964; 87: 233-262.
2. Maurice-Williams, R. S.: Micturition symptoms in frontal tumours. J Neurol Neurosurg Psychiatry. 1974; 37: 431-436
3. Lang, E. W., Chesnut, R. M., Hennerici, M.: Urinary retention and space-occupying lesions of the frontal cortex. Eur Neurol. 1996;36:43-47
4. Fayeye O, Sankaran V, Sherlala K, Choksey M.: Pligodendrioma presenting with intradural spinal metastases: an unusual case of cauda equina syndrome. Journal of Clinical Neuroscience 2010; 17: 265-267
5. Ueki K. Disturbances of micturition observed in some patients with brain tumor. Neurol Med Chir 1960; 2: 25-33.
6. Renier WO, Gabreels FJ. Evaluation of diagnosis and non-surgical therapy in 24 children with a pontine tumour. Neuropediatrics 1980; 11: 262-73.
7. Toba K, Ouchi Y, Orimo H, Iimura O, Sasaki H, Nakamura Y, Takasaki M, Kuzuya F, Sekimoto H, Yoshioka H, Ogiwara T, Kimura I, Ozawa T, Fujishima M.. Urinary incontinence in elderly inpatients in Japan: a comparison between general and geriatric hospitals. Aging (Milano) 1996; 81:47-54.
8. Campbell AJ, Reinken J, McCosh L. Incontinence in the elderly: prevalence and prognosis. Age Ageing 1985; 142:65-70.
9. Horimoto Y, Matsumoto M, Akatsu H, Ikari H, Kojima

K, Yamamoto T, Otsuka Y, Ojika K, Ueda R, Kosaka K. Autonomic dysfunctions in dementia with Lewy bodies. J Neurol 2003; 250(5):530-533.

10. Sugiyama T, Hashimoto K, Kiwamoto H, Ohnishi N, Esa A, Park YC, Kurita T. Urinary incontinence in senile dementia of the Alzheimer type (SDAT). Int J Urol 1994;1:337-340.
11. McGrother C, Resnick M, Yalla SV, Kirschner-Hermanns R, Broseta E, Muller C, Welz-Barth A, Fischer GC, Mattelaer J, McGuire EJ. Epidemiology and etiology of urinary incontinence in the elderly. World J Urol 1998;16 (Suppl 1):S3-S9.
12. Madersbacher H, Awad S, Fall M, Janknegt RA, Stohrer M, Weisner B. Urge incontinence in the elderly-supraspinal reflex incontinence. World J Urol 1998;16 (Suppl 1):S35-S43.
13. Olsen CG, Clasen ME. Senile dementia of the Binswanger's type. Am Fam Physician 1998;58:2068-2074.
14. Ransmayr GN, Holliger S, Sclletterer K, Heldler H, Deible M, Poewe W, Madersbacher H, Kiss G. Lower urinary tract symptoms in dementia with Lewy bodies, Parkinson disease, and Alzheimer disease. Neurology 2008; 70: 299-303.
15. Honig LS, Mayeux R. Natural history of Alzheimer's disease. Aging (Milano) 2001;13:171-182.
16. Cacabelos R, Rodríguez B, Carrera C, Caamaño J, Beyer K, Lao JI, Sellers MA . APOE-related frequency of cognitive and noncognitive symptoms in dementia. Methods Find Exp Clin Pharmacol 1996; 18(10):693-706.
17. Leung KS, Ng MF, Pang FC, Au SY. Urinary incontinence: an ignored problem in elderly patients. Hong Kong Med J 1997; 31:27-33.
18. Mitchell S J, Woodthorpe, J. Young mentally handicapped adults in three London boroughs: prevalence and degree of disability. J Epidemiol Community Health 1981; 35(1):59-64.).
19. Reid A H, Ballinger B R, Heather B B. Behavioural syndromes identified by cluster analysis in a sample of 100 severely and profoundly retarded adults. Psychol Med. 1978; 8:399-412.
20. Yang PY, Meng NH, Chou EC. Voiding dysfunction in children with mental retardation. Neurourol Urodyn 2010; 29: 1272-1275.
21. de Waal KH, Tinselboer BM, Evenhuls HM, Penning C. Unnoticed post-void residual urine volume in people with moderate to severe intellectual disabilities: prevalence and risk factors. J Intellectual Disability Research 2009; 53: 772-779.
22. McNeal DM, Hawtrey CE, Wolraich ML, Mapel JR.. Symptomatic neurologic bladder in a cerebral-palsied population. Dev Med Child Neurol. 1983 ; 25:612-616
23. Decter RM, Bauer SB, Khoshbin S, Dyro FM, Krarup C, Colodny AH, Retik AB. Urodynamic assessment of children with cerebral palsy. J Urol. 1987; 138:1110-1112.
24. Richardson I Palmer LS Clinical and urodynamic spectrum of bladder function in cerebral palsy. J Urology 2009; 182: 1945-1948.
25. Jonas S, Brown J. Neurologic bladder in normal pressure hydrocephalus. Urology. 1975; 5: 44-50
26. Black P M. Idiopathic normal-pressure hydrocephalus. Results of shunting in 62 patients. J Neurosurg. 1980; 52: 371-377
27. Mulrow CD, Feussner JR, Williams BC, Vokaty KA. The value of clinical findings in the detection of normal pressure hydrocephalus. J Gerontol. 1987; 42: 277-279.
28. Sakakibara R, Kanda T, Sekido T, Uchiyama T, Awa Y, Ito T, Yamamoto T, Yamanshi T, Yuasa T, Shirai K, Hattoir T. Mechanism of bladder dysfunction in idiopathic normal pressure hydrocephalus. Neurourol Urodyn 2008; 27: 507-510.
29. Murnaghan GF. Neurogenic disorders of the bladder in Parkinsonism. Br J Urol 1961;33:403-409
30. Campos-Sousa RN, Quagliato E, da Silva BB, de Carvalho RM Jr, Ribeiro SC, de Carvalho DFl Urinary symptoms in Parkinson's disease: prevalence and associated factors. Arq Neuropsiquiatr. 2003; 61: 359-363 .
31. Salinas JM, Berger Y, De La Rocha RE, Blaivas JG. Urological evaluation in the Shy Drager syndrome. J Urol 1986;135:741-743.
32. Saymour ZM, Gomes CM, Barbosa ER, Lopes RI, Sallem FS, Trigo-Tocha FE, Bruschini H, Srougl M. Voiding dysfunction in patients with Parkinson's disease: impact of neurological impairment and clinical parameters. Neurourol Urodyn 2009; 28: 510-515.
33. Chandiramani VA, Palace J, Fowler CJ. How to recognize patients with parkinsonism who should not have urological surgery. Br J Urol. 1997 ; 80: 100-104
34. Hattori T, Yasuda K, Kita K, Hirayama K. Voiding dysfunction in Parkinson's disease. Jpn J Psychiatry Neurol 1992; 46: 181-186.
35. Gray R, Stern G, Malone-Lee J. Lower urinary tract dysfunction in Parkinson's disease: changes relate to age and not disease. Age Ageing 1995; 24: 499-504.
36. Araki I, Kuno S. Assessment of voiding dysfunction in Parkinson's disease by the international prostate symptom score. J Neurol Neurosurg Psychiatry 2000; 68: 429-433.
37. Lemack GE, Dewey RB, Roehrborn CG, O'Suilleabhain PE, Zimmern PE. Questionnaire-based assessment of bladder dysfunction in patients with mild to moderate Parkinson's disease. Urology 2000; 56: 250-254.
38. Sakakibara R, Shinotoh H, Uchiyama T, Sakuma M, Kashiwado M, Yoshiyama M, Hattori T. Questionnaire-based assessment of pelvic organ dysfunction in Parkinson's disease. Auton Neurosci 2001; 92: 76-85.
39. Bloch FJ, Pichon B, Bonnet AM, Pichon J, Vidailget M, Roze E, Perrigot M. Urodynamic analysis in multiple system atrophy: characterisation of detrusor sphincter dyssynergia. Neurology 2010; 257: 1986-1991.
40. Currie CT. Urinary incontinence after stroke. Br Med J 1986;293:1322-1323.
41. Codine PH, Pellissier J, Manderscheidt JC, Costa P, Enjalbert M, Perrigot M. Les troubles urinaires au cours des hémiplegies vasculaires. In: Pellisier J ed Hémiplegie vasculaire et médicine de rééducation. Paris: Masson, 1988, pp. 261-269.
42. Barer DH. Continence after stroke: useful predictor or goal of therapy? Age Ageing 1989;18:183-191.
43. Sakakibara R, Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance after acute hemispheric stroke: analysis of the lesion site by CT and MRI. J Neurol Sci 1996c; 137: 47-56.
44. Nakayama H, Jørgensen HS, Pedersen PM, Raaschou HO, Olsen TS. Prevalence and risk factors of incontinence after stroke: The Copenhagen Stroke Study. Stroke. 1997 Jan;28(1):58-62.
45. Khan Z, Hertanu J., Yang WC, Melman A, Leiter E. Predictive correlation of urodynamic dysfunction and brain injury after cerebrovascular accident. J Urol 1981; 126: 86-8.
46. Tsuchida S, Noto H, Yamaguchi O, Itoh M. Urodynamic studies on hemiplegic patients after cerebrovascular accident. Urology 1983; 21: 315-8.
47. Kuroiwa Y, Tohgi H, Ono S, Itoh M. Frequency and urgency of micturition in hemiplegic patients; relationship to hemisphere laterality of lesions. J Neurol 1987; 234: 100-102.

48. Khan Z, Starer P, Yang WC, Bhola A. Analysis of voiding disorders in patients with cerebrovascular accidents. Urology 1990; 35: 263-270

49. Taub NA, Wolfe CD, Richardson E, Burney PG. Predicting the disability of first-time stroke sufferers at 1 year. 12-month follow-up of a population-based cohort in southeast England. Stroke 1994; 25: 352-357.

50. Borrie MJ, Campbell AJ, Caradoc-Davies TH, Spears GF.. Urinary incontinence after stroke: a prospective study. Age Ageing 1986; 15: 177-181

51. Sakakibara R., Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance and the pontine tegmental lesion: urodynamic and MRI analyses of vascular cases. J Neurol Sci 1996; 141: 105-110.

52. Kim TG, Yoo KH, Jeon SH, Lee HL, Chang SG. Effect of dominant hemispheric stroke on detrusor function in patients with lower urinary tract symptoms. Int J Urology 2010; 17: 656-660, 2010.

53. Giannantoni A, Slivestro D, Siracusano S, Azicnuda E, D'Ippolito M, Rigon J, Sabatini U, Bini V, Formisan R. Urologic dysfunction and neurologic outcome in coma survivors after severe traumatic brain injury in the postacute and chronic phase. Arch Phys Med Rehab. 2011; 92: 1134-1138.

54. Litwiller S E, Frohman E M, Zimmern P E.: Multiple sclerosis and the urologist. J Urol. 1999 Mar;161(3):743-57.

55. Giannantoni A, Scivoletto G, Di Stasi SM, Grasso MG, Finazzi Agrò E, Collura G, Vespasiani G. LUT dysfunction and disability status in patients with multiple sclerosis. Arch Phys Med Rehabil 1999; 80: 437-441.

56. Hinson JL, Boone TB. Urodynamics and multiple sclerosis. Urol Clin North Am. 1996; 23: 475-481.

57. DasGupta R, Fowler C.J.: Sexual and urological dysfunction in multiple sclerosis: a better understanding and improved therapies. Cur Opin Neurol 2002, 15: 271-278

58. De Seze M, Ruffion A, Denys P, Jospeh PA, Perrouin-Verbe G. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. Multip Scler 2007; 13: 915-928.

59. Onal B, Siva A, Buldu I, Demirkesen O, Centinel B. Voiding dysfunction due to multiple sclerosis: a large scale retrospective analysis. Int Braz Urol 2009; 35: 326-333.

60. Bemelmans BL, Hommes OR, Van Kerrebroeck PE, Lemmens WA, Doesburg WH, Debruyne FM. Evidence for early LUT dysfunction in clinically silent multiple sclerosis J Urol 1991; 145: 1219-1224.

61. Lemack GE, Hawker K, Frohmman E. Incidence of upper tract abnormalities in patients with neurovesical dysfunction secondary to multiple sclerosis: analysis of risk factors at initial urologic evaluation. Urology 2005; 65: 854-857.

62. Lemack GE, Frohman E, Ramnarayan P. Women with voiding dysfunction secondary to bladder outlet dyssynergia in the setting of multiple sclerosis don not demonstrate significantly elevated intravesical pressures. Urology 2007; 69: 893-897.

63. Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey? Spinal Cord. 2006 Sep;44(9):523-529.

64. Jeong SJ, Cho SY, Oh SJ. Spinal cord/brain injury and neurogenic bladder. Urol Clin NA 2010; 37: 537-546.

65. McGuire EJ. Urodynamics of the neurogenic bladder. Urol Clin NA. 2010; 37: 537-546.

66. Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. A UK general practice database study of prevalence and mortality of people with neural tube defects. Clin Rehabil 2000;14:627-630.

67. Selzman AA, Elder JS, Mapstone TB. Urologic consequences of myelodysplasia and other congenital abnormalities of the spinal cord. Urol Clin North Am 1993;20:485-504.

68. Smith, E.: Spina Bifida and the total care of spinal myelomeningocoele. Springfield, IL: CC Thomas, pp. 92-123.

69. van Gool JD, Dik P, de Jong TP. Bladder-sphincter dysfunction in myelomeningocele. Eur J Pediatr 2001;160:414-420.

70. Wyndaele JJ, De Sy W. Correlation between the findings of a clinical neurological examination and the urodynamic dysfunction in children with myelodysplasia. J Urol. 1985 Apr;133(4):638-640

71. Bartolin Z, Gilja I, Bedalov G, Savic I. 1998. Bladder function in patients with lumbar intervertebral disc protrusion. J Urol 159:969-971.

72. O'Flynn KJ, Murphy R,Thomas DG. 1992.Neurologic bladder dysfunction in lumbar intervertebral disc prolapse. Br J Urol 69:38-40.

73. Jennett WB. A study of 25 cases of compression of the cauda equina by prolapsed intervertebral discs. J Neurol Neurosurg Psychiatry 1956; 19:109-116.

74. Tay ECK, Chacha PB. Midline prolapse of a lumbar intervertebral disc with compression of the cauda equina. J Bone Joint Surg Br 1979; 61: 43-46.

75. Nielsen B, de Nully M, Schmidt K, Hansen RI. A urodynamic study of cauda equina syndrome due to lumbar disc herniation. Urol Int. 1980; 35: 167-170

76. O'Flynn KJ, Murphy R,Thomas DG. Neurologic bladder dysfunction in lumbar intervertebral disc prolapse. Br J Urol. 1992 ; 69: 38-40.

77. Bartels RH, de Vries J. Hemi-cauda equina syndrome from herniated lumbar disc: a neurosurgical emergency? Can J Neurol Sci. 1996 ; 23: 296-299

78. Goldman HB, Appell RA. Voiding dysfunction in women with lumbar disc prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10:134-138.

79. Ahn UM, Ahn NU, Buchowski JM, Garrett ES, Sieber-AN, Kostuik JP. Cauda equina syndrome secondary to lumbar disc herniation: a meta-analysis of surgical outcomes. Spine. 2000 Jun 15;25(12):1515-1522.

80. Shapiro S. Medical realities of cauda equina syndrome secondary to lumbar disc herniation. Spine. 2000 ;25:348-351.

81. Olivero WC, Wang H, Hanigan WC, Henderson JP, Tracy PT, Elwood PW, Lister JR, Lyle L. Cauda equina syndrome from lumbar disc herniation. J Sp Dis and Ther 2009; 22: 202-206.

82. Rosomoff HL, Johnston JD, Gallo AE, Ludmer M, Givens FT, Carney FT, Kuehn CA. Cystometry in the evaluation of nerve root compression in the lumbar spine. Surg Gynecol Obstet 1963; 117: 263-270

83. Kawaguchi Y, Kanamori M, Ishihara H, Ohmori K, Fujiuchi Y, Matsui H, Kimura T . Clinical symptoms and surgical outcome in lumbar spinal stenosis patients with neurologic bladder. J Spinal Disord. 2001;14: 404-410.

84. Tammela T L, Heiskari M J, Lukkarinen O A.: Voiding dysfunction and urodynamic findings in patients with cervical spondylotic spinal stenosis compared with severity of the disease. Br J Urol. 1992;70:144-148.

85. Inui Y, Doita M, Ouchi K, Tsukuda M, Fujita N, Kurosaka M. Clinical and radiological features of lumbar spinal stenosis and disc herniation with neurologic bladder. Spine. 2004; 29: 869-873.

86. Cong ML Gong WM, Zhang QG, Sun BW, Liu SH, Li L, Zhang LB, Jia TH. Urodynamic study of bladder function for patients with lumbar spinal stenosis treated by surgical decompression. J Int Med Research 2010; 38: 1149-1155.

87. Boulis NM, Mian FS, Rodriguez D, Cho E, Hoff JT. Urinary retention following routine neurosurgical spine procedures. Surg Neurol. 2001 ; 55: 23-27.

88. Brooks ME, Moreno M, Sidi A, Braf ZF. Urologic complications after surgery on lumbosacral spine. Urology. 1985; 26: 202-204.

89. Ellenberg M. Development of urinary bladder dysfunction in diabetes mellitus. Ann Intern Med 1980;92:321-323.

90. Frimodt-Moller C. Diabetic cystopathy: epidemiology and related disorders. Ann Intern Med 1980; 92:318-321.

91. Hampel C, Gillitzer R, Pahernik S, Melchior S, Thüroff JW. Diabetes mellitus and bladder function. What should be considered? Urologe A. 2003 ; 42:1556-1563.

92. Bradley WE. Diagnosis of urinary bladder dysfunction in diabetes mellitus. Ann Intern Med 1980;92: 323-326. Schuckit M. In: Isselbacher KJ, et al. eds Harrison's principles of internal medicine. New York: McGraw-Hill 1981, pp. 1475-1478.

93. Bansal R, Agarwal MM, Modi M, Mandal AK, Singh SK. Urodynamic profile of diabetic patients with lower urinary tract symptoms: association of diabetic cystopathy with autonomic and peripheral neuropathy. Urology 2011; 77: 699-705.

94. Barter F, Tanner AR. Autonomic neuropathy in an alcoholic population. Postgrad Med J 1987; 63: 1033-1036.

95. Chen PH, Hsueh HF, Hong CZ. Herpes zoster-associated voiding dysfunction: a retrospective study and literature review. Arch Phys Med Rehabil 2002;83:1624-1628.

96. Greenstein A, Matzkin H, Kaver I, Braf Z. Acute urinary retention in herpes genitalis infection. Urodynamic evaluation. Urology 1988;31:453-456.

97. Grbavac Z, Gilja I, Gubarev N, Bozicevic D. Neurologic and urodynamic characteristics of patients with Guillain-Barre syndrome. Lijec Vjesn 1989; 111:17-20.

98. Sakakibara R, Hattori T, Kuwabara S, Yamanishi T, Yasuda K. Micturitional disturbance in patients with Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry 1997; 63:649-653.

99. Lichtenfeld P. Autonomic dysfunction in the Guillain-Barré syndrome. Am J Med 1971;50:772-780.

100. Sakakibara R, Uchiyama T, Yoshiyama M, Yamanishi T, Hattori T.Urinary dysfunction in patients with systemic lupus erythematosis. Neurourol Urodyn. 2003; 22 (6): 593-596.

101. Min, J. K., Byun, J. Y., Lee, S. H. et al.: Urinary bladder involvement in patients with systemic lupus erythematosus: with review of the literature. Korean J Intern Med, 2000;15: 42-49.

102. Asia S. Martellotto G. Belen R. Sesin AM. Gamrom S. Drenkard C. Obstructive uropathy as the only manifestation of flare in a patient with systemic lupus erythematosus and anti-phospholipid syndrome. Lupus 2008; 17:46-49.

103. Khan Z, Singh VK, Yang WC. Neurologic bladder in acquired immune deficiency syndrome (AIDS). Urology 1992; 40:289-291.

104. Voiding problems in patients with HIV infection and AIDS. Mardirosoff C, Dumont L. Bowel and bladder dysfunction after spinal bupivacaine. Anesthesiology 2001; 95:1306.

105. Dinh A. Salomon J. Schoindre Y. Mathez D. Denys P. Durand MC. Bernard L Acute urinary retention due to viral coinfections (HIV, HBV, VZV). Journal of the International Association of Physicians in AIDS Care: JIAPAC. 2010; 9:20-22.

106. Hollabaugh RS, Jr., Steiner MS, Sellers KD, Samm BJ, Dmochowski RR. Neuroanatomy of the pelvis: implications for colonic and rectal resection. Dis Colon Rectum 2000; 43:1390-1397.

107. Baumgarner GT, Miller HC. Genitourinary complications of abdominoperineal resection. South Med J 1976; 69:875-877.

108. Eickenberg HU, Amin M, Klompus W, Lich R, Jr. Urologic complications following abdominoperineal resection. J Urol 1976; 1152:180-182.

109. Pocard M, Zinzindohoue F, Haab F, Caplin S, Parc R, Tiret E. A prospective study of sexual and urinary function before and after total mesorectal excision with autonomic nerve preservation for rectal cancer. Surgery. 2002 ;131:368-372

110. Kim NK., Aahn TW., Park JK., Lee KY., Lee WH., Sohn SK.; Min JS. Assessment of sexual and voiding function after total mesorectal excision with pelvic autonomic nerve preservation in males with rectal cancer. Dis Colon Rectum. 2002; 45 : 1178-1185.

111. Parys BT, Woolfenden KA, Parsons KF. Bladder dysfunction after simple hysterectomy: urodynamic and neurological evaluation. Eur Urol 1990; 172:129-133.

112. Sekido N, Kawai K, Akaza H. LUT dysfunction as persistent complication of radical hysterectomy. Int J Urol 1997; 4:259-264.

113. Zanolla R, Monzeglio C, Campo B, Ordesi G, Balzarini A, Martino G. Bladder and urethral dysfunction after radical abdominal hysterectomy: rehabilitative treatment. J Surg Oncol 1985; 28:190-194.

114. Seski JC, Diokno AC. Bladder dysfunction after radical abdominal hysterectomy. Am J Obstet Gynecol 1977;128:643-651.

115. Lin H H, Sheu B C, Lo M C , Huand SC. Abnormal urodynamic findings after radical hysterectomy or pelvic irradiation for cervical cancer. Int J Gynaecol Obstet 1998; 63: 169 – 174

116. Oda Y. Todo Y. Hanley S. Hosaka M. Takeda M. Watari H. Kaneuchi M. Kudo M. Sakuragi N. Risk factors for persistent low bladder compliance after radical hysterectomy. International Journal of Gynecological Cancer. 2011; 21:167-172.

117. Kuwabara Y, Suzuki M, Hashimoto M, Furugen Y, Yoshida K, Mitsuhashi N. New method to prevent bladder dysfunction after radical hysterectomy for uterine cervical cancer. J Obstet Gynaecol Res 2000; 261:1-8.

118. Wu J. Liu X. Hua K. Hu C. Chen X. Lu X. Effect of nerve-sparing radical hysterectomy on bladder function recovery and quality of life in patients with cervical carcinoma. International Journal of Gynecological Cancer 2010; 20:905-909.

CII. Specific diagnostics

1. Stöhrer M, Castro-Diaz D, Chartier-Kastler E, Del Popolo G, Kramer G, Pannek J, Radziszewski P, Wyndaele JJ. EAU Guidelines on Neurogenic Urinary Tract Dysfunction, In: EAU Guidelines. Edition presented at the 23rd EAU Congress, Milan, Italy. ISBN-13: 978-90-70244-91-0. http://www.uroweb.org/professional-resources/guidelines/

2. Stohrer M, Goepel M, Kondo A, Kramer G, Madersbacher H, Millard R, Rossier A, Wyndaele JJ. The standardization of terminology in neurogenic lower urinary tract dysfunction with suggestions for diagnostic procedures. Neurourol Urodyn 1999; 18:139-158.

3. Linsenmeyer TA, Oakley A. Accuracy of individuals with spinal cord injury at predicting urinary tract infections based on their symptoms. J Spinal Cord Med. 2003 ; 26:352-357

4. Pannek J. Treatment of urinary tract infection in persons with spinal cord injury: guidelines, evidence, and

clinical practice. A questionnaire-based survey and review of the literature. J Spinal Cord Med. 2011; **34**(1): 11-5.

5. Naoemova I, De Wachter S, Wuyts FL, Wyndaele JJ .Reliability of the 24-h sensation-related bladder diary in women with urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19: 955-959
6. Lombardi G, Del Popolo G. Clinical outcome of sacral neuromodulation in incomplete spinal cord injured patients suffering from neurogenic lower urinary tract symptoms. Spinal Cord. 2009; **47**(6): 486-91.
7. Wyndaele, J. J.: Correlation between clinical neurological data and urodynamic function in spinal cord injured patients. Spinal Cord 1997; 35: 213- 216
8. Schurch B, Schmid DM, Karsenty G, Reitz A. Can neurologic examination predict type of detrusor sphincter-dyssynergia in patients with spinal cord injury? Urology. 2005 ; 65: 243-246
9. Wyndaele J J, De Sy W A. Correlation between the findings of a clinical neurological examination and the urodynamic dysfunction in children with myelodysplasia. J Urol 1985; 133: 638- 640
10. Bross S, Honeck P, Kwon ST, Badawi JK, Trojan L, Alken P Correlation between motor function and lower urinary tract dysfunction in patients with infantile cerebral palsy. Neurourol Urodyn. 2007; 26: 222-227.
11. Wyndaele J J. A critical review of urodynamic investigations in spinal cord injury patients. Paraplegia 1984; 22: 138-144
12. Biering-Sørensen F, Craggs M, Kennelly M, Schick E, Wyndaele JJ. International Urodynamic Basic Spinal Cord Injury Data Set. Spinal Cord. 2008 Jan 29.
13. Nguyen HT, Sencan A, Silva A, Carvas FA, Bauer SB. Urodynamic studies are recommended in children with central nervous system tumors regardless of location. J Urol. 2010; **184**(6): 2516-20. **13a**. Wein A, Barrett DM. Etiologic possibilities for increased pelvic floor electromyography activity during cystometry. J Urol. 1982 May: **127**:949-52
14. Sundin T, Petersén I. Cystometry and simultaneous electomyography from the striated urethral and anal sphincters and from levator ani. Invest Urol. 1975;13:40-46
15. Perkash I. Detrusor-sphincter dyssynergia and dyssynergic responses: recognition and rationale for early modified transurethral sphincterotomy in complete spinal cord injury lesions. J Urol. 1978;120:469-474
16. Rodriquez AA, Awad EA, Price MM. Electromyogram-gas cystometrogram: its use in the management of neurologic bladder of spinal cord injury. Arch Phys Med Rehabil. 1978;59:451-454
17. Mayo ME, Kiviat MD. Increased residual urine in patients with bladder neuropathy secondary to suprasacral spinal cord lesions. J Urol. 1980;123:726-728
18. Perlow DL, Diokno AC. Predicting LUT dysfunctions in patients with spinal cord injury. Urology. 1981 ;18:531-535
19. Koyanagi T, Arikado K, Takamatsu T, Tsuji I. Experience with electromyography of the external urethral sphincter in spinal cord injury patients. J Urol. 1982 ;127:272-276
20. Blaivas JG, Sinha HP, Zayed AA, Labib KB. Detrusor-external sphincter dyssynergia: a detailed electromyographic study. J Urol. 1981;125:545-548
21. Rudy DC, Awad SA, Downie JW. External sphincter dyssynergia: an abnormal continence reflex. J Urol. 1988; **140**(1): 105-10
22. Aoki H, Adachi M, Banya Y, Sakuma Y, Seo K, Kubo T, Ohori T, Takagane H, Suzuki Y. Evaluation of neurologic bladder in patients with spinal cord injury using a CMG.EMG study and CMG.UFM.EMG study. Hinyokika Kiyo. 1985;31:937-948
23. Kirby RS. Studies of the neurologic bladder. Ann R Coll Surg Engl. 1988 ;70:285-288
24. Pavlakis AJ, Siroky MB, Wheeler JS Jr, Krane RJ. Supplementation of cystometrography with simultaneous perineal floor and rectus abdominis electromyography. J Urol. 1983 ;129:1179-81
25. Yamamoto T, Sakakibara R, Uchiyama T, Liu Z, Ito T, Awa Y, Yamamoto K, Kinou M, Yamanishi T, Hattori T. When is Onuf's nucleus involved in multiple system atrophy? A sphincter electromyography study. J Neurol Neurosurg Psychiatry. 2005 ;76:1645-1648.
26. Rapidi CA, Karandreas N, Katsifotis C, Benroubi M, Petropoulou K, Theodorou C. A combined urodynamic and electrophysiological study of diabetic cystopathy. Neurourol Urodyn. 2006; 25:32-38.
27. Schafer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn. 2002; **21**(3): 261-74
28. Bruschini H, Almeida FG, Srougi M. Upper and lower urinary tract evaluation of 104 patients with myelomeningocele without adequate urological management. World J Urol. 2006; 24: 224-228.
29. Moslavac S, Dzidic I, Kejla Z. Neurogenic detrusor overactivity: Comparison between complete and incomplete spinal cord injury patients. Neurourol Urodyn. 2008 May 28. [Epub ahead of print]
30. Abrahamsson K, Olsson I, Sillén U. Urodynamic findings in children with myelomeningocele after untethering of the spinal cord. J Urol. 2007 ;177:331-334
31. Kang HS, Wang KC, Kim KM, Kim SK, Cho BK. Prognostic factors affecting urologic outcome after untethering surgery for lumbosacral lipoma. Childs Nerv Syst. 2006; 22:1111-1121
32. Perkash I, Friedland GW. Ultrasonographic detection of false passages arising from the posterior urethra in spinal cord injury patients. J Urol. 1987;137:701-702
33. Perkash I, Friedland GW. Principles of modern urodynamic studies. Invest Radiol. 1987;22:279-289
34. Ko HY, Lee JZ, Park HJ, Kim H, Park JH. Comparison between conventional cystometry and stimulated filling cystometry by diuretics in a neurologic bladder after spinal cord injury. Am J Phys Med Rehabil. 2002 ;81:731-735
35. De Gennaro M, Capitanucci ML, Silveri M, Mosiello G, Broggi M, Pesce F. Continuous (6 hour) urodynamic monitoring in children with neurologic bladder. Eur J Pediatr Surg. 1996 ;6 Suppl 1:21-24
36. Zermann DH, Lindner H, Huschke T, Schubert J. Diagnostic value of natural fill cystometry in neurologic bladder in children. Eur Urol. 1997;32:223-228
37. Martens FM, van Kuppevelt HJ, Beekman JA, Heijnen IC, D'Hauwers KW, Heesakkers JP. No primary role of ambulatory urodynamics for the management of spinal cord injury patients compared to conventional urodynamics. Neurourol Urodyn. 2010; 29(8): 1380-6
38. Sakakibara R, Fowler CJ, Hattori T, Hussain IF, Swinn MJ, Uchiyama T, Yamanishi T. Pressure-flow study as an evaluating method of neurologic urethral relaxation failure. J Auton Nerv Syst. 2000;80:85-88
39. Nitti VW, Adler H, Combs AJ. The role of urodynamics in the evaluation of voiding dysfunction in men after cerebrovascular accident. J Urol. 1996;155:263-266
40. Sakakibara R, Hattori T, Uchiyama T, Yamanishi T, Ito H, Ito K. Neurologic failures of the external urethral sphincter closure and relaxation; a videourodynamic study. Auton Neurosci. 2001;86:208-215.
41. Madersbacher H. Combined pressure, flow, EMG and X-ray studies for the evaluation of neurologic bladder disturbance: technique. Urol Int. 1977;32:176-183.
42. Zerin J M, Lebowitz RL, Bauer S B. Descent of the

bladder neck: a urographic finding in denervation of the urethral sphincter in children with myelodysplasia. Radiology. 1990;174:833-836

43. Ockrim J, Laniado ME, Khoubehi B, Renzetti R, Finazzi Agrò E, Carter SS, Tubaro A. Variability of detrusor overactivity on repeated filling cystometry in men with urge symptoms: comparison with spinal cord injury patients. BJU Int. 2005;95:587-590 .

44. Wyndaele J J. Is impaired perception of bladder filling during cystometry a sign of neuropathy? Br J Urol. 1993;71:270-273

45. Lee, S. W. & Kim, J. H. 2008. The significance of natural bladder filling by the production of urine during cystometry. Neurourol Urodyn, 27, 772-4.

46. Wyndaele J J. Studies of bladder sensitivity in patients with myelodysplasia. Paraplegia. 1992; 30:333-335.

47. Martens FM, van Kuppevelt HJ, Beekman JA, Rijkhoff NJ, Heesakkers JP. Limited value of bladder sensation as a trigger for conditional neurostimulation in spinal cord injury patients. Neurourol Urodyn. 2010; 29(3): 395-400.

48. Ersoz M, Akyuz M. Bladder-filling sensation in patients with spinal cord injury and the potential for sensation-dependent bladder emptying. Spinal Cord. 2004 ;42:110-116

49. Shin JC, Chang WH, Jung TH, Yoo JH, Park SN. The determination of sensation-dependent bladder emptying time in patients with complete spinal cord injury above T11. Spinal Cord. 2008;46:210-215.

50. Lemack GE, Frohman EM, Zimmern PE, Hawker K, Ramnarayan P. Urodynamic distinctions between idiopathic detrusor overactivity and detrusor overactivity secondary to multiple sclerosis. Urology. 2006; 67:960-964.

51. Ayyildiz A, Huri E, Nuhoğlu B, Germiyanoğlu C. Unexpected complication after cystometry in the hypocompliant urinary bladder: formation of a knot in the double lumen urethral catheter--a case report. Int Urol Nephrol. 2006;38:527-529

52. Blok BF, Al Zahrani A, Capolicchio JP, Bilodeau C, Corcos J. Post-augmentation bladder perforation during urodynamic investigation. Neurourol Urodyn. 2007;26:540-542.

53. Pannek J, Nehiba M. Morbidity of urodynamic testing in patients with spinal cord injury: is antibiotic prophylaxis necessary? Spinal Cord. 2007;45:771-774

54. Latthe PM, Foon R, Toozs-Hobson P. Prophylactic antibiotics in urodynamics: a systematic review of effectiveness and safety. Neurourol Urodyn. 2008;27:167-173.

55. Deffontaines Rufin S, Jousse M, Verollet D, Guinet A, Ismael SS, Amarenco G. Cold perception of the bladder during ice water test. Study on 120 patients. Ann Phys Rehabil Med. 2010; 53(9): 559-67

56. Van Meel TD, De Wachter S, Wyndaele JJ. The effect of intravesical oxybutynin on the ice water test and on electrical perception thresholds in patients with neurogenic detrusor overactivity. Neurourol Urodyn. 2010; 29(3): 391-4

57. Geirsson G, Lindstrom S, Fall M. Pressure, volume and infusion speed criteria for the ice-water test. Br J Urol 1994; 73: 498-503

58. Geirsson G, Fall M. The ice-water test in the diagnosis of detrusor-external sphincter dyssynergia. Scand J Urol Nephrol 1995; 29: 457-461

59. Ishigooka M, Hashimoto T, Hayami S, Suzuki Y, Ichiyanagi O, Nakada T. Thermoreceptor mediated bladder sensation in patients with diabetic cystopathy. Int Urol Nephrol 1997; 29: 551-555

60. Ronzoni G, Menchinelli P, Manca A , de Giovanni l.: The ice-water test in the diagnosis and treatment of the neurologic bladder. Br J Urol 1997; 79: 698-701

61. Chancellor MB, Lavelle J, Ozawa H, Jung SY, Watanabe T, Kumon H. Ice-water test in the urodynamic evaluation of spinal cord injured patients. Tech Urol 1998; 4: 87-91

62. Van Meel T, De Wachter S, Wyndaele JJ Repeated ice water tests and electrical perception threshold determination to detect a neurologic cause of detrusor overactivity. Urology. 2007; 70: 772-776.

63. Ismael SS, Epstein T, Bayle B, Denys P, Amarenco G. Bladder cooling reflex in patients with multiple sclerosis. J Urol. 2000; 164: 1280-1284

64. De Wachter S, Van Meel T, Wyndaele JJ. Study of the afferent nervous system and its evaluation in women with impaired detrusor contractility treated with bethanechol. Urology. 2003; 62: 54-58

65. Lapides J, Friend CR, Ajemian EP, Reus WF. A new method for diagnosing the neurologic bladder. Med Bull (Ann Arbor). 1962 ; 28: 166-180

66. Blaivas JG, Labib KB, Michalik SJ, Zayed AA. Failure of bethanechol denervation supersensitivity as a diagnostic aid. J Urol. 1980; 123:199-201

67. Penders L.The bethanechol test in the diagnosis of neurologic bladder. 60 cases. J Urol (Paris). 1983 ; 89: 309-315.

68. Pavlakis AJ, Siroky MB, Krane RJ. Neurologic detrusor areflexia: correlation of perineal electromyography and bethanechol chloride supersensitivity testing. J Urol. 1983 ; 129: 1182-1184

69. Sidi AA, Dykstra DD, Peng W. Bethanechol supersensitivity test, rhabdosphincter electromyography and bulbocavernosus reflex latency in the diagnosis of neurologic detrusor areflexia. J Urol. 1988 ;140 : 335-337

70. Sakakibara R, Uchiyama T, Asahina M, Suzuki A, Yamanishi T, Hattori T. Micturition disturbance in acute idiopathic autonomic neuropathy. J Neurol Neurosurg Psychiatry. 2004 ; 75: 287-291

71. Wheeler JS Jr, Culkin DJ, Canning JR.: Positive bethanechol supersensitivity test in neurologically normal patients. Urology 1988; 31: 86-89

72. Wheeler JS Jr, Culkin DJ, Walter JS, Flanigan RC. Female urinary retention. Urology. 1990; 35: 428-432

73. Mahajan ST, Fitzgerald MP, Kenton K, Shott S, Brubaker L Concentric needle electrodes are superior to perineal surface-patch electrodes for electromyographic documentation of urethral sphincter relaxation during voiding. BJU Int. 2006 ; 97:117-120

74. Nordling J, Meyhoff HH. Dissociation of urethral and anal sphincter activity in neurologic bladder dysfunction. J Urol. 1979;122:352-356

75. Koyanagi T, Arikado K, Takamatsu T, Tsuji I. Experience with electromyography of the external urethral sphincter in spinal cord injury patients. J Urol. 1982 ;127:272-276.

76. Podnar S. Neurophysiology of the neurogenic lower urinary tract disorders. Clin Neurophysiol. 2007 ;118:1423-1437

77. Fowler CJ, Kirby RS, Harrison MJ, Milroy EJ, Turner-Warwick R.. Individual motor unit analysis in the diagnosis of disorders of urethral sphincter innervation. J Neurol Neurosurg Psychiatry. 1984 ;47:637-641

78. Vodusek D B. Individual motor unit analysis in the diagnosis of urethral sphincter innervation. J Neurol Neurosurg Psychiatry. 1989 ;52:812-813

79. Ziemann U, Reimers C D. Anal sphincter electromyography, bulbocavernosus reflex and pudendal somatosensory evoked potentials in diagnosis of neurologic lumbosacral lesions with disorders of bladder and large intestine emptying and erectile dysfunction. Nervenarzt. 1996 ;67:140-146.

80. Fowler CJ. Investigational techniques. Eur Urol. 1998;34 Suppl 1:10-12

81. Kavia RB, Datta SN, Dasgupta R, Elneil S, Fowler CJ. Urinary retention in women: its causes and management. BJU Int. 2006; 97(2): 281-7

82. Opisso E, Borau A, Rijkhoff NJ. Urethral sphincter EMG-controlled dorsal penile/clitoral nerve stimulation to treat neurogenic detrusor overactivity. J Neural Eng. 2011; 8(3): 036001

83. De EJ, Patel CY, Tharian B, Westney OL, Graves DE, Hairston JC. Diagnostic discordance of electromyography (EMG) versus voiding cystourethrogram (VCUG) for detrusor-external sphincter dyssynergy (DESD). Neurourol Urodyn. 2005;24:616-21

84. Wenzel BJ, Boggs JW, Gustafson KJ, Creasey GH, Grill WM. Detection of neurogenic detrusor contractions from the activity of the external anal sphincter in cat and human. Neurourol Urodyn. 2006;25:140-147

85. Hansen J, Borau A, Rodríguez A, Vidal J, Sinkjaer T, Rijkhoff NJ. Urethral sphincter EMG as event detector for neurogenic detrusor overactivity. IEEE Trans Biomed Eng. 2007; 54: 1212-1219

86. Light J K, Faganel J, Beric A. Detrusor areflexia in suprasacral spinal cord injuries. J Urol. 1985 ;134:295-297

87. Ito T, Sakakibara R, Yasuda K, Yamamoto T, Uchiyama T, Liu Z, Yamanishi T, Awa Y, Yamamoto K, Hattori T. Incomplete emptying and urinary retention in multiple-system atrophy: when does it occur and how do we manage it? Mov Disord. 2006; 21: 816-823

88. Sakakibara R, Uchiyama T, Arai K, Yamanishi T, Hattori T. Lower urinary tract dysfunction in Machado-Joseph disease: a study of 11 clinical-urodynamic observations. J Neurol Sci. 2004; 218: 67-72

89. Durufle A, Petrilli S, Nicolas B, Robineau S, Guillé F, Edan G, Gallien P. Effects of pregnancy and child birth on urinary symptoms and urodynamics in women with multiple sclerosis. Int Urogynecol J Pelvic Floor Dysfunct. 2006; 17: 352-355.

90. Karaman MI, Kaya C, Caskurlu T, Guney S, Ergenekon E. Urodynamic findings in children with cerebral palsy. Int J Urol. 2005; 12:717-720

91. La Joie WJ, Cosgrove MD, Jones WG. Electromyographic evaluation of human detrusor muscle activity in relation to abdominal muscle activity. Arch Phys Med Rehabil. 1976; 57: 382-386

92. Kaplan E, Nanninga B.: Electromyography of the human urinary bladder. Electromyogr Clin Neurophysiol. 1978; 18: 63-68

93. Kinder M, Gommer E, Janknegt R, van Waalwijk van Doorn E. Recording the detrusor electromyogram is still a difficult and controversial enterprise. Neurourol Urodyn. 1998; 17: 571-3

94. Walter JS, Wheeler JS Jr, Dunn RB.Dynamic bulbocavernosus reflex: dyssynergia evaluation following J Am Paraplegia Soc. 1994 ;17:140-145

95. Kaiho Y, Namima T, Uchi K, Nakagawa H, Aizawa M, Orikasa S.Electromyographic study of the striated urethral sphincter by using the bulbocavernosus reflex: study of the normal voluntary voiding and the involuntary sphincter relaxation. Nippon Hinyokika Gakkai Zasshi. 1999 ; 90: 893-900

96. Kaiho Y, Namima T, Uchi K, Nakagawa H, Aizawa M, Takeuchi A, Nishimura Y, Ohnuma T, Orikasa S.Electromyographic study of the striated urethral sphincter by using the bulbocavernosus reflex: study of the normal voluntary voiding and the involuntary sphincter relaxation]. Nippon Hinyokika Gakkai Zasshi. 2000; 91:715-722

97. Niu X, Shao B, Ni P, Wang X, Chen X, Zhu B, et al. Bulbocavernosus reflex and pudendal nerve somatosensory-evoked potentials responses in female patients with nerve system diseases. J Clin Neurophysiol. 2010; 27: 207-11

98. Schmid DM, Curt A, Hauri D, Schurch B. Motor evoked potentials (MEP) and evoked pressure curves (EPC) from the urethral compressive musculature (UCM) by functional magnetic stimulation in healthy volunteers and patients with neurogenic incontinence. Neurourol Urodyn. 2005;24:117-127

99. Di Lazzaro V, Pilato F, Oliviero A, Saturno E, Dileone M, Tonali PA. Role of motor evoked potentials in diagnosis of cauda equina and lumbosacral cord lesions. Neurology. 2004 ;63:2266-2271

100. Andersen JT, Bradley WE.: Abnormalities of bladder innervation in diabetes mellitus. Urology. 1976; 7: 442-448.

101. Vereecken RL, De Meirsman J, Puers B, Van Mulders J. Electrophysiological exploration of the sacral conus J Neurol. 1982;227:135-144

102. Carbone A, Palleschi G, Parascani R, Morello P, Conte A, Inghilleri M.et al.: Modulation of viscero-somatic H-reflex during bladder filling: a possible tool in the differential diagnosis of neurologic voiding dysfunctions. Eur Urol. 2002 ;42:281-288.

103. Badr G, Carlsson CA, Fall M, Friberg S, Lindström L, Ohlsson B. Cortical evoked potentials following stimulation of the urinary bladder in man. Electroencephalogr Clin Neurophysiol. 1982 ;54:494-498

104. Galloway NT, Chisholm GD, McInnes A. Patterns and significance of the sacral evoked response (the urologist's knee jerk). Br J Urol. 1985;57:145-147.

105. Mochida K, Shinomiya K, Andou M.Urodynamic and electrophysiologic study of the urinary disturbances caused by cervical myelopathy. J Spinal Disord. 1996 ; 9:141-145

106. Curt A, Rodic B, Schurch B, Dietz V. Recovery of bladder function in patients with acute spinal cord injury: significance of ASIA scores and somatosensory evoked potentials. Spinal Cord. 1997;35:368-373

107. Mazo EB, Sokolova AA, Krivoborodov GG, Shkol'nikov ME, Moiseev PP. The role of somatosensory evoked potentials in prognosis of efficacy of tibial neuromodulation in patients with hyperactive urinary bladder. Urologiia. 2005 ;5:49-52 .

108. Kaneko K, Kato Y, Kojima T, Imajyo Y, Taguchi T Epidurally recorded spinal cord evoked potentials in patients with cervical myelopathy and normal central motor conduction time measured by transcranial magnetic stimulation. Clin Neurophysiol. 2006;117:1467-1473.

109. Kurstjens GA, Borau A, Rodríguez A, Rijkhoff NJ, Sinkjaer T. Intraoperative recording of electroneurographic signals from cuff electrodes on extradural sacral roots in spinal cord injured patients.J Urol. 2005 ;174:1482-1487

110. Frankl-Hochwart L, Zuckerkandl O. Die nervösen Erkrankungen der Blase. In: Spezielle Pathologie und Therapie. Edited by v. Northnagel. Wien: Holder, 1899

111. Markland C, Chou S, Swaiman KF, Westgate HD, Bradley WE. Evaluation of neurologic urinary dysfunction. Surg Forum 1965;16:504-507

112. Kiesswetter, H. Mucosal sensory threshold of urinary bladder and urethra measured electrically. Urol Int. 1977;32:437-448

113. Powell PH, Feneley RC. The role of urethral sensation in clinical urology. Br J Urol. 1980;52:539-541

114. Frimodt-Moller, C. A new method for quantitative evaluation of bladder sensibility. Scand J Urol Nephrol. 1972;6:Suppl 15:135-134

115. Wyndaele J J. Is abnormal electrosensitivity in the LUT a sign of neuropathy? Br J Urol. 1993; 72: 575-579.

116. De Wachter S, Wyndaele J J. Quest for standardisation of electrical sensory testing in the LUT: the influ-

ence of technique related factors on bladder electrical thresholds. Neurourol Urodyn. 2003;22:118-122.

117. Ukimura O, Ushijima S, Honjo H, Iwata T, Suzuki K, Hirahara N, Okihara K, Mizutani Y, Kawauchi A, Miki T. Neuroselective current perception threshold evaluation of bladder mucosal sensory function. Eur Urol. 2004 ;45:70-76

118. De Laet K, De Wachter S, Wyndaele JJ. Current perception thresholds in the lower urinary tract: Sine- and square-wave currents studied in young healthy volunteers. Neurourol Urodyn. 2005;24:261-266

119. Schurch B, Curt A, Rossier A B. The value of sympathetic skin response recordings in the assessment of the vesicourethral autonomic nervous dysfunction in spinal cord injured patients. J Urol 1997;157:2230-2233

120. Rodic B, Curt A, Dietz V, Schurch B. Bladder neck incompetence in patients with spinal cord injury: significance of sympathetic skin response. J Urol. 2000; 163:1223-1227.

CIII. Conservative treatment

1. Bothig R, Hirschfeld S, Thietje R. Quality of life and urological morbidity in tetraplegics with artificial ventilation managed with suprapubic or intermittent catheterisation. Spinal Cord. 2012 Mar: 50:247-51

2. Drake MJ. Re: Influences on renal function in chronic spinal cord injured patients. J Urol. 2001 Jun: 165:2006

3. Drake MJ, Cortina-Borja M, Savic G, Charlifue SW, Gardner BP. Prospective evaluation of urological effects of aging in chronic spinal cord injury by method of bladder management. Neurourol Urodyn. 2005: 24:111-6

4. Cameron AP, Wallner LP, Forchheimer MB, et al. Medical and psychosocial complications associated with method of bladder management after traumatic spinal cord injury. Arch Phys Med Rehabil. 2011 Mar: 92:449-56

5. Jamison J, Maguire S, McCann J. Catheter policies for management of long term voiding problems in adults with neurogenic bladder disorders. Cochrane Database Syst Rev. 2011: 12:CD004375

6. Colli J, Lloyd LK. Bladder neck closure and suprapubic catheter placement as definitive management of neurogenic bladder. J Spinal Cord Med. 2011: 34:273-7

7. El-Masri WS, Chong T, Kyriakider AE, Wang D. Long-term follow-up study of outcomes of bladder management in spinal cord injury patients under the care of the Midlands Centre for Spinal Injuries in Oswestry. Spinal Cord. 2012 Jan: 50:14-21

8. Pan D, Troy A, Rogerson J, Bolton D, Brown D, Lawrentschuk N. Long-term outcomes of external sphincterotomy in a spinal injured population. J Urol. 2009 Feb: 181:705-9

9. Pannek J, Gocking K, Bersch U. Clinical usefulness of the memokath stent as a second-line procedure after sphincterotomy failure. J Endourol. 2011 Feb: 25:335-9

10. Mehta S, Hill D, Foley N, et al. A Meta-Analysis of Botulinum Toxin Sphincteric Injections in the Treatment of Incomplete Voiding After Spinal Cord Injury. Arch Phys Med Rehabil. 2012; 93: 597-603

11. Khastgir J, Drake MJ, Abrams P. Recognition and effective management of autonomic dysreflexia in spinal cord injuries. Expert Opin Pharmacother. 2007 May: 8:945-56. **11a** Perkash I. Transurethral sphincterotomy provides significant relief in autonomic dysreflexia in spinal cord injured male patients: long-term followup results. J Urol. 2007 Mar: 177:1026-9

12. Di Benedetto P. Clean intermittent self-catheterization in neuro-urology. Eur J Phys Rehabil Med. 2011 Dec: 47:651-9

13. Xu DF, Zhang S, Wang CZ, et al. Low-frequency electrotherapy for female patients with detrusor underactivity due to neuromuscular deficiency. Int Urogynecol J. 2012; 23: 1007-15

14. Abrams P, Agarwal M, Drake M, et al. A proposed guideline for the urological management of patients with spinal cord injury. BJU Int. 2008 Apr: 101:989-94

15. Bladder management for adults with spinal cord injury: a clinical practice guideline for health-care providers. J Spinal Cord Med. 2006: 29:527-73

16. Generao SE, Dall'era JP, Stone AR and Kurzrock EA. Spinal cord injury in children: long-term urodynamic and urological outcomes. J Urol 2004; 172: 1092-4, discussion 1094.

17. Kochakarn W, Ratana-Olarn K, Lertsithichai P and Roongreungsilp U. Follow-up of long-term treatment with clean intermittent catheterization for neurogenic bladder in children. Asian J Surg 2004; 27: 134-6.

18. Dromerick AW and Edwards DF. Relation of postvoid residual to urinary tract infection during stroke rehabilitation. Arch Phys Med Rehabil 2003; 84: 1369-72.

19. Wyndaele JJ. Intermittent catheterisation and intermittent self-catheterization have become properly introduced. Eur Urol 2007; 52: 220.

20. Guttmann L and Frankel H. The value of intermittent catheterisation in the early management of traumatic paraplegia and tetraplegia. Paraplegia 1966; 4: 63-84.

21. De Ridder DJ, Everaert K, Fernandez LG, Valero JV, Duran AB, Abrisqueta ML *et al.* Intermittent catheterisation with hydrophilic-coated catheters (SpeediCath) reduces the risk of clinical urinary tract infection in spinal cord injured patients: a prospective randomised parallel comparative trial. Eur Urol 2005; 48: 991-5.

22. Bjerklund-Johansen T, Hultling C, Madersbacher H, Del Popolo G and Amarenco G. A novel product for intermittent catheterisation: its impact on compliance with daily life--international multicentre study. Eur Urol 2007; 52: 213-20.

23. Kovindha A, Mai WN and Madersbacher H. Reused silicone catheter for clean intermittent catheterization (CIC): is it safe for spinal cord-injured (SCI) men? Spinal Cord 2004; 42: 638-42.

24. Getliffe K, Fader M, Allen C, Pinar K and Moore KN. Current evidence on intermittent catheterization: sterile single-use catheters or clean reused catheters and the incidence of UTI. J Wound Ostomy Continence Nurs 2007; 34: 289-96.

25. Lindehall B, Abrahamsson K, Jodal U, Olsson I and Sillen U. Complications of clean intermittent catheterization in young females with myelomeningocele: 10 to 19 years of followup. J Urol 2007; 178: 1053-5.

26. Lindehall B, Abrahamsson K, Hjalmas K, Jodal U, Olsson I and Sillen U. Complications of clean intermittent catheterization in boys and young males with neurogenic bladder dysfunction. J Urol 2004; 172: 1686-8.

27. Chen Y, DeVivo MJ and Lloyd LK. Bladder stone incidence in persons with spinal cord injury: determinants and trends, 1973-1996. Urology 2001; 58: 665-70.

28. Oh SJ, Ku JH, Jeon HG, Shin HI, Paik NJ and Yoo T. Health-related quality of life of patients using clean intermittent catheterization for neurogenic bladder secondary to spinal cord injury. Urology 2005; 65: 306-10.

29. Oh SJ, Shin HI, Paik NJ, Yoo T and Ku JH. Depressive symptoms of patients using clean intermittent catheterization for neurogenic bladder secondary to spinal cord injury. Spinal Cord 2006; 44: 757-62.

30. Ozawa H, Uematsu K, Ohmori H, Kondo A, Iwatsubo E and Takasaka S. [Long-term usefulness and safety

of the contemporary balloon catheter]. Nippon Hinyokika Gakkai Zasshi 2005; 96: 541-7.

31. Pannek J. Transitional cell carcinoma in patients with spinal cord injury: a high risk of malignancy? Urology 2002; 59: 240-4.

32. Wall BM, Dmochowski RR, Malecha M, Mangold T, Bobal MA and Cooke CR. Inducible nitric oxide synthase in the bladder of spinal cord injured patients with a chronic indwelling urinary catheter. J Urol 2001; 165: 1457-61.

33. Hamid R, Bycroft J, Arya M and Shah PJ. Screening cystoscopy and biopsy in patients with neuropathic bladder and chronic suprapubic indwelling catheters: is it valid? J Urol 2003; 170: 425-7

34. Stern JA and Clemens JQ. Osteomyelitis of the pubis: a complication of a chronic indwelling catheter. Urology 2003; 61: 462.

35. Biering-Sorensen F, Bagi P and Hoiby N. Urinary tract infections in patients with spinal cord lesions: treatment and prevention. Drugs 2001; 61: 1275-87.

36. Siroky MB. Pathogenesis of bacteriuria and infection in the spinal cord injured patient. Am J Med 2002; 113 Suppl 1A: 67S-79S.

37. Ahluwalia RS, Johal N, Kouriefs C, Kooiman G, Montgomery BS and Plail RO. The surgical risk of suprapubic catheter insertion and long-term sequelae. Ann R Coll Surg Engl 2006; 88: 210-3.

CIV. Pharmacotherapy

1. Nicholas RS, Friede T, Hollis S, Young CA. Anticholinergics for urinary symptoms in multiple sclerosis. Cochrane Database Syst Rev. 2009:CD004193.

2. Bennett N, O'Leary M, Patel AS, Xavier M, Erickson JR and Chancellor MB. Can higher doses of oxybutynin improve efficacy in neurogenic bladder? J Urol 2004; 171: 749-51.

3. Franco I, Horowitz M, Grady R, Adams RC, de Jong TP, Lindert K *et al.* Efficacy and safety of oxybutynin in children with detrusor hyperreflexia secondary to neurogenic bladder dysfunction. J Urol 2005; 173: 221-5.

4. Gajewski JB, Awad SA. Oxybutynin versus propantheline in patients with multiple sclerosis and detrusor hyperreflexia. J Urol. 1986 May: 135:966-8

5. 3. Stohrer M, Murtz G, Kramer G, Schnabel F, Arnold EP and Wyndaele JJ. Propiverine compared to oxybutynin in neurogenic detrusor overactivity--results of a randomized, double-blind, multicenter clinical study. Eur Urol 2007; 51: 235-42.

6. Grigoleit U, Murtz G, Laschke S, Schuldt M, Goepel M, Kramer G *et al.* Efficacy, tolerability and safety of propiverine hydrochloride in children and adolescents with congenital or traumatic neurogenic detrusor overactivity--a retrospective study. Eur Urol 2006; 49: 1114-20; discussion 1120-1.

7. Schulte-Baukloh H, Murtz G, Henne T, Michael T, Miller K and Knispel HH. Urodynamic effects of propiverine hydrochloride in children with neurogenic detrusor overactivity: a prospective analysis. BJU Int 2006; 97: 355-8.

8. Mazo EB, Krivoborodov GG, Shkol'nikov ME, Babanina GA, Kozyrev SV and Korshunov ES. [Trospium chloride in the treatment of idiopathic and neurogenic detrusor overactivity]. Urologiia 2005; 56-9.

9. Mazo EB and Babanina GA. [Trospium chloride (spasmex) in the treatment of lower urinary tract symptoms in patients with neurogenic hyperactive urinary bladder caused by vertebrogenic lesions]. Urologiia 2007; 15-9.

10. Drutz HP, Appell RA, Gleason D, Klimberg I and Radomski S. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct 1999; 10: 283-9.

11. Horstmann M, Schaefer T, Aguilar Y, Stenzl A and Sievert KD. Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage. Neurourol Urodyn 2006; 25: 441-5.

12. 10. Ethans KD, Nance PW, Bard RJ, Casey AR and Schryvers OI. Efficacy and safety of tolterodine in people with neurogenic detrusor overactivity. J Spinal Cord Med 2004; 27: 214-8.

13. Chapple CR, Rechberger T, Al-Shukri S, Meffan P, Everaert K, Huang M *et al.* Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU Int 2004; 93: 303-10.

14. Chapple CR, Cardozo L, Steers WD and Govier FE. Solifenacin significantly improves all symptoms of overactive bladder syndrome. Int J Clin Pract 2006; 60: 959-66.

15. van Rey F, Heesakkers J. Solifenacin in multiple sclerosis patients with overactive bladder: a prospective study. Adv Urol. 2011: 2011:834753

16. Amend B, Hennenlotter J, Schafer T, Horstmann M, Stenzl A, Sievert KD. Effective treatment of neurogenic detrusor dysfunction by combined high-dosed antimuscarinics without increased side-effects. Eur Urol. 2008 May: 53:1021-8

17. Kay G, Crook T, Rekeda L, et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. Eur Urol. 2006 Aug: 50:317-26

18. Staskin D, Kay G, Tannenbaum C, et al. Trospium chloride has no effect on memory testing and is assay undetectable in the central nervous system of older patients with overactive bladder. Int J Clin Pract. 2010 Aug: 64:1294-300

19. Brendler CB, Radebaugh LC and Mohler JL. Topical oxybutynin chloride for relaxation of dysfunctional bladders. J Urol 1989; 141: 1350-2.

20. George J, Tharion G, Richar J, Macaden AS, Thomas R and Bhattacharji S. The effectiveness of intravesical oxybutynin, propantheline, and capsaicin in the management of neuropathic bladder following spinal cord injury. Scientific World Journal 2007; 7: 1683-90.

21. Evans RJ. Intravesical therapy for overactive bladder. Curr Urol Rep 2005; 6: 429-33.

22. Saito M, Watanabe T, Tabuchi F, Otsubo K, Satoh K, Miyagawa I. Urodynamic effects and safety of modified intravesical oxybutynin chloride in patients with neurogenic detrusor overactivity: 3 years experience. Int J Urol. 2004 Aug: 11:592-6

23. Hayashi A, Saito M, Okada S, et al. Treatment with modified intravesical oxybutynin chloride for neurogenic bladder in children. J Pediatr Urol. 2007 Dec: 3:438-42

24. Guerra LA, Moher D, Sampson M, Barrowman N, Pike J, Leonard M. Intravesical oxybutynin for children with poorly compliant neurogenic bladder: a systematic review. J Urol. 2008 Sep: 180:1091-7

25. Van Meel TD, De Wachter S, Wyndaele JJ. The effect of intravesical oxybutynin on the ice water test and on electrical perception thresholds in patients with neurogenic detrusor overactivity. Neurourol Urodyn. 2010 Mar: 29:391-4

26. Scheepe JR, de Jong BW, Wolffenbuttel KP, Arentshorst ME, Lodder P, Kok DJ. The effect of oxybutynin on structural changes of the obstructed guinea pig bladder. J Urol. 2007 Oct: 178:1807-12

27. Fader M, Glickman S, Haggar V, Barton R, Brooks R and Malone-Lee J. Intravesical atropine compared to oral oxybutynin for neurogenic detrusor overactivity:

a double-blind, randomized crossover trial. J Urol 2007; 177: 208-13.

28. Lecci A, Giuliani S, Meini S and Maggi CA. Nociceptin and the micturition reflex. Peptides 2000; 21: 1007-21.

29. Lazzeri M, Calo G, Spinelli M, Malaguti S, Guerrini R, Salvadori S *et al.* Daily intravesical instillation of 1 mg nociceptin/orphanin FQ for the control of neurogenic detrusor overactivity: a multicenter, placebo controlled, randomized exploratory study. J Urol 2006; 176: 2098-102.

30. MacDonald R, Monga M, Fink HA, Wilt TJ. Neurotoxin treatments for urinary incontinence in subjects with spinal cord injury or multiple sclerosis: a systematic review of effectiveness and adverse effects. J Spinal Cord Med. 2008: 31:157-65

31. de Seze M, Gallien P, Denys P, et al. Intravesical glue cidic capsaicin versus glucidic solvent in neurogenic detrusor overactivity: a double blind controlled randomized study. Neurourol Urodyn. 2006: 25:752

32. Giannantoni A, Di Stasi SM, Stephen RL, Bini V, Costantini E and Porena M. Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study. J Urol 2004; 172: 240-3.

33. Gevaert T, Vandepitte J, Hutchings G, Vriens J, Nilius B, De Ridder D. TRPV1 is involved in stretch-evoked contractile changes in the rat autonomous bladder model: a study with piperine, a new TRPV1 agonist. Neurourol Urodyn. 2007: 26:440-50; discussion 51-3

34. Santos-Silva A, Charrua A, Cruz CD, Gharat L, Avelino A, Cruz F. Rat detrusor overactivity induced by chronic spinalization can be abolished by a transient receptor potential vanilloid 1 (TRPV1) antagonist. Auton Neurosci. 2011 Jan 26: 166:35-8

35. Andrade EL, Forner S, Bento AF, et al. TRPA1 receptor modulation attenuates bladder overactivity induced by spinal cord injury. Am J Physiol Renal Physiol. 2011 May: 300:F1223-34

36. Artim DE, Bazely F, Daugherty SL, et al. Nitro-oleic acid targets transient receptor potential (TRP) channels in capsaicin sensitive afferent nerves of rat urinary bladder. Exp Neurol. 2011 Nov: 232:90-9

37. Karsenty G, Denys P, Amarenco G, et al. Botulinum toxin A (Botox) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. Eur Urol. 2008: 53:275-87

38. Apostolidis A, Dasgupta P, Denys P, et al. Recommedations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus panel report. Eur Urol. 2009: 55:100-20

39. Mangera A, Andersson KE, Apostolidis A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). Eur Urol. 2011 Oct: 60:784-95

40. Duthie JB, Vincent M, Herbison GP, Wilson DI, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Database Syst Rev. 2011: 12:CD005493

41. Schurch B, de Seze M, Denys P, et al. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol. 2005 Jul: 174:196-20

42. Ehren I, Volz D, Farrelly E, et al. Efficacy and impact of botulinum toxin A on quality of life in patients with neurogenic detrusor overactivity: a randomised, placebo-controlled, double-blind study. Scand J Urol Nephrol. 2007: 41:335-40

43. Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2011 Oct: 60:742-50

44. Herschorn S, Gajewski J, Ethans K, et al. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: a randomized, double-blind trial. J Urol. 2011 Jun: 185:2229-35

45. Grosse J, Kramer G, Jakse G. Comparing two types of botulinum-A toxin detrusor injections in patients with severe neurogenic detrusor overactivity: a case-control study. BJU Int. 2009 Sep: 104:651-6

46. Grise P, Ruffion A, Denys P, Egon G, Chartier Kastler E. Efficacy and tolerability of botulinum toxin type A in patients with neurogenic detrusor overactivity and without concomitant anticholinergic therapy: comparison of two doses. Eur Urol. 2010 Nov: 58:759-66

47. Abdel-Meguid TA. Botulinum toxin-A injections into neurogenic overactive bladder--to include or exclude the trigone? A prospective, randomized, controlled trial. J Urol. 2010 Dec: 184:2423-8

48. Gomes CM, de Castro Filho JE, Rejowski RF, et al. Experience with different botulinum toxins for the treatment of refractory neurogenic detrusor overactivity. Int Braz J Urol. 2010 Jan-Feb: 36:66-74

49. Ginsberg DA, Gousse A, Keppenne V, et al. Phase 3 Efficacy and Safety Study of OnabotulinumtoxinA in Patients With Urinary Incontinence Due to Neurogenic Detrusor Overactivity. J Urol. 2011: Abstracts, American Urological Association Annual Meeting

50. Grosse J, Kramer G, Stohrer M. Success of repeat detrusor injections of botulinum a toxin in patients with severe neurogenic detrusor overactivity and incontinence. Eur Urol. 2005 May: 47:653-9

51. Karsenty G, Reitz A, Lindemann G, Boy S, Schurch B. Persistence of therapeutic effect after repeated injections of botulinum toxin type A to treat incontinence due to neurogenic detrusor overactivity. Urology. 2006 Dec: 68:1193-7

52. Reitz A, Denys P, Fermanian C, Schurch B, Comperat E, Chartier-Kastler E. Do repeat intradetrusor botulinum toxin type a injections yield valuable results? Clinical and urodynamic results after five injections in patients with neurogenic detrusor overactivity. Eur Urol. 2007: 52:1729-35

53. Del Popolo G, Filocamo MT, Li Marzi V, et al. Neurogenic detrusor overactivity treated with english botulinum toxin a: 8-year experience of one single centre. Eur Urol. 2008: 53:1013-20

54. Stoehrer M, Wolff A, Kramer G, et al. Treatment of neurogenic detrusor overactivity with botulinum toxin A: the first seven years. Urol Int. 2009: 83:379-85

55. Giannantoni A, Mearini E, Del Zingaro M, Porena M. Six-year follow-up of botulinum toxin A intradetrusorial injections in patients with refractory neurogenic detrusor overactivity: clinical and urodynamic results. Eur Urol. 2009 Mar: 55:705-11

56. Ghalayini IF, Al-Ghazo MA, Elnasser ZA. Is efficacy of repeated intradetrusor botulinum toxin type A (Dysport) injections dose dependent? Clinical and urodynamic results after four injections in patients with drug-resistant neurogenic detrusor overactivity. Int Urol Nephrol. 2009 Jan 31: 41:805-13

57. Khan S, Game X, Kalsi V, et al. Long-term effect on quality of life of repeat detrusor injections of botulinum neurotoxin-A for detrusor overactivity in patients with multiple sclerosis. J Urol. 2011 Apr: 185:1344-9

58. Kuo HC, Liu SH. Effect of repeated detrusor onabotulinumtoxinA injections on bladder and renal function in patients with chronic spinal cord injuries. Neurourol Urodyn. 2011 Nov: 30:1541-5

59. Deffontaines-Rufin S, Weil M, Verollet D, Peyrat L, Amarenco G. Botulinum toxin A for the treatment of neurogenic detrusor overactivity in multiple sclerosis patients. Int Braz J Urol. 2011 Sep-Oct: 37:642-8

60. Schulte-Baukloh H, Bigalke H, Miller K, et al. Botulinum neurotoxin type A in urology: antibodies as a cause of therapy failure. Int J Urol. 2008 May: 15:407-15; discussion 15

61. Naumann M, Carruthers A, Carruthers J, et al. Meta-analysis of neutralizing antibody conversion with onabotulinumtoxinA (BOTOX(R)) across multiple indications. Mov Disord. 2010 Oct 15: 25:2211-8

62. Hegele A, Frohme C, Varga Z, Olbert P, Kranz J, Hofmann R. Antibodies after botulinum toxin a injection into musculus detrusor vesicae: incidence and clinical relevance. Urol Int. 2011: 87:439-44

63. Schulte-Baukloh H, Herholz J, Bigalke H, Miller K, Knispel HH. Results of a BoNT/A Antibody Study in Children and Adolescents after Onabotulinumtoxin A (Botox(R)) Detrusor Injection. Urol Int. 2011: 87:434-8

64. Kajbafzadeh AM, Nikfarjam L, Mahboubi AH, Dianat S. Antibody Formation Following Botulinum Toxin Type A (Dysport) Injection in Children With Intractable Bladder Hyper-reflexia. Urology. 2010 Jul: 76:233-7

65. Giannantoni A, Rossi A, Mearini E, Del Zingaro M, Porena M, Berardelli A. Botulinum toxin A for overactive bladder and detrusor muscle overactivity in patients with Parkinson's disease and multiple system atrophy. J Urol. 2009 Oct: 182:1453-7

66. Kulaksizoglu H, Parman Y. Use of botulinim toxin-A for the treatment of overactive bladder symptoms in patients with Parkinsons's disease. Parkinsonism Relat Disord. 2010 Sep: 16:531-4

67. Giannantoni A, Conte A, Proietti S, et al. Botulinum toxin type A in patients with Parkinson's disease and refractory overactive bladder. J Urol. 2011 Sep: 186:960-4

68. Kuo HC. Therapeutic effects of suburothelial injection of botulinum a toxin for neurogenic detrusor overactivity due to chronic cerebrovascular accident and spinal cord lesions. Urology. 2006 Feb: 67:232-6

69. Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol. 2010 Dec: 184:2416-22

70. Ruffion A, Capelle O, Paparel P, Leriche B, Leriche A, Grise P. What is the optimum dose of type A botulinum toxin for treating neurogenic bladder overactivity? BJU Int. 2006 May: 97:1030-4

71. Mehnert U, Birzele J, Reuter K, Schurch B. The effect of botulinum toxin type a on overactive bladder symptoms in patients with multiple sclerosis: a pilot study. J Urol. 2011 Sep: 184:1011-6

72. Apostolidis A, Mourad S, Thompson C, Yan X, Haag-Molkenteller C. A Dose-Exploration Study Of The Efficacy and Safety Of OnabotulinumtoxinA in Patients With Urinary Incontinence Due To Neurogenic Detrusor Overactivity. Neurourol Urodyn. 2011: Abstracts, 41st Annual Meeting of the International Continence Society

73. Schurch B, Denys P, Kozma CM, Reese PR, Slaton T, Barron RL. Botulinum toxin A improves the quality of life of patients with neurogenic urinary incontinence. Eur Urol. 2007: 52:850-8

74. Schurch B, Stohrer M, Kramer G, Schmid DM, Gaul G, Hauri D. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol. 2000: 164:692-7

75. Karsenty G, Carsenac A, Boy S, Reitz A, Tournebise H, Bladou F *et al.* Botulinum toxin- A (BTA) in the treatment of neurogenic detrudor overcativity (NDOI)- A prospective randomized study to compare 30 vs. 10 injection sites. Eur Urol 2007; 2: 245.

76. Chuang YC, Tyagi P, Huang CC, et al. Urodynamic and immunohistochemical evaluation of intravesical botulinum toxin A delivery using liposomes. J Urol. 2009 Aug: 182:786-92

77. Kajbafzadeh AM, Montaser-Kouhsari L, Ahmadi H, Sotoudeh M. Intravesical electromotive botulinum toxin type A administration: part I--Experimental study. Urology. 2011 Jun: 77:1460-4

78. Kajbafzadeh AM, Ahmadi H, Montaser-Kouhsari L, Sharifi-Rad L, Nejat F, Bazargan-Hejazi S. Intravesical Electromotive Botulinum Toxin Type A Administration-Part II: Clinical Application. Urology. 2011 Aug 26: 77:439-45

79. Gamé X, Bentaleb Y, Thiry-Escudie I, et al. Detrusor injections of Botulinum toxin A in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infections. Eur Urol. 2008; 53: 613-8

80. Wefer B, Ehlken B, Bremer J, et al. Treatment outcomes and resource use of patients with neurogenic detrusor overactivity receiving botulinum toxin A (BOTOX) therapy in Germany. World J Urol. 2010 Jun: 28:385-90

81. Mascarenhas F, Cocuzza M, Gomes CM, Leao N. Trigonal injection of botulinum toxin-A does not cause vesicoureteral reflux in neurogenic patients. Neurourol Urodyn. 2008: 27:311-4

82. Alloussi SH, Lang C, Eichel R, et al. Videourodynamic changes of botulinum toxin A in patients with neurogenic bladder dysfunction (NBD) and idiopathic detrusor overactivity (IDO) refractory to drug treatment. World J Urol. 2011 Aug 13:

83. Caremel R, Courtois F, Charvier K, Ruffion A, Journel NM. Side effects of intradetrusor botulinum toxin injections on ejaculation and fertility in men with spinal cord injury: preliminary findings. BJU Int. 2011 Oct 7:

84. De Laet K, Wyndaele JJ. Adverse events after botulie num A toxin injection for neurogenic voiding disorders. Spinal Cord. 2005 Jul: 43:397-9

85. Girlanda P, Vita G, Nicolosi C, Milone S, Messina C. Botulinum toxin therapy: distant effects on neuromuscular transmission and autonomic nervous system. J Neurol Neurosurg Psychiatry. 1992: 55:844-5

86. Dutton JJ. Botulinum-A toxin in the treatment of craniocervical muscle spasms: short- and long-term, local and systemic effects. Surv Ophthalmol. 1996: 41:51-65

87. Schnitzler A, Genet F, Durand MC, et al. Pilot study evaluating the safety of intradetrusor injections of botulinum toxin type A: investigation of generalized spread using single-fiber EMG. Neurourol Urodyn. 2011 Nov: 30:1533-7

88. Comperat E, Reitz A, Delcourt A, Capron F, Denys P, Chartier-Kastler E. Histologic Features in the Urinary Bladder Wall Affected from Neurogenic Overactivity - A Comparison of Inflammation, Oedema and Fibrosis With and Without Injection of Botulinum Toxin Type A. Eur Urol. 2006 Feb 6: 50:1058-64

89. Apostolidis A, Jacques TS, Freeman A, et al. Histoo logical Changes in the Urothelium and Suburothelium of Human Overactive Bladder following Intradetrusor Injections of Botulinum Neurotoxin Type A for the Treatment of Neurogenic or Idiopathic Detrusor Overactivity. Eur Urol. 2008: 53:1245-53

90. Pascali MP, Mosiello G, Boldrini R, Salsano ML, Castelli E, De Gennaro M. Effects of botulinum toxin type a in the bladder wall of children with neurogenic bladder dysfunction: a comparison of histological features before and after injections. J Urol. 2011 Jun: 185:2552-7

91. Apostolidis A. Taming the Cannabinoids: New Poten-

tial in the Pharmacologic Control of Lower Urinary Tract Dysfunction. Eur Urol. 2012 Oct 6: 61:107-9

92. Tyagi V, Philips BJ, Su R, et al. Differential expression of functional cannabinoid receptors in human bladder detrusor and urothelium. J Urol. 2009 Apr: 181:1932-8

93. Gratzke C, Streng T, Park A, et al. Distribution and function of cannabinoid receptors 1 and 2 in the rat, monkey and human bladder. J Urol. 2009 Apr: 181:1939-48

94. Gratzke C, Streng T, Stief CG, et al. Effects of cane nabinor, a novel selective cannabinoid 2 receptor agonist, on bladder function in normal rats. Eur Urol. 2010 Jun: 57:1093-100

95. Gratzke C, Streng T, Stief CG, et al. Cannabinor, a selective cannabinoid-2 receptor agonist, improves bladder emptying in rats with partial urethral obstruction. J Urol. 2011 Feb: 185:731-6

96. Capasso R, Aviello G, Borrelli F, et al. Inhibitory Effect of Standardized Cannabis sativa Extract and Its Ingredient Cannabidiol on Rat and Human Bladder Contractility. Urology. 2011 Feb 8:

97. Walczak JS, Cervero F. Local activation of cannabinoid CB1 receptors in the urinary bladder reduces the inflammation-induced sensitization of bladder afferents. Mol Pain. 2011 May 9: 7:31

98. Strittmatter F, Gandaglia G, Benigni F, et al. Expression of fatty acid amide hydrolase (FAAH) in human, mouse and rat urinary bladder and effects by FAAH-inhibition on bladder function in awake rats. Eur Urol. 2012: 61:98-106

99. Adhikary S, Li H, Heller J, et al. Modulation of inflammatory responses by a cannabinoid-2-selective agonist after spinal cord injury. J Neurotrauma. 2011 Dec: 28:2417-27

100. Stankovich E, Borisov VV and Demina TL. [Tamsuloc sin in the treatment of detrusor-sphincter dyssynergia of the urinary bladder in patients with multiple sclerosis]. Urologia 2004; 48-51.

101. Abrams P, Amarenco G, Bakke A, Buczynski A, Castro-Diaz D, Harrison S *et al.* Tamsulosin: efficacy and safety in patients with neurogenic lower urinary tract dysfunction due to suprasacral spinal cord injury. J Urol 2003; 170: 1242-51.

102. Dykstra DD, Sidi AA, Scott AB, Pagel JM, Goldish GD. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. J Urol. 1988 May: 139:919-22

103. Chen SL, Bih LI, Chen GD, Huang YH, You YH. Comparing a transrectal ultrasound-guided with a cystoscopy-guided botulinum toxin a injection in treating detrusor external sphincter dyssynergia in spinal cord injury. Am J Phys Med Rehabil. 2011 Sep: 90:723-30

104. de Seze M, Petit H, Gallien P, et al. Botulinum a toxin and detrusor sphincter dyssynergia: a double-blind lidocaine-controlled study in 13 patients with spinal cord disease. Eur Urol. 2002 Jul: 42:56-62

105. Schulte-Baukloh H, Schobert J, Stolze T, Sturzebecher B, Weiss C, Knispel HH. Efficacy of botulinum-A toxin bladder injections for the treatment of neurogenic detrusor overactivity in multiple sclerosis patients: an objective and subjective analysis. Neurourol Urodyn. 2006: 25:110-5

106. Gallien P, Reymann JM, Amarenco G, Nicolas B, de Seze M and Bellissant E. Placebo controlled, randomised, double blind study of the effects of botulinum A toxin on detrusor sphincter dyssynergia in multiple sclerosis patients. J Neurol Neurosurg Psychiatry 2005; 76: 1670-6.

107. Safari S, Jamali S, Habibollahi P, Arshadi H, Nejat F, Kajbafzadeh AM. Intravesical Injections of Botulinum Toxin Type A for Management of Neuropathic Bladder: A Comparison of Two Methods. Urology. 2010 Jul: 76:225-30

CV. Electrostimulation

1. Mehnert U, Boy S, Svensson J, Michels L, Reitz A, Candia V *et al.* Brain activation in response to bladder filling and simultaneous stimulation of the dorsal clitoral nerve--an fMRI study in healthy women. Neuroimage 2008; 41: 682-9.

2. Gladh G, Mattsson S, Lindstrom S. Anogenital electrical stimulation as treatment of urge incontinence in children. BJU Int. 2001 Mar: 87:366-71

3. Trsinar B, Kraij B. Maximal electrical stimulation in children with unstable bladder and nocturnal enuresis and/or daytime incontinence: a controlled study. Neurourol Urodyn. 1996: 15:133-42

4. Spinelli M, Malaguti S, Giardiello G, Lazzeri M, Tarantola J and Van Den Hombergh U. A new minimally invasive procedure for pudendal nerve stimulation to treat neurogenic bladder: description of the method and preliminary data. Neurourol Urodyn 2005; 24: 305-9

5. Spinelli M, Giardiello G, Arduini A, van den Hombergh U. New percutaneous technique of sacral nerve stimulation has high initial success rate: preliminary results. Eur Urol. 2003 Jan: 43:70-4

6. Spinelli M, Giardiello G, Gerber M, Arduini A, van den Hombergh U, Malaguti S. New sacral neuromodulation lead for percutaneous implantation using local anesthesia: description and first experience. J Urol. 2003 Nov: 170:1905-7

7. Reitz A, Gobeaux N, Mozer P, Delmas V, Richard F, Chartier-Kastler E. Topographic Anatomy of a New Posterior Approach to the Pudendal Nerve for Stimulation. Eur Urol 2006; 51: 1350-5

8. Wheeler JS, Jr., Walter JS and Zaszczurynski PJ. Bladder inhibition by penile nerve stimulation in spinal cord injury patients. J Urol 1992; 147: 100-3

9. Dalmose AL, Rijkhoff NJ, Kirkeby HJ, Nohr M, Sinkjaer T and Djurhuus JC. Conditional stimulation of the dorsal penile/clitoral nerve may increase cystometric capacity in patients with spinal cord injury. Neurourol Urodyn 2003; 22: 130-7.

10. Hansen J, Media S, Nohr M, Biering-Sorensen F, Sinkjaer T and Rijkhoff NJ. Treatment of neurogenic detrusor overactivity in spinal cord injured patients by conditional electrical stimulation. J Urol 2005; 173: 2035-9.

11. Ohlsson BL, Fall M, Frankenberg-Sommar S. Effects of external and direct pudendal nerve maximal electrical stimulation in the treatment of the uninhibited overactive bladder. Br J Urol. 1989 Oct: 64:374-80

12. Goldman HB, Amundsen CL, Mangel J, et al. Dorsal genital nerve stimulation for the treatment of overactive bladder symptoms. Neurourol Urodyn. 2008: 27:499-50

13. Horvath EE, Yoo PB, Amundsen CL, Webster GD, Grill WM. Conditional and continuous electrical stimulation increase cystometric capacity in persons with spinal cord injury. Neurourol Urodyn. 2010 Mar: 29:401-7

14. Opisso E, Borau A, Rodriguez A, Hansen J, Rijkhoff NJ. Patient controlled versus automatic stimulation of pudendal nerve afferents to treat neurogenic detrusor overactivity. J Urol. 2008 Oct: 180:1403-8

15. Martens FM, Heesakkers JP, Rijkhoff NJ. Minimal invasive electrode implantation for conditional stimulation of the dorsal genital nerve in neurogenic detrusor overactivity. Spinal Cord. 2011 Apr: 49:566-72

16. Reitz A, Schmid DM, Curt A, Knapp PA, Schurch B. Afferent fibers of the pudendal nerve modulate sympathetic neurons controlling the bladder neck. Neurourol Urodyn. 2003: 22:597-601

17. Fjorback MV, Rijkhoff N, Petersen T, Nohr M, Sinkjaer T. Event driven electrical stimulation of the dorsal penile/clitoral nerve for management of neurogenic

detrusor overactivity in multiple sclerosis. Neurourol Urodyn. 2006: 25:349-55

18. Andrews BJ and Reynard JM. Transcutaneous posterior tibial nerve stimulation for treatment of detrusor hyperreflexia in spinal cord injury. J Urol 2003; 170: 926.

19. Krivoborodov GG, Gekht AB and Korshunova ES. [Tibial neuromodulation in the treatment of neurogenic detrusor hyperactivity in patients with Parkinson's disease]. Urologia 2006; 3-6.

20. Gobbi C, Digesu GA, Khullar V, El Neil S, Caccia G, Zecca C. Percutaneous posterior tibial nerve stimulation as an effective treatment of refractory lower urinary tract symptoms in patients with multiple sclerosis: preliminary data from a multicentre, prospective, open label trial. Mult Scler. 2011 Dec: 17:1514-9

21. Kabay S, Kabay SC, Yucel M, et al. The clinical and urodynamic results of a 3-month percutaneous posterior tibial nerve stimulation treatment in patients with multiple sclerosis-related neurogenic bladder dysfunction. Neurourol Urodyn. 2009: 28:964-8

22. Kabay SC, Kabay S, Yucel M, Ozden H. Acute urodynamic effects of percutaneous posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with Parkinson's disease. Neurourol Urodyn. 2009: 28:62-7

23. de Seze M, Raibaut P, Gallien P, et al. TranscutaneR ous posterior tibial nerve stimulation for treatment of the overactive bladder syndrome in multiple sclerosis: results of a multicenter prospective study. Neurourol Urodyn. 2011 Mar: 30:306-11

24. Rijkhoff NJ. Re: Kabay et al.: Acute effect of posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with multiple sclerosis: urodynamic study. (Urology 2008;71:641-645). Urology. 2008 Nov: 72:1186

25. Baumer T, Lange R, Liepert J, Weiller C, Siebner HR, Rothwell JC *et al.* Repeated premotor rTMS leads to cumulative plastic changes of motor cortex excitability in humans. Neuroimage 2003; 20: 550-60.

26. Centonze D, Petta F, Versace V, Rossi S, Torelli F, Prosperetti C *et al.* Effects of motor cortex rTMS on lower urinary tract dysfunction in multiple sclerosis. Mult Scler 2007; 13: 269-71.

27. Brusa L, Finazzi Agro E, Petta F, et al. Effects of inhibiA tory rTMS on bladder function in Parkinson's disease patients. Mov Disord. 2009 Feb 15: 24:445-8

28. Lemack GE, Dewey RB, Jr., Roehrborn CG, O'Suilleabhain PE and Zimmern PE. Questionnaire-based assessment of bladder dysfunction in patients with mild to moderate Parkinson's disease. Urology 2000; 56: 250-4.

29. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C *et al.* Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003; 349: 1925-34.

30. Seif C, Herzog J, van der Horst C, Schrader B, Volkmann J, Deuschl G *et al.* Effect of subthalamic deep brain stimulation on the function of the urinary bladder. Ann Neurol 2004; 55: 118-20.

31. Dalmose AL, Bjarkam CR, Sorensen JC, Djurhuus JC and Jorgensen TM. Effects of high frequency deep brain stimulation on urine storage and voiding function in conscious minipigs. Neurourol Urodyn 2004; 23: 265-72.

32. Herzog J, Weiss PH, Assmus A, Wefer B, Seif C, Braun PM *et al.* Subthalamic stimulation modulates cortical control of urinary bladder in Parkinson's disease. Brain 2006; 129: 3366-75.

33. Herzog J, Weiss PH, Assmus A, Wefer B, Seif C, Braun PM *et al.* Improved sensory gating of urinary bladder afferents in Parkinson's disease following subthalamic stimulation. Brain 2008; 131: 132-45.

34. Kessler TM, Burkhard FC, Z'Brun S, Stibal A, Studer UE, Hess CW *et al.* Effect of thalamic deep brain stimulation on lower urinary tract function. Eur Urol 2008; 53: 607-12.

35. Hagerty JA, Richards I, Kaplan WE. Intravesical electrotherapy for neurogenic bladder dysfunction: a 22-year experience. J Urol. 2007 Oct: 178:1680-3

CVI. Surgical treatment of urinary incontinence

1. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, Lycklama a Nijholt AA, Siegel S, Jonas U, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol 2007;178:2029-2034.

2. Schiotz HA. One month maximal electrostimulation for genuine stress incontinence in women. Neurourol Urodyn 1994;13:43-50.

3. Madersbacher H. Intravesical electrical stimulation for the rehabilitation of the neuropathic bladder. Paraplegia 1990;28:349-352.

4. Merrill DC. The treatment of detrusor incontinence by electrical stimulation. J Urol 1979;122:515-517.

5. Vodusek DB, Light JK, Libby JM. Detrusor inhibition induced by stimulation of pudendal nerve afferents. Neurourol Urodyn 1986;5:381-390.

6. Vodusek DB, Plevnik S, Janez J, Vrtacnik P. Detrusor inhibition on selective pudendal nerve stimulation in the perineum. Neurourol Urodyn 1988;6:389-393.

7. Tanagho EA, Schmidt RA, Orvis BR. Neural stimulah tion for control of voiding dysfunction: a preliminary report in 22 patients with serious neuropathic voiding disorders. J Urol 1989;142:340-345.

8. Leng WW, Chancellor MB. How sacral nerve stimulation neuromodulation works. Urol Clin North Am 2005;32:11-18.

9. Bemelmans BL, Mundy AR, Craggs MD. Neuromodulation by implant for treating lower urinary tract symptoms and dysfunction. Eur Urol 1999;36:81-91.

10. Chartier-Kastler EJ, Ruud Bosch JL, Perrigot M, Chancellor MB, Richard F, Denys P. Long-term results of sacral nerve stimulation (S3) for the treatment of neurogenic refractory urge incontinence related to detrusor hyperreflexia. J Urol 2000;164:1476-1480.

11. Blok BF, Groen J, Bosch JL, Veltman DJ, Lammertsma AA. Different brain effects during chronic and acute sacral neuromodulation in urge incontinent patients with implanted neurostimulators. BJU Int 2006;98:1238-1243.

12. Braun PM, Baezner H, Seif C, Boehler G, Bross S, Eschenfelder CC, et al. Alterations of cortical electrical activity in patients with sacral neuromodulator. Eur Urol 2002;41:562-566; discussion 566-567.

13. Dasgupta R, Critchley HD, Dolan RJ, Fowler CJ. Changes in brain activity following sacral neuromodulation for urinary retention. J Urol 2005;174:2268-2272.

14. Kruse MN, de Groat WC. Spinal pathways mediate coordinated bladder/urethral sphincter activity during reflex micturition in decerebrate and spinalized neonatal rats. Neurosci Lett 1993;152:141-144.

15. Wallace PA, Lane FL, Noblett KL. Sacral nerve neuromodulation in patients with underlying neurologic disease. Am J Obstet Gynecol 2007;197:96 e91-95.

16. Bosch RJL, Groen J. Treatment of refractory urge urinary incontinence with sacral spinal nerve stimulation in multiple sclerosis patients. Lancet 1996;348:717-719.

17. Bosch RJL, Groen J. Neuromodulation: urodynamic effects of sacral (S3) spinal nerve stimulation in patients with detrusor instability or detrusor hyperflexia. Behav Brain Res 1998;92:141-150.

18. Spinelli M, Bertapelle P, Cappellano F, Zanollo A, Carone R, Catanzaro F, et al. Chronic sacral neuromodulaC tion in patients with lower urinary tract symptoms: results from a national register. J Urol 2001;166:541-545.

19. Hohenfellner M, Humke J, Hampel C, Dahms S, Matzel K, Roth S, et al. Chronic sacral neuromodulah tion for treatment of neurogenic bladder dysfunction: long-term results with unilateral implants. Urology 2001;58:887-892.

20. Scheepens WA, Jongen MM, Nieman FH, de Bie RA, Weil EH, van Kerrebroeck PE. Predictive factors for sacral neuromodulation in chronic lower urinary tract dysfunction. Urology 2002;60:598.

21. Bross S, Braun PM, Weiss J, Martinez Portillo FJ, Knoll T, Seif C, et al. The role of the carbachol test and concomitant diseases in patients with nonobstructive urinary retention undergoing sacral neuromodulation. World J Urol 2003;20:346-349.

22. Spinelli M, Malaguti S, Giardiello G, Lazzeri M, Tarantola J, Van Den Hombergh U. A new minimally invasive procedure for pudendal nerve stimulation to treat neurogenic bladder: description of the method and preliminary data. Neurourol Urodyn 2005;24:305-309.

23. Schurch B, Reilly I, Reitz A, Curt A. Electrophysiological recordings during the peripheral nerve evaluation (PNE) test in complete spinal cord injury patients. World J Urol 2003;20:319-322.

24. Zvara P, Sahi S, Hassouna MM. An animal model for the neuromodulation of neurogenic bladder dysfunction. Br J Urol 1998;82:267-271.

25. Guys JM, Haddad M, Planche D, Torre M, Louis-Borrione C, Breaud J. Sacral neuromodulation for neurogenic bladder dysfunction in children. J Urol 2004;172:1673-1676.

26. Sievert KD, Amend B, Gakis G, et al. Early sacral neuromodulation prevents urinary incontinence after complete spinal cord injury. Ann Neurol. 2010 Jan: **67**:74-84

27. Chaabane W, Guillotreau J, Castel-Lacanal E, et al. Sacral neuromodulation for treating neurogenic bladder dysfunction: clinical and urodynamic study. Neurourol Urodyn. 2011 Apr: **30**:547-50

28. Chartier-Kastler EJ, Denys P, Chancellor MB, Haertig A, Bussel B, Richard F. Urodynamic monitoring during percutaneous sacral nerve neurostimulation in patients with neurogenic detrusor hyperreflexia. Neurourol Urodyn 2001;20:61-71.

29. Bertapelle P, Bodo G, Carone R. Detrusor acontractility in urinary retention: detrusor contractility test as exclusion criteria for sacral neurostimulation. J Urol. 2008 Jul: **180**:215-6

30. Aboseif S, Tamaddon K, Chalfin S, Freedman S, Mourad MS, Chang JH, et al. Sacral neuromodulation in functional urinary retention: an effective way to restore voiding. BJU Int 2002;90:662-665.

31. Dasgupta R, Wiseman OJ, Kitchen N, Fowler CJ. Long-term results of sacral neuromodulation for women with urinary retention. BJU Int 2004;94:335-337.

32. Goodwin RJ, Swinn MJ, Fowler CJ. The neurophysiology of urinary retention in young women and its treatment by neuromodulation. World J Urol 1998;16:305-307.

33. von Heyden B, Steinert R, Bothe HW, Hertle L. Sacral neuromodulation for urinary retention caused by sexual abuse. Psychosom Med 2001;63:505-508.

34. DeLaere KP, Debruyne FM, Michiels HG, Moonen WA. Prolonged bladder distension in the management of the unstable bladder. J Urol 1980;124:334-337.

35. Janknegt RA, Moonen WA, Schreinemachers LM. Transection of the bladder as a method of treatment in adult enuresis nocturna. Br J Urol 1979;51:275-277.

36. Mundy AR. Long-term results of bladder transection for urge incontinence. Br J Urol 1983;55:642-644.

37. Mundy AR. Bladder transection for urge incontinence associated with detrusor instability. Br J Urol 1980;52:480-483.

38. Westney OL, Lee JT, McGuire EJ, Palmer JL, Cespedes RD, Amundsen CL. Long-term results of Ingelman-Sundberg denervation procedure for urge incontinence refractory to medical therapy. J Urol 2002;168:1044-1047.

39. Cespedes RD, Cross CA, McGuire EJ. Modified Ingelman-Sundberg bladder denervation procedure for intractable urge incontinence. J Urol 1996;156:1744-1747.

40. Brindley GS, Polkey CE, Rushton DN. Sacral anterior root stimulators for bladder control in paraplegia. Paraplegia 1982;20:365-381.

41. Brindley GS, Polkey CE, Rushton DN, Cardozo L. Sacral anterior root stimulators for bladder control in paraplegia: the first 50 cases. J Neurol Neurosurg Psychiatry 1986;49:1104-1114.

42. Vignes JR, De Seze M, Sesay M, Barat M, Guerin J. [Anterior sacral root stimulation with dorsal rhizotomy (Brindley technique)]. Neurochirurgie 2003;49:383-394.

43. Bauchet L, Segnarbieux F, Martinazzo G, Frerebeau P, Ohanna F. [Neurosurgical treatment of hyperactive bladder in spinal cord injury patients]. Neurochirurgie 2001;47:13-24.

44. Egon G, Barat M, Colombel P, Visentin C, Isambert JL, Guerin J. Implantation of anterior sacral root stimulators combined with posterior sacral rhizotomy in spinal injury patients. World J Urol 1998;16:342-349.

45. Kutzenberger J, Domurath B, Sauerwein D. Spastic bladder and spinal cord injury: seventeen years of experience with sacral deafferentation and implantation of an anterior root stimulator. Artif Organs 2005;29:239-241.

46. Clarke SJ, Forster DM, Thomas DG. Selective saø cral neurectomy in the management of urinary incontinence due to detrusor instability. Br J Urol 1979;51:510-514.

47. Torrens MJ, Griffith HB. The control of the uninhibited bladder by selective sacral neurectomy. Br J Urol 1974;46:639-644

48. Torrens MJ. The effect of selective sacral nerve blocks on vesical and urethral function. J Urol 1974;112:204-205.

49. Rockswold GL, Bradley WE, Chou SN. Differential sacral rhizotomy in the treatment of neurogenic bladder dysfunction. Preliminary report of six cases. J Neurosurg 1973;38:748-754.

50. Opsomer RJ, Klarskov P, Holm-Bentzen M, Hald T. Long term results of superselective sacral nerve resection for motor urge incontinence. Scand J Urol Nephrol 1984;18:101-105.

51. Torrens M, Hald T. Bladder denervation procedures. Urol Clin North Am 1979;6:283-293.

52. Lucas MG, Thomas DG, Clarke S, Forster DM. Long-term follow-up of selective sacral neurectomy. Br J Urol 1988;61:218-220.

53. Mertens P, Sindou M. [Microsurgical sacral drezotomy for the treatment of hyperactive bladder]. Neurochirurgie 2003;49:399-403.

54. Sindou M. [Selective posterior radicellotomy in the treatment of spasticity]. Neurochirurgie 1977;23:359-366.

55. Hohenfellner M, Pannek J, Botel U, Dahms S, Pfitzenmaier J, Fichtner J, et al. Sacral bladder denervation for treatment of detrusor hyperreflexia and autonomic dysreflexia. Urology 2001;58:28-32.

56. Dogliotti AM. Traitement des syndromes douloureux de la périphérie par l'alcoolisation sous-arachnoïdienne des racines postérieurs à leur émergence de la moelle épinière. Presse Med 1931;39:1219-1251.

57. Bors E, Comarr AE, Moulton SH. The role of nerve blocks in the management of traumatic cord bladder: spinal anaesthesia, subarachnoïd alcohol injections, pudendal nerve anaesthesia and vesical neck anaesthesia. J Urol 1950;63:653-666.

58. Hoch M, Leriche A, Paparel P, Morel-Journel N, Ruffion A. [Chemical destruction of sacral nerve roots by alcohol injection for the treatment of overactive bladder]. Prog Urol 2006;16:584-587.

59. Glémain P, Rivière C, Robert R, Buzelin JM. Dénervation chirurgicale et hyperactivité vésicale. London: Elsevier, 1998.

60. Alloussi S, Loew F, Mast GJ, Alzin H, Wolf D. Treatment of detrusor instability of the urinary bladder by selective sacral blockade. Br J Urol 1984;56:464-467.

61. Alloussi S, Loew F, Mast GJ, Jung P, Schwertfeger K, Steffens J, et al. Value of selective reversible sacral nerve blockade in the diagnosis and treatment of the urge syndrome. Eur Urol 1990;17:30-34.

62. Muller SC, Frohneberg D, Schwab R, Thuroff JW. Selective sacral nerve blockade for the treatment of unstable bladders. Eur Urol 1986;12:408-412.

63. Mulcahy JJ, Young AB. Long-term follow-up of percutaneous radiofrequency sacral rhizotomy. Urology 1990;35:76-77.

64. Ferreira RS, Levi d'Ancona CA, Dantas-Filho VP, Rodrigues Netto N, Jr., Miyaoka R. [Percutaneous radiofrequency sacral rhizotomy in the treatment of neurogenic detrusor overactivity in spinal cord injured patients]. Actas Urol Esp. 2011 Jun: **35**:325-30

65. Tanagho EA, Schmidt RA, Orvis BR. Neural stimulation for control of voiding dysfunction: a preliminary report in 22 patients with serious neuropathic voiding disorders. J Urol 1989;142:340-345.

66. Li JS, Hassouna M, Sawan M, Duval F, Elhilali MM. Electrical stimulation induced sphincter fatigue during voiding. J Urol 1992;148:949-952.

67. Rijkhoff NJ, Wijkstra H, van Kerrebroeck PE, Debruyne FM. Selective detrusor activation by sacral ventral nerve-root stimulation: results of intraoperative testing in humans during implantation of a Finetech-Brindley system. World J Urol 1998;16:337-341.

68. Brindley GS. The first 500 patients with sacral anterior root stimulator implants: general description. Paraplegia 1994;32:795-805.

69. van der Aa HE, Alleman E, Nene A, Snoek G. Sacral anterior root stimulation for bladder control: clinical results. Arch Physiol Biochem 1999;107:248-256.

70. Martens FM, den Hollander PP, Snoek GJ, Koldewijn EL, van Kerrebroeck PE, Heesakkers JP. Quality of life in complete spinal cord injury patients with a Brindley bladder stimulator compared to a matched control group. Neurourol Urodyn. 2011 Apr: **30**:551-5

71. Schurch B, Rodic B, Jeanmonod D. Posterior sacral rhizotomy and intradural anterior sacral root stimulation for treatment of the spastic bladder in spinal cord injured patients. J Urol 1997;157:610-614.

72. Barat M, Egon G, Daverat P, Colombel P, Guerin J, Ritz M, et al. [Electrostimulation of anterior sacral nerve roots in the treatment of central neurogenic bladders. G.S. Brindley's technique. Results of the 40 first French cases]. J Urol (Paris) 1993;99:3-7.

73. Van Kerrebroeck PE, Koldewijn EL, Rosier PF, Wijkstra H, Debruyne FM. Results of the treatment of neurogenic bladder dysfunction in spinal cord injury by sacral posterior root rhizotomy and anterior sacral root stimulation. J Urol 1996;155:1378-1381.

74. Creasey GH, Grill JH, Korsten M, U HS, Betz R, Anderson R, et al. An implantable neuroprosthesis for restoring bladder and bowel control to patients with spinal cord injuries: a multicenter trial. Arch Phys Med Rehabil 2001;82:1512-1519.

75. Vignes JR, Liguoro D, Sesay M, Barat M, Guerin J. Dorsal rhizotomy with anterior sacral root stimulation for neurogenic bladder. Stereotact Funct Neurosurg 2001;76:243-245

76. Noll F, Sauerwein D, Stohrer M. Transurethral sphincterotomy in quadriplegic patients: long-term-follow-up. Neurourol Urodyn 1995;14:351-358.

77. Juma S, Mostafavi M, Joseph A. Sphincterotomy: long-term complications and warning signs. Neurourol Urodyn 1995;14:33-41.

78. Chancellor M, Rivas D. Complications related to sphincter stent used to the management of detrusor-sphincter dyssynergia. In: Yachia D, editor. Stenting the urinary system. Oxford: Isis Medical Media, 1998:437-443.

79. Parikh A, Milroy E. Precautions and complications in the use of the Urolume Wallstent. Eur Urol 1995;27:1-7.

80. Gross AJ, Sauerwein DH, Kutzenberger J, Ringert RH. Penile prostheses in paraplegic men. Br J Urol 1996;78:262-264.

81. Carson CC. Complications of penile prostheses and complex implantations. In: Carson C, Kirby R, Goldestein I, editors. Textbook of erectile dysfunction. Oxford: Isis Medical Media, 1999:435-450.

82. Lundberg PO, Brackett NL, Denys P, Chartier-Kastler E, Sonksen J, Vodusek DB. Neurological disorders: erectile and ejaculatory dysfunction (Committee 17). In: Jardin A, Wagner G, Khoury S, Giuliano F, Padma-Nathan H, Rosen R, editors. Erectile dysfunction. Plymouth: Health Publication Ltd, 2000:591-645.

83. Emmett JL, Daut RV, Dunn JH. Role of the external urethral sphincter in the normal bladder and cord bladder. J Urol 1948;59:439-454.

84. Ross JC, Damanski M, Giddons N. Resection of the external urethral sphincter in the paraplegic-preliminary report. J Urol 1958;79:742-746.

85. Archimbaud JP. Les complications urinaires des dysfonctionnements vésico-sphinctériens neurologiques. In: d'Urologie AF, editor. Les dysfonctonnements vésico-sphinctériens neurologiques. Paris: Masson, 1974:153-162.

86. Cukier J, Leger P, Benhamou G, Lacombe, Maury M, Couvelaire R. [Surgical myotomy of the striated sphincter of the urethra. A new sub-pubic approach. Study of the pathology of the striated sphincter in paraplegics]. J Urol Nephrol (Paris) 1971;77:27-50.

87. Reynard JM, Vass J, Sullivan ME, Mamas M. Sphincterotomy and the treatment of detrusor-sphincter dyssynergia: current status, future prospects. Spinal Cord 2003;41:1-11.

88. Dollfus P, Jurascheck F, Adli G, Chapus A. Impairment of erection after external sphincter resection. Paraplegia 1976;13:290-293.

89. Crane DB, Hackler RH. External sphincterotomy: its effect on erections. J Urol 1976;116:316-318.

90. Yalla SV, Fam BA, Gabilondo FB, Jacobs S, Di Benedetto M, Rossier AB, et al. Anteromedian external urethral sphincterotomy: technique, rationale and complications. J Urol 1977;117:489-493.

91. Kiviat MD. Transurethral sphincterotomy: relationship of site of incision to postoperative potency and delayed hemorrhage. J Urol 1975;114:399-401.

92. Chancellor MB, Gajewski J, Ackman CF, Appell RA, Bennett J, Binard J, et al. Long-term followup of the North American multicenter UroLume trial for the treat-

ment of external detrusor-sphincter dyssynergia. J Urol 1999;161:1545-1550.

93. Vapnek JM, Couillard DR, Stone AR. Is sphincterotomy the best management of the spinal cord injured bladder? J Urol 1994;151:961-964.

94. Ricottone AR, Pranikoff K, Steinmetz JR, Constantino G. Long-term follow-up of sphincterotomy in the treatment of autonomic dysreflexia. Neurourol Urodyn 1995;14:43-46.

95. Pan D, Troy A, Rogerson J, Bolton D, Brown D, Lawrentschuk N. Long-term outcomes of external sphincterotomy in a spinal injured population. J Urol. 2009 Feb: 181:705-9

96. Pannek J, Gocking K, Bersch U. Clinical usefulness of the memokath stent as a second-line procedure after sphincterotomy failure. J Endourol. 2011 Feb: 25:335-9

97. Shaw JPR, Milory EJG, Timoney AG, Mitchel N. Permanent external sphincter stents in spinal injured patients. Br J Urol 1990;66:297-302.

98. Yachia D. Temporary metal stents in bladder outflow obstruction. J Endourol 1997;11:459-465.

99. Badlani G. Role of permanent stents. J Endourol 1997;11:473-475.

100. Chartier-Kastler E, De Petriconi R, Bussel B, Richard F, Denys P. Etude de faisabilité de la prothèse endouréthrale transsphinctérienne striée DiaboloTM dans le traitement de la dyssynergie vésicosphincterienne striée. Prog Urol 2002;12:59A.

101. Game X, Chartier-Kastler E, Ayoub N, Even-Schneider A, Richard F, Denys P. Outcome after treatment of detrusor-sphincter dyssynergia by temporary stent. Spinal Cord 2008;46: 74-7.

102. Pannek J, Gocking K, Bersch U. Clinical usefulness of the memokath stent as a second-line procedure after sphincterotomy failure. J Endourol. 2011 Feb: **25**:335-9

103. Hamid R, Arya M, Wood S, Patel HR, Shah PJ. The use of the Memokath stent in the treatment of detrusor sphincter dyssynergia in spinal cord injury patients: a single-centre seven-year experience. Eur Urol 2003;43:539-543.

104. Low AI, McRae PJ. Use of the Memokath for detrusor-sphincter dyssynergia after spinal cord injury--a cautionary tale. Spinal Cord 1998;36:39-44.

105. Mehta SS, Tophill PR. Memokath stents for the treatment of detrusor sphincter dyssynergia (DSD) in men with spinal cord injury: the Princess Royal Spinal Injuries Unit 10-year experience. Spinal Cord 2006;44:1-6.

106. Shah NC, Foley SJ, Edhem I, Shah PJ. Use of Memokath temporary urethral stent in treatment of detrusor-sphincter dyssynergia. J Endourol 1997;11:485-488.

107. Vaidyanathan S, Soni BM, Oo T, Sett P, Hughes PL, Singh G. Long-term result of Memokath urethral sphincter stent in spinal cord injury patients. BMC Urol 2002;2:12.

108. Corujo M, Badlani G. Epithelialization of permanent stents. J Endourol 1997;11:477-480.

109. Chancellor M, Rivas D, Watanabe T, Bennet J, Foote J, Green B, et al. Reversible clinical outcome after sphincter stent removal. J Urol 1996;155:1992-1994.

110. Gajewski J, Chancellor M, Ackman D, al. e. Removal of Urolume endoprosthesis: experience of the north american study group for detrusor-sphincter dyssynergia application. J Urol 2000;163:773-776.

111. Elkassaby AA, Al-Kandari AM, Shokeir AA. The surgical management of obstructive stents used for urethral strictures. J Urol 2007;178:204-207.

112. Rodriguez E, Jr., Gelman J. Pan-urethral strictures can develop as a complication of UroLume placement for bulbar stricture disease in patients with hypospadias. Urology 2006;67:1290 e1211-1292.

113. Shah DK, Kapoor R, Badlani GH. Experience with urethral stent explantation. J Urol 2003;169:1398-1400.

114. Wilson T, Lemack G, Dmochowski R. Urolume stents: lessons learned. J Urol 2002;167:2477-2480.

115. Abdul-Rahman A, Ismail S, Hamid R, Shah J. A 20-year follow-up of the mesh wallstent in the treatment of detrusor external sphincter dyssynergia in patients with spinal cord injury. BJU Int. 2010 Nov: 106:1510-3

116. Chancellor M, Rivas D, Abdill C, al. e. Prospective comparison of external sphincter balloon dilatation and prosthesis placement with external sphincterotomy in spinal cord injured men. Arch Phys Med Rehabil 1994;75:297-305.

117. Rivas DA, Chancellor MB, Bagley D. Prospective comparison of external sphincter prosthesis placement and external sphincterotomy in men with spinal cord injury. J Endourol 1994;8:89-93.

118. McFarlane JP, Foley SJ, Shah PJR. Balloon dilatation in the treatment of detrusor sphincter dyssynergia. Spinal Cord 1997;35:96-98.

119. Chancellor MB, Bennett C, Simoneau AR, Finocchiaro MV, Kline C, Bennett JK, et al. Sphincteric stent versus external sphincterotomy in spinal cord injured men: prospective randomized multicenter trial. J Urol 1999;161:1893-1898.

120. Rivas DA, Chancellor MB, Staas WE, Jr., Gomella LG. Contact neodymium:yttrium-aluminum-garnet laser ablation of the external sphincter in spinal cord injured men with detrusor sphincter dyssynergia. Urology 1995;45:1028-1031.

121. Perkash I. Use of contact laser crystal tip firing Nd:YAG to relieve urinary outflow obstruction in male neurogenic bladder patients. J Clin Laser Med Surg 1998;16:33-38.

122. Chancellor MB, Rivas DA, Abdill CK, Karasick S, Ehrlich SM, Staas WE. Prospective comparison of external sphincter balloon dilatation and prosthesis placement with external sphincterotomy in spinal cord injured men. Arch Phys Med Rehabil. 1994 Mar: **75**:297-305

123. Ke QS, Kuo HC. Transurethral incision of the bladder neck to treat bladder neck dysfunction and voiding dysfunction in patients with high-level spinal cord injuries. Neurourol Urodyn. 2010 Jun: **29**:748-52

124. Mahfouz W, Corcos J. Management of detrusor external sphincter dyssynergia in neurogenic bladder. Eur J Phys Rehabil Med. 2011 Dec: **47**:639-50

125. Horton CE, Sadove RC, Jordan GH, Sagher U. Use of the rectus abdominis muscle and fascia flap in reconstruction of epispadias/exstrophy. Clin Plast Surg 1988;15:393-397.

126. Parkash S, Bhandari M. Rectus abdominis myocutaneous island flap for bridging defect after cystectomy for bladder exstrophy. Urology 1982;20:536-537.

127. Celayir S, Kilic N, Elicevik M, Buyukunal C. Rectus abdominis muscle flap (RAMF) technique for the management of bladder exstrophies: late clinical outcome and urodynamic findings. Br J Urol 1997;79:276-278.

128. Ninkovic M, Stenzl A, Schwabegger A, Bartsch G, Prosser R, Ninkovic M. Free neurovascular transfer of latisstmus dorsi muscle for the treatment of bladder acontractility: II. Clinical results. J Urol 2003;169:1379-1383.

129. Stenzl A, Ninkovic M, Kolle D, Knapp R, Anderl H, Bartsch G. Restoration of voluntary emptying of the bladder by transplantation of innervated free skeletal muscle. Lancet 1998;351:1483-1485.

130. Stenzl A, Ninkovic M, Willeit J, Hess M, Feichtinger H, Schwabegger A, et al. Free neurovascular transfer of latissimus dorsi muscle to the bladder. I. Experimental studies. J Urol 1997;157:1103-1108.

131. Gakis G, Ninkovic M, van Koeveringe GA, et al. Functional detrusor myoplasty for bladder acontractility: long-term results. J Urol. 2011 Feb: **185**:593-9

132. Catz A, Luttwak ZP, Agranov E, Ronen J, Shpaser R, Paz A, et al. The role of external sphincterotomy for patients with a spinal cord lesion. Spinal Cord 1997;35:48-52.

133. Fontaine E, Hajri M, Rhein F, Fakacs C, Le Mouel MA, Beurton D. Reappraisal of endoscopic sphincterotomy for post-traumatic neurogenic bladder: a prospective study. J Urol 1996;155:277-280.

134. Namiki T. Transurethral sphincteroresection in traumatic tetraplegia. Urol Int 1984;39:286-291.

135. Ruutu M, Lehtonen T. External sphincterotomy in patients with spinal cord injury. Ann Chir Gynaecol 1982;71:250-254.

136. Carrion HM, Brown BT, Politano VA. External sphincterotomy at the 12 o'clock position. J Urol 1979;121:462-463.

137. Fabian KM. Der intraprostatische „partielle Katheter"(urologische Spirale). Urologe [A] 1980;19:236-238.

138. Nissenkorn I. Experience with a new self retaining intraurethral catheter in patients with urinary retention: a preliminary report. J Urol 1989;142:92-94.

139. Soni BM, Vaidyanatham S, Krishnan KR. Use of Memokath, a second generation urethral stent for relief of urinary retention in male spinal cord injured patients. Paraplegia 1994;32:480-488.

140. Juma S, Niku S, Broda K, Joseph A. Urolume urethral wallstent in the treatment of detrusor sphincter dyssynergia. Paraplegia 1994;32:616-621.

141. Parra R. Treatment of posterior urethral strictures with a Titanium urethral stent. J Urol 1991;146:937-1000.

142. Juan Garcia F, Salvador S, Montoto A, Lion S, Balvis B, Rodriguez A, et al. Intraurethral stent prosthesis in spinal cord injured patients with sphincter dyssynergia. Spinal Cord 1999;37:54-57.

143. Chartier-Kastler EJ, Ruud Bosch JL, Perrigot M, Chancellor MB, Richard F, Denys P. Long-term results of sacral nerve stimulation (S3) for the treatment of neurogenic refractory urge incontinence related to detrusor hyperreflexia. J Urol 2000;164:1476-1480.

144. Denys P, Thiry-Escudie I, Ayoub N, Even-Schneider A, Benyahya S, Chartier-Kastler E. Urethral stent for the treatment of detrusor-sphincter dyssynergia: evaluation of the clinical, urodynamic, endoscopic and radiological efficacy after more than 1 year. J Urol 2004;172:605-607.

145. Juan Garcia FJ, Salvador S, Montoto A, Lion S, Balvis B, Rodriguez A, et al. Intraurethral stent prosthesis in spinal cord injured patients with sphincter dyssynergia. Spinal Cord 1999;37:54-57.

146. Hamid R, Arya M, Patel HR, Shah PJ. The mesh wallstent in the treatment of detrusor external sphincter dyssynergia in men with spinal cord injury: a 12-year follow-up. BJU Int 2003;91:51-53.

147. Shah NC, Foley SJ, Edhem I, Shah PJ. Use of Memokath temporary urethral stent in treatment of detrusor-sphincter dyssynergia. J Endourol. 1997 Dec: **11**:485-8

148. Austin PF, Westney OL, Leng WW, McGuire EJ, Ritchey ML. Advantages of rectus fascial slings for urinary incontinence in children with neuropathic bladders. J Urol 2001;165:2369-2371

149. Barthold JS, Rodriguez E, Freedman AL, Fleming PA, Gonzalez R. Results of the rectus fascial sling and wrap procedures for the treatment of neurogenic sphincteric incontinence. J Urol 1999;161:272-274.

150. Gosalbez R, Castellan M. Defining the role of the bladder-neck sling in the surgical treatment of urinary incontinence in children with neurogenic incontinence. World J Urol 1998;16:285-291.

151. Kakizaki H, Shibata T, Shinno Y, Kobayashi S, Matsumura K, Koyanagi T. Fascial sling for the management of urinary incontinence due to sphincter incompetence. J Urol 1995;153:644-647.

152. Belloli G, Campobasso P, Mercurella A. Neuropathic urinary incontinence in pediatric patients: management with artificial sphincter. J Pediatr Surg 1992;27:1461-1464.

153. Bersch U, Gocking K, Pannek J. The Artificial Urinary Sphincter in Patients with Spinal Cord Lesion: Description of a Modified Technique and Clinical Results. Eur Urol 2009; 55:687-93

154. Castera R, Podesta ML, Ruarte A, Herrera M, Medel R. 10-Year experience with artificial urinary sphincter in children and adolescents. J Urol 2001;165:2373-2376.

155. Elliott DS, Barrett DM. Mayo Clinic long-term analysis of the functional durability of the AMS 800 artificial urinary sphincter: a review of 323 cases. J Urol 1998;159:1206-1208.

156. Fulford SC, Sutton C, Bales G, Hickling M, Stephenson TP. The fate of the ‚modern' artificial urinary sphincter with a follow-up of more than 10 years. Br J Urol 1997;79:713-716.

157. Gonzalez R, Merino FG, Vaughn M. Long-term results of the artificial urinary sphincter in male patients with neurogenic bladder. J Urol 1995;154:769-770.

158. Herndon CD, Rink RC, Shaw MB, Simmons GR, Cain MP, Kaefer M, et al. The Indiana experience with artificial urinary sphincters in children and young adults. J Urol 2003;169:650-654; discussion 654.

159. Kryger JV, Leverson G, Gonzalez R. Long-term results of artificial urinary sphincters in children are independent of age at implantation. J Urol 2001;165:2377-2379.

160. Lai HH, Hsu EI, Teh BS, Butler EB, Boone TB. 13 years of experience with artificial urinary sphincter implantation at Baylor College of Medicine. J Urol 2007;177:1021-1025.

161. Levesque PE, Bauer SB, Atala A, Zurakowski D, Colodny A, Peters C, et al. Ten-year experience with the artificial urinary sphincter in children. J Urol 1996;156:625-628.

162. Lopez Pereira P, Somoza Ariba I, Martinez Urrutia MJ, Lobato Romero R, Jaureguizar Monroe E. Artificial urinary sphincter: 11-year experience in adolescents with congenital neuropathic bladder. Eur Urol 2006;50:1096-1101; discussion 1101.

163. Patki P, Hamid R, Shah PJ, Craggs M. Long-term efficacy of AMS 800 artificial urinary sphincter in male patients with urodynamic stress incontinence due to spinal cord lesion. Spinal Cord 2006;44:297-300.

164. Simeoni J, Guys JM, Mollard P, Buzelin JM, Moscovici J, Bondonny JM, et al. Artificial urinary sphincter implantation for neurogenic bladder: a multi-institutional study in 107 children. Br J Urol 1996;78:287-293.

165. Singh G, Thomas DG. Artificial urinary sphincter in patients with neurogenic bladder dysfunction. Br J Urol 1996;77:252-255.

166. Snodgrass WT, Elmore J, Adams R. Bladder neck sling and appendicovesicostomy without augmentation for neurogenic incontinence in children. J Urol 2007;177:1510-1514.

167. Dave S, Pippi Salle JL, Lorenzo AJ, Braga LH, Peralta-Del Valle MH, Bagli D, et al. Is long-term bladder deterioration inevitable following successful isolated bladder outlet procedures in children with neuropathic bladder dysfunction? J Urol 2008;179:1991-1996; discussion 1996.

168. Kryger JV, Gonzalez R, Barthold JS. Surgical management of urinary incontinence in children with neurogenic sphincteric incompetence. J Urol. 2000 Jan: **163**:256-63

169. Dyer L, Franco I, Firlit CF, Reda EF, Levitt SB, Palmer LS. Endoscopic injection of bulking agents in children with incontinence: dextranomer/hyaluronic acid copolymer versus polytetrafluoroethylene. J Urol. 2007 Oct: **178**:1628-31

170. Godbole P, Mackinnon AE. Expanded PTFE bladder neck slings for incontinence in children: the long-term outcome. BJU Int 2004;93:139-141

171. Malizia AA, Jr., Reiman HM, Myers RP, et al. Migration and granulomatous reaction after periurethral injection of polytef (Teflon). Jama. 1984 Jun 22-29: **251**:3277-81

172. Claes H, Stroobants D, Van Meerbeek J, Verbeken E, Knockaert D, Baert L. Pulmonary migration following periurethral polytetrafluoroethylene injection for urinary incontinence. J Urol. 1989 Sep: **142**:821-2

173. Wan J, McGuire EJ, Bloom DA, Ritchey ML. The treatment of urinary incontinence in children using glutaraldehyde cross-linked collagen. J Urol. 1992 Jul: **148**:127-30

174. Sundaram CP, Reinberg Y, Aliabadi HA. Failure to obtain durable results with collagen implantation in children with urinary incontinence. J Urol. 1997 Jun: **157**:2306-7

175. Block CA, Cooper CS, Hawtrey CE. Long-term efficacy of periurethral collagen injection for the treatment of urinary incontinence secondary to myelomeningocele. J Urol. 2003 Jan: **169**:327-9

176. Bomalaski MD, Bloom DA, McGuire EJ, Panzl A. Glutaraldehyde cross-linked collagen in the treatment of urinary incontinence in children. J Urol. 1996 Feb: **155**:699-702

177. Perez LM, Smith EA, Parrott TS, Broecker BH, Massad CA, Woodard JR. Submucosal bladder neck injection of bovine dermal collagen for stress urinary incontinence in the pediatric population. J Urol. 1996 Aug: **156**:633-6

178. Leonard MP, Decter A, Mix LW, Johnson HW, Coleman GU. Treatment of urinary incontinence in children by endoscopically directed bladder neck injection of collagen. J Urol. 1996 Aug: **156**:637-40; discussion 40-1

179. Chernoff A, Horowitz M, Combs A, Libretti D, Nitti V, Glassberg KI. Periurethral collagen injection for the treatment of urinary incontinence in children. J Urol. 1997 Jun: **157**:2303-5

180. Kassouf W, Capolicchio G, Berardinucci G, Corcos J. Collagen injection for treatment of urinary incontinence in children. J Urol. 2001 May: **165**:1666-8

181. Halachmi S, Farhat W, Metcalfe P, Bagli DJ, McLorie GA, Khoury AE. Efficacy of polydimethylsiloxane injection to the bladder neck and leaking diverting stoma for urinary continence. J Urol. 2004 Mar: 171:1287-90

182. Lottmann HB, Margaryan M, Bernuy M, et al. The effect of endoscopic injections of dextranomer based implants on continence and bladder capacity: a prospective study of 31 patients. J Urol. 2002 Oct: 168:1863-7; discussion 7

183. Hamid R, Arya M, Khastgir J, Patel HR, Shah PJ. The treatment of male stress urinary incontinence with polydimethylsiloxane in compliant bladders following spinal cord injury. Spinal Cord. 2003 May: 41:286-9

184. Guys JM, Breaud J, Hery G, Camerlo A, Le Hors H, De Lagausie P. Endoscopic injection with polydimethylsiloxane for the treatment of pediatric urinary incontinence in the neurogenic bladder: long-term results. J Urol. 2006 Mar: 175:1106-10

185. Caione P, Capozza N. Endoscopic treatment of urinary incontinence in pediatric patients: 2-year experience with dextranomer/hyaluronic acid copolymer. J Urol. 2002 Oct: 168:1868-71

186. Misseri R, Casale AJ, Cain MP, Rink RC. Alternative uses of dextranomer/hyaluronic acid copolymer: the efficacy of bladder neck injection for urinary incontinence. J Urol. 2005 Oct: 174:1691-3; discussion 3-4

187. Dean GE, Kirsch AJ, Packer MG, Scherz HC, Zaontz MR. Antegrade and retrograde endoscopic dextranomer/hyaluronic Acid bladder neck bulking for pediatric incontinence. J Urol. 2007 Aug: 178:652-5

188. Henly DR, Barrett DM, Weiland TL, O'Connor MK, Malizia AA, Wein AJ. Particulate silicone for use in periurethral injections: local tissue effects and search for migration. J Urol. 1995 Jun: **153**:2039-43

189. Stenberg AM, Sundin A, Larsson BS, Lackgren G, Stenberg A. Lack of distant migration after injection of a 125iodine labeled dextranomer based implant into the rabbit bladder. J Urol. 1997 Nov: **158**:1937-41

190. Lottmann HB, Margaryan M, Lortat-Jacob S, Bernuy M, Lackgren G. Long-term effects of dextranomer endoscopic injections for the treatment of urinary incontinence: an update of a prospective study of 61 patients. J Urol. 2006 Oct: **176**:1762-6

191. Karsenty G, Chartier-Kastler E, Mozer P, Even-Schneider A, Denys P, Richard F. A novel technique to achieve cutaneous continent urinary diversion in spinal cord-injured patients unable to catheterize through native urethra. Spinal Cord 2007; 46: 305-310.

192. Castellan M, Gosalbez R, Labbie A, Ibrahim E, Disandro M. Bladder neck sling for treatment of neurogenic incontinence in children with augmentation cystoplasty: long-term followup. J Urol 2005;173:2128-2131; discussion 2131.

193. Albouy B, Grise P, Sambuis C, Pfister C, Mitrofanoff P, Liard A. Pediatric urinary incontinence: evaluation of bladder wall wraparound sling procedure. J Urol 2007;177:716-719.

194. Karsenty G, Chartier-Kastler E, Mozer P, Even-Schneider A, Denys P, Richard F. A novel technique to achieve cutaneous continent urinary diversion in spinal cord-injured patients unable to catheterize through native urethra. Spinal Cord 2007; 46: 305-310

195. Castellan M, Gosalbez R, Labbie A, Ibrahim E, Disandro M. Bladder neck sling for treatment of neurogenic incontinence in children with augmentation cystoplasty: long-term followup. J Urol 2005;173:2128-2131; discussion 2131.

196. Albouy B, Grise P, Sambuis C, Pfister C, Mitrofanoff P, Liard A. Pediatric urinary incontinence: evaluation of bladder wall wraparound sling procedure. J Urol 2007;177:716-719.

197. Harris SE, Guralnick ML, O'Connor RC. Urethral Erosion of Transobturator Male Sling. Urology 2008.

198. Ordorica R, Rodriguez AR, Coste-Delvecchio F, Hoffman M, Lockhart J. Disabling complications with slings for managing female stress urinary incontinence. BJU Int 2008.

199. Velemir L, Amblard J, Jacquetin B, Fatton B. Urethral erosion after suburethral synthetic slings: risk factors, diagnosis, and functional outcome after surgical management. Int Urogynecol J Pelvic Floor Dysfunct 2008.

200. Hamid R, Khastgir J, Arya M, Patel HR, Shah PJ. Experience of tension-free vaginal tape for the treatment of stress incontinence in females with neuropathic bladders. Spinal Cord. 2003 Feb: **41**:118-21

201. Scott FB, Bradley WE, Timm GW. Treatment of urinary incontinence by implantable prosthetic sphincter. Urology 1973;1:252-259.

202. Chartier-Kastler E, Ayoub N, Richard F, Ruffion A. [Prosthetic surgery for stress urinary incontinence due

to neurogenic sphincter incompetence]. Prog Urol 2007;17:600-608.

203. Salomon J, Gory A, Bernard L, Ruffion A, Denys P, Chartier-Kastler E. [Urinary tract infection and neurogenic bladder]. Prog Urol 2007;17:448-453

204. Bersch U, Gocking K, Pannek J. The artificial urinary sphincter in patients with spinal cord lesion: description of a modified technique and clinical results. Eur Urol. 2009 Mar: **55**:687-93

205. Herndon CD, Rink RC, Shaw MB, Cain MP, Casale AJ. Experience with non-cycled artificial urinary sphincters. BJU Int 2004;93:1049-1052

206. Diokno AC, Sonda LP. Compatibility of genitourinary prostheses and intermittent self-catheterization. J Urol 1981;125:659-660.

207. Game X, Bram R, Abu Anz S, et al. Laparoscopic insertion of artificial periprostatic urinary sphincter. Urology. 2009 Feb: **73**:442 e1-3

208. Jumper BM, McLorie GA, Churchill BM, Khoury AE, Toi A. Effects of the artificial urinary sphincter on prostatic development and sexual function in pubertal boys with meningomyelocele. J Urol 1990;144:438-442; discussion 443-434.

209. Petit J, Olivier F, Callenaere C, Camier B. [The treatment of sterility due to retrograde ejaculation, using implantation of a pericervical sphincter prosthesis. Apropos of a case]. Prog Urol 1994;4:423-425

210. Young HH. An operation for the cure of incontinence of urine. Surg Gynecol Obstet 1919;28:84-90

211. Dees JE. Congenital epispadias with incontinence. J Urol 1949;62:513-522.

212. Leadbetter GW, Jr. Surgical Correction of Total Urinary Incontinence. J Urol 1964;91:261-266.

213. Sidi AA, Reinberg Y, Gonzalez R. Comparison of artificial sphincter implantation and bladder neck reconstruction in patients with neurogenic urinary incontinence. J Urol 1987;138:1120-1122.

214. Jones JA, Mitchell ME, Rink RC. Improved results using a modification of the Young-Dees-Leadbetter bladder neck repair. Br J Urol 1993;71:555-561

215. Tanagho EA. Bladder neck reconstruction for total urinary incontinence: 10 years experience. J Urol 1981;125:321-326

216. Gallagher PV, Mellon JK, Ramsden PD, Neal DE. Tanagho bladder neck reconstruction in the treatment of adult incontinence. J Urol. 1995 May: **153**:1451-4

217. Kropp KA, Angwafo FF. Urethral lengthening and reimplantation for neurogenic incontinence in children. J Urol 1986;135:533-536.

218. Mollard P, Mouriquand P, Joubert P. Urethral lengthening for neurogenic urinary incontinence (Kropp's procedure): results of 16 cases. J Urol 1990;143:95-97.

219. Snodgrass W. A simplified Kropp procedure for incontinence. J Urol 1997;158:1049-1052.

220. Salle JL, de Fraga JC, Amarante A, Silveira ML, Lambertz M, Schmidt M, et al. Urethral lengthening with anterior bladder wall flap for urinary incontinence: a new approach. J Urol 1994;152:803-806.

221. Salle JL, McLorie GA, Bagli DJ, Khoury AE. Urethral lengthening with anterior bladder wall flap (Pippi Salle procedure): modifications and extended indications of the technique. J Urol 1997;158:585-590.

222. Mouriquand PD, Sheard R, Phillips N, White J, Sharma S, Vandeberg C. The Kropp-onlay procedure (Pippi Salle procedure): a simplification of the technique of urethral lengthening. Preliminary results in eight patients. Br J Urol 1995;75:656-662.

223. Mollard P, Gauriau L, Bonnet JP, Mure PY. Continent cystostomy (Mitrofanoff's procedure) for neurogenic bladder in children and adolescent (56 cases: long-term results). Eur J Pediatr Surg 1997;7:34-37.

224. Shpall AI, Ginsberg DA. Bladder neck closure with lower urinary tract reconstruction: technique and long-term followup. J Urol 2004;172:2296-2299

225. Barqawi A, de Valdenebro M, Furness PD, 3rd, Koyle MA. Lessons learned from stomal complications in children with cutaneous catheterizable continent stomas. BJU Int. 2004 Dec: **94**:1344-7

226. De Vocht TF, Chrzan R, Dik P, Klijn AJ, De Jong TP. Long-term results of bulking agent injection for persistent incontinence in cases of neurogenic bladder dysfunction. J Urol. 2010 Feb: **183**:719-23

227. Gormley EA, Bloom DA, McGuire EJ, Ritchey ML. Pubovaginal slings for the management of urinary incontinence in female adolescents. J Urol 1994;152:822-825; discussion 826-827.

228. Elder JS. Periurethral and puboprostatic sling repair for incontinence in patients with myelodysplasia. J Urol 1990;144:434-437

229. Murphy S, Rea D, O'Mahony J, et al. A comparison of the functional durability of the AMS 800 artificial urinary sphincter between cases with and without an underlying neurogenic aetiology. Ir J Med Sci. 2003 Jul-Sep: **172**:136-8

230. Shankar KR, McGillivray D, Turnock RR, Rickwood AM. Superior transperitoneal dissection for inserting artificial sphincter bladder neck cuffs. BJU Int. 2001 Nov: **88**:797-8

231. Stohrer M, Castro-Diaz D, Chartier-Kastler E, Kramer G, Mattiasson A, Wyndaele JJ. Guidelines on neurogenic lower urinary tract dysfunction. Prog Urol. 2007 May: **17**:703-55

232. Mikulicz V. Zur operation der angerborenen blasensplate. Zentralbl Chir 1889;26:641-643.

233. Lapides J, Diokno AC, Silber SJ, Lowe BS. Clean, intermittent self-catheterization in the treatment of urinary tract disease. Trans Am Assoc Genitourin Surg 1971;63:92-96.

234. Game X, Karsenty G, Chartier-Kastler E, Ruffion A. [Treatment of neurogenic detrusor hyperactivity: enterocystoplasty]. Prog Urol 2007;17:584-596.

235. Meng MV, Anwar HP, Elliott SP, Stoller ML. Pure laparoscopic enterocystoplasty. J Urol 2002;167:1386.

236. Gill IS, Rackley RR, Meraney AM, Marcello PW, Sung GT. Laparoscopic enterocystoplasty. Urology 2000;55:178-181.

237. Gundeti MS, Acharya SS, Zagaja GP, Shalhav AL. Paediatric robotic-assisted laparoscopic augmentation ileocystoplasty and Mitrofanoff appendicovesicostomy (RALIMA): feasibility of and initial experience with the University of Chicago technique. BJU Int. 2011 Mar: **107**:962-9

238. Simforoosh N, Tabibi A, Basiri A, Noorbala MH, Danesh AD, Ijadi A. Is ureteral reimplantation necessary during augmentation cystoplasty in patients with neurogenic bladder and vesicoureteral reflux? J Urol 2002;168:1439-1441.

239. Lopez Pereira P, Martinez Urrutia MJ, Lobato Romera R, Jaureguizar E. Should we treat vesicoureteral reflux in patients who simultaneously undergo bladder augmentation for neuropathic bladder? J Urol 2001;165:2259-2261.

240. Soylet Y, Emir H, Ilce Z, Yesildag E, Buyukunal SN, Danismend N. Quo vadis? Ureteric reimplantation or ignoring reflux during augmentation cystoplasty. BJU Int 2004;94:379-380.

241. Nasrallah PF, Aliabadi HA. Bladder augmentation in patients with neurogenic bladder and vesicoureteral reflux. J Urol 1991;146:563-566.

242. Hayashi Y, Kato Y, Okazaki T, Lane GJ, Kobayashi H,

Yamataka A. The effectiveness of ureteric reimplantation during bladder augmentation for high-grade vesicoureteric reflux in patients with neurogenic bladder: long-term outcome. J Pediatr Surg 2007;42:1998-2001.

243. Wang JB, Liu CS, Tsai SL, Wei CF, Chin TW. Augmentation cystoplasty and simultaneous ureteral reimplantation reduce high-grade vesicoureteral reflux in children with neurogenic bladder. J Chin Med Assoc. 2010 Jul: **74**:294-7

244. Misseri R, Rosenbaum DH, Rink RC. Reflux in cystoplasties. Arch Esp Urol. 2008 Mar: **61**:213-7

245. Gonzalez R, Buson H, Reid C, Reinberg Y. Seromuscular colocystoplasty lined with urothelium: experience with 16 patients. Urology 1995;45:124-129.

246. De Badiola F, Ruiz E, Puigdevall J, Lobos P, Moldes J, Lopez Raffo M, et al. Sigmoid cystoplasty with argon beam without mucosa. J Urol 2001;165:2253-2255.

247. Lima SV, Araujo LA, Vilar FO. Nonsecretory intestinocystoplasty: a 10-year experience. J Urol 2004;171:2636-2639; discussion 2639-2640.

248. Shakeri S, Aminsharifi A, Jahanabadi Z. Application of appendicular-based cecal flap for less invasive augmentation cystoplasty: a novel technique. Urol Int. 2009: **83**:271-6

249. Aminsharifi A, Shakeri S, Yousofzade J, Pakbaz S. In situ reversed ileocystoplasty for less invasive augmentation cystoplasty: an experimental study. Urol Int. 2011: **86**:273-7

250. Shekarriz B, Upadhyay J, Demirbilek S, Barthold JS, Gonzalez R. Surgical complications of bladder augmentation: comparison between various enterocystoplasties in 133 patients. Urology 2000;55:123-128.

251. Chartier-Kastler EJ, Mongiat-Artus P, Bitker MO, Chancellor MB, Richard F, Denys P. Long-term results of augmentation cystoplasty in spinal cord injury patients. Spinal Cord 2000;38:490-494.

252. Hasan ST, Marshall C, Robson WA, Neal DE. Clinical outcome and quality of life following enterocystoplasty for idiopathic detrusor instability and neurogenic bladder dysfunction. Br J Urol 1995;76:551-557.

253. Gundeti MS, Acharya SS, Zagaja GP, Shalhav AL. Paediatric robotic-assisted laparoscopic augmentation ileocystoplasty and Mitrofanoff appendicovesicostomy (RALIMA): feasibility of and initial experience with the University of Chicago technique. BJU Int. 2011 Mar: **107**:962-9

254. Erickson BA, Dorin RP, Clemens JQ. Is nasogastric tube drainage required after reconstructive surgery for neurogenic bladder dysfunction? Urology 2007;69:885-888.

255. Gurung PM, Attar KH, Abdul-Rahman A, Morris T, Hamid R, Shah PJ. Long-term outcomes of augmentation ileocystoplasty in patients with spinal cord injury: a minimum of 10 years of follow-up. BJU Int. 2012 Apr: **109**:1236-42

256. Khoury AE, Salomon M, Doche R, Soboh F, Ackerley C, Jayanthi R, et al. Stone formation after augmentation cystoplasty: the role of intestinal mucus. J Urol 1997;158:1133-1137.

257. Mathoera RB, Kok DJ, Nijman RJ. Bladder calculi in augmentation cystoplasty in children. Urology 2000;56:482-487.

258. DeFoor W, Minevich E, Reddy P, Sekhon D, Polsky E, Wacksman J, et al. Bladder calculi after augmentation cystoplasty: risk factors and prevention strategies. J Urol 2004;172:1964-1966.

259. Zhang H, Yamataka A, Koga H, Kobayashi H, Lane GJ, Miyano T. Bladder stone formation after sigmoidocolocystoplasty: statistical analysis of risk factors. J Pediatr Surg 2005;40:407-411.

260. Terai A, Ueda T, Kakehi Y, Terachi T, Arai Y, Okada Y, et al. Urinary calculi as a late complication of the Indiana continent urinary diversion: comparison with the Kock pouch procedure. J Urol 1996;155:66-68.

261. Palmer LS, Franco I, Kogan SJ, Reda E, Gill B, Levitt SB. Urolithiasis in children following augmentation cystoplasty. J Urol 1993;150:726-729.

262. Ginsberg D, Huffman JL, Lieskovsky G, Boyd S, Skinner DG. Urinary tract stones: a complication of the Kock pouch continent urinary diversion. J Urol 1991;145:956-959.

263. Stein R, Lotz J, Fisch M, Beetz R, Prellwitz W, Hohenfellner R. Vitamin metabolism in patients with a Mainz pouch I: long-term followup. J Urol 1997;157:44-47.

264. Akerlund S, Delin K, Kock NG, Lycke G, Philipson BM, Volkmann R. Renal function and upper urinary tract configuration following urinary diversion to a continent ileal reservoir (Kock pouch): a prospective 5 to 11-year followup after reservoir construction. J Urol 1989;142:964-968.

265. Roth S, Semjonow A, Waldner M, Hertle L. Risk of bowel dysfunction with diarrhea after continent urinary diversion with ileal and ileocecal segments. J Urol 1995;154:1696-1699.

266. Somani BK, Kumar V, Wong S, Pickard R, Ramsay C, Nabi G, et al. Bowel dysfunction after transposition of intestinal segments into the urinary tract: 8-year prospective cohort study. J Urol 2007;177:1793-1798.

267. Feng AH, Kaar S, Elder JS. Influence of enterocystoplasty on linear growth in children with exstrophy. J Urol 2002;167:2552-2555; discussion 2555.

268. Gerharz EW, Preece M, Duffy PG, Ransley PG, Leaver R, Woodhouse CR. Enterocystoplasty in childhood: a second look at the effect on growth. BJU Int 2003;91:79-83.

269. Mingin GC, Nguyen HT, Mathias RS, Shepherd JA, Glidden D, Baskin LS. Growth and metabolic consequences of bladder augmentation in children with myelomeningocele and bladder exstrophy. Pediatrics 2002;110:1193-1198.

270. Vajda P, Pinter AB, Harangi F, Farkas A, Vastyan AM, Oberritter Z. Metabolic findings after colocystoplasty in children. Urology 2003;62:542-546; discussion 546.

271. Shaw J, Lewis MA. Bladder augmentation surgery--what about the malignant risk? Eur J Pediatr Surg 1999;9 Suppl 1:39-40.

272. Metcalfe PD, Cain MP, Kaefer M, Gilley DA, Meldrum KK, Misseri R, et al. What is the need for additional bladder surgery after bladder augmentation in childhood? J Urol 2006;176:1801-1805; discussion 1805.

273. Castellan M, Gosalbez R, Perez-Brayfield M, et al. Tumor in bladder reservoir after gastrocystoplasty. J Urol. 2007 Oct: **178**:1771-4; discussion 4

274. Higuchi TT, Granberg CF, Fox JA, Husmann DA. Augmentation cystoplasty and risk of neoplasia: fact, fiction and controversy. J Urol. 2010 Dec: **184**:2492-6

275. Kokorowski PJ, Routh JC, Borer JG, Estrada CR, Bauer SB, Nelson CP. Screening for malignancy after augmentation cystoplasty in children with spina bifida: a decision analysis. J Urol. 2011 Oct: **186**:1437-43

276. DeFoor W, Tackett L, Minevich E, Wacksman J, Sheldon C. Risk factors for spontaneous bladder perforation after augmentation cystoplasty. Urology 2003;62:737-741.

277. Blok BF, Al Zahrani A, Capolicchio JP, Bilodeau C, Corcos J. Post-augmentation bladder perforation during urodynamic investigation. Neurourol Urodyn 2007;26:540-542.

278. Flood HD, Malhotra SJ, O'Connell HE, Ritchey MJ, Bloom DA, McGuire EJ. Long-term results and complications using augmentation cystoplasty in recon-

structive urology. Neurourol Urodyn 1995;14:297-309.

279. Singh G, Thomas DG. Enterocystoplasty in the neuropathic bladder. Neurourol Urodyn 1995;14:5-10

280. McInerney PD, DeSouza N, Thomas PJ, Mundy AR. The role of urodynamic studies in the evaluation of patients with augmentation cystoplasties. Br J Urol 1995;76:475-478.

281. Herschorn S, Hewitt RJ. Patient perspective of long-term outcome of augmentation cystoplasty for neurogenic bladder. Urology 1998;52:672-678.

282. Blaivas JG, Weiss JP, Desai P, Flisser AJ, Stember DS, Stahl PJ. Long-term followup of augmentation enterocystoplasty and continent diversion in patients with benign disease. J Urol 2005;173:1631-1634

283. Mor Y, Leibovitch I, Golomb J, Ben-Chaim J, Nadu A, Pinthus JH, et al. [Lower urinary tract reconstruction by augmentation cystoplasty and insertion of artificial urinary sphincter cuff only: long term follow-up]. Prog Urol 2004;14:310-314.

284. Close CE. Autoaugmentation gastrocystoplasty. BJU Int 2001;88:757-761.

285. Dewan PA, Anderson P. Ureterocystoplasty: the latest developments. BJU Int 2001;88:744-751.

286. Abdel-Azim MS, Abdel-Hakim AM. Gastrocystoplasty in patients with an areflexic low compliant bladder. Eur Urol 2003;44:260-265.

287. DeFoor W, Minevich E, Reeves D, Tackett L, Wacksman J, Sheldon C. Gastrocystoplasty: long-term followup. J Urol 2003;170:1647-1649; discussion 1649-1650.

288. Husmann DA, Snodgrass WT, Koyle MA, Furness PD, 3rd, Kropp BP, Cheng EY, et al. Ureterocystoplasty: indications for a successful augmentation. J Urol 2004;171:376-380.

289. Mahony DT, Laferte RO. Studis of enuresis. IV. Multiple detrusor myotomy: a new operation for the rehabilitation of severe detrusor hypertrophy and hypercontractility. J Urol 1972;107:1064-1067.

290. Ivancic V, Defoor W, Jackson E, et al. Progression of renal insufficiency in children and adolescents with neuropathic bladder is not accelerated by lower urinary tract reconstruction. J Urol. 2010 Oct: **184**:1768-74

291. Basiri A, Otoukesh H, Simforoosh N, Hosseini R, Farrokhi F. Kidney transplantation in children with augmentation cystoplasty. J Urol. 2007 Jul: **178**:274-7

292. Basiri A, Otookesh H, Hosseini R, Simforoosh N, Moghaddam SM. Kidney transplantation before or after augmentation cystoplasty in children with high-pressure neurogenic bladder. BJU Int. 2009 Jan: **103**:86-8

293. Mahony DT, Laferte RO. Studis of enuresis. IV. Multiple detrusor myotomy: a new operation for the rehabilitation of severe detrusor hypertrophy and hypercontractility. J Urol. 1972 Jun: **107**:1064-7

294. Cartwright PC, Snow BW. Bladder autoaugmentation: partial detrusor excision to augment the bladder without use of bowel. J Urol 1989;142:1050-1053.

295. Ehrlich RM, Gershman A. Laparoscopic seromyotomy (auto-augmentation) for non-neurogenic neurogenic bladder in a child: initial case report. Urology 1993;42:175-178.

296. McDougall EM, Clayman RV, Figenshau RS, Pearle MS. Laparoscopic retropubic auto-augmentation of the bladder. J Urol 1995;153:123-126.

297. Mammen T, Balaji KC. Robotic transperitoneal detrusor myotomy: description of a novel technique. J Endourol 2005;19:476-479.

298. Poppas DP, Uzzo RG, Britanisky RG, Mininberg DT. Laparoscopic laser assisted auto-augmentation of the pediatric neurogenic bladder: early experience with urodynamic followup. J Urol 1996;155:1057-1060.

299. Oge O, Tekgul S, Ergen A, Kendi S. Urothelium-preserving augmentation cystoplasty covered with a peritoneal flap. BJU Int 2000;85:802-805.

300. Perovic SV, Djordjevic ML, Kekic ZK, Vukadinovic VM. Detrusorectomy with rectus muscle hitch and backing. J Pediatr Surg 2003;38:1637-1641.

301. Frey P, Lutz N, Leuba AL. Augmentation cystoplasty using pedicled and de-epithelialized gastric patches in the mini-pig model. J Urol 1996;156:608-613.

302. Nguyen DH, Mitchell ME, Horowitz M, Bagli DJ, Carr MC. Demucosalized augmentation gastrocystoplasty with bladder autoaugmentation in pediatric patients. J Urol 1996;156:206-209.

303. Kumar SP, Abrams PH. Detrusor myectomy: long-term results with a minimum follow-up of 2 years. BJU Int 2005;96:341-344.

304. Leng WW, Blalock HJ, Fredriksson WH, English SF, McGuire EJ. Enterocystoplasty or detrusor myectomy? Comparison of indications and outcomes for bladder augmentation. J Urol 1999;161:758-763.

305. MacNeily AE, Afshar K, Coleman GU, Johnson HW. Autoaugmentation by detrusor myotomy: its lack of effectiveness in the management of congenital neuropathic bladder. J Urol 2003;170:1643-1646; discussion 1646.

306. Marte A, Di Meglio D, Cotrufo AM, Di Iorio G, De Pasquale M, Vessella A. A long-term follow-up of autoaugmentation in myelodysplastic children. BJU Int 2002;89:928-931.

307. Potter JM, Duffy PG, Gordon EM, Malone PR. Detrusor myotomy: a 5-year review in unstable and non-compliant bladders. BJU Int 2002;89:932-935.

308. Rawashdeh YF, Jorgensen TM, Olsen LH, Djurhuus JC. The outcome of detrusor myotomy in children with neurogenic bladder dysfunction. J Urol 2004;171:2654-2656.

309. Stohrer M, Kramer G, Goepel M, Lochner-Ernst D, Kruse D, Rubben H. Bladder autoaugmentation in adult patients with neurogenic voiding dysfunction. Spinal Cord 1997;35:456-462.

310. Rivas DA, Chancellor MB, Huang B, Epple A, Figueroa TE. Comparison of bladder rupture pressure after intestinal bladder augmentation (ileocystoplasty) and myomyotomy (autoaugmentation). Urology 1996;48:40-46.

311. Aboushwareb T, McKenzie P, Wezel F, Southgate J, Badlani G. Is tissue engineering and biomaterials the future for lower urinary tract dysfunction (LUTD)/pelvic organ prolapse (POP)? Neurourol Urodyn. 2011 Jun: **30**:775-82

312. Fraser M, Thomas DF, Pitt E, Harnden P, Trejdosiewicz LK, Southgate J. A surgical model of composite cystoplasty with cultured urothelial cells: a controlled study of gross outcome and urothelial phenotype. BJU Int. 2004 Mar: **93**:609-16

313. Caione P, Capozza N, Zavaglia D, Palombaro G, Boldrini R. In vivo bladder regeneration using small intestinal submucosa: experimental study. Pediatr Surg Int. 2006 Jul: **22**:593-9

314. Ayyildiz A, Akgul KT, Huri E, et al. Use of porcine small intestinal submucosa in bladder augmentation in rabbit: long-term histological outcome. ANZ J Surg. 2008 Jan-Feb: **78**:82-6

315. Ayyildiz A, Nuhoglu B, Huri E, Ozer E, Gurdal M, Germiyanoglu C. Using porcine acellular collagen matrix (Pelvicol) in bladder augmentation: experimental study. Int Braz J Urol. 2006 Jan-Feb: **32**:88-92; discussion -3

316. Pattison M, Webster TJ, Leslie J, Kaefer M, Haber-

stroh KM. Evaluating the in vitro and in vivo efficacy of nano-structured polymers for bladder tissue replacement applications. Macromol Biosci. 2007 May 10: **7**:690-700

317. Jayo MJ, Jain D, Ludlow JW, et al. Long-term durability, tissue regeneration and neo-organ growth during skeletal maturation with a neo-bladder augmentation construct. Regen Med. 2008 Sep: **3**:671-82

318. Jayo MJ, Jain D, Wagner BJ, Bertram TA. Early cellular and stromal responses in regeneration versus repair of a mammalian bladder using autologous cell and biodegradable scaffold technologies. J Urol. 2008 Jul: **180**:392-7

319. Korossis S, Bolland F, Southgate J, Ingham E, Fisher J. Regional biomechanical and histological characterisation of the passive porcine urinary bladder: Implications for augmentation and tissue engineering strategies. Biomaterials. 2009 Jan: **30**:266-75

320. Jack GS, Zhang R, Lee M, Xu Y, Wu BM, Rodriguez LV. Urinary bladder smooth muscle engineered from adipose stem cells and a three dimensional synthetic composite. Biomaterials. 2009 Jul: **30**:3259-70

321. Domingos AL, Tucci S, Jr., Garcia SB, de Bessa J, Jr., Cologna AJ, Martins AC. Use of a latex biomembrane for bladder augmentation in a rabbit model: biocompatibility, clinical and histological outcomes. Int Braz J Urol. 2009 Mar-Apr: **35**:217-24; author reply 25

322. Mondalek FG, Ashley RA, Roth CC, et al. Enhanced angiogenesis of modified porcine small intestinal submucosa with hyaluronic acid-poly(lactide-co-glycolide) nanoparticles: from fabrication to preclinical validation. J Biomed Mater Res A. 2010 Sep 1: **94**:712-9

323. Roth CC, Mondalek FG, Kibar Y, et al. Bladder reo generation in a canine model using hyaluronic acid-poly(lactic-co-glycolic-acid) nanoparticle modified porcine small intestinal submucosa. BJU Int. 2011 Jul: **108**:148-55

324. Mauney JR, Cannon GM, Lovett ML, et al. Evaluation of gel spun silk-based biomaterials in a murine model of bladder augmentation. Biomaterials. 2011 Jan: **32**:808-18

325. Gomez P, 3rd, Gil ES, Lovett ML, et al. The effect of manipulation of silk scaffold fabrication parameters on matrix performance in a murine model of bladder augmentation. Biomaterials. 2011 Oct: **32**:7562-70

326. Turner A, Subramanian R, Thomas DF, et al. Transplantation of autologous differentiated urothelium in an experimental model of composite cystoplasty. Eur Urol. 2011 Mar: **59**:447-54

327. Yoo JJ, Olson J, Atala A, Kim B. Regenerative medicine strategies for treating neurogenic bladder. Int Neurourol J. 2011 Sep: **15**:109-19

328. Zhang Y, Kropp BP, Moore P, et al. Coculture of bladder urothelial and smooth muscle cells on small intestinal submucosa: potential applications for tissue engineering technology. J Urol. 2000 Sep: **164**:928-34; discussion 34-5

329. Dahms SE, Piechota HJ, Dahiya R, Lue TF, Tanagho EA. Composition and biomechanical properties of the bladder acellular matrix graft: comparative analysis in rat, pig and human. Br J Urol. 1998 Sep: **82**:411-9

330. Bolland F, Korossis S, Wilshaw SP, et al. Development and characterisation of a full-thickness acellular porcine bladder matrix for tissue engineering. Biomaterials. 2007 Feb: **28**:1061-70

331. Barrington JW, Dyer R, Bano F. Bladder augmentation using Pelvicol implant for intractable overactive bladder syndrome. Int Urogynecol J Pelvic Floor Dysfunct 2006;17:50-53.

332. Atala A, Bauer SB, Soker S, Yoo JJ, Retik AB. Tissue-engineered autologous bladders for patients needing cystoplasty. Lancet 2006;367:1241-1246.

333. Chen JL, Kuo HC. Long-term outcomes of augmentation enterocystoplasty with an ileal segment in patients with spinal cord injury. J Formos Med Assoc. 2009 Jun: **108**:475-80

334. Quek ML, Ginsberg DA. Long-term urodynamics followup of bladder augmentation for neurogenic bladder. J Urol 2003;169:195-198.

335. Medel R, Ruarte AC, Herrera M, Castera R, Podesta ML. Urinary continence outcome after augmentation ileocystoplasty as a single surgical procedure in patients with myelodysplasia. J Urol 2002;168:1849-1852.

336. Nomura S, Ishido T, Tanaka K, Komiya A. Augmentation ileocystoplasty in patients with neurogenic bladder due to spinal cord injury or spina bifida. Spinal Cord 2002;40:30-33.

337. Arikan N, Turkolmez K, Budak M, Gogus O. Outcome of augmentation sigmoidocystoplasty in children with neurogenic bladder. Urol Int 2000;64:82-85.

338. Venn SN, Mundy AR. Long-term results of augmentation cystoplasty. Eur Urol 1998;34 Suppl 1:40-42.

339. Mast P, Hoebeke P, Wyndaele JJ, Oosterlinck W, Everaert K. Experience with augmentation cystoplasty. A review. Paraplegia 1995;33:560-564.

340. Khoury JM, Timmons SL, Corbel L, Webster GD. Complications of enterocystoplasty. Urology 1992;40:9-14.

341. Luangkhot R, Peng BC, Blaivas JG. Ileocecocystoplasty for the management of refractory neurogenic bladder: surgical technique and urodynamic findings. J Urol 1991;146:1340-1344.

342. Robertson AS, Davies JB, Webb RJ, Neal DE. Bladder augmentation and replacement. Urodynamic and clinical review of 25 patients. Br J Urol 1991;68:590-597.

343. Hendren WH, Hendren RB. Bladder augmentation: experience with 129 children and young adults. J Urol 1990;144:445-453; discussion 460.

344. Sidi AA, Becher EF, Reddy PK, Dykstra DD. AugmenA tation enterocystoplasty for the management of voiding dysfunction in spinal cord injury patients. J Urol 1990;143:83-85.

345. Lockhart JL, Bejany D, Politano VA. Augmentation cystoplasty in the management of neurogenic bladder disease and urinary incontinence. J Urol 1986;135:969-971.

346. Asayama K, Kihara K, Shidoh T, Shigaki M, Ikeda T. The functional limitations of tetraplegic hands for intermittent clean self-catheterisation. Paraplegia 1995;33:30-33.

347. Mollard P, Gauriau L, Bonnet JP, Mure PY. Continent cystostomy (Mitrofanoff's procedure) for neurogenic bladder in children and adolescent (56 cases: long-term results). Eur J Pediatr Surg 1997;7:34-37.

348. Zommick JN, Simoneau AR, Skinner DG, Ginsberg DA. Continent lower urinary tract reconstruction in the cervical spinal cord injured population. J Urol 2003;169:2184-2187.

349. Koyle MA, Mingin GC, Furness PD, 3rd, Malone PSJ. The Mitrofanoff (flap valve) principle: application in contemporary continent urinary and gastrointestinal reconstruction. AUA update series 2004;23:273-279.

350. Mills RD, Studer UE. Metabolic consequences of continent urinary diversion. J Urol 1999;161:1057-1066.

351. Mitrofanoff P. [Trans-appendicular continent cystostomy in the management of the neurogenic bladder]. Chir Pediatr 1980;21:297-305.

352. Monti PR, Lara RC, Dutra MA, de Carvalho JR. New techniques for construction of efferent conduits based on the Mitrofanoff principle. Urology 1997;49:112-115.

353. Casale AJ. A long continent ileovesicostomy using a single piece of bowel. J Urol 1999;162:1743-1745.

354. Dodat H, Denis E, Pelizzo G, Dubois R, Carlioz P, Chavrier Y. [Continent urinary diversion using a tubulized sigmoid segment. An alternative to trans-appendicular diversion]. Prog Urol 1998;8:58-61.

355. Cain MP, Rink RC, Yerkes EB, Kaefer M, Casale AJ. Long-term followup and outcome of continent catheterizable vesicocstomy using the Rink modification. J Urol 2002;168:2583-2585.

356. Close CE, Mitchell ME. Continent gastric tube: new techniques and long-term followup. J Urol 1997;157:51-55.

357. Mor Y, Kajbafzadeh AM, German K, Mouriquand PD, Duffy PG, Ransley PG. The role of ureter in the creation of Mitrofanoff channels in children. J Urol 1997;157:635-637.

358. Castellan MA, Gosalbez R, Labbie A, Ibrahim E, Disandro M. Outcomes of continent catheterizable stomas for urinary and fecal incontinence: comparison among different tissue options. BJU Int 2005;95:1053-1057.

359. Perovic S. Continent urinary diversion using preputial penile or clitoral skin flap. J Urol 1996;155:1402-1406.

360. Karsenty G, Chartier-Kastler E, Mozer P, Even-Schneider A, Denys P, Richard F. A novel technique to achieve cutaneous continent urinary diversion in spinal cord-injured patients unable to catheterize through native urethra. Spinal Cord 2007.

361. Sylora JA, Gonzalez R, Vaughn M, Reinberg Y. Intermittent self-catheterization by quadriplegic patients via a catheterizable Mitrofanoff channel. J Urol 1997;157:48-50.

362. Walsh K, Troxel SA, Stone AR. An assessment of the use of a continent catheterizable stoma in female tetraplegics. BJU Int 2004;94:595-597.

363. Moreno JG, Chancellor MB, Karasick S, King S, Abdill CK, Rivas DA. Improved quality of life and sexuality with continent urinary diversion in quadriplegic women with umbilical stoma. Arch Phys Med Rehabil 1995;76:758-762.

364. Mor Y, Quinn FM, Carr B, Mouriquand PD, Duffy PG, Ransley PG. Combined Mitrofanoff and antegrade continence enema procedures for urinary and fecal incontinence. J Urol 1997;158:192-195.

365. Franc-Guimond J, Gonzalez R. Simplified technique to create a concealed catheterizable stoma: the VR flap. J Urol 2006;175:1088-1091.

366. Tekant G, Emir H, Eroglu E, Esenturk N, Buyukunal C, Danismend N, et al. Catheterisable continent urinary diversion (Mitrofanoff principle)--clinical experience and psychological aspects. Eur J Pediatr Surg 2001;11:263-267.

367. Watanabe T, Rivas DA, Smith R, Staas WE, Jr., Chancellor MB. The effect of urinary tract reconstruction on neurologically impaired women previously treated with an indwelling urethral catheter. J Urol 1996;156:1926-1928.

368. Touma NJ, Horovitz D, Shetty A, Caumartin Y, De Maria J, Luke PP. Outcomes and quality of life of adults undergoing continent catheterizable vesicostomy for neurogenic bladder. Urology 2007;70:454-458.

369. Thomas JC, Dietrich MS, Trusler L, DeMarco RT, Pope JCt, Brock JW, 3rd, et al. Continent catheterizable channels and the timing of their complications. J Urol 2006;176:1816-1820; discussion 1820.

370. Liard A, Seguier-Lipszyc E, Mathiot A, Mitrofanoff P. The Mitrofanoff procedure: 20 years later. J Urol 2001;165:2394-2398.

371. Narayanaswamy B, Wilcox DT, Cuckow PM, Duffy PG, Ransley PG. The Yang-Monti ileovesicostomy: a problematic channel? BJU Int 2001;87:861-865.

372. De Ganck J, Everaert K, Van Laecke E, Oosterlinck W, Hoebeke P. A high easy-to-treat complication rate is the price for a continent stoma. BJU Int 2002;90:240-243.

373. Pons M, Messaoudi R, Fiquet C, et al. Use of cutaneous flap for continent cystostomy (daoud technique). J Urol. 2010 Sep: **184**:1116-21

374. Wiesner C, Bonfig R, Stein R, Gerharz EW, Pahernik S, Riedmiller H, et al. Continent cutaneous urinary diversion: long-term follow-up of more than 800 patients with ileocecal reservoirs. World J Urol 2006;24:315-318.

375. Carr LK, Webster GD. Kock versus right colon continent urinary diversion: comparison of outcome and reoperation rate. Urology 1996;48:711-714.

376. Pazooki D, Edlund C, Karlsson AK, Dahlstrand C, Lindholm E, Tornqvist H, et al. Continent cutaneous urinary diversion in patients with spinal cord injury. Spinal Cord 2006;44:19-23.

377. Blaivas JG, Weiss JP, Desai P, Flisser AJ, Stember DS, Stahl PJ. Long-term followup of augmentation enterocystoplasty and continent diversion in patients with benign disease. J Urol 2005;173:1631-1634.

378. Stein R, Wiesner C, Beetz R, Pfitzenmeier J, Schwarz M, Thuroff JW. Urinary diversion in children and adolescents with neurogenic bladder: the Mainz experience. Part II: Continent cutaneous diversion using the Mainz pouch I. Pediatr Nephrol 2005;20:926-931.

379. Plancke HR, Delaere KP, Pons C. Indiana pouch in female patients with spinal cord injury. Spinal Cord 1999;37:208-210.

380. Abdallah MM, Bissada NK, Hamouda HM, Bissada AN. Long-term multi-institutional evaluation of Charleston pouch I continent cutaneous urinary diversion. J Urol 2007;177:2217-2220.

381. De Troyer B, Van Laecke E, Groen LA, Everaert K, Hoebeke P. A comparative study between continent diversion and bladder neck closure versus continent diversion and bladder neck reconstruction in children. J Pediatr Urol. 2010 Apr: **7**:209-12

382. Spahn M, Kocot A, Loeser A, Kneitz B, Riedmiller H. Last resort in devastated bladder outlet: bladder neck closure and continent vesicostomy--long-term results and comparison of different techniques. Urology. 2010 May: **75**:1185-92

383. Wille MA, Zagaja GP, Shalhav AL, Gundeti MS. Continence outcomes in patients undergoing robotic assisted laparoscopic mitrofanoff appendicovesicostomy. J Urol. 2011 Apr: **185**:1438-43

384. Vian E, Soustelle L, Viale S, Costa P. [A technique of continent vesicostomy with ileocystoplasty: study of 32 patients]. Prog Urol. 2009 Feb: **19**:116-21

385. Welk BK, Afshar K, Rapoport D, MacNeily AE. Complications of the catheterizable channel following continent urinary diversion: their nature and timing. J Urol. 2008 Oct: **180**:1856-60

386. Mhiri MN, Bahloul A, Chabchoub K. [Mitrofanoff appendicovesicostomy in children: indication and results]. Prog Urol 2007;17:245-249.

387. Chulamorkodt NN, Estrada CR, Chaviano AH. Continent urinary diversion: 10-year experience of Shriners Hospitals for Children in Chicago. J Spinal Cord Med 2004;27 Suppl 1:S84-87.

388. Barqawi A, de Valdenebro M, Furness PD, 3rd, Koyle MA. Lessons learned from stomal complications in children with cutaneous catheterizable continent stomas. BJU Int 2004;94:1344-1347.

389. Lemelle JL, Simo AK, Schmitt M. Comparative study of the Yang-Monti channel and appendix for continent diversion in the Mitrofanoff and Malone principles. J Urol 2004;172:1907-1910.

390. Kochakarn W, Muangman V. Mitrofanoff procedure

incombination with enterocystoplasty for detrusor hyperreflexia with external sphincter dyssynergia: one-year experience of 12 cases. J Med Assoc Thai 2001;84:1046-1050.

391. Harris CF, Cooper CS, Hutcheson JC, Snyder HM, 3rd. Appendicovesicostomy: the mitrofanoff procedure-a 15-year perspective. J Urol 2000;163:1922-1926.

392. Cain MP, Casale AJ, King SJ, Rink RC. Appendicovesicostomy and newer alternatives for the Mitrofanoff procedure: results in the last 100 patients at Riley Children's Hospital. J Urol 1999;162:1749-1752

393. Wiener JS, Antonelli J, Shea AM, et al. Bladder augmentation versus urinary diversion in patients with spina bifida in the United States. J Urol. 2011 Jul: **186**:161-5

394. Pfister C, Prapotnich D, Mombet A, Veillon B, Brisset JM, Vallancien G. [Technique and results of the "Mini-Bricker" urinary tract diversion after total cystectomy for bladder tumors]. Prog Urol 1994;4:953-958.

395. Beurton D, Fontaine E, Grall J, Houlgatte A, Cukier J. [Cutaneous trans-jejunal ureterostomy: an original technique used in 29 patients]. Prog Urol 1992;2:381-390.

396. Hubert J, Chammas M, Larre S, Feuillu B, Cheng F, Beis JM, et al. Initial experience with successful totally robotic laparoscopic cystoprostatectomy and ileal conduit construction in tetraplegic patients: report of two cases. J Endourol 2006;20:139-143.

397. Hubert J, Feuillu B, Beis JM, Coissard A, Mangin P, Andre JM. Laparoscopic robotic-assisted ileal conduit urinary diversion in a quadriplegic woman. Urology 2003;62:1121.

398. Potter SR, Charambura TC, Adams JB, 2nd, Kavoussi LR. Laparoscopic ileal conduit: five-year follow-up. Urology 2000;56:22-25.

399. Yohannes P, Khan A, Francis K, Sudan R. Robot-assisted Bricker ileoureteral anastomosis during intracorporeal laparoscopic ileal conduit urinary diversion for prostatocutaneous fistula: case report. J Endourol 2004;18:269-272.

400. Ramalingam M, Senthil K, Ganapathy Pai M. Laparoscopy-assisted ileal conduit in sacral agenesis. J Laparoendosc Adv Surg Tech A. 2008 Apr: **18**:335-9

401. Guillotreau J, Game X, Castel-Lacanal E, Mallet R, De Boissezon X, Malavaud B, et al. [Laparoscopic cystectomy and transileal ureterostomy for neurogenic vesicosphincteric disorders. Evaluation of morbidity]. Prog Urol 2007;17:208-212.

402. Chaykovska L, Deger S, Wille A, et al. Kidney transplantation into urinary conduits with ureteroureterostomy between transplant and native ureter: single-center experience. Urology. 2009 Feb: **73**:380-5

403. Kato H, Hosaka K, Kobayashi S, Igawa Y, Nishizawa O. Fate of tetraplegic patients managed by ileal conduit for urinary control: long-term follow-up. Int J Urol 2002;9:253-256

404. Chartier-Kastler EJ, Mozer P, Denys P, Bitker MO, Haertig A, Richard F. Neurogenic bladder management and cutaneous non-continent ileal conduit. Spinal Cord 2002;40:443-448.

405. Malone PR, Stanton SL, Riddle PR. Urinary diversion for incontinence--a beneficial procedure? Ann R Coll Surg Engl 1985;67:349-352.

406. Samellas W, Rubin B. Management of Upper Urinary Tract Complications in Multiple Sclerosis by Means of Urinary Diversion to an Ileal Conduit. J Urol 1965;93:548-552.

407. Hetet JF, Rigaud J, Karam G, Glemain P, Le Normand L, Bouchot O, et al. [Complications of Bricker ileal conduit urinary diversion: analysis of a series of 246 patients]. Prog Urol 2005;15:23-29; discussion 29.

408. Singh G, Wilkinson JM, Thomas DG. Supravesical diversion for incontinence: a long-term follow-up. Br J Urol 1997;79:348-353.

409. Legrand G, Roupret M, Comperat E, Even-Schneider A, Denys P, Chartier-Kastler E. Functional outcomes after management of end-stage neurological bladder dysfunction with ileal conduit in a multiple sclerosis population: a monocentric experience. Urology. 2011 Oct: **78**:937-41

410. Malek RS, Burke EC, Deweerd JH. Ileal conduit urinary diversion in children. J Urol 1971;105:892-900.

411. Schwarz GR, Jeffs RD. Ileal conduit urinary diversion in children: computer analysis of followup from 2 to 16 years. J Urol 1975;114:285-288.

412. Heath AL, Eckstein HB. Ileal conduit urinary diversion in children. A long term follow-up. J Urol (Paris) 1984;90:91-96.

413. Pitts WR, Jr., Muecke EC. A 20-year experience with ileal conduits: the fate of the kidneys. J Urol 1979;122:154-157.

414. Shapiro SR, Lebowitz R, Colodny AH. Fate of 90 children with ileal conduit urinary diversion a decade later: analysis of complications, pyelography, renal function and bacteriology. J Urol 1975;114:289-295.

415. Arnarson O, Straffon RA. Clinical experience with the ileal conduit in children. J Urol 1969;102:768-771.

416. Erickson BA, Dorin RP, Clemens JQ. Is nasogastric tube drainage required after reconstructive surgery for neurogenic bladder dysfunction? Urology 2007;69:885-888.

417. Somani BK, Kumar V, Wong S, Pickard R, Ramsay C, Nabi G, et al. Bowel dysfunction after transposition of intestinal segments into the urinary tract: 8-year prospective cohort study. J Urol 2007;177:1793-1798.

418. Fazili T, Bhat TR, Masood S, Palmer JH, Mufti GR. Fate of the leftover bladder after supravesical urinary diversion for benign disease. J Urol 2006;176:620-621.

419. Bennett CJ, Young MN, Adkins RH, Diaz F. Comparison of bladder management complication outcomes in female spinal cord injury patients. J Urol 1995;153:1458-1460.

420. Cass AS, Luxenberg M, Gleich P, Johnson CF. A 22-year followup of ileal conduits in children with a neurogenic bladder. J Urol 1984;132:529-531.

421. Stonehill WH, Dmochowski RR, Patterson AL, Cox CE. Risk factors for bladder tumors in spinal cord injury patients. J Urol 1996;155:1248-1250.

422. Djavan B, Litwiller SE, Milchgrub S, Roehrborn CG. Mucinous adenocarcinoma in defunctionalized bladders. Urology 1995;46:107-110.

423. Yap RL, Weiser A, Ozer O, Pazona J, Schaeffer A. Adenocarcinoma arising from a defunctionalized bladder. J Urol 2002;167:1782-1783.

424. Yang CC, Clowers DE. Screening cystoscopy in chronically catheterized spinal cord injury patients. Spinal Cord 1999;37:204-207.

425. Hamid R, Bycroft J, Arya M, Shah PJ. Screening cystoscopy and biopsy in patients with neuropathic bladder and chronic suprapubic indwelling catheters: is it valid? J Urol 2003;170:425-427.

426. Neulander EZ, Rivera I, Eisenbrown N, Wajsman Z. Simple cystectomy in patients requiring urinary diversion. J Urol 2000;164:1169-1172.

427. Laven BA, O'Connor RC, Gerber GS, Steinberg GD. Long-term results of endoureterotomy and open surgical revision for the management of ureteroenteric strictures after urinary diversion. J Urol 2003;170:1226-1230.

428. Poulakis V, Witzsch U, De Vries R, Becht E. Cold-knife

endoureterotomy for nonmalignant ureterointestinal anastomotic strictures. Urology 2003;61:512-517; discussion 517.

429. Watterson JD, Sofer M, Wollin TA, Nott L, Denstedt JD. Holmium: YAG laser endoureterotomy for ureterointestinal strictures. J Urol 2002;167:1692-1695.

430. Kouba E, Sands M, Lentz A, Wallen E, Pruthi RS. Incidence and risk factors of stomal complications in patients undergoing cystectomy with ileal conduit urinary diversion for bladder cancer. J Urol 2007;178:950-954.

431. Ahmed S, Boucaut HA. Urinary undiversion in 35 patients with neurogenic bladder and an ileal conduit. Aust N Z J Surg 1987;57:753-761.

432. Ahmed S, Carney A. Urinary undiversion in myelomeningocele patients with an ileal conduit diversion. J Urol 1981;125:847-852.

433. Borden TA, Woodside JR. Urinary tract undiversion in a patient with an areflexic neurogenic bladder: management with intermittent catheterization. J Urol 1980;123:956-958.

434. Menon M, Elder JS, Manley CB, Jeffs RD. Undiverting the ileal conduit. J Urol 1982;128:998-1000.

435. Breza J, Hornak M, Bardos A, Zvara P. Transformation of the Bricker to a continent urinary reservoir to eliminate severe complications of uretero-ileostomy performed in eight patients among 200 Bricker. Ann Urol (Paris) 1995;29:227-231.

436. Cordonnier JJ. Ileocystostomy: followup evaluation of 14 cases. J Urol 1962;87:60-62.

437. Cordonnier JJ. Ileocystostomy for neurogenic bladder. J Urol 1957;78:605-610.

438. Schwartz SL, Kennelly MJ, McGuire EJ, Faerber GJ. Incontinent ileo-vesicostomy urinary diversion in the treatment of lower urinary tract dysfunction. J Urol 1994;152:99-102.

439. Mutchnik SE, Hinson JL, Nickell KG, Boone TB. Ileovesicostomy as an alternative form of bladder management in tetraplegic patients. Urology 1997;49:353-357.

440. Abrahams HM, Rahman NU, Meng MV, Stoller ML. Pure laparoscopic ileovesicostomy. J Urol 2003;170:517-518.

441. Atan A, Konety BR, Nangia A, Chancellor MB. Advantages and risks of ileovesicostomy for the management of neuropathic bladder. Urology 1999;54:636-640.

442. Rivas DA, Karasick S, Chancellor MB. Cutaneous ileocystostomy (a bladder chimney) for the treatment of severe neurogenic vesical dysfunction. Paraplegia 1995;33:530-535.

443. Gudziak MR, Tiguert R, Puri K, Gheiler EL, Triest JA. Management of neurogenic bladder dysfunction with incontinent ileovesicostomy. Urology 1999;54:1008-1011.

444. Leng WW, Faerber G, Del Terzo M, McGuire EJ. Long-term outcome of incontinent ileovesicostomy management of severe lower urinary tract dysfunction. J Urol 1999;161:1803-1806.

445. Hsu TH, Rackley RR, Abdelmalak JB, Tchetgen MB, Madjar S, Vasavada SP. Laparoscopic ileovesicostomy. J Urol 2002;168:180-181.

446. Vanni AJ, Cohen MS, Stoffel JT. Robotic-assisted ileovesicostomy: initial results. Urology. 2009 Oct: **74**:814-8

447. Vanni AJ, Stoffel JT. Ileovesicostomy for the neurogenic bladder patient: outcome and cost comparison of open and robotic assisted techniques. Urology. 2011 Jun: **77**:1375-80

448. Tan HJ, Stoffel J, Daignault S, McGuire EJ, Latini JM. Ileovesicostomy for adults with neurogenic bladders: Complications and potential risk factors for adverse outcomes. Neurourol Urodyn 2007.

449. Gauthier AR, Jr., Winters JC. Incontinent ileovesicostomy in the management of neurogenic bladder dysfunction. Neurourol Urodyn 2003;22:142-146.

450. Hellenthal NJ, Short SS, O'Connor RC, Eandi JA, Yap SA, Stone AR. Incontinent ileovesicostomy: Long-term outcomes and complications. Neurourol Urodyn. 2009: **28**:483-6

451. Zimmerman WB, Santucci RA. Ileovesicostomy: update. Arch Esp Urol. 2011 Apr: **64**:207-18

452. Petrou SP. Incontinent ileovesicostomy in the management of neurogenic bladder dysfunction. Int Braz J Urol 2003;29:185-186.

453. Blocksom BH, Jr. Bladder pouch for prolonged tubeless cystostomy. J Urol 1957;78:398-401.

454. Lapides J, Ajemian EP, Lichtwardt JR. Cutaneous vesicostomy. 1960. J Urol 2002;167:1147-1151; discussion 1152.

455. Lapides J, Koyanagi T, Diokno A. Cutaneous vesicostomy: 10-year survey. J Urol 1971;105:76-80.

456. Allen TD. Vesicostomy for the temporary diversion of the urine in small children. J Urol 1980;123:929-931.

457. Cohen JS, Harbach LB, Kaplan GW. Cutaneous vesicostomy for temporary urinary diversion in infants with neurogenic bladder dysfunction. J Urol 1978;119:120-121

458. Lee MW, Greenfield SP. Intractable high-pressure bladder in female infants with spina bifida: clinical characteristics and use of vesicostomy. Urology 2005;65:568-571.

459. Mandell J, Bauer SB, Colodny AH, Retik AB. Cutaneous vesicostomy in infancy. J Urol 1981;126:92-93.

460. Morrisroe SN, O'Connor RC, Nanigian DK, Kurzrock EA, Stone AR. Vesicostomy revisited: the best treatment for the hostile bladder in myelodysplastic children? BJU Int 2005;96:397-400.

461. Snyder HM, 3rd, Kalichman MA, Charney E, Duckett JW. Vesicostomy for neurogenic bladder with spina bifida: followup. J Urol 1983;130:724-726.

462. Jayanthi VR, McLorie GA, Khoury AE, Churchill BM. The effect of temporary cutaneous diversion on ultimate bladder function. J Urol 1995;154:889-892.

463. Sonda LP, Solomon MH. Twenty-year outcome of cutaneous vesicostomy. J Urol 1980;124:326-328.

464. Pannek J. Vesicostomy in adult meningomyelocele patients. Reappraisal of an old technique. Int Urol Nephrol 1999;31:643-645.

465. Lacreuse I, Becmeur F, Dheu C, Moog R, Terzic J, Fischbach M. Endoscopic Mic-Key button placement for continent vesicostomy. J Laparoendosc Adv Surg Tech A 2010; 20: 297-9

466. Johnston JH. Temporary cutaneous ureterostomy in the management of advanced congenital urinary obstruction. Arch Dis Child 1963;38:161-166.

467. Lister J, Cook RC, Zachary RB. Operative management of neurogenic bladder dysfunction in children: ureterostomy. Arch Dis Child 1968;43:672-678.

468. Kogan BA, Gohary MA. Cutaneous ureterostomy as a permanent external urinary diversion in children. J Urol 1984;132:729-731.

469. MacGregor PS, Kay R, Straffon RA. Cutaneous ureterostomy in children--long-term followup. J Urol 1985;134:518-520.

470. Sarduy GS, Crooks KK, Smith JP, Wise HA, 2nd. Results in children managed by cutaneous ureterostomy. Urology 1982;19:486-488.

471. Chitale SV, Chitale VR. Bilateral ureterocutaneostomy

with modified stoma: long-term follow-up. World J Urol 2006;24:220-223.

472. Lindstedt E, Mansson W. Transuretero-ureterostomy with cutaneous ureterostomy for permanent urinary diversion. Scand J Urol Nephrol 1983;17:205-207.

D. Neurological faecal incontinence

DI. Epidemiology

1. Saunders LL, Selassie AW, Hill EG, Nicholas JS, Varma AK, Lackland DT, Patel SJ. J Trauma. 2009;66:184-90

2. Williams R, Rigby AS, Airey M, Robinson M, Ford H. Multiple sclerosis: its epidemiological, genetic, and health care impact. J Epidemiol Comm Health 1995;49: 563 –569.

3. Lang AE, Lozano AM. Medical Progress: Parkinson's disease. Parts 1 and 2. NEJM. 1998:339:1130-1143:1044-1053

4. Glickmann S, Kamm MA. Bowel dysfunction in spinal cord injury patients. Lancet 1996; 347:1651-1653.

5. Hinds JP, Eidelmann BH, Wald A. Prevalence of bowel dysfunction in multiple sclerosis. A population study. Gastroenterology 1990; 98: 1538-1542.

6. Edwards LL, Quigley EEM, Pfeier RF. Gastrointestinal dysfunction in Parkinson´s disease: frequency and pathophysiology. Neurology 1992; 42: 726-732.

7. DeVivo MJ. Epidemiology of traumatic spinal cord injury. In: Kirshblum S, Campagnolo DI, DeLisa JA, eds. *Spinal Cord Medicine*. Baltimore, Md: Lippincott Williams & Wilkins; 2002:69-81

8. Avery JD, Avery JA. Malignant spinal cord compression: a hospice emergency. *Home Healthc Nurse*. 2008;26:457-61

9. Biering-Sørensen F, Pedersen V, Clausen S. Epidemiology of spinal cord lesions in Denmark. Paraplegia 1990; 28: 105-111

10. Krogh K, Nielsen J, Djurhuus JC *et al*.. Colorectal function in patients with spinal cord lesions. Dis Colon Rectum 1997; 40: 1233-1239

11. Finnerup NB, Faaborg P, Krogh K, Jensen TS. Abdominal pain in long-term spinal cord injury. Spinal Cord 2008; 46: 198-203

12. Bakke H, Myhr KM, Gronning M, Nyland H. Bladder, bowel and sexual dysfunction in patients with multiple sclerosis – a cohort study. Scand J Urol Nephrol Suppl 1996; 179: 61-66.

13. Krogh K, Ostergaard K, Sabroe S, Laurberg S. Clinical aspects of bowel symptoms in Parkinson´s disease. Acta Neurol Scand 2008; 117: 60-64

14. Doshi VS, Say JH, Young SH, Doraisamy P. Complications of stroke in patients: a study carried out at the Rehabilitation Medicine Service, Change General Hospital. Singapore Med J 2003; 44: 643-652

DII. Neurophysiology

1. Sun WM, MacDonagh R, Forster D *et al*. Anorectal function in patients with complete spinal transsection before and after sacral posterior rhizotomy. Gastroenterology 1995; 108: 990-998.

2. Lynch AC, Anthony A, Dobbs DR, Frizelle FA. Anorectal physiology following spinal cord injury. Spinal Cord 2000; 38: 573-580.

3. Nino-Murcia M, Stone J, Chang P, Perkash I. Colonic transit in spinal cord injured patients. Invest Radiol 1990; 25: 109-112.

4. Krogh K, Mosdal C, Laurberg S. Gastrointestinal and segmental colonic transit times in patients with acute and chronic spinal cord lesions. Spinal Cord 2000; 38: 615-621s

5. Aaronson MJ, Freed MM, Burakoff R. Colonic myoelectric activity in persons with spinal cord injury. Dig Dis Sci 1985; 30: 295-300

6. Krogh K, Olsen N, Christensen P, Madsen JL, Laurberg S. Colorectal transport during defecation in patients with lesions of the sacral spinal cord. Neurogastroenterol Motil 2003; 15: 25-31

7. Vallès M, Vidal J, Clavé P, Mearin F. Bowel dysfunction in patients with motor complete spinal cord injury: clinical, neurological, and pathophysiological associations.Am J Gastroenterol. 2006 Oct;101(10):2290-9

8. Freckner B, Ihre T. Influence of autonomic nerves on the internal anal sphincter in man. Gut 1976; 17: 306-312

9. Craggs M, Balasubramaniam AV, Chung EAL, Emmanuel AV. Aberrant reflexes and function of the pelvic organs following spinalcord injury in man. Auton Neurosci 2006; 126-127: 355-370

10. Ashraf W, Wszolek ZK, Pfeier RF *et al*. Anorectal function in fluctuating (on-off) Parkinson´s disease: evaluation by combined anorectal manometry and electromyography. Mov Disord 1995; 10: 650-657.

11. Singaram C, Ashraf W, Gaumintz EA *et al*. Dopaminergic defect of enteric nervous system in Parkinson´s disease patients with chronic constipation. Lancet 1995; 346: 861-864s.

12. Edwards LL, Quigley EM, Hanred RK *et al*. Characterization of swallowing and defecation in Parkinson´s disease. Am J Gastroenterol 1994; 89: 15-25.

13. Kupsky WJ, Grimes MM, Sweetig J *et al*. Parkinson´s disease and megacolon: Concentric hyaline inclusions (Lewi bodies) in enteric ganglion cells. Neurology 1987; 37: 1253-1255s.

14. Abbott RD, Petrovitch H, White LR *et al*. Frequency of bowel movements and the future risk of Parkinson´s disease. Neurology 2001; 57: 456-462.

DIII. Assessment

1. Jorge JMN, Wexner SD. Etiology and management of faecal incontinence. Dis Colon Rectum 1993; 36: 77-97.

2. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. Gut 1999; 44: 77-80

3. Krogh K, Christensen P, Sabroe S, Laurberg S. Neurogenic bowel dysfunction score. Spinal Cord 2006; 44: 625-631

DIV. Conservative management

1. Wyndaele JJ, Maderbacher H, Castro D, Igawa Y, Kovindha A., Radziszewski P, Stone A, Wiesel P. *Neurologic urinary and fecal incontinence*. In: Incontinence. Abrams P, Cardozo L, Khoury S, Wein A (Editors), Plymouth, HEALTH Publications 2004; Volume 2, Chapter 17, 1059-1162.

2. Wyndaele JJ, Kovindha A, Maderbacher H, Radziszewski P, Ruffion A, Schurch B, Castro D, Igawa Y, Sakakibara P, Perkash I. *Neurologic urinary and fecal incontinence.* In: Incontinence. Abrams P, Cardozo L, Khoury S, Wein A (Editors), Plymouth, HEALTH Publications 2009; Chapter 10, 793-960

3. Krassioukov A, Eng JJ, Claxton G, Sakakibara BM, Shum S. Neurogenic bowel management after spinal cord injury: a systematic review of the evidence. Spinal Cord. 2010;48:718-733.

4. Coggrave M, Norton C, Wilson-Barnett J. Management of neurogenic bowel dysfunction in the community after spinal cord injury: a postal survey in the United Kingdom. Spinal Cord. 2009;47:323-330

5. Emmanuel A. Managing neurogenic bowel dysfunction. Clin Rehabil. 2010; 24:483-8.

6. Coggrave MJ, Norton C. The need for manual evacuation and oral laxatives in the management of neurogenic bowel dysfunction after spinal cord injury: a randomized controlled trial of a stepwise protocol. Spinal Cord. 2010 ;48:504-510

7. Krogh K, Jensen MB, Gandrup P, et al. Efficacy and tolerability of prucalopride in patients with constipation due to spinal cord injury. Scand J Gastroenterol. 2002 Apr: **37**:431-6

8. McClurg D, Hagen S, Hawkins S, Lowe-Strong A. Abdominal massage for the alleviation of constipation symptoms in people with multiple sclerosis: a randomized controlled feasibility study. Mult Scler. 2011 ;17:223-233.

9. Ayaş S, Leblebici B, Sözay S, Bayramoğlu M, Niron EA.The effect of abdominal massage on bowel function in patients with spinal cord injury. Am J Phys Med Rehabil. 2006 ;85:951-955.

10. Christensen P, Krogh K, Buntzen S, Payandeh F, Laurberg S. Long-term outcome and safety of transanal irrigation for constipation and fecal incontinence. Dis Colon Rectum. 2009;52:286-292

11. Faaborg PM, Christensen P, Kvitsau B, Buntzen S, Laurberg S, Krogh K. Long-term outcome and safety of transanal colonic irrigation for neurogenic bowel dysfunction. Spinal Cord. 2009 ;47:545-549. .

12. Ausili E, Focarelli B, Tabacco F, Murolo D, Sigismondi M, Gasbarrini A, Rendeli C.Transanal irrigation in myelomeningocele children: an alternative, safe and valid approach for neurogenic constipation.Spinal Cord. 2010 ;48:560-565.

13. Neel KF.Total endoscopic and anal irrigation management approach to noncompliant neuropathic bladder in children: a good alternative. J Urol. 2010;184:315-318.

14. Christensen P, Andreasen J, Ehlers L.Cost-effectiveness of transanal irrigation versus conservative bowel management for spinal cord injury patients. Spinal Cord. 2009 ; 47:138-143.

15. Emmanuel A. Review of the efficacy and safety of transanal irrigation for neurogenic bowel dysfunction. Spinal Cord. 2010; 48: 664-673

16. Bond C, Youngson G, MacPherson I, Garrett A, Bain N, Donald S, Macfarlane TV. Anal plugs for the management of fecal incontinence in children and adults: a randomized control trial. J Clin Gastroenterol. 2007;41:45-53.

17. Tsai PY, Wang CP, Chiu FY, Tsai YA, Chang YC, Chuang TY.Efficacy of functional magnetic stimulation in neurogenic bowel dysfunction after spinal cord injury. J Rehabil Med. 2009;41:41-47.

18. Kajbafzadeh AM, Sharifi-Rad L, Nejat F, Kajbafzadeh M, Talaei HR.Transcutaneous interferential electrical stimulation for management of neurogenic bowel dysfunction in children with myelomeningocele. Int J Colorectal Dis. 2011 Nov 9. Epub

19. Fu G, Liao LM, Lü Z, Li JJ, Wu J, Ju YH, Li D, Liang WL, Han CS, Xiong ZS, Shi WB. Neuromodulation for treatment for neurogenic bowel dysfunction. Zhonghua Wai Ke Za Zhi (Chinese) 2009;47:128-131.

DV. Surgical treatment

1. Matzel KE, Stadelmaier U, Hohenfellner M, Gall FP. Electrical stimulation of sacral spinal nerves for treatment of faecal incontinence. Lancet. 1995 Oct 28;346(8983):1124-7.

2. Matzel KE, Bittorf B, Stadelmaier U, Hohenberger W. [Sacral nerve stimulation in the treatment of faecal incontinence] Chirurg. 2003 Jan;741:26-32.

3. Ripetti V, Caputo D, Ausania F, Esposito E, Bruni R, Arullani A. Sacral nerve neuromodulation improves physical, psychological and social quality of life in patients with fecal incontinence. Tech Coloproctol. 2002;6(3):147-52.

4. Rasmussen OO, Christiansen J. [Sacral nerve stimulation in fecal incontinence] Ugeskr Laeger. 2002 Aug 12;164(33):3866-8.

5. Kenefick NJ, Vaizey CJ, Cohen RC, Nicholls RJ, Kamm MA. Medium-term results of permanent sacral nerve stimulation for faecal incontinence.Br J Surg. 2002 Jul;89(7):896-901.

6. Matzel KE, Stadelmaier U, Hohenfellner M, Hohenberger W. Chronic sacral spinal nerve stimulation for fecal incontinence: long-term results with foramen and cuff electrodes.Dis Colon Rectum. 2001 Jan;441:59-66.

7. Rosen HR, Urbarz C, Holzer B, Novi G, Schiessel R. Sacral nerve stimulation as a treatment for fecal incontinence. Gastroenterology. 2001 Sep;121(3):536-41.

8. Ganio E, Ratto C, Masin A, Luc AR, Doglietto GB, Dodi G, Ripetti V, Arullani A, Frascio M, BertiRiboli E, Landolfi V, DelGenio A, Altomare DF, Memeo V, Bertapelle P, Carone R, Spinelli M, Zanollo A, Spreafico L, Giardiello G, deSeta F. Neuromodulation for fecal incontinence: outcome in 16 patients with definitive implant. The initial Italian Sacral Neurostimulation Group (GINS) experience. Dis Colon Rectum. 2001;44(7):965-70.

9. Leroi AM, Michot F, Grise P, Denis P. Effect of sacral nerve stimulation in patients with fecal and urinary incontinence. Dis Colon Rectum. 2001;44(6):779-89.

10. Ganio E, Luc AR, Clerico G, Trompetto M. Sacral nerve stimulation for treatment of fecal incontinence: a novel approach for intractable fecal incontinence. Dis Colon Rectum. 2001 May;44(5):619-29; discussion 629-31.

11. Malouf AJ, Vaizey CJ, Nicholls RJ, Kamm MA. Permanent sacral nerve stimulation for fecal incontinence. Ann Surg. 2000 Jul;2321:143-8.

12. Rosen HR, Urbarz C, Holzer B et al. Sacral nerve stimulation as a treatment for fecal incontinence. Gastroenterology 2001; 121:536.

13. Kessler TM, Madersbacher H, Kiss G . Prolonged sacral neuromodulation testing using permanent leads: a more reliable patient selection method?_Eur Urol. 2005 May;47(5):660-5

14. Jarrett ME. Neuromodulation for constipation and fecal incontinence Urol Clin North Am. 2005 Feb;32(1):79-87

15. Holzer B, Rosen HR, Novi G, Ausch C, Hölbling N, Schiessel R Sacral nerve stimulation for neurogenic faecal incontinence_Br J Surg. 2007 Jun;94(6):749-53

16. Lombardi G, Del Popolo G, Cecconi F, Surrenti E, Macchiarella A. Clinical outcome of sacral neuromodulation in incomplete spinal cord-injured patients suffering from neurogenic bowel dysfunctions. Spinal Cord 2010 Feb. 48(2):154-9.

17. Malone PS, Ransley PG, Kiely EM. Preliminary report: the antegrade continence enema. Lancet. 1990 Nov 17;336(8725):1217-8.

18. Teichman JM, Zabihi N, Kraus SR, Harris JM, Barber DB. Long-term results for Malone antegrade continence enema for adults with neurologic bowel disease. Urology. 2003 Mar;61(3):502-6.

19. Dey R, Ferguson C, Kenny SE, Shankar KR, Coldicutt P, Baillie CT, Lamont GL, Lloyd DA, Losty PD, Turnock RR. After the honeymoon--medium-term outcome of antegrade continence enema procedure. J Pediatr Surg. 2003 Jan;381:65-8;

20. Liard A, Bocquet I, Bachy B, Mitrofanoff P. [Survey on satisfaction of patients with Malone continent cecostomy] Prog Urol. 2002 Dec;12(6):1256-60.

21. Aksnes G, Diseth TH, Helseth A, Edwin B, Stange M, Aafos G, Emblem R. Appendicostomy for antegrade enema: effects on somatic and psychosocial functioning in children with myelomeningocele. Pediatrics. 2002 Mar;109(3):484-9

22. Liloku RB, Mure PY, Braga L, Basset T, Mouriquand PD. The left Monti-Malone procedure: Preliminary results in seven cases. J Pediatr Surg. 2002 Feb;372:228-31.

23. Tackett LD, Minevich E, Benedict JF, Wacksman J, Sheldon CA. Appendiceal versus ileal segment for antegrade continence enema. J Urol. 2002 Feb;167(2 Pt 1):683-6.

24. Perez M, Lemelle JL, Barthelme H, Marquand D, Schmitt M. Bowel management with antegrade colonic enema using a Malone or a Monti conduit--clinical results.Eur J Pediatr Surg. 2001;11(5):315-8.

25. Kajbafzadeh AM, Chubak N. Simultaneous Malone antegrade continent enema and Mitrofanoff principle using the divided appendix: report of a new technique for prevention of stoma complications. J Urol. 2001 Jun;165(6 Pt 2):2404-9.

26. Van Savage JG, Yohannes P. Laparoscopic antegrade continence enema in situ appendix procedure for refractory constipation and overflow fecal incontinence in children with spina bifida. J Urol. 2000 Sep;164(3 Pt 2):1084-7.

27. Bruce RG, el-Galley RE, Wells J, Galloway NT. Antegrade continence enema for the treatment of fecal incontinence in adults: use of gastric tube for catheterizable access to the descending colon. J Urol. 1999 Jun;161(6):1813-6.

28. Robertson RW, Lynch AC, Beasley SW, Morreau PN. Early experience with the laparoscopic ace procedure. Aust N Z J Surg. 1999 Apr;69(4):308-10.

29. Teichman JM, Harris JM, Currie DM, Barber DB. Malone antegrade continence enema for adults with neurologic bowel disease. J Urol. 1998 Oct;160(4):1278-81.

30. Meier DE, Foster ME, Guzzetta PC, Coln D. Antegrade continent enema management of chronic fecal incontinence in children. J Pediatr Surg. 1998 Jul;33(7):1149-51; discussion 1151-2.

31. Driver CP, Barrow C, Fishwick J, Gough DC, Bianchi A, Dickson AP. The Malone antegrade colonic enema procedure: outcome and lessons of 6 years' experience.Pediatr Surg Int. 1998 Jul;13(5-6):370-2.

32. Hensle TW, Reiley EA, Chang DT. The Malone antegrade continence enema procedure in the management of patients with spina bifida. J Am Coll Surg. 1998 Jun;186(6):669-74.

33. Levitt MA, Soffer SZ, Pena A. Continent appendicostomy in the bowel management of fecally incontinent children. J Pediatr Surg. 1997 Nov;32(11):1630-3.

34. Goepel M, Sperling H, Stohrer M, Otto T, Rubben H. Management of neurologic fecal incontinence in myelodysplastic children by a modified continent appendiceal stoma and antegrade colonic enema. Urology. 1997 May;49(5):758-61.

35. Dick AC, McCallion WA, Brown S, Boston VE. Antegrade colonic enemas.Br J Surg. 1996 May;83(5):642-3.

36. Ellsworth PI, Webb HW, Crump JM, Barraza MA, Stevens PS, Mesrobian HG. The Malone antegrade colonic enema enhances the quality of life in children undergoing urological incontinence procedures. J Urol. 1996 Apr;155(4):1416-8.

37. Koyle MA, Kaji DM, Duque M, Wild J, Galansky SH. The Malone antegrade continence enema for neurologic and structural fecal incontinence and constipation.J Urol. 1995 Aug;154(2 Pt 2):759-61.

38. Squire R, Kiely EM, Carr B, Ransley PG, Duffy PG. The clinical application of the Malone antegrade colonic enema. J Pediatr Surg. 1993 Aug;28(8):1012-5.

39. Casale AJ, Metcalfe PD, Kaefer MA, Dussinger AM, Meldrum KK, Cain MP, Rink RC. Total continence reconstruction: a comparison to staged reconstruction of neuropathic bowel and bladderJ Urol. 2006 Oct;176(4 Pt 2):1712-5.

40. Herndon CD, Rink RC, Cain MP, Lerner M, Kaefer M, Yerkes E, Casale AJ. In situ Malone antegrade continence enema in 127 patients: a 6-year experience J Urol. 2004 Oct;172(4 Pt 2):1689-91

41. Bar-Yosef Y, Castellan M, Joshi D, Labbie A, Gosalbez R. Total continence reconstruction using the artificial urinary sphincter and the Malone antegrade continence enema. J Urol 2011 Apr; 185(4):1444-7

42. Rongen MJ, Uludag O, El Naggar K, Geerdes BP, Konsten J, Baeten CG. Long-term follow-up of dynamic graciloplasty for fecal incontinence. Dis Colon Rectum. 2003 Jun;46(6):716-21.

43. Wexner SD, Baeten C, Bailey R, Bakka A, Belin B, Belliveau P, Berg E, Buie WD, Burnstein M, Christiansen J, Coller J, Galandiuk S, Lange J, Madoff R, Matzel KE, Pahlman L, Parc R, Reilly J, Seccia M, Thorson AG, Vernava AM 3rd. Long-term efficacy of dynamic graciloplasty for fecal incontinence. Dis Colon Rectum. 2002 Jun;45(6):809-18.

44. Bresler L, Reibel N, Brunaud L, Sielezneff I, Rouanet P, Rullier E, Slim K. [Dynamic graciloplasty in the treatment of severe fecal incontinence. French multicentric retrospective study] Ann Chir. 2002 Sep;127(7):520-6.

45. Matzel KE, Madoff RD, LaFontaine LJ, Baeten CG, Buie WD, Christiansen J, Wexner S; Dynamic Graciloplasty Therapy Study Group. Complications of dynamic graciloplasty: incidence, management, and impact on outcome. Dis Colon Rectum. 2001;44(10):1427-35.

46. Baeten CG, Bailey HR, Bakka A, Belliveau P, Berg E, Buie WD, Burnstein MJ, Christiansen J, Coller JA, Galandiuk S, LaFontaine LJ, Lange J, Madoff RD, Matzel KE, Pahlman L, Parc R, Reilly JC, Seccia M, Thorson AG, Vernava AM 3rd, Wexner S. Safety and efficacy of dynamic graciloplasty for fecal incontinence: report of a prospective, multicenter trial. Dynamic Graciloplasty Therapy Study Group. Dis Colon Rectum. 2000;43(6):743-51.

47. Madoff RD, Rosen HR, Baeten CG, LaFontaine LJ, Cavina E, Devesa M, Rouanet P, Christiansen J, Faucheron JL, Isbister W, Kohler L, Guelinckx PJ, Pahlman L. Safety and efficacy of dynamic muscle plasty for anal incontinence: lessons from a prospective, multicenter trial. Gastroenterology. 1999;116:549-56.

48. Sielezneff I, Malouf AJ, Bartolo DC, Pryde A, Douglas S. Dynamic graciloplasty in the treatment of patients with faecal incontinence. Br J Surg. 1999;861:61-5.

49. Christiansen J, Rasmussen OO, Lindorff-Larsen K. Dynamic graciloplasty for severe anal incontinence. Br J Surg. 1998;851:88-91.

50. Geerdes BP, Heineman E, Konsten J, Soeters PB, Baeten CG. Dynamic graciloplasty. Complications and management. Dis Colon Rectum. 1996;39(8):912-7.

51. Baeten CG, Geerdes BP, Adang EM, Heineman E, Konsten J, Engel GL, Kester AD, Spaans F, Soeters PB. Anal dynamic graciloplasty in the treatment of intractable fecal incontinence. N Engl J Med. 1995 Jun 15;332(24):1600-5.

52. Ortiz H, Armendariz P, DeMiguel M, Solana A, Alos R, Roig JV. Prospective study of artificial anal sphincter and dynamic graciloplasty for severe anal incontinence. Int J Colorectal Dis. 2003 Jul;18(4):349-54.

53. Chapman AE, Geerdes B, Hewett P, Young J, Eyers T, Kiroff G, Maddern GJ. Systematic review of dynamic graciloplasty in the treatment of faecal incontinence. Br J Surg. 2002;892:138-53

54. Christiansen J, Lorentzen M. Implantation of artificial sphincter for anal incontinence. Lancet. 1987 Aug 1;2(8553):244-5.

55. Wong WD, Congliosi SM, Spencer MP, Corman ML, Tan P, Opelka FG, Burnstein M, Nogueras JJ, Bailey HR, Devesa JM, Fry RD, Cagir B, Birnbaum E, Fleshman JW, Lawrence MA, Buie WD, Heine J, Edelstein PS, Gregorcyk S, Lehur PA, Michot F, Phang PT, Schoetz DJ, Potenti F, Tsai JY. The safety and efficacy of the artificial bowel sphincter for fecal incontinence: results from a multicenter cohort study. Dis Colon Rectum. 2002 Sep;45(9):1139-53.

56. Parker SC, Spencer MP, Madoff RD, Jensen LL, Wong WD, Rothenberger DA. Artificial bowel sphincter: long-term experience at a single institution. Dis Colon Rectum. 2003 Jun;46(6):722-9.

57. Michot F, Costaglioli B, Leroi AM, Denis P. Artificial anal sphincter in severe fecal incontinence: outcome of prospective experience with 37 patients in one institution. Ann Surg. 2003 Jan;2371:52-6.

58. Devesa JM, Rey A, Hervas PL, Halawa KS, Larranaga I, Svidler L, Abraira V, Muriel A. Artificial anal sphincter: complications and functional results of a large personal series.Dis Colon Rectum. 2002 Sep;45(9):1154-63.

59. Ortiz H, Armendariz P, DeMiguel M, Ruiz MD, Alos R, Roig JV. Complications and functional outcome following artificial anal sphincter implantation. Br J Surg. 2002 Jul;89(7):877-81.

60. Altomare DF, Dodi G, La Torre F, Romano G, Melega E, Rinaldi M. Multicentre retrospective analysis of the outcome of artificial anal sphincter implantation for severe faecal incontinence. Br J Surg. 2001 Nov;88(11):1481-6.

61. O'Brien PE, Skinner S. Restoring control: the Acticon Neosphincter artificial bowel sphincter in the treatment of anal incontinence. Dis Colon Rectum. 2000 Sep;43(9):1213-6.

62. Lehur PA, Roig JV, Duinslaeger M. Artificial anal sphincter: prospective clinical and manometric evaluation. Dis Colon Rectum. 2000 Aug;43(8):1100-6.

63. Christiansen J, Rasmussen OO, Lindorff-Larsen K. Long-term results of artificial anal sphincter implantation for severe anal incontinence. Ann Surg. 1999 Jul;2301:45-8.

64. Vaizey CJ, Kamm MA, Gold DM, Bartram CI, Halligan S, Nicholls RJ. Clinical, physiological, and radiologia cal study of a new purpose-designed artificial bowel sphincter. Lancet. 1998 Jul 11;352(9122):105-9.

65. Lehur PA, Glemain P, Bruley des Varannes S, Buzelin JM, Leborgne J. Outcome of patients with an implanted artificial anal sphincter for severe faecal incontinence. A single institution report. Int J Colorectal Dis. 1998;132:88-92.

66. Lehur PA, Michot F, Denis P, Grise P, Leborgne J, Teniere P, Buzelin JM. Results of artificial sphincter in severe anal incontinence. Report of 14 consecutive implantations. Dis Colon Rectum. 1996 Dec;39(12):1352-5.

67. Wong WD, Jensen LL, Bartolo DC, Rothenberger DA. Artificial anal sphincter. Dis Colon Rectum. 1996 Dec;39(12):1345-51.

68. Lehur PA, Meurette G. The artificial bowel sphincter in the treatment of severe fecal incontinence in adults. 2007

69. Michot F, Tuech J-J, Lefebure B, Bridoux V, Denis P. A new implantation procedure of artificial sphincter for anal incontinence: the transvaginal approach. Dis. Colon Rectum. 2007; 50:1-4.

70. Devesa JM, Rey A, Hervas Pl, Halawa KS, Larrañaga I, Svider L, Abraira V, Muriel A. Artificial anal sphincter: complications and functional results of a large personal series. Dis Colon. Rectum 2002 Sep; 45(9):1154-63.

71. Branagan G, Tromans A, Finnis D. Effect of stoma formation on bowel care and quality of life in patients with spinal cord injury. Spinal Cord. 2003 Dec;41(12):680-3.

72. Safadi BY, Rosito O, Nino-Murcia M, Wolfe VA, Perkash I. Which stoma works better for colonic dysmotility in the spinal cord injured patient? Am J Surg. 2003 Nov;186(5):437-42.

73. Rosito O, Nino-Murcia M, Wolfe VA, Kiratli BJ, Perkash I. The effects of colostomy on the quality of life in patients with spinal cord injury: a retrospective analysis. J Spinal Cord Med. 2002 Fall;25(3):174-83.

74. Randell N, Lynch AC, Anthony A, Dobbs BR, Roake JA, Frizelle FA. Does a colostomy alter quality of life in patients with spinal cord injury? A controlled study. Spinal Cord. 2001 May;39(5):279-82.

75. Kelly SR, Shashidharan M, Borwell B, Tromans AM, Finnis D, Grundy DJ. The role of intestinal stoma in patients with spinal cord injury. Spinal Cord. 1999 Mar;37(3):211-4.

76. Stone JM, Wolfe VA, Nino-Murcia M, Perkash I. Coe lostomy as treatment for complications of spinal cord injury. Arch Phys Med Rehabil. 1990 Jun;71(7):514-8.

77. Saltzstein RJ, Romano J. The efficacy of colostomy as a bowel management alternative in selected spinal cord injury patients. J Am Paraplegia Soc. 1990 Apr;132:9-13.

78. Frisbie JH, Tun CG, Nguyen CH. Effect of enterosG tomy on quality of life in spinal cord injury patients. J Am Paraplegia Soc. 1986 Jan-Apr;9(1-2):3-5.

79. Rosito O, Nino-Murcia M, Wolfe VA, et al. The effects of colostomy on the quality of life in patients with spinal cord injury: a retrospective analysis. J Spinal Cord Med 2002;25:174

80. Safadi BY, Rositoa O, Nino-Murcia M, et al. Which stoma works better for colonic dysmotility in the spinal cord injured patient? Am J Surg 2003;186:437

81. Frisbie JH, Ahmed N, Hirano I, Klein MA, Soybel DI. Diversion colitis in patients with myelopathy: clinical, endoscopic, and histopathological findings. J Spinal Cord Med. 2000 Summer;232:142-9.

82. Lai JM, Chuang TY, Francisco GE, Strayer JR. Diversion colitis: a cause of abdominal discomfort in spinal cord injury patients with colostomy. Arch Phys Med Rehabil. 1997 Jun;78(6):670-1.

83. Harig JM, Soergel KH, Komorowski RA, Wood CM. Treatment of diversion colitis with short-chain-fatty acid irrigation. N Engl J Med. 1989 Jan 5;3201:23-8.

84. Eggenberger JC, Farid A. Diversion Colitis. Curr Treat Options Gastroenterol. 2001 Jun;4(3):255-259.

85. Hocevar B, Gray M. Intestinal diversion (colostomy or ileostomy) in patients with severe bowel dysfunction following spinal cord injury. J Wound Ostomy Continence Nurs. 2008 Mar-Apr; 35(2):159-66.

86. Mackey P, Mackey L, Kennedy ML, King DW, Newstead GL, Douglas PR, Lobowski DZ. Postanal repair - do the long-term results justify the procedure? Colorectal Dis. 2010 Apr; 12(4):367-72.

E. Specific neurological diseases

E-I to VII

1. Grossmann H, Bergmann C, Parker S. Dementia: A Brief Review. Mt Sinai J Med. 2006: 73:985-92

2. Honig L, Mayeux R. Natural history of Alzheimer's disease. Aging 2001: 13:171-82

3. Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. IV: Disorders of behaviour. Br J Psychiatry. 1990: 157:86-94
4. Cacabelos R, Rodriguez B, Carrrera C, et al. APOE-related frequency of cognitive and noncognitive symptoms in dementia. Methods Find Exp Clin Pharmacol. 1996: 18:693-706
5. Sakakibara R, Uchiyama T, Yamanishi T, Kishi M. Dementia and lower urinary dysfunction: with a reference to anticholinergic use in elderly population. Int J Urol. 2008 15:778-88
6. Hutchinson S, Leger-Krall S, Skodol Wilson H. Toileting: a bio-behavioral challenge in Alzheimer's dementia care. J Gerontol Nurs. 1996: 22:18-27
7. Tariot P. Medical management of advanced dementia. J Am Geriatr Soc. 2003: 51 Suppl:S305-13
8. Areosa S, Sherriff F. Memantine for dementia. Cochrane Database Syst Rev. 2003: 3:CD003154
9. Ransmayr G, Holliger S, Schletterer K, et al. Lower urinary tract symptoms in dementia with Lewy bodies, Parkinson disease, and Alzheimer disease. Neurology. 2008 70:299-303
10. Del Ser T, Munoz D, Hachinsky V. Temporal pattern of cognitive decline and incontinence is different in Alzheimer's disease and diffuse Lewy body disease. Neurology 1996: 46:682-6
11. Nobili F, Copello F, Buffoni F, et al. Timing of disease progression by quantitative EEG in Alzheimer's patients. J Clin Neurophysiol. 1999: 16:556-73
12. Nobili F, Copello F, Buffoni F, et al. Regional cerebral blood flow and prognostic evaluation in Alzheimer's disease. Dement Geriatr Cogn Disord. 2001: 122:89-97
13. Sugiyama T, Hashimoto K, Kiwamoto H. Urinary incontinence in senile dementia of the Alzheimer type (SDAT). Int J Urol. 1994: 1:337- 40
14. Haddad F, Curd G, Meyers J. Alzheimer's disease with refluxes. Urol Int. 1987: 422:155-7
15. Franssen E, Souren L, Torossian C, Reisberg B. Utility of developmental reflexes in the differential diagnosis and prognosis of incontinence in Alzheimer's disease. J Geriatr Psychiatry Neurol. 1997: 101:22-8
16. Lancioni G, Singh N, OReilly M, et al. Persons with mild or moderate Alzheimer's disease learn to use urine alarms and prompts to avoid large urinary accidents. Research in Developmental Disabilities. 2011: 32:1998.2004
17. Shinotoh H, Aotsuka A, Fukushi K, et al. Effect of donepezil on brain acetylcholinesterase activity in patients with AD measured by PET. Neurology 2001: 56:408-10
18. Burns A, Rossor M, Hecker J, et al. The effects of donepezil in 17 Alzheimer's disease: Results from a multinational trial. Dementia and Geriatric Cognitive-Disorders. 1999: 10:237-44
19. Rogers S, Farlow M, Doody R, Mohs R, Friedhoff L. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 1998: 50:136-45
20. Becker R. Therapy of the cognitive deficit in Alzheimer's disease; the cholinergic system. In RE B, E G eds, Cholinergic basis for Alzheimer therapy. Boston Birkhäuser Boston, 1991:1-22
21. Sakakibara R, Uchiyama T, Yoshiyama M, Yamanishi T, Hattori T. Preliminary Communication: Urodynamic Assessment of Donepezil Hydrochloride in Patients with Alzheimer's Disease. Neurourol Urodyn. 2005: 24:273-5
22. Komatsu K, Yokoyama O, Otsuka N, Kodama K, Yotsuyanagi S, Niikura S. Central muscarinic mechanism of bladder overactivity associated with Alzheimer type senile dementia. NeurourolUrodyn. 2000: 4:539- 40
23. Sakakibara R, Ogata T, Uchiyama T, et al. How to manage overactive bladder in elderly individuals with dementia? A combined use of donepezil, a central AChE inhibitor, and propiverine, a peripheral muscarine receptor antagonist. J Am Geriatr Soc. 2009 57:1515-7
24. Sink K, Thomas Jr, Xu H, Craig B, Kritchevsky S, Sands L. Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes. J Am Geriatr Soc. 2008: 56:847-53
25. Yamamoto S, Maruyama S, Ito Y, et al. Effect of oxybutynin and imidafenacin on central muscarinic receptor occupancy and cognitive function: a monkey PET study with [(11)C](+)3-MPB. Neuroimage. 2011 58:1-9
26. Lieu P, Chia H, Heng L, Ding Y, Choo P. Carer-assisted intermittent urethral catheterisation in the management of persistent retention of urine in elderly women. Ann Acad med Singapore. 1996: 25:562-265
27. Fratiglioni L, Launer L, Andersen K, et al. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic diseases in the Elderly. Research Group. Neurology 2000: 54:S 4- S 9
28. van Dijk E, Breteler M, Schmidt R, et al. . The association between blood pressure, hypertension, and cerebral white matter lesions cardiovascular determinants of dementia study. Hypertension. 2004: 44
29. Sakakibara R, Panicker J, Fowler C, et al. "Vascular incontinence" and normal-pressure hydrocephalus: two common elderly incontinence with brain etiologies. Current Drug Therapy. 2012:
30. Hénon H, Durieu I, Guerouaou D, Lebert F, Pasquier F, Leys D. Poststroke dementia : inicidence and relationship to prestroke cognitive decline. Neurology 2001: 57:1216-22
31. Hofman A, Ott A, Breteler M, et al. A therosclerosis, apolipoprotein E and prevalence of dementia and Alzheimer's disease in the Rotterdam study. Lancet 1997: 349:151-4
32. Thom D, Haan M, Van Den Eeden S. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. Age Ageing. 1997: 26:367-74
33. Wardlaw J. Blood-brain barrier and cerebral small vessel disease. J Neurol Sci 2010: 299:66-71
34. Lee S, Scott A. Hypoxia positron emission tomography imaging with 18F-fluoromisonidazole. Semin Nucl Med. 2007: 37:451-61
35. Hentschel F, Damian M, Krumm B, Froelich L. White matter lesions - age-adjusted values for cognitively healthy and demented subjects. Acta Neurol Scand. 2007: 115:174-80
36. Tullberg M, Fletcher E, DeCarli C, et al. White matter lesions impair frontal lobe function regardless of their location. Neurology. 2004: 63:246-53
37. Hanyu H, Shimuzu S, Tanaka Y, Takasaki M, Koizumi K, Abe K. Cerebral blood flow patterns in Binswanger's disease: a SPECT study using three-dimensional stereotactic surface projections. J Neurol Sci. 2004: 220:79-84
38. Sakakibara R, Fowler C, Hattori T. Voiding and MRI analysis of the brain. Int Urogynecol J Pelvic Floor Dysfunct. 1999: 10:192-9
39. Fowler C, Griffiths D. A decade of functional brain imaging applied to bladder control. Neurourol Urodyn. 2010: 29:49-55
40. Sakakibara R, Tsunoyama K, Takahashi O, et al. Real-time measurement of oxyhemoglobin concentration changes in the frontal micturition area: an fNIRS study. Neurourol Urodyn. 2010: 29:757-64

41. Fowler C, Griffiths D, de Groat W. The neural control of micturition. Nat Rev Neurosci. 2008: 9:453-66

42. Griffiths D, Tadic S. Bladder control, urgency, and urge incontinence: evidence from functional brain imaging. Neurourol Urodyn. 2008: 27:466-74

43. Jirovec M, Wells T. Urinary incontinence in nursing home residents with dementia: the mobility-cognition paradigm. Appl Nurs Res. 1990: 3:112-7

44. Yoshimura N, Yoshida O, Yamamoto S, Mori H, Majima M, Mui K. Evaluation of urinary incontinence among the nursing home elderly. Hinyokika Kiyo. 1991: 37:689-94

45. Eustice S, Roe B, Paterson J. Prompted voiding for the management of urinary incontinence in adults. Cochrane Database Syst Rev. 2000: 2:CD002113

46. Suzuki Y, Machida T, Oishi Y, et al. Countermeasures for urinary incontinence in patients with senile dementia: correlation between urinary incontinence severity, senile dementia severity, and activity of daily living. Hinyokika Kiyo. 1992: 38:291-5

47. Sugiyama T, Matsuda H, Oonishi N, et al. Anticholinergic therapy of urinary incontinence and urinary frequency associated with the elderly - with special reference to dementia. Nippon Hinyokika Gakkai Zasshi. 1993: 84:1068-73

48. Yonou H, Kagawa H, Oda A, Nagano M, Gakiya M, Niimura K. Transurethral resection of the prostate for patients with dementia. Hinyokika Kiyo. 1999: 45:241-4

49. McKeith I, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy boides (DLB): report of the consortium on DLB international workshop. Neurology 1996: 47 1113-24

50. Spillantini M, Schmidt M, Lee V, Trojanowski J, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. Nature 1997: 388:839-40

51. McKeith I, Dickson D, Lowe J, et al. Diagnosis and management of dementia with Lewy Bodies: third report of the DLB consortium. Neurology 2005: 65 1863-72

52. Merdes A, Hansen L, Jeste D, et al. Influence of Alzheimer pathology on clinical diagnostic accurancy in dementia with Lewy bodies. Neurology 2003: 60:1586-90

53. Lippa C, Fujiwara H, Mann D, Giasson B, Baba MSchmidt M, Nee LE OCB, Pollen DA, St George-Hyslop P, Ghetti B, Nochlin D, Bird TD, Cairns NJ, Lee VM, Iwatsubo T, Trojanowski JQ. Lewy bodies contain altered alpha-synuclein in brains of many familial Alzheimer's disease patients with mutations in presenilin and amyloid precursor protein genes. Am J Pathol. 1998: 153:1365-370

54. Thaisetthawatkul P, Boeve B, Benarroch E, et al. Autonomic dysfunction in dementia with Lewy bodies. Neurology 2007: 62:1804-8

55. Ratnavalli E, Brayne C, Dawson K, Hodges J. The prevalence of frontotemporal dementia. Neurology 2002: 58:1615-21

56. Gustafson L. Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis. Arch Gerontol Geriatr. 1987: 6:209-23

57. Varma A, Adams W, Lloyd J, et al. Diagnostic patterns of regional atrophy on MRI and regional cerebral blood flow change on SPECT in young onset patients with Alzheimer's disease, frontotemporal dementia and vascular dementia. Acta Neurol Scand. 2002: 105:261-9

58. Hellström L, Ekelund P, Milsom I, Skoog I. The influence of dementia on the prevalence of urinary and faecal incontinence in 85-year-old men and women. Arch Gerontol Geriatrics. 1994: 19:11-20

59. Marmarou A, Black P, Bergsneider M, Klinge P, Relkin N. International NPH Consultant Group. International NPH Consultant Group. Guidelines for management of idiopathic normal pressure hydrocephalus: progress to date. Acta Neurochir Suppl. 2005:237-40

60. Hakim S, Adams R. The special clinical problem of symptomatic occult hydrocephalus with normal cerebrospinal pressure. J Neurol Sci. 1965: 2:307-32

61. Iseki C, Kawanami T, Nagasawa H, et al. Asymptomatic ventriculomegaly with features of idiopathic normal pressure hydrocephalus on MRI (AVIM) in the elderly: a prospective study in a Japanese population. J Neurol Sci. 2009 15:54-7

62. Sakakibara R, Kanda T, Sekido T, et al. Mechanism of bladder dysfunction in idiopathic normal pressure hydrocephalus. Neurourol Urodyn. 2008: 27:507-10

63. Jonas S, Brown J. Neurogenic bladder in normal pressure hydrocephalus. Urology 1975: 5:44-50

64. Ahlberg J, Noren L, Blomstrand C, Wikkelso C. Outcome of shunt operation on urinary incontinence in normal pressure hydrocephalus predicted by lumber puncture. J Neurol Neurosurg Psychiatry. 1988: 51:105-8

65. de Groat W. Integrative control of the lower urinary tract: preclinical perspective. Br J Pharmacol. 2006: 147:S25-S40

66. Owler B, Momjian S, Czosnyka Z, et al. Normal pressure hydrocephalus and cerebral blood flow: a PET study of baseline values. J Cereb Blood Flow Metab. 2004: 24:17-23

67. Sasaki H, Ishii K, Kono A, et al. Cerebral perfusion pattern of idiopathic normal pressure hydrocephalus studied by SPECT and statistical brain mapping. Ann Nucl Med. 2007: 21:39-45

68. Walter C, Hertel F, Neumann E, Morsdorf M. Alteration of cerebral perfusion in patients with idiopathic normal pressure hydrocephalus measured by 3D perfusion weighted magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 2005: 252:1465-71

69. Sakakibara R, Uchida Y, Ishii K, et al. Correlation of right frontal hypoperfusion and urinary dysfunction in iNPH: A SPECT study. Neurourol Urodyn. 2011 Oct 28. [Epub ahead of print]

70. Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, Kaufmann H, Klockgether T, Lang AE, Lantos PL, Litvan I, Mathias CJ, Oliver E, Robertson D, Schatz I, Wenning GK. Consensus statement on the diagnosis of multiple system atrophy. J Auton Nerv Syst 1998; 74: 189-192.

71. Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy–Drager syndrome). J Neurol Sci 1989; 94:79-100.

72. Beck RO, Betts CD, Fowler CJ. Genitourinary dysfunction in multiple system atrophy: clinical features and treatment in 62 cases. J Urol 1994; 151: 1336-41.

73. Sakakibara R, Hattori T, Uchiyama T, Kita K, Asahina M, Suzuki A, Yamanishi T. Urinary dysfunction and orthostatic hypotension in multiple system atrophy: Which is the more common and earlier manifestation? J Neurol Neurosurg Psychiatry 1999; 67: 1-5.

74. Wenning GK, Ben Shlomo Y, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy: an analysis of 100 cases. Brain 1994; 117:835–845.

75. Kirchhof K, Apostolidis AN, Mathias CJ, Fowler CJ. Erectile and urinary dysfunction may be the presenting features in patients with multiple system atrophy: a retrospective study. Impotence Research 2003; 15: 293-298.

76. Sakakibara R, Hattori T, Tojo M, Yamanishi T, Yasuda

K, Hirayama K. Micturitional disturbance in multiple system atrophy Jpn J Psychiat Neurol 1993; 47: 3; 591-598.

77. Incomplete emptying and urinary retention in multiple system atrophy: when does it occur and how do we manage it? Mov Disord 2006; 21: 6; 816-823.

78. Benarroch EE, Schmeichel AM. Depletion of corticotrophin-releasing factor neurons in the pontine micturition area in multiple system atrophy. Ann Neurol 2001; 50: 640-645.

79. Yamamoto T, Sakakibara R, Uchiyama T, Liu Z, Ito T, Awa Y, Yamanishi T, Hattori T. When is Onuf's nucleus involved in multiple system atrophy; a sphincter electromyography study. J Neurol Neurosurg Psychiatry 2005; 76: 1645-1648.

80. Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry 2001; 71: 600-606.

81. Stocchi F, Carbone A, Inghilleri M, Monge A, Ruggieri S, Berardelli A, Manfredi M. Urodynamic and neurof physiological evaluation in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry 1997; 62:507-511.

82. Sakakibara R, Uchida Y, Uchiyama T, Yoshiyama M, Yamanishi T, Hattori T. Reduced cerebellar vermis acu tivation in response to micturition in multiple system atrophy; 99mTc-labeled ECD SPECT study. Eur J Neurol 2004; 11: 705-708.

83. Bannister R, Mathias CJ. Clinical features and investigation of the primary autonomic failure syndromes. In: Bannister R, Mathias CJ, eds. Autonomic failure, 3rd edn. Oxford: Oxford Medical Publications, 1992: 531–547.

84. Yamamoto T, Sakakibara R, Uchiyama T, Liu Z, Ito T, Awa Y, Yamanishi T, Hattori T. Neurological diseases that cause detrusor hyperactivity with impaired contractile function. Neurourol Urodynam 2006; 25; 356-360.

85. Ozawa T, Oyanagi K, Tanaka H, Horikawa Y, Takahashi H ,Morita T, Tsuji S. Suprachiasmal nucleus in a patient with multiple system atrophy with abnormal circadian rhythm of arginine vasopressin secretion into plasma. J Neurol Sci 1998; 154:116–121.

86. Mathias CJ, Fosbraey P, DaCosta DF, Thomley A, Bannister R. The effect of desmopressin on nocturnal polyuria, overnight weight loss, and morning postural hypotension in patients with autonomic failure. BMJ 1986; 293: 353-356.

87. Palace J, Chandiramani VA, Fowler CJ. Value of sphincter electromyography in the diagnosis of multiple system atrophy. Muscle and Nerve 1997; 20: 1396-1403.

88. Reduced genital sensitivity in female patients with multiple system atrophy of parkinsonian type. 2003; 18: 430-432.

89. Hahn KH, Ebersbach G.: Sonographic Assessment of Urinary Retention in Multiple System Atrophy and Idiopathic Parkinson's Disease. Movement Disorders 2005, 20, 1499-1502.

90. How to recognize patients with parkinsonism who should not have urological surgery. 1997; 80: 100-104.

91. Sakakibara R, Matsuda S, Uchiyama T, Yoshiyama M, Yamanishi T, Hattori T. The effect of intranasal desmopressin on noctu rnal waking in urination in multiple system atrophy patients with nocturnal polyuria. Clin Auton Res 2003; 13: 106-108.

92. Sakakibara R, Hattori T, Uchiyama T, Suenaga T, Takahashi H, Yamanishi T, Egoshi K, Sekita N. Are alpha-blockers involved in lower urinary tract dysfunction in multiple system atrophy? A comparison of prazosin and moxisylyte. J Auton Nerv Syst 2000; 79: 191-195.

93. Sakakibara R, Uchiyama T, Asahina M, Yamanishi T, Hattori T. Amezinium metilsulfate, a sympathomie metic agent, may increase the risk of urinary retention in multiple system atrophy. Clin Auton Res 2003; 13: 51-53.

94. Yamamoto T, Sakakibara R, Yamanaka Y, Uchiyama T, Asahina M, Liu Z, Ito T, Koyama Y, Awa Y, Yamamoto K, Kinou M, Hattori T. Pyridostigmine in autonomic failure: can we treat postural hypotension and bladder dysfunction with one drug? Clin Auton Res 2006; 16: 296-298.

95. Sakakibara R, Odaka T, Uchiyama T, Asahina M, Yamaguchi K, Yamaguchi T, Yamanishi T, Hattori T. Colonic transit time, sphincter EMG and rectoanal videomanometry in multiple system atrophy. Mov Disord 2004; 19: 924-929.

96. Stocchi F, Badiali D, Vacca L,Dlba L, Bracci F, Ruggieri S, Torti M, Berardelli A, Corazziari E. Anorectal function in multiple system atrophy and Parkinson's disease. Mov Disord 2000; 15: 71-76.

97. Bardoux N, Leroi AM, Touchais JY, Weber J, Denis P. Difficult defecation and/or faecal incontinence as a presenting feature of neurologic disorders in four patients. Neurogastroenterol Mot 1997; 9: 13-18.

98. Eichhorn TE, Oertel WH. Macrogol 3350/electrolyte improves constipation in Parkinson's disease and multiple system atrophy. Mov Disord 2001; 16: 1176-1177.

99. Sakakibara R, Yamaguchi T, Uchiyama T et al. Calcii um polycarbophil improves constipation in primary autonomic failure and multiple system atrophy subjects. Mov Disord. 2007; 22: 1672-1673.

100. Liu, Z., Sakakibara R, Odaka T, Uchiyama T, Yamamoto T, Ito T, Asahina M, Yamaguchi K, Yamaguchi T, Hattori T. Mosapride citrate, a novel 5-HT4 agonist and partial 5-HT3 antagonist, ameliorates constipation in parkinsonian patients. Mov Disord 2005; 20: 680-686.

101. Sakakibara R, Odaka T, Liu Z, Uchiyama T, Yamaguchi K, Yamaguchi T, Asahina M, Yamamoto T, Ito T, Hattori T. Dietary herb extract dai-kenchu-to ameliorates constipation in parkinsonian patients (parkinson's disease and multiple system atrophy). Mov Disord 2005; 20: 261-262

102. Chaudhuri K, Healy D, Schapira A. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006: 5:235-45

103. Hattori T, Yasuda K, Kita K, Hirayama K. Voiding dysfunction in Parkinson's disease. Jpn J Psychiatry Neurol. 1992: 46:181-6

104. Gray R, Stern G, Malone-Lee J. Lower urinary tract dysfunction in Parkinson's disease: changes relate to age and not disease. Age Ageing. 1995: 24:499-504

105. Araki I, Kuno S. Assessment of voiding dysfunction in Parkinson's disease by the international prostate symptom score. J Neurol Neurosurg Psychiatry. 2000: 68:429-33

106. Lemack G, Dewey R, Roehrborn C, O'Suilleabhain P, Zimmern P. Questionnaire-based assessment of bladder dysfunction in patients with mild to moderate Parkinson's disease. Urology 2000: 56:250-4

107. Campos-Sousa R, Quagliato E, da Silva B, De CJ, Ribeiro S, de Carvalho D. Urinary symptoms in Parkinson's disease: prevalence and associated factors. Arq Neuropsiquiatr. 2003: 61:359-63

108. Sakakibara R, Shinotoh H, Uchiyama T, et al. Questionnaire-based assessment of pelvic organ dysfunction in Parkinson's disease. Auton Neurosci. 2001: 92:76-85.

109. Uchiyama T, Sakakibara R, Yamamoto T, et al. Urinary dysfunction in early and untreated Parkinson's disease. J Neurol Neurosurg Psychiatry. 2011 Jun 13. [Epub ahead of print].

110. Sakakibara R, Shinotoh H, Uchiyama T, et al. Questionnaire-based assessment of pelvic organ dysfunction in Parkinson's disease. Auton Neurosci. 2001: **92**:76-85

111. Sakakibara R, Tateno F, Kishi M, Tsuyuzaki Y, Uchiyama T, Yamamoto T. Pathophysiology of bladder dysfunction in Parkinson's disease. Neurobiol Dis. 2011 Oct 10. [Epub ahead of print]

112. Fowler C, Griffiths D, de Groat W. The neural control of micturition. Nat Rev Neurosci. 2008: 9:453-66

113. Sakakibara R, Shinotoh H, Uchiyama T, Yoshiyama M, Hattori T, Yamanishi T. SPECT imaging of the dopamine transporter with [123I]-beta-CIT reveals marked decline of nigrostriatal dopaminergic function in Parkinson's disease with urinary dysfunction. J Neurol Sci. 2001: 187:55-9.

114. Dalmose AL, Bjarkam CR, Sorensen JC, Djurhuus JC, Jorgensen TM. Effects of high frequency deep brain stimulation on urine storage and voiding function in conscious minipigs. Neurourol Urodyn 2004; 23: 265-272

115. Winge K, Friberg L, Werdelin L, Nielsen K, Stimpel H. Relationship between nigrostriatal dopaminergic degeneration, urinary symptoms, and bladder control in Parkinson's disease. Eur J Neurol. 2005: 12:842-50

116. Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry. 2001: 71: 600-6

117. Defreitas G, Lemack G, Zimmern P, Dewey R, Roehrborn C, O'Suilleabhain P. Distinguishing neurogenic from non-neurogenic detrusor overactivity: a urodynamic assessment of lower urinary tract symptoms in patients with and without Parkinson's disease. Urology. 2003: 62:651-5

118. Chandiramani V, Palace J, Fowler C. How to recognize patients with parkinsonism who should not have urological surgery. Br J Urol. 1997: 80:100-4

119. O'Sullivan S, Holton J, Massey L, Williams D, Revesz T, Lees A. Parkinson's disease with Onuf's nucleus involvement mimicking multiple system atrophy. J Neurol Neurosurg Psychiatry. 2008: 79:232-4

120. Sakakibara R, Ito T, Uchiyama T, et al. Lower urinary tract function in dementia of Lewy body type (DLB). J Neurol Neurosurg Psychiatry. 2005: 76:729-32

121. Magerkurth C, Schnitzer R, Braune S. Symptoms of autonomic failure in Parkinson's disease: prevalence and impact on daily life. Clin Auton Res. 2005: 15 76-82

122. Matsui H, Nishinaka K, Oda M, Komatsu K, Kubori T, Udaka F. Does cardiac metaiodobenzylguanidine (MIBG) uptake in Parkinson's disease correlate with major autonomic symptoms? Parkinsonism Relat Disord. 2006: 12:284-8

123. Balash Y, Peretz C, Leibovich G, Herman T, Hausdorff J, Giladi N. Falls in outpatients with Parkinson's disease: frequency, impact and identifying factors. J Neurol Neurosurg Psychiatry. 2005: 252: 1310-5

124. Kuno S, Mizuta E, Yamasaki S, Araki I. Effects of pergolide on nocturia in Parkinson fs disease: three female cases selected from over 400 patients. Parkinsonism Related Disord. 2004: 10:181-7

125. Yamamoto M. Pergolide improves neurogenic bladder in patients with Parkinson's disease. Mov Disord. 1997: 12:328

126. Brusa L, Petta F, Pisani A, et al. Central acute D2 stimulation worsens bladder function in patients with mild Parkinson's disease. J Urol 2006: 175:202-6

127. Uchiyama T, Sakakibara R, Hattori T, Yamanishi T. Short-term effect of a single levodopa dose on micturition disturbance in Parkinson's disease patients with the wearing-off phenomenon. Mov Disord. 2003: 18:573-8

128. Ishizuka O, Mizusawa H, Nishizawa O. Roles of dopaminergic receptors in bladder and erectile function at the spinal level. Asian J Androl 2002: 4:287-90

129. Uchiyama T, Sakakibara R, Yoshiyama M, et al. Biphasic effect of apomorphine, an anti-parkinsonian drug, on bladder function in rats. Neuroscience. 2009: 162:1333-8

130. Katzenschlager R, Sampaio C, Costa J, Lees A. Anticholinergics for symptomatic management of Parkinson's disease. Cochrane Database Syst Rev. 2003: 2:CD003735

131. Donnellan C, Fook L, McDonald P, Playfer J. Oxybutynin and cognitive dysfunction. BMJ 1997: 315:1363-4

132. Sakakibara R, Uchiyama T, Yamanishi T, Kishi M. Dementia and lower urinary dysfunction: with a reference to anticholinergic use in elderly population. Int J Urol. 2008: 15:778-88

133. Sakakibara R, Nakazawa K, Uchiyama T, Yoshiyama M, Yamanishi T, Hattori T. Micturition-related electrophysiological properties in the substantia nigra pars compacta and the ventral tegmental area in cats. Auton Neurosci. 2002: 102:30-8

134. Herzog J, Weiss P, Assmus A, et al. Improved sensory gating of urinary bladder afferents in Parkinson's disease following subthalamic stimulation. Brain 2008: 131:132-45

135. Fritsche H, Ganzer R, Schlaier J, Wieland W, Brawanski A, Lange M. Acute urinary retention in two patients after subthalamic nucleus deep brain stimulation (STN-DBS) for the treatment of advanced Parkinson's disease. Mov Disord. 2009: 24:1553-4

136. Giannantoni A, Rossi A, Mearini E, Del Zingaro M, Porena M, Berardelli A. Botulinum toxin A for overactive bladder and detrusor muscle overactivity in patients with Parkinson's disease and multiple system atrophy. J Urol. 2009: 182:1453-7

137. Kulaksizoglu H, Parman Y. Use of botulinim toxin-A for the treatment of overactive bladder symptoms in patients with Parkinson's disease. Parkinsonism Relat Disord. 2010: 16:531-4

138. Myers D, Arya L, Friedman J. Is urinary incontinence different in women with Parkinson's disease? Int Urogynecol J Pelvic Floor Dysfunct. 1999: 10:188-1891

139. Pfeiffer R. Gastrointestinal, Urological, and Sexual Dysfunction in Parkinson's Disease. Mov Disord. 2010: 25 Suppl 1:S94-S7

140. Ogawa E, Sakakibara R, Kishi M, Tateno F. Constipation triggered the malignant syndrome in Parkinson's disease. Neurol Sci. 2011 Jul 20 [Epub ahead of print]

141. Sakakibara R, Kishi M, Ogawa E, et al. Bladder, bowel, and sexual dysfunction in Parkinson's disease. Parkinsons Dis. 2011: Epub 2011 Sep 12.

142. Wang S, Fuh J, Shan D, et al. Sympathetic skin response and R-R interval variation in Parkinson's disease. Mov Disord. 1993: 8:151-7

143. Yokoyama T, Hasegawa I. Ileus in Parkinson's disease. Neurological Medicine. 2007: 66:6-11

144. Tateno F, Sakakibara R, Kishi M, et al. Incidence of emergency intestinal pseudo-obstruction in Parkinson's disease. J Am Geriatr Soc. 2011 59:2373-5

145. Abbott R, Petrovitch H, White L, et al. Frequency of bowel movements and the future risk of Parkinson's disease. Neurology 2001: 57:456-62

146. Braak H, Rub U, Del Tredici K. Cognitive decline correlates with neuropathological stage in Parkinson's disease. J Neurol Sci. 2006: 248:255-8

147. Hansen M. Neurohumoral control of GI motility. Physiol Res. 2003: 52:1-30

148. Kupsky W, Grimes M, Sweeting J, Bertsch R, Cote L. Parkinson's disease and megacolon; concentric hyaline inclusions (Lewy bodies) in enteric ganglion cells. Neurology 1987: 37:1253-5

149. Wakabayashi K TH, Ohama E, Ikuta F. Parkinson's disease: an immunohistochemical study of Lewy body-containing neurons in the enteric nervous system. Acta Neuropathol. 1990: 79:581-3

150. Singaram C, Ashraf W, Gaumnitz E, et al. Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. Lancet 1995: 346:861-4

151. Jost W. Gastrointestinal dysfunction in Parkinson's Disease. J Neurol Sci. 2010 289:69-73

152. Stocchi F, Carbone A, Inghilleri M, et al. Urodynamic and neurophysiological evaluation in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry. 1997: 62:507-11

153. Mathers S, Kempster P, Law P, et al. Anal sphincter dysfunction in Parkinson's disease. Arch Neurol. 1989: 46:1061-4

154. Astarloa R, Mena M, Sanchez V, de la Vega L, de Yebenes J. Clinical and pharmacological effects of a diet rich in insoluble fiber on Parkinson's disease. Clin Neuropharmacol. 1992: 15:375-80

155. Ashraf W, Pfeiffer R, Park F, Lof J, Quigley E. Constipation in Parkinson's disease; objective assessment and response to psyllium. Mov Disord. 1997: 12:946-51

156. Eichhorn T, Oertel W. Macrogol 3350/electrolyte improves constipation in Parkinson's disease and multiple system atrophy. Mov Disord. 2001: 16:1176-7

157. Sakakibara R, Yamaguchi T, Uchiyama T, et al. . Calcium polycarbophil improves constipation in primary autonomic failure and multiple system atrophy subjects. Mov Disord. 2007: 22:1672-3

158. Tateno F, Sakakibara R, Yokoi Y, et al. Levodopa ameliorated anorectal constipation in de novo Parkinson's disease: The QL-GAT study. Parkinsonism Relat Disord. 2011 Jun 24. [Epub ahead of print]

159. Shimada J, Sakakibara R, Uchiyama T, et al. Intestinal pseudo-obstruction and neuroleptic malignant syndrome in a case of parkinsonian patient with chronic constipation. Eur J Neurol. 2006: 13:306-12

160. Shindler J, Finnerty G, Towlson K, Dolan A, Davies C, Parkes J. Domperidone and levodopa in Parkinson's disease. Br J Clin Pharmacol. 1984: 18:959-62

161. Djaldetti R, Koren M, Ziv I, Achiron A, Melamed E. Effect of cisapride on response fluctuations in Parkinson's disease. Mov Disord. 1995: 10:81-4

162. Liu Z, Sakakibara R, Odaka T, et al. Mosapride citrate, a novel 5-HT4 agonist and partial 5-HT3 antagonist, ameliorates constipation in parkinsonian patients. Mov Disord. 2005: 20:680-6

163. Sullivan K, Staffetti J, Hauser R, Dunne P, Zesiewicz T. Tegaserod (Zelnorm) for the treatment of constipation in Parkinson's disease. Mov Disord. 2006: 21:115-6

164. Sakakibara R, Odaka T, Liu Z, et al. Dietary herb extract Dai-Kenchu-To ameliorates constipation in parkinsonian patients. Mov Disord 2005: 20:261-2

165. Cadeddu F, Bentivoglio A, Brandara F, Marniga G, Brisinda G, Maria G. Outlet type constipation in Parkinson's disease: results of botulinum toxin treatment. Aliment Pharmacol Ther. 2005: 22:997-1003

166. Not used

167. Di Carlo A, Lamassa M, Baldereschi M, et al. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. Stroke. 2003 **34**:1114-9

168. Wade D, Hewer R. Outlook after an acute stroke: urinary incontinence and loss of consciousness compared in 532 patients. Q J Med. 1985 **56**::601-8

169. Barer D, Mitchell J. Predicting the outcome of acute stroke: do multivariate models help? . Q J Med. 1989 **70**:27-39

170. Pettersen R, Stien R, Wyller T. Post-stroke urinary incontinence with impaired awareness of the need to void: clinical and urodynamic features. BJU Int. 2007 **99**:1073-7

171. Nakayama H, Jorgensen H, Pedersen P, Raaschou H, Olsen T. Prevalence and risk factors of incontinence after stroke. The Copenhagen Stroke Study. Stroke. 1997 **28**:58-62

172. Edwards D, Hahn M, Dromerick A. Post stroke urinary loss, incontinence and life satisfaction: when does post-stroke urinary loss become incontinence? Neurourol Urodyn. 2006: **25**:39-45

173. Andrew J, Nathan P. Lesions on the Anterior Frontal Lobes and Disturbances of Micturition and Defaecation. Brain. 1964 **87**:233-62

174. Khan Z, Starer P, Yang W, Bhola A. Analysis of voiding disorders in patients with cerebrovascular accidents. Urology. 1990 **35**:265-70

175. Tsuchida S, Noto H, Yamaguchi O, Itoh M. Urodynamic studies on hemiplegic patients after cerebrovascular accident. Urology. 1983 Mar: **21**:315-8

176. Kuroiwa Y, Tohgi H, Ono S, Itoh M. Frequency and urgency of micturition in hemiplegic patients: relationship to hemisphere laterality of lesions. J Neurol Neurosurg Psychiatry. 1987 **234**:100-2

177. Sakakibara R, Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance after acute hemispheric stroke: analysis of the lesion site by CT and MRI. J Neurol Sci. 1996 **137**:47-56

178. Maurice-Williams R. Micturition symptoms in frontal tumours. J Neurol Neurosurg Psychiatry. 1974 **37**:431-6

179. Daviet J, Borie M, Salle J, et al. Epidemiology and prognostic significance of bladder sphincter disorders after an initial cerebral hemisphere vascular accident. Ann Readapt Med Phys. 2004 **47**:531-6

180. Mochizuki H, Saito H. Mesial frontal lobe syndromes: correlations between neurological deficits and radiological localizations. Tohoku J Exp Med. 1990 **161 Suppl**:231-9

181. Yamamoto S, Soma T, Hatayama T, Mori H, Yoshimura N. Neurogenic bladder induced by brain abscess. Br J Urol. 1995 **76**:272

182. Lang EW, Chesnut RM, Hennerici M. Urinary retention and space-occupying lesions of the frontal cortex. Eur Neurol. 1996: **36**:43-7

183. Yokoyama O, Mizuno H, Komatsu K, Akino H, Tanase K, Namiki M. Role of glutamate receptors in the development and maintenance of bladder overactivity after cerebral infarction in the rat. J Urol. 2004 **171**:1709-14

184. Holman E. Difficult urination associated with intracranial tumors of posterior fossa. A physiologica and clinical study. Arch Neurol Psychiat. 1926 **371**:15

185. Ueki K. Disturbances of mictrurition observed in some patients with brain tumor. Neurol Med Chir. 1960 **2**:25

186. Renier W, Gabreels F. Evaluation of diagnosis and non-surgical therapy in 24 children with a pontine tumour. Neuropediatrics. 1980 **11**:262-73

187. Betts C, Kapoor R, Fowler C. Pontine pathology and voiding dysfunction. Br J Urol. 1992 **70**:100-2

188. Manente G, Melchionda D, Uncini A. Urinary retention in bilateral pontine tumour: evidence for a pontine micturition centre in humans. J Neurol Neurosurg Psychiatry. 1996 Nov: **61**:528-9

189. Sakakibara R, Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance and the pontine tegmental lesion: urodynamic and MRI analyses of vascular cases. J Neurol Sci. 1996 **141**:105-10

190. Sakakibara R, Hattori T, Fukutake T, Mori M, Yamanishi T, Yasuda K. Micturitional disturbance in herpetic brainstem encephalitis; contribution of the pontine micturition centre. J Neurol Neurosurg Psychiatry. 1998 **64**:269-72

191. Patel M, Coshall C, Lawrence E, Rudd A, Wolfe C. Recovery from poststroke urinary incontinence: associated factors and impact on outcome. J Am Geriatr Soc. 2001 **49**:1229-33

192. Tibaek S, Gard G, Jensen R. Pelvic Floor Muscle Training Is E!ective in Women With Urinary Incontinence After Stroke: A Randomised, Controlled and Blinded Study. Neurourol Urodynam. 2005: **24**:348-57

193. Herr-Wilbert I, Imhof L, Hund-Georgiadis M, Wilbert D. Assessment-guided therapy of urinary incontinence after stroke. Rehabil Nurs. 2010 **35**:248-53

194. Thomas L, Cross S, Barrett J, et al. Treatment of urinary incontinence after stroke in adults. Cochrane Database Syst Rev. 2008: **CD004462**

195. Kuo H. Therapeutic effects of suburothelial injection of botulinum a toxin for neurogenic detrusor overactivity due to chronic cerebrovascular accident and spinal cord lesions. Urology 2006: **67**:232-6

196. Herbaut A. Neurogenic urinary retention. Int Urogynecol J. 1993: 4:221-8

197. Sakakibara R, Hattori T, Uchiyama T, Kamura K, Yamanishi T. Uro-neurological assessment of spina bifida cystica and occulta. Neurourol Urodynam. 2003: 22

198. Swinn M, Lowe E, Fowler C. The clinical features of non-psychogenic urinary retention (Fowler's syndrome). Neurourol Urodynam. 1998: 17:383-4

199. Yamanishi T, Yasuda K, Sakakibara R, et al. Urinary retention due to Herpes Simplex infections. Neurourol Urodynam. 1998: 17:613-9

200. Sakakibara R, Uchiyama T, Liu Z, et al. Meningitis-retention syndrome; an unrecognized clinical condition. J Neurol. 2005: 252:1495-9

201. Sakakibara R, Yamanishi T, Uchiyama T, Hattori T. Acute urinary retention due to benign inflammatory nervous diseases. J Neurol. 2006 253:1103-10

202. Schwarz S, Mohr A, Knauth M, Wildemann B, Storch-Hagenlocher B. Acute disseminated encephalomyelitis. A follow-up study of 40 adult patients. Neurology. 2001: 56:1313-8

203. Kawamura M, Kaku H, Takayama N, Ushimi T, Kishida S. AcuteUrinaryRetention Secondaryto AsepticMeningoencephalitis in an Infant - a Case Report. Brain Nerve. 2007: 59:1287-91

204. Sakakibara R, Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance in acute disseminated encephalomyelitis (ADEM). J Auton Nerv Syst. 1996: 60:200-5

205. Panicker J, Nagaraja D, Kovoor J, Nair K, Subbakrishna D. Lower urinary tract dysfunction in acute disseminated encephalomyelitis. Mult Scler. 2009 15:1118-22

206. Pradhan S, Gupta RK, Kapoor R, Shashank S, Kathuria MK. Parainfectious conus myelitis. J Neurol Sci. 1998: 161:156-62

207. Kinoshita A, Kaseda S, Yagi K, Oda M, Tanabe H. A case of acute disseminated encephalomyelitis with pathology-proven acute demyelinating lesion in the peripheral nervous system. Clin Neurol. 1994: 34:892-7

208. Kusuhara T, Nakajima M, Inoue H, Takahashi M, Yamada T. Parainfectious encephalomyeloradiculitis associated with herpes simplex virus 1 DNA in cerebrospinal fluid. Clin Infect Dis. 2002: 34:1199-205

209. Hiraga A, Sakakibara R, Mori M, Yamanaka Y, Ito S, Hattori T. Urinary retention can be the sole initial manifestation of acute myelitis. J Neurol Sci. 2006 251:110-2

210. Hiraga A, Sakakibara R, Mori M, Suzuki A, Hattori T. Bilateral lesion in the lateral columns and complete urinary retention: association with the spinal cord descending pathway for micturition. Neurourol Urodynam. 2005: 24:398-89

211. Zenda T, Soma R, Muramoto H, et al. Acute urinary retention as an unusual manifestation of aseptic meningitis. Internal Medicine. 2002: 41:392-4

212. Tascilar N, Aydemir H, Emre U, Unal A, Ataso T, Ekem S. Unusual combination of reversible splenial lesion and meningitis-retention syndrome in aseptic meningomyelitis. Clinics. 2009: 64:932-7

213. Furugen M, Yamashiro S, Tamayose M, et al. Elsberg syndrome with eosinophilic meningoencephalitis caused by Angiostrongylus cantonensis. Intern Med. 2006: 45:1333-6

214. Hsu J, Chuang S, Chen C, Huang M. Sacral myeloradiculitis (Elsberg syndrome) secondary to eosinophilic meningitis caused by Angiostrongylus cantonensis. BMJ Case Rep. 2009:pii: bcr10.2008.1075

215. Ntziora F, Alevizopoulos A, Konstantopoulos K, Kanellopoulou S, Bougas D, Stravodimos K. AsepticMeningitis with Urinary Retention: A Case Report. Case Reports in Medicine. 2011: ID 741621:3 pages

216. Takahashi O, Sakakibara R, Kishi M, et al. Herbal medicine-induced meningitis-retention syndrome. Intern Med. 2010: 49:1813-6

217. Ito Y, Uchida Y, Tamai N, Nakajima F. Two cases of urinary retention secondary to benign inflammatory nervous diseases. Hinyokika Kiyo. 2009 55:655-9

218. Kim T, Whang J, Lee S, Choi J, Park S, Lee J. Acute Urinary Retention due to Aseptic Meningitis: Meningitis-Retention Syndrome. Int Neurourol J. 2010 14:122-4.

219. Tateno F, Sakakibara R, Sugiyama M, et al. Meningitis-retention syndrome: first case of urodynamic follow-up. Intern Med. 2011: 50:1329-32

220. Fujita K, Tanaka T, Kono S, et al. Urinary Retention Secondary to Listeria Meningitis. Inter Med. 2008: 47:1129-31

221. Kennedy F, Elsberg CA, Lambert CI. A peculiar undescribed disease of the nerves of the cauda equina. Am J Med Sci. 1913: 147:645-67

222. Burton M, Anslow P, Gray W, Donaghy M. Selective hypertrophy of the cauda equina nerve roots. J Neurol 2002: 249:337-40

223. Dyck P, Windebank A. Diabetic and nondiabetic lumbosacral radiculoplexus neuropathies: new insights into pathophysiology and treatment. Muscle Nerve. 2002: 25:477-91

224. Tenembaum S, Chitnis T, Ness J, Hahn JS. Acute disseminated encephalomyelitis. Neurology. 2007 Apr 17: 68:S23-36

225. Wender M. Acute disseminated encephalomyelitis (ADEM). J Neuroimmunol. 2011 Feb: 231:92-9

226. Schkrohowsky JG, Hoernschemeyer DG, Carson BS, Ain MC. Early presentation of spinal stenosis in achondroplasia. J Pediatr Orthop 2007; 27(2): 119-22.

227. Johnsson KE, Sass M. Cauda equina syndrome in lumbar spinal stenosis: case report and incidence in Jutland, Denmark. J Spinal Disord Tech 2004; 17(4): 334-5.

228. Goh KJ, Khalifa W, Anslow P, Cadoux-Hudson T, Donaghy M. The clinical syndrome associated with lumbar spinal stenosis. Eur Neurol 2004; 52(4): 242-9.

229. Inui Y, Doita M, Ouchi K, Tsukuda M, Fujita N, Kurosaka M. Clinical and radiologic features of lumbar spinal

stenosis and disc herniation with neuropathic bladder. Spine 2004;29(8): 869-73.

230. Jensen RL. Cauda equina syndrome as a postoperative complication of lumbar spine surgery. Neurosurg Focus 2004; 16(6): e7.

231. Imran Y, Halim Y. Acute cauda equina syndrome secondary to free fat graft following spinal decompression. Singapore Med J 2005; 46(1)25-7.

232. Tubbs RS, Oakes WJ, Blount JP. Isolated atlantal stenosis in a patient with idiopathic growth hormone deficiency, and Klippel-Feil and Duane's syndromes. Childs Nerv Syst 2005; 21(5):421-4.

233. Alvarez JA, Hardy RH Jr. Lumbar spine stenosis: a common cause of back and leg pain. Am Fam Physician 1998; 57(8):1825-34, 1839-40.

234. Miyata M, Mizunaga M, Taniguchi N, Kaneko S, Yachiku S, Atsuta Y. Neuropathic bladder dysfunction in patients with ossification of the posterior longitudinal ligament. Int J Urol 1998; 5(6): 540-5.

235. Yamanishi T, Yasuda K, Sakakibara R, Murayama N, Hattori T, Ito H. Detrusor overactivity and penile erection in patients with lower lumbar spine lesions. Eur Urol 1998; 34(4): 360-4.

236. Lee TT, Manzano GR, Green BA. Modified open-door cervical expansive laminoplasty for spondylotic myelopathy: operative technique, outcome, and predictors for gait improvement. J Neurosurg 1997; 86(1): 64-8.

237. Jennett WB. A study of 25 cases of compression of the cauda equina by prolapsed intervertebral discs. J NeurolNeurosurg Psychiatry 1956;19:109-116.

238. Tay ECK, Chacha PB. Midline prolapse of a lumbar intervertebral disc with compression of the cauda equina. J Bone Joint Surg Br 1979;61: 43-46.

239. Nielsen B, de Nully M, Schmidt K, Hansen I. A urodynamic study of cauda equina syndrome due to lumbar disc herniation.Urol Int 1980; 35:167-170.

240. O'Flynn KJ, Murphy R,Thomas DG. Neurogenic bladder dysfunction in lumbar intervertebral disc prolapse. Br J Urol 1992.;69:38-40.

241. Bartels RH, de Vries J.. Hemi-cauda equina syndrome from herniated lumbar disc: a neurosurgical emergency? Can J Neurol Sci 1996; 23:296-299.

242. Goldman HB, Appell RA. Voiding dysfunction in women with lumbar disc prolapse. Int Urogynecol J 1999;10:134-138.

243. Ahn UM, Ahn NU, Buchowski JM, Garrett ES, SieberAN, Kostuik JP. Cauda equina syndrome secondiary to lumbar disc herniation: a metaanalysis of surgical outcomes. Spine 2000; 25:1515-1522

244. Shapiro S. Medical realities of cauda equina syndrome secondary to lumbar disc herniation. Spine 2000; 25:348-351.

245. Kostuik JP, Harrington I, Alexander D, Rand W, Evans D.. Cauda equina syndrome and lumbar disc herniation. J Bone Joint Surg Am 1986; 68: 386-391.

246. Yamanishi T, Yasuda K,Yuki T, Sakakibara R, Uchiyama T,Kamai T, Tsujii T, Yoshida K. Urodynamic evaluation of surgical outcome in patients with urinary retention due to central lumbar disc prolapse. Neurouro Urodyn 2003, 22: 670-675.

247. McCarthy MJ, Aylott CE, Grevitt MP, Hegarty J.Cauda equina syndrome: factors affecting long-term functional and sphincteric outcome. Spine 2007; 32:207-216.

248. Fanciullacci F, Sandri S, Politi P, Zanollo A. . Clinical, urodynamic and neurophysiological findings in patients with neuropathic bladder due to a lumbar intervertebral disc protrusion. Paraplegia 1989; 27:354-358.

249. Fanciullacci F. Urodynamic findings with disc protrusion. Int Urogynecol J 1994; 5:106-111.

250. Inui Y, Doita M, Ouchi K, Tsukuda M, Fujita N, Kurosaka M. Clinical and radiological features of lumber spinal stenosis and disc herniation with neurogenic bladder. Spine 2004; 29: 869-873.

251. Yamanishi T, Yasuda K, Sakakibara R, Murayama N, Hattori T, Ito H. Detrusor overactivity and penile erection in patients with lower lumbar spine lesions. Eur Urol 1998; 34: 360-364.

252. Dong D, Xu Z, Shi B, Chen J, Jiang X, Wang H. Clinical significance of urodynamic studies in neurogenic bladder dysfunction caused by intervertebral disk hernia. Neurouro Urodyn 2006; 25: 446-450.

253. Bell DA, Collie D, Statham PF. Cauda equina syndrome: what is the correlation between clinical assessment and MRI scanning? Br J Neurosurg 2007; 21:201-203.

254. Kennedy JG, Sole KE, McGrath A, Stephens MM, Walsh MG, McManus F. Predictors of outcome in cauda equina syndrome. Eur Spine J 1999; 8: 317-322.

255. Postacchini F. Management of herniation of the lumbar disc. J Bone Joint Surg Br 1999; 81:567-576.

256. Henriques T, Olerud C, Petren-Mallmin M, Ahl T. Cauda equine syndrome as a postoperative complication in five patients operated for lumbar disc herniation. Spine 2001; 26:293-297.

257. Bartolin Z, Gilja I, Bedalov G, Savic I. . Bladder funcG tion in patients with lumbar intervertebral disc protrusion. J Urol 1998; 159:969-971.

258. Bartolin Z, Vilendecic M, Derezic D. Bladder function after surgery for lumbar intervertebral disc protrusion. J Urol 1999; 161:1885-1887.

E-VIII. Neuropathies and muscle disorders

1. Hughes RA, Cornblath DR. Guillain-Barré syndrome. Lancet. 2005; 366: 1653-1666.

2. Hughes RA, Wijdicks EFM, Benson E, Cornblath DR. Hahn AF, Meythaler JM, Sladky JT, Barohn RJ, Stevens JC. Supportive care for patients with Guillain-Barré syndrome. Arch Neurol. 2005; 62: 1194-1198.

3. Asahina M, Kuwabara S, Suzuki A, Hattori T. Autonomic function in demyelinating and axonal subtypes of Guillain-Barré syndrome. Acta Neurol Scand 2002; 105: 44-50. **3A**. Asbury AK, Cornblath DR. Assesss ment of current diagnostic criteria for Guillain-Barre syndrome. Ann Neurol. 1990: 27 Suppl:S21-4

4. Sakakibara R, Hattori T, Kuwabara S, Yamanishi T, Yasuda K. Micturitional disturbance in patients with Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1997; 63: 649-653. 4. Sakakibara R, Uchiyama T, Kuwabara S, et al. Prevalence and mechanism of bladder dysfunction in Guillain-Barre Syndrome. Neurourol Urodyn. 2009: **28**:432-7

5. Guillain G, Barré JA, Strohl A. Sur un syndrome de radiculo-névrite avec hyperalbuminose du liquode céphalo-rachidien sans réaction cellulaire; remarques sur les caractéres cliniques et graphiques des réflexes tendineux. Bell Mém Soc Méd Paris 1916; 40: 1462-1470.

6. Guillain G. Radiculoneuritis with acellular hyperalbuminosis of the cerebrospinal fluid. Arch Neurol Psychiat 1936; 36: 975-990.

7. Sawai S, Sakakibara R, Uchiyama T, Liu Z, Yamamoto T, Ito T, Kuwabara S, Kanai K, Asahina M, Yamanaka T, Odaka T, Yamaguchi T, Hattori T. Acute motor axonal neuropathy presenting with bowel, bladder, and erectile dysfunction. J Neurol. 2007; 254: 250-252.

8. Sakakibara R, Uchiyama T, Tamura N, Kuwabara S, Asahina M, Hattori T. U rinary retention and sympathetic sphincter obstruction in axonal Guillain-Barre syndrome. Muscle Nerve. 2007; 35: 111-115. **8A**. de Jager AE, Sluiter HJ. Clinical signs in severe Guillain-

Barre syndrome: analysis of 63 patients. J Neurol Sci. 1991 Aug: **104**:143-50

9. Lichtenfeld P. Autonomic dysfunction in the Guillain-Barré syndrome. Am J Med 1971; 50: 772–780.

10. Kogan BA, Solomon MH, Diokno AC. Urinary retention secondary to Landry- Guillain-Barré syndrome. J Urol 1981; 126: 643-644.

11. Wheeler JS, Siroky MB, Pavlakis A, Krane RJ. The urological aspects of the Guillain-Barré syndrome. J Urol 1984; 131: 917-919.

12. Gabavac Z, Gilja I, Gubarev N, Bozicević D. Neurologic and urodynamic characteristics of patients with Guillain-Barré syndrome. Lijec Vjesn. 1989; 111: 17-20.

13. Muller HD, Beckmann A, Schroder JM. Inflammatory infiltrates in the spinal cord of patients with Guillain-Barre syndrome. Acta Neuropathol (Berl). 2003; 106: 509-517. **13A**. Burakgazi AZ, Alsowaity B, Burakgazi ZA, Unal D, Kelly JJ. Bladder dysfunction in peripheral neuropathies. Muscle Nerve. 2012 Jan: **45**:2-8

14. Crino PB, Zimmerman R, Laskowitz D, Raps EC, Rostami AM. Magnetic resonance imaging of the cauda equina in Guillain-Barré syndrome. Neurology. 1994; 44: 1334-1336.

15. Kuwabara S, Nakata M, Sung JY, Mori M, Kato N, Hattori T, Koga M, Yuki N. Hyperreflexia in axonal Guillain-Barre syndrome subsequent to Campylobacter jejuni enteritis. J Neurol Sci. 2002; 199: 89-92.

16. Zochodne DW. Autonomic involvement in Guillain-Barré syndrome; a review. Muscle Nerve 1994; 17: 145-1155. 16. Muller HD, Beckmann A, Schroder JM. Inflammatory infiltrates in the spinal cord of patients with Guillain-Barre syndrome. Acta Neuropathol. 2003 Dec: **106**:509-17. 16A. Wosnitzer MS, Walsh R, Rutman MP. The use of sacral neuromodulation for the treatment of non-obstructive urinary retention secondary to Guillain-Barre syndrome. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Sep: **20**:1145-7

17. Burns TM, Lawn ND, Low PA, Camilleri M, Wijdicks EFM. Adynamic ileus in severe Guillain–barre´ syndrome. Muscle Nerve 2001; 24: 963–965.

18. Lobrano A, Blanchard K, Abell TL, Minocha A, Boone W, Wyatt-Ashmead J, Fratkin J, Subramony C, Wee Jr A,. di Nardo G, Barbara G, Stanghellini V, de Giorgio R. Postinfectious gastroparesis related to autonomic failure: a case report. Neurogastroenterol Motil 2006; 18: 162–167.

19. Gazulla Abio J, Benavente Aguilar I. Paraparesis, hyperprolactinemia and adynamic ileus in Guillain-Barre syndrome. Neurologia. 2004; 19: 396-400.

20. Sawai S, Sakakibara R, Uchiyama T, Liu Z, Yamamoto T, Ito T, Kuwabara S, Kanai K, Asahina M, Yamanaka T, Odaka T, Yamaguchi T, Hattori T. Acute motor axonal neuropathy presenting with bowel, bladder, and erectile dysfunction. J Neurol 2007; 254; 250-252.

21. Nowe T, Hüttemann K, Engelhorn T, Schellinger PD, Köhrmann M. Paralytic ileus as a presenting symptom of Guillain-Barré syndrome. J Neurol. 2008; 255: 756-757.

22. Herlenius G, Wilczek HE, Larsson M, Ericzon BG. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. Transplantation. 2004 Jan 15: **77**:64-71

23. Lobato L, Ventura A, Beirao I, et al. End-stage renal disease in familial amyloidosis ATTR Val30Met: a definitive indication to combined liver-kidney transplantation. Transplant Proc. 2003 May: **35**:1116-20

24. Ito T, Sakakibara R, Ito S, et al. Mechanism of cona stipation in familial amyloid polyneuropathy: a case report. Intern Med. 2006: **45**:1173-5

25. Adams D, Samuel D, Goulon-Goeau C, et al. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. Brain. 2000 Jul: **123 (Pt 7)**:1495-504

26. Saini J, Axelrod FB, Maayan C, Stringer J, Smilen SW. Urinary incontinence in familial dysautonomia. Int Urogynecol J Pelvic Floor Dysfunct. 2003 Aug: **14**:209-13

27. Miura S, Shibata H, Kida H, et al. Hereditary motor and sensory neuropathy with proximal dominancy in the lower extremities, urinary disturbance, and paroxysmal dry cough. J Neurol Sci. 2008 Oct 15: **273**:88-92

28. Sakakibara R, Uchiyama T, Asahina M, Suzuki A, Yamanishi T, Hattori T. Micturition disturbance in acute idiopathic autonomic neuropathy. J Neurol Neurosurg Psychiatry. 2004 Feb: **75**:287-91

29. Gibbons CH, Freeman R. Antibody titers predict clinical features of autoimmune autonomic ganglionopathy. Auton Neurosci. 2009 Mar 12: **146**:8-12

30. Sakakibara R, Hattori T, Uchiyama T, Asahina M, Yamanishi T. Micturitional disturbance in pure autonomic failure. Neurology. 2000 Jan 25: **54**:499-501

31. Waterman SA. Autonomic dysfunction in Lambert-Eaton myasthenic syndrome. Clin Auton Res. 2001 Jun: **11**:145-54

32. Sandler PM, Avillo C, Kaplan SA. Detrusor areflexia in a patient with myasthenia gravis. Int J Urol. 1998 Mar: **5**:188-90

33. Kaya C, Karaman MI. Case report: a case of bladder dysfunction due to myasthenia gravis. Int Urol Nephrol. 2005: **37**:253-5

34. Vernino S, Cheshire WP, Lennon VA. Myasthenia gravis with autoimmune autonomic neuropathy. Auton Neurosci. 2001 May 14: **88**:187-92

35. MacLeod M, Kelly R, Robb SA, Borzyskowski M. Bladder dysfunction in Duchenne muscular dystrophy. Arch Dis Child. 2003 Apr: **88**:347-9

36. Caress JB, Kothari MJ, Bauer SB, Shefner JM. Urinary dysfunction in Duchenne muscular dystrophy. Muscle Nerve. 1996 Jul: **19**:819-22

37. Abercrombie JF, Rogers J, Swash M. Faecal incontinence in myotonic dystrophy. J Neurol Neurosurg Psychiatry. 1998 Jan: **64**:128-30

38. Pelliccioni G, Scarpino O, Piloni V. Procainamide for faecal incontinence in myotonic dystrophy. J Neurol Neurosurg Psychiatry. 1999 Aug: **67**:257-8

39. Sakakibara R, Hattori T, Tojo M, Yamanishi T, Yasuda K, Hirayama K. Micturitional disturbance in myotonic dystrophy. J Auton Nerv Syst. 1995 Mar 18: **52**:17-21

40. Nishino I, Spinazzola A, Papadimitriou A, et al. Mitochondrial neurogastrointestinal encephalomyopathy: an autosomal recessive disorder due to thymidine phosphorylase mutations. Ann Neurol. 2000 Jun: **47**:792-800

41. Barrett TG, Bundey SE. Wolfram (DIDMOAD) syndrome. J Med Genet. 1997 Oct: **34**:838-41. Barrett TG, Scott-Brown M, Seller A, Bednarz A, Poulton K, Poulton J. The mitochondrial genome in Wolfram syndrome. J Med Genet. 2000 Jun: **37**:463-6.

42. Parys BT, Woolfenden KA, Parsons KF. Bladder dysfunction after simple hysterectomy: urodynamic and neurological evaluation. *Eur Urol* 1990; 172:129-133.

43. Sekido N, Kawai K, Akaza H. LUT dysfunction as persistent complication of radical hysterectomy. *Int J Urol* 1997; 4(3):259-264.

44. Axelsen SM, Bek KM, Petersen LK. Urodynamic and ultrasound characteristics of incontinence after radical hysterectomy. Neurourol Urodyn 2007; 26(6):794-799.

45. Jackson SL, Scholes D, Boyko EJ, Abraham L, Fihn SD. Predictors of urinary incontinence in a prospective cohort of postmenopausal women. Obstet Gynecol 2006; 108(4):855-862.

46. Plotti F, Angioli R, Zullo MA, et al. Update on urodynamic bladder dysfunctions after radical hysterectomy for cervical cancer. Crit Rev Oncol Hematol. 2011 Nov: **80**:323-9

47. Eickenberg HU, Amin M, Klompus W, Lich R, Jr. Urologic complications following abdominoperineal resection. *J Urol* 1976; 1152:180-182.

48. Baumgarner GT, Miller HC. Genitourinary complications of abdominoperineal resection. *South Med J* 1976; 69(7):875-877.

49. Pocard M, Zinzindohoue F, Haab F, Caplin S, Parc R, Tiret E. A prospective study of sexual and urinary function before and after total mesorectal excision with autonomic nerve preservation for rectal cancer. Surgery. 2002 Apr;131(4):368-72

50. Kim NK., Aahn TW., Park JK., Lee KY., Lee WH., Sohn SK.; Min JS. Assessment of sexual and voiding function after total mesorectal excision with pelvic autonomic nerve preservation in males with rectal cancer. Dis Colon Rectum. 2002 Sep; 45 (9): 1178-85.

51. Turoldo A., Balani A., Roseano M. et al., 2003 Functional complication of the LUT after curative exeresis for cancer of the rectum. Tumori 89 (4) Suppl.: 98-102.

52. Lim JF, Tjandra JJ, Hiscock R, Chao MW, Gibbs P. Preoperative chemoradiation for rectal cancer causes prolonged pudendal nerve terminal motor latency. Dis Colon Rectum 2006; 49(1):12-19.

53. Langer R, Neuman M, Ron-el R, Golan A, Bukovsky I, Caspi E. The effect of total abdominal hysterectomy on bladder function in asymptomatic women. Obstet Gynecol. 1989 Aug: **74**:205-7

54. Fitzpatrick M, O'brien C, O'connell PR, O'Herlihy C. Patterns of abnormal pudendal nerve function that are associated with postpartum fecal incontinence. Am J Obstet Gynecol 2003; 189(3):730-735.

55. Sangwan YP, Coller JA, Barrett RC, Roberts PL, Murray JJ, Schoetz DJ, Jr. Can manometric parameters predict response to biofeedback therapy in fecal incontinence? Dis Colon Rectum 1995; 38(10):1021-1025.

56. Sangwan YP, Coller JA, Schoetz DJ, Roberts PL, Murray JJ. Spectrum of abnormal rectoanal reflex patterns in patients with fecal incontinence. Dis Colon Rectum 1996; 39(1):59-65.

57. Nordling J, Meyhoff HH, Hald T, Gerstenberg T, Walter S, Christensen NJ. Urethral denervation supersene sitivity to noradrenaline after radical hysterectomy. *Scand J Urol Nephrol* 1981; 151:21-24.

58. Hollabaugh RS, Jr., Steiner MS, Sellers KD, Samm BJ, Dmochowski RR. Neuroanatomy of the pelvis: implications for colonic and rectal resection. *Dis Colon Rectum* 2000; 43(10):1390-1397.

59. Junginger T, Kneist W, Heintz A. Influence of identification and preservation of pelvic autonomic nerves in rectal cancer surgery on bladder dysfunction after total mesorectal excision. *Dis Colon Rectum* 2003; 46(5):621-628.

60. Smith PH, Ballantyne B. The neuroanatomical basis for denervation of the urinary bladder following major pelvic surgery. *Br J Surg* 1968; 55(12):929-933.

61. Tong XK, Huo RJ. The anatomical basis and prevention of neurologic voiding dysfunction following radical hysterectomy. Surg Radiol Anat 1991; 132:145-148.

62. Yabuki Y, Asamoto A, Hoshiba T, Nishimoto H, Nishikawa Y, Nakajima T. Radical hysterectomy: An anatomic evaluation of parametrial dissection. Gynecol Oncol 2000; 771:155-163.

63. Ito E, Saito T. Nerve-preserving techniques for radical hysterectomy. Eur J Surg Oncol 2004; 30:1137-1140.

64. Zanolla R, Monzeglio C, Campo B, Ordesi G, Balzarini A, Martino G. Bladder and urethral dysfunction after radical abdominal hysterectomy: rehabilitative treatment. J Surg Oncol. 1985 Mar: **28**:190-4

65. Sakuragi N, Todo Y, Kudo M, Yamamoto R, Sato T. A systematic nerve-sparing radical hysterectomy technique in invasive cervical cancer for preserving postsurgical bladder function. Int J Gynecol Cancer 2005; 15:389-397.

66. Kuwabara Y, Suzuki M, Hashimoto M, Furugen Y, Yoshida K, Mitsuhashi N. New method to prevent bladder dysfunction after radical hysterectomy for uterine cervical cancer. J Obstet Gynaecol Res 2000; 261:1-8.

67. Kneist W, Junginger T. Long-term urinary dysfunction after mesorectal excision: a prospective study with intraoperative electrophysiological confirmation of nerve preservation. Eur J Surg Oncol 2007; 33:1068-1074.

68. Zanolla R, Monzeglio C, Campo B, Ordesi G, Balzarini A, Martino G. Bladder and urethral dysfunction after radical abdominal hysterectomy: rehabilitative treatment. J Surg Oncol 1985; 28:190-194.

69. Martins FE, Boyd SD. Artificial urinary sphincter in patients following major pelvic surgery and/or radiotherapy: are they less favorable candidates? J Urol 1995; 153:1188-1193

70. Ratto C, Grillo E, Parello A, Petrolino M, Costamagna G, Doglietto GB. Sacral neuromodulation in treatment of fecal incontinence following anterior resection and chemoradiation for rectal cancer. Dis Colon Rectum 2005; 48:1027-1036

E-IX. Multiple sclerosis

1. Nortvedt MW, Riise T, Myhr KM, Landtblom AM, Bakke A, Nyland HI. Reduced quality of life among multiple sclerosis patients with sexual disturbance and bladder dysfunction. Mult Scler. 2001 Aug: 7:231-5

2. Bonniaud V, Raibaut P, Guyatt G, Amarenco G, Parratte B. [Symptom and quality of life assessment in urinary disorders]. Ann Readapt Med Phys. 2005 Jul: 48:392-403

3. Bonniaud V, Parratte B, Amarenco G, Jackowski D, Didier JP, Guyatt G. Measuring quality of life in multiple sclerosis patients with urinary disorders using the Qualiveen questionnaire. Arch Phys Med Rehabil. 2004 Aug: 85:1317-23

4. Bonniaud V, Jackowski D, Parratte B, et al. Quality of life in multiple sclerosis patients with urinary disorders: discriminative validation of the English version of Qualiveen. Qual Life Res. 2005 Mar: 14:425-31

5. Marrie RA, Cutter G, Tyry T, Vollmer T, Campagnolo D. Disparities in the management of multiple sclerosis-related bladder symptoms. Neurology. 2007 Jun 5: 68:1971-8

6. Hinson JL, Boone TB. Urodynamics and multiple sclerosis. Urol Clin North Am. 1996 Aug: 23:475-81

7. Amarenco G, Kerdraon J, Denys P. [Bladder and sphincter disorders in multiple sclerosis. Clinical, urodynamic and neurophysiological study of 225 cases]. Rev Neurol (Paris). 1995 Dec: 151:722-30

8. Betts CD, D'Mellow MT, Fowler CJ. Urinary symptoms and the neurological features of bladder dysfunction in multiple sclerosis. J Neurol Neurosurg Psychiatry. 1993 Mar: 56:245-50

9. Giannantoni A, Scivoletto G, Di Stasi SM, Grasso MG, Vespasiani G, Castellano V. Urological dysfunctions and upper urinary tract involvement in multiple sclerosis patients. Neurourol Urodyn. 1998: 17:89-98

10. Gonor SE, Carroll DJ, Metcalfe JB. Vesical dysfunction in multiple sclerosis. Urology. 1985 Apr: 25:429-31

11. Philp T, Read DJ, Higson RH. The urodynamic characteristics of multiple sclerosis. Br J Urol. 1981 Dec: 53:672-5

12. Kurtzke JF, Beebe GW, Nagler B, Auth TL, Kurland LT, Nefzger MD. Studies on the natural history of multiple sclerosis. 6. Clinical and laboratory findings at first diagnosis. Acta Neurol Scand. 1972: 48:19-46

13. Miller H, Simpson CA, Yeates WK. Bladder Dysfunction in Multiple Sclerosis. Br Med J. 1965 May 15: 5445:1265-9

14. Sliwa JA, Bell HK, Mason KD, Gore RM, Nanninga J, Cohen B. Upper urinary tract abnormalities in multiple sclerosis patients with urinary symptoms. Arch Phys Med Rehabil. 1996 Mar: 77:247-51

15. Giannantoni A, Scivoletto G, Di Stasi SM, et al. Lower urinary tract dysfunction and disability status in patients with multiple sclerosis. Arch Phys Med Rehabil. 1999 Apr: 80:437-41

16. Bart S, De Seze M, Chartier-Kastler E, Ruffion A. [Lower urinary tract dysfunction and multiple sclerosis]. Prog Urol. 2007 May: 17:358-64

17. de Seze M, Ruffion A, Denys P, Joseph PA, Perrouin-Verbe B. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. Mult Scler. 2007 Aug: 13:915-28

18. Andersen JT, Bradley WE. Abnormalities of detrusor and sphincter function in multiple sclerosis. Br J Urol. 1976 Jun: 48:193-8

19. Perrigot M, Richard F, Veaux-Renault V, Chatelain C, Kuss R. [Bladder sphincter disorders in multiple sclerosis: symptomatology and evolution. 100 cases]. Sem Hop. 1982 Nov 25: 58:2543-6

20. Awad SA, Gajewski JB, Sogbein SK, Murray TJ, Field CA. Relationship between neurological and urological status in patients with multiple sclerosis. J Urol. 1984 Sep: 132:499-502

21. Bemelmans BL, Hommes OR, Van Kerrebroeck PE, Lemmens WA, Doesburg WH, Debruyne FM. Evidence for early lower urinary tract dysfunction in clinically silent multiple sclerosis. J Urol. 1991 Jun: 145:1219-24

22. Bradley WE. Urinary bladder dysfunction in multiple sclerosis. Neurology. 1978 Sep: 28:52-8

23. De Ridder D, van Poppel H, Demonty L, et al. Bladder cancer in patients with multiple sclerosis treated with cyclophosphamide. J Urol. 1998 Jun: 159:1881-4

24. Eardley I, Nagendran K, Lecky B, Chapple CR, Kirby RS, Fowler CJ. Neurophysiology of the striated urethral sphincter in multiple sclerosis. Br J Urol. 1991 Jul: 68:81-8

25. Gallien P, Robineau S, Nicolas B, Le Bot MP, Brissot R, Verin M. Vesicourethral dysfunction and urodynamic findings in multiple sclerosis: a study of 149 cases. Arch Phys Med Rehabil. 1998 Mar: 79:255-7

26. Goldstein I, Siroky MB, Sax DS, Krane RJ. Neurouros logic abnormalities in multiple sclerosis. J Urol. 1982 Sep: 128:541-5

27. Hennessey A, Robertson NP, Swingler R, Compston DA. Urinary, faecal and sexual dysfunction in patients with multiple sclerosis. J Neurol. 1999 Nov: 246:1027-32

28. Kasabian NG, Krause I, Brown WE, Khan Z, Nagler HM. Fate of the upper urinary tract in multiple sclerosis. Neurourol Urodyn. 1995: 14:81-5

29. Koldewijn EL, Hommes OR, Lemmens WA, Debruyne FM, van Kerrebroeck PE. Relationship between lower urinary tract abnormalities and disease-related parameters in multiple sclerosis. J Urol. 1995 Jul: 154:169-73

30. Mayo ME, Chetner MP. Lower urinary tract dysfunction in multiple sclerosis. Urology. 1992 Jan: 39:67-70

31. Porru D, Campus G, Garau A, et al. Urinary tract dysfunction in multiple sclerosis: is there a relation with disease-related parameters? Spinal Cord. 1997 Jan: 35:33-6

32. Summers JL. Neurogenic bladder in the woman with multiple sclerosis. J Urol. 1978 Nov: 120:555-6

33. De Ridder D, Vermeulen C, De Smet E, Van Poppel H, Ketelaer P, Baert L. Clinical assessment of pelvic floor dysfunction in multiple sclerosis: urodynamic and neurological correlates. Neurourol Urodyn. 1998: 17:537-42

34. Litwiller SE, Frohman EM, Zimmern PE. Multiple sclerosis and the urologist. J Urol. 1999 Mar: 161:743-57

35. Amarenco G. [Vesico-sphincter disorders of nervous origin]. Rev Prat. 1995 Feb 1: 45:331-5

36. Araki I, Matsui M, Ozawa K, Takeda M, Kuno S. Relationship of bladder dysfunction to lesion site in multiple sclerosis. J Urol. 2003 Apr: 169:1384-7

37. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov: 33:1444-52

38. Sirls LT, Zimmern PE, Leach GE. Role of limited evaluation and aggressive medical management in multiple sclerosis: a review of 113 patients. J Urol. 1994 Apr: 151:946-50

39. Buchanan RJ, Martin RA, Wang S, Ju H. Analyses of nursing home residents with multiple sclerosis at admission and one year after admission. Mult Scler. 2004 Feb: 10:74-9

40. McGuire EJ, Savastano JA. Urodynamic findings and long-term outcome management of patients with multiple sclerosis-induced lower urinary tract dysfunction. J Urol. 1984 Oct: 132:713-5

41. Kirchhof K, Fowler CJ. The value of the Kurtzke Functional Systems Scales in predicting incomplete bladder emptying. Spinal Cord. 2000 Jul: 38:409-13

42. Kragt JJ, Hoogervorst EL, Uitdehaag BM, Polman CH. Relation between objective and subjective measures of bladder dysfunction in multiple sclerosis. Neurology. 2004 Nov 9: 63:1716-8

43. Grasso MG, Pozzilli C, Anzini A, Salvetti M, Bastianello S, Fieschi C. Relationship between bladder dysfunction and brain MRI in multiple sclerosis. Funct Neurol. 1991 Jul-Sep: 6:289-92

44. Pozzilli C, Grasso MG, Bastianello S, et al. Structural brain correlates of neurologic abnormalities in multiple sclerosis. Eur Neurol. 1992: 32:228-30

45. Ukkonen M, Elovaara I, Dastidar P, Tammela TL. Urodynamic findings in primary progressive multiple sclerosis are associated with increased volumes of plaques and atrophy in the central nervous system. Acta Neurol Scand. 2004 Feb: 109:100-5

46. Leruitte A, Ketelaer P, Vereecken R. [Micturitional disorders in multiple sclerosis (author's transl)]. Urol Int. 1976: 31:230-8

47. Araki I, Zakoji H, Komuro M, et al. Lower urinary tract symptoms in men and women without underlying disease causing micturition disorder: a cross-sectional study assessing the natural history of bladder function. J Urol. 2003 Nov: 170:1901-4

48. Redelings MD, McCoy L, Sorvillo F. Multiple sclerosis mortality and patterns of comorbidity in the United States from 1990 to 2001. Neuroepidemiology. 2006: 26:102-7

49. Amarenco G, Bosc S, Boiteau F. [Urologic complications of multiple sclerosis. 180 cases]. Presse Med. 1996 Jun 22: 25:1007-10

50. Barbalias GA, Nikiforidis G, Liatsikos EN. Vesicourethral dysfunction associated with multiple sclerosis: clinical and urodynamic perspectives. J Urol. 1998 Jul: 160:106-11

51. Blaivas JG, Barbalias GA. Detrusor-external sphincter dyssynergia in men with multiple sclerosis: an ominous urologic condition. J Urol. 1984 Jan: 131:91-4

52. Petersen T, Pedersen E. Neurourodynamic evaluation of voiding dysfunction in multiple sclerosis. Acta Neurol Scand. 1984 Jun: 69:402-11

53. Linsenmeyer TA, Oakley A. Accuracy of individuals with spinal cord injury at predicting urinary tract infections based on their symptoms. J Spinal Cord Med. 2003 Winter: 26:352-7

54. Bakke A, Malt UF. Psychological predictors of symptoms of urinary tract infection and bacteriuria in patients treated with clean intermittent catheterization: a prospective 7-year study. Eur Urol. 1998: 34:30-6

55. Hillman LJ, Burns SP, Kraft GH. Neurological worsening due to infection from renal stones in a multiple sclerosis patient. Mult Scler. 2000 Dec: 6:403-6

56. Metz LM, McGuinness SD, Harris C. Urinary tract infections may trigger relapse in multiple sclerosis. Axone. 1998 Jun: 19:67-70

57. Game X, Castel-Lacanal E, Bentaleb Y, et al. Botulinum toxin A detrusor injections in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infections. Eur Urol. 2008 Mar: 53:613-8

58. Andersen JT, Bradley WE. The syndrome of detrusor-sphincter dyssynergia. J Urol. 1976 Oct: 116:493-5

59. Blaivas JG, Bhimani G, Labib KB. Vesicourethral dysfunction in multiple sclerosis. J Urol. 1979 Sep: 122:342-7

60. Franz DA, Towler MA, Edlich RF, Steers WD. Functional urinary outlet obstruction causing urosepsis in a male multiple sclerosis patient. J Emerg Med. 1992 May-Jun: 10:281-4

61. Groah SL, Weitzenkamp DA, Lammertse DP, Whiteneck GG, Lezotte DC, Hamman RF. Excess risk of bladder cancer in spinal cord injury: evidence for an association between indwelling catheter use and bladder cancer. Arch Phys Med Rehabil. 2002 Mar: 83:346-51

62. Pannek J. Transitional cell carcinoma in patients with spinal cord injury: a high risk malignancy? Urology. 2002 Feb: 59:240-4

63. Subramonian K, Cartwright RA, Harnden P, Harrison SC. Bladder cancer in patients with spinal cord injuries. BJU Int. 2004 Apr: 93:739-43

64. West DA, Cummings JM, Longo WE, Virgo KS, Johnson FE, Parra RO. Role of chronic catheterization in the development of bladder cancer in patients with spinal cord injury. Urology. 1999 Feb: 53:292-7

65. Desgrippes A, Meria P, Cortesse A, Cochand-Priollet B, Cariou G. [Epidermoid carcinoma of the bladder]. Prog Urol. 1998 Jun: 8:321-9

66. van Poppel H, Stessens R, de Vos R, van Damme B. Isolated condyloma acuminatum of the bladder in a patient with multiple sclerosis: etiological and pathological considerations. J Urol. 1986 Nov: 136:1071-3

67. Wiedemann A, Diekmann WP, Holtmann G, Kracht H. Report of a case with giant condyloma (Buschke-Lowenstein tumor) localized in the bladder. J Urol. 1995 Apr: 153:1222-4

68. Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. Renal failure in patients with neurogenic lower urinary tract dysfunction. Neuroepidemiology. 2001 May: 20:138-43

69. Saint S, Kaufman SR, Rogers MA, Baker PD, Ossenkop K, Lipsky BA. Condom versus indwelling urinary catheters: a randomized trial. J Am Geriatr Soc. 2006 Jul: 54:1055-61

70. Eckford SB, Kohler-Ockmore J, Feneley RC. Long-term follow-up of transvaginal urethral closure and suprapubic cystostomy for urinary incontinence in women with multiple sclerosis. Br J Urol. 1994 Sep: 74:319-21

71. Sheriff MK, Foley S, McFarlane J, Nauth-Misir R, Craggs M, Shah PJ. Long-term suprapubic catheterisation: clinical outcome and satisfaction survey. Spinal Cord. 1998 Mar: 36:171-6

72. Weld KJ, Dmochowski RR. Effect of bladder management on urological complications in spinal cord injured patients. J Urol. 2000 Mar: 163:768-72

73. Ciancio SJ, Mutchnik SE, Rivera VM, Boone TB. Urodynamic pattern changes in multiple sclerosis. Urology. 2001 Feb: 57:239-45

74. Piazza DH, Diokno AC. Review of neurogenic bladder in multiple sclerosis. Urology. 1979 Jul: 14:33-5

75. Parratte B, Bonniaud V, Vuillier F, Tatu L, Rumbach L, Monnier G. [Urinary disorders, functional exploration of the urinary tract, and multiple sclerosis]. Rev Neurol (Paris). 2002 Oct: 158:1019-24

76. Wheeler JS, Jr., Siroky MB, Pavlakis AJ, Goldstein I, Krane RJ. The changing neurourologic pattern of multiple sclerosis. J Urol. 1983 Dec: 130:1123-6

77. Andrews KL, Husmann DA. Bladder dysfunction and management in multiple sclerosis. Mayo Clin Proc. 1997 Dec: 72:1176-83

78. Nortvedt MW, Riise T, Frugard J, et al. Prevalence of bladder, bowel and sexual problems among multiple sclerosis patients two to five years after diagnosis. Mult Scler. 2007 Jan: 13:106-12

79. Chia YW, Fowler CJ, Kamm MA, Henry MM, Lemieux MC, Swash M. Prevalence of bowel dysfunction in patients with multiple sclerosis and bladder dysfunction. J Neurol. 1995 Jan: 242:105-8

80. Munteis E, Andreu M, Tellez MJ, Mon D, Ois A, Roquer J. Anorectal dysfunction in multiple sclerosis. Mult Scler. 2006 Apr: 12:215-8

81. Bakke A, Myhr KM, Gronning M, Nyland H. Bladder, bowel and sexual dysfunction in patients with multiple sclerosis--a cohort study. Scand J Urol Nephrol Suppl. 1996: 179:61-6

82. Hinds JP, Eidelman BH, Wald A. Prevalence of bowel dysfunction in multiple sclerosis. A population survey. Gastroenterology. 1990 Jun: 98:1538-42

83. Johanson JF, Lafferty J. Epidemiology of fecal incontinence: the silent affliction. Am J Gastroenterol. 1996 Jan: 91:33-6

84. Munteis E, Andreu M, Martinez-Rodriguez J, Ois A, Bory F, Roquer J. Manometric correlations of anorectal dysfunction and biofeedback outcome in patients with multiple sclerosis. Mult Scler. 2008 Mar: 14:237-42

85. Basilisco G, Barbera R, Vanoli M, Bianchi P. Anorectal dysfunction and delayed colonic transit in patients with progressive systemic sclerosis. Dig Dis Sci. 1993 Aug: 38:1525-9

86. Weber J, Grise P, Roquebert M, et al. Radiopaque markers transit and anorectal manometry in 16 patients with multiple sclerosis and urinary bladder dysfunction. Dis Colon Rectum. 1987 Feb: 30:95-100

87. Chia YW, Gill KP, Jameson JS, et al. Paradoxical puborectalis contraction is a feature of constipation in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 1996 Jan: 60:31-5

E-X. Spinal cord lesions

1. Dahlberg A, Perttilä I, Wuokko E, Ala-Opas M. Bladder management in persons with spinal cord lesion. Spinal Cord 2004; 42: 694-8.

2. Hansen RB, Biering-Sørensen F, Kristensen JK. Blade der emptying over a period of 10-45 years after a traumatic spinal cord injury. Spinal Cord 2004; 42: 631-7.

3. Patki P, Woodhouse J, Hamid R, Shah J, Craggs M. Lower urinary tract dysfunction in ambulatory patients with incomplete spinal cord injury. J Urol 2006; 175(5): 1784-7.

4. Drake MJ, Cortina-Borja M, Savic G, Charlifue SW, Gardner BP. Prospective evaluation of urological effects of aging in chronic spinal cord injury by method of bladder management. Neurourol Urodyn. 2005: **24**:111-6

5. Podnar S, Trsinar B, Vodusek DB. Bladder dysfunction in patients with cauda equina lesions. Neurourol Urodyn 2006; 25(1): 23-31.

6. Pontari MA, Braverman AS, Ruggieri MR Sr. The M2 muscarinic receptor mediates in vitro bladder contractions from patients with neurogenic bladder dysfunction. Am J Physiol Regul Integr Comp Physiol 2004; 286(5): R874-80.

7. Haferkamp A, Freund T, Wagener N, Reitz A, Schurch B, Doersam J, Schumacher S, et al. Distribution of neuropeptide Y-containing nerves in the neurogenic and non-neurogenic detrusor. BJU Int 2006; 97(2): 393-9.

8. Oner-Iyidoğan Y, Koçak H, Gürdöl F, Koçak T, Erol B. Urine 8-isoprostane F2alpha concentrations in patients with neurogenic bladder due to spinal cord injury. Clin Chim Acta 2004; 339(1-2): 43-7.

9. Schmid DM, Reitz A, Curt A, Hauri D, Schurch B. Urethral evoked sympathetic skin responses and viscerosensory evoked potentials as diagnostic tools to evaluate urogenital autonomic afferent innervation in spinal cord injured patients. J Urol 2004; 171(3): 1156-60.

10. Schmid DM, Curt A, Hauri D, Schurch B. Motor evoked potentials (MEP) and evoked pressure curves (EPC) from the urethral compressive musculature (UCM) by functional magnetic stimulation in healthy volunteers and patients with neurogenic incontinence. Neurourol Urodyn 2005; 24(2): 117-27.

11. Dai CF, Xiao CG. Electrophysiological monitoring and identification of neural roots during somatic-autonomic reflex pathway procedure for neurogenic bladder. Chin J Traumatol 2005; 8(2): 74-6.

12. Ockrim J, Laniado ME, Khoubehi B, Renzetti R, Finazzi Agrò E, Carter SS, et al. Variability of detrusor overactivity on repeated filling cystometry in men with urge symptoms: comparison with spinal cord injury patients. BJU Int 2005; 95(4): 587-90.

13. Chou FH, Ho CH, Chir MB, Linsenmeyer TA. Normal ranges of variability for urodynamic studies of neurogenic bladders in spinal cord injury. J Spinal Cord Med 2006; 29(1): 26-31.

14. Generao SE, Dall'era JP, Stone AR, Kurzrock EA. Spinal cord injury in children: long-term urodynamic and urological outcomes. J Urol 2004; 172(3): 1092-4, discussion 1094.

15. Ersoz M, Akyuz M. Bladder-filling sensation in patients with spinal cord injury and the potential for sensation-dependent bladder emptying. Spinal Cord 2004 Feb; 42(2): 110-6.

16. Ukimura O, Ushijima S, Honjo H, Iwata T, Suzuki K, Hirahara N, Okihara K, Mizutani Y, Kawauchi A, Miki T. Neuroselective current perception threshold evaluation of bladder mucosal sensory function. Eur Urol 2004 Jan; 45(1): 70-6.

17. Schurch B, Schmid DM, Karsenty G, Reitz A. Can neurologic examination predict type of detrusor sphincter-dyssynergia in patients with spinal cord injury? Urology 2005 Feb; 65(2): 243-6.

18. De EJ, Patel CY, Tharian B, Westney OL, Graves DE, Hairston JC. Diagnostic discordance of electromyography (EMG) versus voiding cystourethrogram (VCUG) for detrusor-external sphincter dyssynergy (DESD). Neurourol Urodyn 2005; 24(7): 616-621.

19. Wenzel BJ, Boggs JW, Gustafson KJ, Creasey GH, Grill WM. Detection of neurogenic detrusor contractions from the activity of the external anal sphincter in cat and human. Neurourol Urodyn 2006; 25(2): 140-7.

20. Vaidyanathan S, Singh G, Soni BM, Hughes PL, Mansour P, Oo T, Bingley J, Sett P. Do spinal cord injury patients always get the best treatment for neuropathic bladder after discharge from regional spinal injuries centre? Spinal Cord 2004 Aug; 42(8): 438-442.

21. Kovindha A, Sivasomboon C, Ovatakanont P. Extravasation of the contrast media during voiding cystourethrography in a long-term spinal cord injury patient. Spinal Cord 2005 Jul; 43(7): 448-9.

22. Stoffel JT, McGuire EJ. Outcome of urethral closure in patients with neurologic impairment and complete urethral destruction. Neurourol Urodyn 2006; 25(1): 19-22.

23. Frost F, Roach MJ, Kushner I, Schreiber P. Inflammatory C-reactive protein and cytokine levels in asymptomatic people with chronic spinal cord injury. Arch Phys Med Rehabil 2005; 86(2): 312-7.

24. Linsenmeyer TA, House JG, Millis SR. The role of ab, normal congenitally displaced ureteral orifices in causing reflux following spinal cord injury. J Spinal Cord Med 2004; 27(2): 116-9.

25. Linsenmeyer MA, Linsenmeyer TA. Accuracy of bladder stone detection using abdominal x-ray after spinal cord injury. J Spinal Cord Med 2004; 27(5): 438-42.

26. Matlaga BR, Kim SC, Watkins SL, Kuo RL, Munch LC, Lingeman JE. Changing composition of renal calculi in patients with neurogenic bladder. J Urol 2006; 175(5): 1716-9.

27. Ke HL, Lin HY, Jang MY, Wu WJ. Hair as the nidus for bladder calculi formation complicating suprapubic cystostomy catheterization: a case report. Kaohsiung J Med Sci 2006; 22(5): 243-6.

28. Ku JH, Jung TY, Lee JK, Park WH, Shim HB. Risk factors for urinary stone formation in men with spinal cord injury: a 17-year follow-up study. BJU Int 2006; 97(4): 790-3.

29. Ost MC, Lee BR. Urolithiasis in patients with spinal cord injuries: risk factors, management, and outcomes. Curr Opin Urol 2006;16(2): 93-9.

30. Ozawa H, Uematsu K, Ohmori H, Kondo A, Iwatsubo E, Takasaka S. Long-term usefulness and safety of the contemporary balloon catheter. Nippon Hinyokika Gakkai Zasshi 2005; 96(5): 541-7.

31. Linsenmeyer MA, Linsenmeyer TA. Accuracy of predicting bladder stones based on catheter encrustation in individuals with spinal cord injury. J Spinal Cord Med 2006; 29(4): 402-5.

32. Jayawardena V, Midha M. Significance of bacteriuria in neurogenic bladder. J Spinal Cord Med 2004; 27(2): 102-5.

33. Svensson E, Ertzgaard P, Forsum U. Bacteriuria in spinal cord injured patients with neurogenic bladder dysfunction. Ups J Med Sci 2004; 109(1): 25-32.

34. Levendoglu F, Ugurlu H, Ozerbil OM, Tuncer I, Ural O. Urethral cultures in patients with spinal cord injury. Spinal Cord 2004; 42(2): 106-9.

35. Waites KB, Canupp KC, DeVivo MJ. Microbiology of the urethra and perineum and its relationship to bacteriuria in community-residing men with spinal cord injury. J Spinal Cord Med 2004; 27(5): 448-52.

36. Ku JH, Jung TY, Lee JK, Park WH, Shim HB. Influence of bladder management on epididymo-orchitis in patients with spinal cord injury: clean intermittent catheterization is a risk factor for epididymo-orchitis. Spinal Cord 2006; 44(3): 165-9.

37. Nambiar PK, Lander S, Midha M, Ha C. Fournier gangrene in spinal cord injury: a case report. J Spinal Cord Med 2005; 28(2): 121-4.

38. Vaidyanathan S, Hughes PL, Mansour P, Soni BM, Singh G, Watt JW, et al. Pseudo-tumours of the urinary tract in patients with spinal cord injury/spina bifida. Spinal Cord 2004; 42(5): 308-12.

39. Oh SJ, Ku JH, Jeon HG, Shin HI, Paik NJ, Yoo T. Health-related quality of life of patients using clean intermittent catheterization for neurogenic bladder secondary to spinal cord injury. Urology 2005; 65(2): 306-10.

40. Oh SJ, Shin HI, Paik NJ, Yoo T, Ku JH. Depressive symptoms of patients using clean intermittent catheterization for neurogenic bladder secondary to spinal cord injury. Spinal Cord 2006; 44(12): 757-62.

41. Patki P, Hamid R, Somayaji S, Bycroft J, Shah PJ, Craggs M. Long-term urological outcomes in paediatric spinal cord injury. Spinal Cord 2006; 44(12): 729-33.

42. Nosseir M, Hinkel A, Pannek J. Clinical usefulness of urodynamic assessment for maintenance of bladder function in patients with spinal cord injury. Neurourol Urodyn 2007; 26(2): 228-33.

43. Bycroft J, Hamid R, Bywater H, Patki P, Craggs M, Shah J. Variation in urological practice amongst spinal injuries units in the UK and Eire. Neurourol Urodyn 2004; 23(3): 252-6.

44. Sepahpanah F, Burns SP, McKnight B, Yang CC. Role of creatinine clearance as a screening test in persons with spinal cord injury. Arch Phys Med Rehabil 2006; 87(4): 524-8.

45. Gignoux A, Chartier-Kastler E, Ruffion A. Specific features of the early diagnosis of prostate cancer in the presence of neurogenic bladder. Prog Urol 2007; 17(3): 457-61.

46. Ruffion A, Comperat E, Roupret M, Chartier-Kastler E. Bladder cancer and neurogenic bladder. Prog Urol 2007; 17(3): 431-5.

47. Wyndale JJ, Castro D, Madersbacher H, Chartier-Kastler E, lgawa Y, Kovindha A, et al. Neurologic urinary and faecal incontinence. In Abrams P, Cardozo L, Khoury S, et al editors: Incontinence, Vol 2, Management. Paris: Health Publication Ltd 2005. p. 1059-1162.

48. Consortium for Spinal Cord Medicine. Bladder management for adults with spinal cord injury: a clinical practice guideline for health-care providers. J Spinal Cord Med. 2006; 29(5): 527-73.

49. Mizuno K, Tsuji T, Kimura A, Liu M, Masakado Y, Chino N. Twenty-seven years of complication-free life with clean intermittent self-catheterization in a patient with spinal cord injury: A case report. Arch Phys Med Rehabil 2004; 85(10): 1705-7.

50. Oz B, Olmez N, Memis A, Oruk G. Differential diagnosis of polyuria and polydipsia in a patient with spinal cord injury. Am J Phys Med Rehabil 2005; 84(10): 817-20.

51. Polliack T, Bluvshtein V, Philo O, Ronen J, Gelernter I, Luttwak ZP, Hart J, Catz A. Clinical and economic consequences of volume- or time-dependent intermittent catheterization in patients with spinal cord lesions and neuropathic bladder. Spinal Cord 2005; 43(10): 615-9.

52. Jamison J, Maguire S, McCann J. Catheter policies for management of long term voiding problems in adults with neurogenic bladder disorders. Cochrane Database Syst Rev. 2004; (2): CD004375.

53. De Ridder DJ, Everaert K, Fernández LG, Valero JV, Durán AB, Abrisqueta ML, et al. Intermittent catheteriL sation with hydrophilic-coated catheters (SpeediCath) reduces the risk of clinical urinary tract infection in spinal cord injured patients: a prospective randomised parallel comparative trial. Eur Urol 2005 Dec; 48(6): 991-5.

54. Bjerklund Johansen T, Hultling C, Madersbacher H, Del Popolo G, Amarenco G; LoFric Primo Study Group. A novel product for intermittent catheterisation: its impact on compliance with daily life--international multicentre study. Eur Urol 2007; 52(1): 213-20. **54a** Kovindha A, Na Chiang Mai W, Madersbacher H. Reused silicone catheter for clean intermittent (CIC): is it safe for spinal cord-injured (SCI) men? Spinal Cord 2004; 42: 638-42.

55. Ethans KD, Nance PW, Bard RJ, Casey AR, Schryvers OI. Efficacy and safety of tolterodine in people with neurogenic detrusor overactivity. J Spinal Cord Med 2004; 27(3): 214-8.

56. Bennett N, O'Leary M, Patel AS, Xavier M, Erickson JR, Chancellor MB. Can higher doses of oxybutynin improve efficacy in neurogenic bladder? J Urol 2004; 171(2 Pt 1): 749-51.

57. Horstmann M, Schaefer T, Aguilar Y, Stenzl A, Sievert KD. Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage. Neurourol Urodyn 2006; 25(5): 441-5.

58. Reitz A, Schurch B. Intravesical therapy options for neurogenic detrusor overactivity. Spinal Cord 2004; 42(5): 267-72.

59. Giannantoni A, Mearini E, Di Stasi SM, Costantini E, Zucchi A, Mearini L, Fornetti P, Del Zingaro M, Navarra P, Porena M. New therapeutic options for refractory neurogenic detrusor overactivity. Minerva Urol Nefrol 2004; 56(1): 79-87.

60. Lazzeri M, Spinelli M, Zanollo A, Turini D. Intravesical vanilloids and neurogenic incontinence: ten years experience. Urol Int 2004; 72(2): 145-9.

61. de Sèze M, Wiart L, de Sèze MP, Soyeur L, Dosque JP, Blajezewski S, Moore N, Brochet B, Mazaux JM, Barat M, Joseph PA. Intravesical capsaicin versus resiniferatoxin for the treatment of detrusor hyperreflexia in spinal cord injured patients: a double-blind, randomized, controlled study. J Urol 2004 Jan; 171(1): 251-5.

62. Watanabe T, Yokoyama T, Sasaki K, Nozaki K, Ozawa H, Kumon H. Intravesical resiniferatoxin for patients with neurogenic detrusor overactivity. Int J Urol 2004 Apr; 11(4): 200-5.

63. Silva C, Silva J, Ribeiro MJ, Avelino A, Cruz F. Urodynamic effect of intravesical resiniferatoxin in patients with neurogenic detrusor overactivity of spinal origin: results of a double-blind randomized placebo-controlled trial. Eur Urol 2005; 48(4): 650-5.

64. Shin JC, Kim YW, Park CI, Kang SW, Yang SC. Effect of the intravesical resiniferatoxin instillation evaluated by the ice provocative urodynamic study. Spinal Cord 2006; 44(5): 309-14.

65. Reitz A, Knapp PA, Müntener M, Schurch B. Oral nitric oxide donors: a new pharmacological approach to detrusor-sphincter dyssynergia in spinal cord injured patients? Eur Urol 2004; 45(4): 516-20.

66. Linsenmeyer TA, Harrison B, Oakley A, Kirshblum S, Stock JA, Millis SR. Evaluation of cranberry supplement for reduction of urinary tract infections in individuals with neurogenic bladders secondary to spinal cord injury. A prospective, double-blinded, placebo-controlled, crossover study. J Spinal Cord Med 2004; 27(1): 29-34.

67. Waites KB, Canupp KC, Armstrong S, DeVivo MJ. Effect of cranberry extract on bacteriuria and pyuria in persons with neurogenic bladder secondary to spinal cord injury. J Spinal Cord Med 2004; 27(1): 35-40.

68. Lee BB, Haran MJ, Hunt LM, Simpson JM, Marial O, Rutkowski SB, Middleton JW, Kotsiou G, Tudehope M, Cameron ID. Spinal-injured neuropathic bladder antisepsis (SINBA) trial. Spinal Cord 2007 Aug; 45(8): 542-50.

69. Schlager TA, Ashe K, Hendley JO. Effect of a phose phate supplement on urine pH in patients with neurogenic bladder receiving intermittent catheterization. Spinal Cord 2005 Mar; 43(3): 187-9.

70. Salomon J, Denys P, Merle C, Chartier-Kastler E, Perronne C, Gaillard JL, Bernard L. Prevention of urinary tract infection in spinal cord-injured patients: safety

and efficacy of a weekly oral cyclic antibiotic (WOCA) programme with a 2 year follow-up--an observational prospective study. J Antimicrob Chemother 2006 Apr; 57(4): 784-8.

71. Waites KB, Canupp KC, Roper JF, Camp SM, Chen Y. Evaluation of 3 methods of bladder irrigation to treat bacteriuria in persons with neurogenic bladder. J Spinal Cord Med 2006; 29(3): 217-26.

72. Lavano A, Volpentesta G, Aloisi M, Veltri C, Piragine G, Signorelli CD. Use of chronic sacral nerve stimulae tion in neurological voiding disorders. J Neurosurg Sci 2004 Dec; 48(4): 157-9.

73. Kutzenberger J, Domurath B, Sauerwein D. Spastic bladder and spinal cord injury: seventeen years of experience with sacral deafferentation and implantation of an anterior root stimulator. Artif Organs 2005 Mar; 29(3): 239-41.

74. Hansen J, Media S, Nøhr M, Biering-Sørensen F, Sinkjaer T, Rijkhoff NJ. Treatment of neurogenic detrusor overactivity in spinal cord injured patients by conditional electrical stimulation. J Urol 2005; 173(6): 2035-9.

75. Dvorak MF, Fisher CG, Hoekema J, Boyd M, Noonan V, Wing PC, et al. Factors predicting motor recovery and functional outcome after traumatic central cord syndrome: a long-term follow-up. Spine 2005 15; 30(20): 2303-11.

76. Liem NR, McColl MA, King W, Smith KM. Aging with a spinal cord injury: factors associated with the need for more help with activities of daily living. Arch Phys Med Rehabil 2004; 85: 1567-1577.

77. Ng C, Prott G, Rutkowski S, Li Yueming, Hansen R, Kellow J, et al. Gastrointestinal symptoms in spinal cord injury: relationships with level of injury and psychologic factors. Dis Colon Rectum 2005; 48(8): 1562-1568.

78. Tongprasert S, Kovindha A. Impact of neurogenic bowel dysfunction in spinal cord injured patient. J Thai Rehabil 2006; 16(2): 75-84.

79. Vallès M, Vidal J, Clavé P, Mearin F. Bowel dysfunction in patients with motor complete spinal cord injury: clinical, neurological, and pathophysiological associations. Am J Gastroenterol 2006; 101(10): 2290-9.

80. Pagliacci MC, Franceschini M, Di Clemente B, Agosti M, Spizzichino L. A multicentre follow-up of clinical aspects of traumatic spinal cord injury. Spinal Cord 2007; 45: 404-410.

81. Gallia GL, Burger PC, Suk I, Bagley CA, Wolinsky JP, Garonzik IM, Gokaslan ZL. Concomitant conus medullaris ependymoma and filum terminale lipoma: case report. Neurosurgery 2006; 58(6): E1214.

82. Dhall SS, Tumialán LM, Brat DJ, Barrow DL. Spinal intradural clear cell meningioma following resection of a suprasellar clear cell meningioma. Case report and recommendations for management. J Neurosurg 2005; 103(3): 559-63.

83. Połczyńska K, Bień E, Stefanowicz J, Drozyńska E, Szołkiewicz A, Stachowicz-Stencel T, Sierota D, Kaczorowska-Hać B, Kosiak W, Balcerska A. Neurologic symptoms in the course of neuroblastoma in children. Own observations. Med Wieku Rozwoj 2005; 9(3 Pt 2): 477-86.

84. Rodriguez FJ, Crum BA, Krauss WE, Scheithauer BW, Giannini C. Venous congestive myelopathy: a mimic of neoplasia. Mod Pathol. 2005 May;18(5):710-8.

85. Tanaka ST, Stone AR, Kurzrock EA. Transverse myelitis in children: long-term urological outcomes. J Urol 2006; 175(5): 1865-8.

86. Post NH, Wisoff JH, Thorne CH, Weiner HL. Transient syringomyelia leading to acute neurological deterioration after repair of a lipomyelomeningocele: case report. Neurosurgery 2007; 61(2): E426.

87. Aldrete JA, Ferrari H. Myelopathy with syringomyelia following thoracic epidural anaesthesia. Anaesth Intensive Care 2004; 32(1): 100-3.

88. Podnar S. Bilateral vs. unilateral electromyographic examination of the external anal sphincter muscle. Neurophysiol Clin 2004; 34(3-4): 153-7.

89. Li WC, Xiao CG. Anorectal functions in patients with lumbosacral spinal cord injury. Chin J Traumatol 2006 Aug; 9(4): 217-22.

90. Korsten MA, Fajardo NR, Rosman AS, Creasey GH, Spungen AM, Bauman WA. Difficulty with evacuation after spinal cord injury: colonic motility during sleep and effects of abdominal wall stimulation. J Rehabil Res Dev 2004; 41(1): 95-100.

91. Furlan JC, Fehlings MG. A Web-based systematic review on traumatic spinal cord injury comparing the “citation classics” with the consumers’ perspectives. J Neurotrauma 2006; 23: 156-69.

92. Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma 2004; 21: 1371- 83.

93. Anderson KD, Borisoff JF, Johnson RD, Stiens SA, Elliott SL. The impact of spinal cord injury on sexual function: concerns of the general population. Spinal Cord 2007; 45: 328-37.

94. Anderson KD, Borisoff JF, Johnson RD, Stiens, S.A., Elliott, S.L. Spinal cord injury influences psychogenic as well as physical components of female sexual ability. Spinal Cord 2007, 45:349-59.

95. Krogh K, Christensen P, Sabroe S, Laurberg S. Neurogenic bowel dysfunction score. Spinal Cord 2006; 44(10): 625-31.

96. Tongprasert S, Kovindha A. Impact of neurogenic bowel dysfunction in spinal cord injured patient. J Thai Rehabil 2006; 16(2): 75-84.

97. Luther SL, Nelson AL, Harrow JJ, Chen F, Goetz LL. A comparison of patient outcomes and quality of life in persons with neurogenic bowel: standard bowel care program vs colostomy. J Spinal Cord Med 2005; 28(5): 387-93.

98. Consortium for Spinal Cord Medicine: Clinical practice guidelines: Neurogenic bowel management in adults with spinal cord injury. J Spinal Cord Med 1998; 21(3): 248-293.

99. Korsten MA, Singal AK, Monga A, Chaparala G, Khan AM, Palmon R, et al. Anorectal stimulation causes increased colonic motor activity in subjects with spinal cord injury. J Spinal Cord Med 2007; 30(1): 31-35.

100. Furusawa K, Sugiyama H, Ikeda A, Tokuhiro A, Koyoshi H, Takahashi M, et al. Autonomic dysreflexia during a bowel program in patients with cervical spinal cord injury. Acta Med Okayama 2007; 61(4): 221-7.

101. Uchikawa K, Takahashi H, Deguchi G, Liu M. A washing toilet seat with a CCD camera monitor to stimulate bowel movement in patients with spinal cord injury Am J Phys Med Rehabil 2007; 86(3): 200-4.

102. Christensen P, Bazzocchi G, Coggrave M, Abel R, Hultling C, Krogh K, Media S, Laurberg S. A randomized, controlled trial of transanal irrigation versus conservative bowel management in spinal cord-injured patients. Gastroenterology 2006; 131(3): 738-47.

103. Ayaş S, Leblebici B, Sözay S, Bayramoğlu M, Niron EA. The effect of abdominal massage on bowel function in patients with spinal cord injury. Am J Phys Med Rehabil 2006; 85(12): 951-5.

104. Coggrave M, Wiesel PH, Norton C. Management of faecal incontinence and constipation in adults with central neurological diseases. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD002115.

105. Korsten MA, Rosman AS, Ng A, Cavusoglu E, Spungen AM, Radulovic M, et al. Infusion of neostigmine-

glycopyrrolate for bowel evacuation in persons with spinal cord injury. Am J Gastroenterol 2005; 100: 1560-5.

106. Singal AK, Rosman AS, Bauman WA, Korsten MA. Recent concepts in the management of bowel problems after spinal cord injury. Adv Med Sci 2006; 51: 15-22.

E-XI. Myelomeningocoele

1. Kaneoya F, Mine M, Ishizaka K, Gotoh S, Yokokawa M, Hiraga S. Neurologic bladder dysfunction due to spina bifida and sacral dysgenesis manifested itself in middle age. Report of a case. Nippon Hinyokika Gakkai Zasshi. 1990 ;81:1091-4

2. Yamamura A, Niwa J, Hashi K, Nakamura T. Tethered cord syndrome of adult onset: report of a case and a review of the literature. No Shinkei Geka. 1989;17:69-73

3. Almodhen F, Capolicchio JP, Jednak R, El Sherbiny M. Postpubertal urodynamic and upper urinary tract changes in children with conservatively treated myelomeningocele. J Urol 2007; 178(4 Pt 1):1479-1482.

4. Taskinen S, Valanne L, Rintala R. Effect of spinal cord abnormalities on the function of the LUT in patients with anorectal abnormalities. J Urol. 2002 Sep;168(3):1147-9

5. Cahill RA, Kiely EA. The spectrum of urological disease in patients with spina bifida. Ir J Med Sci. 2003 ;172:180-4

6. Altaweel W, Jednack R, Bilodeau C, Corcos J. Repeated intradetrusor botulinum toxin type A in children with neurogenic bladder due to myelomeningocele. J Urol 2006; 175(3 Pt 1):1102-1105.

7. Bruschini H, Almeida FG, Srougi M. Upper and lower urinary tract evaluation of 104 patients with myelomeningocele without adequate urological management. World J Urol 2006; 24(2):224-228.

8. Olsson I, Dahl M, Mattsson S, Wendelius M, Astrom E, Westbom L. Medical problems in adolescents with myelomeningocele (MMC): an inventory of the Swedish MMC population born during 1986-1989. Acta Paediatr 2007; 96(3):446-449.

9. Muller T, Arbeiter K, Aufricht C. Renal function in meningomyelocele: risk factors, chronic renal failure, renal replacement therapy and transplantation. Curr Opin Urol. 2002 ;12:479-84.

10. Lemelle J. L., Guillemin F., Aubert D. et al. (2006) : A multicentre study of the management of disorders of defecation in patients with spina bifida Neurogastroenterol Motil 2006, 18, 123–128

11. Younoszai MK.: Stooling problems in patients with myelomeningocele South Med J 1992; 85: 718–724.

12. Eire PF, Cives RV, Gago MC : Fecal incontinence in children with spina bifida: the best conservative treatment Spinal Cord 1998; 36: 774–6

13. Shandling B., Gilmour RF: The enema continence catheter in spina bifida: successful bowel management. J Pediatr Surg 1987; 22: 271–273

14. Sang Won Han, Myoung Jim Kim, Jang Hwan Kim et al.: Intravesical electrical stimulation improves neurogenic bowel dysfunction in children with spina bifida, J. Urol. 2004;171: 2648–2650

15. Wald A.: Biofeedback for neurogenic fecal incontinence: rectal sensation is determinant of outcome. J Pediatr Gastroenterol Nutr 1983; 2: 302–306

16. Van WF, Kuijpers JHC, Bleijenberg G.: Biofeedback treatment is ineffective in neurogenic fecal incontinence.Dis Colon Rectum 1996; 39: 992–994

17. Malone PS, Ransley PG, Kiely EM: Preliminary report: The Antegrade Continence Enema.Lancet 1990; 336: 1217–1218

18. Casale A. J, Metcalfe P.D., Kaefer M.A. et al.. Total Continence Reconstruction: A comparison to Staged Reconstruction of Neuropathic Bowel and BladderJ. Urol 2006; 176: 1712–1715

19. Schmidt RA, Kogan BA, Tanagho EA. Neuroprostheses in the management of incontinence on myelomeningocele patients. J. Urol 1990; 143: 779–782

20. Parkin PC, Kirpalani HM, Rosenbaum PL, Fehlings DL, Van Nie A, Willan AR, King D. Development of a health-related quality of life instrument for use in children with spina bifida. Qual Life Res. 1997 ;6:123-32

E-XII. Systemic and other conditions

1. Sakakibara R, Uchiyama T, Yoshiyama M, Yamanishi T, Hattori T.Urinary dysfunction in patients with systemic lupus erythematosis.Neurourol Urodyn. 2003; 22 : 593-6.

2. Yu HJ, Lee WC, Lee KL, Chen MY, Chen CY, Chen J. Voiding dysfunction in women with systemic lupus erythematosus. Arthritis Rheum 2004; 50:166-172.

3. Duran-Barragan S, Ruvalcaba-Naranjo H, Rodriguez-Gutierrez L, et al. Recurrent urinary tract infections and bladder dysfunction in systemic lupus erythematosus. Lupus. 2008 Dec: **17**:1117-21

4. Erol B, Avci A, Eken C, Ozgok Y. Urinary retention, erectile dysfunction and meningitis due to sacral herpes zoster: a case report and review of the literature. Urol Int. 2009: **82**:238-41

5. Chen, PH, Hsueh HF, Hong CZ. Herpes zoster-associated voiding dysfunction: a retrospective study and literature review. Arch Phys Med Rehabil. 2002 ; 83: 1624-8.

6. Game X, Bigay-Game L, Bialek D, Sailler L, Astudillo L, Rischmann P. [Urinary retention secondary to herpes zoster infection]. Prog Urol 2004; 14:224-226.

7. Julia JJ, Cholhan HJ. Herpes zoster-associated acute urinary retention: a case report. Int Urogynecol J Pelvic Floor Dysfunct 2007; 18:103-104.

8. Khan Z, Singh VK, Yang WC. Neurologic bladder in acquired immune deficiency syndrome (AIDS). Urology 1992; 40(3):289-291.

9. Shin JK, Newman LS, Gebbie KM, Fillmore HH. Quality of care measurement in nursing home AIDS care: a pilot study. J Assoc Nurses AIDS Care 2002; 132:70-76.

10. Gyrtrup HJ, Kristiansen VB, Zachariae CO, Krogsgaard K, Colstrup H, Jensen KM. Voiding problems in patients with HIV infection and AIDS. Scand J Urol Nephrol 1995; 29(3):295-298.

11. Cohen BA, McArthur JC, Grohman S, Patterson B, Glass JD. Neurologic prognosis of cytomegalovirus polyradiculomyelopathy in AIDS. Neurology. 1993 Mar: 43:493-9

12. Mahieux F, Gray F, Fenelon G, Gherardi R, Adams D, Guillard A et al. Acute myeloradiculitis due to cytomegalovirus as the initial manifestation of AIDS. J Neurol Neurosurg Psychiatry 1989; 522:270-274.

13. Matsumoto R, Nakagawa S, Nakayama J, Hashimoto T, Shindo M. [A case of acquired immune deficiency syndrome presenting acute lumbosacral polyradiculopathy due to opportunistic infection of cytomegalovirus]. Rinsho Shinkeigaku 1998; 38(7):653-657.

14. Gyrtrup HJ, Kristiansen VB, Zachariae CO, Krogsgaard K, Colstrup H, Jensen KM. Voiding problems in patients with HIV infection and AIDS. Scand J Urol Nephrol. 1995 Sep: **29**:295-8

15. Begara Morillas FJ, Salinas CJ, Silmi MA, Espinosa FB, Fernandez LC, Roca A, V et al. [Vesicourethral

dysfunction in the acquired immunodeficiency syndrome (AIDS)]. Arch Esp Urol 1995; 48(9):915-921.

16. Menendez V, Valls J, Espuna M, Perez A, Barranco MA, Carretero P. Neurologic bladder in patients with acquired immunodeficiency syndrome. Neurourol Urodyn 1995; 14(3):253-257.

17. Snijders F, de Boer JB, Steenbergen B, Schouten M, Danner SA, van Dam FS. Impact of diarrhoea and faecal incontinence on the daily life of HIV-infected patients. AIDS Care; 1998, 10: 629-637.

18. Garber SJ, Christmas TJ, Rickards D. Voiding dysfunction due to neurosyphilis. Br J Urol. 1990 Jul: **66**:19-21.

19. Hattori T, Yasuda K, Kita K, Hirayama K. Disorders of micturition in tabes dorsalis. Br J Urol. 1990 May: **65**:497-9.

20. Frimodt-Moller C. Diabetic cystopathy: epidemiology and related disorders. Ann Intern Med 1980; 92:318-321.

21. Jackson SL, Scholes D, Boyko EJ, Abraham L, Fihn SD. Urinary incontinence and diabetes in postmenopausal women. Diabetes Care 2005; 28: 1730-1738

22. Lewis CM, Schrader R, Many A, Mackay M, Rogers RG. Diabetes and urinary incontinence in 50- to 90-year-old women: a cross-sectional population-based study. Am J Obstet Gynecol 2005; 193: 2154-58

23. Van Poppel H, Stessens R, Van Damme B, Carton H, Baert L. Diabetic cystopathy: neuropathological examination of urinary bladder biopsies. Eur Urol. 1988;15:128-31

24. Pittenger G, Vinik A. Nerve growth factor and diabetic neuropathy. Exp Diabesity Res 2003;4:271–85.

25. Cheng JT, Tong YC. Alterations of nerve-growth factor and p75(NTR) expressions in urinary bladder of fructose-fed obese rats. Neurosci Lett 2008;441:25–8.

26. Fayyad AM, Hill SR, Jones G. Urine production and bladder diary measurements in women with type 2 diabetes mellitus and their relation to lower urinary tract symptoms and voiding dysfunction. Neurourol Urodyn 2010; 29: 354–358.

27. Yamaguchi C, Sakakibara R, Uchiyama T, Yamamoto T, Ito T, Liu Z, Awa Y, Yamamoto K, Nomura F, Yamanishi T, Hattori T. Overactive bladder in diabetes: a peripheral or central mechanism? Neurourol Urodyn.2007; 26: 807-813.

28. Daneshgari F, Liu G, Birder L, et al. Diabetic bladder dysfunction: Current translational knowledge. J Urol 2009;182:S18–26.

29. Ishigooka M, Hashimoto T, Hayami S, Suzuki Y, Ichiyanagi O, Nakada T. Thermoreceptor mediated bladder sensation in patients with diabetic cystopathy. Int Urol Nephrol 1997; 29:551-555.

30. Ueda T, Yoshimura N, Yoshida O. Diabetic cystopathy: relationship to autonomic neuropathy detected by sympathetic skin response. J Urol 1997; 1572:580-584.

31. Beylot M, Marion D, Noel G. Ultrasonographic determination of residual urine in diabetic subjects: relationship to neuropathy and urinary tract infection. Diabetes Care 1982; 5:501-505.

32. Ho C-H, Tai H-C, Yu H-J. Urodynamic findings in female diabetic patients with and without overactive bladder symptoms. Neurourol Urodyn 2010; 29: 424–427, March 2010.

33. Daniels DH, Powell CR, Braasch MR, Kreder KJ. Sacral neuromodulation in diabetic patients: Success and complications in the treatment of voiding dysfunction. Neurourol Urodyn 2010; 29: 578–581.

34. Caruana BJ, Wald A, Hinds JP, Eidelman BH et al.: Anorectal sensory and motor function in neurologic fecal incontinence: comparison between multiple sclerosis and diabetes mellitus. Gastroenterology 1991; 100: 465-470.

35. Nakayama H, Jørgensen HS, Pedersen PM, Raaschou HO, Olsen TS, et al.: Prevalence and risk factors of incontinence after stroke. The Copenhagen Stroke Study. Stroke1997, 28: 58-62.

36. Schiller LR, Santa Ana CA, Schmulen AC, Hendler RS, Harford WV, Fordtran JS., et al.: Pathogenesis of fecal incontinence in diabetes mellitus: evidence for internal-anal-sphincter dysfunction. N Engl J Med 1982, 307: 1666-1671.

37. Russo A, Botten R, Kong MF, Chapman IM, Fraser RJ, Horowitz M, Sun WM., et al.: Effects of acute hyperglycaemia on anorectal motor and sensory function in diabetes mellitus. Diabet Med 2004; 21: 176-182.

38. Talley NJ, Young L, Bytzer P, Hammer J, Leemon M, Jones M, Horowitz M., et al.: Impact of chronic gastrointestinal symptoms in diabetes mellitus on health-related quality of life. Am J Gastroenterol 2001; 96: 71-76.

Committee 11

Incontinence in the Frail Elderly

Chair

Adrian S. Wagg, (Canada)

Members

Liang Kung Chen, (Taiwan)

Ruth Kirschner – Hermanns, (Germany)

George A. Kuchel, (USA)

Theodore Johnson 2nd, (USA)

Joan Ostaszkiewicz, (Australia)

Alayne Markland, (USA)

Mary H. Palmer,(USA)

George Szonyi, (Australia)

CONTENTS

A. General considerations

I. INTRODUCTION

II. SEARCH STRATEGIES

III. DEFINING THE FRAIL OLDER POPULATION

B. Urinary Incontinence in frail older people

I. AETIOLOGY AND ASSESSMENT

II. ASSESSMENT OF THE FRAIL OLDER PERSON WITH UI

III. FACTORS IN MANAGEMENT

IV. TREATMENT OF URINARY INCONTINENCE IN THE FRAIL ELDERLY

V. NOCTURIA IN THE OLDER ADULT

VI. MODELS OF CARE FOR THE FRAIL ELDERLY WITH UI

C. FAECAL INCONTINENCE

I.BACKGROUND

II.PREVALENCE AND RISK FACTORS FOR FAECAL INCONTINENCE

III.THE AGEING LOWER BOWEL AND PATHOPHYSIOLOGY IN OLDER ADULTS WITH FAECAL INCONTINENCE

REFERENCES

Incontinence in the Frail Elderly

Adrian S. Wagg, M.D.

Liang Kung Chen, Ruth Kirschner – Hermanns, George A. Kuchel, Theodore Johnson 2nd, Joan Ostaszkiewicz, RN, Alayne Markland, Mary H. Palmer, George Szonyi.

A. General considerations

I. INTRODUCTION

Older people have the highest known prevalence of urinary incontinence (UI) of any group, other than those with specific neurological disease (e.g., spinal cord injury). As the proportion of older people in the populations of the developed world increases, so will the absolute numbers of those with either urinary (UI) or faecal incontinence (FI) or lower urinary tract symptoms.[1] Even if improvement in physical functioning among older people continues, and research in the field is able to demonstrate continuing benefit whilst containing costs, the impact on future health care and long-term care costs will still be profound.[2] Early signals suggest however that the decrease in disability for older people observed in the last two decades of the twentieth century has not been seen in those aged 40 – 64 years[3].

No matter how one defines "older" or "elderly," this population is characterized by its variety, ranging from active, community-dwelling, working, healthy nonagenarians to bed-bound, chronically ill, functionally- and cognitively-impaired persons in their late 60's. Because the healthier group is closer in phenotype and physiology to middle aged than to frailer older people, information relating to the management of urinary and faecal incontinence in this group is integrated into the other ICI chapters. This chapter focuses on frailer older people, emphasizing not only the different aetiologies and treatment of UI and FI, but the additional issues of disease burden, disability, altered responses to drug therapy, the role of caregivers, and goals and organisation of care. This chapter is aimed at all those who work with the frail elderly, and is also intended to be relevant to specialists who may find standard approaches ineffective in this population.

The committee took the view that where there is a paucity of data reflecting the efficacy or utility of approaches to the treatment of UI or FI in frail older adults, interventions aimed at community dwelling, fitter older adults should be employed with due regard to the likely benefits, harms, feasibility, expectations and outcomes of treatment, rather than be denied any intervention. The pathophysiology of UI in the frail elderly requires a broader conception of "disease," centreing on patient-level factors rather than just the bladder or bowel and its neurological control. UI and FI in frail older people is normally a result of multiple interacting risk factors, including age-related physiological changes, comorbidity, polypharmacy and common pathways between them. Furthermore, the impact of urinary or faecal incontinence in the frail elderly includes functional impairment, and extends beyond the affected individual to their caregivers, leading to caregiver stress and an increased likelihood of institutionalisation. Therefore, assessment in frail persons requires a broader scope. Failure to address the multifactorial nature of disease and treatment limits not only clinical care and research, but also important opportunities to improve function and quality of life[4]. Treatment is usually multicomponent, and must address the many associated factors and shared underlying impairments with other geriatric syndromes (for example, by combining lower extremity exercise with prompted voiding)[5]. Drug therapy must be placed in the context of altered pharmacology, polypharmacy, and an increased susceptibility to adverse effects. Effective management may also require system-level approaches, with different models of care (e.g., for institutionalised persons).

The challenge in providing a review of UI in frail older people is the relative dearth of Level 1 evidence for interventions; the frail present multiple challenges for research (not the least of which is substantial trial drop-out due to intervening illness and death) and there is still a systematic problem in including older people in clinical trials[6]. Over and above this problem is the ***continuing paucity of new clinical trials,*** despite the clear epidemiological imperative that the oldest-old are the fastest growing group of affected individuals. Intervention studies and outcomes need to be more broadly based, incorporating caregivers, a range of care settings, alternative models of care, and goals of care unique to this population[7].

II. SEARCH STRATEGIES

Overview

Given the broad range of this report, we used multiple searches using the following MESH terms (in caps) and phrases, alone and in combination, using the PubMed and Ovid search engines: AGED, AGED OVER 80, ACTIVITIES OF DAILY LIVING, DEPRESSION, elderly, FALLS , frail, FRAIL ELDERLY, FRAILTY, function, geriatrics, LONG TERM CARE, MEDICATIONS, NURSING HOME, older, QUALITY OF LIFE, RANDOMIZED CONTROLLED TRIAL; and BLADDER, GYNAECOLOGICAL SURGICAL PROCEDURES, PELVIC FLOOR, PROSTATE, STRESS INCONTINENCE, SURGERY, URETHRA, URINARY INCONTINENCE, URINATION DISORDERS, UROGYNECOLOGY, UROLOGY, VAGINA, VOIDING DYSFUNCTION , nocturia OR nocturia OR "night-time voiding" OR "nighttime voiding" OR "nocturnal voiding" OR "nighttime voids" OR "night-time voids" OR "nocturnal voids" OR "night-time frequency" OR "night-time frequency" OR "nocturnal frequency" OR "nighttime urination" OR "night-time urination" OR "nocturnal urination" OR "night-time micturition" OR "night-time micturition" OR "nocturnal micturition" OR "night-time polyuria" OR "night-time polyuria" OR "nocturnal polyuria" OR nocturia) OR ((noctur* OR night*) AND (void* OR urination OR micturition OR polyuria OR pollakiuria OR "LUTS" OR "lower urinary tract symptoms" OR "BPH" OR "benign prostatic hyperplasia")) AND ("aged, 80 or over" OR aging OR elderly OR older OR "very old" OR senior OR "all aged" OR geriatric OR frail OR aged) AND ("double blind method" OR "double blind" OR placebos OR placebo OR "controlled clinical trial" OR "randomized controlled trial" OR "random allocation" OR "single blind method" OR "research design" OR "exp clinical trials" OR "clinical trial" OR "single blind" OR "double blind" or "triple blind" OR "single mask*" OR "double mask*" or "triple mask*") (longitudinal OR "natural history" OR cohort OR incidence OR remission OR progression OR prospective OR "community-based" OR "population-based" OR epidemiol* OR "follow-up"); TOLTERODINE; OXYBUTYNIN; SOLIFENACIN; PROPIVERINE; TROSPIUM, IMIDAFENACIN; DARIFENACIN; FESOTERODINE; Ovid Expert Search Filter; Publication years 2004-11. We included, where possible, information from non-English language articles where an English language abstract with sufficient information was available. References in retrieved articles were reviewed for additional relevant articles. We also searched the Cochrane Database and National Guideline Clearinghouse for relevant systematic reviews, meta-analyses, and evidence-based recommendations.

III. DEFINING THE FRAIL OLDER POPULATION

1. FRAILTY

Who, then, are the frail elderly? Consistent with increasing consensus in the geriatric literature, we define "frail older persons" as those over the age of 65 with a clinical presentation or phenotype combining impaired physical activity, mobility, balance, muscle strength, motor processing, cognition, nutrition, and endurance (including feelings of fatigue and exhaustion) [8-10] . Frailty is not, however, synonymous with disability and comorbidity. In one study, among persons meeting strict phenotypic criteria for fragility, only 22% also had both comorbidity and disability, 46% had comorbidity without disability, 6% disability without comorbidity, and 27% had neither comorbidity nor disability [9]. Frail people usually have multiple chronic medical conditions, take multiple medications, require care from others and assistance to perform some or all of the personal activities of daily living (PADLs) (e.g., bathing, dressing, toileting, and mobility), are often homebound or institutionalised They have a high risk of intercurrent disease, increased disability, hospitalisation, and death [1,8]. For example, in the US, 10% of all persons over 65 require help or supervision with at least one ADL,[11] and the total prevalence of frail elders has been estimated at 6.1%.[12] From the United Kingdom Hertfordshire cohort study of men and women aged between 65-74, the prevalence of frailty was 8.5% among women and 4.1% among men [13].

Several studies suggest that the relationship between UI and frailty is not unidirectional. Incident UI in those over age 65 has been associated with a two-fold increased risk of impairment in ADLs, instrumental activities of daily living (IADLs – e.g., transportation, finances, shopping, laundry, housekeeping), and poor performance on three physical measures, suggesting that incident UI may be an early marker of the onset of frailty [12]. In a population-based study of older Mexican Americans, incident but not prevalent UI was independently associated with functional decline in ADLs, IADLs, and physical performance [14]. Another population-based study found an association between UI and IADL decline, but not ADL decline, nursing home admission, or death, after adjustment for age and comorbidity [2]. The authors suggest that the relationship between UI and adverse outcomes may be mediated by baseline illness severity and functional impairment [2]. A recent Portuguese study showed that older people who presented with either "slowness" or "exhaustion" had a risk of UI almost five times greater than those without [15].

2. IMPACT OF UI ON MORBIDITY AND INSTITUTIONALISATION

UI in frail persons can have much more severe consequences than in healthy older persons. Although one early study suggested that older persons with UI had a higher mortality risk, [16] subsequent studies that more fully adjusted for comorbidity and functional status have not found any association. [2,12, 17,18] Several multivariate studies suggest that patients with new onset UI at the time of stroke have higher rates of death or disability at 2 years (OR 4.43; 95% CI 1.76 to 11.2)[19] to 5years (OR 3.21 [95% CI 1.04−9.91]), [20] especially if UI persists (OR 7.47 [95% CI 2.29−24.42]).[20]

Given its association with frailty, it is not surprising that UI remains a risk factor for nursing home admission, despite global variation in services and temporal changes in elder care. Studies showing a significant association between UI and institutionalisation have been done in: Finland (men [not women] with urgency UI);[21] Germany;[22] New Zealand (persons > age 65);[23] US (men more than women,[24] after hip fracture,[25] among Hispanic elderly,[14] and patients attending a dementia clinic[26]); Japan (men only)[27], and Hong Kong[28]. Two studies failed to find a significant association after controlling for comorbidity, using US[2] and Canadian databases.[29] It is estimated that the fraction of US NH admissions attributable to UI in men is 0.10 (95% CI 0.08–0.13) and in women 0.06 (95% CI 0.05–0.09).[30] The prevalence of UI at NH admission in the U.S. shows small area variation of almost 50% and differs by race,[31] suggesting that patient and caregiver factors and local resources affect the role UI plays in institutionalisation. An important methodological issue for such studies is the erroneously low prevalence of UI found in administrative long-term care databases when UI is defined by physician diagnosis in the medical record.[32, 33] Another issue, particularly in studies of institutionalisation in persons with dementia, is the failure to include UI as a risk factor [34] or defining it only by a composite function score [35]. The significant association of faecal incontinence and institutionalisation (odds ratio 1.79, 95% CI: 1.00-3.20), in one Canadian study was lost when adjusted for cognition, ADL dependence, and self-reported health[36], although a survey of US geriatricians found that the presence of faecal incontinence was more likely to result in a referral to a nursing home than not [37].

B. Urinary Incontinence in frail older people

I. AETIOLOGY AND ASSESSMENT

1. BACKGROUND

The aetiology of UI in frail older adults is grounded in the concept of a classic geriatric syndrome, involving multiple interacting risk factors, including age-related changes, comorbidity, and potentially common pathways between them. This section addresses all of these components.

2. QUALITY OF THE DATA

The data on the aetiology of UI in the frail elderly population is limited, and observational studies of varying quality constitute much of this literature. Additionally, longitudinal studies of large numbers of frail individuals are difficult to carry out because of paucity in recruitment and the high rate of natural attrition. Despite the lack of such studies, many relatively large, careful descriptive studies and case series, as well as expert consensus processes, have made important contributions to our understanding of the aetiology of UI in this population.

3. UI AS A GERIATRIC SYNDROME

In older adults, especially those who are frail, UI is considered to be a geriatric syndrome, because many of its risk factors are not directly related to the genitourinary tract.[38, 39] Geriatric syndromes have been defined as ‘‘multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges”.[38] Thus, large numbers of different baseline as well as precipitating risk factors may interact with each other in influencing the ability of an older individual to remain continent in the face of common daily challenges (**Figure 1**). This multifactorial complexity, combined with the fact that most individual risk factors typically account for only a small proportion of the overall risk, have greatly complicated the development of a pathophysiological framework for the study of common geriatric syndromes.[38]

Nevertheless, because common risk factors (e.g. lower and upper extremity weakness, sensory and affective impairment) may be shared by different geriatric syndromes (such as UI, falls, and functional dependence) [40], they may represent particularly attractive sites for intervention development.[38] For example, as proposed by Kuo and Lipsitz,[41] the presence of brain white matter hyperdensities within critical periventricular and subcortical regions could represent key risk factors for the development of different geriatric syndromes such as falls, impairment in executive cognitive function, depressive symptoms, and UI. In fact, recent functional magnetic resonance imaging (fMRI) studies have begun to identify central nervous system areas that are particularly relevant to urgency [42-44]. Therefore, failure of activation within orbitofrontal regions may contribute to an older individuals’ decreased ability to suppress urgency [44]. Connectivity pathways within the right insula and anterior cingulate gyrus may also play a role in maintaining continence,[43, 44] supporting the concept that declines in connectivity[45] and

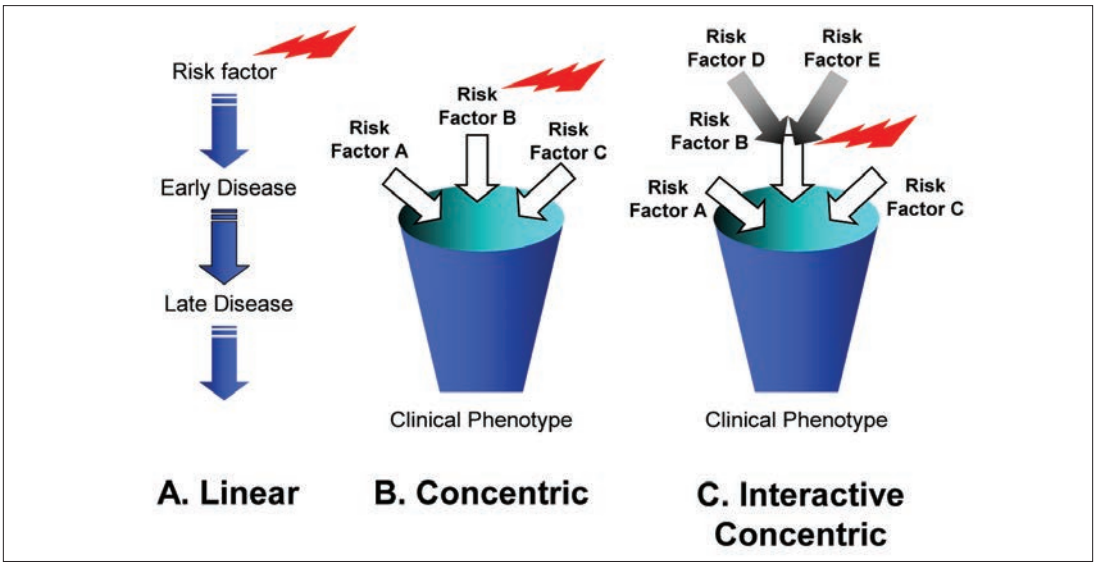


Figure 1. Mechanistic of Geriatric Syndromes

coordination[46] between different brain regions represent early critical events in aging. These findings suggest the possibility that interventions to prevent the development of white matter hyperintensities, such as control of vascular risk factors, could also prevent UI.

4. AGE-RELATED CHANGES RELEVANT TO UI IN THE FRAIL ELDERLY

Age-related changes in the LUT can function as risk factors for the development, continuation, and worsening of UI in frail elderly persons (**Table 1**). At the same time, they rarely are alone sufficient to cause UI, and in some persons have no effect on lower urinary tract symptoms (LUTS) or UI. Furthermore, the literature on "normal" LUT ageing has many potentially confounding methodological limitations. Normal ageing changes are difficult to study, because longitudinal data including large numbers of individuals spanning many years are necessary to definitively separate "normal LUT ageing" from confounding factors and comorbidity. Cross sectional studies are subject to confounding by comorbidity and time-dependent cohort effects, such as change in labour and delivery practices. Thus, to date many studies actually describe "age-related" associations, as opposed to normal ageing. Other limitations include: derivation of much of the cellular and neurochemical data from animal studies; morphologic studies based on cadavers with unknown parity, comorbidity, and LUT symptoms; "age-effects" derived from studies of symptomatic persons; and use of surgical patients at tertiary centres as "normal" controls. Even the definition of "normal" can be difficult: is it continence, absence of LUTS, lack of comorbid disease, or normal physiological testing [47]? The following sections focus on findings from more robust and, where possible, confirmatory studies.

a) Bladder. Understanding age-related changes in the bladder is complicated by a paucity of longitudinal data, variable definitions of "normal," and use of potentially biased (and symptomatic) referral populations. It is difficult to isolate such factors as the role of decreased blood flow, poor voiding habits, comorbidity, central and peripheral nervous system innervation, and reflex patterns as determinants of bladder function in older persons. The research focus has been urodynamic function, neurohumoural responsiveness of detrusor smooth muscle, and ultrastructure. While the key role of the urothelium and afferent systems on micturition are increasingly appreciated (See Committee 2, Cell Biology; Committee 3, Neural Control; and Committee 4, Pathophysiology), there are only limited human data on urothelial changes with age. Urodynamic changes associated with age have typically included smaller voided volume, increased residual volume, smaller bladder capacity, and increased involuntary detrusor contractions (detrusor overactivity (DO)). Correlations with age are often small, suggesting that other factors are at least as important [48]. Urodynamic findings may not relate to symptoms: in a urodynamic study of community-based healthy persons over age 55, DO was found in 42% of continent women, one-third of whom were totally free of LUTS [47]. In another study, charts of 53 consecutive females over age 80 undergoing multichannel urodynamics according to ICS standards were retrospectively analyzed. All of these elderly patients presented with LUT symptoms, yet in 11% urodynamic studies were reported as being normal, with considerable other discordance between symptoms and urodynamic findings [49].

Nevertheless, in a cross-sectional study involving ambulatory, cognitively intact, community-dwelling older female volunteers, maximum urethral closure pressure, detrusor contraction strength, and urine flow rate all declined significantly with age, regardless of whether DO was present or not [50]. The ability of the bladder to empty efficiently also declines in healthy older men and women who have no evidence of bladder outlet obstruction (BOO) or significant confounding disease [47, 51]. A variety of different risk factors associated both with ageing and common comorbid conditions may contribute to age-related declines in detrusor contractile function, which may ultimately lead to detrusor underactivity [52, 53]. Decreased contractile function during voiding in older persons is associated with lower urine flow rates and a small increase in post voiding residual volume (PVR) (generally to < 50 ml) [54]. Even in men with BOO, an elevated PVR may reflect decreased bladder contractility rather than obstructed voiding [55]. While some studies suggest a myogenic origin of impaired contractility, others suggest that impaired blood supply, with concomitant ischemic-reperfusion injury causing patchy denervation, leads to decreased contractility (see Committee 3, Neural Control). More recently, Smith highlighted the potential contribution of age- and disease-related declines in bladder afferent sensory activity in contributing to impaired voiding performance seen with detrusor underactivity [56]. Incomplete bladder emptying from all such causes can reduce functional bladder capacity, and thereby contribute to the urinary frequency and nocturia common in frail older persons [52]. The recent development of a model allowing continuous uroflow in mice has led to studies evaluating the impact of normal aging on overall LUT performance [57, 58]. While aging did not influence measures of detrusor expulsive strength, pre-contraction pressures, intervoid intervals, per-void volumes and voiding flow rates all increased with aging [57]. Moreover, aged animals demonstrated

Table 1. Age-related changes that can contribute to UI in frail elderly persons

Age-Related Change	Potential Effects on Continence
Bladder ultrastructure on electron microscopy	
Dysjunction pattern	Bladder overactivity and urgency UI
Muscle and axon degeneration	Impaired bladder contractility, increased residual urine, and decreased functional bladder capacity
Bladder function	
Decreased capacity	Increased likelihood of urinary symptoms and UI
Decrease sensation of filling	
Increased detrusor overactivity	
Decreased bladder contractile function	
Increased residual urine	
Urethra	
Decreased closure pressure in women	Increased likelihood of stress and urgency UI
Prostate	
Increased incidence of benign prostatic obstruction	Increased likelihood of urinary symptoms and UI
Increased incidence of prostate cancer	
Decreased oestrogen (women)	Increased incidence of urogenital atrophy and related symptoms
	Increased incidence of recurrent urinary tract infections
Increased night-time urine production	Increased likelihood of nocturia and night-time UI
Altered central and peripheral neurotransmitter concentrations and actions	Increased likelihood of lower urinary tract dysfunction
Altered immune function	Increased likelihood of recurrent urinary tract infections
Increased prevalence of white matter hyperintensities in brain	Increased prevalence of severe urge / urgency, link to cognitive impairment and impaired mobility

a decreased homeostatic capacity to respond to the challenge of continuous bladder filling, with indirect measures suggesting a role for decreased bladder volume sensitivity [57, 59].

In human studies, the observation that bladder volume at the initial desire to void declines with age may be confounded by comorbid conditions and concurrent medications [60]. Furthermore, unlike the positive association between detrusor contraction strength and DO found in younger subjects, older adults fail to demonstrate this DO-associated increase in detrusor contractility [61]. Moreover, many frail older persons with UI present with a combination of DO on filling and poor contractility during voiding, an association termed detrusor hyperactivity with impaired contractility (DHIC) [52, 62, 63]. In such cases, the bladder contraction does not empty the bladder fully, leaving a large PVR otherwise not explained by BOO. Because DHIC symptoms can include urgency UI, stress and mixed UI, dribbling, frequency, and nocturia, they may be mistaken for other conditions. At the same time, DHIC may be mistaken for DO with normal contractility because significant detrusor underactivity may be present in the absence of any relevant symptoms.

Ultrastructural studies demonstrate cellular changes associated with age-related changes in detrusor function. One series of such studies involved symptomatic and asymptomatic persons aged 65 to 96, using urodynamic testing and electron microscopy of bladder biopsy specimens, which were read in a blinded fashion using explicit protocols [54, 64-68] A consistent, one-to-one correlation between specific urodynamic findings and bladder ultrastructure was observed, although there has been considerable debate about the veracity of these findings and they have not been reproduced and have been disputed by the findings of a later study which found the ultrastructural changes described evenly distributed between normal women (n = 15) and women with detrusor overactivity (n = 22) .[69] The small number of asymptomatic patients with no DO, normal contractility, and no obstruction, detrusor muscle fascicles were largely intact, with two distinctive ultrastructural findings that may be related to ageing alone: muscle cell membranes characterized by numerous “dense bands” and markedly depleted caveolae, and slightly widened spaces between muscle cells with limited content of collagen and elastin. Depletion of caveolae may be related to de-differentiation of muscle cells, which could eventually result in the reversion of actively contractile cells to inactive, synthetically immature cells. A similar phenomenon has been reported in atherosclerotic blood vessels and postmenopausal myometrium, and may be related to reports of increased collagen in bladders from older women [54, 70]. Moreover, lack of oestrogen contributes to, and oestrogen replacement reverses, both caveolar depletion and detrusor fibrosis [71, 72]. Thus, both ageing and post-menopausal decline in oestrogen levels may contribute to bladder muscle cell differentiation and contractile function [52].

The natural history of these ultrastructural changes remains largely unknown. From the ultrastructural studies described above, a subset of 23 patients was followed longitudinally [67]. The previously observed one-to-one correlation between ultrastructure and function was maintained, but it was unclear whether urodynamic or ultrastructural changes occurred first in subjects who developed or had a change in LUTS. The pattern of dense-bands and nondisruptive muscle cell degeneration varied over time: the DO with dysjunction pattern developed in some subjects, and impaired detrusor contractility and the corresponding degeneration pattern was observed to progress in severity or develop. Other investigators have found similar results but without the one-to-one correlation (e.g., see Brierly et al [73]). Clearly, further work is needed understand the associations between changes in ultrastructure,urodynamic features and clinical syndromes.

In addition to such alterations in ultrastructure, a variety of changes involving relevant nerve fibres, receptors and signalling pathways have also been described in bladder tissues from aged animals, and to lesser extent human biopsies. For example, with aging overall, sympathetic nerve fibre density may decrease [74, 75]. Bladder biopsies from older subjects with normal urodynamic profiles typically show little or no evidence of axonal degeneration and the density of some CGRP-positive sensory nerves is maintained in old age, yet the impact of aging on other categories of sensory fibres or on motor fibres remains unknown [54, 74]. Examples of other changes include decreased contractility and calcium fluxes in response to cholinergic agonists or depolarization [76]; increased responsiveness to adrenergic agonists with increased expression of the alpha 1D-adrenergic receptor [75]; declines in phosphodiesterase 5 (PDE5) levels and possibly signaling [77]; as well as decreased P2X1 purinergic receptor expression [78]. Unfortunately, the interpretation and generalisability of these findings is often limited by a failure to include intermediate age-points which would allow investigators to distinguish changes attributable to aging as opposed to maturational processes [79, 80].

b) Urethra. Due to their common embryological origin, the urethra undergoes age-related mucosal and stromal changes similar to the vagina, and urethral changes in older women can be partially inferred from examination of vaginal tissue. Because of the difficulty of obtaining non-cadaveric urethral tissue, data on urethral smooth and striated muscle changes with age are complicated by confounding factors and definitions of controls.

Urethral closure pressure decreases with age [81, 82]. Based on a sample of 82 women aged 20-70, urethral closure pressure was found to decrease by 15 cmH2O per decade [83]. A number of anatomical and physiologic changes may account for this decline. Mucosal thinning and lack of proteoglycans reduce urethral wall apposition; this also may contribute to retrograde movement of perineal bacteria into the bladder causing urinary tract infections [84]. These mucosal changes may extend up to the bladder trigone, causing irritation of sensory afferent nerves, and possibly triggering DO [85]. The submucosal venous plexus in the proximal urethra loses its corkscrew shape, the number and volume of arterial vessels decrease, and vascular pulsations lessen.[86] Several studies, using different measurement techniques, have shown that urethral vascular density and blood flow decrease with age, but not vascular flow velocity [87-89]. However, age explained only 9% of the variability in vascular density in one study [90], and none of the studies controlled for vascular risk factors such as hypertension and diabetes. The relative importance of decreased vascular volume versus hypoxia on urethral functional integrity is unclear. Other alterations in the urethral stroma are increased volume of connective tissue, decreased ratio of proteoglycans to collagen, and decrease in nerve density [91, 92].

Cadaver studies suggest that the number and density of urethral striated muscle fibres decrease with age, especially in the ventral wall of the proximal urethra [93, 94]. These authors estimated that striated fibres decrease by 1% per year. Large inter-individual variations were observed, with age and parity accounting for only a small part of the variability, suggesting that other yet to be defined factors are important. These studies also found that cross-sectional striated muscle fibre area decreased while fibre diameter was preserved. Another cadaver study by the same group found that circular smooth muscle width was 25%-50% higher in younger women (aged 20-39 years) than older (aged 70-89), and that younger women had higher fibre counts [95]. Smooth muscle loss in the older women correlated with loss of striated muscle in the anterior urethra. Moreover, a recent study raised the possibility that TNF-alphamay contribute to age-related rhabdosphincter satellite cell death and muscle loss with aging [96]. Urethral sensation, measured as current perception thresholds, was significantly higher in older women in two studies (by the same authors), one comparing 48 asymptomatic women and 13 with urgency UI [85], and another in asymptomatic women [97]. The authors concluded that age-related LUT sensory neuropathy could contribute to the higher prevalence of overactive bladder (OAB) symptoms with age; however, urethral sensation thresholds were higher in women with urgency UI when controlled for age and parity [85], and the “asymptomatic” older women may have had urodynamic DO [97].

With age, the urethral meatus generally moves toward the vaginal introitus, and may be difficult to see if there is considerable introital stenosis. Caruncles -benign violaceous soft swellings-often appear at the meatus, and are not problematic unless they cause discomfort or obstruction. Urethral diverticula can be a diagnostic challenge, especially in older women, because the symptoms (dysuria, pain, UI, frequency, urgency, dyspareunia) may be attributed to postmenopausal changes, age, OAB, or urgency UI [98]. Diverticula should be considered in women who have repeatedly failed “conventional” UI treatment. Diagnosis requires imaging by voiding cystourethrography, ultrasound, or magnetic resonance scans. Urethral obstruction is relatively uncommon in older women, and is nearly always secondary to other LUT dysfunction (e.g., pelvic organ prolapse) or is iatrogenic (from LUT/pelvic surgery or radiation. In men, age-related decrease in striated sphincter muscle cell density occurs as well, [99, 100] and has been associated with increased muscle cell apoptosis [99] . While some investigations describe an increase in resting prostatic urethral pressure with age, [101] others note the increase occurs only to the sixth decade then subsequently decreases, along with a shortening of sphincteric urethral length [102]. These discrepancies may reflect differences in prostate volume and morphology.

c) Pelvic floor. Pelvic floor changes in normal older men have not been well studied. In women, the effect of age on pelvic floor structure and function is difficult to differentiate from the effects of hormonal status and parity [103]. A number of studies are cross sectional rather than longitudinal, and focus on symptomatic women. For example, a questionnaire study of over 4,000 community women aged 25-84 found no association between age and stress UI (SUI), OAB, or anal UI, after adjustment for obesity, birth history, menopause, and hormone use [104]. Similarly, in a random sample of 343 Austrian women aged 18-79 years, impaired pelvic muscle contraction (graded by the Modified Oxford Scale) was weakly associated with parity and body mass index but not age [105]. In contrast, a recent study combining an interview, physical exam and transperineal ultrasound identified age as a weak ($r = -0.25$) but statistically significant predictor of pelvic muscle weakness and levator ani morphometry even after controlling for obvious confounders [106]. Evidence of denervation and changes in pelvic striated muscle fibre number, type, and diameter have been found in asymptomatic and nulliparous women (see Committee 2, Cell Biology). For example, in a sample of 82 nulliparous women, neither levator function (measured by resting vaginal closure force and augmentation of vaginal closure force) nor pelvic organ support (on pelvic exam) showed an association with age [85]. A his-

tomorphometric study, using levator ani muscle from 94 female cadavers (aged 15-58), 10 male cadavers (aged 23-35), and 24 women undergoing pelvic surgery, found that myogenic cell damage was associated with both parity and age (</> age 35), but there was no difference between nulliparous women, men, and women with pelvic organ prolapse and/or UI [107]. Total collagen content in pelvic muscle and fascia declines with age, with increased cross-linking and decreased elasticity, [108] but this association does not imply a direct causative effect of "ageing." Constipation may independently contribute to pelvic floor dysfunction in older women [109, 110].

d) Vagina. The prevalence of age-related changes in the vagina varies with hormonal status, coexistent vascular disease, and the continuation or lack of sexual activity [111]. The postmenopausal decrease in oestrogen plays a part in many age-associated vaginal changes. Oestrogen is trophic for much of the LUT in women, with oestrogen receptors found in the vagina, vestibule, distal urethra, bladder trigone, pelvic muscles, and ligamentum rotundum [112]. Yet, as the Women's Health Initiative trial has shown, one cannot assume that the association between low oestrogen levels and physiological changes implies that hormone replacement will reverse these changes, restore function, or reduce symptoms [113, 114]. Moreover, the data are equivocal whether and how LUT oestrogen receptors change in number, density, or function with age [86].

Following menopause, the vaginal epithelium loses the majority of its superficial and intermediate layers. Mucosal thinning may be associated with inflammation, evident as erythema, telangiectasia, petechiae, friability, and erosions. This may be responsible for urgency and frequency in some frail elderly women. In addition, there is loss of epithelial glycogen and lubrication, and mucosal pH increases from 4.5-5.5 to 7.0-7.4. [¬68] These changes can lead to loss of normal adherent flora (lactobacillus), colonisation with pathogenic organisms such as E. coli and enterococci, and the observed increase in bacteriuria and recurrent symptomatic urinary tract infections (UTIs) in older women [115].

Vaginal blood flow, which is important for mucosal integrity and submucosal fullness, decreases with age. Whether this is oestrogen-related, and/or due to concomitant vascular disease is not known. Collagen and lipofuscin deposition in the stroma increases, and may be accompanied by invasion by lymphocytes and plasma cells [115]. The combined epithelial and stromal changes are associated with vaginal wall thinning and flattening of rugae [112]. The vaginal vault may shorten and narrow, and the introital opening decrease (and in severe cases become stenotic), which may make vaginal examination, intercourse, and use of pessaries difficult. However, it is not clear that vaginal shortening is clinically relevant: in one case series of over 3,000 women attending a general clinic, total vaginal length decreased by only 0.08 cm every 10 years [116]. Vaginal shape also may be altered by POP. Because of the multiple potential confounding factors discussed above, a causal relationship between urogenital atrophy and urogenital symptoms/LUTS should not be automatically assumed. Very few randomised trials of oestrogen (oral or topical) for urogenital symptoms include women over age 75, use patient-defined outcomes in addition to physiological measures, or evaluate quality of life outcomes [117]. There are insufficient data to provide an evidence-based approach to symptomatic urogenital atrophy in older women. Oral oestrogen should not be used, but expert opinion supports topical oestrogen treatment (cream, intravaginal tablets, or oestrogen-impregnated pessary-like ring). The validation of vaginal self-swab collection specimen collection offers new opportunities for extending relevant questions to epidemiological studies of older women living in the community [118].

e) Prostate. Histological benign prostate hyperplasia (BPH) is strongly age-related [119], and may lead to prostate enlargement (BPE) and outlet obstruction (BOO). While many LUT changes in women are associated with lower oestrogen levels, BPH results from the development of an oestrogen-predominant hormonal milieu in the prostate. The trophic prostatic androgen, dihydrotestosterone, is formed by the 5-α reduction of testosterone. Dihydrotesterone levels decrease with age, while oestradiol concentrations increase in the prostate stroma and remain constant in epithelial tissues, leading to an increase in the oestradiol/dihydrotesterone ratio and promoting stromal proliferation [120, 121]. Epithelial hyperplasia in turn is mediated by an array of stromal factors [122].

Histological BPH occurs in nearly 80% of men by age eighty [119]. Mean prostate volume increases with age but is very variable; its strongest predictor is prostate specific antigen level of >1.4-2 ng/mL [123]. LUTS in men increase linearly over time, with the fastest increase during the seventh decade, such that by age 80 approximately one-third of men have received treatment for moderate to severe LUTS [124]. Natural history studies and randomized intervention trials, however, consistently demonstrate that symptomatic progression of benign prostate disease is not inevitable. LUTS remit in about one-third of symptomatic men without treatment [125]. Approximately one-third to one-half of affected men develops DO. Thus, even in the presence of demonstrable BPE and/or BOO, the aetiology of LUTS is multifactorial, making prostate-related LUTS in older men a diagnosis of exclusion. Nevertheless, age-stratified normative values for prostate

volume, PSA level, as well as indicators of clinical symptoms, quality of life measures and urodynamic parameters may help in such decisions [126].

Although most patients are asymptomatic at the time of prostate cancer diagnosis, this is another possible cause of LUTS, including urgency UI, in older men. However, evaluation for prostate cancer in frail elderly men is rarely if ever indicated, given the high likelihood of limited remaining life expectancy.

The evidence is contradictory as to whether prostatic inflammation, either acute or chronic, contributes to urinary retention and LUTS in frail older men. In a single institution case series of 374 men undergoing TURP for acute urinary retention (AUR) or LUTS, pathological evidence of acute inflammation was significantly more common men presenting with AUR than LUTS (70% vs. 45%) [127]. However, in a much smaller case series of 70 men presenting with AUR, there was no association between inflammation from prostate infarction and AUR [128]. Nevertheless, a recent study demonstrated phenotypic changes and an increased differential expression of a variety of genes involved in inflammation and oxidative stress within glandular adjacent stroma microdissected from young and aged mouse prostates [129]. Such changes may play a role in promoting the development of BPH, BPE and cancer in aged prostates [130].

f) Other changes. The role of various neurotransmitters in the central and peripheral nervous system in UI is under active investigation (see Committee, Cell Biology). Nevertheless, age-related changes in the actions of these neurotransmitters, their receptors, or the cellular events they stimulate may contribute to the development of UI in frail older persons.

The prevalence of both asymptomatic bacteriuria and UTIs increase with age [115], and the two are often found together in the frail elderly. Age-related changes in immune function, vaginal epithelium, faecal incontinence, and insufficient hygiene related to disability, cognitive impairment, and/or lack of caregivers may predispose the frail elderly to bacteriuria and recurrent UTIs. However, the role of otherwise asymptomatic bacteriuria (often found in association with pyuria) [131], in the aetiology of UI in frail elderly people remains unclear [132]. Treating otherwise asymptomatic bacteriuria in frail elderly patients with chronic, stable UI does not, in general, reduce UI severity [133]. UTI symptoms may be subtle and non-specific in this population, and include worsening of UI, altered mental status in patients with dementia, decreased oral intake, or a minor but important decline in functional ability [133]. At the same time, current consensus criteria for UTI are poorly sensitive and only fairly specific for UTI in frail elderly. In a prospective cohort of 340 nursing home residents, in which UTI was defined as pyuria (>10 white cells) with >100,000 colony forming units on culture, the McGeer, Loeb, and revised Loeb UTI criteria had sensitivities of only 19-30% and specificities of 79-89% [134].

5. FACTORS OUTSIDE THE LOWER URINARY TRACT CAUSING OR CONTRIBUTING TO UI

Of 8,688 participants in the English longitudinal study of ageing, of whom 4,417 had one or more diagnoses, there were shortfalls in receipt of basic recommended care, most noticeable in areas associated with disability and frailty [135], A hallmark of UI in the frail elderly population is the wide variety of factors and conditions outside the lower urinary tract that can cause or contribute to leakage (**table 2**).

a) Medications. Older people consume a high proportion of prescribed medications. Those over 65 years of age comprise between 12 – 16% of the population in the US, UK and Canada but consume 32%, 50% and 45% of prescribed medications respectively and are therefore at greater risk of experiencing adverse events associated with their use [136-141]. The risk of difficulty in controlling urination in community dwelling older women taking medications with LUT effects was about 30% higher compared to those who did not take such medications (OR 1.31 [95% CI 1.05–1.21]) Overall, 20.5% of these women reported incident incontinence at Year 4 (3 years from baseline). We found one additional study since the 4th ICI which examined 959 elderly community dwelling women from the Health, Aging and Body Composition Study, multivariate logistic regression analyses revealed that current users of alpha blockers (adjusted odds ratio (AOR) =4.98, 95% confidence interval (CI) =1.96-12.64) and oestrogen (AOR=1.60, 95% CI=1.08-2.36) had a greater risk of urinary incontinence than nonusers. There was no greater risk of UI associated with current use of anticholinergics, central nervous system medications, or diuretics [142]. Many classes of medications commonly prescribed for the frail elderly can cause or contribute to the development of UI (**Table 3**). The possibility that UI could be caused by a medication should be taken into account before prescribing drug treatment for UI in older persons.

b) Co-morbid conditions and functional impairment: The prevalence of urinary incontinence (UI) is increased in the presence of frailty. The elderly are prone to frailty and commonly have co-morbid medical illnesses. In a large population-based observation study UI (defined as use of pads) was independently associated with one or more other geriatric conditions (cognitive impairment, injurious falls, dizziness, vision impairment, hearing impairment) in 60%, two or more conditions in 29% and three or more in 13% [143].

In a sample of 572 older Latinos participating in a programme to increase walking, medical comorbidity was independently associated with higher rates of UI (OR 1.66). A higher degree of physical activity was independently associated with lower rates of UI (OR

Table 2. Comorbid conditions that can cause or contribute to UI in frail elderly persons

Conditions	Comments	Implications for Management
Comorbid medical illnesses		
Diabetes mellitus	Poor control can cause polyuria and precipitate or exacerbate incontinence; also associated with increased likelihood of urgency incontinence and diabetic neuropathic bladder	Better control of diabetes can reduce osmotic diuresis and associated polyuria, and improve incontinence
Degenerative joint disease	Can impair mobility and precipitate urgency UI	Optimal pharmacologic and non-pharmacologic pain management can improve mobility and toileting ability
Chronic pulmonary disease	Associated cough can worsen stress UI	Cough suppression can reduce stress incontinence and cough-induced urgency UI
Congestive heart failure Lower extremity venous insufficiency	Increased night-time urine production at night can contribute to nocturia and UI	Optimizing pharmacologic management of congestive heart failure, sodium restriction, support stockings, leg elevation, and a late afternoon dose of a rapid acting diuretic may reduce nocturnal polyuria and associated nocturia and night-time UI
Sleep apnoea	May increase night-time urine production by increasing production of atrial natriuretic peptide	Diagnosis and treatment of sleep apnoea, usually with continuous positive airway pressure devices, may improve the condition and reduce nocturnal polyuria and associated nocturia and UI
Severe constipation and faecal impaction	Associated with "double" incontinence (urine and faecal)	Appropriate use of stool softeners Adequate fluid intake and exercise Disimpaction if necessary
Neurological and psychiatric conditions		
Stroke	Can precipitate urgency UI and less often urinary retention; also impairs mobility	UI after an acute stroke often resolves with rehabilitation; persistent UI should be further evaluated Regular toileting assistance essential for those with persistent mobility impairment Optimizing management may improve mobility and improve UI
Parkinson's disease	Associated with urgency UI; also causes impaired mobility and cognition in late stages	Regular toileting assistance essential for those with mobility and cognitive impairment in late stages Patients presenting with all three symptoms should be considered for brain imaging to rule out this condition, as it may improve a ventricular-peritoneal shunt
Normal pressure hydrocephalus	Presents with UI, along with gait and cognitive impairments	Regular toileting assistance essential for those with mobility and cognitive impairment in late stages
Dementia (Alzheimer's, multi-infarct, others)	Associated with urgency UI; impaired cognition and apraxia interferes with toileting and hygiene	Optimizing pharmacologic and non-pharmacologic management of depression may improve UI
Depression	May impair motivation to be continent; may also be a consequence of incontinence	
Medications	See Table 3	Discontinuation or modification of drug regimen
Functional impairments		
Impaired mobility Impaired cognition	Impaired cognition and/or mobility due to a variety of conditions listed above and others can interfere with the ability to toilet independently and precipitate UI	Regular toileting assistance essential for those with severe mobility and/or cognitive impairment
Environmental factors		
Inaccessible toilets Unsafe toilet facilities Unavailable caregivers for toileting assistance	Frail, functionally impaired persons require accessible, safe toilet facilities, and in many cases human assistance in order to be continent	Environmental alterations may be helpful; supportive measures such as pads may be necessary if caregiver assistance is not regularly available

UI = urinary incontinence

0.77). Hypertension, congestive heart failure, arthritis, depression and anxiety were associated with a higher prevalence of UI. A linear correlation was found between prevalence of UI and the number of comorbid conditions. (correlation coefficient =0.81) [144].

A decline in physical health has been associated with an increase in the incidence of incontinence. [145] In an observational study of 6,361 community-dwelling women, aged 65 and older, participating in the study of Osteoporotic Fractures, after adjusting for confounders, women with recent physical function decline (a worsening of 1 standard deviation from baseline) were more likely to report weekly incontinence (OR 1.3) for decline in walking speed over 6 metres and (OR 1.4) to stand from sitting. [146]. The Nurses' Health Study found that moderate-intensity physical activity including walking resulted in a 20-25% reduction in the risk of developing UI in older women [147].

Likewise, impaired cognition is associated with an increased likelihood of UI. For example in a UK cross-sectional survey of over 15,051 subjects, persons with cognitive impairment (Mini Mental State Exam score <= 23, prevalence 18%) were significantly more likely to have UI (adjusted odd ratio [OR] 1.3), impaired hearing (OR 1.7), poor vision (OR 1.7) have had at least two falls in the previous six months (OR 1.4), and report poorer health (OR 1.9) [148].

Comorbid conditions can affect incontinence through multiple mechanisms e.g. diabetes mellitus, present in approximately 15-20% of frail elderly,

Table 3. Medications that can cause or contribute to UI in frail elderly persons

Medications	**Effects on Continence**
Alpha adrenergic agonists	Increase smooth muscle tone in urethra and prostatic capsule and may precipitate obstruction, urinary retention, and related symptoms
Alpha adrenergic antagonists	Decrease smooth muscle tone in the urethra and may precipitate stress urinary incontinence in women
Angiotensin converting enzyme inhibitors	Cause cough that can exacerbate UI
Anticholinergics	May cause impaired emptying, urinary retention, and constipation that can contribute to UI. May cause cognitive impairment and reduce effective toileting ability.
Calcium channel blockers	May cause impaired emptying, urinary retention, and constipation that can contribute to UI. May cause dependent ooedema which can contribute to nocturnal polyuria
Cholinesterase inhibitors	Increase bladder contractility and may precipitate urgency UI
Diuretics	Cause diuresis and precipitate UI
Lithium	Polyuria due to diabetes insipidus
Opioid analgesics	May cause urinary retention, constipation, confusion, and immobility, all of which can contribute to UI
Psychotropic drugs Sedatives Hypnotics Antipsychotics Histamine$_1$ receptor antagonists	 May cause confusion and impaired mobility and precipitate UI Anticholinergic effects Confusion
Selective serotonin re-uptake inhibitors	Increase cholinergic transmission and may lead to urinary UI
Others Gabapentin Glitazones Non-steroidal anti-inflammatory agents	 Can cause ooedema, which can lead to nocturnal polyuria and cause nocturia and night-time UI

UI = urinary incontinence

may cause UI by diabetes associated LUT dysfunction (DO , OAB, cystopathy and incomplete bladder emptying) or by poor diabetic control (hyperglycaemia causing osmotic diuresis and polyuria). The Nurses Health Studies, NHS and NHS II [149] showed an increase in weekly urgency incontinence (OR 1.4) in women with type 2 diabetes compared to those without. Findings from the NHANES 2001-2002 Survey showed that prevalence of UI was significantly higher in women with impaired fasting glucose and diabetes mellitus compared to those with normal fasting glucose. Two microvascular complications caused by diabetes - peripheral neuropathic pain and macroalbuminuria (approaching significance) were associated with weekly UI.[150]

See **Table 2** as to how comorbid medical conditions can contribute to UI

***c) Neurological and psychiatric disorders*:** A more detailed summary of neurological disorders and their impact on UI is covered in Chapter X. Neurological and psychiatric disorders are highly prevalent in the frail elderly. Neurological conditions in the elderly commonly associated with urinary incontinence include stroke, dementia of the Alzheimer's type (AD), multi-infarct dementia or a combination of the two, Diffuse Lewy body (DLB) disease and Parkinson's disease. Less common conditions include Normal Pressure Hydrocephalus and Multiple System Atrophy (MSA). Each of these conditions is associated with the development of brain lesions that can interfere with the normal ability to inhibit voiding as well as affecting cognition. These conditions are associated with impaired mobility and also affect the ability to toilet independently.

In Alzheimer's disease UI is often associated with severe cognitive decline whereas in DLB it usually precedes severe cognitive impairment [4]. Occurrence of UI was significantly earlier 3.2 yrs in DLB compared with 5.9 yrs in Alzheimer's dementia [151].

Normal pressure hydrocephalus should be considered as a diagnosis in any frail elderly person who presents with new onset of UI in association with gait disturbance and cognitive impairment. A subset of these patients benefit from surgical implantation of a cerebrospinal fluid shunt [152].

LUTS, UI and urodynamic DO are common in older persons with Parkinson's disease. A logistic regression analysis of 3,414 Parkinson's disease patients found a significant correlation of orthostatic hypotension and urinary incontinence with age and duration of the disease. The presence of UI in people with Parkinson's may in turn increase their risk for disability: in one series of patients with Parkinson's, UI increased the risk of falling by nearly six-fold. Urinary symptoms are often non-responsive to L Dopa therapy and there is an increased risk of cognitive decline in people with Parkinson's disease when given anticholinergic agents [153, 154].

Multiple system Atrophy presents with a combination of impaired autonomic function, Parkinsonism (MSA-P) or cerebellar ataxia (MSA-C) or both [155]. It frequently begins with bladder dysfunction and erectile dysfunction in males. It is associated with bladder symptoms of DO and often progressing to incomplete emptying. The early appearance of LUTS and high post void residuals may help in pointing to a diagnosis of MSA-P rather than Parkinson's disease [156].

With the introduction of magnetic resonance brain imaging into routine clinical practice, reports in older patients have increasingly emphasized the presence of structural abnormalities involving the white matter[157]. Terminology has also undergone a great change, moving away from subcortical atherosclerotic encephalopathy (Binswanger's disease, a specific and relatively rare form of dementia), towards leukoaraiosis [158] and, most recently, to the concept of white matter signal abnormalities (WMSA).[157, 159]. A dichotomous diagnosis of "cerebral white matter lesions" on CT scans provided by a radiologist demonstrated no relationship to the presence or absence of UI. A semi-quantitative measure of global WMSA appears to be associated with increased urgency UI and nocturnal frequency [160]. In 699 non-disabled elderly subjects with WMSA on MRI there was a significant difference in prevalence of urgency but not incontinence between mild and severe groups [161]. WMH have been linked to severity rather than to the presence of incontinence [162].

d) Depression. As in younger people, the frail elderly with UI have a higher risk of depression, a finding that has been replicated across cultures. Depression in older persons with UI may be under-diagnosed and under-treated: in one study of homebound adults with UI and severe depression, only 35% carried a previous diagnosis of depression and only 34% had been prescribed an antidepressant [163]. UI may add to the burden of depression by decreasing life satisfaction and self-rated health and by its association in frail elders with comorbidity. [164-167]

Studies of the association of depression and UI in older persons are consistent across several depression measures. The validated Centre for Epidemiologic Studies-Depression scale was used in two U.S. studies: a cross-sectional analysis of nearly 10,000 community-based people found an adjusted risk ratio for depression with UI 1.39 [95% CI 1.24, 1.55]) [168]. A large community-based study of older Mexican Americans reported an adjusted OR for depression of 1.94 [95% CI 1.46-2.59]) [169] . The emotional disturbances and social isolation subscales of the Nottingham Health Profile Questionnaire was associated with urgency but not stress urinary incontinence and have included studies in Asia [145, 170]. Although no association between UI and depression was found in a Korean study of

135 community living elderly aged greater than 85 years, it used a higher cut-off (>7) on the Geriatric Depression Scale and, unlike many other studies, found no association between UI and mobility[171]. Self-report of depression or sadness has and has not been associated with UI. [172-174]

Psychological distress, assessed by the General Health Questionnaire, was associated with UI in African Americans (adjusted OR 5.60 [95% CI 1.88–16.67]), but not in whites, in a cross-sectional study of community based older persons with mean age 67 years[175]. However, a longitudinal analysis of the same population over 13 years found that people with UI and psychological distress were more likely to report UI-specific functional impairment (e.g., avoidance of social activities, shopping, and physical activities) (adjusted OR 6.55 [95% CI 1.94-22.12]). Additionally, persons with UI and condition-specific functional loss were more likely to develop psychological distress (OR 3.66 [95% CI 1.61–8.33]) [176].

EpiLUTs, a large cross-sectional internet study, showed significant impairments in mental health and HRQOL when different urinary symptoms were combined [177, 178].The US sample of the EpiLUTS study, involving 2,485 men and 2,877 women aged 65 and older, found OAB was associated with significant impairment in HRQOL. Rates of Anxiety of >7 on the HADS-A were 16.4% for men and 23.6% for women with OAB compared to 3.3% and 8.6% with minimal or no symptoms. Similarly rates for depression on the HADS-D were 17.3% and 15.7% for OAB compared to 4% and 6.4% in those with no or minimal symptoms. [179]

A case controlled study of 100 elderly men attending a Urology outpatients, matched with 100 age matched controls from the community and Geriatric outpatient clinics, found those with moderate to severe LUTS had worse HRQOL. This was evident in a number of ageing male symptoms including depression, decline in feelings of general well-being, decreased sexual performance and decreased muscle strength [180].

The direction of the causal relationship between UI and depression in frail persons is unclear, as nearly all of these studies were cross-sectional. The results of the one available longitudinal study suggested that it is not UI itself but UI-specific functional loss (e.g., avoidance of social activities, attending church, etc.) that is most closely associated with psychological distress, even after controlling for important covariates [163].

e) Falls: Overactive bladder (OAB), present in up to 20% of older adults, and its component symptoms of urinary urgency and urinary incontinence, urinary frequency, and nocturia have been identified repeatedly as risk factors for falls among community-dwelling older adults [181-186]. Mixed incontinence (a combination of urgency and stress incontinence) has also been associated with falls risk in women 70 years and older [187].

In hospital, the need to use the toilet has been reported to increase falls, especially among older patients [188]. Urinary incontinence is also associated with falls in institutionalized older persons [189, 190].

f) Stroke: Conservative interventions (e.g. bladder training, pelvic floor muscle training and prompted voiding) have been shown to have some effect in Cochrane systematic reviews, but have not had their effectiveness demonstrated with stroke patients. UI may have particular prognostic implications after stroke, being associated with greater mortality, a poorer functional recovery and an increased likelihood of institutionalization than those following strokes who regain continence. Of 1,187 patients aged 60–96 with stroke, those with low bladder maintenance scores (more dysfunction) fared worse with rehabilitation than those with higher scores [191]. A survey of stroke unit practice in Australia showed that less than half had a formal plan for continence care and in the UK, as part of the national sentinel audits of stroke, there was little advance in continence care [192, 193]. A comparative study of stroke nursing found a dearth of evidence and treatment focused on containment and social continence, highlighting the need for systematic assessment and management [194].

g) Recommendations for research

Further research is required to:

1. Examine the effect of treatment for UI in older people with Parkinson's disease
2. Examine the temporal association and mechanism underlying falls and UI in frail older persons
3. Examine the effect of structured treatment for UI in older people following stroke.

h) Recommendations for practice

1. Clinicians need to assess and manage co-existing co morbid conditions which are known to have an impact on continence status or the ability to successfully toilet.

6. ENVIRONMENTAL FACTORS

This section addresses those factors unrelated to underlying pathophysiology which affect continence status in frail older persons.

- The physical environment
- Processes of and/or quality of care
    - o assessment
    - o practices that reduce mobility
    - o toileting assistance
    - o staffing levels and skill mix
    - o use and misuse of continence products

In this section we defined processes of care as the instrumental procedures involved in the assessment and management of incontinence relating to frail older persons.

a) The physical environment

Although the physical environment is considered a risk factor for incontinence in frail older adults, there is limited research on this topic. We located seven publications with evaluative data on this topic: two of these studies were conducted over 40 years ago [195, 196] prior to the establishment of internationally agreed standards for reporting trial data. Three were published from a series of projects conducted in the USA to examine the impact of the physical environment on specific problems of people with Alzheimer's disease and related disorders [197-199]. One qualitative study was identified that employed an ethnographic design [200]. Each of these studies involved individuals in long-term care institutions. One study evaluated the prevalence and risk factors for incontinence in a sample of 5,418 community-dwelling frail older adults who were receiving home care services [201]. Environmental barriers as well as the use of physical restraints, along with UTIs were the most common reversible risk factors for urinary incontinence: increasing the risk of urinary incontinence by over 50% [201]. In this study, environmental hazards included a lack of access to the toilet, unavailability of grab rails, inappropriate toilet seat height, inadequate lighting, and inadequate toileting substitutes such as commodes or urinals.

Attempts to evaluate the effects of enhancing the physical environment of long-term care on rates of incontinence were first reported by Chanfreau-Rona [195, 196]. In both studies, the intervention involved enhancing visual access to the toilet by painting toilet doors in bright colours and strategically locating pictorial signs and other visual cues. In addition, staff were asked to accompany residents to the toilet at predetermined 'peak times' and to employ operant conditioning techniques to reinforce residents' appropriate toileting behaviour. In the first of these trials, 24 elderly female residents, most of whom had cognitive impairment, were purposively assigned to either the intervention, or to usual care for seven weeks [195]. The same procedures were repeated in a subsequent trial (1986), [196]. Although reductions in incontinence were noted for residents in the experimental groups compared to the control groups, the extent to which these reductions were related to the intervention is difficult to determine as both studies lacked power and did not control for confounding factors. Nonetheless, these studies represent an early, multifaceted intervention that involved evaluating the effect of changes to the physical environment to reduce incontinence in among frail older adults in long-term care.

According to the findings of a series of projects conducted by Namazi and colleagues, the overall physical environment has a considerable impact on the well being and quality of life of individuals with Alzheimer's' Disease (AD), affecting their ability to function in the face of incontinence, distraction and disorientation [197]. One of the projects focused on the clinical utility of using environmental cues (i.e. signage, colour differentiation and images) in a dementia-specific unit to assist compensate for resident' visuo-perceptual deficits [198]. The most effective environmental cue in terms of orienting individuals with AD to the toilet was a combination of using a sign with the word 'toilet', together with 'wayfinding' arrows on the floor. No single strategy was suitable for all individuals with AD due to the variability in the ability of individuals with AD to perform all of the tasks associated with successful toileting. The researchers therefore recommended "to maximize the remaining strengths of those who are afflicted with AD, each component of the morphology which creates difficulties for AD patients must be identified and treated individually". In essence, individuals with AD may need individually targeted cues that address identified specific areas deficit.

In a second project, Namazi and colleagues [199] systematically examined toilet use in a dementia-specific unit under two conditions: with the toilet highly visible to residents, and with the toilet concealed. The frequency of toilet use increased when toilets were visually accessible during the 45 hours of observation. Visibility and accessibility of toilets may be an important factor in supporting individuals to maintain continence.

Toilet accessibility also featured highly in a qualitative study conducted by Sacco-Peterson and Borell [200]. Using ethnographic methods, the researchers collected over 200 hours of field observational data and conducted in-depth interviews with nine residents. They reported that different aspects of the facility's physical and socio-cultural environment influenced residents' abilities to maintain autonomy in self-care. For example, there was an inadequate number of toilets, inadequate privacy for toileting, inappropriate toilet heights, excessive distances to the toilet, and a lack of call light, toilet paper, soap, paper towels, lighting and commodes. Despite the challenges of negotiating this 'defeating ward geography', many residents attempted to participate autonomously in toileting, whilst others were deterred because of a fear of falling.

b) Processes and quality of care

In a systematic review of the prevalence and risk factors for urinary incontinence in nursing homes Offerman and colleagues [202] identified 46 risk factors for urinary incontinence in nursing homes. These factors were grouped into 1) locomotion, 2) cognitive function and 3) drugs. However, in addition to these risk factors, the reviewers stated "differences in the care process and quality of care can also influence urinary incontinence prevalence;

reasons for a less-than-optimal approach in nursing homes may include, for example, inadequate knowledge of and skills for urinary incontinence in general, inability to use guidelines for urinary incontinence care, insufficient staffing and poor communication among healthcare professionals" (p. 291). They recommended that risk factors related to care processes be further investigated.

Two studies offer qualitative data on how processes of care in nursing homes may represent a risk factor for incontinence. For example, descriptive information derived from semi-structured interviews with six elderly women from two nursing homes in Canada, suggests that some residents experience an environment characterised by rituals and routines, pad rationing, limited assistance with pad changing, restrictions on the type of products available, set times for toileting and pad changes, ageism, and a lack of recognition of attempts to maintain continence [203] Sacco-Peterson and Borell [200] also found that 'toileting assistance was provided at set times, and 'if residents required more assistance other than at set times, pads were used'. Pad use also correlated with residents' mobility level, rather than their cognitive or continence status. Additionally, night-time use of pads often started following a fall at night. Residents did not divulge their difficulties to staff, and were reluctant to ask for help and thus staff members were unaware of residents 'difficulties and efforts. Residents valued the capacity to exercise some power and autonomy with regard to self care, and didn't want to be 'a bother to the nurse'. Thus, their attempts to maintain continence may be undermined by care processes that unintentionally diminish an individual's independent toileting.

c) Assessment

A comprehensive assessment to determine type and causes of incontinence is an essential precursor to appropriate management. However, many people with incontinence do not have access to this assessment, and are therefore at risk of remaining incontinent (**Table 4**). This finding is consistent for older adults across different countries and settings.

d) Knowledge

A lack of knowledge about incontinence and its management may operate as an antecedent to care processes that inadvertently promote incontinence. A number of studies reveal gaps in nurses' and nursing aides' knowledge about and attitudes toward older people with incontinence in long-term [204-224], as well as acute care [221, 225-229]. Other research highlights gaps in medical practitioners' knowledge about incontinence [230-234]. For example, a survey of general practitioners (GPs) knowledge of investigation modalities and treatment options for individuals with faecal incontinence in the UK, found that only 32% were aware of at least one investigation, and 32% were aware of at least one form of surgical treatment [230]. In a cross-sectional national survey to determine knowledge, attitudes, and management of urinary incontinence among family physicians in Canada, less than half (46.0%, 284/617) indicated that they had a clear understanding of incontinence and just 37.9% (232/612) had an organized plan for incontinence problems [234]. Szonyi and Millard [232] reported a significant improvement in GPs knowledge about incontinence following receipt of an education package.

Knowledge about incontinence and its management in the general community is also lacking, especially amongst men, those aged 85 and older, and those with lower levels of education [235]. For instance, a nation-wide consumer survey conducted in the USA in 2000, found four in ten people (41%) thought that loss of bladder control was a disease and a similar percentage (38%) believed it was a natural part of ageing [236].

e) Processes of care that reduce functional status

Impaired functional ability can cause or contribute to incontinence in frail older persons. Care processes that restrict or minimise mobility and the ability to function constitute a critical risk factor. The use of physical restraints is one such practice. Although restraint-free care has been recommended as standard, restraints remain widely used in long-term care – ranging from 12-47% internationally [237]. In a multivariate analysis of data from 2,014 residents from 270 USA Medicaid-certified nursing homes, Brandeis and colleagues (1997) identified that urinary incontinence was independently associated with impairment in ADLs (OR = 4.2; CI = 3.2,5.6), dementia (OR = 2.3;CI = 1.8,3.0), the use of anti-anxiety/hypnotic medications (OR = .7;CI = .5,1.0) (all $P < .04$) and the use of restraints of the trunk (OR = 1.7; CI = 1.5,2.0), restrained to a chair (OR = 1.4; CI = 1.2,1.6), and bedrails (OR = 1.3; CI = 1.1,1.5). Similarly, in a community–based sample of frail older adults, the use of physical restraints was a key reversible risk factor for urinary incontinence [201].

f) Lack of toileting assistance

An obvious, yet often overlooked risk factor for incontinence is a lack of toileting opportunities and assistance for individuals who are care-dependent. Research from USA shows that the frequency of toileting assistance actually provided in nursing homes is too low to maintain continence [238].

In recent years, the UK media has drawn attention to the fact that many people in hospital do not receive timely assistance to use the toilet: a situation that contributed to the establishment of the "Dignity in Care Campaign" – launched in 2006. In response to concerns about neglect in aspects of personal and healthcare, the British Geriatrics Society proposed that the ability to use the toilet in private was in fact, a marker of human rights, and developed a

Table 4. Evaluative studies on assessment of incontinence in frail older adults

Study	Objective	Sample	Method	Findings
[943] Du Moulin et al., 2009	To assess the prevalence of UI and gain insights into care issues	2866 patients (mean age 80 ± 7.2yrs) living at home receiving home care in Holland	Survey + audit of medical records	Type of UI was diagnosed in 49% of patients. Management did not differ for patients with and without a diagnosis of UI type
[614] Georgiou et al., 2001	To evaluate the recommended outcome measures in clinical practice	1125 residents in 17 residential homes, 14 nursing homes and 5 long-stay wards in UK.	Analysis of data on the UI section of the Royal College of Physicians Continuous Assessment Review and Evaluation Scheme audit tool	Rates of full clinical assessment were • 48% for people in residential homes • 24% for people in nursing homes • 36% for people in long-stay wards
[254] Rodriguez et al., 2007	To explore continence prevalence, knowledge and care	66 care homes in Birmingham, UK	Survey completed by managers or other senior staff	Only two respondents gave information indicative of a full assessment. Most respondents had difficulty identifying the process of assessment.
[257] Pringle-Specht et al., 2002	To determine patterns and treatment of urinary incontinence	145 residents with dementia (mean age 83.3yrs) from 13 special care units in long-term care facilities in USA	Retrospective audit of residents' medical histories using 'Incontinence Patterns Tool' (IPT)	55% of residents with UI and dementia had a documented care plan for treatment of UI 2.1% (n=3) had a current medical diagnosis of bladder incontinence
[245] Wagg et al., 2008	To assess the quality of continence care for older people	Patients from 138 primary care trusts, 195 secondary care trusts, and 27 care homes in UK	Audit of patients' clinical records	Poorly documented aspects of a clinical assessment across all settings: rectal examinations and post-void residual urine volumes. In secondary care trusts, 919/3509 (25%) of histories had documentation of an assessment to determine UI type or cause
[944] Watson et al., 2003	To assess the use of the Agency for Healthcare Policy and Research Guideline for managing UI in nursing homes	200 residents with new UI or newly admitted with UI from 52 nursing homes in upstate New York, USA	Retrospective chart review and Nursing Assistance screening interviews	4 new cases of UI per 100 beds over 12 weeks UI Guideline standards met 20% of cases (0-45%). Aspects of assessment rarely performed • rectal examination (15%) • digital examination of prostate (15%) • pelvic examination (2%)

"Behind Closed Doors Campaign". The aim of the campaign was to empower, educate and influence providers and policy makers to adopt a more proactive stance to demand better continence care. A more recent campaign, again led by the British Geriatrics Society, titled "Do not forget the person" was launched in March, 2010. The extent to which such awareness raising activities affect day-to-day care processes in the absence of structural change and resources requires evaluation.

Structured toileting programmes require a staff to patient ratio of 1:5. A lack of staffing or institutional understaffing represents a key risk factor for incontinence among individuals who are dependent on another person to use the toilet. Factors which have been identified in the success (or otherwise) of such programmes are covered in Section 7.

g) Staffing levels and skill mix

Estimating and achieving the optimal level and skill mix of any workforce is a challenge. In long-term care where residents' have chronic health problems and complex health needs, this problem is exacerbated by a high staff turnover. Nurses consistently cite inadequate staffing levels as a major barrier to continence care [239-243]. The extent to which patients and residents' continence care needs are considered in formulas designed to establish the right staffing level and skill mix is unclear. The time, resources, knowledge and skill required to conduct an assessment, and offer active, effective management and manage incontinent episodes require consideration in service planning.

h) Use and misuse of continence aids

For many people, continence aids represent a means by which they can achieve effective and discrete containment of incontinence, minimise physical discomfort and optimise psychological and social function [244]. At the same time, overuse and misuse of continence aids, may represent a risk factor for incontinence and, for pads, urinary tract infection. Although continence aids have an important place in the control of incontinence, their use in the general community, in hospital settings, and in long-term care institutions is widespread (**Table 5**). For example, in the largest and widest audit of continence care conducted in the UK and involving over 6,000 patients across primary and secondary care trusts, and care homes, containment strategies (i.e. the use of continence aids) far exceeded all other forms of documented continence management [245].

- ***Community / home care / primary care***

Extrapolating data from users of absorbent pads in one area in Sweden, Samuelsson and colleagues [246] found 6.4% of all women and 2.4% of all men in the country, used continence aids: equating to 3.7% of the total population. Most of these users were aged over 75 years of age and 21% lived in special accommodation. Other studies have examined use of continence aids in targeted populations. For example, among individuals receiving home care services in European countries, rates of continence aid use vary from 29-52% (mean 39%) [247] to 57% [248]. And across primary care trusts in the UK, containment strategies are used by 48% of patients [245].

- ***Acute care / hospital / secondary care***

Rates of continence aid use in elderly patients in acute care across a number of countries are similar and range from 55.1% in Italy [249], 56% in the UK [245] to 60% in Singapore [250] and Australia [251]. Not only are they widely used but they are often used indiscriminately. One of the earliest studies to draw attention to an overreliance on pad use was conducted by Starer and Libow [252]who found more residents using pads than those with incontinence. More recently, Ostaszkiewicz and colleagues found that in the inpatient care setting, pads were inappropriately used for some patients, and were underused for others [251]. Of 121 patients who were using pads at the times of the survey, 50(41%) reported no UI or FI in the preceding 24-hours. However, 18% of patients who had no pad did report such an episode. This mismatch between incontinence and pad use has been noted in other research. [253] [249]

- ***Long-term care / nursing homes / skilled nursing facilities / residential aged care / care homes***

We located six studies that provided data on the use of continence aids in long term care facilities. These were conducted in the UK [245, 254], the USA [255-257], and in Norway [258]. Wagg and colleagues reported that of 488 residents from 27 care homes included in the national audit of continence care in the UK, 307 (63%) used a containment strategy to manage their incontinence [245]. Roderiguez and colleagues reported similar rates based on interview data from managers of 66 care homes in Birmingham [254].

In the USA, Brandeis and colleagues reported a higher rate of pad use (84%) in their sample of 2,014 residents from 270 Medicaid-certified nursing homes[255]. Eighty-four percent were managed with pads/briefs, and more than one third of incontinent patients were managed with two modalities. A recent evaluation of the use of urinary collection devices by 57,302residents from five skilled nursing facilities found that pad use remained relatively stable over a 12 month period [256]. Pad use among a sample of 11,549 newly admitted 75-84 year old residents was 58.7% at admission and 61.1% twelve months later. This rate was higher for residents aged 85 years of age and older (i.e. 60.3% at admission and 62.6% one year later). In a survey of patterns and treatments of urinary incontinence in 13 special care units in the USA, Pringle-Specht and colleagues (2002) re-

Table 5. Evaluative studies on the use of continence aids (pads and briefs)

Community / home care / primary care				
Study	Objective	Sample	Method	Results
[943] Du Moulin et al., 2009	To assess the prevalence of UI and gain insights into care issues	2866 patients (mean age 80 ± 7.2yrs) living at home and receiving home care in Holland	Survey + audit of medical records	Pads were used by 59.2% of patients with diagnosis of UI type and by 55.8% of patients with no diagnosis of UI type
[945] Samuelsson et al., 2001	To study age- and sex specific use and costs of freely available incontinence aids in Sweden	2542 women & 1292 men living in their homes (including special accommodation) in a county of Sweden who were using incontinence aids	Audit of incontinence aid prescriptions – data extrapolated to general population	Incontinence aid use 367000 (3.7%) of all people in Sweden 6.4%-women /2.4%-men in the county 765000 (66%) in special accommodation Costs 925 million SK 50% of cost attributable to those aged 80 yrs or >
[247] Sorbye et al., 2008	To determine prevalence and characteristics associated with UI	4010 randomly selected older persons (mean age 82.3 ± 7.3 yrs) living at home in one of 11 European countries and using home care agencies	Cross sectional survey using the International Resident Assessment Instrument for Home Care (RAI-HC)	39% used pads (highest usage in France -52% / lowest usage in Norway and Czech Republic – 29%) Pad use correlated with need for toileting assistance (p<0.001)
[245] Wagg et al., 2008	To assess the quality of continence care for older people	2717 patients from 138 primary care trusts in UK	Audit of patients' clinical records	Containment strategies were used by 1294/2717 (48%) of patients
Acute care / hospital / secondary care				
Study	Objective	Sample	Method	Results
[250] Kadir, 2004	To determine the incidence and appropriateness of incontinence aid use	333 elderly patients in an acute hospital (Singapore)	Survey – patient self report	200/333 (60%) - using some form of aid 101 (50.1%) could have been managed with alternatives
[249] Palese et al., 2007	To evaluate the incidence of pad use and explore appropriateness and reasons for use	396 patients (mean age 76.8 ± 11.8yrs) admitted to medical units in 2 acute care units in Italy	Survey – interview + clinical assessment 3 x day each day during hospitalization	Inpatient use of pads – 218/396 (55.1%). Of this cohort, 120/396 (30.3%) had incontinence prior to admission Rationale for pad use: urinary incontinence associated with acute confusion or dementia
[251] Ostaszkiewicz, et al., 2008	To determine the prevalence of UI & FI + pad use + documentation of incontinence	447 inpatients (mean age 70 ± 18.7yrs) admitted to 3 acute and 1 subacute care hospitals in Australia	Point prevalence survey + an audit of medical records	266/446 (60%)- using a continence product/ device 50/121 (41%) of patients using pads had no UI or FI in the preceding 24 hrs. 18/113 (16%) patient with UI or FI in preceding 24 hrs had no continence product/device
[245] Wagg et al., 2008	To assess the quality of continence care for older people	3683 patients from 195 secondary care trusts (hospitals) in UK	Audit of patients' clinical records	2070/3683 (56%) patients used containment strategies
[253] Zisberg 2011	To determine incidence of incontinence brief [pad] use	465 older patients (mean age 78.6 ± 5.8 yrs) who were not using incontinence briefs prior to admission to medical acute care units in a 900 bed teaching hospital in Israel	Admission interview and then every day after first 48 hrs	65/465(14%) used incontinence briefs during most of their hospitalization. Brief use was associated with low mobility
Long-term care / nursing homes / skilled nursing facilities / residential aged care / care homes				
Study	Objective	Sample	Method	Results
[255] Brandeis et al., 1997	To describe the frequency and correlates of potentially treatable causes of urinary incontinence	2014 residents (mean age 84.3 ± 8.7) from 270 Medicaide-certified nursing homes in USA	Review of MDS data / Interview with the nursing home staff, and interaction and observation of residents	990/2014 (49%) of residents were incontinent. Of these, 84.0% were managed by pads/briefs. More than one-third (n = 350) of the incontinent residents were managed with two modalities
[258] Omi et al., 2010	To determine daily pad usage & association with UTI, and fluid intake	153 residents (mean age 83 ± 8.2 yrs) from 6 nursing homes in Norway	Number and weight of pads per/resident calculated over 2 days	118/153 (77%) used pads 36/48(75%) men 82/105(78%) women Average number of pad changes p/day-2.7 UTI correlated with pad use but not fluid intake or number of pad changes
[254] Roderiguez et al., 2007	To explore incontinence prevalence, knowledge and care	66 care homes in Birmingham, UK	Questionnaire to care home managers	Several methods to manage incontinence were cited however briefs and pads accounted for over 50% of responses

ported that 72% (n=105) of residents used a continence aid: the most common type of aid being a continence brief or pad (n=93) [257].

According to Omli and colleagues who estimated the daily pad usage of 153 elderly residents from six nursing homes in Norway, 77% of residents use pads [258]. Omli and colleagues also found that residents' pads were changed infrequently (i.e. an average of 2.3 times a day (range 0.5-8.0) for female residents and 3.1 times a day for male residents (range 1.0-9.0). Moreover, urinary tract infections were associated with pad use (41 vs. 11%; P = 0.001): but not with fluid intake or number of pads changes. Residents pad usage did not correlate well with the volume of their incontinence:

As inappropriate use of continence aids may contribute to onset, or continuation of, incontinence, it is important that clinicians who advocate or authorise their use, are familiar with evidence-based guidelines that advocate an active approach to diagnosing and treating incontinence.

i) Recommendations for research

Further research is required to:

1. explore the physical environment as a risk factor for UI in frail older adults, and to evaluate the effect of modifying the environment.
2. explore the extent to which socio-cultural factors and care processes in particular, influence frail older adults' abilities to maintain autonomy and continence.
3. identify the association between fear of falling, reduced mobility, and UI in frail older persons.
4. evaluate the effect of awareness raising activities that aim to enhance day-to-day continence care processes in healthcare settings.

j) Recommendations for practice

1. Environmental cues such as toilet visibility, signage, colour differentiation and images should be used to compensate for visuo-perceptual deficits in frail older adults with cognitive impairment.
2. As remaining physical strength and exterity varies in individuals with cognitive impairment, each component of the toileting process which creates difficulties for such patients should be identified and treated individually.
3. Awareness raising activities should be conducted to enhance day-to-day continence care processes in healthcare settings.
4. Ensure that the time, resources, knowledge and skill required to conduct an assessment, and offer active, effective management and manage UI episodes are considered in service planning.
5. Continue to address gaps in healthcare practitioners' knowledge about preventing and managing incontinence in frail older persons.
6. As inappropriate use of continence aids may contribute to onset or continuation of UI, clinicians who advocate or authorise their use, should be familiar with evidence-based guidelines that advocate an active approach to prevention, diagnosis and treatment.

II. ASSESSMENT OF THE FRAIL OLDER PERSON WITH UI

Recommendations for the basic assessment of the frail elderly persons with UI are summarised in the algorithm (see Summary Document). Because UI in the frail elderly is multifactorial, it is essential to conduct a comprehensive assessment with the goal of identifying all potential contributing factors. Collaboration among primary care physicians, geriatricians, surgical specialists, nurses, other health professionals, and caregivers, both formal and informal is usually necessary for optimal assessment and management.

Since the last Consultation, the European Association of Urology published guidelines on UI which include those for frail older men and women. These are largely based on the findings of the 4th ICI [259].The UK NICE guidelines for the management of lower urinary tract symptoms in men contain no specific recommendations for older men but are perhaps more age applicable than those which exist for UI in women.[260, 261] The US government sets minimum quality standards for UI assessment and management in long term care, but these standards, along with basic fundamental principles of UI, are poorly understood by long term staff [262]. Two groups, the US Assessing Care of Vulnerable Elders (ACOVE) project and the UK Clinical Effectiveness and Evaluation Unit, have developed quality performance measures for UI care in frailer older persons, using structured literature review and expert panel review.[263-267] These measures are not guidelines *per se*, and in some instances lack sufficient detail. Although both groups have demonstrated using their measures that UI assessment and care by practitioners in the US and the UK is poor, and of a lower standard than that afforded to younger adults, there is evidence that integrated services are more likely to provide a higher standard of UI care [268] Thus, there is an urgent need to re-establish the fundamentals of UI assessment and management for all personnel who care for frail older persons with UI and ensure that there is adequate service provision.

1. COMPONENTS

a) Identification of frail older persons. Health care providers can screen older patients with UI for

frailty using the Vulnerable Elders Survey, which can be administered in person or by phone [269]. Persons with a score of 3 or greater have four-fold increase in the risk of death and functional decline compared with persons with lower scores. A patient self reported scale in which those people classified as either frail or pre-frail had higher frequency of hospitalization, a higher probability of co-morbidity and higher mortality than those classified as non-frail has recently been reported [270]. However, caution still needs to be exercised when classifying an older individual as frail as there is considerable heterogeneity within this group [271].

b) Primary care assessment. Physician education using a modified version of the ACOVE model to reach a large group of primary care physicians resulted in between 80% and 92% of them planning to make a change in their practice behaviour [272], although no formal assessment of carry through was undertaken. Geriatricians' and primary care physicians' (PCPs) UI assessments were compared in a randomized multicentre study involving 364 subjects, 42% of whom self-reported UI to the investigators. Geriatricians were significantly more likely to detect UI (59% of cases vs. 16%), regardless of the severity of UI, and were more likely to refer to Continence Programmes (25%); all referrals by PCPs were to urologists.[273] An assessment strategy based on clinical evaluation, simple cystometry, and several criteria for referral was compared with urodynamic diagnosis. Approximately 25% of patients met criteria for referral, half of patients accepted urodynamic evaluation, yet urodynamics changed the treatment plan in only 12% of the patients who did not met the *a priori* criteria for referral [274].

Practice patterns and adherence to US UI guidelines were evaluated by retrospective chart review of 300 consecutive patients aged >65y, seen by either an internist or geriatrician for UI at a tertiary care centre. Geriatricians ordered more testing, such as urodynamics, before referring patients to a surgical specialist. [275] Overall, primary care practitioners rarely follow the US Agency for Healthcare Research and Quality UI guidelines (now obsolete), [276] and nursing home practitioners rarely follow the Federal guidance for UI care regarding recommended physical examination, PVR testing, urinalysis, and identification of potentially reversible causes [277]. Okamura and colleagues investigated the diagnosis and treatment of lower urinary tract symptoms (LUTS) by general practitioners (GPs) according to the "Practical manual for LUTS evaluation and treatment in the elderly For GPs (Japanese)" and found adherence to the manual, reinforced by educational and promotional activities resulted better treatment outcomes [278, 279].

A systematic review of articles identified only 5 studies meeting eligibility criteria, and all were in women. None of studies found sufficient diagnostic evidence (defined as positive > 5 and negative likelihood ratios < 0.02) for different types of UI. The best was a general population study reporting the utility of history and exam for the diagnosis of SUI (positive and negative likelihood ratios 3.23 and 0.40, respectively) [280]. Adding a nurse practitioner to general practitioner care for adult patients with UI can reduce the impact of UI [281].

c) Cough stress test. We found no additional evidence on the utility of the cough stress test since the last consultation. Utility of the cough stress test was studied in 97 incontinent female long-term care residents using blinded comparison with single channel cystometry. Of the 77% in whom single channel cystometry diagnosis was congruent with the stress test (i.e., urodynamic DO with negative cough test, no DO and positive cough test), all were correctly classified; no woman with SUI was missed nor were any with DO misclassified.[282] An analysis, 200 older women with UI found that provocative full-bladder cough test was as effective as radiographic or urodynamic pressure measurement in detecting SUI. Clinical diagnosis incorporating the cough test with leakage symptoms was 78% accurate, with only 6% false negatives for SUI, but was only 44% accurate with 45% false negatives for urgency UI [283].

d) Postvoid residual measurement. We identified no studies evaluating the impact of PVR measurement on clinical diagnosis and treatment outcomes. One study of 100 patients consecutively admitted to a geriatric ward found that 34% had PVR > 50 mL; these patients tended to have more UI (57% vs. 38%, p >.05), greater functional dependency, and a higher mortality rate (36% vs. 9%).[284] A study of the residual urine in a randomly selected community dwelling sample of men and women aged 75 years of age found more than 10 ml of residual urine in 91 of the 92 men (median 90 ml; range 10-1502 ml), and in 44 of the 48 women (median 45 ml; range 0-180 ml). The significance of this single measurement could not be estimated [285].

e) Urodynamic testing. Urodynamic testing is feasible and safe, even in frail nursing home residents. [63] There is no evidence, however, that urodynamic diagnosis changes the outcome of treatment. Expert guidelines have recommended urodynamic testing before surgical or minimally invasive UI treatment in frail elders [286].

f) Ultrasound estimation of bladder weight. A single study of men attending the uroflow clinic of mean age 65 (range 23 – 90) detected no statistically significant differences in ultrasound estimated bladder weight between men with Qmax <10mL/min versus those with >15mL/min [287].

2. SUMMARY OF EVIDENCE

1. Active case finding and screening for UI should be done in all frail older persons because many do not spontaneously report their symptoms. (Level 1).
2. Screening for frailty is possible with short screening instruments (Level 1).
3. Current quality of primary care assessment of UI in frail elders is poor (Level 2).
4. Cough stress test has moderate accuracy in frail institutionalized women (Level 2).
5. No recommendation is possible on the utility of PVR testing in the assessment of UI in frail elderly (Level 4).
6. Urodynamic testing is feasible in frail older people (Level 1) but it is unlikely to change management or outcomes except, perhaps, in those considered for surgical treatment of UI (Level 4).

3. RECOMMENDATIONS FOR EVALUATION (SEE ALGORITHM)

The essential first step is to actively case find in the frail elderly, as the condition is generally underreported. The second is to identify treatable, potentially reversible conditions and other factors (medications, environment) that can cause or contribute to UI. Although UI associated with such factors has been commonly called "transient UI," for most frail elderly it is a chronic and often progressive condition. It is important to evaluate for such contributing factors because their amelioration may improve UI directly, make UI more amenable to other interventions, and overall improve the patient's (and carer's) quality of life.[288]

The common, treatable, potentially reversible conditions that can contribute to UI in frail older people can be defined by the mnemonic DIPPERS ((Delirium, Infection [urinary tract), Pharmaceuticals, Psychological, Excess fluid (in/out), Restricted mobility, and Stool impaction [and constipation]). This is a useful aid to teach and remember these conditions [289]. Cognisance must be made of the potential to overtreat asymptomatic bacteriuria as apparent infection because of the risk of adverse outcome [290].

III. FACTORS IN MANAGEMENT

1. BACKGROUND

This section highlights the issues that distinguish management of incontinence in frail older people from that of healthier older adults. These include preferences for care, goals of care, determination of costs and benefits, special issues in drug treatment, and issues unique to frail elderly men. They incorporate knowledge of physiological, psychological, sociological, and economic changes associated with frailty and advanced age, and reflect the importance of patient-centred goals and the role of caregivers in this population. These factors provide the context of continence care and should be incorporated into the management of all incontinent frail persons, regardless of the choice of specific treatment.

2. ROLE OF COMORBIDITY IN MANAGEMENT DECISIONS

Many frail older people will have co-existing disability and comorbidity, both of which can influence the clinical presentation and assessment of UI, as well as responsiveness to interventions. Frail older people are not only at higher risk for unintended adverse effects from treatment (e.g., fulminate *Clostridium difficile* colitis from antibiotics used to treat otherwise asymptomatic bacteriuria), but also may realise additive benefits in domains other than UI [291] from UI treatment that is aimed at underlying comorbidity and impairment (e.g., topical oestrogen for irritating urogenital atrophy reduces recurrent UTIs); and a nursing home exercise programme done in the course of toileting improves both physical function and UI [5]). Likewise, management of chronic cough from obstructive pulmonary disease may benefit stress urinary incontinence.

3. DEFINING OUTCOMES FOR TREATMENT

Outcome measures must be fundamentally different from those used in healthy older persons, because of the heterogeneity of this frail population regarding comorbidity, remaining life expectancy (RLE), patient perceptions, personal values, and the involvement of caretakers and proxy decision makers. Unfortunately, intervention studies in the frail elderly remain focused on objective disease related variables and seldom, if at all, take account of these factors. Additionally, comorbidity is frequently used as an exclusion criterion in therapeutic trials. A review of care home residents' views on continence showed that they valued having independent bowel and bladder function, but believed incontinence to be inevitable and intractable. Residents often had low expectations, and declined further evaluation and treatment [292]. There are no data on frail older peoples' expectations from specific treatments.

Although quality of life (QoL) is a key concern for UI in all persons (see Committee 5, Initial Assessment Including Quality of Life), and has special relevance in frail elderly with limited RLE, there are few validated QoL outcome measures applicable to this population. Only one validated UI-related QoL measure is derived specifically from patient-based data among persons older than 65, and these subjects were community-dwelling and relatively healthy [293]. None of the ICI-endorsed UI-related QoL measures have been validated in oldest-old or cognitively and/or functionally impaired persons. Traditional UI QoL domains—e.g.,

impact on IADLs, travel, sexual relations—are often not relevant to frail elderly, and there could be significant "floor effects" for social and role function domains. One alternative QoL domain for frail elderly is social interaction, especially for nursing home residents;[294] an analysis of cross sectional and longitudinal data from over 100,000 US nursing home residents found that prevalent and especially incident UI had negative impact on social interactions, particularly among persons with moderate ADL impairment [294]. An analysis of older Medicare beneficiaries over 65 years of age, and including those over 85, found significant impairment of QoL, in accordance with that found in younger people [295].

The profound question when considering UI outcomes in frail older persons is, "Is complete cure ever possible?" In short, this depends on patient factors, specific treatment(s), and the target outcome. While no geriatrician endorses "ageism" and therapeutic nihilism, research evidence suggests that complete dryness is unlikely for certain frail patients, particularly frail institutionalised persons with severe cognitive and functional impairment. Even "intractable" UI is amenable to interventions that may improve the patient's urinary and bowel function and quality of life [4]. The Frail Elderly Committee of the Third ICI introduced an alternative continence paradigm for frail elderly (**Figure 2**), which subsequently was generalised for all persons with UI [296]. In this paradigm, people with "dependent continence" are dry as a result of ongoing assistance, behavioural treatment, and/or medications. UI would return if the interventions ceased, a situation analogous to chronic disease models [297] such as "controlled hypertension" or "controlled diabetes." Persons with "independent continence" are cured without need for ongoing treatment (e.g., dry after successful anti-incontinence surgery). For patients who are unable to achieve independent or dependent continence, "contained incontinence" should be possible by use of appropriate products such pads, catheters, and appliances (See Committee 20, Management Using Continence Products), thus providing "social continence" or "accepted incontinence."[298, 299] The balance between the degrees of continence achieved may vary as UI severity changes, and are dependent upon patient and caregiver preferences. All of these continence outcomes encompass a common need: to be both realistic and hopeful about UI in frail elders while avoiding nihilism and neglect; maintaining comfort and dignity and preventing avoidable complications of UI.

Although the ICS standardisation document on outcomes in older patients is now over 10 years old, little progress has been made and many of the identified needs still pertain (see Recommendations for Research) [7].

4. ROLE OF REMAINING LIFE EXPECTANCY IN TREATMENT DECISIONS

Remaining life expectancy (RLE) is a key yet often misunderstood concept in treatment decisions for frail older people. RLE is *not* uniformly short in this population; moreover, there is a demographic trend of increasing RLE, with a smaller proportion of persons spending their remaining years living with disability [300]. Evidence shows that many health care professionals will underestimate life expectancy[301]. Reference to actuarial tables produced for insurance purposes is often enlightening. Incorporation of RLE into treatment decisions in urology and gynaecology has been studied only in relation to cancer treatment. Only two studies, both in prostate cancer, examined specialists' ability to estimate RLE. Canadian urologists were more accurate in estimating longer RLE: using scenarios based on actual patient data, 31% were accurate within 1 year, 67% within 3 years, and 82% in estimating greater than or less than 10 years in 82% of responses [302]. Comprehensive Geriatric Assessment can help estimate remaining life expectancy and can help predict treatment-related morbidity and mortality in older men with prostate cancer [303].

Walter and Covinsky [304] developed a graphical tool for estimating quintiles of RLE by age. Medical conditions most closely associated with shorter RLE are class III/IV congestive heart failure, end-stage renal disease, and oxygen-dependent chronic obstructive pulmonary disease. Estimates of RLE are significantly affected by frailty and cognitive impairment [305]. Functional status has a dramatic impact on life expectancy. For example, 75-year-old men and women without limitations have life expectancies 5 years longer than those with ADL limitation and more than 1 year longer than those limited in mobility [306]. Alzheimer's dementia decreases RLE profoundly (by nearly 75%) among older persons who otherwise would be in the top quintile of RLE [307]. Compared to older persons with at most one IADL deficit, persons with more deficits have significantly higher 5-year mortality (with two deficit, adjusted RR 1.46 [95% CI 1.20 – 1.78] ; with three or more deficits, adjusted RR 1.64 [1.26 – 2.14]) [305].

5. PREFERENCES FOR CARE

Because there are multiple treatment options available for frail older adults with UI, and individualised care should be emphasised, obtaining patients' and carers' opinions regarding preferences and goals for care is essential for quality care planning. It should not be assumed that persons with cognitive impairment are unable to make their care preferences known or participate in treatment decisions and all reasonable efforts to help them to do so should be made.

Preferences for toileting and changing were studied in 111 nursing home residents with UI; residents

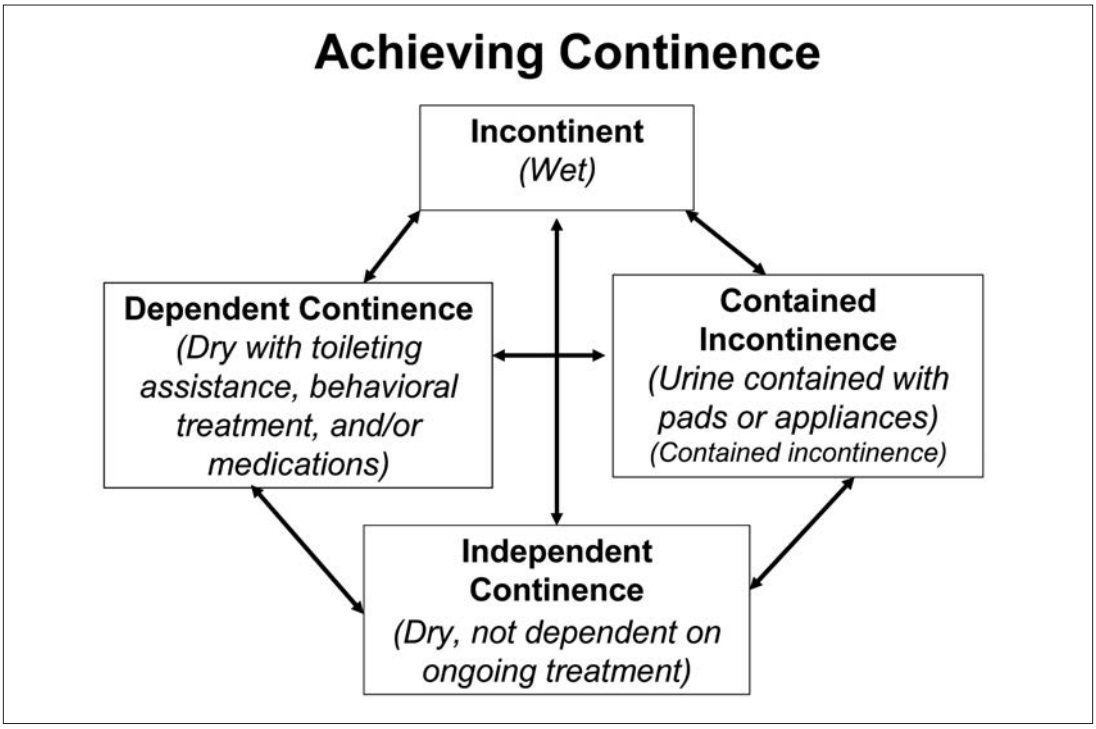


Figure 2. A Paradigm for Continence

preferred an average of 2 pad changes, 1.5 toilet assists, and 2 walking assists more than they actually received, yet even these levels were lower than guidelines recommend, suggesting that residents may have reduced expectations based on their experience [308]. In a second, residents of board-and-care facilities and two nursing homes, their family members, and facility nursing staff were given definitions of and information about five UI treatment options (indwelling catheter, prompted voiding, adult diapers, electrical stimulation, and medications) [309]. Respondents were asked their preferences between pairs of treatment options (e.g., "diapers" versus prompted voiding). Most of the board-and-care respondents were continent, although some were undergoing UI treatment at an outpatient clinic. Patients and family members were evenly divided between "definitely" and "probably" preferring prompted voiding versus diapers. Almost 80% of nursing staff, however, preferred prompted voiding to diapers. Families perceived staff members as unwilling to perform prompted voiding, and some thought prompted voiding was degrading to the resident and that it was bothersome to be asked to go to the toilet frequently. Using a similar method, a German study with 117 geriatric hospital patients (mean age 85; 43% with UI), 72 staff members, and 71 family members, found that most patients preferred diapers (79%), medications (78%), and scheduled toileting (79%) over urinary catheters, and 64% preferred scheduled toileting [310]. When choosing between diapers and medication, equal proportions preferred each option. Patients with greater functional dependence were more likely to prefer catheters, and those with experience with diapers were more likely to prefer medications and toileting. Notably, spouses showed moderate to almost perfect agreement with patient preferences, but those of other family proxies had only slight to fair agreement. In a qualitative study of 25 women with pelvic floor dysfunction living in residential facilities, residents expressed a desire to live with their problem rather than undergo assessment and management, emphasizing the need to include the patient in management decisions at the outset [311].

6. COSTS AND BENEFITS OF UI TREATMENT IN FRAIL ELDERLY

An overall discussion regarding UI-related costs is covered by Committee 22, Economics of Incontinence. The following discusses UI cost issues specific to the frail elderly.

a) Estimating Costs. For the majority of developed countries, the greatest increase in population is occurring in the oldest old, those > age 85. This group has the highest prevalence of UI, and accordingly the increased prevalence of lower urinary tract symptoms will result in higher UI care costs. Such an increase has already been observed between 1992 and 1998 amongst US women aged > 65 [312]. The costs of care for older persons has

been estimated at double that for people under 65, but care for those older persons living in institutions was less than for community dwelling individuals [313]. Likewise, the cost of OAB in five European countries is estimated to rise by one billion Euros between 2000 and 2020,[314] and in the US it has been estimated that by 2030 the greatest increase in demand for UI care (81%) will be in older women aged 60-89 with OAB symptoms [315]. In one US study using of a community managed care population, the presence of OAB and comorbidity doubled the associated costs of UI care [316]. In South Korea, the estimated cost of treating overactive bladder was 117 billion Korean Won (KRW) in 2006 and 145 billion in 2007. The estimated total cost in treating stress urinary incontinence was 122 billion KRW in 2006 and 59 billion in 2007 [317].

Costs can be expressed as direct costs, indirect costs, and intangible costs [318]. Previous estimates have focused on diagnostic costs, treatment (including routine care and pads), and consequence costs (skin irritation, urinary tract infection, falls, fractures, additional nursing home and hospital admissions, longer hospital length of stay). Direct healthcare costs are most often estimated but there is a lack of meaningful research into indirect costs and those related to comorbidity in the frail elderly. Intangible costs have not been considered in these estimates because of their subjective nature and the methodological difficulty of collection and estimation. Much of the evidence for the cost of UI in older persons has been gathered from either epidemiological surveys or analyses of claims from insurance databases; these have often involved many assumptions or complicated formulae to calculate final costs. There is a consistent theme that the cost of caring for older adults with UI will increase, but the estimated magnitude of this increase is variable.

For the frail elderly, especially those in long term care, cost calculation is especially complex. The greatest costs for UI care in nursing homes are by far nursing labour costs [319]. Extrapolated costs for nursing home admission due to UI was $6 billion (2000 US dollars),[30] with institutional costs of UI management and consequences of $5 billion (2000 U.S. dollars). [320] In one small 6-month study, the mean daily cost of UI care, including direct nursing care, indirect nursing overhead, and supplies, was $9.09 (+ $ 10.52) per resident (2003 U.S. dollars) [321]. The costs for UI pads alone in Dutch long-term care have been estimated at 160 million Euros [322]. In an Australian subacute care setting, the costs of daily UI care was $49 AU, with most spent on staff wages [323]. In Canada, researchers found that 1% increase in UI prevalence was associated with an 11-12% increase in costs [324]. The extra nursing time needed to maintain toileting programmes contributes to high costs [325]. Routine garment and laundry costs may be lower than estimated because in practice residents are not changed as often as needed. In addition, for prompted voiding to remain effective, such things as regular refresher education programmes for staff or wet sensors may be necessary, and thus are rarely considered in cost estimates. Moreover, the time period over which the costs and benefit are calculated needs to be explicit because both benefit and costs will change, and patient morbidity and mortality need to be considered. The costs of correcting functional and medical causes of UI are rarely considered. Also, the potential differential in costs across the span of cognitive and functional impairment has seldom been assessed,[326] despite evidence that UI care costs are closely related to the degree of functional impairment [327]. Some surveys suggest that the costs of care for younger community dwelling adults outweighs that associated with the elderly, but there are wide variations of estimates depending upon the population studies [328].

Costs related to caregivers of frail persons with UI living in the community include lost wages, decreased productivity (both within and outside of the home), the additional number of caretaking hours when a frail person develops UI,[329] and the cumulative effect of increased strain and burden, along with any resultant illness. Overall, there is still limited data on costs of UI treatment in other residential (such as assisted living or rest homes) and acute care settings [330 (2004)],costs may vary by access to care. Because so many frail elderly are homebound or live in institutions, they often do not have the same access to the UI therapies as other populations. Their health care providers may be limited to primary care physicians, community nurses, and care assistants or aides with little to no expertise in UI management. Specialist consultation may be minimally available in home or long term care settings, leading to a focus solely on behavioural management and/or containment products. An assessment of a multi-component intervention based upon absorbent products, a structured skin care regimen, and nursing advice on incontinence associated dermatitis revealed that incontinent residents used an average of 5.19 absorbent products, at a mean cost of € 1.79 per day. Following introduction of the intervention, the mean number of absorbent products consumed per day was 2.02 per incontinent patient, at a mean cost of € 0.97 per day [331].

Cost relates strongly to reimbursement, which varies considerably from country to country, depending not only on structure of the health system but special programmes for the aged and persons with UI (see Models of Care below). Within particular countries, there may be further variation based on insurance, co-insurance, drug versus procedure coverage and incentives, access to care, programmes for vulnerable populations, and urban/rural differences.

b) Benefit and effectiveness of treatment. The ability to define the benefit of UI treatment in frail older people is highly dependent on the individual, their caregivers, and the health care system. Out-

comes research indicates that patients value quality of life, which encompasses many domains besides reduction in UI (See Committee 6, Symptom and Quality of Life Assessment). Even cognitively impaired people can still express treatment preferences [310, 332], so it is also possible to evaluate domains of quality of life (e.g., social interaction) [294] and assess treatment satisfaction directly or behaviourally. At the same time, we found no data on the value or utilities frail elderly or their caregivers assign to varying degrees of UI (with or without treatment intervention) versus "dryness." Standard outcomes such as quality adjusted life years (QALYs) may overestimate effectiveness in older people,[333] not just because of potentially different utilities, but because of the altered importance of "years of life saved" in a population with variable and sometimes limited remaining life expectancy.

The need for novel and specific outcomes for use in both trials of UI interventions and clinical care of incontinent frail elderly people continues. Outcomes measured by single item tools of perceived benefit or satisfaction with treatment are unlikely to be generalisable across the heterogeneous older population. It should not be assumed that perceived benefit of treatment can be measured with the same tools across cultures and health systems, unless such tools are sensitive to differences in such things as reimbursement and provision of continence services and supplies. The association between expectations, preferences, and outcomes needs to be prospectively studied in relevant ad representative populations. New approaches and tools to assess UI-specific quality of life in cognitively-impaired frail elderly are needed, as well as better understanding of the interaction between functional impairment and the impact of UI [294]. When QALYs are included as an outcome in UI treatment trials in older persons, they should be specifically analysed by age and also possibly health status.

7. ISSUES IN DRUG TREATMENT

a) Age-related changes in pharmacology. Specific age-related changes in pharmacokinetics, alteration in drug absorption, distribution, metabolism and clearance, and their potential effect on UI drugs, are shown in **Table 6**. Age-related pharmacokinetic changes are rarely considered in planning the duration of time off previous UI medications, placebo-run in periods, and wash-out periods in UI drug trials in older persons. The numerous factors potentially affecting drug clearance in such patients, as well as previous and/or cross-over compounds, may confound observed drug effects. Age-related changes in pharmacodynamics have been described for benzodiazepines, beta-adrenergic agents, and opiates [334, 335] but there are few available data concerning change, even in these, other than for limited numbers of community dwelling older people.

b) Availability of low dose agents. One effect of the under-representation (if not exclusion) of frail older persons in UI drug studies is a lack of knowledge regarding minimal effective drug doses for this population. The age-related changes in pharmacology noted above suggest that some UI drugs may be effective at lower than standard doses in frail elderly with concomitant decreased adverse effects [336]. This issue is especially relevant for extended-release preparations, which cannot be divided into smaller doses. There are some data supporting the effective use of low dose oxybutynin in older persons, but such studies are exceptional [337, 338].

c) Inappropriate polypharmacy. Approximately 60% of people over age 65 take at least one prescribed medication, and about one-third take more than five prescribed drugs. In addition, many take over-the-counter and naturopathic or herbal agents, with the rate of use varying across countries and cultures. The likelihood of adverse drug reactions (ADEs) and drug interactions rises exponentially as the number of medications increases. This has led to the recommendation in geriatric prescribing to "subtract before adding," to consider whether target symptoms might be due to medications before adding another drug targeting those symptoms. This approach is relevant in geriatric UI, as UI may have been precipitated and/or worsened by medications (see **Table 3**). Changes to existing drug regimens should be considered in the management of UI in all frail older people. The national audit of continence care in the United Kingdom reported that of older adults, mean age 80 years, only 27.5% (2082/7572) had documented evidence of a medication review [339].

d) Adverse drug effects. ADEs are extremely common in older persons,[340] with rates up to 35% among community-dwelling persons aged > 65 in the US [341], and up to two-thirds of long term care residents [342]. In a recent UK study, 59% of ADEs requiring hospital admission involved patients aged > 60 [343]. Factors associated with higher ADEs in the elderly are higher drug doses, age-related pharmacological changes, polypharmacy, comorbid conditions, and the interactions between them and female sex [344, 345]. Older people are at higher risk of ADEs from antimuscarinics because of age, and comorbidity-related changes in muscarinic receptor number and distribution, blood-brain barrier transport, and drug metabolism [346]. Whereas antimuscarinic ADEs in younger persons are bothersome, in the frail elderly they can result in serious morbidity such as sedation, heat intolerance, delirium, and falls.[4]

A major antimuscarinic ADE of concern in frail adults is cognitive decline, yet there is little data about its actual incidence or prevalence. Cognitive effects may be under-detected because they are clinically subtle, neither asked about nor reported by the patient, or mistaken for age-related diseases

Table 6. Pharmacokinetic changes in older persons

Parameter	Age-associated Changes	UI Drugs Potentially affected
Absorption	Minimal quantitative change despite ↓ gastric motility, yet little known regarding effect on slow-release agents	Extended release preparations
	↓ Skin thickness	Transdermal preparations
Distribution	Decrease in lean body mass leads to ↓ Vd /↓T½ for hydrophilic drugs and ↑Vd/↑T½ for lipophilic agents	Lipophilic agents, tricyclic antidepressants
	Decreased protein binding in frail patients with low albumin, leading to higher concentration of free drug	Tolterodine
Hepatic metabolism	↓ Phase I reactions (oxidation/ reduction)	Tricyclic antidepressants
	No change in Phase II reactions (glycosylation)	
	↓ Hepatic blood flow and ↓ hepatic mass, leading to reduced clearance for agents with first-pass metabolism	Oxybutynin Tolterodine Solifenacin Darifenacin
	Stereoselective selectivity in metabolism (hypothetical)	Enantiomers
	Cytochrome P450	Oxybutynin Tolterodine Solifenacin Darifenacin
Clearance	Decrease in renal clearance	Tolterodine

Vd = volume of distribution, T½ = half life

and ageing [347, 348]. Persons with pre-existing cognitive impairment (especially from conditions known to affect central cholinergic pathways) may be at greater risk for this ADE although there are some data to suggest that those with established dementia may not experience cognitive decline following therapy with anticholinergic agents [349]. Actual incidence rates of cognitive impairment with antimuscarinic agents for UI are difficult to estimate because of probable under-reporting [64], the different measures used across studies, failure to specify the measure in published trials, the use of proxy measures (such as quantitative EEG), and differences in psychometrics and clinical relevance of self-report, physiologic, and performance measures of cognition.

Xerostomia is common in older people [350]. A study of 175 acutely hospitalized community dwelling older people (mean (SD) 82 (5.7) years) and 252 outpatients (mean (SD) 77 (5.7) years) found that 63% of the hospitalized elderly and 57% of outpatients complained of dry mouth. Dry mouth was more common amongst those on multiple medications [351]. In general, older people, women and those taking multiple medications are more likely to report the symptom . Antimuscarinics clearly may exacerbate this condition, leading to concerns about deteriorating dental health and a 2011 warning to the Food and Drug Administration from the American Dental Association [352]. Meta-analyses of bladder antimuscarinics show minor variations in the incidence of dry mouth from clinical trials, with oxybutynin associated with the highest prevalence [353]. A recent subcut analysis of a randomized controlled trial of solifenacin, 5mg/day, versus oxybutynin 5mg tid, examined the tolerability of both drugs in subjects under and over the age of 65 years, the study found that dry mouth was no more common amongst those over the age of 65 but was more common and more severe with oxybutynin [354]. In those over 75 years of age treated with 8mg versus 4mg of fesoterodine from a pooled analysis of data from registration trials, dry mouth was more common in the older aged sample [355].

Another antimuscarinic ADE to which the frail elderly may be predisposed is decreased visual accommodation, yet this has been specifically evaluated only in young healthy volunteers,[356] and

drug trials typically report only "blurred vision," without further characterization.

The incidence of increased PVR as an ADE is seldom reported in clinical trials of antimuscarinics for UI or OAB. When it has been reported, the magnitude of increase is seldom of clinical significance. The incidence of acute urinary retention with antimuscarinics in general is low, but it has not been systematically evaluated in the frail elderly. There is no consensus as to what constitutes a sufficiently high PVR to preclude antimuscarinic treatment or to require dose adjustment of an already prescribed agent. If urinary frequency or UI worsens after an antimuscarinic is started or increased, then PVR should be checked because an increased PVR will lower functional bladder capacity and worsen UI. PVR should be monitored in frail older men treated with antimuscarinics who may not reliably report change in LUTS or voiding difficulty. The majority of men with clinically relevant outlet obstruction are excluded from treatment trials and the results of these should be viewed in that light.

***e) Drug interactions*.** Because frail older people take higher numbers of drugs and usually have several comorbid conditions, drug interactions are more common [357]. All antimuscarinic agents for UI will have additive side effects when combined with other anticholinergic agents. Antimuscarinics could potentially alter the absorption of other drugs by slowing gastrointestinal motility.

Drug-drug interactions for oxybutynin, solifenacin, darifenacin, and tolterodine include potent CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, cyclosporin, and vinblastine). Fesoterodine, a prodrug that is converted to tolterodine by non specific esterases, is also dependent upon CY3A4 for its excretion. There is one case report of interaction between tolterodine and warfarin in 2 older patients, [358] which has not been seen in healthy volunteers. Naturopathic/ herbal preparations should also be considered for potential interactions, especially in areas where these agents are used frequently.

There is still uncertainty regarding interactions between antimuscarinic agents for UI and cholinesterase inhibitors (CEIs) used for dementia. There is evidence CEIs can cause or worsen UI from a case report [359] and also a case series of 216 consecutive patients with probable Alzheimer's disease attending a memory treatment centre [360]. In the latter, CEI treatment was overall associated with 7% risk of new UI: the highest risk was observed in patients with more behaviour problems, and lower risk in patients who demonstrated positive cognitive and/or behavioural response to CEI. Further evidence for an interaction between antimuscarinics and CEIs comes from a database study of nursing home residents in one US state [361]. Residents with dementia, newly treated with cholinesterase inhibitors, were more likely to then be prescribed a bladder antimuscarinic than those residents with dementia not given a cholinesterase inhibitor, an example of a geriatric "prescribing cascade."[362] Concomitant use of antimuscarinics (extended release oxybutynin and tolterodine) and cholinesterase inhibitors in nursing home residents was associated with a decline in ADL function in the most functionally able residents but there was no worsening of cognition, probably because the cognitive measure (MDS-COG) was inadequately sensitive. More importantly, there was no case of delirium observed [363]. A recent study in which the primary objective was to assess the cognitive impact of trospium chloride in older people with dementia treated with galantamine over a six month period. The study hypothesised that galantamine in combination would not result in any adverse outcome such as that reported by Sink [363]. 46 subjects with UI and dementia were enrolled, 10 withdrew from the study. No effect on cognition or activities of daily living was detected over the duration of the study. A within group analysis demonstrated an improvement in nocturia and reduction in pad use in this combination group [364]. A small study reported some positive effect of the treatment of UI with propiverine in subjects with probable AD taking cholinesterase inhibitors [365]. Although intuitively illogical, given the opposing pharmacological actions, there seems to be no reason not to use bladder antimuscarinics for older people with dementia. The current weight of evidence appears to be that a positive outcome in terms of bladder control can be achieved without a significant detriment in either cognition of activities of daily living.

Drugs also may interact with comorbid conditions (drug-disease interactions), such as diseases that affect hepatic or renal metabolism and clearance, slow gastric motility (e.g., advanced diabetes), predispose to delirium, or are associated with impaired central cholinergic transmission (Alzheimer's and Parkinson's diseases).

f) Potentially inappropriate drugs for older persons. Efforts at quality improvement for older populations have led to the development in several countries of expert consensus guidelines regarding inappropriate drugs for older persons,[366, 367] although the continuing relevance of these guidelines has been questioned and alternative systems suggested [368, 369]. A revised Beers criteria was introduced in 2012 [370]. These guidelines focus on drugs with lower risk-benefit ratios and higher potential for drug-drug and drug-disease interactions, and are used for nursing home regulation and quality performance measurement. The concerns regarding oxybutynin and tolterodine in causing urinary retention have been removed. All bladder antimuscarinics are included because of their risk of causing constipation and darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine and

trospium are noted with respect to their anticholinergic properties.

8. SPECIAL ISSUES UNIQUE TO FRAIL OLDER MEN.

Although their ranks thin into the ninth decade, men still comprise a significant portion of frail older persons. The prevalence of UI increases in men after age 80, going from about one-third of the rate in women to the same. Over the past ten years, the prevalence of UI in US male nursing home residents aged 65-74 has increased to a greater extent than in female residents (from 39% to 60%, compared with 45% to 59%) [371]. At the same time, frail men are under-represented in UI treatment trials, whether behavioural, pharmacological, or surgical (see also Committee 15: Surgery for Urinary Incontinence in Men). Since the time of the last ICI, the European Association of Urology has summarized their recommendations (2012) for Urinary incontinence in frail/older men and women [372]

This under representation is unfortunate, because results from treatment trials in frail women cannot be directly extrapolated to men for several reasons:

- **Differences in comorbidity:** frail older women have higher rates of functional impairment and chronic disease and geriatric syndromes which may mean that frail men may be more likely to respond to behavioural intervention [373, 374]. For older adults who become incontinent, a composite measure of physical performance (rising from a chair, walking, balance) is a better predictor of UI incidence in men than in women [375].

- **Differences in the relationship between UI and cognition:** one systematic urodynamic study of nursing home residents with UI found a significant association between DO and more severe cognitive impairment in women, but not in men (although power was likely low, as the number of men was only 17) [63].

- **Differences in caregivers:** more older men have living spouses who can provide care, with a potential impact on the risk and type of caregiver burden associated with UI management.

- **Prostate cancer:** nearly all men in their ninth decade have histological evidence of prostate cancer. However, it is not clear that frail elderly men have an increased risk of prostate cancer-specific mortality, especially given that their RLE is primarily affected by comorbid conditions. The need to screen for and treat prostate cancer diminishes with functional status, comorbidity, and RLE [376]. At the same time, more men are living with the sequelae of prostate cancer treatment, particularly stress UI after radical surgery.

- **Benign prostate disease:** the prevalence of histological BPH, BPE, and BOO increase with age, and is associated with LUTS, UI, and DO. In the urodynamic study cited above, 29% of men had BOO and 59% had DO as the predominant cause of UI, versus 4% BOO and 61% DO in women [63].

- **Risk of urinary retention:** because of age-related decrease in detrusor contractile function and increased likelihood of BPE and BOO, it is often assumed that frail elderly men have a higher prevalence and risk of urinary retention. However, this has never been demonstrated. Among NH residents with UI, the prevalence of underactive detrusor was similar in women and men (38% and 41%, respectively), despite the higher prevalence of BOO in men [63].

- **Differences in device usage:** A nationally-representative survey of adults in the US showed that older men were nearly three times less likely than older women to use pads to contain leakage (15% vs. 45%) [377]. Newer data from Scandinavia, where some countries provide absorptive pads as part of the health care benefit, showed that this gap might be narrowing (22% vs. 48%), and that increased functional impairment was associated with greater pad usage [378]. In a survey of patients recruited from family practice clinics in the Netherlands, the gender difference for pad usage by older adults with UI was even higher, with 4 out of 5 women using pads versus 1 of 9 men using pads [379]. Men are also more likely to be users of indwelling catheters, both in the long-term care setting [256] and in the community [378].

- **Differences in medical treatments:** there are medications that might be used by only one gender, or might have distinct side effect profiles. Alpha-blockers in particular should be cautiously considered in men with suspected outlet obstruction from prostate disease, due to their potential side effects of causing orthostatic hypotension. (Grade C) [372]. The interactions of UI and other conditions with regards to orthostatic hypotension and risk of falls merits attention. In a German registry of 3,414 patients with Parkinson's disease, for those with urinary incontinence (716; 21%), orthostatic hypotension was reported for 14% of the men, yet only 9% of the women [380]. On the other hand, for women and men who had strokes and urinary incontinence, both were equally more likely to sustain a fall after stroke, though women were more likely to sustain an injury (OR 1.5) than were men [381].

- **Differences in surgical treatments:** there are gender-specific devices and surgical approaches that do require active management on the part of the patient. In particular, certain frail older men might not be appropriate for placement of an artificial urinary sphincter due to co-morbidity, medications and cognitive and/or functional impairment would not allow for the individual to manage the device on his own (Grade C) [372].

Despite the issues noted above, evaluation and management of UI in most frail older men follows the same roadmap as for frail women (see Algorithm).

9. SUMMARY OF THE EVIDENCE

1. Patients and caregivers have clear preferences for the type of UI management, and they are often discordant between the two groups **(Level 2)**
2. Age-related changes in pharmacokinetics affect antimuscarinic drugs for UI and should be incorporated into treatment planning. **(Level 1-2)**
3. Drugs may be effective at lower doses in frailer compared with healthier older persons **(Level 3)**
4. Polypharmacy increases the chance of adverse reactions to drug therapy. **(Level 1)**
5. Adverse drug events are more common in the frail elderly. **(Level 2)**
6. Drug-drug and drug-disease interactions are common in frail older persons **(Level 1-3).**
7. The economic burden of UI in frail elderly, as well as the cost-benefit, cost-effectiveness, and cost-utility of its treatment, has been incompletely characterised **(Level 4)**
8. The majority of drugs for treatment of overactive bladder remain flagged as potentially inappropriate medications for older people **(Level 3-4)**.

IV. TREATMENT OF URINARY INCONTINENCE IN THE FRAIL ELDERLY

1. LIFESTYLE INTERVENTIONS

As treatable and potentially treatable correlates of and risk factors for UI are determined, interventions that ameliorate their effects have been devised. Several lifestyle interventions have been evaluated in healthier older and younger women, including dieting and medication to help with weight loss, dietary modification, fluid selection and management, and constipation management (See Committee 12, Adult Conservative Management). Although many health care professionals advocate lifestyle interventions to treat UI,[382-385] we did not locate any studies investigating these interventions for the frail elderly. Some of these interventions may be inappropriate for or impractical to use in frail older people, for example weight loss, yet advanced age alone should not preclude use of lifestyle interventions if assessment warrants this. Inadequate fluid intake and dehydration are common in long-term care residents [386] . Dehydration may actually increase the risk of UI in frail elders, because of its significant association with constipation and delirium, both known risk factors for UI [387-389].

a) Quality of data and results.

We located articles addressing lifestyle interventions for UI in older women, but the number of oldest-old subjects was very small, few to none appeared to be frail, and no studies stratified results by age. Two very small older trials and one recent small RCT [390] raise the possibility that increased hydration for incontinent frail elderly may actually decrease UI [391, 392].

b) Summary of the evidence (see **Table 7***)*

1. No recommendations are possible regarding lifestyle interventions for UI in the frail elderly (Level 4)

2. BEHAVIOURAL INTERVENTIONS

Behavioural interventions have been especially designed for frail older people with cognitive and physical impairments that may affect their ability to learn new behaviours or to actively participate in self-care activities. These interventions evolved from classical behavioural change theory, using antecedent and/or consequent conditioning to shape the desired behaviour. Because behavioural interventions have no side effects, they have been the mainstay of UI treatment in the frail elderly [393]. Behavioural

Table 7. Lifestyle Interventions.

Intervention	Authors	Study Design	Sample	Methods	Results
Fluid management	Kincade et al, 2007[383]	Two arm, randomized trial	224 community-dwelling women aged 18 years and older with UI	Self monitoring was individualized and women were counselled on fluid consumption, quick pelvic floor muscle contraction, management of constipation and voiding frequency.	After adjusting for age, hormone status, and race women in the self-monitoring group had statistically significant less urine loss (average 13.3g less urine loss) than women in the wait list group.
Caffeine reduction	Bryant et al, 2002 [946]	Prospective randomized controlled trial	95 consecutive adults with UI coming to two continence nurse advisors	Treatment group received education regarding caffeine reduction; control received no information.	Caffeine intake was significantly reduced in treatment group and frequency and urgency was significantly improved compared to control group one month post intervention.
Multifactorial intervention: food and fluid intake, exercice, prompted voiding	Schnelle, Leung, Rao, Beuscher, Keeler, Clift & Simmons, 2010[390]	Randomized controlled trial	112 residents (average age 86 years) in 12 nursing homes	Prompted voiding, physical activity. mobility endurance, food and fluid ake (i.e., offering fluids and snacks of choice between meals)	Significant improvement in UI frequency and percent of appropriate toiletings. Individuals with lower Mini Mental Status Examination (MMSE) scores responded well to treatment.

interventions, also called voiding programmes, used predominantly in frail adults, ***all of which require active caregiver participation***, include:

- ***Prompted voiding***, involving prompts to toilet with contingent social approval, is designed to increase patient requests for toileting and self-initiated toileting, and decrease the number of UI episodes. It was first used in the 1980s for incontinent nursing home residents [394].

- ***Habit retraining***, which requires the identification of the incontinent person's individual toileting pattern, including UI episodes, usually by means of a bladder diary. A toileting schedule is then devised to pre-empt UI episodes. There is no attempt in habit retraining to alter an individual's voiding pattern [395, 396] ***Timed voiding*** involves toileting an individual at fixed intervals, such as every 3 hours. This is considered a passive toileting programme; no attempts are made at patient education or reinforcement of behaviours, or to re-establish voiding patterns [397]. Other terms used to describe timed voiding are scheduled toileting, routine toileting, and fixed toileting [393, 397]. ***Combined toileting and exercise therapy.*** Functional Intervention Training incorporates strengthening exercises into toileting routines by nursing home care aides (nursing assistants) [398]. Another combination intervention, administered by occupational or physical therapist, involves toileting and mobility skills [399].

Cognitive and functional impairments common in frail elderly persons may preclude the use of some of these interventions. In addition, the context in which care is provided has been implicated in the provision of continence care [400-402]. Staff buy-in for the intervention is considered an important component to behavioural interventions [403]. Consideration of organisational and social factors and interplay among older adults, by the healthcare team, is considered important to implementation of evidence-based practices [404].

Although pelvic floor muscle rehabilitation has not been studied extensively in frail older persons, age and frailty alone should not preclude their use in appropriate patients with sufficient cognition to participate [405, 406]. Similarly, a combined behavioural modification programme involving pelvic floor muscle exercises, bladder training, and information about lifestyle modifications that prevented UI in community-dwelling older women aged between 55 and 80 years[407], could be effective in some frail older women, but we located no studies that reported on promotion or maintenance of urinary continence in frail older adults.

a) Quality of data

Since the last ICI, we identified a metastudy of systematic reviews for bladder training, prompted voiding, habit retraining, and timed voiding using a metastudy framework [396]. This metastudy confirmed our earlier findings. The majority of trials included in the systematic reviews did not determine the type of UI, or sufficiently describe whether comorbidity that possibly contributed to UI was evaluated or treated. Randomised trials in long term care have overwhelmingly depended on research personnel to supervise or conduct the interventions. Studies repeatedly show that, once a trial ends, the long-term care staff rarely maintains the intervention at the same level, if at all. Outcome evaluation is usually limited to "wet checks" (percentage of times the patient is found to be wet on a set schedule) and not UI, and no studies report cure or patient-based outcomes, such as satisfaction with treatment and quality of life. No studies reported impact on caregivers. One trial investigated the effects of prompted voiding, exercise, fluid and food intake on faecal and urinary incontinence. Trained research staff provided the intervention 5-days a week between 7am to 3:30pm for 12 consecutive weeks [390]. Few intervention studies have been conducted with incontinent hospitalised and homebound frail elders. One study with hospitalised older patients found that the main intervention used for urinary incontinence was absorbent products [408]. Incident urinary incontinence at hospital discharge was associated with absorbent product use during hospitalisation [409].

Limitations in many studies include: small samples with low power to detect significant differences; variable terminology and operational definitions making comparisons across studies difficult. Additionally, there is little ethnic or cultural diversity; much data are limited to women, especially in nursing home trials. There is little focus on night-time UI; little consideration as to the psychological impact of toileting programmes on patients and caregivers, and no long-term follow up [393, 410]. Many studies excluded frail older adults with terminal illness, inability to respond to a one-step command, or poor language ability [411-414]. Ethical concerns for human subjects prohibits withholding treatment, thus true "control" groups were nearly impossible to create. Two studies used delayed treatment as controls [413, 414] The frequency of the intervention varied across studies as well, with toileting conducted every two hours over 12-hour, 14-hour, and 24-hour schedules [394].

b) Efficacy (**Table 8**)

Prompted voiding is more effective, in the short-term, than no intervention for improving daytime dryness in nursing home residents and some home care clients (Level 1) [415]. A three-day trial of prompted voiding should be initiated, and the intervention should be continued, but only in those that achieve appropriate toileting rates (the number of times the resident voided into the toilet divid-

Table 8. Behavioural interventions

Intervention	Authors	Study Design	Sample	Methods	Results
Prompted Voiding					
	Palmer, 2005[394]	Systematic literature review	1 quasi-experimental, 1 repeated measures, 1 prospective case series, and 1 systematic (Cochrane) review	Sample, methods, and results were examined to address: is prompted voiding effective in reducing wetness episodes and increasing requests for toileting?	Different prompted voiding protocols were used limiting comparison across studies. Sample sizes were small and mainly white elderly female long-term care residents participated. Staff adherence to the protocol was important to its success. Little evidence exists that self-initiated requests for toileting is increased. Wetness episodes decreased in the short-term.
	Eustice, Roe, & Paterson, 2000 [415]	Cochrane Review update	Nine trials included, N = 674 older adults.	Literature searched according to protocol (all randomized or quasi-experimental studies). Two reviewers evaluated studies for methodological quality; third reviewer proof read the review.	Insufficient evidence to reach firm conclusions for practice. Suggestive evidence exists for short-term benefit from prompted voiding, longer effects are not known.
	Schnelle, Leung, Rao, Beuscher, Keeler, Clift & Simmons, 2010[390])	RCT	112 nursing home residents in 12 nursing homes in USA	Prompted voiding, exercise and mobility endurance, food and fluid intake administered by trained research staff for 5 days a week from 7am to 3:30pm over 12-week period. Frequency of urinary and fecal incontinence and constipation were outcome variables.	Urinary incontinence frequency and number of appropriate toiletings improved.
Habit Retraining					
	Ostaszkiewicz, Chestney & Roe, 2004 [947]938]	Cochrane Review	Four trials included, N = 378.	Literature searched and evaluated per protocol. Trials too heterogeneous to for meta-analysis.	Adherence to habit retraining protocols is difficult for staff. Evidence is too limited to judge if improvements in continence make habit re-training protocols worth investment.
	Nikoletti, Young & King, 2004 [948]	Randomized controlled trial	41 elderly incontinent patients on acute care rehabilitation units in Australian hospitals	Patients in the treatment group were monitored for 72-hours with an electronic device. Patients in the control group received standard habit training. Prescribed voiding times for both groups (control and monitoring group) were developed and continence outcomes were measured.	No statistically significant improvements in self-reported or carer reported UI frequency. Significant reduction in self-reported and carer reported severity of UI in one-month follow up of treatment group. Missing data and problems with using the electronic monitoring device were noted.

Table 8: Behavioural interventions (continued)

Intervention	Authors	Study Design	Sample	Methods	Results
Timed Voiding					
	Ostaszkiewicz, Johnston & Roe, 2004 [420]	Cochrane Review	Two trials met inclusion criteria, N= 298 female subjects with reduced mobility and cognitive impairments.	Literature searched and evaluated per protocol.	Nighttime incontinence was significantly lower in intervention group. Data were considered too few to make a recommendation for or against timed voiding.
Mobility and Toileting Interventions					
	Ouslander, Griffiths, McConnell, Riolo, Kutner & Schnelle, 2005 [5]	Randomized controlled trial cross-over design.	102 residents in four Veterans Affairs nursing home	Research staff implemented the Functional Incidental Training (FIT) intervention four times daily, five days a week for eight weeks.	FIT improved endurance, strength and UI; 64 residents completed the intervention.
	Van Houten, Achterberg & Ribbe, 2007 [399]	Randomized single blinded trial.	57 dependent women with no cognitive impairment with longstanding UI living in 24 long-term care institutions.	Physiotherapists or occupational therapist administered the intervention to the treatment group for an individualized eight-week long programme of mobility and toileting skills.	Intervention group experienced 37.7% reduction in the daily amount of urine loss, but results were not statistically significant.
Prevention Interventions					
	Diokno et al, 2004 [407]	Randomized controlled trial comparing behavioural modification programme (BMP) to no treatment group.	Ambulatory postmenopausal continent volunteer women, N = 359.	Women in BMP intervention group received educational sessions and individualized evaluations of knowledge, adherence and skills.	At 12 months follow up, women in BMP group had significantly better continence status, pelvic muscle strength and displacement score.

ed by the total number of voids) of > 66%, or a wet check rate (number of times the resident was wet when physically checked) of <20% [416]. All others should be managed by check and change. This approach allows prompted voiding to be targeted just to the approximately one-third of residents who are eligible for and respond to prompted voiding, and could help decrease the considerable time and labour costs now used for inappropriate, unsuccessful toileting [417]. The 2005 revised US guidelines for continence care in nursing homes approved this approach as quality care [418]. Prompted voiding with food and fluid management and exercise was effective in reducing UI frequency and increasing the number of appropriate toileting episodes. Those nursing home residents with less cognitive impairment (higher Mini Mental Status Examination scores) showed lower improvement than those with more cognitive impairment [390].

The large majority of prompted voiding trials were conducted in the United States. No data are available about the long-term effects of prompted voiding and there is no evidence relating to the adoption of such programmes in other jurisdictions.

There is insufficient evidence to determine if ***timed voiding*** improves continence (Level 4) [419]. No additional intervention studies on timed voiding were located since the previous International Consultation. Several of the studies included in a systematic review had only female subjects with cognitive impairment, and included use of additional interventions such as antimuscarinic drugs (propantheline or flavoxate), staff education, bedside commodes, and absorbent products.

There is insufficient evidence to determine if ***habit retraining*** improves continence (Level 4) [420, 421].

Functional Incidental Training (FIT) incorporates endurance and strengthening exercises (e.g., sit-to-stand, bicep curls) while an aide conducts prompted voiding with a resident. FIT significantly improves physical endurance and UI (measured by wet check). Across several different long-term populations, FIT led to a 38% reduction in daily urine loss [5, 398, 399]. However, all FIT efficacy trials relied on trained research nursing staff, FIT costs more than usual care, and it may be difficult to implement in nursing homes without changes in existing staffing levels, limiting its generalisability [5, 422, 423].

Operant behavioural strategies have shown some effectiveness in improving UI in long-term care residents (Level B) [394, 395]. The underlying principle is that behaviour is modified by its consequences, even in frail adults [424]. A balance must be struck, however, between encouraging self-care activities and patient preferences for care and functional ability, on-going evaluation of the frail older person's status, and treatment effectiveness.

c) Summary of evidence

1. Prompted voiding is effective in the short-term treatment of daytime UI in nursing home residents and home-care clients when caregivers comply with the protocol **(Level 1)**.
2. Prompted voiding is ineffective and should not be used for people who need the assistance of more than one person to transfer; these people should be managed with "check and change." **(Level 1)**.
3. Prompted voiding should not be continued in eligible persons who have less than a 20% reduction in wet checks **(Level 1)** or toilet successfully less than two-thirds of the time after a three day trial; these people should be managed with "check and change." **(Level 1)**.
4. Interventions combining toileting and exercise, decrease wet checks and improve endurance in nursing home residents, including those with psychiatric disease **(Level 1)**.
5. Interventions combining prompted voiding, exercise, fluid and food intake interventions improve UI frequency and appropriate toileting **(Level 1)**.
6. It is uncertain whether habit retraining reduces UI in frail older persons **(Level 4)**.
7. It is uncertain whether timed voiding reduces UI in frail older persons **(Level 4)**.
8. There are no proven interventions to reduce night-time UI in frail older persons **(Level 4)**.
9. There are no proven interventions to reduce the incidentce ofUI in hospitalized frail older persons **(Level 4)**.

d) Interventions with caregivers and long term care staff

Acute care patients have preferences for urinary incontinence treatment that is significantly discordant to hospital staff. For example, nurses and physicians preferred scheduled toileting over diapers more than did the patients [310]. The authors suggested that communication about treatment preferences should occur.

3. INTERVENTIONS WITH LONG TERM CARE STAFF AND CAREGIVERS

Many frail elderly people rely on family, caregivers, or residential and/or nursing staff for toileting assistance and personal care. These carers may not be available as frequently as necessary for the frail elder to maintain continence, and even if available they may not be able or willing to provide the needed assistance. Research has shown that the frequency of toileting assistance actually provided in US nursing homes is too low to maintain continence [425, 426]. There is dissonance between

nursing home surveyors, nursing staff, and nursing home administrators' knowledge and beliefs about UI and its management, which may be an important barrier to effective UI care [427]. A number of studies suggest that nurses in acute and long-term care settings continue to provide urine containment interventions rather than promoting continence [249, 250, 253, 255-258, 428-432]. For example, 99% of residents with UI in one study facility wore absorbent products and only 3% had received UI treatment [433]. Moreover, nursing staff preferences for UI management (toileting) often conflict with those of residents and their families' patient treatment preferences (medications and garments) [309, 310, 434]. Acute care patients' preferences for urinary incontinence treatment also differ from hospital staff preferences [310]. For example, nurses and physicians preferred scheduled toileting over diapers more than did the patients [310]. The authors suggested that communication about treatment preferences should occur.

In long term care, a two-pronged behavioural intervention to UI care, one geared towards the resident and the other geared towards staff members, appears necessary [435-437]. Nursing assistants play a key role in the success of behavioural programmes, and organisational schemes need to be devised to create incentives for them to keep residents continent [438]. Direct care providers will be unlikely to implement programmes unless residents and their families advocate for them [439]. This advocacy, however, appears unlikely if, based on their experiences, nursing home residents have reduced expectations and do not anticipate receiving sufficiently frequent and prompt toileting, and therefore express no desire for more frequent toileting [426]. One documented barrier to toileting programmes in long term care is their labour intensity. Bladder training programmes are considered one of the three most time consuming activities for long-term care staff [321].

A number of approaches have been trialled in an attempt to promote continence and to improve the management of incontinence care in long term care facilities. One involves a specialty practice exemplar model to improve continence care in long-term care, with a nursing faculty member with expertise in the assessment and treatment of UI having a clinical practice in a facility. Graduate nursing students, working with this individual, focus on the Minimum Data Set Resident Assessment Protocol for UI. Assessment and treatment skills ultimately are transferred to the facility nursing staff members through several mechanisms, including staff education and improved continence care systems [440]. Quality assurance programmes using incontinence quality indicators have also been proposed [441]. A clinical leadership model in the sub-acute setting in Australia used a staff empowerment and mentorship model to make evidence based changes related to continence care during the patient's stay and on discharge [442]. The effectiveness of clinical leaders may depend on a number of factors including, but not limited to their educational preparation for the role; the extent to which they feel supported; and; maintenance of the role (i.e. succession planning).

a) Quality of data.

Several authors point to the difficulty of conducting research in long-term care settings [435, 436, 443]. Factors such as staffing ratios, changes in administrative and regulatory policies, and fiscal issues are beyond researchers' control. Several investigators report that staff compliance was less than total, and some experienced problems with staff training. For instance, in one study several staff members did not attend group-training sessions and needed one-on-one training, and other staff members did not perform the protocol or document its use, especially when staffing levels were low [436]. Little staff intervention research to improve continence in older persons has been conducted in the acute-care setting.

b) Results

1. Interventions With Long-Term Care Staff

A recent systematic review of the management of incontinence and promotion of continence in older people in care homes concluded that use of incontinence pads and toileting programmes comprised the most common management strategies, and assessment processes were inconsistently used [444]. Assessment protocols are a key first step in the process of identifying residents' individual continence care needs. A number of assessment tools have been developed for this purpose. They include, but are not limited to:

- the Resident Assessment Instrument/Minimum Data Set (RAI/MDS) used in US nursing homes;
- the 'Continence, History, Assessment, Medications, Mobility, Plan' (CHAMMP) tool, developed to support the use of the RAI/MDS [445],
- the 'Capital Health Authority (CHA) Screening Tool' for use within community and clinical settings in Canada, [446], and
- the Continence Assessment Tools for Residential Aged Care' for use within Australian long-term care settings [447].

Toileting assistance programmes also play a central role in optimising continence for frail older adults in long term care settings. One group of researchers investigated the effect of a scheduled toileting programme on the incidence of nursing home staff injury, using a quasi-experimental design using a 75 bed unit and a similar comparison unit [448]. Fifty residents in the intervention unit were selected to participate based on an assessment indicating their eligibility for a toileting pro-

gramme. Mechanical lifts were purchased for the intervention unit in anticipation of an increase in toilet transfers. Regular toileting increased from 12% pre-intervention to 67% in the intervention and 26% in the comparison unit. Staff injuries related to toileting did not increase in the intervention group, and the staff also noted less resident agitation. A pre-post test trial of toileting assistance programmes involving 153 elderly residents in Japan also reported improvements in residents' continence status following a multifaceted intervention. Managerial support was key to the success of the intervention, as was the involvement of a clinical leader on each unit to oversee the protocol [449].

Although toileting assistance programmes are effective in reducing incontinence rates when implemented, and in-service classes on UI may change staff knowledge and attitudes about UI, in-service-classes alone do not improve resident toileting. In one study, only 70% of toileting assists were completed [435]. The authors noted that staff members believed that toileting was "not worthwhile" for some residents. In a randomised study using advanced practice nurses (with post-graduate training) to work with staff to implement evidence-based protocols, residents in the intervention arm experienced significantly greater improvement in UI compared with those receiving usual care [450].

In response to knowledge deficits, some researchers have developed and trialled education and awareness-raising strategies, designed to enhance knowledge, that would subsequently lead to improvements in practice that would, in turn, enhance the quality of continence care in long-term care [205, 208, 220, 403, 451-455]. For example, a number of countries have established post-graduate and continuing education courses that prepare nurses and physiotherapists to address the broad spectrum of continence issues.

However, the association between improved knowledge and improved practice is not straightforward. Some researchers reported improvements in knowledge that did not translate into improvements in practice [205, 220, 453]. Cognisant of this dilemma, Henderson and Kashka [212] examined the association between knowledge, beliefs, attitudes and practice about incontinence in a sample of 126 nurses from hospital, home health and long-term care settings in Texas, USA, using a tool titled 'the Urinary Incontinence Scales'. Using a multiple regression analysis, they found that although participants' knowledge and belief were positively associated with their self-reported practice, attitude alone had a direct effect on self-rated practice [212], thus highlighting the need for educational strategies that address the effective behaviours associated with caring for incontinent persons. In response to this finding, and to greater calls for UI content in nursing curricula, as part of a larger educational programme on rehabilitation, one researcher designed a novel six hour experiential learning activity for nursing students to experience wearing an absorbent incontinence product [452].Twenty-one senior nursing students volunteered to participate in the pilot trial. Using the Urinary Incontinence Scales to measure participants' attitudes, beliefs, knowledge and practice, the researchers reported a post-test median increase of < 1% in attitude scores; 3.6% in belief scores; 4.4% in knowledge scores, and 47.6% in practice scores.

Given the longstanding challenges surrounding the uptake of evidence into practice, in 2005, Stolee and colleagues conducted a qualitative study to explore the factors within the work environment that impacted the effectiveness of continuing education. Data were derived from a series of focus groups with a sample of 35 staff and managers of long term care facilities, in Ontario, to collect information about facts affecting transfer of learning. This information was collated and a Delphi approach was used with 34 experts in long term care to validate and refine the list of factors. The need for managerial support was ranked as the most important factor. This was followed by: sufficient resources to implement new learning; the learner's belief in the practicality of training; integration of the learning into ongoing practice; staff feeling valued; on-the-job reinforcement of learning; knowing change of practice is supported; seeing benefits of new approaches; and attitudes toward elderly people [456]. Whilst all of the above mentioned resource factors are important to optimise evidence-based continence care practice, a number of researchers draw attention to the need for theory to inform improvements in the quality of care [395, 457-462]. However, many translation of research into practice models for LTC rely on the belief that usual care staff are able to implement better care if they know what to do and are properly motivated [463]. One of the key steps in the process of translating evidence-based knowledge into practice is to identify potential barriers to change [464].

Research literature on UI in long-term care identifies extensive barriers to UI care [433, 463, 465]. A staff survey revealed that nursing assistants believed prompted voiding was very helpful to residents in reducing the frequency and volume of incontinent voids, but that inadequate staffing, staff work load, turnover, and absenteeism were significant barriers to prompted voiding. They believed that increased numbers of staff, improved communication, ongoing education, and alternative modes of care delivery were necessary to facilitate prompted voiding. Overall, staff believed toileting programmes improved resident quality of life but the realities of long-term care made them difficult to implement [466]. Nursing assistants believed that UI was a normal part of ageing and that nothing could be done for it, 99% of residents with UI in the study facility wore absorbent products and only 3% had received UI treatment [433].

A further challenge to continence care in long term care is the fact that differences may exist between documented care, reported care, and actual care. For example, when staff perceptions regarding completed toileting assistance were compared to research staff observations, staff over-inflated the percent of toilet assists they completed (stating 80-90% when the observed was 70%) [467]. Staff members also believed that residents were happier with a prompted voiding programme, yet only 52% thought the programme improved residents' continence. In another study, long-term care facility residents reported a mean of 1.8 daily assists to the toilet, regardless of whether they were on a toileting programme or not [439].

Another approach to translating evidence based protocols into practice, to enhance continence care for individuals living in long term care, involves the use of quality management programmes. Schnelle and colleagues tested a computerised quality management programme for prompted voiding in a convenience sample of 85 residents in eight US nursing homes [468]. Each facility was asked to identify staff members for the following roles: main contact person; quality control specialist; two licensed personnel who would conduct UI assessments; and two nursing/health care assistants who would implement the prompted voiding intervention. Information on the computer system included UI assessment and residents wetness rates. Research staff monitored the database and provided the nursing staff feedback by telephone consultation. The programme was effective in improving dryness for six months while research staff monitored the database, but only one facility continued the programme after the research ended [465]. The researchers noted that current incentives for nursing homes to maintain UI management systems are insufficient.

One disincentive that needs to be addressed, at a resource and policy level, is the fact that toileting assistance programmes require statistically significantly more staff time than the practice of checking and changing residents' pads. Engst and colleagues reported that the latter practice was four minutes duration for residents who were soiled and in bed, compared to six minutes to provide residents with toileting assistance [448]. Schnelle and colleagues have also reported a cost disincentive for maintaining residents' functional ability to walk to the toilet [469]. In an analysis of the cost and time involved in changing residents' pads, compared with implementing prompted voiding, or a functional improvement program (FIT), these researchers found that changing residents pads involved an average of 5.5 minutes, compared with 7.7 for prompted voiding and 13.7 for FIT [398]. Although FIT resulted in significantly better outcomes for residents in terms of their strength, mobility and continence, it relied on a staff to resident ratio of one aide to five residents [470]. These resource costs may however be offset over time by improvements in residents' functional abilities. Another cost minimisation strategy is to identify and target residents who are most likely to benefit.

As reduced mobility is a major risk factor for incontinence, further attention should be directed toward developing, implementing and evaluating interventions that increase residents' functional skills, or at the very least, minimise their functional decline, and prevent falls. van Houten and colleagues [399] report reductions in the daily loss of urine for elderly dependent women randomized to an 8-week individualised training programme of mobility and toileting skills. Two systematic reviews affirm the value of rehabilitation and falls minimisation strategies for frail older adults in long-term care [189, 471]. Given the association between the use of restraint and incontinence in long-term care settings, interventions designed to prevent and reduce restraint use should also be adopted.

Interventions for continence care in frail older adults should also aim to minimise the incidence of incontinence-associated dermatitis (IAD). Palese and Carniel [472] describe a three-phased multi-intervention incontinence care programme in a long-term care facility in Northern Italy that reduced the incidence of IAD, and the number, and cost of absorbent products. The intervention consisted of an assessment process, the introduction of new absorbent continence aids, a structured skin care regimen and advice and education from a Continence Nurse Advisor. To this end, it is important to use tools that help staff differentiate between IAD and pressure ulcers such as the Pressure Ulcer Classification (PUCLAS) education tool [473].

2. Interventions To Manage Night-Time Incontinence In Long-Term Care

Night-time sleep in long-term care residents is often fragmented and disrupted [474-479] and much of this fragmentation and disruption is caused by noise, light and incontinence care routines [476-478]. There is some evidence to suggest residents may spend long periods of time in bed overnight (returning to bed after dinner about 6.30pm and waking between 0600-0700hrs), and staff conduct pre-scheduled rounds to reposition residents and change their pads [478]. In this study, although senior staff stated that such rounds were conducted every two hours during the night; the number of observed rounds was 0.3 - 4.5 per resident [478].

Interventions that have been trialled in an attempt to enhance the quality and duration of sleep for residents' with incontinence include:

- a daytime physical activity programme [480]
- a daytime physical activity programme combined with a night staff behaviour programme aimed at reducing noise, light and sleep-disruptive care practices [481].

- a two or four hourly incontinence care schedule based on an individualised assessment of each resident's skin health [482].
- an individualised incontinence care routine combined with feedback to usual care staff about methods to reduce noise levels [483].
- a two or four hourly prompted voiding schedule based on an individualised assessment of each resident's skin health [484].
- a four or eight hourly pad changing regime based on an individualised assessment of each resident's skin health [485].

The combined findings of these trials suggest that continence care at night in long-term care settings can, and should be individualized based on an assessment of residents' skin health; their ability to spontaneously move in bed; and on their sleep/wake status. It should also be based on an assessment of residents' preferences. Whilst toileting assistance should be available to residents' during the night as well as day, one study suggests that prompted voiding is not effective or well tolerated at night. The researchers concluded that 'in general, incontinent nursing home residents are not responsive to prompted voiding at night, even when the prompts are carried out so as to be minimally disruptive to sleep [486]. Clearly, further research is needed about residents' preferences for nighttime continence care.

One of the main reasons for residents' sleep disruption is due to the time-honoured practice of waking residents with incontinence to check their continence status and to reposition them in order to minimise the risk of pressure ulcers. The Agency for HealthCare Policy and Research Agency, (now the Agency for Healthcare Research and Quality) identified incontinence as a risk factor for pressure ulcers in its now archived Clinical Practice Guideline for Pressure Ulcers in Adults (1992). The guideline also recommends that 'any individual in bed who is assessed to be at risk for developing pressure ulcers should be repositioned at least every two hours if consistent with overall patient goals'. However, advances in the design and absorbency of pads and of pressure relieving devices, may mitigate the number of times residents' need such care. Fader and colleagues randomly assigned 81 residents of residential homes in the UK to either a four or an eight hourly nighttime pad changing regime [485]. They found no evidence that the less frequent pad changing regime had an effect on skin erythema or on skin pH. However, residents on the less frequent pad changing regime had wetter skin (P=0.01; 95% CI: 2.89-21.39) and five residents developed grade 2 ulcers. Further research on this issue is warranted to guide practice.

3. Interventions With Caregivers

Family caregivers of frail elders with UI report a high level of physical fatigue (70%) [487]. This is particularly so for family caregivers of individuals with UI and dementia [488]. Upton and Reed conducted a qualitative study on caring in the context of incontinence and dementia and reported that the relentless nature of incontinence was psychologically draining and demanding on caregivers. This was particularly the case if the care-recipient had challenging behaviours; in which case, incontinence typically presented as a behavioural problem [488]. Similar findings were reported by Hutchinson and colleagues [489] who used an ethnographic design, to examine the range and variation of toileting problems and management strategies used by family and employed caregivers of individuals with Alzheimer's' Disease (AD). The researchers reported that toileting emerged as a complex event with many stages and as a task that was unaesthetic and unpleasant for caregivers and clients. It also occasionally triggered a severe emotional response from the person with AD. Caregiver's responses were variable, however, some read cues and interpreted toileting behaviours. These findings from qualitative research draw attention to the complexities of managing incontinence in the context of dementia.

Family caregivers report embarrassment and social isolation as their most frequent emotional responses to UI, and a need for information about resources.[487] In a small pilot study, caregivers at home felt that the requirements of a behavioural protocol were more than they could manage [490]. However, in contrast to long term care staff, family caregivers were adherent with prompted voiding 89% of the time, and 93% were somewhat or completely satisfied with the decrease in UI [491]. Using data from a cross-sectional survey of the Dutch national prevalence measurement of Health Care Problems, Du Moulin and colleagues found that more than half incontinent older adults (mean age 80) living at home and receiving home care services, had no diagnosis of the type of incontinence. The most common management strategy, regardless of diagnosis, was the use of pads [492].

c) Recommendations for practice

- Family, caregivers, or residential and/or nursing staff dealing with different levels of UI (mild, moderate, catheter managed) have different educational needs and require different levels of support.
- Interventions to support family caregivers of individuals with UI may need to be adapted to suit formal carers or staff in long-term care so that they accommodate the organisational context.
- a one-size fits all approach will not accommodate the diverse needs of older people in long term residential care.

- Interventions or approaches to caring for an individual with UI and cognitive impairment need to be tailored to the person's unique abilities and disabilities.
- Interventions for UI should be theory-based, multi-component, interdisciplinary and person-centred.

4. PHARMACOLOGICAL TREATMENT

a) Background

This section deals with the management of the frail elderly. The pharmacological management of UI in healthy older persons is discussed in Chapter 10, Drug Treatment. Specific treatments for bladder outlet obstruction and associated LUTS in frail elderly men are outside the scope of this chapter; special issues in the care of frail older men with UI are discussed above.

Frail persons with UI should be considered for drug treatment only following a comprehensive evaluation of remediable causative factors, and if they are appropriate for and have had a trial of behavioural and lifestyle interventions. Drug treatment should not generally be used for persons who make no attempt to toilet when aided, become agitated with toileting, or are so functionally and cognitively impaired that there is no prospect of meaningful benefit. Even so, a recent study of US nursing home residents suggested that only a small proportion of incontinent residents potentially suitable for drug therapy ever received it [493].

b) Quality of data

Since the last ICI we located a further 13 randomised placebo controlled trials (RCTs) of antimuscarinic medication, involving subjects over the age of 80. As before, the majority of studies addressing frail older people are of only modest quality, reflecting their vintage. The available RCTS were predominantly done in the US, with a small number in Europe, the UK, Germany, Taiwan and Japan. . All focus on antimuscarinic treatment of presumed urgency UI. UI diagnosis was overwhelmingly symptom-based; only three studies included urodynamic evaluation. There have been two large studies of older people, one in Europe and one in the US; the latter targeted at frail older people identified by the VES-13 [494] For most studies however, it was impossible to identify whether subjects were frail, even though the spread of co-morbid condition and co-existing medication suggests a representative sample of community dwelling older people except where the study was performed in an institutional environment, in which it is reasonable to assume a high prevalence of functional and cognitive dependence.

The methods of blinding and randomisation in RCTs were seldom specified. Other than those conducted by the pharmaceutical industry, most studies were generally small and potentially under-powered, and others lost power because of high dropout rates due to illness and death (inevitable in trials with frail elderly persons). Because of these issues, many RCTs provide only Level 2 evidence. Some larger studies in older persons without clear frailty are included here, to recognise an increasing emphasis on including older persons in drug trials.

Precise descriptions of the target population - including the definition of "frail persons" and a comprehensive description of the degree of cognitive and functional impairment - were usually absent. Although some investigators included information on patients' functional and cognitive status, as well as comorbid conditions, the descriptions were often only qualitative, and none addressed these issues adequately in the analyses. Explicit, concurrent behavioural therapy was used in most nursing home studies, yet may have occurred in many others although these are usually specifically prohibited in trials managed by the pharmaceutical industry. Combination therapy and high comorbidity could have attenuated differences between drug and placebo, and make it difficult to compare results directly with studies in healthy older and younger persons. Outcomes in care home studies were universally assessed by UI frequency (pad-weighing, bladder diaries, and wet-checks), and none reported quality of life outcomes.

In at least six studies, investigators treated subjects with "urinary tract infection" (usually defined as pyuria and bacteriuria in the presence of UI) before initiating antimuscarinic therapy, and one study excluded such subjects. In another, investigators treated urogenital atrophy with oestrogen prior to antimuscarinic therapy, possibly leading to an additional amelioration of symptoms. However, no other reversible causes were addressed prior to entry or randomisation in most studies.

The generally low quality of these trials reflects not just study design, but the larger issue of the difficulty of doing large, prospective intervention trials in frail populations. Moreover, UI in frail elderly is universally a multifactorial problem involving a large number of factors beyond the bladder. Thus, the expectation that drug therapy targeted solely at urodynamic DO or SUI would markedly improve/cure UI in this population is unlikely to be realised. Additionally, the reporting of adverse events relevant to managing older people appears to be deficient. A meta-analysis examining the measurement and reporting of CNS outcomes showed that, 77% (242/314) of eligible trials identified, neither measured nor reported CNS outcomes. Of the remaining 23%, it was difficult to ascertain whether CNS adverse events were systematically measured or spontaneously reported. Only one of 72 trials objectively measured changes in cognitive performance. Age-stratified analyses of CNS outcomes from trials

in adults aged 65 and older with overactive bladder were found in only eight publications [495].

c) Results

Results from randomised trials are summarised in **Table 9**; the following sections discuss specific drugs in detail.

1. Oxybutynin

The majority of older studies in frail older persons used immediate-release oxybutynin (oxybutynin-IR). There are two studies of extended release oxybutynin (oxybutynin-ER), one examining cognitive effects in nursing home residents with dementia and urgency UI,[496] and the other involving community-dwelling women over age 65 [497] Published trials of the efficacy of transdermal oxybutynin included subjects up to age 100 and in institutional care settings, but did not stratify results by age or comorbidity [498].

The pharmacokinetics of oxybutynin-IR and its active metabolite, N-desethyloxybutynin, in one study tended to show greater plasma levels and bioavailability with increasing frailty and age.[499] Another found peak levels in 21 octogenarians similar to those reported in young normal males (12.5 ng/mL vs. 8.9 ng/mL) [500]. A study of the pharmacokinetics of transdermal oxybutynin showed no significant difference in plasma levels between young and old (up to 77 years) subjects [501].

- **Efficacy.** An early, small (n=15) trial of **oxybutynin-IR** and habit training in long-term care residents showed no effect on UI episodes.[502] However, in a subsequent and larger study in long-term care residents study who had failed prompted voiding alone, the addition of titrated oxybutynin-IR resulted in a significant but modest reduction versus placebo.[503] Wet-checks decreased from 27% at baseline to 20% on drug and 24% on placebo, leading the authors to conclude that the improvement was not clinically significant, especially given the continuing requirement for nursing intervention. However, their *a priori* definition of "clinically significant improvement" (one or fewer episodes of daytime UI) was achieved by 40% on drug but only 18% on placebo ($p<0.05$). The dose generally associated with improvement was 2.5 mg three times daily. In another controlled study of UI in long-term care residents (n=24), there was little effect of oxybutynin-IR 5 mg twice daily given for 8 days, but all residents were toileted 10 times daily, and the dose may have been too high and given too infrequently.[504] In a randomised two month trial in frail community-dwelling elderly, oxybutynin-IR plus bladder training was subjectively and objectively superior to bladder training alone in improving urinary frequency (95% CI 6-27 fewer voids per 2 weeks) but not UI.[505] Insufficient information was available regarding a Japanese study in 75 "elderly" patients to assess the population and outcomes.[506] A study in 416 community dwelling older persons, including the fitter elderly, found 68% reported a partial or complete symptomatic cure with 2.5 mg three times daily; 30% of subjects experienced ADEs, but only 10% withdrew because of them.[337]

Only one of the two identified RCTs in frailer older people examined the efficacy of **oxybutynin-ER**. [497] The other examined the effect on cognition [496] and is discussed below. No published RCTs of **transdermal oxybutynin** in the frail elderly were found, and *post hoc* sub-analysis of efficacy in subjects over the age of 65 has been published only in abstract form. In a small Japanese case series (n=13, mean age 75) in persons with urgency UI and cystometric DO, **intravesical oxybutynin** caused no significant increase in mean bladder capacity one hour after installation of 5 mg oxybutynin at pH 5.85. [507] In four patients who continued twice daily installation, two had UI "disappear" and one "markedly decrease" (duration until effect not noted). No patient developed an "increased PVR" (not defined).

- ***Predictors of efficacy.*** Predictors of efficacy were studied in one study in persons with urgency UI and urodynamic DO (n=41, mean age 79) treated with 2-4 weeks of oxybutynin-IR (5-15 mg/day).[508] Factors associated with baseline urine loss (by pad weighing) were impaired cognitive orientation (on the Cambridge Mental Disorders of the Elderly Examination), number of daily voids, and fluid intake. Persistent urine loss after treatment was associated with impaired orientation, reduced sensation of bladder filling during cystometry, and most significantly global cortical under-perfusion on single photon emission computed tomography scan, suggesting that cortical factors are the main determinant of the severity of urgency UI before and after oxybutynin. In a study of 80 older patients (mean age 74), patients with dementia (by Hasegawa dementia scale) were less likely than cognitively intact patients to report subjective improvement in UI with antimuscarinic agents, despite similar objective outcomes.[509] However, these results could reflect treatment-associated cognitive effects.

- ***Adverse reactions.*** A comparative sub-analysis of oxybutynin IR versus solifenacin in subjects below or above 65 years of age (mean 71 years in >65 year age group) showed subjects receiving oxybutynin IR at a fixed dose of 15mg/day were over eight times more likely to have dry mouth than were those receiving solifenacin 5mg /day, irrespective of age (OR 8.88; 95% CI 3.91–20.17) [354] (Note that the median dose of oxybutynin used in clinical practice is 5mg bid). A comparative study against once daily trospium chloride conducted in subjects up to the age of 91, but with mean age 61 (SD 12.4) years showed oxybutynin to be non- inferior to trospium in terms of resolution of UI episodes, but was associated with twice the incidence of dry mouth (7.7% versus 4.1%) [510].

Table 9. Evaluable drug trials in frail older people (see text for explanation)

Drug	Study	Design	Setting and pts	Results	Comments
Oxybutynin	Minassian 2007 [497]	prospective randomized 12-week, open-label study to investigate the effectiveness of extended release versus immediate release oxybutynin	community-dwelling female population over the age of 65	72 women (23%) were enrolled over 34 months (33 in the immediate release group, and 39 in the extended release group). The study was stopped prematurely	
	Sand 2007 [949]	randomized, open-label, assessing health-related quality-of-life (HRQoL) and safety with oxybutynin transdermal system (OXY-TDS)	community-based study of 2878 participants aged >/=18 years who had been given a diagnosis of OAB.	There were clinically meaningful and statistically significant improvements in nine of 10 domains in KHQ at the study end; the greatest improvements were in Incontinence Impact (-13.5), Symptom Severity (-12.4), and Role Limitations (-13.3).	No age stratification, not obviously a frail element to the study sample
	Lackner 2011[950]	efficacy of oral extended-release oxybutynin for urge urinary incontinence	4 week trial in 50 older female nursing home residents with mild to severe cognitive impairment.	both groups achieved a significant median decrease in mean urinary incontinence episodes and urinary frequency at 4 weeks (P = .01-.05).	No between group differences in any outcome
Solifenacin	Herschorn 2011[354]	randomized, multicentre, prospective, double-blind, double-dummy study to compare the incidence and severity of dry mouth and other adverse events in patients ≤ 65 years and >65	132 subjects with ≥ 1 urgency episode per 24 h, with or without urgency incontinence, and ≥ 8 micturitions per 24 h for ≥ 3 months.	incidence and severity of dry mouth and other adverse events with solifenacin were similar between younger and older patients. solifenacin 5 mg/day was associated with fewer episodes and lower severity of dry mouth, and a lower discontinuation rate	adverse events were evaluated in subgroups of patients ≤ 65 years and >65 years. No stratification otherwise

Table 9. Evaluable drug trials in frail older people (see text for explanation) (continued)

Drug	Study	Design	Setting and pts	Results	Comments
Darifenacin	Chapple 2007 [951]	RCT assessing efficacy, tolerability, safety and quality of life in 400 subjects mean age 72 years	randomized (2:1) to 12 weeks of double-blind treatment with darifenacin 7.5 mg once daily for 2 weeks, then optional titration to 15 mg daily or placebo with sham titration	Mean urgency urinary incontinence episodes decreased significantly with both darifenacin (-88.6%) and placebo (-77.9%; p > 0.05), QoL assessments revealed significant improvements with darifenacin versus placebo	Unsure re “frailty” of sample
Fesoterodine	Wagg 2010 [527]	RCT, efficacy and PRO comparing fesoterodine to placebo	794 community dwelling men and women >65 (1/3 >75)	improvement in urgency episodes (-1.92 v -3.47, p<0.001), micturitions (-0.93 v -1.91, p<0.001), nocturnal micturition (-0.27 v -0.51, p=0.003), severe urgency episodes (-1.55, -2.40, p<0.001), and incontinence pad use The response on the treatment benefit scale, OAB-S, PPBC, and UPS significantly greater in fesoterodine group	Community dwelling sample, including very elderly, no assessment of frailty, largely cognitively intact
	DuBeau 2012 [528]	12 week double blind, placebo controlled study	562 people of mean age 75 years fulfilling definition of vulnerable elderly	mean reductions in UUI episodes at week 12 versus placebo -0.65 (0.21), p<0.0018) and 24h micturition frequency -0.84 (0.23), p<0.0003)	

Cognitive side effects from oxybutynin have been reported in older persons. In one case series, four older men with Parkinson's disease and mild-severe cognitive impairment developed confusion, psychosis, hallucinations, behavioural disturbance, and/or paranoia after receiving oxybutynin-IR (5-15mg/day), which resolved when oxybutynin was stopped.[511] Of note, each patient was also on L-dopa (co-beneldopa) and selegiline, and the observed effects could reflect drug-drug interactions. However, these results are belied by a large RCT in which oxybutynin-ER 5 mg daily did not cause more delirium than placebo in NH residents with UI and dementia [496].

There are case reports of reversible peripheral neuropathy confirmed by re-exposure in a 70 year old woman taking oxybutynin-IR 5-7.5 mg/day[512] and recurrent heat stroke associated with oxybutynin in one elderly patient.[513] Few studies have addressed cardiac effects. A small study of older persons in the community with UI (n=20, mean age 75) found no change in resting heart rate or electrocardiograph evidence of either prolonged PR interval or QTc, or QTc dispersion after 4 weeks of oxybutynin-IR (mean daily dose 7.6 mg [range 2.5-10 mg]).[514] Using a large administrative utilisation database, no association was found between antimuscarinics (oxybutynin, flavoxate, hyoscyamine) and ventricular arrhythmia and sudden death.[515] Post-marketing adverse events with extended release oxybutynin include tachycardia and hallucinations.

2. Tolterodine

Since the last ICI, we identified no further studies of tolterodine for OAB/ DO. Analysis of the studies of tolterodine in "older patients " does not allow any conclusion to be drawn about the frail elderly. For example, "older" patients in one RCT of **tolterodine-ER** were all community-dwelling, able to complete a 7-day bladder diary, had a high prevalence of previous antimuscarinic treatment (53-57%), and a low prevalence of arthritis (15-18%), unlike most frail older persons.[516] Although several trials include elderly persons in their ninth and tenth decades,[516-518] mean age (~64 years) was much lower, persons with "[unspecified] disease which the investigator thought made the patient unsuitable" and/or "renal disease" were excluded, and results were not stratified by age. In a secondary analysis of a large, open label German trial of **tolterodine-IR** 2 mg twice daily, higher age was significantly associated with "less favourable efficacy."[519] However, the absolute difference in odds was only 0.019, there was no association of tolerability with age, only mean age is described, and UI frequency was based on patient report, not bladder diaries, all of which fail to add up to a clinically meaningful difference. In a non-randomised study, tolterodine was given to 48 nursing home residents who did not respond to toileting alone; 31 of these patients had a 29% increase in dryness (versus 16% in residents on toileting alone) [484]. We did locate a trial of 1 year duration of the addition of tolterodine ER 4mg to alpha blocker or 5 ARA therapy in older men (mean age 74.9 years) which resulted in a between group, statistically significant decrease in the storage symptom score on the IPSS [520].

- ***Adverse reactions.*** There are no prospective systematic data on tolerability in frail patients. There have been case reports of hallucinations (73 year old woman with dementia [521]) and worsening memory,[522] including a 65 year old cognitively intact woman.[523] There is a case reports of delirium when tolterodine was given with a cholinesterase inhibitor [524]. Analysis of prescription-event monitoring in the UK (mean patient age 63) found a significant association between age (>74 years) and psychiatric events and tachycardia (odds ratios not given) [525]. In a similar database study, the age- and sex-adjusted risk of hallucinations with tolterodine was 4.85 (95% CI 2.72-8.66) compared with 10 other drugs (acarbose, alendronate, famotidine, 3 proton pump inhibitors, finasteride, meloxicam, misoprostol, and nizatidine) chosen for presumed lack of antimuscarinic, cardiovascular, and CNS activity, and available in the database. Important confounders such as other drugs and comorbidity were not evaluated. Similar to oxybutynin-ER, post-marketing information on tachycardia and hallucinations was added to the tolterodine-ER package insert in 2003.

3. Fesoterodine

Since the 4th ICI we located four studies of age related pharmacokinetics in younger versus older subjects (although not frail), a pooled analysis demonstrating efficacy of fesoterodine in subjects over the age of 65, stratified into >65 and >75year age groups, a large prospective study which reported the efficacy of fesoterodine in subjects stratified by age (>65 and >75) years of age and a prospective study in the frail elderly [355, 526]The pharmacokinetic study found no clinically meaningful effect on 5-HMT, the active metabolite of fesoterodine pharmacokinetics or pharmacodynamics after single-dose administration of fesoterodine 8 mg. The efficacy of fesoterodine has also been studied in a European trial in 794 elderly men and women with OAB [527], 47% were men. Forty-six percent of subjects reported urgency incontinence episodes at baseline, and 64% had prior treatment with antimuscarinics. At week 12, the improvement from baseline in urgency episodes (-1.92 v -3.47, $p<0.001$), micturitions (-0.93 v -1.91, $p<0.001$), nocturnal micturition (-0.27 v -0.51, $p=0.003$), severe urgency episodes (-1.55, -2.40, $p<0.001$), and incontinence pad use were statistically significantly greater with fesoterodine than with placebo. The responses on the treatment benefit scales, OAB-S, PPBC, and UPS were also significantly greater in those in the fesoterodine group versus placebo. The effect of fesoterodine has

also been assessed in vulnerable older people as assessed by the Vulnerable Elders Survey Survey [269], which identifies those at risk of death in the following two years. This 12 week double blind, placebo controlled study including 562 people of mean age 75 years resulted in mean reductions in UUI episodes at week 12 versus placebo (-0.65 (0.21), p<0.0018) and 24h micturition frequency (-0.84 (0.23), p<0.0003) [528].

- ***Adverse effects:*** The cognitive safety of fesoterodine has been assessed in a single small study of cognitively intact older subjects, using alprazolam as an active control and placebo. There were no statistically significant changes in performance on a computer assisted battery of cognitive tests versus placebo [529].

4. Solifenacin

We located a sub-cut analysis from a Canadian study which reported tolerability of solifenacin versus oxybutynin in older subjects, reported above [354]. Otherwise, there were no further relevant studies. Pharmacokinetics of solifenacin have been evaluated in 23 older subjects (mean age 68); t_{max} was longer and there was a higher maximum plasma concentration, but the differences from results in younger patients were small and deemed by the authors to be clinically irrelevant.[530]. A secondary analysis of pooled Phase III data in patients aged 65 and older (all community dwelling and fit, mean age 72) found similar efficacy to that reported for younger and middle aged persons [531]. However, direct comparison with subjects < 65 yrs from the same pooled trials was not done. Adverse effects in older frailer patients have not been specifically reported. However, data from an open-label, 12-week trial in patients treated by community urologists found that overall treatment-emergent adverse events were more likely in patients aged >80 years (OR 3.9 [95% CI 1.3-11.5]) and taking concomitant medications (OR 1.8 [95% CI 1.2-2.6]) [532]. Patients with concurrent medications were more likely to be male and on average about 12-14 years older, have comorbid disease, and be administered higher doses of solifenacin, yet had no observed increase in heart rate or blood pressure with solifenacin.

- ***Adverse effects:*** The cognitive safety of a single dose of 10mg solifenacin was tested versus placebo and 10mg oxybutynin IR in an exploratory study in 12 cognitively intact older subjects. Solifenacin showed no evidence of impaired cognition or self-ratings of mood and alertness versus placebo [533]. In a 3-way crossover design, chronic dosing of 5mg solifenacin, placebo and 5mg bid of oxybutynin were compared using a similar battery of tests in 23 older subjects with mild cognitive impairment. There was no statistically significant effect on cognition of solifenacin versus placebo. Oxybutynin 5mg bid was associated with impairment in power and speed of attention in a *post hoc* analysis of pooled time points at 1+2h post dose [534].

5. Darifenacin

We located one RCT of darifenacin for OAB in persons aged ≥65 (mean 72), in which there was no statistically significant difference between drug and placebo for the primary end point, UI frequency. [535] There were statistically significant improvements with drug for urinary frequency (-25.3% vs. -18.5% with placebo; p < 0.01) and quality of life, as measured by OAB-q and patient perception of bladder condition. A 2 year extension study in subjects >65 was reported, showing maintenance of OAB symptom improvement over the 2-year period with 44.4% patients achieving > or = 90% reduction in incontinence episodes at 2 years for the 64% (137/214) subjects remaining in the study [536].

- ***Adverse effects.*** Cognitive adverse effects of darifenacin have been prospectively studied in a series of trials. The first was a 3-period crossover RCT in 129 older subjects (mean age 71, 54% of those screened), 88% of whom had comorbid medical conditions and 93% were on other medications.[537] Cognition was assessed using a standardized computerised test battery. Darifenacin at variable doses did not adversely affect cognition compared to placebo, but results were aggregated so that patients did not serve as their own controls. A subsequent study in cognitively intact older persons (n = 49, mean age 66) using a similar computer cognitive test battery compared titrated darifenacin and oxybutynin-ER with placebo over 3 weeks.[538] Oxybutynin-ER but not darifenacin or placebo adversely affected the primary endpoint, delayed recall on the Name-Face Association test. However, oxybutynin was titrated one week earlier than darifenacin, and to a final dose (20 mg daily) much higher than is commonly used in clinical practice. Also, there were no differences between the two drugs and placebo for many other domains of the cognitive battery.

6. Trospium Chloride

Although often promoted for use in the elderly because of the reduced likelihood that the drug crosses the blood-brain barrier, we found no studies that evaluated the agent specifically in frail older persons. All studies have included “younger elderly,” but even the most recent has not stratified results by age [539].

- ***Adverse effects:*** The effect of 60mg trospium chloride once daily over 10 days on either learning or memory was assessed in 12 cognitively intact older people (>65 – 75 years). There was no change in standardised testing. Additionally, no trospium was detectable in the CSF of the subjects at day 10 [540, 541]. As part of a larger study of trospuim chloride 20mg bid, 36 (26 completed). Subjects with UUI and dementia, treated with galantamine and trospium) were examined. Subjects with severe dementia were excluded in this

non-randomised, open label study. There was no observable decrement in either cognition, but only measured by MMSE, or ability in terms of activities of daily living in the dually treated group [364].

7. Propiverine

In 46 patients with dementia (mean age 81), there was a 40% decrease in urgency UI with propiverine 20 mg/day for 2 weeks,[542] similar to two small Japanese trials [543, 544]and a German trial in 98 patients.[545] The agent's high protein binding, extensive first pass metabolism, 15-hour half life (in normal younger persons), and renal clearance [542] need to be considered if used in frail older people. There have been no new trials reporting on either efficacy or tolerability in older people.

8. Imidafenacin

There have been no pharmacokinetic studies of imidafenacin in older people [546]. However, a population pharmacokinetic analysis demonstrated that oral clearance was decreased with advancing age, increasing hepatic function parameters (AST and ALP), food intake, and itraconazole co-administration. The absorption rate constant was decreased with food intake [547]. The drug is metabolised by the CYP3A4 system, and it is affected by drugs which inhibit this system [546] . There appears to be no affect on digoxin pharmacokinetics in healthy volunteers [548]. There are no trial data on older patients using this agent.

9. Duloxetine

There was a statistically significantly reduced rate of clearance of duloxetine in patients over age 65, based on a study in 12 fit women aged 65-77.[549] The authors felt the differences were not clinically significant given the "similar safety profile" of the drug in older and younger women. In three large RCTs in women with SUI, aged 24-83 years, n = 494 [none frail];[550] with OAB, aged 21-84 years [none frail], n = 306 [551];and with mixed UI, up to age 85[552]), duloxetine decreased UI and urinary frequency, but none stratified outcomes or adverse effects by age. In a newer randomised controlled study of 265 community dwelling older women, 134 treated with duloxetine, of whom 20% had mild cognitive impairment as classified by the modified mini-mental state exam [553], duloxetine treatment led to a statistically significant decrease in incontinence episode frequency (median percent change 51.6%) versus placebo (32.1%) for stress predominant mixed symptoms, but did not reach significance for stress urinary incontinence (53% v 42%) [554]. Duloxetine is neither approved by the US FDA nor recommended by the UK National Institute of Healthcare and Clinical Excellence.

10. Mirabegron

There are no trials of mirabegron in the frail elderly. There are data on the comparative pharmacokinetics in older people, but not specifically the frail elderly. In available studies, there were no statistically significant differences in mirabegron exposure between older volunteers aged 55 years and above and younger volunteers (18-45 years). Similar results were obtained for those aged 65 years and above. AUC was predicted to be 11% higher in a subject aged 90 years of age [555]

11. Oestrogen

Oral oestriol 3 mg/day was compared to placebo for 12 weeks in 34 women aged 75 [84]. The group was highly self-selected; complete results were available for 11 with SUI, 12 with urgency UI, and 8 with mixed. Two-thirds of urgency UI and 75% of mixed UI patients reported improvement; there was no effect on SUI. Four patients reported metrorrhagia and mastodynia. A 10 week crossover trial comparing quinestradol 0.25 mg four times a day with placebo in 18 women in long-term care (type of UI not reported) found a mean 12% decrease in UI episodes vs 22% increase with placebo.[556] The combination of conjugated oestrogen 0.625 mg/day and progesterone 2.5 mg/day was evaluated in a 6 month, placebo-controlled trial in 32 female NH residents with predominantly urgency UI, who also received prompted voiding [557]. In the 21 women who finished the trial, there was no difference in wet checks between drug and placebo despite increased serum oestrogen levels and partial oestrogen effect on vaginal cytology and pH in the women on drug. Two women on the drug developed vaginal spotting, and 10% developed breast tenderness. Similar lack of efficacy despite vaginal changes were found in a case series of 9 frail women (mean age 83) with urgency or mixed UI using an oestrogen-implanted vaginal ring (Estring ®) [558].

12. Miscellaneous Medications

Readers interested in agents which are seldom used in clinical practice should refer to the 4th International Consultation on Incontinence for data relevant to frail older people for information on:

Emepronium bromide, Flavoxate, Propantheline, Imipramine, Flurbiprofen, Procaine haematoporphyrin.

13. Comparative Trials

We found no studies that compared antimuscarinic agents in frail older persons. Other comparative studies in community dwelling elderly, where relevant, are mentioned above.

d) Summary of the evidence

1. Short-term treatment with oxybutynin-IR has small to moderate efficacy in reducing urinary frequency and urgency UI when added to behavioural therapy in long term care residents. **(Level 2)**

2. Low dose oxybutynin-ER does not cause delirium in cognitively impaired nursing home residents **(Level 1**)

3. Oxybutynin-IR has been associated with cognitive adverse effects in persons with dementia and/or Parkinson's disease **(Level 3)**, although the incidence and prevalence are unknown **(Level 4)**

4. Oxybutynin has been associated with tachycardia **(Level 3)**, but not associated with QTc prolongation **(Level 3)** or ventricular arrhythmia **(Level 2)**

5. Oxybutynin is less effective in persons with impaired orientation, cerebral cortical under-perfusion, and reduced bladder sensation **(Level 2)**

6. Oxybutynin is less well tolerated, versus solifenacin, in older people **(level 2)**

7. Fesoterodine is effective in ameliorating the symptoms of OAB in frail older people, identified by VES-13 **(level 1).** There is insufficient evidence to determine the efficacy, tolerability, and safety of the following agents in the frail elderly **(Level 4)**:

    a. Intravesical oxybutynin

    b. Transdermal oxybutynin

    c. Trospium

    d. Tolterodine

    e. Darifenacin

    f. Solifenacin

    g. Mirabegron

    h. Duloxetine

    i. Oral and topical oestrogen

8. Tolterodine is associated with cognitive impairment and tachycardia **(Level 3)**, although the incidence and prevalence are unknown. **(Level 4)**

9. Solifenacin (5mg/day) is associated with no impairment of cognition in older persons with mild cognitive impairment versus placebo **(level 2)**

e) Recommendations for practice

• A global assessment of the cognitive and "at risk" status of the patient should be undertaken. Unfortunately, the MMSE and ADAS-Cog seem to be insensitive to change in cognitive impairment due to bladder antimuscarinics [527, 559]. Patients that might be at risk of impaired cognition have been well described [348] and consist of those with mild cognitive impairment, long-standing type II diabetes, alcohol misuse, dementia and Parkinson's disease. Those with Parkinson's disease may be exquisitely sensitive [560]. These individuals will need to be carefully assessed, both prior to, and shortly after, initiation of treatment with bladder antimuscarinics. Treatment may necessarily depend upon a global assessment of cognition during the clinical assessment and, if possible, a carer's impression of change. In addition to the of likely benefit from drug treatment, considering the life expectancy and wishes of the patient, account should be taken of total anticholinergic load, as this clearly increases the likelihood of cognitive impairment. There is evidence of cognitive safety of these drugs, for the most part in cognitively intact older adults, and therefore, prescribing bladder antimuscarinics as single agents is, on the whole, probably safe.

• Those studies using high doses (20mg) of oxybutynin are associated with an increased likelihood of causing cognitive impairment, which may not be apparent to either the patient or the clinician. This drug should probably be avoided in the elderly at high dose, and in those at cognitive risk, in any case. The other antimuscarinics should be initiated carefully, at the lowest dose for tolerability, with dose increases where indicated for efficacy, and reviewed early.

• The length of exposure to anticholinergics seems to be important, studies suggest a lack of decline in those with established dementia [349, 561] , but with exposures of at least two years, there is a reported increase in mortality [562-564]. To what extent this is explained by case mix, comorbidity or other factors is not known and will be the subject of further research. Consideration should be given to limiting the overall exposure of antimuscarinics, particularly if in combination with other drugs with anticholinergic properties.

5. SURGICAL TREATMENT IN THE FRAIL ELDERLY

a) Background

Despite ongoing reports concerning the aetiology and pathophysiology of UI in older people, information on surgical management of the frail elderly is scarce [565, 566]. Nevertheless, currently, surgical management of stress incontinence (SUI) in elderly women is the same as in younger stress-incontinent patients [567, 568]. However, the outcomes of anti-incontinence surgery in frail elderly patients may be affected by inherent co-morbidities, as well as impaired bladder and pelvic floor function. There are still very few studies of gynaecological surgery in older frail women, surgical treatment for post-prostatectomy UI in frail men, and minimally invasive procedures, or peri-operative care (including prevention of common postoperative complications) in urological and gynaecological patients. We reviewed the available data and general issues regarding peri-operative care which could improve surgical outcomes in this group. Aspects of surgical treatment of UI in healthy older persons are also covered in 13: Surgery for Urinary Incontinence in Men, Chapter 14: Surgery for Urinary Incontinence in Women, and Chapter 15: Surgery for Pelvic Organ Prolapse.

In providing an evidence-based summary on this topic, we have taken advantage of the recent literature review and research recommendations from

the American Geriatrics Society, New Frontiers in Geriatrics Research: An Agenda for Surgical and Related Medical Specialties. [569]. This project involved systematic literature reviews that were used to generate summary statements and recommendations for research. Their findings and recommendations pertinent to the frail elderly regarding surgical treatment of geriatric UI, geriatric gynaecological surgery, and general care of the geriatric surgical patient are included in the summary statements below. Data supporting these conclusions are available in the monograph [570].

b) Incontinence surgery in frail elderly women

Surgical intervention is considered to be the most efficient and durable approach for the treatment of SUI. A wide variety of surgical techniques have been described, among which the mid-urethral sling procedures have gained worldwide popularity. Since the last ICI report on UI surgical treatment in frail elderly appeared, there are few new data on which to base appropriate recommendations for this group. Several studies have used U.S. national hospital discharge databases to examine surgical rates, but unfortunately they either age-adjusted results [571] or used relatively young cut-off points (e.g., </> 50 years) [572]. Even in series that do specifically look at elderly women (mean age 78, range 68-90), most patients are cognitively intact (95%) [573]. Cognitive impairment appears to bias against having surgery: in one study, only 0.11% of operations for UI were done in women with dementia, cerebrovascular disease, or hemiplegia combined. Despite the fact that absolute numbers of ambulatory UI surgery cases in women increased from 1994-1996, the percent done in those aged > 80 years remained the same (4-5%) [574], with the same proportions for pelvic organ prolapse surgery (5%) [575]. In the US, surgery rates in elderly women vary by region and race [576].

One single-centre, community-based series of 54 patients aged 70 years and above provides a picture of this surgical population. Twenty-eight percent of patients were aged > 80, four resided in a nursing home or assisted living facility, 82% had significant comorbidities, and 32% were classified as American Society of Anaesthesiology class III risk. Intra-operative complications occurred in 11% of patients; postoperatively, 11% required intensive care monitoring, 6% had serious complications, 7% became delirious, and 9% experienced a slow return of bowel function. The authors concluded that discharge planning was especially important for these patients, and recommended presurgical planning with regard to discharge destination and likely need for assistance [577].

Although higher complication rates generally reflect the comorbidity common in frail elders (10.4% complication rate with comorbidity vs. 5.8% without it, p<.001) [572], some studies have found age protective (in one, age >73 years is associated with lower risk of vaginal cuff infection and recurrent prolapse following vaginal sacrospinous fixation [578]). The morbidity and mortality for geriatric patients undergoing anti-UI procedures appear to be similar to those of other major non-cardiac surgical procedures [569]. Mortality is inconsistently associated with increased age, and most strongly related to cardiac or cancer complications [579]. Many studies do not uniformly control for the impact of comorbidity on mortality [579]. Pre-operative administration of oestrogen appears ineffective in promoting wound healing [580]. Patient-controlled analgesia provides adequate pain control and sedation and increased patient satisfaction compared with standard fixed-dose and time administered medications in cognitively intact geriatric patients [580]. Choice of anaesthetic agent may affect postoperative cognition and urinary retention. The use of methyl naltrexone to treat opioid-related urinary retention or constipation may become an important adjunct to surgical care in frailer patients [581]. There are few age-specific data on outcomes available, and no studies systematically examine quality of life, functional outcome, or discharge destination.

With the advent of newer “minimally invasive” procedures, there has come some modicum of use in older, albeit, not frail patients. Injection of bulking agents in women appears to be as little effective in younger women as in elderly patients and age does not appear to relate to outcomes [569]. There are several published reports examining outcomes of tension-free vaginal tape (TVT) in the elderly population. However, most of these studies are limited by short term follow-up, small patient groups and confounding variables [582-584]. Hellberg *et al.* showed that at three months, women ≥ 75 years old had a cure rate of 81.6% compared with a rate of 92.8% in women <75 years old. At later follow-up, regardless of duration since the TVT procedure, the proportion of women with cure for ‘any’ incontinence decreased with increasing age. Women ≥ 75 years old had a cure rate of 55.7%, compared with 79.9% in women < 60 years old (p= 0.0001) [585]. In one single institutional study, authors showed no significant difference in cure rate (85% vs. 91.3%, respectively). However, follow-up was only 10.4 months [586]. In a randomized controlled trial of tension-free vaginal tape (TVT) versus 6-month wait-list control, the intervention group at 6 months had a statistically significantly greater improvement in mean I-QOL score, patient satisfaction score, and urinary problem score [587]. There was no objective measure of cure. Peri-operative complications were common, with bladder perforation by needle in one-in-five (22.6%) which required 24 hours of indwelling catheterisation; urinary retention (12.9%), and less than 5% with either a urinary tract infection or new urinary urgency (3.2%). In an uncontrolled case series examining the use of the suprapubic arch (SPARC) sling procedure, the outcomes in 43

older women (ages 65-91) were separately examined. Objective cure rate was evaluated by clinical and urodynamic examination and subjective cure rate by using a visual analogue score.At a mean follow-up of 36 months (range, 12 - 54 months), objective and subjective cure rates in 997 women were 91% and 95%, respectively [588]. There was statistically significant improvement in pad weight and pad numbers (from a mean of 5 to 0) and the visual analogue score. No severe intra- or post-operative complications were observed, and no patient developed *de novo* urgency UI. In a case series, long-term clinical outcomes following placement of a retropubic mid-urethral sling (SPARC) in patients aged 70 and over were compared with outcomes of a younger cohort. Overall success rate after a follow-up of 4 years was 83.2% in the younger group and 53.1% in the group of older patients (p= 0.0003) [589]. In a comparative prospective single-centre study examining safety and efficacy of TVT-O in elderly versus younger stress-incontinent women, after mean follow-up of 30±17 months early and late postoperative morbidity was similar in both groups, except for significantly more cases of postoperative recurrent UTIs among the elderly women (13.7% vs. 6.2%). Incidence of persistent urodynamically confirmed overt SUI was similar in both age groups (5%). However, asymptomatic urodynamic SUI was significantly more common among elderly patients (19% vs. 3.7%, P<0.05). The incidence of persistent OAB was similar in both groups (68% and 62%, respectively), while *de novo* OAB was significantly more common in elderly patients (11.9% vs. 4.7%, P<0.05) [590].

c) Incontinence surgery in frail elderly men

No specific conclusions can be drawn regarding surgical treatment of UI in frail men. Typical studies of anti-UI surgery in elderly men are very small or fail to stratify results by age and/or comorbidity [591, 592]. One small study (n=46) found that advanced age was not a risk factor for poor outcome after collagen injection for post-prostatectomy UI [593], while another (n=12, mean age 80 years) of trans-urethral resection prostatectomy (TURP) for obstruction-associated urgency UI concluded that cognitively impaired men demonstrated the greatest UI improvement [594]. In a single-institution case series of men aged > 80 years old undergoing TURP (68% of whom had urinary retention), 80% were satisfied with their outcome. Of the men with retention, 80% were able to void with a small PVR by six weeks. Complication rates were 41% (early) and 22% (late) [595]. Urodynamic evaluation of post-prostatectomy UI was recommended prior to surgical treatment, such as implantation of an artificial sphincter [592].

d) General issues in surgical care of the frail elderly

Important factors in the surgical care of frail patients include: preoperative risk stratification (e.g., American Society of Anaesthesiology class, Charlson index, Modified Cardiac Risk Index , Burden of Illness Score [596]; ensuring adequate nutrition, especially when patients cannot take oral feeding or become delirious; proactive management of comorbid heart disease, diabetes, and pulmonary disease; prevention [597, 598],recognition [599], and treatment of postoperative delirium [600]; adequate pain assessment and treatment, especially in cognitively impaired persons [601]; recognition of the hazards of prolonged bed rest [602] and the prevention [603] and treatment of functional impairment; use of specialised care units for the elderly [604]; and discharge planning regarding rehabilitation, need for assistance, and site of discharge. All need to be actively considered and dealt with in any plan of surgical care of frail elderly patients.

e) Summary of evidence

1. No studies were identified regarding gynaecological surgery in institutionalised elderly women. **(Level 4)**

2. Exogenous administration of oestrogen is ineffective in promoting wound healing after gynaecological surgery in older women. **(Level 3)**

3. Injection of bulking agents for SUI appears to give minor benefit in women, however the technique is minimally invasive and age does not appear to correlate with outcomes.**(Level 3)**

4. No studies were identified that evaluate functional or quality of life outcomes after UI surgery in frail older persons **(Level 4)**

5. Risks of morbidity and mortality for frail patients undergoing anti-UI procedures are similar to those of other major non-cardiac surgical procedures. **(Level 2)**

6. Surgical mortality risks are still low in elderly persons, and when deaths do occur, they are often due to cardiac or cancer complications. **(Level 2-3)**

7. Operative mortality is inconsistently associated with increased age, and many studies do not uniformly control for comorbid conditions. **(Level 2-3)**

8. Patient-controlled analgesia provides adequate pain control and sedation and increased patient satisfaction compared with standard fixed-dose and time-administered medications in cognitively intact geriatric patients. **(Level 2)**

9. Choice of agent for patient-controlled analgesia may affect postoperative cognition. **(Level 3)**

10. Some case series and waitlist-controlled trials suggest that minimally invasive surgical approaches may be useful in older adults, yet these trials may have little to do with whether surgical treatments are appropriate in the frail elderly **(Level 3)**

f) Recommendations for management

a. Age alone is not a contraindication to surgical treatment of UI **(Grade C)**.

b. Urodynamic evaluation should be done before considering surgical treatment of UI in frail older persons **(Grade B)**.

c. Preoperative risk should be stratified using established indices **(Grade A)**.

d. Ensure adequate post-operative nutrition, especially in patients who cannot take oral feeding or who become delirious **(Grade C)**.

e. Programmes to prevent post-operative delirium should be utilised **(Grade A)** along with proactive use of established measures to diagnose delirium **(Grade A)**.

f. Pain assessment in cognitively impaired persons should use measures specially-designed for this population **(Grade B)**.

g. Proactive preventative approaches to hospitalisation-related functional impairment should be used **(Grade A)**.

h. Specialised care units may improve selective outcomes for frail older patients **(Grade A)**.

i. Discharge planning should begin before surgery takes place **(Grade C)**.

j. Patient controlled analgesia can be used in cognitively-intact frail older persons **(Grade B)**.

k. Analgesic agents associated with delirium (e.g., meperidine) should be avoided **(Grade B)**.

l. Long-term outcomes before the operation should be discussed with the patient **(Grade C)**.

g) Recommendations for research

- Inclusion of older-old and frailer patients in surgical studies, with stratification of outcomes by age, comorbidity, oestrogen status (women), and urodynamic findings
- Prospective studies to determine the magnitude and severity of common geriatric complications following anti-incontinence surgery
- Develop and validate guidelines for identifying frail elders who would benefit from gynaecological/ urological anti-incontinence surgery

6. CATHETERS

a) Background

The use of indwelling urethral catheters (IDC) is clinically indicated in a limited set of circumstances (see Box 1) and should not be considered as a substitute for nursing care of the frail older person with incontinence [605]. Despite this recommendation, a number of studies report potentially inappropriate IDC use in frail older adults. The information in this section reviews research on rates of IDC use in the frail elderly; the appropriateness of IDC use in this population; complications (morbidity and mortality); management recommendations and recommendations for research. Detailed discussion of key issues related to catheters more broadly, including intermittent catheterisation, is provided in Chapter 20.

Box 1. Appropriate Indications for Indwelling Urethral Catheter Use

- Patient has acute urinary retention or bladder outlet obstruction
- Need for accurate measurements of urinary output in critically ill patients
- Perioperative use for selected surgical procedures:
- Patients undergoing urological surgery or other surgery on contiguous structures of the genitourinary tract
- Anticipated prolonged duration of surgery (catheters inserted for this reason should be removed in PACU)
- Patients anticipated to receive large-volume infusions or diuretics during surgery
- Need for intraoperative monitoring of urinary output
- To assist in healing of open sacral or perineal wounds in incontinent patients
- Patient requires prolonged immobilisation (e.g., potentially unstable thoracic or lumbar spine, multiple traumatic injuries such as pelvic fractures)
- To improve comfort for end of life care if needed

Healthcare Infection Control Practices Advisory Committee [2009]

b) Quality of the data

Some of the difficulties in conducting research on use of IDCs are discussed in Chapter20… We located a number of articles on the use of catheters in frail older persons. These largely described the prevalence of catheters in this population. Few studies addressed the specific complications associated with IDC in frail older adults. It is therefore difficult to determine the relative effect of frailty and ageing on the incidence and prevalence of IDC complications. There is a lack of research on the use of catheters for individuals with terminal illness (i.e. end of life care), and for different cultural groups of frail older persons. Although intermittent catheterisation is associated with fewer risks compared to IDC use, there is limited research on its use in this older group. Guidelines and recommendations that apply

to the IDC use in other populations equally apply to IDC use in frail older adults. Catheter use should be avoided wherever possible and only adopted for those in whom alternative strategies are unsuitable or unsatisfactory, after careful assessment of the patient and their particular problem [606].

c) Rates of IDC use in frail older adults

Despite the presence of guidelines cautioning their use, IDCs are used to manage urinary incontinence and other conditions in a substantial number of frail older persons in long-term care facilities, in the community, and in acute care. The lowest rate reported in the reviewed literature was 3% of women in Swedish nursing homes [607] and the highest was 38.1% in frail older community-dwelling women in Italy who were listed on a Home Health Agency database [608]. In a one-day point prevalence survey conducted in 2009 involving 2625 residents from 78 nursing homes in Sweden, 50 (3%) of women and 135 (16%) of men had an IDC. Just over half (58%) had had their IDC at the time of admission to the facility. For many of those who had their IDC inserted since their admission, the catheter was inserted during a temporary stay at hospital [607].

Data from the US Department of Health & Human Services, Centres for Medicare and Medicaid Services (third quarter of 2010) [609] indicates that, in the USA, 7% of residents in long-term care facilities have an IDC, however rates vary between states (4.5% to 12.3%). This finding compares with 7-10% of residents in 1987 [610] and research reported in 2003, from the USA National Nursing Home Survey for 1995 to 1999, on the prevalence of urinary incontinence among female nursing home residents, when 9.5% to 11.7%% had an IDC or ostomy [611]. A web-based point prevalence survey of nursing home-associated infections (NHAI) conducted in 2005 in 133 USA Veteran Affairs homes, [612] found 1233 (10.7%) of 11475 residents had an IDC and was reproduced in a follow-up survey conducted by the same researchers in 2007 [613]. Rogers and colleagues [256] analysed data from 57,302 residents admitted to skilled nursing facilities in USA in 2003, and reported that 0.5 million nursing home residents have some form of catheter, and rates vary from 12.6% at admission to 4.5% ($P<0.001$) at annual assessment. IDC use was associated with male sex, and with conditions such as paraplegia, quadriplegia, multiple sclerosis, diabetes mellitus, renal failure, skin conditions, deep vein thrombosis, aphasia, or end-stage disease, obesity, taking more medications, as well as those who are comatose.

Rates of IDC use in nursing homes in the UK appear relatively stable over time. Based on 2001 survey data from 1125 residents in different healthcare settings for the elderly, 5% (0-20%) of individuals living in residential homes in the UK had an IDC, 10% (0-44%) in nursing homes, and 6% (0-20%) in long-stay wards [614]. Similar rates were reported by McNulty and colleagues in 2003 based on a sample of 4900 residents from registered nursing homes [615]. and from a more recent survey involving 3190 residents from 92 homes, where 8% of resident had an IDC, although rates varied considerably with one facility having up to 47% of residents with an IDC [616]. In 57% of care homes, residents received their IDC as a hospital inpatient [616]. A more recent audit of continence care in UK conducted across England, Wales, and Northern Ireland estimated that 13% (62/488) of individuals living in care homes had an IDC [245]. These rates are consistent with IDC rates in individuals living in long-term care facilities in Canada, which range from 5% to 10% [617].

Estimating the prevalence of IDC use in frail older adults living in the community is more difficult as community samples differ, as do methods to define and measure IDC use. With the exception of one study, prevalence data do not differentiate between IDC use among frail and non-frail older community-dwelling individuals. One of the earliest reports on rates of IDC use in the community was based on a sample of individuals receiving district nursing home care in the UK. During the four weeks of data collection (Feb 1987) a total of 1709 patients were being attended by the district nursing services, with 61 (4%) known to have an IDC. In a larger context, the population for the health authority was 178,300 of whom 61 (0.03%) were patients aged from 22-95 years living in the community and had an indwelling urethral catheter (mean age 67.6 years, SD 19.56)." (p44) [618]. A more recent prospective, population-based survey of 4 010 older people >65 years of age (mean age 82.3) receiving home care in 11 European countries, found that 5.4% (range 0–23%) of their sample had an IDC [619]. IDC use was more common in men than in women (11.5% versus 3.3%). Rates also differed between countries, ranging from 0% in the Netherlands to 23% in Italy. High rates of IDC use in Italy were also reported in data from 12 Home Health Agencies that provided care for 1004 frail older community-dwelling women (mean (SD) age 83.3 (9.5) years). The researchers reported that in this sample the prevalence of incontinent patients with a catheter was 38.1% [608].

Although some frail older adults are catheterised during an admission to acute care, others are admitted with an IDC in situ. Lakhan and colleagues conducted a prospective cohort study to identify the prevalence of geriatric syndromes at preadmission, admission and discharge, and to determine the incidence of new and significant worsening of existing syndromes at admission and discharge. In their sample of 577 patients aged 70 and older who were admitted to a general medical unit of large acute care hospitals, 22/577 (3.8%) had a pre-morbid IDC (within three days prior to the acute illness precipitating admission). IDC rates increased to 98/577 (17%) in the admission period, and decreased to

47/577 (8.1%) at discharge. Although rates of IDC use decreased before patients were discharged from acute care hospitals, more elderly patients were discharged with an IDC than those who were admitted with an IDC [620].

d) IDC for end of life care

Incontinence is experienced by many patients toward the latter stages of a terminal illness. Although IDCs are indicated 'to improve comfort for end of life care if needed' [605], we found little evidence about managing incontinence for end of life care, or about IDC use in this context. According to the findings of one study, involving 61 patients with terminal illness due to cancer admitted to a palliative care unit (PCU), IDCs may be used in up to 75% of such patients [621]. In this study, 38% (n=23) admitted to the PCU had an IDC in situ prior to their admission and another 36% (n=22) were catheterised during their admission. Complications associated with the use of IDCs in this cohort included: bacteriuria (n=28), encrustation (n=8), bladder spasms (n=4), fever (n=2), and urethritis (n=2). Despite these complications, staff cited 'patient comfort' as the main rationale for the use of an IDC. Clearly, further research is warranted to guide clinical care in this area.

- **The appropriateness of IDC use in frail older adults**

Despite guidelines for appropriate IDC use, a number of studies report potentially inappropriate IDC use in older adults. For example, Landi and colleagues report that of their sample of frail older community-dwelling women with urinary incontinence and IDCs, 50% were catheterised without any reasonable justification [608]. Overuse of IDCs is however not limited to community-dwelling frail older adults. Two studies draw attention to potentially inappropriate IDC use for older people admitted to acute care hospital settings. Gokula and colleagues for example found appropriate indications for IDC use for only 46% of 2845 elderly patients admitted to a large teaching hospital in the US [622]. They reported that only 13% of charts contained information on the reason for the catheter and 33% of charts contained no written order for catheterisation. Similar findings were reported for 133 elderly patients who had an IDC inserted whilst inpatients of a 450-bed, tertiary-care university hospital in central Thailand. Twenty-eight percent of medical records lacked information about the reason for the IDC. The presence of urinary incontinence was cited as a reason in 18% of cases [623].

Anomalies in the use of IDCs were also reported by McNulty and colleagues who found that "almost all homes (114/124, 92%) stated they had an infection control policy, however 31% (38/124) had no written policy on urinary catheter care" [615]. In a later qualitative examination of reasons for variation in IDC use in care homes, McNulty and colleagues found that 'care homes with a lower urinary catheterisation prevalence, had a more proactive approach to management of continence, using structured toileting regimes and encouraging residents' mobility' [624] (p. 709).

- **Complications - morbidity and mortality**

The complications associated with IDCs are well documented and are comprehensively addressed in Chapter20….. However, with respect to frail older adults with an IDC, Kunin and colleagues report the morbidity associated with use of an IDC in residents of a skilled nursing facility is threefold even after adjusting for other factors [625]. This finding also holds true for community-dwelling frail older adults with an IDC [608]. Among residents of Department of Veteran Affairs (VA) long term care facilities in the USA, 1205 of 10939 residents had an IDC and of these, 135 (11.2%) had a nursing home-associated infection. Residents with some form of indwelling device had a three-fold increased risk of a nursing home-associated infection ($P < .0001$). These factors make it imperative that IDCs are used to manage incontinence only when other methods of managing have been excluded.

e) Management recommendations

As noted in Chapter 20, IDCs should be avoided wherever possible and only adopted for those in whom alternative strategies are unsuitable or unsatisfactory, after careful assessment of the patient and their particular problem [606]. Interventions designed to minimise IDC in frail older adults are the same as those for other populations of IDC users. Interventions include, but are not limited to: the development and dissemination of guidelines, quality indicators, and regulatory initiatives; educational approaches; and promoting intermittent catheterisation as an alternative method of management. Interventions to minimize and address complications associated with IDCs are comprehensively addressed in Chapter 20.

Another approach designed to decrease the inappropriate use of IDCs, and to ensure optimal IDC management is the use of assessment protocols. Regulatory processes in the USA mandate that all newly admitted Medicare/Medicaid funded residents receive an assessment using a standardised form called the Minimum Data Set (MDS). A further level of assessment is triggered when/if a resident is newly incontinent and the Resident Assessment Instrument Minimum Data Set is completed (RAI-MDS). This assessment information in turn, acts as a prompt for staff to design an individualised care plan based on direct contact with residents, appropriate staff, and through use of observation, interviews and record reviews. The MDS and RAI are now used in a number of other countries, including Canada and Iceland, and other countries have developed their own assessment instruments. Ideally, these assessment

instruments should prompt staff to enquire about whether the residents' IDC is medically warranted, and to identify IDC related problems, and care plans should contain information about an individualised IDC care plan (including the frequency of IDC changes and ongoing maintenance).

The assessment process used in the USA is strengthened by the fact that it is linked to quality indicators. Since, 2005 facilities have been required to use information from the residents' comprehensive assessment to provide assurances that:

- o IDCs are used for only medically valid reasons;
- o IDCs are removed as soon as clinically warranted;
- o efforts are applied to restore or improve bladder function as much as possible; and
- o efforts are made to prevent infection while the IDC is inserted [626].

It remains to be seen if these measures will reduce IDC rates in long-term care, and how they will impact day-to-day IDC use and care at the clinical interface. However, similar regulatory approaches should be considered by government and health agencies in other countries.

f) Intermittent catheterisation as an alternative to IDC in frail older adults

Intermittent catheterisation (IC) involves the act of passing a catheter into the bladder to drain urine via the urethra, or a catheterisable channel such as a Mitrofanoff diversion. It avoids many of the problems associated with IDC. Many patients with neurological urinary incontinence perform IC. While IC is performed using a sterile technique in healthcare environments, some patients intermittently catheterise themselves using a clean technique in their own home environment. Advanced age should not constitute a barrier to IC. Pilloni and colleagues (2005) for example, found that of 21 elderly patients in whom IC was initiated because of voiding dysfunction, 12 learnt to catheterised themselves, seven were catheterised by their partners and two by nurses. The majority (18/21) reported improvements in their quality of life [627].

g) Research recommendations

- Further research is required on:
  - o Rates of IDC use in various populations (especially in community-dwelling frail older adults and those admitted to acute care)
  - o Managing incontinence for end-of-life care
  - o The effectiveness of interventions to minimise inappropriate use of IDCs such as the development and dissemination of guidelines, educational approaches; the development and dissemination of quality indicators; and regulatory initiatives; and intermittent catheterisation Efficacy and effectiveness of specific devices and procedures to prevent complications from long term indwelling catheters in frail elderly

V. NOCTURIA IN THE OLDER ADULT

1. BACKGROUND

Nocturia is defined as waking at night from sleep one or more times to void, with each void being preceded and followed by sleep.[628] Having a standardised definition is meaningful for the field, but this specific definition is problematic for several reasons. While a single episode of awakening to urinate would be considered nocturia, patients are more likely to be experience significant bother and have decreased quality of life [629], or consult a provider about nocturia if they have three or more episodes.[630] Many clinical trials include only participants with two or more episodes [631]. Additionally, if only a void interrupting sleep and preceding sleep counts, the annoying situation of waking to void and not being able to return to sleep again would not be nocturia, but would still be disruptive [632]. This definition does not take into account the wide range of sleep patterns of older adults. Since some older adults will spend six hours sleeping while others might spend twelve hours in bed, having three episodes of nocturia would be very different for these individuals [633].

Several detailed reviews on nocturia [634, 635] and two convened consensus conferences reports [631, 636] have helped summarise and update the current knowledge regarding nocturia. Even with these sources, the prevalence, impact, pathophysiology, diagnostic assessment, and treatment of nocturia differ meaningfully with respect to the older adult and the frail elderly [633] and merit a targeted discussion. As is the case with urinary incontinence, nocturia often results from the reduced physiological reserve of multiple systems. Because of this fact, diagnostic assessment must be detailed and comprehensive, and multi-component interventions may be necessary for successful treatment.

2. QUALITY OF THE DATA

There are multiple, quality sources of epidemiological data across a broad range of countries and cultures regarding the prevalence of nocturia and associated risk factors. There is a smaller, but growing, body of evidence regarding the incidence and impact of nocturia. In particular, studies of the pathophysiology of nocturia in the elderly have generally been small and disease-focused, examining a single, potential underlying cause of nocturia. As with UI, there are limited data on optimal diagnostic assessment, and therefore recommendations are generally based on expert opinion.[628, 637] The evidence base regarding treatment, particularly with

respect to the frail, is somewhat thin. While there are some treatment RCTs, they are small, include few very elderly subjects. The treatment literature regarding vasopressin and its analogues is robust, yet use of the therapy in the older patient continues to be limited because of the side effect of hyponatraemia. We located no randomised controlled trial data on the effectiveness of multi-component interventions for nocturia in the elderly.

3. PREVALENCE, INCIDENCE, AND IMPACT

The prevalence of nocturia increases with age, and has been reported to be as high as 90% for one episode per night in persons over age 80.[638-643] The prevalence of two or more episodes among men between 70 and 79 is nearly 50 percent.[643, 644] This increasing prevalence is largely due to age-related conditions that underlie the pathophysiology of nocturia (see below). With respect to gender, nocturia for young adults is more common in women than in men, but this gender ratio reverses after age 60 when more men have nocturia.[644] For those over 75 years of age, the prevalence of nocturia of at least two or more times is much more common in men (70%) than in women (50%) [645].

While higher age is associated with more nocturia, what happens to nocturia, as an individual ages, is a slightly different question. Nocturia is more prevalent in older populations, yet the concept of incidence of nocturia is difficult as the condition both “begins” and “resolves” over time and varies due to imprecision of self-reporting and estimates as to the frequency over a past period of time. In one recent study, participants recorded their urination frequency and voided volumes. Over a 2-year period, the incidence rate of nocturia of an average of two or more times per night was 23.9% and the resolution rate was 36.7%. For the oldest adults participating (70-78 years), they had the highest nocturia incidence (47.1%) and the lowest resolution rate (26.2%) compared to their younger counterparts [646].

Recent data have also highlighted that the prevalence of nocturia in older adults differs by racial group. Multiple population-based epidemiological studies have shown a higher prevalence of nocturia in older men and women who are African-American when compared to whites [643, 647, 648]. While controlling for socioeconomic factors eliminated the differences in prevalence between non-Hispanic whites and Hispanics, differences persisted, although somewhat attenuated, between blacks and whites [649].

Nocturia is also associated with chronic medical conditions such as hypertension and diabetes,[650, 651] advancing renal insufficiency [652, 653] and cardiovascular disease.[654, 655] Clinically, nocturia may be the herald symptom of significant underlying medical conditions and problems, which, if overlooked, might result in significant morbidity and even mortality [631]. Therefore, an older patient bringing up nocturia should be evaluated not only for the causes of nocturia, but also for unrecognised comorbidity, including cardiovascular disease, sleep apnoea, restless leg syndrome, moderate alcohol usage, poor nocturnal glycaemic control, and conditions causing nighttime pain [631].

Nocturia is associated with other important conditions. Nocturia has been shown to be associated with accidental falls.[185, 656] Frail elderly persons with nocturia, who also have gait and balance disorders and other risk factors for falls, are clearly at increased risk for falls [657], injury and hip fracture [658], and consequent morbidity [659]. Despite these facts, no nocturia treatment trials to date have evaluated any impact on fall reduction. Nocturia also has adverse effects on quality of life [660], including an increased risk of depression and poor self-rated health, probably as the result of the impact on sleep [661]. Adults with nocturia also complain that nocturia “makes them feel old” and they worry about falling at night [662] Older individuals described nocturia as simultaneously debilitating, frustrating, distressing and puzzling [663].

To better appreciate the deleterious effects of nocturia, it is important to understand the effects of disrupted sleep [636, 664] When a group of 1,424 elderly individuals, ages 55–84 were presented with a checklist of symptoms that potentially disrupt sleep, nocturia was chosen by 53% of the sample as a self-perceived cause of “every night or almost every night”. Nocturia was cited four times as frequently as pain, which was the next most identified cause of sleep disruption [665]. There is growing evidence to suggest that bother from nocturia is related to the number of trips to the bathroom, but also with the difficulty experienced in trying to return to sleep.[632, 664, 666] In particular, those with nocturia who report difficulty going back to sleep, the prevalence of falls is higher [666]. While the relationship between nocturia and sleep disruption might appear to be self-evident, other lower urinary tract symptoms are also highly correlated with sleep disturbances. [667]

There has been recent and meaningful development in understanding the impact of nocturia on quality of life. A condition-specific instrument commonly used for assessing the impact of nocturia is the ICIQ-NQOL [668], which was developed using a pool of only men (average age 68.2, age range 32-88) recruited from urology practices. Given the absence of women and the likely predominance of men with benign prostatic enlargement as informants, there remains a chance that the instrument does not broadly represent the experiences of all individuals who have nocturia. Other focus groups and one-on-one interviews performed independently with a broader representation of both men and women did demonstrate similar themes, suggesting content validity.[662] Two missing themes,

however, were that nocturia was an “indication of getting older” and made them fearful of falling. Use of the Nocturia Nocturnal Enuresis and Sleep-interruption Questionnaire, which was specifically developed in older men and older women (60-80), showed a greater impact of nocturia in the younger elderly and a greater bother among women compared to men.[663] Use of the generic quality of life instrument, the 15-D, demonstrated statistically significant and clinically meaningful decreases in 15D score and in all 15D dimensions except eating with increasing nocturia.[629] In this study, older women were less bothered by nocturia than were younger women; older and younger men were equally bothered [629].

Notable recent work has shown nocturia to be associated with mortality [659, 669, 670]. It is unlikely that nocturia directly contributes to mortality; nocturia certainly marks other conditions (poorly controlled diabetes mellitus, congestive heart failure, worsening renal insufficiency) associated with bad outcomes. Whether or not these associated conditions should be statistically controlled for is not clear, as they might represent a part of the causal pathway. The association with mortality when examined across the age spectrum shows a stronger relationship with younger than with older individuals [669]. With careful controlling for comorbidities, this association between mortality and nocturia sometimes remains independently significant [671] and other times does not [672]. Though much of the impact of nocturia is believed to result from its impact on sleep, nocturia remains independently associated with mortality even with controlling for sleep disordered breathing [673].

4. PATHOPHYSIOLOGY

The pathophysiology of nocturia is considered to be multifactorial; this is the case for nocturia in elderly persons as well. In age-adjusted analyses from a large survey in Finland, no single factor related to nocturia was present in greater than 50% of those with nocturia [674]. The factors with the greatest impact at the population level were (urinary) urgency, “benign prostatic hyperplasia”, and snoring for men, and overweight and obesity, urgency, and snoring for women [674].

A commonly used framework for clinical diagnosis and treatment is that nocturia can be related to one or a combination of three primary underlying causes, all of which increase with age: low bladder capacity usually as a component of OAB, DO, urgency UI, or BOO in men; nocturnal polyuria; and primary sleep disorders.[634, 635, 675] Nocturia was shown in retrospective analysis of 213 cases (mean age 72) who had detrusor overactivity, out of a total of 777 men studied using pre-operative urodynamics to be highly associated with volume at which the first detrusor contraction occurred [676]. Somewhat in contrast, in one prospective case series of 987 ambulatory women aged 55-75 years, a higher post void residual (>200 mL, 100-199 mL, 50-99 mL versus <50 mL) was not associated with reporting more nocturia [677].

The proportion of 24-hour urine volume produced at night increases with age, even among healthy older adults free of overt comorbid conditions.[678, 679] Studies of frail elderly have shown that the proportion of urine produced at night is close to 50%, rather than less than 30% as in young healthy adults. [680-682] Nocturnal polyuria (NP) is more common in older compared to younger nocturics [683-685] In some elderly persons, this is due to mobilisation of excess volume caused by peripheral oedema, which may be due to venous insufficiency, medications, and/or heart failure. In the case of calcium channel blockers, women younger than 55 years of age, but not older women or men, were shown to have higher rates of nocturia in cross-sectional analyses [686]. In that same study, both hydrochlorothiazide and loop-diuretic usage in men were associated with higher rates of nocturia.

Some studies have suggested that there is an abnormality in the secretion and/or action of arginine vasopressin (AVP) or a loss of the normal diurnal rhythm (with inappropriately low values at night) in many elderly patients with nocturia. [687, 688], which may approach as many as 4% [687]. Another, however, failed to find an association between AVP deficiency (detected by water deprivation testing) and nocturnal polyuria in a series of elderly persons with nocturia. [689] Other research suggests that some frail elderly persons with nocturia have high atrial natriuretic peptide (ANP) levels at night; [690, 691] however, these investigators did not use echocardiography or brain natriuretic peptide levels to detect occult heart failure.

Sleep disordered breathing and sleep apnoea, have also been associated with nocturia and nocturnal UI in the elderly.[690, 692-694] Community-based elderly populations who have higher levels of sleep disordered breathing (>25 breathing events per hour), have nearly double the number of nocturia episodes compared with those with low rates of sleep apnoea [695]. Nocturia is so tightly associated with sleep apnoea that in a population of adult patients presenting to a sleep clinic, it performed similarly as a screening question for OSA when compared to asking about “snoring’ [696]; whether or not this held true for the subset of older patients was not reported. Whether this relates to increased ANP production,[690] mechanical forces on the bladder generated during apnoea events,[693] or other mechanism(s) is unknown.

5. DIAGNOSTIC ASSESSMENT

The approach to the assessment of nocturia should be similar to that for UI described above. Special considerations include:

- A frequency-volume chart of at least 24 hours duration that includes timing and volume of each void at night as well as during the day, as well as a specific indication of when the individual went to bed with the intention of going to sleep at night and awoke in the morning. Some patients may find this difficult to perform,[697] but face-to-face explanation of the procedure, a hand-held urinal or a receptacle to place in the toilet to measure volumes, and involvement of caregivers may improve compliance and accuracy.

- Additional questions in the history that focus on the possibility of a primary sleep disorder, such as asking about sleep quality, daytime sleepiness, snoring, and leg movements at night (this history is enhanced by questioning the bed partner).

- Additional history and focused physical examination related to volume overload (e.g., lower extremity venous insufficiency, congestive heart failure); in some cases additional testing such as an echocardiogram or a brain natriuretic peptide level may be helpful in ruling out the latter diagnosis.

6. TREATMENT

While many clinical investigations are trials of single agents, experts [633] would argue that treatment of nocturia in elderly patients should be based on a holistic approach informed by identification of multiple potential underlying causes. There is, unfortunately, little high quality evidence for most treatments, and certainly with respect to combined treatments, for nocturia in this age group. As well, cure, or the complete resolution of nocturia, is infrequently achieved in either clinical practice or research.

The most common primary outcome in clinical trials is reduction in nocturia episodes, as measured by voiding diary or self-reported, average nocturia over a given period of time. Some trials have reported the percent of participants who achieving a 33% [698] or 50% [689, 699-702] reduction in nocturia from the baseline level or the percent of individuals having a reduction equal to 1.0 fewer mean nightly episodes of nocturia [699, 701, 702]. There are few treatments that offer robust reductions of nocturia, with most ranging from 0 to 0.8 fewer episodes of nocturia. The net reduction of an intervention, subtracting the benefit seen in the control or placebo arm is often even smaller. Whether this is due to regression to the mean due to random variation in the symptom of nocturia or a result of monitoring and recording night-time voids is unclear. Patient-level outcomes related to general satisfaction questions, nocturia-related bother, and nocturia-specific quality of life are therefore even more meaningful. Most trials examining nocturia as an outcome were performed prior to the validation testing of the ICIQ-NQOL instrument.[668] An additional important target for therapy is reduction in bother due to nocturia. Unfortunately, there have been few meaningful successes in relating the number of nocturia episodes to the hours spent in bed, which may vary considerably in older persons. [633]

There are several approaches to drug therapy for elderly patients with nocturia; most of the published guidelines suggest targeting “primary” or “principal” causes of nocturia (e.g., nocturnal polyuria). Because older adults with nocturia have multiple potential causes, treatment often will require combination treatment. While some trials may report statistical significance for reduction in nocturia, the clinical meaningfulness of these changes is suspect.[703] Although no specific data are available on RCTs of multi-component interventions, elderly patients with nocturia may benefit from an approach to treatment [704] that combines behavioural strategies, therapy for medical and sleep disorders, and nocturia-specific drug therapy. In another uncontrolled study, lifestyle modifications of 1) restriction of fluid intake, 2) refraining from excess hours in bed, 3) moderate daily exercise and 4) keeping warm in bed resulted in a positive reduction of nocturia from 3.6 episodes per night to 2.7 for 56 participants aged 59-85 (mean age 74.5, 84% male) [705]

a) Behavioural approaches and treatment of comorbidity.

The use of specific behavioural strategies (e.g. altering fluid intake, reducing sodium intake, leg elevation for oedema) on nocturia in older patients have largely been made on the basis of consensus. Using bedside commodes or urinals, and minimising the distance necessary to reach a toilet and providing a safe, adequately lit path may be helpful in reducing the risk of night-time falls related to nocturia, especially in those with underlying gait instability and other risk factors for falls.

The first secondary data analysis of a RCT which demonstrated that behavioural therapy, with an emphasis on pelvic floor muscle exercises and urgency suppression strategies, showed that nocturia was reduced in women (mean age 68) with urgency-predominant UI.[699] The median reduction of 0.5 episodes per night was significantly more effective than drug treatment with oxybutynin IR titrated from 2.5mg per day to 5.0 mg three times a day, (0.3 episodes) or placebo (no reduction). A second secondary data analysis of an RCT, that did not show benefit with respect to the primary endpoint of urgency incontinence in women (mean age 55), did not show benefit of behavioural therapy when added to tolterodine 4 mg LA for nocturia. [706] An additional RCT in men (mean age 64) examined the impact of the addition of either titrated bladder relaxant therapy (oxybutynin XL 5-30mg) versus behavioural therapy for pelvic floor muscle exercise in whose 24 hour urinary frequency was not resolved with alpha-blocker therapy. In this trial, nocturia was a secondary outcome. In this study, the behavioral group showed greater reductions in nocturia (mean

= -0.70 vs. -0.32 episodes/night; P = .05) [707]. There are currently no trials of pelvic floor muscle exercises or urgency suppression strategies where individuals were enrolled on the basis of having nocturia with reduction in nocturia as the primary outcome.

b) Pharmacotherapy

1. Antimuscarinic therapy

Members of a recent nocturia consensus conference agreed on the following statements with regards to overactive bladder and antimuscarinics: 1) most patients with nocturia do not have overactive bladder; 2) most patients with OAB do have nocturia; 3) antimuscarinics are not usually efficacious for nocturia; and 4) antimuscarinics may be effective for nocturnal voids due to urgency.[631] In general, if the history, bladder diary, and physical examination suggest that nocturia is related primarily or in part to OAB/DO/urgency UI, then treatment with an antimuscarinic agent should be considered (see Pharmacological Treatment above). There are several trials examining the effect of antimuscarinics for nocturia reduction, including trials of oxybutynin-IR, [699] solifenacin, [708] and tolterodine [709, 710]. Four recent trials have compared placebo to active drug for nocturia without statistical improvement. [711-714] There is evidence to suggest that these agents may be best used in combination with other therapies [715] rather than as single modality therapy. Even when agents from this category have shown statistically significant reductions in nocturia, the net benefit of reduction in nocturia (above that effect shown with placebo) is only by 0.0 to 0.3 episodes. A recent "positive" trial showed a statistical advantage of solifenacin 10 mg over placebo of a net difference of -0.12 episodes per night.[716] Tolterodine demonstrated statistical reduction in nocturia accompanied by urinary urgency (but not overall nocturia). [710] The clinical importance of nocturnal urgency is evident to the patient with the symptom ("I would like to not wake up and have to rush to the bathroom"), but this outcome is not fully nor well established within the literature. Use of anticholinergic medications should be used with caution in at-risk individuals as they may cause worsening of confusion.

2. Agents directed towards benign prostatic obstruction

Alpha-adrenergic agents used in patients with symptoms suggestive of BPO have a modest impact on nocturia, with a mean reduction of slightly less than one episode per night.[689, 717]. 5-alpha reductase inhibitors [689] and saw palmetto (Serenoa repens, saw palmetto berry extract) [718] have not shown statistical benefit for nocturia except in one study within one subset of participants age >70.[719] This statistical advantage did not persist beyond one year, and the net benefit compared to placebo was a difference of < 0.2 fewer nocturia episodes.

3. Other medication approaches

Among postmenopausal women, one uncontrolled trial of oestradiol in combination with a progestogen showed a dramatic reduction in nocturia over 6 months, [720] but this was not replicated in another RCT. [721] There are few studies that have focused on treatment of nocturia with the use of medications for sleep. One RCT evaluated melatonin for treatment of nocturia associated with BOO in older men. [722] Melatonin showed only a trend towards reduction in nocturia compared to placebo (-.03 and -0.05 episodes from baseline 3.1 episodes, respectively) but did significantly reduce reported bother from nocturia. A second study compared the addition of either melatonin or a sedative hypnotic (rilmazafone) to older men and women (mean age 72) who were already taking a medication for nocturia, and found the addition of either treatment further reduced nocturia one episode (from 3.5 to 2.5 in both groups) [723]. Reducing volume overload associated with lower extremity venous insufficiency or congestive heart failure with a late afternoon dose of a rapid acting diuretic may be helpful in reducing nocturnal polyuria and nocturia in selected patients. [724, 725] Diuretics (specifically bumetanide and furosemide) have been conferred Level 2 evidence, Grade C recommendation by the Committee for Establishment of the Clinical Guidelines for Nocturia of the Neurogenic Bladder Society. [726] Treating sleep apnoea with continuous positive airway pressure can reduce nocturia severity, but these trials have not usually included the frail elderly. [727] Treatment with very short-acting benzodiazepines for patients with primary insomnia, and with dopaminergic agonists for patients with restless leg syndrome, may improve sleep quality, but there are no data to support these approaches.

4. Anti-diuresis treatment Desmopressin

Most older patients with nocturia have increased nocturnal urine output, which is less common in younger patients [685]. This having been said, the value of classification of patients (according to the presence or absence of NP) has not been demonstrated to be a meaningful predictor of efficacy, or lack of benefit, for any treatment, including prediction of response to desmopressin [636]. A large number of studies over the last 20 years have examined the potential role of exogenous AVP (desmopressin or DDAVP) for the treatment of nocturia in older patients [681, 698, 701, 702, 728-743] (**table 10**). While many have been uncontrolled case series involving relatively small numbers of subjects, more are robust RCTs. In some cases, however, the inclusion criteria, outcome measures, and route, dosing, and duration of DDAVP treatment have varied considerably. The first two, large RCTS using oral DDAVP employed essentially identical designs, with one conducted in men [702] and the other in women. [701] While these trials included some patients older

Table 10. Selected studies of desmopressin (DDAVP) for nocturia involving older patients (last 5 years)

Reference No. (Yr.)	Study Design	N	Sex	Age Mean, (SD)	Nocturia Definition	DDAVP Dose[1]	Outcomes	Level of Evidence
van Kerrebroeck 2007 [952]	RCT, placebo controlled Dose titration	127	70%M	63.4 (12.8)	> or =2 voids/night	0.1, 0.2, 0.4 mg	39% reduction in the mean number of nocturnal voids with desmopressin vs. 15% with placebo, p<0.0001 duration of the first sleep period prolonged by 108 min with desmopressin vs. 41 min with placebo; p<0.0001)	2
Johnson 2007 [953]	double-blinded, placebo-controlled, crossover trial of individually titrated oral ddAVP.	14	NS	74 (5)	any nighttime void between going to bed and morning awakening	0.1, 0.2, 0.4 mg	NUV in subjects receiving ddAVP treatment was significantly lower than at baseline (197mL reduction,) and than in subjects taking placebo (126mL less,). NUVof subjects at baseline and of those taking placebo were not significantly different	3
Wang 2011 [738]	long-term efficacy and safety of low dose oral desmopressin in elderly patients with benign prostatic hyperplasia	126	M	74.5 (5.99)	2 or more voids nightly nocturnal polyuria =nocturnal uri ne volume greater than 30% of total daily urine volume	0.1	decrease of 2 or more voids per night) achieved by 35 (61.40%) patients receiving desmopressin and by 8 (13.80%) on placebo (p _0.001).	2
Fu 2011 [740]	randomized double-blind treatment period. with DDAVP and staggered furosemide	80	58 men and 22 women,	67 (8)	at least two voids per night	0.1, 0.2, 0.4mg	46% patients in the study group compared with 4 (10%) patients in the control group reported that the treatment had a 50% or greater reduction in the number of nocturnal voids	2

than 75, the mean age of the participants was closer to “middle” rather than “old” age (65 and 57, respectively). Both found significant reductions in nocturia and nocturnal urine volume, and increases in mean duration of self-reported first night-time sleep episode. However, there were some unusual elements of the trial design. The randomised controlled portion was preceded by an open-label dose-titration run-in, with the subsequent exclusion of subjects who did not experience >20% reduction in nocturnal urine volume or who were intolerant to the medication. Although this approach may be useful for targeting therapy in clinical practice, it raises questions about selection bias and the generalisability of the results. Most individuals in DDAVP oral tablet trials were titrated up to an oral dosage of 0.4 mg, [701, 702] yet older patients can have a significant reduction in night-time urine with much lower doses of 0.1 or 0.2 mg orally.[738, 739, 744]. A major concern related to DDAVP treatment in elderly patients is fluid retention (which can exacerbate underlying cardiovascular disease) and hyponatraemia. In one study, one of the 57 individuals randomized to 0.1 mg DDAVP for year was described as having a “consciousness disturbance due to hyponatraemia (116 mmol/l)” which left him unable to “complete the protocol” (Wang 2011). Many older persons may have pre-existent hyponatraemia due to a variety of medical conditions and drugs and will develop renal insufficiency or congestive heart failure. One review [745] found the incidence of hyponatraemia with DDAVP in older persons to be 0-9% (depending on definition), with the exception of the RCT in men discussed above, in which the incidence of any hyponatraemia was 22% (4% with sodium < 130 mmol/L). Because so few frail elderly were included in these trials, the actual incidence of clinically significant hyponatraemia from DDAVP that might occur with monitoring outside of a clinical trial is unknown. A further review of pooled trial results found that the incidence of hyponatraemia in subjects with normal baseline sodium was <1% (3/336 subjects) in persons < 65 and 8% (22/260) in those >65, and 75% (6/8) in older patients with a low baseline serum sodium.[746] Pharmacodynamic studies in younger older men (aged 55-70) found that DDAVP had a prolonged half-life which was in part responsible for hyponatraemia. [747] DDAVP is not useful in frail older persons in nursing homes with nocturia and/or night-time UI because of the lack of efficacy for reducing night-time voids and the very high rate of hyponatraemia [744].

Several attempts at delivering the efficacy of antidiuretic therapy without the side effects have focused on the dosing, mechanism of achieving anti-diuresis, half-life of the agent, and delivery system. Since the last ICI review, data about the efficacy and safety of an orally-disintegrating tablet formulation of DDAVP have been published [698]. The theoretical advantages of such a formulation would be the ability to deliver smaller and consistent level of the drug. The study design evaluated co-primary outcomes of decrease in night-time voids from baseline versus placebo and the ability to achieve a 33% decline in baseline nocturia. Participants were stratified by age <65 and ≥ 65, with 500 individuals over 65 in the study having safety endpoints. At enrolment, all participants needed to have a serum sodium of >135 mmol/L, an estimated creatinine clearance of greater than 60 ml/min (the largest single reason for exclusion during screening, 15%), and a post void residual of less than 150 mL, and, for men only, a peak uroflow of >5 mL/second. The results showed that for men, the minimal effective dosage was 100 microgrammes (-1.38 versus -0.84 for placebo) and for women it was 25 microgrammes (-1.22 versus -0.88 for placebo). Side effects appeared in a dose-dependent fashion, that depended upon both age (older had higher side effects) and gender (women had higher side effects). For those participants over 65 years of age, the following percentages of participants had a reduction of sodium of either 125-130 or <125: on 100 microgrammes, 14.1% and 4.7%; on 50 microgrammes, 6.6% and 2.6%; for 25 microgrammes, 2.6% and 0%. While the 2011 nocturia treatment consensus guidelines [631] stated that ”the mechanisms behind desmopressin-induced hyponatraemia are well understood”, newer information suggests that the hyponatraemia in women is not fully explained by pharmacokinetic profiles [748]. For elderly individuals, antidiuretic therapy via DDAVP orally absorbable tablets still has a narrow therapeutic window where the dosage that allows for efficacy in the absence of meaningful and potentially serious side effects may be difficult to find.

There have also been trials with staggered DDAVP and diuretics, which have greatly reduced nocturia [740]. Of the participants who completed the trial, 5% had hyponatraemia, not counting individuals who had hyponatraemia during run in.

c) Surgical and procedural treatments

Posterior tibial nerve stimulation has been used in OAB trials. A recent trial [749] demonstrated in 214 individuals a favorable outcome for nocturia reduction in the active treatment group (2.9 at baseline to 2.1 with treatment) that was statistically superior to the effect of sham (2.9 to 2.6, net benefit of active over placebo -0.4 reduction). Of note, there were more individuals over 65 years of age (50%) compared to the sham group (41%) biasing against demonstrating benefit if it were true that older adults responded less well; whether or not these gains are maintained without ongoing treatment is not known [750].

Surgical approaches to treatment of nocturia have long been recognized to be effective, yet overall symptoms improve more than does nocturia specifically. The evidence from trials shows that older patients with the highest symptom scores prior to surgery benefit the most from transurethral resection of the prostate [751], yet nocturia often persists and may

be the least responsive symptom for improvement following the procedure [751-753]. Yet, surgery does reduce lower urinary tract symptoms and may result in reductions in nocturia and improvement in symptom specific QOL [754] In one consecutive group of 56 patients treated with either TURP or radical prostatectomy (mean age 69) for persistent symptoms despite six months of medical therapy. The group monitored postoperative nocturia counts, hours of undisturbed sleep, and the ICIQ-NQOL which were compared to baseline. In this uncontrolled series, patients had significant improvements in all measured domains, including a 0.8 episode reduction per night [755]. The NQOL outcome measure was most favorable in individuals with the greatest reductions in nocturia or the most uninterrupted sleep. One study used a retrospective evaluation of 298 patients (mean age 70) over a 10-year period, and found that younger men with lower preoperative urinary maximum flow rates had the best post-operative results [753]. Not surprisingly, symptoms post-operatively were not strongly correlated with objective urodynamic findings [756]. On average, less than half of the men operated on had a reduction of nocturia by 50% or more [753]. In a rare RCT where 66 men, aged 52–81 years (mean 68.6), who were believed to have nocturia solely due to "benign prostatic hyperplasia" and who had received no previous treatments of any type, were randomized in a 1:1 fashion to either alpha-blocker therapy (tamsulosin 0.4 mg) or TURP. The prostate volumes and baseline nocturia nearly differed in a statistically significant manner at baseline (51 cm3 and 2.0 mean nocturia episodes versus 59 cm3 and 2.4 for those allocated to surgery). Both groups had a reduction of nocturia to 1.5 (3 months) and 1.4 (6 months), as well as statistical improvements in the ICIQ-NQOL. No treatment was superior to the other and both were statistically significantly improved from baseline [754].

7. SUMMARY OF EVIDENCE

- Late afternoon administration of a diuretic may reduce nocturia in persons with lower extremity venous insufficiency or congestive heart failure unresponsive to other interventions. **(Level 2)**
- If OAB, DO, and/or urgency UI is felt to be a major contributor to nocturia, antimuscarinic agents should be considered. **(Level 3)**
- If nocturia is due to insomnia alone, then a very-short acting sedative hypnotic may be considered. **(Level 3)**
- DDAVP should not be used in frail elderly because of the risk of hyponatraemia. **(Level 1)**

8. RECOMMENDATIONS FOR MANAGEMENT

- Nocturia investigations should be carried out utilising both frequency-volume charts and validated questionnaires capturing QoL and bother related specifically to nocturia (e.g. NQoL).

9. RECOMMENDATIONS FOR RESEARCH FOR NOCTURIA IN THE ELDERLY [636]

- Validation and clarification of the definitions of both nocturia (in regards to any night awakening owing to the desire to pass urine, the ICS definition, vs. the more clinically bothersome nocturia, of 2 or more episodes)
- Studies to elucidate the reason for awakening
- Ways in which to understand, and potentially diminish, the robust effect of placebo/control arms
- Epidemiological research regarding studies of nocturia involving the following aspects: incidence/natural history, bother, effect on quality of life
- Research regarding what would be a clinically significant improvement
- Further clinical trials examining the impact of sleep focused treatments
- Trials examining the effects of multiple incremental and multicomponent therapies for nocturia
- Algorithms for both initial and subsequent (e.g., cause-specific) management of frail elderly, and men versus women would seem to be desirable.

VI. MODELS OF CARE FOR THE FRAIL ELDERLY WITH UI

1. BACKGROUND

Globally, frail elderly persons receive personal, nursing and medical care in a variety of healthcare and residential settings that employ many different models of continence care. While there continue to be very few studies, and fewer randomised clinical trials that directly examine these models in relation to UI prevention and management, a discussion of selected models is useful in identifying the challenges and opportunities to improve continence care for this population. This descriptive section briefly outlines four models of UI care particularly relevant to the frail elderly: home care, continence nurse advisors, collaborative practices between advance practice nurses and physicians, and long term institutional care. The care of incontinent frail elders in the acute care and assistive living settings is also discussed. A comprehensive review of global models of care is outside the purview of this section. Of note, we located little new information since the 4th ICI. Our findings were confirmed by a systematic literature review of 7 studies that investigated conservative interventions for frail non-institutionalised older adults, some of whom however lived in assisted living, senior apartments, and homes for the elderly, or attended adult day care [757].

2. HOME CARE

Most care for the frail elderly who live at home is provided by informal caregivers such as spouses,

children, other relatives, and in some cases neighbours or friends. Overall, there has been little research on UI interventions for this population but one trial found that behavioural interventions can be effective in selected frail homebound persons with UI and motivated caregivers [758]. Another trial, included in the systematic literature review mentioned above, found comprehensive geriatric assessment (CGA) was effective in resolving UI in 23% and improving incontinence in 44.6% [759]. Overall, however, the informal nature of care at home may lead to important barriers to effective continence care. Firstly, caregivers may not be available 24 hours per day, and thus regular toileting assistance may only be intermittently available. Toileting programmes (e.g., prompted voiding), intermittent catheterisation, and pessary use therefore may be impossible to implement consistently. Secondly, many caregivers for frail persons are, in fact frail, themselves. Spouses and adult children may have medical illnesses and/or functional problems making toileting assistance physically difficult and continence care stressful for them. An internet-based survey with Japanese family caregivers revealed that caring for a family member with incontinence resulted in significantly higher Zarit Caregiver Burden Interview (ZBI) scores than for those caring for a continent family member [760].) In 11 European regions, informal caregivers caring for incontinent older adults were 2.2 times more likely to report feelings of stress or burden [378]. Thirdly, even among caregivers who are physically capable and available to assist with continence care, negative attitudes, lack of knowledge and educational resources may pose substantial barriers to providing the required care.

Trained, paid caregivers for the frail elderly living at home are variably available throughout the world. Such services may include nurses to teach patients and caregivers UI care and management of intermittent or indwelling catheterisation, health care aides or personal care assistants who can assist with continence care, and provision of continence care supplies (e.g., pads and catheter supplies). In the US, for example, Medicare (health insurance for persons aged > 65) does not pay for ongoing UI care, only some catheter care and supplies and need-based home skilled nursing and physical therapy, and usually only on a limited basis and following hospitalisation. In a survey of Dutch older adults, > 65 years (mean age 80 years, standard deviation 7.2) who were receiving home care agency services, 46% (n=2866) had urinary incontinence. UI type was diagnosed in 49.8%. Types of UI were as follows: 13.1% stress UI, 33.4% urgency UI, 18.1% mixed UI, and 35.4% functional UI. Use of pads was the most commonly used intervention with scheduled toileting the second most frequently used intervention. In addition, for older adults who had a diagnosis for UI type, only 11% received special skin care [492]. In a study with 4010 older adults who were receiving home care, 1478 (36.8%) were incontinent of urine and the use of pads ranged from 29% to 52% among 11 home care sites in Europe [378]. Thus, even for older adults receiving home care, UI management often remains focused on containment by using pads and other protective products. These can be expensive if not provided or reimbursed through available health services or insurance. Research is needed to determine the magnitude of the problem of frail elders who do not engage in practices to protect skin integrity and devise homemade alternatives to pads, which are neither effective, comfortable, nor safe (especially to prevent incontinence-associated dermatitis [761]. A study conducted in the Netherlands with 19 home health agencies found that 38% of agencies documented the input of a continence nurse to care, but no association between quality systems and UI outcomes was found. The authors defined quality systems as management activities designed to monitor, assess and improve the quality of care [762]. With the demand for home care services expected to increase, these agencies will provide services for an increasing number of frail elderly patients with continence concerns.

3. CONTINENCE NURSE ADVISORS AND NURSE-LED MODELS

In many countries (e.g., UK, Australia, Sweden and Canada, among others), continence nurse advisors who can provide extremely valuable services for frail elderly with UI are available. Continence nurse advisors are highly trained in the assessment and management of both urinary and faecal incontinence. They are generally funded by the government and function as public health nurses for a region associated with one or more hospitals. They serve as advisors and provide education to physicians, nurses, and other health care professionals, as well as patients and their caregivers. They may also assist hospital staff in the assessment and management of UI in the hospitalised frail elderly, and coordinate follow up care in the home or in an outpatient clinic. One Canadian study found that continence nurse advisors had a positive impact in improving management of UI in older persons [763]. Data suggest that continence nurse led services are effective for the general population, but there are no specific data for frail older people [764].

4. COLLABORATIVE PRACTICES BETWEEN ADVANCE PRACTICE NURSES AND PHYSICIANS

In many countries, publicly supported continence nurse advisors are not available. However, other models have developed that generally involve collaborative practices between nurses with special interest, advanced training, and expertise in continence care and physicians (usually a urologist, gynaecologist, or geriatrician). These collaborations can be vital for providing optimal continence care for the frail elderly because of the multi-component therapy required. Such nurses may provide reim-

bursable services in private offices and clinics; provide education, consultation, and/or direct services to nursing homes or other long term care facilities, and assisted living facilities; and assist with the assessment and management of UI to frail elders in their homes. The complexity of healthcare delivery systems and needs of medically complex frail older adults are acknowledged in calls for optimal continence care delivered through multidisciplinary teams [404]. An analysis conducted with data from the 2006 National Audit of Continence Care for Older People in England and Wales found that integrated services, those that included organisational structure and clinical care processes for continence care which met national quality standards, provided higher quality of care [268] . Reimbursement for advance practice nurses and their ability to provide direct care independently of a physician varies across countries, and in some case within countries (e.g., in the US their scope of practice can vary by state). Evidence from a randomised controlled trial of a nurse-led continence service (for women aged 40 years and over) revealed clinical and statistically significance decrease in the urinary symptoms of urgency, frequency and UI [765]. The nurses in this study were specially trained, used evidence-based interventions and behavioural techniques with motivation and reinforcement. The nurses also consulted with a medical team. Although this model was used in independently living women, it shows promise for use in community-dwelling frail older people. In some countries there are specialty organisations for continence nursing (e.g., the US, Wound Ostomy Continence Nurses Society and Society of Urological Nurses and Associates; Canada, Canadian Continence Nurse Advisors; UK, Association for Continence Advice). Although little data on the effectiveness of these organisations in terms of improving patient care exist, they are becoming more widespread (e.g., Israel and Italy).

5. INSTITUTIONAL LONG TERM CARE

Long term care for the frail elderly is provided in a variety of types of institutional settings throughout the world. Continence care here is dependent upon many factors, including: type of resident (those requiring long-term skilled and personal care, short-term rehabilitation, post-hospitalisation care); physical environment; the organisational culture and leadership commitment to providing high quality care; the number, education, and motivation of direct care staff; access to physicians with interest in and understanding of continence care; and financial and regulatory incentives to provide appropriate continence care. Nursing home staffing continues to be a major barrier to translating research on prompted voiding and other interventions (see sections on Behavioural interventions and Environmental factors) into practice, and because resource constraints are stringent and will become more challenging with the rapid growth in the frail elderly population [766]. One study found that one staff member to five residents was necessary to implement combined toileting assistance with an exercise programme for physically dependent residents [470]. However, the residents' ability to maintain continence or improve may depend not only on the number of staff available, but also on their knowledge, skill, and interest and how these staff members are deployed. A systematic review on the impact of nursing workload and staffing on establishing healthy work environments for example, found a positive association between the knowledge and level of staff, and patient outcomes. Specifically, a greater proportion of regulated staffing (i.e. registered nurses, enrolled nurses, practical or vocational nurses) is associated with improved outcomes related to the Functional Independence Measure score, the Short Form Health Survey (SF-36) vitality score, patient satisfaction with nursing care, patient adverse events (including atelectasis, pressure ulcers, falls, pneumonia, postsurgical and treatment infection and urinary tract infections) [767]. Moreover, improved patient outcomes in relation to falls, pneumonia, pressure ulcers, urinary tract infection, length of stay and postoperative infection rates are associated with increased hours of registered nurse employment. The section on Interventions with Long-term Care Staff above, reviews studies of interventions with nursing home staff to improve continence care. These interventions have generally met with limited success because they have not incorporated either contextual or patient-level factors into their interventions, but have merely concentrated upon facilitation [768].

Three broad strategies have been employed to improve the quality of continence care for frail elderly nursing homes residents. The first are standardised approaches to identification, assessment, and management of UI. One is the Resident Assessment Instrument for nursing facilities, whose use is mandated in the US and other countries [418].) The Resident Assessment Instrument combines information from the Minimum Data Set (including data on individual resident demographics, medical conditions, function, cognition, and care needs) with Resident Assessment Protocols for specific conditions and impairments. The continence section of the Minimum Data Set is generally accurate in identifying incontinent patients, but not for determining the type or severity of UI or determining especially smaller changes in continence over time [769]. The original version of the Resident Assessment Protocol for UI was partially validated in a sample of approximately 100 frail, incontinent patients in one large academically-affiliated US nursing home [770]. In other countries, such as Australia and the UK, the use of clinical assessment tools in nursing homes is not mandated. They are in certain cases however, linked to accreditation processes and funding, providing a financial incentive for nursing homes to document an assessment and care plan

that addresses residents' continence care needs. The National Audit of continence Care for Older People reported on the extent to which nursing homes adhered to a suite of continence assessment and management standards based on ICI and national criteria [265].

Another approach is national guidance directives, such as that for surveyors who conduct yearly quality evaluations of all US nursing homes. A revision of the US guidance to surveyors for UI and catheter use in 2005 attempted to replace the existing emphasis on nursing documentation of continence care plans with an emphasis on UI assessment and provision of patient-focused care [418]. However, a subsequent study found that both surveyors and nursing home staff did not understand this shift in emphasis, and that the dissonance between these two groups in basic UI knowledge and elements of the guidance was a barrier to any change in quality of UI care [427]. Despite the existence and dissemination of guidelines, several studies document an ongoing discrepancy between their recommendations and regulations and the continence care actually delivered in the US [277, 425, 458, 771] and UK [265, 772].

The second strategy has been the use of principles of continuous quality improvement and total quality management developed for business management [773]. The key elements of these approaches are education and involvement of direct care staff, identification of a "continence champion" and team to implement the programme, and the continuous collection and analysis of quantitative outcome data using principles of statistical quality control. Quality assurance programmes using UI quality indicators have also been proposed [263]. One study successfully used a computerised assessment and quality improvement software program and external oversight to maintain a 50% reduction in UI in eight diverse, geographically dispersed US nursing homes [440]. A second implemented a quality improvement programme in five diverse US nursing homes, but UI reduction was more modest (20-30%) in this effort to translate research into practice [484]. In a recent major quality improvement in NHs initiative, the Centres for Medicare and Medicaid Services (CMS) in the United States use publicly disclosed quality measures (QMs) for nursing homes. Low risk incontinence (i.e., percent of low risk long stay residents with loss of bladder or bowel control) was associated with the percent of residents readmitted and the percent of residents incontinent of urine on admission to the facility [774].

The third approach is a specialty practice exemplar model for continence care, with an academic nursing faculty member with expertise in the assessment and treatment of UI engaged in clinical UI practice in a long-term care facility (see Interventions with Long-term Care Staff, above): graduate nursing students working with this individual focus on the Resident Assessment Protocol for UI. UI assessment and management skills are transferred to the facility nursing staff members through several mechanisms, including staff education and improved continence care systems [398]. This approach to improving continence care in nursing homes can be facilitated through collaborative partnerships between academia and the nursing home sector. Proponents of this type of collaboration claim it has the potential to facilitate culture change in nursing homes; to transform the perceptions and images of nursing homes in academia and the community, as exemplary places for quality and care and quality of life; and to promote evidence-based care, interdisciplinary collaboration, and resident-centred care [775-777]. For example, they can also potentially support the development of clinical leaders to introduce change at the clinical interface [778].

The concept of using clinical leaders, and/or nurses with advanced knowledge and skill, to improve the evaluation and treatment of UI in nursing homes is not new [277, 453, 767, 779, 780]. Watson and colleagues for example report a quasi-experimental pre-post design to test the effectiveness of using nurse practitioners to translate the Agency for Health Care Research and Quality Urinary Incontinence Guideline into practice for residents from nursing homes in upstate New York. Although the intervention was inconsistently implemented, 8.4% of residents' (n=25) became continent: largely due to treatment of reversible causes such as constipation [781].

6. OTHER INSTITUTIONAL SETTINGS

Other institutional settings that warrant attention in the context of models of care for improving the management of UI in frail older adults are: 1) acute care settings and 2) assisted living communities.

Acute care is a form of secondary health care which involves an active approach to managing a short-term, but urgent health problem. It is generally delivered by a range of health care professionals in a hospital setting. Older adults comprise the largest proportion of people admitted to acute care and as the population ages, the number of frail older adults requiring hospitalisation will increase. A recent prospective cohort study of 577 patients (mean age 82 +/- 6.9 years) admitted to general medical wards of three acute care hospitals in Brisbane, Australia, found UI rates of 43.8% (243/555) premorbid, 36.7% (176/479) during admission, and 35.3%(187/530) at discharge [782]. Moreover, of 438 patients at the time of discharge, 38 (12.8%) had new onset UI. One group of patients with a high risk for developing UI in hospital are female hip fracture patients. A secondary analysis of data from 6516 hospitalised women with a fractured hip revealed 21% became incontinent during hospitalisation [783]. Risk factors in this group included admission from a nursing home or other long-term care facility (odds ratio

[OR] 1.68, 95% confidence interval [CI] 1.29–2.19), confusion (OR 3.44, 95% CI 2.79–4.24), use of a wheelchair or device for walking (OR 1.53, 95% CI 1.29–1.83), and prefracture dependence on others for ambulation (OR 2.51, 95% CI 1.64–3.85).

Other research on UI in acute care draws attention to an overreliance on continence aids, and inadequate attention to identifying and addressing potentially contributing factors. For example, Ostaszkiewicz and colleagues conducted a point-prevalence survey of 447 hospitalised older adults in acute and subacute care settings in Australia and found 60% with a continence product or device, however, 50 (41%) patients with an absorbent pad denied having experienced UI or FI in the preceding 24 hours [430]. By contrast, 113 patients (16%) who reported UI or FI in the same period had no continence product or device. Hospital inpatient notes and admission notes also lacked information about patients' continence status. Similar findings were reported for elderly patients admitted to hospitals in Israel [409] Switzerland, [408] , and Italy [784]. Zisberg and colleagues [409] conducted a prospective cohort study of 352 patients aged 70 and older who were continent prior to admission to an acute care hospital. They found, 17.1% developed UI during their hospitalization, and in a multivariate analysis, the use of a urinary catheter or diaper were associated with the development of UI (4.26 95%CI 1.53-11.83 and 2.62 95%CI 1.17-5.87 respectively). Zurcher and colleagues [408] surveyed 78 elderly inpatients in a Swiss hospital and found 41 (51%) screened positive for UI, yet only 10 (24%) of nursing records documented the presence of UI. Moreover, the use of absorbent pads was the only intervention documented. The number of patients who declined to be asked about their continence status was minimal (n=5). Palese and colleagues also drew attention to a mismatch between UI and absorbent pad use, which occurred for 34% of patients admitted to medical wards in two Italian hospitals [784]. Factors that contribute to the lack of screening and assessment of incontinence, and overreliance on containment strategies for UI in acute care include: healthcare practitioners' lack of knowledge and skills, [428, 785-787] negative attitudes toward older adults with incontinence, or the belief that UI is not a priority [788, 789].

Whilst existing research indicates the need for UI to be treated as a potentially preventable complication of hospitalisation, it does not offer specific information about the continence status and continence care needs of hospitalised frail older adults as a specific subgroup. As incident UI is a marker for frailty, and functional decline, it is important to focus clinical and research attention on this vulnerable population [790, 791]. Dowling-Castronovo and colleagues provide a standard of practice protocol for managing UI in older hospitalised adults [792]. However to the best of our knowledge, there is no evaluative research on the use of these or other protocols for managing either daytime or night-time UI in acute care, especially in the frail elderly. There is a similar lack of published literature on models of care. Staff management protocols that involve using clinical champions, goal setting, self monitoring, and industrial quality control techniques, that have been trialled and evaluated in other settings (i.e. nursing homes), may apply to acute care.

Assisted living communities are social care residential models, in which older persons are provided primarily IADL assistance (meals, laundry, cleaning), and are becoming more common (primarily in the developed world). There is substantial variation in the functional status and medical care needs of their residents, the availability of nursing and physician care, reimbursement, regulation, and whether and how residents are allowed to age "in place" versus being transferred to nursing facilities should their care needs substantially increase. In some countries and localities, assisted living residents may substantially resemble the nursing home population. There are no data on the quality of management of UI for frail elderly residing in assisted living facilities, or intervention trials specifically in this population. The US National Association for Continence (www.nafc.org) has published a "blueprint" for continence care in assisting living facilities, based primarily on expert opinion.

7. RESEARCH RECOMMENDATIONS

1. Compare the efficacy of specific models of UI care for the frail elderly around the world.
2. Determine the factors associated with the effectiveness of care models in countries with different health care systems.
3. Develop and evaluate protocols for managing UI in frail elderly persons in acute care.
4. Differentiate frail from non-frail older adults in research on UI.
5. Replicate clinical trials and quality improvement initiatives to reduce urinary incontinence in a variety of healthcare settings with larger samples.
6. Identify specific models of care for UI in frail elderly persons in specific healthcare delivery settings: acute care, nursing home and assistive living, and primary care settings.
7. Determine system-level, group-level and individual-level quality indicators and outcomes for different models of care for UI in frail elderly persons.
8. Determine the factors associated with the effectiveness of care models in countries with different health care systems

C. FAECAL INCONTINENCE

I. BACKGROUND

FI in older people is a distressing and social isolating symptom and is associated with a possible increased risk of morbidity,[320, 793] mortality,[794, 795] and dependency [793, 795-797]. Frailty, defined by having multiple comorbid chronic illnesses and/or limitations to physical activity, is an independent risk factor for FI [798, 799]. Many older individuals with FI will not volunteer the problem to their general practitioner or nurse, and regrettably, health care providers do not routinely enquire about the symptom.[800] This 'hidden problem' can therefore lead to a downward spiral of psychological distress, dependency, and poor health. The condition can especially take its toll on informal care providers of home-dwelling patients, [801] with FI being a reason for requesting nursing home placement [802].

Even when older people are noted by health care professionals to have FI, the condition is often managed with the use of absorptive or containment products, especially in the long-term care setting where it is most prevalent. Current surveys show that the level of awareness regarding appropriate assessment and treatment options is limited among primary care physicians [803]. The importance of identifying treatable causes of FI in frail older people, rather than just managing passively (e.g. pads provision without assessment) is strongly emphasized in national and international guidance,[320, 804] but audits show that adherence to such guidance is generally poor, with non-integrated services, and sub-optimal delivery by professionals of even basic assessment and care [268].

This section covers specific issues for frail older people with FI. Since frail older adults frequently have co-existing urinary incontinence, evaluation and management of urinary incontinence and FI should be considered simultaneously [805-809]. Healthy older people should be managed using the interventions covered in the Chapter 16 on the "Management of Faecal Incontinence."

For the previous ICI report, the literature review covered the period 1966 to 2008. We identified new population-based studies on the prevalence and incidence rates of faecal incontinence specifically including frail, older adults (**Table 11**). Table 10 includes all studies published through December 2011, which met the following criteria: (1) sample representative of the general population (not a convenience sample or sample recruited from a specialty/primary care medical clinic or other setting in which there is a probable selection bias), (2) sample involving specific models of care for the older adult, and (3) sample of specific disease or co-morbid condition (i.e., home care, long term care).

The PUBMED.gov database was searched up to December 2011 using the following keywords:

(i) 'anal, bowel, faecal, faecal' and 'incontinence'

(ii) constipation

(iii) 'urinary' and 'incontinence'

(iv) laxatives, enemas, suppositories

(iv) other relevant phrases such as 'comprehensive geriatric assessment' ' stroke'

(v) level of care, 'nursing home,' institutionalisation', long-term care,' 'acute care,' 'hospitalisation'

Additional articles were identified by examining reference lists, and the Cochrane other recent systematic reviews.

II. PREVALENCE AND RISK FACTORS FOR FAECAL INCONTINENCE

In 2007, the Centre for Disease Control commissioned the University of Minnesota to prepare a systematic review of the prevalence and risk factors associated with FI for the State of the Science Conference on the Prevention of Faecal and Urinary Incontinence [810]. Their inclusion criteria differed from ours and did not focus on the frail older adult. The studies identified in both of these publications were reviewed for this report.

1. PREVALENCE ESTIMATES FOR FAECAL INCONTINENCE

(FI) prevalence estimates for faecal incontinence vary widely: 2.2% to 25% in the general community-dwelling population, 9-30% in older, frail adults, 18% to 33% in acute care settings, and may approach up to 50% in long term care and institutionalised settings. Incident FI varies from 6% to 17% in community dwelling populations, with less information known about incident rates in specific care settings. The variability in the prevalence rates may be related to the case definition and the frequency of FI reported. Case definition may include flatal incontinence, as well as loss of solid and liquid stool. Often, passive FI, or seepage, is not differentiated from solid or liquid stool FI in prevalence studies. A few studies have also defined a category of soiling of underwear only. In this review, FI refers to the loss of solid or liquid stool or mucus. Studies are specified that use other definitions, such as flatal incontinence or anal incontinence and soiling.

2. PREVALENCE AND INCIDENCE ESTIMATES OF FI IN COMMUNITY-DWELLING OLDER ADULTS.

FI is strongly associated with aging in many studies, and studies only involving older adults have higher prevalence estimates. The National Health and Nutrition Examination Survey (NHANES) in

Table 11. Population-based Surveys of FI in Older Adults

Source	Design	Prevalence/Incidence	Risk Factors	Notes
Whitehead et al (2008)	US representative sample of 2229 women and 2079 men, aged 20+ years. FI assessed with the FISI. FI defined as any involuntary loss of mucus, liquid, or solids in the last month.	**Prevalence** among older adults aged 70+: **15.3%** overall No gender differences	Age Loose stool consistency >21 bowel movements/week – women Inability to do activity – women Chronic illnesses – women Poor self-rated health – men Urinary incontinence - men	Cross-sectional, population-based national survey. No subgroup analysis for risk factors in older adults.
Rey et al (2009)	Random sample of 5,400 adults aged 50 yrs and older from Olmstead Co, MN. Respondents (n=1540, 64%) answered questions on FI at baseline in 1993 and 674 responded a mean of 9 years later.	**10-year incidence rate was 7%** for any FI	Urgency with bowel movements Self-reported diarrhoea Incomplete evacuation Pelvic radiation	Community sample, not population-based No separate analyses by gender Mean age of sample at follow up was 67±9 years
Markland et al (2010)	1000 Medicare beneficiaries age 65+ in 3 counties of Alabama. In-person interviews at baseline and 4-years. Gender/race stratified. FI excluded flatus.	**4-year Incidence** rates reported. 17% overall for any FI 6% for monthly FI No gender differences	White race/ethnicity - women Chronic diarrhoea – women Urinary incontinence – men and women Depression – women	Population-based longitudinal study with in-person interviews Mean age of 78 ± 5 years
Joh et al (2010)	Convenience-based survey in adult senior centers and health centers in Korea, n=981, mean age 73.6±6.8 years	**Prevalence of FI in the previous 3 months, 15.5%.** No differences in men and women, p=0.08	Urinary incontinence – men and women Hemorrhoids – men and women Poor self-rated health – men Diabetes – women Infrequent dietary fiber - women	Community sample, not population-based
Sharma et al (2011)	Postal survey of 2000 adults, 18 years and older in New Zealand, mean age 51.6 years	**Prevalence of monthly liquid or solid stool was 12.6%**	Study did not assess risk factors, only variations in prevalence by 3 scales	No gender or age group sub-analyses
AlAmeel (2010)	Population-based Canadian Health and Aging Study, n=8917, among adults 65 years of age and older	**4% overall prevalence rate** for any FI in the past year	Older age More common among women Poorer self-rated health More dependency in ADLs Cognitive impairment	Population-based study No increased mortality or institutionalization after 10 years when adjusting for all significant confounding factors No separate analyses by gender

the United States (US) provides one of the best estimates of FI prevalence to date because it surveyed both sexes, all major races represented in the US, and a range of older adults by age decade (55-69 and 70 years of age and older) [811]. NHANES also provided separate estimates for different types of FI (e.g., solid, liquid, mucus, and flatus) and frequencies of stool loss. The age-adjusted prevalence of FI (defined as accidental loss of solid, liquid, or mucus incontinence in the month preceding the interview) in the non-institutionalised population of the United States is 8.9% of women and 7.7% of men, with higher rates in older adults (15.3% in women and 15.5% in men aged 70 years of age and older). Liquid stool incontinence was the most common type of FI reported in the NHANES data. Rates of FI in older, frail adults are not gender-specific, with recent studies suggesting equal rates of FI among older men and women [797, 798, 811-815], and differences in survey methods make it difficult to interpret observed differences [793, 811, 812, 816-818].

New additions to the literature include prevalence estimates of urinary incontinence and FI in populations receiving specialty services in the home, such as home health care/home visits by physicians and other care providers. Using the Outcome and Assessment Information Set (OASIS), a standardised and administrative assessment tool used to document patient needs in home care settings in the United States, urinary incontinence was identified in 27%-33% of home health care patients and 7%-9% had FI on admission to the home health agency/provider [819].

Rates of incident (i.e., rate of new onset) FI in non-institutionalised populations have been reported in two recent studies [817, 818]. Both studies surveyed older adults in the community and reported FI incidence rates after 4 and 9 years, respectively, from the initial survey period [817, 818]. Incident rates for FI occurring in the last year were 17% (95% confidence interval 13.7% to 20.1%) after 4-years in one study (n=557)[817] and 6.3% (95% confidence interval 4.5% to 8.6%) after 9-years in the other (n=683).[818] For FI occurring at least monthly, the incidence rate was 6% (95% confidence interval 4.0% to 8.3%) after 4-years [817]. Differing FI incidence rates may be due to the age range of those surveyed at baseline. In the Markland *et al* study, the average age of those surveyed was 77.7 years at 4-years, whereas the Rey et al study surveyed adults 50 years and older at baseline. FI incidence rates have also been reported in specific populations followed over varying time periods. Rates of incident FI in institutionalised older adults was 7.5% at 1-year (n=1186), [794] with another study finding an incidence rate of 5.4% 1-year after hospitalisation for an acute brain injury (n=1013),[820] and a smaller study finding a rate of 10.2% 5.5 years after a lateral sphincterotomy for an anal fissure (n=62) [821].

3. PREVALENCE ESTIMATES OF FI IN HOSPITALIZED OLDER ADULTS.

Like the variability of prevalence rates of FI in community-dwelling population, hospitalized older adult populations also vary depending on the type of acute care setting or hospital setting, type of populations being studied (i.e. those under surveillance for certain types of infections), and duration of the hospital stay. Rates of FI in hospital or acute care settings range from 18-33%. In one study, the rates of FI in the acute care setting for adults (mean age of 67 years) was 33% (50/152 with diarrhoea under surveillance for infections) [822]. In another study, FI (17.6%) was almost as common as urinary incontinence (19.7%) in 608 hospitalised adults (age range 4 years to over 80 years) [823]. Older age was associated with a 4-fold increase in FI in hospitalised adults [823].

4. PREVALENCE AND INCIDENCE ESTIMATES OF FI IN LONG-TERM CARE RESIDENTS.

Few studies were identified that reported prevalence rates of FI in nursing home or long-term care resident facilities. Data are often limited by the type of facility described or administrative data that report FI rates [805, 824-828]. Prior estimates of FI in long-term care or institutionalised older adults varied due to the type of facility and administrative data reporting. Recent FI prevalence studies confirm the prior high range of FI (>50% of nursing home residents having FI) reported in the literature [824, 825, 829]. Little is known about the FI incidence rate in this specific population of frail adults, with one study reporting a rate of 20% during a 10-month period after admission [794].

5. FAECAL INCONTINENCE IN OLDER ADULTS – THE “HIDDEN” PROBLEM.

Recent evidence re-affirms that adults with FI do not seek care [830] and that health care practitioners are not likely to inquire or document discussions regarding FI [802,803]. Over 600 geriatricians responded to a US questionnaire on their beliefs, referral patterns, and perceptions on quality of care, and management practices for FI among older adults. Only 54.1% reported screening for FI and over 40% did not feel that FI could be managed conservatively. Only 32.9% believed nursing homes provide good care for FI and 27.1% believed that nursing home care conditions exacerbate FI [831].

Increasing awareness is important aspect of the identification, prevention, and treatment of FI in older adults [320]. Recent public campaigns with public and industry funding have sought to increase awareness of bowel control in the United States and United Kingdom (http://www.bowelcontrol.nih.gov/ and http://www.bowel-control.co.uk). Using appropriate terminology for FI for individuals that is consistent with health literacy levels may be an important factor. Terminology such as "bowel" or "bowel control" may be more appropriate than the term "faecal" or "faecal incontinence." Barriers that prevent adequate identification and treatment include: social and cultural issues about discussing symptoms, perception that treatments may not exist, access to trained health care providers in the community, access to providers in long-term care settings, and access to training and treatment protocols. Given the high prevalence rates of FI in the hospital, home care, and long term care settings, health care practitioners should directly inquire or directly observe bowel control issues and document any findings. Other high risk groups of older adults that should be questioned about bowel control include older adults that have: mobility problems, cognitive impairment/dementia, prior pelvic/lower abdominal radiation exposure, prior anal or rectal surgery, urinary incontinence, chronic constipation, chronic diarrhoea, and co-morbid disorders such as diabetes and stroke.

6. RISK FACTORS ASSOCIATED WITH FI IN OLDER ADULTS.

Age has been established as a risk factor for FI in many population-based studies [797, 808, 811, 832]. Other factors that have been associated with increased rates of FI include: female gender, co-existence of UI, poor general health, physical limitations, cognitive impairment, stool consistency, prior colo-rectal surgery, and high body mass index [798, 833-836]. However, among population-based studies among older adults, risk factors specific to women (e.g. vaginal deliveries, parturition characteristics) are no longer significantly associated with FI when controlling for all other factors [811, 837]. Many diseases and co-morbid disorders are associated with FI and include: diabetes, dementia-related incontinence, irritable bowel syndrome, inflammatory bowel disease, systemic sclerosis, and neurological diseases, such as cerebrovascular disease [797, 818, 833, 838-842]. The association between faecal incontinence and loose stool consistency (diarrhoea) is robust in community-dwelling populations and nursing home studies [811, 817, 818, 826, 836, 837]. As supported by the epidemiological data, the aetiology of faecal incontinence remains multifactorial and treatment depends on the underlying mechanisms or specific co-morbid disorders known to impact bowel function.

III. THE AGEING LOWER BOWEL AND PATHOPHYSIOLOGY IN OLDER ADULTS WITH FAECAL INCONTINENCE

Chapter 4 covers the pathophysiology of FI. This section considers factors specific to frail older people.

1. QUALITY OF DATA

There have been few relevant new studies since the last consultation. The findings from physiological studies of the lower bowel in older adults tend to be variable due to a) a variety of different techniques used in measuring anorectal function, b) unclear definition of the normative range of manometric measures for older people, c) poor matching between cases and controls of clinical factors which may affect gut function (e.g. level of mobility), or inadequate clinical information, d) usually small subject numbers, e) few studies deal with subjects over 80 years, and f) improvements in imaging quality with endoanal ultrasound and MRI. Studies reviewed are cohort case-control to evaluate age-effect [843] [844] [845, 846], young-old healthy subject comparisons [847, 848], and age- and sex-matched case-control studies of continent versus incontinent patients [849-852].

2. ANORECTAL FUNCTION IN HEALTHY OLDER ADULTS

Studies of age effect in healthy volunteers have shown a linear reduction with ageing in squeeze pressures (external anal sphincter tone) in women after the age of 70, and in men from the 9th decade onwards [844] Studies of normal men and women demonstrated a significant but similar linear decrease in anal resting pressure and maximum squeeze pressures in both men and women with increasing age.[853] [854] [855]. Studies of asymptomatic females showed a significant decrease in both anal resting and squeeze pressures with age. [856] [857] [858]. A study comparing young and old continent women found a decrease in anal resting pressure but no decrease in squeeze pressures between the two groups. [852] Age beyond 70 years was associated with reduction in anal resting pressures (internal anal sphincter tone) in both sexes, but to a greater degree in women in some studies [843] [844] [848], but not confirmed in other studies as reaching statistical significance [850, 859] [860].

The internal sphincter thickness and diameter is significantly increased in older versus younger men and women [861] and in nulliparous older women [862]. In addition this was associated with a significant decrease in the external anal sphincter thickness in women [863] [864]. A study of men and women using endoanal MR imaging showed a

significant decrease in the external anal sphincter thickness in men but not women with age [865].

With ageing the enteric nervous system undergoes age-related degeneration. In patients older than 65 years there is >30% loss of enteric neurones when compared to people aged 20 to 35 years. This loss is associated with an increase in fibrous tissue deposition [866]. Increase in thickness of internal sphincter is related to an increase in collagen deposition [867] [868].

There was a significant increase in pudendal nerve latencies with age in women [857] and not men [869].

Rectal motility appears to be unaffected by healthy ageing [847], but there is an age-related increase in anorectal sensitivity thresholds [854] [870] [855]. Rectal compliance was not affected in one study [870] but reduced rectal sensation was associated with reduced rectal compliance in another [858]. Anorectal function in older adults with faecal incontinence.

One study demonstrated prolonged pudendal nerve terminal motor latency (>2.2ms) in 34% of women aged over 50 with FI, though no relationship was observed between pudendal neuropathy and anal resting or squeeze pressures. Advancing age was however related to declining anal resting pressures. [871] Another study similarly found an age-related increase in pudendal neuropathy in incontinent women, again unrelated to squeeze pressures [872]. Single fibre EMG in incontinent patients aged over 78 years showed an increase in polyphasic potentials in the external anal sphincter muscles compared with continent subjects after adjusting for age, indicating some local reinnervation of these muscles following neurogenic damage. [851] A study comparing anorectal function in young (mean age 42) and old (mean age 72) women with FI (patients with constipation and/or pelvic floor dysfunction excluded) showed that older women were more likely to have bilateral pudendal neuropathy, but less likely to have a sphincter deficit of >90 degrees, likely to have had a previous sphincteroplasty and thin perineal body, although the validity of this test is questionable (Committee 7). Anorectal physiology was similar aside from a trend toward lower resting tone in older women [846].

An examination of anorectal function in elderly medically frail incontinent patients and continent age- and sex-matched controls showed that individuals with FI had reduced anal resting pressures. Significantly lower anal resting pressures were found with decreasing mobility in FI elderly [850]. Lower anal resting pressure was correlated with a lower threshold for expulsion of a rectal balloon. Patients with FI and dementia were more likely to exhibit multiple rectal contractions in response to rectal distension, though the role of these 'uninhibited' contractions in causing incontinence was unclear [873].

A similar matched case-control study showed that elderly patients with rectal impaction and soiling had impaired rectal sensation (needing a larger volume before feeling the presence of a rectal balloon and the desire to void), lower rectal pressures during rectal distension, and impaired anal and perianal sensation ('rectal dyschezia') [849]. Resting anal and squeeze pressures were however unimpaired in these patients, and the rectoanal inhibitory response were well-preserved. The authors concluded that overflow FI is primarily due to locally secreted mucus from around an irritative rectal faecal mass leaking out, despite well-preserved anal sphincter integrity.

A study comparing 8 older incontinent women (mean age 71.6 SD 7.5) with 9 older continent women (mean age 71.6 SD 7.5) and 9 younger continent women (mean age 28.7 SD (7.3) found women with FI were more likely to have decreased maximum squeeze pressures and levator ani (LA) defects. (OR 14). LA defects were associated with 26% less force on maximal contraction. Levator and urogenital hiatus measurements on MRI were increased in older women irrespective of continence status. [874]. Older FI females tolerated lower balloon anorectal manometry volumes before urge to defaecate indicative of rectal hypersensitivity [852].

SUMMARY OF EVIDENCE ON FAECAL INCONTINENCE AND THE AGEING GUT

- Anorectal function in healthy older persons is characterised by a tendency towards an age-related reduction in internal anal sphincter tone **(Level 2)**, and a more definite decline in external anal sphincter tone, especially in older women **(Level 3)**, An age-related decline in anorectal sensitivity in women has been observed **(Level 3)**, but rectal motility is well-preserved **(Level 3)**,
- Ageing alone however, appears to have little impact on anorectal function until later old age – from the 7th decade upwards in women and even later in men **(Level 3)**,
- Age-related internal anal sphincter dysfunction (reduced anal resting tone) is an important factor in FI in later old age (Level 3),
- Pudendal neuropathy is an age-related phenomenon in women with FI **(Level 2)**, and a likely predisposing factor for FI **(Level 3)**, although the validity of this test is questioned.
- Stool impaction predisposing to overflow is related to rectal dyschezia in frail older adults, a condition characterised by reduced tone, increased compliance and impaired sensation **(Level 3)**,
- Overflow FI is due primarily to mucus secretion from around a rectal faecal bolus, rather than to impaired sphincter function **(Level 3)**,
- Decrease in mobility is associated with anorectal dysfunction and is a predisposing factor for FI **(Level 3)**,

RECOMMENDATIONS - PATHOPHYSIOLOGY OF FI IN OLDER PEOPLE

1. Overall, the physiological data suggests that FI should not be considered an inevitable consequence of ageing
2. Older adults with FI should be evaluated for age-related reduction in internal and external sphincter function
3. Older patients with FI require a digital examination to identify rectal stool impaction causing overflow
4. Patients who are unaware of the presence of a large faecal bolus in the rectum may have rectal dyschezia, and should be considered at risk of recurrent impaction with overflow

3. CAUSES OF FAECAL INCONTINENCE IN OLDER ADULTS

Stool consistency is important aspect of determining the cause and the associated factors for the evaluation of FI in an older adult [817, 818, 837]. Loose, as well as hard, stool consistency can be related to FI in frail, older adults [794, 825, 875]. Evidence shows that loose stool consistency and chronic diarrhoea are important contributing factors for FI [811, 817, 818, 826, 837]. Loose stool consistency and chronic diarrhoea can result from multiple causes, such as malabsorption syndromes (e.g., lactose intolerance, gluten sensitivity, and fat-malabsorption), acute diarrhoeal illnesses, microcytic colitis, irritable bowel syndrome – with diarrhoea predominant symptoms, and other causes of chronic diarrhoea. Any change in stool consistency along with other warning symptoms (weight loss, bloody stools, change in stool calibre, and painful defaecation) should prompt further evaluation for colorectal cancer. Potential reversible causes of loose stools may include: excessive laxative use, lactose intolerance, drug-related side-effects, bacterial overgrowth, and possible bowel obstruction with “overflow” FI. “Overflow” FI secondary to constipation and stool impaction is also important to consider in older adults, potentially more common in men than women,[876, 877] those with mobility problems, [825, 875, 878] and those that reside in nursing home settings [825, 878].

Overflow incontinence or FI that results from stool impaction can be difficult to diagnose, may be more common in certain frail, older populations, and should be evaluated and treated when suspected. Evidence suggests that constipation and symptoms of constipation are common among nursing home residents with FI [825, 878, 879]. However, the true prevalence of impaction and FI in nursing home residents is not clearly identified. Constipation (according to bowel movement frequency) and associated symptoms (straining and incomplete evacuation) were common among nursing home residents in a 4-site randomized controlled trial to improve FI and urinary incontinence among nursing home resident by giving a multi-component intervention involving toileting assistance, exercise, and dietary snacks [825]. At baseline, 81% of the 111 nursing home study participants had less than 3 bowel movements in 5 days. During the 2-day run-in period where toileting assistance was provided, the number of bowel movements per day increased from 0.3 ± 0.3 to 0.8 ± 1.0 with 11% found to have straining and 21% reporting problems with incomplete evacuation. The average stool consistency rating on the 7-point Bristol Stool Form Scale was 4.2 ± 1.5. Another study that identified factors associated with FI in different health care settings found that 70% of nursing home residents experienced “faecal loading” compared to 63% in rehabilitation wards, 57% in acute care wards, and 20% in the home care setting [878].

Urgency associated with bowel movements is also an important bowel-related factor that should be assessed in older adults. Many studies do not evaluate urgency as an independent risk factor. However, among the studies that evaluated a sense of urgency associated with bowel movements, urgency is consistently and strongly related to FI , having a negative impact on quality of life even after controlling for other known confounding factors [818, 880, 881].

Other bowel-related disorders or complications of prior anorectal surgery can contribute to FI in older adults who otherwise would be continent, especially when functional status, mobility and cognition become impaired. Other bowel related disorders that have been associated with FI in adults (but not limited to the frail older adults) include: haemorrhoids,[876, 882] posterior vaginal prolapse (rectocoele),[837] inflammatory bowel disease,[883] irritable bowel disease,[837, 884] and a strong sense of urgency [880]. Types of prior anorectal surgery that contribute to FI include: haemorrhoid surgery,[876] fistula repair,[885, 886] sphincterotomy for anal fissures,[821] partial or total colectomy,[887] low anorectal resection and re-anastomosis for colo-rectal cancer,[888, 889] prostatectomy,[814] and prior pelvic/perineal radiation [814, 890]. All of these bowel-related disorders and prior surgeries should be part of the focused history in older adults with FI. More studies are needed to identify causal pathways for causing FI in the older adult.

Functional FI, as defined by mobility problems or restraints that restrict accessibility to the toilet despite normal bowel sensation and capacity, is also cited as a common reason for FI in epidemiological studies among community-dwelling older adults and those residing in nursing homes [326, 794, 798, 799, 807, 826-828, 891, 892].

Other causes of FI in older adults can be related to other diseases or co-morbid disorders, especially neurological disease, which increases the risk having FI.

Even after adjusting for age and gender, diabetes mellitus is associated with gastrointestinal symptoms including FI in population-based studies,[813, 840] nursing home residents,[892] and has been associated with impaired rectal sensitivity and sphincter weakness [838].

Neurological diseases that contribute to FI in older adults include cognitive impairment, stroke, traumatic brain injury, and sacral cord dysfunction. Older adults are living longer with significant neurological conditions. Cognitive impairment and dementia have been found to be independent risk factors with FI in older adult populations from epidemiological studies and among those in nursing homes [794, 807, 814, 826]. Having a stroke is an important risk factor for FI, with three and half times the rate of FI, compared to adults who did not have a stroke, in one population-based study [893]. FI affects 30-56% of stroke survivors in the acute period after having a stroke (1-30 days), with a lower prevalence (11%) of FI after 3-months, and 11-22% at 12-months following the initial stroke event [839, 894]. It is unclear whether the functional disability from having a stroke or the disruption in neurological pathways (sensory mechanisms) that promote continence, contributes more to FI among stroke survivors. Traumatic brain injury has also been linked with urinary incontinence and FI, but limited data exist on older adults from registry studies and single site studies [820, 895]. Spinal cord injury (depending on the level of injury) may result in impaired muscular strength of the external anal sphincter, delayed transit time, abnormal defaecation reflexes, and impaired sensation [896].

SUMMARY OF EVIDENCE ON PREVALENCE AND RISK FACTORS FOR FI IN FRAIL OLDER PEOPLE

Summarised below are key points that are specific to the frail elderly population.

- FI affects 1 in 5 older people (aged 65+) living in the community, and half of those reside in care homes **[Level 1]**
- The prevalence of FI increases with age alone, particularly in the 8th decade and beyond **[Level 1]**
- The prevalence of FI is higher in the acute hospital and nursing home setting than in the community **[Level 1]**, thus the group most affected is frail older people.
- The prevalence of FI in frail older men is equal to or greater than in women **[Level 2]**.
- This predominance of older men over women with FI is most striking among nursing home residents **[Level 2]**.
- The prevalence of FI varies dramatically between institutions in nursing home studies **[Level 2]**.
- FI usually coexists with urinary incontinence in frail older people **[Level 1]**
- Aside from age, the following are primary risk factors for FI in older people **[Level 2]**:

  Stool consistency -- Loose stool

  Bowel-related disorders, such has prior rectal surgery

  Impaired mobility

  Dementia

  Neurological disease

  Chronic medical conditions

  Depression

- Loose stool is a primary cause of transient FI in older people **(Level 2)**
- Faecal loading and constipation are clinically linked to FI, but there is little epidemiological work assessing this association (Level 3)
- Physicians and nurses in primary care, acute hospital, and long-term health care settings do not have a high awareness of FI in older people **(Level 2)**
- Within nursing homes, there is a low rate of referral by nursing staff of residents to primary care physicians or continence nurse specialists for further assessment of FI **(Level 2)**,and there is a tendency toward passive management (e.g. use of pads only without further evaluation) **(Level 2)**.Faecal loading is often present in older care home residents with FI **(Level 2)**
- Older people may be reluctant to volunteer the symptoms of FI to their health care provider for social or cultural reasons, or due to a popular misperception that the condition is part of the aging process and therefore 'nothing can be done about it' **(Level 2)**
- FI is associated with reduced quality of life, and poor health perception **(Level 2)**

RECOMMENDATIONS - IDENTIFYING FAECAL INCONTINENCE IN FRAIL OLDER PEOPLE

- Bowel continence status should be established by direct questioning and/or direct observation in:

  o all nursing and residential home residents

  o hospital inpatients aged 65 and over

  o people aged 80 and beyond living at home

  o older adults with impaired mobility

  o older adults with impaired cognition

  o older adults with neurological disease

- o older adults with chronic disease
- o older adults with constipation

- Primary care staff, hospital ward staff, and long-term care staff should routinely enquire about FI in frail older patients
- Enquiry about FI should be systematic and include stool consistency, severity of FI and impact on activities of daily living and quality of life
- Health care providers should be sensitive to cultural and social barriers discouraging patients from talking about the condition
- Frail older patients with restricted ability to access primary care such as nursing home residents, and those with mobility, chronic illness, or cognitive impairments, should be screened for FI through systematic case-finding methods
- Systematic outreach programmes which make it easier for frail older people and those who care for them to volunteer the problem to their primary care provider should be implemented
- There are significant geographical variations in provision of specialist expertise in bowel care (both medical and nursing) nationally and globally, which may affect case-finding in older people
- Further examination of underlying reasons for the variations in prevalence of FI between nursing homes (standards of care, patient case-mix, reporting) is needed
- UI and FI often coexist; continence care workers (e.g. nurse specialists) should be trained in identification and management of faecal as well as urinary incontinence in older people
- Key requirements to improving detection in the practice setting should be implemented:
  - o education of health care workers to embed both a sense of value in identifying FI, plus confidence that the condition can be treated
  - o protocols should be in place clarifying all details of screening enquiry (who will ask, how to ask, when to ask, and who to ask)
  - o patients and carers should have access to educational materials at the point of enquiry

4. EVALUATION OF FAECAL INCONTINENCE IN OLDER ADULTS

The algorithm contained in this chapter delineates a systematic approach to the clinical evaluation of frail older people with FI.

An initial assessment can be undertaken by any suitably trained health care practitioner, often this will be by either a physician or clinical nurse specialist. In the majority of cases, a clinical evaluation will provide sufficient diagnostic information upon which to base further management. There are available tools which can assist in this process [447]. The use of formal testing is hampered by both lack of relevant data in frail older people and the poor correlation between symptoms and abnormalities [897, 898]. Evidence that the assessment of faecal incontinence in older people is poorly done despite the existence of guidelines has been a persistent finding throughout the history of this chapter [339, 772]. What actions need to be taken to ensure that older people receive assessments which are consistent with current guidelines remain to be defined. There is evidence from a survey of US physicians that the presence of FI makes a referral for nursing home placement more likely than if it is not present [37]. Self reports of bowel symptoms are reliable and reproducible in older people including those in long term care [899-901]. Documentation of the type of incontinence experienced is very important, particularly because of the association between faecal incontinence and loose stool [385]. Faecal urgency is closely associated with diarrhoeal illness whereas constant passive leakage of homogenous liquid stool or stained mucus is more characteristic of overflow incontinence around faecal impaction. People with anal sphincter dysfunction tend to lose small amounts of stool. Urgency faecal incontinence tends to predominate when there is underlying external sphincter weakness and those with internal sphincter weakness experience more passive leakage [902]. People with faecal incontinence due to dementia may pass normal stool, particularly after meals, in response to the gastrocolic reflex. Any assessment of faecal incontinence should also include an assessment for constipation. It is important to recognise the constipation subtype of rectal delay in older people, which is said to affect 21% of the community dwelling elderly and may lead to faecal impaction and overflow incontinence [903]. A prolonged evacuation and feeling of anal blockage with the need to evacuate manually are the hallmark symptoms. A majority of the constipated elderly have evacuation problems rather than low stool frequency [904]. Regardless, the clinical definition of constipation relies upon the finding of an excessive amount of stool in the rectum or colon. An objective assessment is especially important in the frail elderly as they may not be able to communicate their symptoms and may, despite constipation, still have regular bowel movements [905]. The frail older person may also have impaired rectal sensation and be unaware of the existence of a full rectum [906, 907] or be unwell, with confusion (or worsening confusion). Older people are also less likely than the young to report a reduction in bowel frequency, abdominal bloating or positional changes to achieve defaecation [908].

Digital rectal examination can assess to a reasonable degree anal sphincter tone and squeeze pressure and appears to be as good as sphincter ma-

nometry in discriminating continent from incontinent people, although not the frail elderly [909]. Constipated patients with an empty rectum on digital examination may have high impaction.

Radiographs of the abdomen should be requested to establish the diagnosis to assess the extent of faecal loading and to rule out an obstruction or sigmoid volvulus. As with any other person, a change in bowel habit with weight loss, anaemia, rectal pain and faecal incontinence should raise the suspicion of an underlying malignancy [910]. Colorectal cancer is associated with both constipation and use of laxatives, although this risk is likely to be complicated by underlying bowel habit. In a retrospective study of 4798 incident cases of colorectal cancer in people aged 30 – 84 from UK datasets, independent predictors in men and women included family history of gastrointestinal cancer, anaemia, rectal bleeding, abdominal pain, appetite and weight loss. Alcohol consumption and recent change in bowel habit were also predictors in men alone [911].

The single symptom of chronic constipation does not usually warrant colonoscopic investigation, however, in the frailer elderly this may be considered as the index of suspicion may be higher. Given the increased difficulty of adequately preparing frail older people for either endoscopy or barium studies [912]; CT colonography may be considered as an alternative investigation where available [913]. Evaluation of the capacity to successfully toilet should include an assessment of mobility, visual acuity, manual dexterity and cognition. If acceptable to the older person, observing the process of transferring to the toilet, manage their clothing, redress and leave the lavatory is a good measure of ability. Caregivers should additionally be aware of the surroundings in which the frail older person lives in terms of access, lighting, distance and clutter. The design of commodes should also be considered in the light of the individual's capabilities.

Faecal incontinence is also associated with the development of pressure ulcers in older people with impaired mobility although whether this is a causal association is still a matter for debate, [914, 915] however, an assessment of skin integrity and provision of appropriate pressure relief is important. A pelvic examination to rule out posterior compartment prolapse is also important given the association between FI and prolapse in older women [916, 917]. There are no bowel specific quality of life assessments validated for use in the frail elderly.

5. TREATMENT OF FI IN OLDER ADULTS.

a) Quality of data

New trials are included on the treatment of FI in frail, older adults. No trials were identified on the prevention of FI in high risk, older adults. Many studies that include older adults have small sample sizes, inadequate power to detect clinically meaningful differences in outcomes, and biased methodology. Given these limitations, FI treatments applicable to older adults were considered and include: multicomponent treatments for FI, treatments aimed at specific populations of older adults (e.g. nursing home populations and stroke survivors), and percutaneous tibial nerve and sacral neuromodulation for FI. Issues related to surgery, bulking agents, biofeedback, containment, and skin care are discussed in other chapters.

b) Multi-component treatments for FI.

Given the multifactorial causes for FI in older adults, few studies existed in the literature involving multicomponent interventions. In 2006, the Cochrane group reported that available trials for FI do not allow for a definitive assessment of the role of pelvic floor muscle training and/or biofeedback therapy in the treatment of FI. The Cochrane report also noted that insufficient data exists that pelvic floor muscle training or biofeedback is any better than other conservative measures such as medication or education [918]. Since the Cochrane report, a recent study by Heymen et al involved a run-in period to improve stool consistency among adults with weekly FI prior to randomization to pelvic floor muscle training or biofeedback [919]. Among the 168 community-dwelling participants (mean age was not reported), FI frequency decreased from 3.4 to 2.0 days/week (41% reduction) and 35 patients (21%) reported adequate relief at the end of run-in. FI severity scores, as measured with the Faecal Incontinence Severity Index (FISI), decreased from 36.9 at baseline to 31.0 at the end of run-in ($p<0.001$). The run-in phase controlled for the effects of improved medical management to normalize stool consistency and this produced adequate relief of FI for 21% of patients. The remaining participants (n=108, mean age 60 years) were randomized to pelvic floor muscle exercises alone or manometric assisted biofeedback. After 3 months, the participants who received biofeedback treatment had a great improvement in improvements in their FI severity scores ($p=0.01$) and fewer days with FI ($p=0.083$) [919]. An additional study comparing different methods of biofeedback concluded that active sensory training is more effective than sham training for participants with "idiopathic" FI [920]. Others have found that the additional of rectal balloon distension sensitivity training did not improve outcomes [921, 922]. Evidence for biofeedback treatment for improving FI in older adults with cognitive impairment or physical limitations/poor functional status was not found.

A systematic review in 2003 identified three trials that compared loperamide versus placebo without any trials among older adults; one in patients with ileoanal pouches, and two in patients with chronic diarrhoea [923]. No controlled studies were identified during this review using anti-diarrhoea medica-

tions for patients initially presenting with the primary complaint of faecal incontinence and there were no controlled studies investigating the treatment of faecal incontinence in older adult populations. In a double blind randomised crossover trial by Lauti *et al* [2008], fibre supplementation was used along with loperamide and specific diet recommendations in participants with the primary complaint of liquid and solid faecal incontinence [924]. Participants (n=63, mean age 59 ±15 years, 91% women) were randomised in a cross-over trial to loperamide along with fibre supplements and advice sheet on diet versus loperamide with an advice sheet on low residue diet and placebo fibre supplements. There was significant improvement in both groups from baseline to 12 weeks in FI severity without group differences between the two treatments. There were also no adverse events reported and very few participants reported dry mouth (specific amounts not reported). Expert opinion suggests that loperamide should be used with caution and close monitoring for faecal impaction in older adults, especially those with chronic co-morbid disorders.

c) Treatment of FI in nursing home settings.

Treatments for FI in nursing home settings also involved the treatment of constipation and faecal loading or faecal impaction. In a French study among 206 nursing home residents in 4 different homes, lactulose alone was compared to lactulose plus daily suppositories along with weekly tap-water enemas for reducing FI episodes. Although there were no differences between the two groups, residents that achieved complete rectal emptying also reduced the number of FI episodes by 35% while also reducing staff workload by 42% (soiled laundry counts). [879] Recently, Schnelle et al (2010) completed a multi-centre, multi-component intervention for improving FI and constipation in cognitively impaired 112 nursing home residents (mean age 86 ± 10 years) [829]. In this controlled trial in 6 nursing homes in the United States (n=112), the intervention was compared to a usual care control group. The intervention group received toileting assistance, exercise, and choice of food/fluid snacks every 2 hours for 8 hours/day for 3 months. Participants in the intervention group compared to the usual care control group had improvements in bowel movement frequency and the percentage of bowel movements in the toilet ($p<0.01$), but not the frequency of FI episodes determined by direct checks from research staff. Urinary incontinence episodes also improved with this intervention ($p<0.05$). Among the 29 nursing home residents who had anorectal manometry, a dyssynergic defecation pattern was identified in 89%. The authors concluded that this multi-component intervention improved some factors associated with FI in nursing home residents, but further work to improve stool consistency and treatments for dyssynergia may be warranted.

d) Treatment of FI in stroke survivors.

In outpatient and inpatient stroke survivors (n=146), Harari et al (2004) completed a randomised, controlled trial to improve FI and constipation symptoms with an intervention based on education booklet for the patient/caregiver along with treatment recommendations to the health care provider and compared this intervention to a usual care control group [925]. After 6-months and 1-year of follow-up, the intervention group compared to the usual care control group were more likely ($p<0.05$) to have 'normal' rated bowel movements on a 7-day bowel diary and more likely to have an increased bowel frequency ($p<0.05$). The intervention group was also more likely to alter their diet and fluid intake to control their bowels.

e) Sacral Neuromodulation/Percutaneous tibial nerve stimulation for FI in older adults.

Recent prospective multi-centre trial data on sacral neuromodulation with a surgically-implanted device shows significant improvements in FI episodes, symptoms, and quality of life [926]. In the larger, multi-centre studies with data at 2- and 3-years, the mean ages were 54.3 ± 11.3 and 60.5 years (range 30-88 years) without subgroup data on the older age participants [927-929]. Evaluating and selecting older adults and adults with specific neurological conditions who may benefit from permanent implantation is an important consideration [930, 931]. Data on sacral neuromodulation for FI and surgical outcomes including adverse events for frail, older adults is limited [932].

Percutaneous tibial nerve stimulation (PTNS) studies for FI have also reported benefits. Among the 8 small, prospective studies (largest study, n=32), involving a total combined sample size of 129 participants, have significant variation in the study population, with large mean age ranges (38 to 60 years), methodology, and outcome measures [933-940]. One prospective study involving 100 participants with a median age of 57 years found that "urge-related" FI and "mixed" FI were more likely to having improvements in a symptom score than those with "passive" FI [941]. Data from adequately powered randomized controlled trials for PTNS treatment for FI are currently ongoing and will add significantly to the existing evidence [942].

6. SUMMARY OF EVIDENCE ON THE TREATMENT OF FI IN FRAIL OLDER PEOPLE

1. Structured multi-component approaches to bowel care did not reduce the frequency of FI in the nursing home setting, but did improve bowel frequency and number of bowel movements in the toilet **(Level 2)**

2. Older people with FI may benefit from biofeed-

back and sphincter strengthening exercises if they are able to comply **(Level 3)**

3. Loperamide can reduce frequency of FI, particularly when associated with loose stool (once infection and other causes have been excluded) but should be used with caution **(Level 2)**

4. Additional fibre supplementation to loperamide may not improve FI outcomes **(Level 2)**

5. Multi-component structured nurse-led assessment and intervention can improve bowel symptoms and alter bowel-related habits in older stroke patients **(Level 2)**

6. More data are needed on the use of sacral neuromodulation in specific higher risk older age populations **(Level 4)**

7. RECOMMENDATIONS - TREATMENT OF FI IN FRAIL OLDER PEOPLE (ALL GRADE C)

1. Loperamide is a useful treatment in FI, in the absence of constipation, but should be used with caution in older adults

2. Causes of loose stool must be identified and treated.

3. All frail older people with FI should have structured multidisciplinary assessment and treatment of their bowel problem.

4. Patient and caregiver education (using verbal and written materials) should be undertaken to promote self-management and other coping mechanisms, and where appropriate self-management (e.g. reducing risk of constipation and impaction through dietary and lifestyle measures, advice on how to take loperamide). Advice on skin care, odour control, and continence aids is also important.

5. Greater emphasis needs to be placed on systematic and effective management of FI in older people backed up by sound communications between all health care providers, especially in the nursing home and acute hospital setting.

6. Education of health care providers with regards to heightening awareness of the problem plus methods of identification, assessment and management of FI in older people should be broad-ranging and include geriatricians, general practitioners, hospital physicians, hospital, community, general practice and long-term care nurses, and related disciplines (physiotherapists, occupational therapists, dieticians, pharmacists).

7. Cyclical national audit with provider accountability, of current practice in managing FI in older people is needed to lay the ground-work for standardised care, and provide a culture of continuous quality improvement. Such audit tools should be developed using standardised consensus methodologies

8. AREAS FOR FURTHER RESEARCH ON FI IN FRAIL OLDER PEOPLE

1. Trials of laxative and nonpharmacological treatment and prevention of faecal impaction and overflow are needed to optimise standards of prescribing and care.

2. Multicomponent interventions to treat FI in frail older people should be evaluated to assess effective ways of FI management in acute care settings

3. Multidisciplinary study assessing the feasibility and efficacy of a step-wise approach to the management of dementia-related FI in nursing home residents

4. Evaluation of case-finding methods for FI in different settings including the fundamentals of staff education, screening protocols, and patient's educational information would be very informative.

5. Testing the feasibility of providing an integrative approach to assessment of FI in the frail older person, including a range of health and social care providers and different health care settings (acute, intermediate or sub-acute, long-term care and community) would be relevant to national implementation of bowel care improvement programmes.

6. Examination of the variability of FI rates between nursing homes within single nation states, (taking into consideration case-mix) will highlight problems areas both organisationally and clinically. Nursing home administrative factors such as resident: nurse staff ratios should be evaluated as a contributing factor to FI.

7. Further epidemiological studies are required to document causes of FI in frail older people in different health care settings. Such studies should include evaluation of unmet need for patients and caregivers.

8. Evaluation of the pathophysiological basis for high prevalence of FI in older men. Evaluation of potentially preventable causes of loose stools in institutionalised older people, and impact of their treatment on FI.

9. Nurse-led initiatives are needed to develop care pathways for assessing of bowel problems in frail older people with a view to establishing integrated service delivery.

10. Examine the research question, 'Do educational interventions by health care providers to informal carers of home-dwelling older people with FI reduce carer burden and improve quality of life for patient and carer?'

REFERENCES

1. Baltes, P.B. and J. Smith, *New frontiers in the future of aging: from successful aging of the young old to the dilemmas of the fourth age.* Gerontology, 2003. **49**(2): p. 123-35.
2. Holroyd-Leduc, J.M., K.M. Mehta, and K.E. Covinsky, *Urinary incontinence and its association with death, nursing home admission, and functional decline.* J Am Geriatr Soc, 2004. **52**(5): p. 712-8.
3. Martin, L.G., R.F. Schoeni, and P.M. Andreski, *Trends in health of older adults in the United States: past, present, future.* Demography, 2010. **47 Suppl**: p. S17-40.
4. Fonda, D., *Improving management of urinary incontinence in geriatric centres and nursing homes. Victorian Geriatricians Peer Review Group.* Austral Clin Rev, 1990. **10**(2): p. 66-71.
5. Ouslander, J.G., et al., *Functional incidental training: a randomized, controlled, crossover trial in Veterans Affairs nursing homes.* J Am Geriatr Soc, 2005. **53**(7): p. 1091-100.
6. McMurdo, M.E., et al., *Improving recruitment of older people to research through good practice.* Age and Ageing, 2011. **40**(6): p. 659-65.
7. Fonda, D., et al., *Outcome measures for research of lower urinary tract dysfunction in frail older people.* Neurourology & Urodynamics, 1998. **17**(3): p. 273-81.
8. Ferrucci, L., et al., *Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report.* Journal of the American Geriatrics Society, 2004. **52**(4): p. 625-34.
9. Fried, L., et al., *Frailty in older adults: evidence for a phenotype.* Journals of Gerontology Series A-Biological Sciences & Medical Sciences, 2001. **56**(3): p. M146-56.
10. Centers for Disease Control National Center for Health Statistics. *Health, United States, 2003 With Chartbook on Trends in the Health of Americans*. June 11, 2004]; Available from: http://www.cdc.gov/nchs/products/pubs/pubd/hus/highlits.pdf.
11. Imuta, H., et al., *The prevalence and psychosocial characteristics of the frail elderly in Japan: a community-based study.* Aging-Clinical & Experimental Research, 2001. **13**(6): p. 443-53.
12. Thom, D.H., M.N. Haan, and S.K. Van Den Eeden, *Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality.* Age & Ageing, 1997. **26**(5): p. 367-74.
13. Syddall, H., et al., *Prevalence and correlates of frailty among community-dwelling older men and women: findings from the Hertfordshire Cohort Study.* Age and Ageing, 2010. **39**(2): p. 197-203.
14. Miles, T.P., et al., *New-onset incontinence and markers of frailty: data from the Hispanic Established Populations for Epidemiologic Studies of the Elderly.* Journals of Gerontology Series A-Biological Sciences & Medical Sciences, 2001. **56**(1): p. M19-24.
15. Silva, V.A., K.L. Souza, and M.J. D'Elboux, *[Urinary incontinence and the criteria of frailness among the elderly outpatients].* Revista da Escola de Enfermagem da U S P, 2011. **45**(3): p. 672-8.
16. Donaldson, L. and C. Jagger, *Survival and functional capacity: three year follow up of an elderly population in hospitals and homes.* Journal of Epidemiology & Community Health, 1983. **37**: p. 176-9.
17. Herzog, A., et al., *Urinary incontinence as a risk factor for mortality.* J Am Geriatr Soc, 1994. **42**: p. 264-8.
18. Johnson, T.n., et al., *Urinary incontinence and risk of death among community-living elderly people: results from the National Survey on Self-Care and Aging.* Journal of Aging & Health, 2000. **12**: p. 25-46.
19. Patel, M., et al., *Natural history and effects on 2-year outcomes of urinary incontinence after stroke.* Stroke, 2001. **32**: p. 122-7.
20. Baztan, J.J., et al., *New-onset urinary incontinence and rehabilitation outcomes in frail older patients.* Age Ageing, 2005. **34**(2): p. 172-175.
21. Nuotio, M., et al., *Predictors of Institutionalization in an Older Population During a 13-Year Period: The Effect of Urge Incontinence.* J Gerontol A Biol Sci Med Sci, 2003. **58**(8): p. M756-762.
22. Welz-Barth, A., C. Garcia-Schurman, and I. Fusgen, *[Incontinence, dementia and multiple morbidity--predictive factors for nursing care requirement and nursing home admission] [German].* Wiener Medizinische Wochenschrift, 1998. **148**(13): p. 305-8.
23. Weatherall, M., T. Slow, and K. Wiltshire, *Risk factors for entry into residential care after a support-needs assessment.* New Zealand Medical Journal, 2004. **117**(1202): p. U1075.
24. Coward, R.T., C. Horne, and C.W. Peek, *Predicting nursing home admissions among incontinent older adults: a comparison of residential differences across six years.* Gerontologist, 1995. **35**(6): p. 732-43.
25. Steiner, J., et al., *Development and validation of a clinical prediction rule for prolonged nursing home residence after hip fracture.* J Am Geriatr Soc, 1997. **45**: p. 1510-4.
26. O'Donnell, B., et al., *ncontinence and troublesome behaviors predict institutionalization in dementia.* Journal of Geriatric Psychiatry & Neurology, 1992. **5**: p. 45-52.
27. Matsumoto, M. and K. Inoue, *Predictors of institutionalization in elderly people living at home: the impact of incontinence and commode use in rural Japan.* Journal of Cross-Cultural Gerontology, 2007. **22**: p. 421-32.
28. Luk, J.K., P.K. Chiu, and L.W. Chu, *Factors affecting institutionalization in older Hong Kong Chinese patients after recovery from acute medical illnesses.* Arch Gerontol Geriatr, 2009. **49**(2): p. e110-4.
29. Hebert, R., et al., *Factors associated with long-term institutionalization of older people with dementia: data From the Canadian Study of Health and Aging.* J Gerontol A Biol Sci Med Sci, 2001. **56**(11): p. M693-699.
30. Morrison, A. and R. Levy, *Fraction of nursing home admissions attributable to urinary incontinence.* Value Health, 2006. **9**(4): p. 272-4.
31. Boyington, J., et al., *Differences in resident characteristics and prevalence of urinary incontinence in nursing homes in the southeastern United States.* Nursing Research., 2007. **56**: p. 97-107.
32. Anger, J.T., et al., *True prevalence of urinary incontinence among female nursing home residents.* Urology, 2006. **67**(2): p. 281-287.
33. Berlowitz, D., H. Brand, and C. Perkins, *Geriatric syndromes as outcome measures of hospital care: can administrative data be used?* J Am Geriatr Soc, 1999. **47**: p. 692-6.
34. Tomiak, M., et al., *Factors associated with nursing-home entry for elders in Manitoba, Canada.* J Gerontol A Biol Sci Med Sci, 2000. **55**(5): p. M279-287.
35. Yaffe, K., et al., *Patient and Caregiver Characteristics and Nursing Home Placement in Patients With Dementia.* JAMA, 2002. **287**(16): p. 2090-2097.
36. AlAmeel, T., M.K. Andrew, and C. MacKnight, *The association of fecal incontinence with institutionalization and mortality in older adults.* The American journal of gastroenterology, 2010. **105**(8): p. 1830-4.
37. Grover, M., et al., *Survey of geriatricians on the effect of fecal incontinence on nursing home referral.* Journal of the American Geriatrics Society, 2010. **58**(6): p. 1058-62.
38. Inouye, S.K., et al., *Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept.* J.Am. Geriatr.Soc., 2007. **55**(5): p. 780-791.

39. DuBeau, C.E., *Beyond the bladder: management of urinary incontinence in older women.* Clin.Obstet.Gynecol., 2007. **50**(3): p. 720-734.

40. Tinetti, M., et al., *Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes.[see comment].* JAMA, 1995. **273**(17): p. 1348-53.

41. Kuo, H.K. and L.A. Lipsitz, *Cerebral white matter changes and geriatric syndromes: is there a link?* J.Gerontol.A Biol. Sci.Med.Sci., 2004. **59**(8): p. 818-826.

42. Griffiths, D., et al., *Brain control of normal and overactive bladder.* J.Urol., 2005. **174**(5): p. 1862-1867.

43. Tadic, S.D., et al., *Abnormal connections in the supraspinal bladder control network in women with urge urinary incontinence.* Neuroimage., 2008. **39**(4): p. 1647-1653.

44. Griffiths, D. and S.D. Tadic, *Bladder control, urgency, and urge incontinence: Evidence from functional brain imaging.* Neurourol.Urodyn., 2007.

45. Hof, P.R. and J.H. Morrison, *The aging brain: morphomolecular senescence of cortical circuits.* Trends Neurosci., 2004. **27**(10): p. 607-613.

46. Andrews-Hanna, J.R., et al., *Disruption of large-scale brain systems in advanced aging.* Neuron, 2007. **56**(5): p. 924-935.

47. Resnick, N.M., Elbadawi, A. E., Yalla, S. V., *Age and the lower urinary tract: what is normal?* . Neurourology and Urodynamics, 1995. **14**: p. 1647.

48. Madersbacher, S., et al., *The aging lower urinary tract: a comparative urodynamic study of men and women.* Urology, 1998. **51**(2): p. 206-12.

49. Bromage, S.J., et al., *Urodynamics in the octogenarian female: is it worthwhile?* Int Urogynecol J Pelvic Floor Dysfunct. **21**(9): p. 1117-21.

50. Pfisterer, M.H., et al., *The effect of age on lower urinary tract function: a study in women.* Journal of the American Geriatrics Society, 2006. **54**(3): p. 405-12.

51. Malone-Lee, J., Wahedna, I., *Characterisation of detrusor contractile function in relation to old-age.* Br J Urol 1993. **72**: p. 873-880.

52. Taylor, J.A., 3rd and G.A. Kuchel, *Detrusor underactivity: Clinical features and pathogenesis of an underdiagnosed geriatric condition.* J Am Geriatr Soc, 2006. **54**(12): p. 1920-32.

53. van Koeveringe, G.A., et al., *Detrusor underactivity: a plea for new approaches to a common bladder dysfunction.* Neurourology and Urodynamics, 2011. **30**(5): p. 723-8.

54. Elbadawi, A., S.V. Yalla, and N.M. Resnick, *Structural basis of geriatric voiding dysfunction. II. Aging detrusor: normal versus impaired contractility.* J Urol, 1993. **150**(5 Pt 2): p. 1657-67.

55. Abrams, P.H. and D.J. Griffiths, *The assessment of prostatic obstruction from urodynamic measurements and from residual urine.* British journal of urology, 1979. **51**(2): p. 129-34.

56. Smith, P.P., *Aging and the underactive detrusor: a failure of activity or activation?* Neurourology and Urodynamics, 2010. **29**(3): p. 408-12.

57. Smith, P.P. and G.A. Kuchel, *Continuous uroflow cystometry in the urethane-anesthetized mouse.* Neurourology and Urodynamics, 2010. **29**(7): p. 1344-9.

58. Smith, P.P., A. Deangelis, and G.A. Kuchel, *Detrusor Expulsive Strength Is Preserved, but Responsiveness to Bladder Filling and Urinary Sensitivity Diminished in the Aging Mouse.* American journal of physiology. Regulatory, integrative and comparative physiology, 2011.

59. Kuchel, G.A., in *Hazzard's Principles of Geriatric Medicine and Gerontology*, J.B. Halter, Hazzard, W. R., Ouslander, J. G., Tinetti, M. E., Wolard, N., Studenski, S., High, K. & Asthana, S. (eds.), Editor 2010, McGraw Hill: New York. p. 621-630.

60. Collas, D., Malone-Lee, JG, *Age associated changes in detrusor sensory function in patients with lower urinary tract symptoms.* Int Urogynecol J Pelvic Floor Dysfunct, 1996. **7**: p. 24-29.

61. Pfisterer, M.H., et al., *The impact of detrusor overactivity on bladder function in younger and older women.* The Journal of urology, 2006. **175**(5): p. 1777-83; discussion 1783.

62. Resnick, N.M. and S.V. Yalla, *Detrusor hyperactivity with impaired contractile function. An unrecognized but common cause of incontinence in elderly patients.* JAMA, 1987. **257**(22): p. 3076-81.

63. Resnick, N.M., S.V. Yalla, and E. Laurino, *The pathophysiology of urinary incontinence among institutionalized elderly persons.* N Engl J Med, 1989. **320**(1): p. 1-7.

64. Elbadawi, A., S.V. Yalla, and N.M. Resnick, *Structural basis of geriatric voiding dysfunction. I. Methods of a prospective ultrastructural/urodynamic study and an overview of the findings.* J Urol, 1993. **150**(5 Pt 2): p. 1650-6.

65. Elbadawi, A., S.V. Yalla, and N.M. Resnick, *Structural basis of geriatric voiding dysfunction. IV. Bladder outlet obstruction.* J Urol, 1993. **150**(5 Pt 2): p. 1681-95.

66. Elbadawi, A., S.V. Yalla, and N.M. Resnick, *Structural basis of geriatric voiding dysfunction. III. Detrusor overactivity.* J Urol, 1993. **150**(5 Pt 2): p. 1668-80.

67. Elbadawi, A., et al., *Structural basis of geriatric voiding dysfunction. VII. Prospective ultrastructural/urodynamic evaluation of its natural evolution.* J Urol, 1997. **157**(5): p. 1814-22.

68. Elbadawi, A., et al., *Structural basis of geriatric voiding dysfunction. VI. Validation and update of diagnostic criteria in 71 detrusor biopsies.* J Urol, 1997. **157**(5): p. 1802-13.

69. Carey, M.P., et al., *A prospective evaluation of the pathogenesis of detrusor instability in women, using electron microscopy and immunohistochemistry.* BJU Int, 2000. **86**(9): p. 970-6.

70. Levy, B.J. and T.N. Wight, *Structural changes in the aging submucosa: new morphologic criteria for the evaluation of the unstable human bladder.* J Urol, 1990. **144**(4): p. 1044-55.

71. Zhu, Q., et al., *Estrogen and postnatal maturation increase caveolar number and caveolin-1 protein in bladder smooth muscle cells.* The Journal of urology, 2004. **171**(1): p. 467-71.

72. Zhu, Q., et al., *Role of ovarian hormones in the pathogenesis of impaired detrusor contractility: evidence in ovariectomized rodents.* The Journal of urology, 2001. **166**(3): p. 1136-41.

73. Brierly, R.D., et al., *A prospective controlled quantitative study of ultrastructural changes in the underactive detrusor.* The Journal of urology, 2003. **169**(4): p. 1374-8.

74. Warburton, A.L. and R.M. Santer, *Sympathetic and sensory innervation of the urinary tract in young adult and aged rats: a semi-quantitative histochemical and immunohistochemical study.* The Histochemical journal, 1994. **26**(2): p. 127-33.

75. Dmitrieva, N., G. Zhang, and H. Nagabukuro, *Increased alpha1D adrenergic receptor activity and protein expression in the urinary bladder of aged rats.* World journal of urology, 2008. **26**(6): p. 649-55.

76. Gomez-Pinilla, P.J., M.J. Pozo, and P.J. Camello, *Aging differentially modifies agonist-evoked mouse detrusor contraction and calcium signals.* Age, 2011. **33**(1): p. 81-8.

77. Muller, D., et al., *Cyclic GMP signaling in rat urinary bladder, prostate, and epididymis: tissue-specific changes with aging and in response to Leydig cell depletion.* Reproduction, 2011. **142**(2): p. 333-43.

78. Chua, W.C., et al., *Age-related changes of P2X(1) receptor mRNA in the bladder detrusor from men with and without bladder outlet obstruction.* Experimental gerontology, 2007. **42**(7): p. 686-92.

79. Coleman, P.D., Finch, C. E., Joseph, J. A., *The need for multiple time points in aging studies.* Neurobiol Aging, 1990. **11**: p. 1-2.

80. Miller, R.A., Nadon, N. L., *Principles Of Animal Use For Gerontological Research*, 2005, American Federation for Aging Research (AFAR).

81. Rud, T., *Urethral pressure profile in continent women from childhood to old age.* Acta obstetricia et gynecologica Scandinavica, 1980. **59**(4): p. 331-5.

82. Hilton, P. and S.L. Stanton, *Urethral pressure measurement by microtransducer: the results in symptom-free women and in those with genuine stress incontinence.* Br J Obstet Gynaecol, 1983. **90**(10): p. 919-33.

83. Trowbridge, E.R., et al., *Effects of aging on lower urinary tract and pelvic floor function in nulliparous women.* Obstetrics and gynecology, 2007. **109**(3): p. 715-20.

84. Samsioe, G., et al., *Occurrence, nature and treatment of urinary incontinence in a 70-year-old female population.* Maturitas, 1985. **7**(4): p. 335-42.

85. Kenton, K., et al., *Aging and overactive bladder may be associated with loss of urethral sensation in women.* Neurourology and Urodynamics, 2007. **26**(7): p. 981-4.

86. Forsberg, J.G., *A morphologist's approach to the vagina--age-related changes and estrogen sensitivity.* Maturitas, 1995. **22**(Suppl): p. S7-S15.

87. Yang, J.M., S.H. Yang, and W.C. Huang, *Functional correlates of Doppler flow study of the female urethral vasculature.* Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 2006. **28**(1): p. 96-102.

88. Siracusano, S., et al., *Application of ultrasound contrast agents for the characterization of female urethral vascularization in healthy pre- and postmenopausal volunteers: preliminary report.* European Urology, 2006. **50**(6): p. 1316-22.

89. Liang, C.C., et al., *Three-dimensional power Doppler measurement of perfusion of the periurethral tissue in incontinent women -- a preliminary report.* Acta Obstet Gynecol Scand, 2006. **85**(5): p. 608-13.

90. Yang, J.M., S.H. Yang, and W.C. Huang, *Functional correlates of Doppler flow study of the female urethral vasculature.* Ultrasound Obstet Gynecol, 2006. **28**(1): p. 96-102.

91. Carlile, A., et al., *Age changes in the human female urethra: a morphometric study.* The Journal of urology, 1988. **139**(3): p. 532-5.

92. Verelst, M., J.M. Maltau, and A. Orbo, *Computerised morphometric study of the paraurethral tissue in young and elderly women.* Neurourol Urodyn, 2002. **21**(6): p. 529-33.

93. Perucchini, D., et al., *Age effects on urethral striated muscle. I. Changes in number and diameter of striated muscle fibers in the ventral urethra.* American journal of obstetrics and gynecology, 2002. **186**(3): p. 351-5.

94. Perucchini, D., et al., *Age effects on urethral striated muscle. II. Anatomic location of muscle loss.* American journal of obstetrics and gynecology, 2002. **186**(3): p. 356-60.

95. Clobes, A., J.O. DeLancey, and D.M. Morgan, *Urethral circular smooth muscle in young and old women.* Am J Obstet Gynecol, 2008. **198**(5): p. 587 e1-5.

96. Hanada, M., et al., *Growth inhibition and apoptosis induction by tumor necrosis factor-alpha in human urethral rhabdosphincter satellite cells.* J Urol, 2010. **183**(6): p. 2445-50.

97. Kenton, K., et al., *Urethral and bladder current perception thresholds: normative data in women.* The Journal of urology, 2007. **178**(1): p. 189-92; discussion 192.

98. Romanzi, L.J., A. Groutz, and J.G. Blaivas, *Urethral diverticulum in women: diverse presentations resulting in diagnostic delay and mismanagement.* J Urol, 2000. **164**(2): p. 428-33.

99. Strasser, H., et al., *Urinary incontinence in the elderly and age-dependent apoptosis of rhabdosphincter cells.* Lancet, 1999. **354**(9182): p. 918-9.

100. Rother, P., et al., *Anatomic basis of micturition and urinary continence. Muscle systems in urinary bladder neck during ageing.* Surgical and radiologic anatomy : SRA, 1996. **18**(3): p. 173-7.

101. Bagi, P., et al., *Pressure/cross-sectional area relations in the proximal urethra of healthy males. Part 1: Elastance and estimated pressure in the uninstrumented urethra.* Eur Urol, 1995. **28**(1): p. 51-7.

102. Hammerer, P., et al., *Urethral closure pressure changes with age in men.* The Journal of urology, 1996. **156**(5): p. 1741-3.

103. Tinelli, A., et al., *Age-related pelvic floor modifications and prolapse risk factors in postmenopausal women.* Menopause, 2010. **17**(1): p. 204-12.

104. Lawrence, J.M., et al., *Prevalence and co-occurrence of pelvic floor disorders in community-dwelling women.* Obstet Gynecol, 2008. **111**(3): p. 678-85.

105. Talasz, H., et al., *Evaluation of pelvic floor muscle function in a random group of adult women in Austria.* International Urogynecology Journal and Pelvic Floor Dysfunction, 2008. **19**(1): p. 131-5.

106. Weemhoff, M., K.L. Shek, and H.P. Dietz, *Effects of age on levator function and morphometry of the levator hiatus in women with pelvic floor disorders.* International urogynecology journal, 2010. **21**(9): p. 1137-42.

107. Jundt, K., et al., *Is the histomorphological concept of the female pelvic floor and its changes due to age and vaginal delivery correct?* Neurourology and Urodynamics, 2005. **24**(1): p. 44-50.

108. Norton, P.A., *Pelvic floor disorders: the role of fascia and ligaments.* Clinical obstetrics and gynecology, 1993. **36**(4): p. 926-38.

109. Spence-Jones, C., et al., *Bowel dysfunction: a pathogenic factor in uterovaginal prolapse and urinary stress incontinence.* Br J Obstet Gynaecol, 1994. **101**(2): p. 147-52.

110. Buntzen, S., et al., *Anal and rectal motility responses to distension of the urinary bladder in man.* International journal of colorectal disease, 1995. **10**(3): p. 148-51.

111. Bachmann, G., *Urogenital ageing: an old problem newly recognized.* Maturitas, 1995. **22 Suppl**: p. S1-S5.

112. Stenberg, A., G. Heimer, and U. Ulmsten, *The prevalence of urogenital symptoms in postmenopausal women.* Maturitas, 1995. **22 Suppl**: p. S17-S20.

113. Rossouw, J.E., et al., *Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.* JAMA : the journal of the American Medical Association, 2002. **288**(3): p. 321-33.

114. Grady, D., et al., *Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II).* JAMA : the journal of the American Medical Association, 2002. **288**(1): p. 49-57.

115. Juthani-Mehta, M., et al., *Diagnostic accuracy of criteria for urinary tract infection in a cohort of nursing home residents.* J Am Geriatr Soc, 2007. **55**: p. 1072-7.

116. Tan, J.S., et al., *Determinants of vaginal length.* American journal of obstetrics and gynecology, 2006. **195**(6): p. 1846-50.

117. Cardozo, L., et al., *A systematic review of estrogens for recurrent urinary tract infections: third report of the hormones and urogenital therapy (HUT) committee.* International Urogynecology Journal and Pelvic Floor Dysfunction, 2001. **12**(1): p. 15-20.

118. Lindau, S.T., et al., *Vaginal self-swab specimen collection in a home-based survey of older women: methods and applications.* The journals of gerontology. Series B, Psychological sciences and social sciences, 2009. **64 Suppl 1**: p. i106-18.

119. Berry, S.J., et al., *The development of human benign prostatic hyperplasia with age.* J Urol, 1984. **132**(3): p. 474-9.

120. Shibata, Y., et al., *Changes in the endocrine environment of the human prostate transition zone with aging: simultaneous quantitative analysis of prostatic sex steroids and comparison with human prostatic histological composition.* Prostate, 2000. **42**(1): p. 45-55.

121. Griffiths, K., *Estrogens and prostatic disease. International Prostate Health Council Study Group.* The Prostate, 2000. **45**(2): p. 87-100.

122. Kramer, G., D. Mitteregger, and M. Marberger, *Is benign prostatic hyperplasia (BPH) an immune inflammatory disease?* Eur Urol, 2007. **51**(5): p. 1202-16.

123. Roehrborn, C.G., et al., *Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group.* Urology, 1999. **54**(4): p. 662-9.

124. Jacobsen, S.J., et al., *Treatment for benign prostatic hyperplasia among community dwelling men: the Olmsted County study of urinary symptoms and health status.* J Urol, 1999. **162**(4): p. 1301-6.

125. McConnell, J.D., M.J. Barry, and R.C. Bruskewitz, *Benign prostatic hyperplasia: diagnosis and treatment. Agency for Health Care Policy and Research.* Clin Pract Guidel Quick Ref Guide Clin, 1994(8): p. 1-17.

126. Berges, R. and M. Oelke, *Age-stratified normal values for prostate volume, PSA, maximum urinary flow rate, IPSS, and other LUTS/BPH indicators in the German male community-dwelling population aged 50 years or older.* World journal of urology, 2011. **29**(2): p. 171-8.

127. Mishra, V.C., et al., *Does intraprostatic inflammation have a role in the pathogenesis and progression of benign prostatic hyperplasia?* BJU Int, 2007. **100**(2): p. 327-31.

128. Anjum, I., et al., *Prostatic infarction/infection in acute urinary retention secondary to benign prostatic hyperplasia.* J Urol, 1998. **160**(3 Pt 1): p. 792-3.

129. Bianchi-Frias, D., et al., *The effects of aging on the molecular and cellular composition of the prostate microenvironment.* PLoS ONE, 2010. **5**(9).

130. Sprenger, C.C., S.R. Plymate, and M.J. Reed, *Aging-related alterations in the extracellular matrix modulate the microenvironment and influence tumor progression.* International journal of cancer. Journal international du cancer, 2010. **127**(12): p. 2739-48.

131. Ouslander, J.G., et al., *Pyuria among chronically incontinent but otherwise asymptomatic nursing home residents.* Journal of the American Geriatrics Society, 1996. **44**(4): p. 420-3.

132. Nicolle, L.E., *Urinary tract infection in geriatric and institutionalized patients.* Curr Opin Urol, 2002. **12**(1): p. 51-5.

133. Ouslander, J.G., et al., *Does eradicating bacteriuria affect the severity of chronic urinary incontinence in nursing home residents?* Ann Intern Med, 1995. **122**(10): p. 749-54.

134. Juthani-Mehta, M., Tinetti, M, Perrelli, E, Towle, V, Quagliarello, V., *Role of dipstick testing in the evaluation of UTI in nursing home residents.* Infect Control Hospi Epidemiol, 2007. **28**: p. 889-91

135. Steel, N., et al., *Self reported receipt of care consistent with 32 quality indicators: national population survey of adults aged 50 or more in England.* BMJ, 2008. **337**: p. a957.

136. Arnett, R.H., 3rd, et al., *National health expenditures, 1988. Office of National Cost Estimates.* Health care financing review, 1990. **11**(4): p. 1-41.

137. Gupta, S., H.M. Rappaport, and L.T. Bennett, *Inappropriate drug prescribing and related outcomes for elderly medicaid beneficiaries residing in nursing homes.* Clinical therapeutics, 1996. **18**(1): p. 183-96.

138. Golden, A.G., et al., *Inappropriate medication prescribing in homebound older adults.* Journal of the American Geriatrics Society, 1999. **47**(8): p. 948-53.

139. O'Connor, K., O'Mahony, D., *Drugs and ageing*. Medicine for older patients: cases and practice., ed. R. Liston, Mulkerrin, E.C. 2003, Dublin: Eireann Healthcare Publications.

140. London., R.C.o.P.o., *Medication for older people*, 1997, Royal College of Physicians: London.

141. Kennerfalk, A., et al., *Geriatric drug therapy and healthcare utilization in the United kingdom.* The Annals of pharmacotherapy, 2002. **36**(5): p. 797-803.

142. Ruby, C.M., et al., *The effect of medication use on urinary incontinence in community-dwelling elderly women.* J Am Geriatr Soc, 2010. **58**(9): p. 1715-20.

143. Cigolle, C.T., et al., *Geriatric conditions and disability: the Health and Retirement Study.* Ann Intern Med, 2007. **147**(3): p. 156-64.

144. Smith, A.L., et al., *Correlates of Urinary Incontinence in Community-Dwelling Older Latinos.* J Am Geriatr Soc, 2010. **58**: p. 1170-1176.

145. Yoshida, Y., et al., *Prevalence and characteristics of urinary incontinence in community-dwelling-elderly as determined by comprehensive health examination and interview for the prevention of geriatric syndrome and bed-ridden state.* Nippon Ronen Igakkai Zasshi - Japanese Journal of Geriatrics, 2007. **44**: p. 83-9.

146. Huang, A., et al., *Study of Osteoporotic Fractures Research Group. Urinary incontinence in older community-dwelling women: the role of cognitive and physical function decline.* Obstetrics & Gynecology, 2007. **109**: p. 909-16.

147. Danforth, K.N., et al., *Physical Activity and Urinary Incontinence Among Healthy, Older Women.* Obstetrics & Gynecology, 2007. **109**: p. 721-727.

148. Rait, G., et al., *Prevalence of cognitive impairment: results from the MRC trial of assessment and management of older people in the community.* Age Ageing, 2005. **34**(3): p. 242-248.

149. Danforth, K.N., et al., *Type 2 Diabetes Mellitus and Risk of Stress, Urge and Mixed Urinary Incontinence.* Journal of Urology, 2009. **181**: p. 193-197.

150. Brown, J.S., et al., *Prevalence and Risk Factors for Urinary Incontinence in Women with type 2 Diabetes and Impaired Fasting Glucose.* Diabetes Care, 2006. **29**: p. 1307-1312.

151. Del-Ser, T., D.G. Munoz, and V. Hachinski, *Temporal pattern of cognitive decline and incontinence is different in Alzheimer's disease and diffuse Lewy body disease.* Neurology, 1996. **46**(3).

152. Meier, U., A. Konig, and C. Miethke, *Predictors of outcome in patients with normal-pressure hydrocephalus.* European Neurology, 2004. **51**(2): p. 59-67.

153. Wullner, U., et al., *Autonomic dysfunction in 3414 Parkinson's disease patients enrolled in the German Network on Parkinson's disease (KNP e V.) the effect of ageing.* European Journal of Neurology, 2007. **14**(1405-1408).

154. Ehrt, U., et al., *Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study.* J Neurol Neurosurg Psychiatry, 2010. **81**(2): p. 160-5.

155. Gilman, S., et al., *Second consensus statement on the diagnosis of multiple system atrophy.* Neurology, 2008. **71**: p. 670-676.

156. Hahn, K. and G. Ebersbach, *Sonographic assessment of urinary retention in multiple system atrophy and idiopathic Parkinson's.* Movement Disorders, 2005. **20**(11): p. 499-502.

157. Pantoni, L., *Leukoaraiosis: from an ancient term to an actual marker of poor prognosis.* Stroke, 2008. **39**(5): p. 1401-1403.

158. Hachinski, V., P. Potter, and H. Merskey, *Leuko-Araiosis.* Arch Neurology, 1987. **44**: p. 21-23.

159. Pantoni, L. and J.H. Garcia, *The significance of cerebral white matter abnormalities 100 years after Binswanger's report. A review.* Stroke, 1995. **26**(7): p. 1293-1301.

160. Sakakibara, R., et al., *Urinary function in elderly people with and without leukoaraiosis: relation to cognitive and gait function.* J.Neurol.Neurosurg.Psychiatry, 1999. **67**(5): p. 658-660.

161. Poggesi, A., et al., *Urinary complaints in Nondisabled Elderly People with Age-related White Matter Changes:The Leukoariasis and Disability (LADIS) Study.* J Am Geriatr Soc, 2008. **56**: p. 1638-1643.

162. Kuchel, G.A., et al., *Localization of the brain white matter hyperintensities and urinary incontinence in community-dwelling older adults.* Journals of Gerontology Series A-Biological Science & Medical Sciences, 2009. **64**(8): p. 902-909.

163. Engberg, S., et al., *Prevalence and recognition of depressive symptoms among homebound older adults with urinary incontinence.* Journal of Geriatric Psychiatry & Neurology, 2001. **14**: p. 130-9.

164. Herzog, A., et al., *Urinary incontinence and psychological distress among older adults.* Psychology & Aging, 1988. **3**: p. 115-21.

165. Cohen, S.J., et al., *Communication between older adults and their physicians about urinary incontinence.* J Gerontol A Biol Sci Med Sci, 1999. **54**(1): p. M34-7.

166. Johnson, T.n., et al., *The association of urinary incontinence with poor self-rated health.* J Am Geriatr Soc, 1998. **46**: p. 693-9.

167. Dugan, E., et al., *The association of depressive symptoms and urinary incontinence among older adults.* J Am Geriatr Soc, 2000. **48**(4): p. 413-6.

168. Fultz, N.H., et al., *The impact of own and spouse's urinary incontinence on depressive symptoms.* Social Science & Medicine, 2005. **60**(11): p. 2537-2548.

169. Black, S., J. Goodwin, and K. Markides, *The association between chronic diseases and depressive symptomatology in older Mexican Americans.* Journals of Gerontology Series A-Biological Sciences & Medical Sciences, 1998. **53**: p. M188-94.

170. Grimby, A., et al., *The influence of urinary incontinence on the quality of life of elderly women.* Age Ageing, 1993. **22**(2): p. 82-9.

171. Song, H. and J. Bae, *Prevalence of urinary incontinence and lower urinary tract symptoms for community-dwelling elderly 85 years of age and older.* Journal of Wound, Ostomy, & Continence Nursing, 2007. **34**: p. 535-41.

172. Fultz, N.H. and A.R. Herzog, *Self-Reported Social and Emotional Impact of Urinary Incontinence.* Journal of the American Geriatrics Society, 2001. **49**(7): p. 892-899.

173. Ko, Y., et al., *The impact of urinary incontinence on quality of life of the elderly.* Am J Managed Care, 2005. **11(4 Suppl)**: p. S103-11.

174. Malmstrom, T.K., et al., *Urinary and fecal incontinence and quality of life in African Americans.* Journal of the American Geriatrics Society, 2010. **58**(10): p. 1941-5.

175. Bogner, H.R., et al., *Urinary Incontinence and Psychological Distress in Community-Dwelling Older Adults.* Journal of the American Geriatrics Society, 2002. **50**(3): p. 489-495.

176. Bogner, H.R., et al., *The temporal relationship between anxiety disorders and urinary incontinence among community-dwelling adults.* J Anxiety Disord, 2010.

177. Coyne, K.S., et al., *The burden of lower urinary tract symptoms: evaluating the effect of LUTS on health-related quality of life, anxiety and depression: EpiLUTS.* BJU international, 2009. **103 Suppl 3**: p. 4-11.

178. Coyne, K.S., et al., *Urinary incontinence and its relationship to mental health and health-related quality of life in men and women in Sweden, the United Kingdom, and the United States.* European Urology, 2012. **61**(1): p. 88-95.

179. Sexton, C.C., et al., *Prevalence and Effect on Health-Related Quality of Life of Overactive Bladder in Older Americans: Results from the Epidemiology of Lower Urinary Tract Symptoms Study.* J Am Geriatr Soc, 2011. **59**: p. 1465-1470.

180. Perchon, L.F.G., et al., *Quality of Life in Elderly Men with Aging Symptoms and Lower Urinary Tract Symptoms (LUTS).* Neurourol.Urodyn., 2011. **30**: p. 1473-1477.

181. Hui-Chi, H., *A checklist for assessing the risk of falls among the elderly.* Journal of Nursing Research, 2004. **12**(2): p. 131-142.

182. Nakagawa, H., Ikeda, Y., Nui, K., Ohmori-Matsuda, K., Nakaya, N., Imanishi, R., Nagatomi, R., Tsuji, I., Arai.Y., *Does nocturia increase fall-related fractures and mortality in a community dwelling elderly population aged 70 years and over? Results of a 3 year prospective cohort study in Japan.* Neuro Urol, 2008. **27**(7): p. 674 - 675.

183. Nakagawa, H., Niu, K., Hozawa, A., Ikeda, Y., Kaiho, Y., Ohmori-Matsuda, K. et al. , *Impact of nocturia on bone fracture and mortality in older individuals: A Japanese longitudinal cohort study.* J Urol, 2010. **184**(4): p. 1413- 1418.

184. Vaughan, C.P., Brown, C.J., Goode, P.S., Burgio, K.L., Allman, R.M., Johnson, T.M.,2nd. , *The association of nocturia with incident falls in an elderly community-dwelling cohort.* Int J Clin Pract, 2010 **64**(5): p. 577-583. .

185. Stewart, R.B., et al., *Nocturia: a risk factor for falls in the elderly.* J Am Geriatr Soc, 1992. **40**(12): p. 1217-20.

186. Coyne, K.S., et al., *The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study.* BJU international, 2009. **104**(3): p. 352-60.

187. Takazawa, K. and K. Arisawa, *Relationship between the type of urinary incontinence and falls among frail elderly women in Japan.* J Med Invest, 2005. **52**(3-4): p. 165-71.

188. Hitcho, E.B., Krauss, M.J., Birge, S., Claiborne- Dunagan, W., Fischer, .I, Johnson, S. et al. , *Characteristics and circumstances of falls in a hospital setting: A prospective analysis.* . J Gen Int Med, 2004. **19**(7): p. 732-739.

189. Cameron, I.D., et al., *Interventions for preventing falls in older people in nursing care facilities and hospitals.* Cochrane database of systematic reviews, 2010(1): p. CD005465.

190. Kron, M., et al., *Risk indicators for falls in institutionalized frail elderly.* American journal of epidemiology, 2003. **158**(7): p. 645-53.

191. Mizrahi, E.H., et al., *Bladder management and the functional outcome of elderly ischemic stroke patients.* Arch Gerontol Geriatr, 2010.

192. Jordan, L.A., et al., *Continence management in acute stroke: a survey of current practices in Australia.* J Adv Nurs, 2010.

193. Wilson, D., et al., *Urinary incontinence in stroke: results from the UK National Sentinel Audits of Stroke 1998-2004.* Age Ageing, 2008. **37**(5): p. 542-6.

194. Booth, J., et al., *Rehabilitation nurses practices in relation to urinary incontinence following stroke: a cross-cultural comparison.* J Clin Nurs, 2009. **18**(7): p. 1049-58.

195. Chanfreau-Rona, D., S. Bellwood, and B. Wylie, *Assessment of a behavioral programme to treat incontinent patients in psychogeriatric wards.* British Journal of clinical Psychology, 1984. **23**(4): p. 273-279.

196. Chanfreau-Rona, D., B. Wylie, and S. Bellwood, *Behaviour treatment of daytime incontinence in elderly male and female patients.* Behavioural Psychotherapy, 1986. **14**(1): p. 13-20.

197. Namazi, K.H., et al., *Environmental modifications in a specially designed unit for the care of patients with Alzheimer's' disease: An overview and introduction.* American Journal of Alzheimer's Disease and other dementias, 1991a. **6**: p. 3-9.

198. Namazi, K.H. and B.D. Johnson, *Environmental effects on incontinence problems in Alzheimer's disease patients* American Journal of Alzheimer's Disease and other dementias, 1991b. **6**: p. 16-21.

199. Namazi, K.H. and B.D. Johnson, *Physical environmental cues to reduce the problems of incontinence in Alzheimer's disease units.* American Journal of Alzheimer's Disease and other dementias, 1991c. **6**.

200. Sacco-Peterson, M. and L. Borell, *Struggles for autonomy in self-care: the impact of the physical and socio-cultural environment in a long-term care setting.* Scandinavian Journal of Caring Sciences, 2004. **18**: p. 376-386.

201. Landi, F.e.a., *Potentially reversible risk factors and urinary incontinence in frail older people living in community.* Age and Ageing, 2003. **32**: p. 194-199.

202. Offermans, M.P.W., et al., *Prevalence of urinary incontinence and associated risk factors in nursing home residents: A systematic review.* Neurourology and Urodynamics, 2009. **28**: p. 288-294.

203. MacDonald, C.D. and L. Butler, *Silent no more: Elderly women's stories of living with urinary incontinence in long-term care.* Journal of Gerontological Nursing, 2007. **33**(1): p. 14-20.

204. Mansson-Lindstrom, A., O. Dehlin, and A. Isacsson, *Urinary incontinence and napkins.* Scandinavian Journal of Caring Sciences, 1992. **6**(4): p. 211-218.

205. Campbell, E.B., et al., *Effect of an incontinence training program on nursing home staff's knowledge, attitudes and behavior.* The Gerontologist, 1991. **3**(6): p. 788-794.

206. Cheater, F., *Nurses' educational preparation and knowledge concerning continence promotion.* Journal of Advanced Nursing, 1992. **17**: p. 328-338.

207. Collette, C., G. Bravo, and L.M. Tu, *Development of a urinary incontinence education program using a competency-based approach and case method.* Journal for Nurses in Staff Development, 2009. **25**(4): p. E5-E10.

208. Collette, C., G. Leclerc, and l. Tu, M., *Effectiveness of a geriatric urinary incontinence educational program for nursing staff.* Nursing Leadership, 2003. **16**(4): p. 99-109.

209. Du Beau, C.E., J.G. Ouslander, and M.H. Palmer, *Knowledge and attitudes of nursing home staff and surveyors about the revised federal guidance for incontinence care.* Gerontologist, 2007. **47**(4): p. 468-479.

210. Freundl, M. and J. Dugas, *Urinary incontinence in the elderly: Knowledge and attitude of long-term care staff: .* Geriatric Nursing, 1992. **March/April**: p. 70-75.

211. Henderson, J.S. and M.S. Kashka, *Development and testing of the urinary incontinence scales.* 19, 1999. **2**(109-119).

212. Henderson, J.S. and M.S. Kashka, *Effect of knowledge, attitude and belief on nurses' practice regarding urinary incontinence in adults.* Urologic Nursing, 2000. **20**(5): p. 291-305.

213. Karlowicz, K.A., *Evaluation of the urinary incontinence scales to measure change after experiential learning: A pilot study.* Urologic Nursing, 2009. **29**(1): p. 40-46.

214. Karlowicz, K.A. and K.L. Palmer, *Engendering student empathy for disabled clients with urinary incontinence through experiential learning.* Urologic Nursing, 2006. **26**(5): p. 373-379.

215. Lekan-Rutledge, D., *Diffusion of innovation: A model for implementation of prompted voiding in long-term care settings.* Journal of Gerontological Nursing, 2000. **26**(4): p. 25-33.

216. Palmer, M.H., *Nurses' knowledge and beliefs about continence interventions in long-term care.* Journal of Advanced Nursing, 1995. **21**: p. 1065-1072.

217. Resnick, B., et al., *Nursing staff beliefs and expectations about continence care in nursing homes.* Journal of Wound, Ostomy and Continence Nursing, 2006. **33**(6): p. 610-618.

218. Saxer, S., et al., *Knowledge, beliefs, attitudes and self-reported practice concerning urinary incontinence in nursing home care.* Journal of Wound, Ostomy & Continence Nursing, 2009. **36**(5): p. 539-544.

219. Saxer, S., et al., *Nurses' knowledge and practice about urinary incontinence in nursing homes.* Nurse Education Today, 2008. **28**: p. 926-934.

220. Stevens, A.B., et al., *Teaching and maintaining behavior management skills with nursing assistants in a nursing home.* The Gerontologist, 1998. **38**(3): p. 379-384.

221. Vinsnes, A.G., et al., *Healthcare personnel's attitudes towards patients with urinary incontinence.* Journal of Clinical Nursing, 2001. **10**: p. 455-462.

222. Vinsnes, A.G., G.E. Harkless, and S. Nyronning, *Unit-based intervention to improve urinary incontinence in frail elderly.* Nursing Science & Research in the Nordic Countries, 2007. **85**(27): p. 53-56.

223. Yu, L.C., et al., *Urinary incontinence: nursing home staff reactions toward residents.* Journal of Gerontological Nursing, 1991. **17**(11): p. 34-41.

224. Williams, K.S., N.J. Crichton, and B. Roe, *Disseminating research evidence. a controlled trial in continence care.* Journal of Advanced Nursing, 1997. **25**: p. 691-698.

225. Connor, P.A. and B.M. Kooker, *Nurses' knowledge, attitudes and practice in managing urinary incontinence in the acute care setting.* Medical Surgical Nursing, 1996. **5**(2): p. 87-117.

226. Norheim, A. and A.G. Vinsnes, *Staff's attitudes towards hospitalised elderly patients with urinary incontinence.* Nordic Journal of Nursing Research & Clinical Studies, 2005. **25**(1): p. 21-25.

227. Mason, M. and S. Tully, *Urinary incontinence in the older acute care population: effects of knowledge, attitudes and beliefs of nurses on continence management.* Perspectives, 2002. **26**(3): p. 4-9.

228. Cooper, G. and E. Watt, *An exploration of acute care nurses' approach to assessment and management of people with urinary incontinence.* Journal of Wound, Ostomy and Continence Nursing, 2003. **30**(6): p. 305-313.

229. Dingwall, L. and E. McLafferty, *Do nurses promote urinary continence in hospitalized older people? An exploratory study.* Journal of Clinical Nursing, 2006. **15**(10): p. 1276-1286.

230. Thekkinkattil, D.K., et al., *Awareness of investigations and treatment of faecal incontinence among the general practitioners: a postal questionnaire survey.* Colorectal Disease, 2007. **10**: p. 263-267.

231. Morbidity And Mortality Weekly Report, *Knowledge, attitudes, and practices of physicians regarding urinary incontinence in persons aged > or = 65 years--Massachusetts and Oklahoma, 1993.* Morbidity And Mortality Weekly Report, 1995. **44**(40): p. 747, 753-4.

232. Szonyi, G. and R. Millard, *Controlled trial evaluation of a General Practitioner education package on incontinence: use of a mailed questionnaire.* British Journal of Urology, 1994. **73**(6): p. 615-620.

233. Albers-Heitner, P., et al., *Adherence to professional guidelines for patients with urinary incontinence by general practitioners: a cross-sectional study.* Journal of Evaluation in Clinical Practice, 2008. **14**: p. 807-811.

234. Swanson, J.G., et al., *Urinary incontinence in Canada: national survey of family physician's knowledge, attitudes and practices.* Canadian Family Physician, 2002. **48**: p. 86-92.

235. Branch, L.G., et al., *Urinary Incontinence knowledge among community-dwelling people 65 years of age and older.* Journal of the American Geriatric Society, 1994. **42**: p. 1258-1262.

236. Muller, N., *What Americans understand and how they are affected by bladder control problems: Highlights of recent nationwide consumer research* Urologic Nursing, 2005. **25**(2): p. 109.

237. Evans, D., J. Wood, and L. Lambert, *A review of physical restraint minimization in the acute and residential care settings.* Journal of Advanced Nursing, 2002. **40**(6): p. 616-625.

238. Schnelle, J.F., et al., *The minimum data set urinary incontinence quality indicators: do they reflect differences in care processes related to incontinence?* Medical Care, 2003. **41**(8): p. 909-922.

239. Funderburg Mather, S. and T. Bakas, *Nursing assistants' perceptions of their ability to provide continence care.* Geriatric Nursing, 2002. **23**(2): p. 76-81.

240. Harke, J.M. and K. Richgels, *Barriers to implementing a continence program in nursing homes.* Clinical Nursing Research, 1992. **1**(2): p. 158-169.

241. Lekan-Rutledge, D., M.H. Palmer, and M. Belyea, *In their own words: Nursing Assistants' perceptions of barriers to implementation of prompted voiding in long-term care.* The Gerontologist, 1998. **38**(3): p. 370-378.

242. Tannenbaum, C., D. Labrecque, and C. Lepage, *Understanding barriers to continence care in institutions.* Canadian Journal on Aging, 2005. **24**(2): p. 151-160.

243. O'Connell, B., et al., *Evaluation of resources for the promotion of continence in long term care: A national consultative approach*, 2005, Deakin University, Australia. p. 2-205.

244. Getliffe, K., et al., *Absorbent products for incontinence: treatment effects and impacts on quality of life.* Journal of Clinical Nursing, 2007. **16**: p. 1936-1945.

245. Wagg, A., et al., *National audit of continence care for older people: management of urinary incontinence* Age and Ageing, 2008. **37**: p. 39-44.

246. Samuelsson, E., L. Mansson, and I. Milsom, *Incontinence aids in Sweden: users and costs.* BJU International, 2001. **88**: p. 893-898.

247. Sørby, L., et al., *Urinary incontinence and use of pads - clinical features and need for help in home care at 11 sites in Europe.* Scandinavian Journal of Caring Sciences, 2008. **23**: p. 33-44.

248. Du Moulin, M.F.M.T., et al., *Urinary incontinence in older adults receiving home care diagnosis and strategies.* Scandinavian Journal of Caring Sciences, 2009. **23**: p. 222-230.

249. Palese, A., et al., *Incontinence pad use in patients admitted to medical wards: an Italian multicenter prospective cohort study.* Journal of Wound, Ostomy & Continence Nursing, 2007. **34**(6): p. 649-654.

250. Kadir, F.S., *The "Pamper" generation: an explorative study into the use of incontinence aids in a local acute peripheral care setting.* Singapore nursing journal, 2004. **31**(4): p. 34-38.

251. Ostaszkiewicz, J., B. O'Connell, and L. Millar, *Incontinence: Managed or mismanaged in hospital settings?* International Journal of Nursing Practice, 2008. **14**: p. 493-500.

252. Starer, P. and L.S. Libow, *Obscuring urinary incontinence: Diapering the elderly.* Journal of the American Geriatric Society, 1985. **33**(12): p. 842-846.

253. Zisberg, A., *Incontinence brief use in acute hospitalized patients with no prior incontinence.* Journal of Wound, Ostomy & Continence Nursing, 2011. **38**(5): p. 559-564.

254. Rodriguez, N.A., C.M. Sackley, and F.J. Badger, *Exploring the facets of continence care: a continence survey of care homes for older people in Birmingham.* Journal of Clinical Nursing, 2007. **16**(5): p. 954-962.

255. Brandeis, G.H., et al., *The prevalence of potentially remediable urinary incontinence in frail older people: A study using the Minimum Data Set.* Journal of the American Geriatric Society, 1997. **45**: p. 179-184.

256. Rogers, M., et al., *Use of urinary collection devices in skilled nursing facilities in five states.* J Am Geriatr Soc, 2008. **56**(5): p. 854-861.

257. Pringle Specht, J.K.P., S. Salsbury-Lyons, and M.L. Maas, *Patterns and treatments of urinary incontinence on special care units.* Journal of Gerontological Nursing, 2002. **28**(5): p. 13-21.

258. Omli, R., et al., *Pad per day usage, urinary incontinence and urinary tract infections in nursing home residents.* Age and Ageing, 2010. **39**(5): p. 549-554.

259. Schroder, A., Abrams, P., Andersson, K-E., Artibani, W., Chapple, C.R., Drake, M.J., Hampel, C., Neisius, A., Tubaro, A., Thuroff, J.W., *Guidelines on urinary incontinence*, J.W. Thuroff, Editor 2010, European Association of Urology.

260. Woodford, H. and J. George, *NICE guidelines on urinary incontinence in women.* Age Ageing, 2007. **36**(3): p. 349-50.

261. Jones, C., J. Hill, and C. Chapple, *Management of lower urinary tract symptoms in men: summary of NICE guidance.* BMJ, 2010. **340**: p. c2354.

262. DuBeau, C.E., *Beyond the bladder: management of urinary incontinence in older women.* Clin Obstet Gynecol, 2007. **50**(3): p. 720-34.

263. Fung, C.H., et al., *Quality indicators for the screening and care of urinary incontinence in vulnerable elders.* J Am Geriatr Soc, 2007. **55 Suppl 2**: p. S443-9.

264. Schnelle, J.F. and R.L. Smith, *Quality indicators for the management of urinary incontinence in vulnerable community-dwelling elders.* Ann Intern Med, 2001. **135**(8 Pt 2): p. 752-8.

265. Wagg, A., et al., *National audit of continence care for older people: management of urinary incontinence.* Age Ageing, 2008. **37**(1): p. 39-44.

266. Wagg, A., et al., *National audit of continence care for older people: results of a pilot study*.* J Eval Clin Pract, 2005. **11**(6): p. 525-32.

267. Wagg, A., et al., *To what extent are national guidelines for the management of urinary incontinence in women adhered? Data from a national audit.* BJOG : an international journal of obstetrics and gynaecology, 2011. **118**(13): p. 1592-600.

268. Wagg, A., et al., *Do self-reported 'integrated' continence services provide high-quality continence care?* Age Ageing, 2009. **38**(6): p. 730-3.

269. Saliba, D., et al., *The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community.* Journal of the American Geriatrics Society, 2001. **49**(12): p. 1691-9.

270. Barreto, P.D., C. Greig, and A.M. Ferrandez, *Detecting and categorizing frailty status in older adults using a self-report screening instrument.* Archives of gerontology and geriatrics, 2011.

271. Montero-Odasso, M., et al., *Identifying mobility heterogeneity in very frail older adults. Are frail people all the same?* Archives of gerontology and geriatrics, 2009. **49**(2): p. 272-7.

272. Warshaw, G.A., et al., *Community physician education in geriatrics: applying the assessing care of vulnerable elders model with a multisite primary care group.* Journal of the American Geriatrics Society, 2010. **58**(9): p. 1780-5.

273. McDowell, B.J., et al., *Identification and intervention for urinary incontinence by community physicians and geriatric assessment teams.* J Am Geriatr Soc, 1994. **42**(5): p. 501-5.

274. Ouslander, J., et al., *Prospective evaluation of an assessment strategy for geriatric urinary incontinence.* J Am Geriatr Soc, 1989. **37**(8): p. 715-24.

275. Torres, C., et al., *Clinical approach to urinary incontinence: a comparison between internists and geriatricians.* Int Urol Nephrol, 2001. **33**(3): p. 549-52.

276. Bland, D.R., et al., *The effects of implementation of the Agency for Health Care Policy and Research urinary incontinence guidelines in primary care practices.* J Am Geriatr Soc, 2003. **51**(7): p. 979-84.

277. Watson, N.M., et al., *Use of the Agency for Health Care Policy and Research Urinary Incontinence Guideline in nursing homes.* J Am Geriatr Soc, 2003. **51**(12): p. 1779-86.

278. Okamura, K., et al., *Diagnosis and treatment of lower urinary tract symptoms in the elderly by general practitioners.* Geriatr Gerontol Int, 2008. **8**(2): p. 119-25.

279. Okamura, K., Nojiri, Y., Ohshima, S. , *Practical Manual for LUTS Evaluation and Treatment in the Elderly for General Practitioners.*, 2005.

280. van Gerwen, M. and A.L. Lagro-Janssen, *[Diagnostic value of patient history and physical examination in elderly patients with urinary incontinence; a literature review].* Ned Tijdschr Geneeskd, 2006. **150**(32): p. 1771-5.

281. Albers-Heitner, P.C., et al., *Effectiveness of involving a nurse specialist for patients with urinary incontinence in primary care: results of a pragmatic multicentre randomised controlled trial.* International journal of clinical practice, 2011. **65**(6): p. 705-12.

282. Resnick, N.M., et al., *Misdiagnosis of urinary incontinence in nursing home women: prevalence and a proposed solution.* Neurourol Urodyn, 1996. **15**(6): p. 599-613; discussion 613-8.

283. Diokno, A.C., T.J. Wells, and C.A. Brink, *Urinary incontinence in elderly women: urodynamic evaluation.* J Am Geriatr Soc, 1987. **35**(10): p. 940-6.

284. Grosshans, C., Y. Passadori, and B. Peter, *Urinary retention in the elderly: a study of 100 hospitalized patients.* J Am Geriatr Soc, 1993. **41**(6): p. 633-8.

285. Bonde, H.V., et al., *Residual urine in 75-year-old men and women. A normative population study.* Scandinavian journal of urology and nephrology, 1996. **30**(2): p. 89-91.

286. *Urinary incontinence guidelines panel*, 1992, US Department of Health and Human Services Agency for Healthcare Quality and Research: Rockville MD.

287. Bright, E., R. Pearcy, and P. Abrams, *Ultrasound estimated bladder weight in men attending the uroflowmetry clinic.* Neurourology and Urodynamics, 2011. **30**(4): p. 583-6.

288. Ouslander, J.G., *Intractable incontinence in the elderly.* BJU Int, 2000. **85 Suppl 3**: p. 72-8; discussion 81-2.

289. DuBeau, C.E., et al., *Incontinence in the frail elderly: report from the 4th International Consultation on Incontinence.* Neurourol Urodyn, 2010. **29**(1): p. 165-78.

290. Nicolle, L.E., *Urinary tract infections in the elderly.* Clin Geriatr Med, 2009. **25**(3): p. 423-36.

291. Ouslander, J.G., *Intractable incontinence in the elderly.* BJU International, 2000. **85**(Suppl 3): p. 72-8; discussion 81-2.

292. Ostaszkiewicz, J., B. O'Connell, and T. Dunning, *Residents' perspectives on urinary incontinence: a review of literature.* Scandinavian journal of caring sciences, 2011.

293. DuBeau, C., D. Kiely, and N. Resnick, *Quality of life impact of urge incontinence in older persons: a new measure and conceptual structure.* J Am Geriatr Soc, 1999. **47**: p. 989-994.

294. DuBeau, C., S. Simon, and J. Morris, *Impact of urinary incontinence on quality of life in nursing home residents.* J Am Geriatr Soc, 2006: p. 1325-33.

295. Hawkins, K., et al., *The prevalence of urinary incontinence and its burden on the quality of life among older adults with medicare supplement insurance.* Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation, 2011. **20**(5): p. 723-32.

296. Fonda, D. and P. Abrams, *Cure sometimes, help always--a "continence paradigm" for all ages and conditions.* Neurourology & Urodynamics, 2006. **25**: p. 290-2.

297. Mitteness, L.S. and J.C. Barker, *Stigmatizing a "normal" condition: urinary incontinence in late life.* Medical Anthropology Quarterly, 1995. **9**(2): p. 188-210.

298. DuBeau, C.E., *Urinary incontinence management: new questions from old assumptions.* Journal of the American Geriatrics Society, 2001. **49**(6): p. 829-30.

299. Houghman, G.W., et al., *Empirical research on informed consent with the cognitively impaired.* Irb: a Review of Human Subjects Research, 2003. **Suppl 25**(5): p. S26-S32.

300. Cai, L. and J. Lubitz, *Was there compression of disability for older Americans from1992 to 2003?* Demography, 2007. **44**: p. 479-495.

301. Wirth, R. and C.C. Sieber, *Health care professionals underestimate the mean life expectancy of older people.* Gerontology, 2012. **58**(1): p. 56-9.

302. Murray, D., et al., *The ten-year rule revisited: accuracy of clinicians' estimates of life expectancy in patients with localized prostate cancer.* Urology, 2002. **60**: p. 258–63.

303. Sajid, S., et al., *Individualized decision-making for older men with prostate cancer: balancing cancer control with treatment consequences across the clinical spectrum.* Seminars in oncology, 2011. **38**(2): p. 309-25.

304. Walter, L. and K. Covinsky, *Cancer screening in elderly patients: a framework for individualized decision making.* JAMA, 2001. **285**: p. 2750-6.

305. Fried, L., et al., *Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study.* JAMA, 1998. **279**: p. 585-92.

306. Keeler, E., et al., *The impact of functional status on life expectancy in older persons.* The journals of gerontology. Series A, Biological sciences and medical sciences, 2010. **65**(7): p. 727-33.

307. Larson, E., et al., *Survival after Initial Diagnosis of Alzheimer Disease.* Ann Intern Med, 2004. **140**: p. 501-509.

308. Simmons, S.F. and J.F. Schnelle, *Strategies to measure nursing home residents' satisfaction and preferences related to incontinence and mobility care: implications for evaluating intervention effects.* Gerontologist, 1999. **39**(3): p. 345-55.

309. Johnson, T.M., et al., *Urinary incontinence treatment preferences in long-term care.[see comment].* Journal of the American Geriatrics Society, 2001. **49**(6): p. 710-8.

310. Pfisterer, M.H., et al., *Geriatric patients' preferences for treatment of urinary incontinence: a study of hospitalized, cognitively competent adults aged 80 and older.* J Am Geriatr Soc, 2007. **55**(12): p. 2016-22.

311. O'Dell, K.K., Jacelon, C., Morse, A.N., *"I'd rather just go on as I am" - pelvic floor care preferences of frail, elderly women in residential care.* Urologic nursing, 2008. **28**(1): p. 36 - 47.

312. Anger, J., et al., *Increasing costs of urinary incontinence among femle Medicare beneficiaries.* J Urol, 2006. **176**: p. 247–51.

313. Wilson, L., et al., *Annual direct cost of urinary incontinence.* Obstet Gynecol, 2001. **98**: p. 398-406.

314. Reeves, P., et al., *The current and future burden and cost of overactive bladder in five European countries.* Eur Urol, 2006. **50**: p. 1050-57.

315. Ouslander, J.G., et al., *Overactive bladder: special considerations in the geriatric population.* American Journal of Managed Care, 2000. **6**(11 Suppl): p. S599-606.

316. Darkow, T., C. Fontes, and T. Williamson, *Costs associated with the management of overactive bladder and related comorbidities.* Pharmacotherapy, 2005. **25**: p. 511–19.

317. Sung, W., et al., *Socioeconomic costs of overactive bladder and stress urinary incontinence in Korea.* International neurourology journal, 2012. **16**(1): p. 23-9.

318. Hu, T.W., et al., *Estimated economic costs of overactive bladder in the United States.* Urology, 2003. **61**(6): p. 1123-8.

319. Schnelle, J.F., et al., *Reduction of urinary incontinence in nursing homes: does it reduce or increase costs?* Journal of the American Geriatrics Society, 1988. **36**(1): p. 34-9.

320. Landefeld, C.S., et al., *National Institutes of Health state-of-the-science conference statement: prevention of fecal and urinary incontinence in adults.* Ann Intern Med, 2008. **148**(6): p. 449-58.

321. Frantz, R.A., et al., *Implementing an incontinence management protocol in long-term care. Clinical outcomes and costs.* Journal of Gerontological Nursing, 2003. **29**(8): p. 46-53.

322. Albers-Heitner, P., et al., *The effects of involving a nurse practitioner in primary care for adult patients with urinary incontinence: the PromoCon study (Promoting Continence).* BMC Health Serv Res, 2008. **8**: p. 84.

323. Morris, A.R., et al., *Costs of managing urinary and faecal incontinence in a sub-acute care facility: a "bottom-up" approach.* Neurourol Urodyn, 2005. **24**(1): p. 56-62.

324. Wodchis, W.P., G.F. Teare, and G.M. Anderson, *Cost and quality: evidence from Ontario long term care hospitals.* Med Care, 2007. **45**(10): p. 981-8.

325. Shih, Y.C., A.G. Hartzema, and S. Tolleson-Rinehart, *Labor costs associated with incontinence in long-term care facilities.* Urology, 2003. **62**(3): p. 442-6.

326. Borrie, M.J. and H.A. Davidson, *Incontinence in institutions: costs and contributing factors.* CMAJ Canadian Medical Association Journal, 1992. **147**(3): p. 322-8.

327. Green, J., et al., *Urinary incontinence in subacute care--a retrospective analysis of clinical outcomes and costs.* Medical Journal of Australia, 2003 **178**: p. 550-3.

328. Onukwugha, E., et al., *The total economic burden of overactive bladder in the United States: a disease-specific approach.* Am J Manag Care, 2009. **15**(4 Suppl): p. S90-7.

329. Langa, K.M., et al., *Informal caregiving time and costs for urinary incontinence in older individuals in the United States.* Journal of the American Geriatrics Society, 2002. **50**(4): p. 733-7.

330. Engberg, S., J. Kincade, and D. Thompson, *Future directions for incontinence research with frail elders.* Nurs Res, 2004. **53**(6 Suppl): p. S22-9.

331. Palese, A. and G. Carniel, *The effects of a multi-intervention incontinence care program on clinical, economic, and environmental outcomes.* Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN, 2011. **38**(2): p. 177-83.

332. Mezey, M., et al., *Decision-making capacity to execute a health care proxy: development and testing of guidelines.* Journal of the American Geriatrics Society, 2000. **48**(2): p. 179-87.

333. Baltussen, R., R. Leidl, and A. Ament, *The impact of age on cost-effectiveness ratios and its control in decision making.* Health Economics, 1996. **5**(3): p. 227-39.

334. Bressler, R. and J.J. Bahl, *Principles of drug therapy for the elderly patient.* Mayo Clinic Proceedings, 2003. **78**(12): p. 1564-77.

335. Avorn, J. and P.A. Rochon, *Principles of pharmacology*, in *Geriatric Medicine: An Evidenced Based Approach*, C. Cassel, et al., Editors. 2003, Spinger: New York. p. 65-81.

336. Rochon, P.A., et al., *Age- and gender-related use of low-dose drug therapy: the need to manufacture low-dose therapy and evaluate the minimum effective dose.* Journal of the American Geriatrics Society, 1999. **47**(8): p. 954-9.

337. Bemelmans, B., L. Kiemeney, and F. Debruyne, *Low-dose oxybutynin for the treatment of urge incontinence: good efficacy and few side effects.* Eur Urol, 2000. **37**: p. 709-713.

338. Malone-Lee, J., D. Lubel, and G. Szonyi, *Low dose oxybutynin for the unstable bladder.* Br Med J, 1992. **304**.

339. Wagg, A., *National Audit of Continence Care*, 2010, Royal College of Physicians of London: London.

340. Cresswell, K., et al., *Adverse drug events in the elderly.* Br Med Bull 2007. **83**: p. 259-274.

341. Hanlon, J.T., et al., *Adverse drug events in high risk older outpatients.* Journal of the American Geriatrics Society, 1997. **45**(8): p. 945-8.

342. Bootman, J.L., D.L. Harrison, and E. Cox, *The health care cost of drug-related morbidity and mortality in nursing facilities.* Archives of Internal Medicine, 1997. **157**(18): p. 2089-96.

343. Patel, H. and et al, *Trends in hospital admissions for adverse drug reactions in England: analysis of national hospital episode statistics 1998-2005.* Clin Pharmacol, 2007. **7**: p. 9.

344. Hofer-Dueckelmann, C., et al., *Adverse drug reactions (ADRs) associated with hospital admissions - elderly female patients are at highest risk.* International journal of clinical pharmacology and therapeutics, 2011. **49**(10): p. 577-86.

345. Rodenburg, E.M., B.H. Stricker, and L.E. Visser, *Sex differences in cardiovascular drug induced adverse reactions causing hospital admissions.* British journal of clinical pharmacology, 2012.

346. Feinberg, M., *The problems of anticholinergic adverse effects in older patients.* Drugs & Aging, 1993. **3**(4): p. 335-48.

347. Kay, G. and et al, *Antimuscarinic drugs for overactive bladder and their potential effects on cognitive function in older patients.* J Am Geriatr Soc, 2005. **53**: p. 2195-2201.

348. Wagg, A., C. Verdejo, and U. Molander, *Review of cognitive impairment with antimuscarinic agents in elderly patients with overactive bladder.* Int J Clin Pract, 2010. **64**(9): p. 1279-86.

349. Fox, C., et al., *The impact of anticholinergic burden in Alzheimer's dementia-the LASER-AD study.* Age and Ageing, 2011. **40**(6): p. 730-5.

350. Hopcraft, M.S. and C. Tan, *Xerostomia: an update for clinicians.* Australian dental journal, 2010. **55**(3): p. 238-44; quiz 353.

351. Pajukoski, H., et al., *Prevalence of subjective dry mouth and burning mouth in hospitalized elderly patients and outpatients in relation to saliva, medication, and systemic diseases.* Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics, 2001. **92**(6): p. 641-9.

352. Gist, R.F., O'Loughlin.K.T. 2011; Available from: http://www.ada.org/sections/newsAndEvents/pdfs/ltr_dry_mouth_110427.pdf.

353. Kessler, T.M., et al., *Adverse event assessment of antimuscarinics for treating overactive bladder: a network meta-analytic approach.* PLoS ONE, 2011. **6**(2): p. e16718.

354. Herschorn, S., et al., *Tolerability of solifenacin and oxybutynin immediate release in older (> 65 years) and younger (</= 65 years) patients with overactive bladder: sub-analysis from a Canadian, randomized, double-blind study.* Current medical research and opinion, 2011. **27**(2): p. 375-82.

355. Kraus, S.R., et al., *Efficacy and tolerability of fesoterodine in older and younger subjects with overactive bladder.* Urology, 2010. **76**(6): p. 1350-7.

356. Chapple, C.R. and L. Nilvebrant, *Tolterodine: selectivity for the urinary bladder over the eye (as measured by visual accommodation) in healthy volunteers.* Drugs in R & D, 2002. **3**(2): p. 75-81.

357. Laroche, M.-L., et al., *Is inappropriate medication use a major cause of adverse drug reactions in the elderly? .* Br J Clin Pharmacol, 2007. **63**: p. 177-186.

358. Colucci, V.J. and M.P. Rivey, *Tolterodine-warfarin drug interaction.* Annals of Pharmacotherapy, 1999. **33**(11): p. 1173-6.

359. Hashimoto, M., et al., *Urinary incontinence: an unrecognised adverse effect with donepezil.* Lancet, 2000. **356**(9229): p. 568.

360. Starr, J., *Cholinesterase inhibitor treatment and urinary incontinence in Alzheimer's disease.* J Am Geriatr Soc, 2007. **55**: p. 800-1.

361. Siegler, E.L. and M. Reidenberg, *Treatment of urinary incontinence with anticholinergics in patients taking cholinesterase inhibitors for dementia.* Clinical Pharmacology & Therapeutics, 2004. **75**(5): p. 484-8.

362. Gill, S.S., et al., *A Prescribing Cascade Involving Cholinesterase Inhibitors and Anticholinergic Drugs.* Arch Intern Med, 2005. **165**(7): p. 808-813.

363. Sink, K., et al., *Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes.* J Am Geriatr Soc, 2008. **56**: p. 847-53.

364. Isik, A.T., et al., *Trospium and cognition in patients with late onset Alzheimer disease.* J Nutr Health Aging, 2009. **13**(8): p. 672-6.

365. Sakakibara, R., et al., *How to manage overactive bladder in elderly individuals with dementia? A combined use of donepezil, a central acetylcholinesterase inhibitor, and propiverine, a peripheral muscarine receptor antagonist.* J Am Geriatr Soc, 2009. **57**(8): p. 1515-7.

366. Fick, D.M., et al., *Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts.* Archives of internal medicine, 2003. **163**(22): p. 2716-24.

367. McLeod, P.J., et al., *Defining inappropriate practices in prescribing for elderly people: a national consensus panel. [see comment].* CMAJ Canadian Medical Association Journal, 1997. **156**(3): p. 385-91.

368. Barry, P., et al., *Inappropriate prescribing in the elderly: a comparison of the Beers criteria and the Improved Prescribing in the Elderly tool (IPET).* J Clin Pharm Ther, 2006. **31**: p. 617-26.

369. O'Mahony, D. and P. Gallagher, *Inappropriate prescribing in the older population: need for new criteria.* Age & Ageing, 2008. **37**: p. 138-141.

370. *American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.* Journal of the American Geriatrics Society, 2012. **60**(4): p. 616-631.

371. Sahyoun, N.R., et al., *The changing profile of nursing home residents: 1985-1997.* Aging Trends, 2001(4): p. 1-8.

372. Thuroff, J.W., et al., *EAU Guidelines on Urinary Incontinence.* Actas urologicas espanolas, 2011. **35**(7): p. 373-388.

373. States, H.U., *Special excerpt trend tables on 65 and older population,*, 2004, National Centre for Health Statistics, Centres for Disease Control and Prevention.

374. Lee, P.G., C. Cigolle, and C. Blaum, *The co-occurrence of chronic diseases and geriatric syndromes: the health and retirement study.* J Am Geriatr Soc, 2009. **57**(3): p. 511-6.

375. Goode, P.S., et al., *Population based study of incidence and predictors of urinary incontinence in black and white older adults.* The Journal of urology, 2008. **179**(4): p. 1449-53; discussion 1453-4.

376. Scherr, D., P.W. Swindle, and P.T. Scardino, *National Comprehensive Cancer Network guidelines for the management of prostate cancer.* Urology, 2003. **61**(2 Suppl 1): p. 14-24.

377. Johnson, T.M., 2nd, et al., *Self-care practices used by older men and women to manage urinary incontinence: results from the national follow-up survey on self-care and aging.* J Am Geriatr Soc, 2000. **48**(8): p. 894-902.

378. Sorbye, L.W., et al., *Urinary incontinence and use of pads--clinical features and need for help in home care at 11 sites in Europe.* Scand J Caring Sci, 2009. **23**(1): p. 33-44.

379. Teunissen, T.A. and A.L. Lagro-Janssen, *Sex differences in the use of absorbent (incontinence) pads in independently living elderly people: do men receive less care?* Int J Clin Pract, 2009. **63**(6): p. 869-73.

380. Wullnera, U., Schmitz-Hubscha, T., Antonyb, G., Fimmersa, R., Spottkea,A., Oertelb, W. H., Deuschlc, G., Klockgethera, T., Eggertb, K. on behalf of the KNP e.V., *Autonomic dysfunction in 3414 Parkinson's disease patients enrolled in the German Network on Parkinson's disease (KNP e.V.): the effect of ageing.* European Journal of Neurology, 2007. **14**: p. 1405-1408

381. Divani, A.A., et al., *Risk factors associated with injury attributable to falling among elderly population with history of stroke.* Stroke, 2009. **40**(10): p. 3286-92.

382. Brown, C.T., et al., *Lifestyle and behavioural interventions for men on watchful waiting with uncomplicated lower urinary tract symptoms: a national multidisciplinary survey.* BJU Int, 2003. **92**(1): p. 53-7.

383. Kincade, J.E., et al., *Randomized clinical trial of efficacy of self-monitoring techniques to treat urinary incontinence in women.* Neurourol Urodyn, 2007. **26**(4): p. 507-11.

384. Landefeld, C.S., *Pragmatic approaches that improve care for geriatric conditions: balancing the promise and the peril of quality indicators.* J Am Geriatr Soc, 2009. **57**(3): p. 556-8.

385. Landefeld, C.S., et al., *National Institutes of Health state-of-the-science conference statement: prevention of fecal and urinary incontinence in adults.* Annals of internal medicine, 2008. **148**(6): p. 449-58.

386. Gaspar, P.M., *Comparison of four standards for determining adequate water intake of nursing home residents.* Research and theory for nursing practice, 2011. **25**(1): p. 11-22.

387. Arnaud, M.J., *Mild dehydration: a risk factor of constipation?* European journal of clinical nutrition, 2003. **57 Suppl 2**: p. S88-95.

388. O'Mahony, R., et al., *Synopsis of the National Institute for Health and Clinical Excellence guideline for prevention of delirium.* Annals of internal medicine, 2011. **154**(11): p. 746-51.

389. Wilson, M.M. and J.E. Morley, *Impaired cognitive function and mental performance in mild dehydration.* European journal of clinical nutrition, 2003. **57 Suppl 2**: p. S24-9.

390. Schnelle, J.F., et al., *A controlled trial of an intervention to improve urinary and fecal incontinence and constipation.* J Am Geriatr Soc, 2010. **58**(8): p. 1504-11.

391. Dowd, T.T., J.M. Campbell, and J.A. Jones, *Fluid intake and urinary incontinence in older community-dwelling women.* J Community Health Nurs, 1996. **13**(3): p. 179-86.

392. Spangler, P.F., T.R. Risley, and D.D. Bilyew, *The management of dehydration and incontinence in nonambulatory geriatric patients.* J Appl Behav Anal, 1984. **17**(3): p. 397-401.

393. Roe, B., et al., *Systematic reviews of bladder training and voiding programmes in adults: a synopsis of findings from data analysis and outcomes using metastudy techniques.* J Adv Nurs, 2007. **57**(1): p. 15-31.

394. Palmer, M.H., *Effectiveness of prompted voiding for incontinent nursing home residents.*, in *Evidence-based practice in nursing & healthcare: A guide to the best practice*, E.F.-O. B. M. Melnyk, Editor 2005, Lippincott Williams & Williams. p. 20 - 30.

395. Palmer, M.H., *Use of health behavior change theories to guide urinary incontinence research.* Nurs Res, 2004. **53**(6 Suppl): p. S49-55.

396. Roe, B., et al., *Systematic reviews of bladder training and voiding programmes in adults: a synopsis of findings on theory and methods using metastudy techniques.* J Adv Nurs, 2007. **57**(1): p. 3-14.

397. Ostaszkiewicz, J., L. Johnston, and B. Roe, *VTimed Voiding for the Management of Urinary Incontinence in Adults.* J Urol, 2005. **173**(4): p. 1262-3.

398. Schnelle, J.F., et al., *Functional Incidental Training, mobility performance, and incontinence care with nursing home residents.* J Am Geriatr Soc, 1995. **43**(12): p. 1356-62.

399. van Houten, P., W. Achterberg, and M. Ribbe, *Urinary incontinence in disabled elderly women: a randomized clinical trial on the effect of training mobility and toileting skills to achieve independent toileting.* Gerontology, 2007. **53**(4): p. 205-10.

400. Booth, J., S. Kumlien, and Y. Zang, *Promoting urinary continence with older people: key issues for nurses.* Int J Older People Nurs, 2009. **4**(1): p. 63-9.

401. Dingwall, L., *Promoting effective continence care for older people: a literature review.* Br J Nurs, 2008. **17**(3): p. 166-72.

402. Wright, J., et al., *Evaluating the context within which continence care is provided in rehabilitation units for older people.* International journal of older people nursing, 2007. **2**(1): p. 9-19.

403. Vinsnes, A.G., Harkless, G. E., & Nyronning, S. , *Unit-based intervention to improve urinary incontinence in frail elderly.* . Nordic Journal of Nursing Research & Clinical Studies, 2007 **27**(3): p. 53.

404. Cheater, F.M., *Overcoming the barriers to optimum continence care: the need for an expanded approach to implementation.* Int J Older People Nurs, 2009. **4**(1): p. 70-5.

405. Hagglund, D., *A systematic literature review of incontinence care for persons with dementia: the research evidence.* J Clin Nurs, 2010. **19**(3-4): p. 303-12.

406. Perrin, L., et al., *Pelvic floor muscle training with biofeedback and bladder training in elderly women: a feasibility study.* J Wound Ostomy Continence Nurs, 2005. **32**(3): p. 186-99.

407. Diokno, A.C., et al., *Prevention of urinary incontinence by behavioral modification program: a randomized, controlled trial among older women in the community.* J Urol, 2004. **171**(3): p. 1165-71.

408. Zurcher, S., S. Saxer, and R. Schwendimann, *Urinary incontinence in hospitalised elderly patients: do nurses recognise and manage the problem?* Nursing research and practice, 2011. **2011**: p. 671302.

409. Zisberg, A., et al., *In-hospital use of continence aids and new-onset urinary incontinence in adults aged 70 and older.* Journal of the American Geriatrics Society, 2011. **59**(6): p. 1099-104.

410. Kraus, S.R., et al., *Vulnerable elderly patients and overactive bladder syndrome.* Drugs Aging, 2010. **27**(9): p. 697-713.

411. Bates-Jensen, B.M., et al., *The effects of an exercise and incontinence intervention on skin health outcomes in nursing home residents.* J Am Geriatr Soc, 2003. **51**(3): p. 348-55.

412. Simmons, S.F. and J.F. Schnelle, *Effects of an exercise and scheduled-toileting intervention on appetite and constipation in nursing home residents.* The journal of nutrition, health & aging, 2004. **8**(2): p. 116-21.

413. Colling, J., et al., *The effects of a continence program on frail community-dwelling elderly persons.* Urol Nurs, 2003. **23**(2): p. 117-22, 127-31.

414. Engberg, S., et al., *Effectiveness of prompted voiding in treating urinary incontinence in cognitively impaired homebound older adults.* J Wound Ostomy Continence Nurs, 2002. **29**(5): p. 252-65.

415. Eustice, S., B. Roe, and J. Paterson, *Prompted voiding for the management of urinary incontinence in adults.* Cochrane database of systematic reviews, 2000(2): p. CD002113.

416. Ouslander, J.G., et al., *Predictors of successful prompted voiding among incontinent nursing home residents.* JAMA, 1995. **273**(17): p. 1366-70.

417. Schnelle, J.F., et al., *Reduction of urinary incontinence in nursing homes: does it reduce or increase costs?* J Am Geriatr Soc, 1988. **36**(1): p. 34-9.

418. *Tag F315*, U.D.o.H.H.S.C.f.M.M. Services., Editor 2005.

419. Ostaszkiewicz, J., B. Roe, and L. Johnston, *Effects of timed voiding for the management of urinary incontinence in adults: systematic review.* J Adv Nurs, 2005. **52**(4): p. 420-31.

420. Ostaszkiewicz, J., L. Johnston, and B. Roe, *Timed voiding for the management of urinary incontinence in adults.* Cochrane Database Syst Rev, 2004(1): p. CD002802.

421. Roe, B., et al., *Translating research on incontinence into practice.* Nurs Res, 2004. **53**(6 Suppl): p. S56-60.

422. Schnelle, J.F., et al., *Does an exercise and incontinence intervention save healthcare costs in a nursing home population?* J Am Geriatr Soc, 2003. **51**(2): p. 161-8.

423. Dubeau, C.E., *Improving urinary incontinence in nursing home residents: are we FIT to be tied?* J Am Geriatr Soc, 2005. **53**(7): p. 1254-6.

424. Baldwin, J., Baldwin, J., *Behavioral principles in everyday life* 2nd ed 1986 Englewood, NJ:: Prentice-Hill.

425. Schnelle, J.F., et al., *A standardized quality assessment system to evaluate incontinence care in the nursing home.* J Am Geriatr Soc, 2003. **51**(12): p. 1754-61.

426. Schnelle, J.F., et al., *The minimum data set urinary incontinence quality indicators: do they reflect differences in care processes related to incontinence?* Medical Care, 2003. **41**(8): p. 909-22.

427. DuBeau, C.E., J.G. Ouslander, and M.H. Palmer, *Knowledge and attitudes of nursing home staff and surveyors about the revised federal guidance for incontinence care.* Gerontologist, 2007. **47**(4): p. 468-79.

428. Dingwall, L. and E. McLafferty, *Do nurses promote urinary continence in hospitalized older people?: An exploratory study.* J Clin Nurs, 2006. **15**(10): p. 1276-86.

429. Schnelle, J.F., J.G. Ouslander, and P.A. Cruise, *Policy without technology: a barrier to improving nursing home care.* Gerontologist, 1997. **37**(4): p. 527-32.

430. Ostaszkiewicz, J., B. O'Connell, and L. Millar, *Incontinence: managed or mismanaged in hospital settings?* International journal of nursing practice, 2008. **14**(6): p. 495-502.

431. Wagg, A., et al., *Continence care for older people in England and Wales: data from a national audit.* J Wound Ostomy Continence Nurs, 2008. **35**(2): p. 215-20.

432. Rodriguez, N.A., C.M. Sackley, and F.J. Badger, *Exploring the facets of continence care: a continence survey of care homes for older people in Birmingham.* J Clin Nurs, 2007. **16**(5): p. 954-62.

433. Watson, N., et al., *Use of the Agency for Health Care Policy and Research Urinary Incontinence Guideline in nursing homes.* J Am Geriatr Soc, 2003. **51**(12): p. 1779-1786.

434. O'Dell, K.K., C. Jacelon, and A.N. Morse, *'I'd rather just go on as I am'--pelvic floor care preferences of frail, elderly women in residential care.* Urol Nurs, 2008. **28**(1): p. 36-47.

435. Colling, J., et al., *The effects of patterned urge-response toileting (PURT) on urinary incontinence among nursing home residents.* Journal of the American Geriatrics Society., 1992. **40**(2): p. 135-41.

436. Creason, N.S., et al., *Prompted voiding therapy for urinary incontinence in aged female nursing home residents.* Journal of Advanced Nursing, 1989. **14**(2): p. 120-6.

437. Schnelle, J.F., et al., *Developing rehabilitative behavioral interventions for long-term care: technology transfer, acceptance, and maintenance issues.* Journal of the American Geriatrics Society, 1998. **46**(6): p. 771-7.

438. Hu, T.W., et al., *A clinical trial of a behavioral therapy to reduce urinary incontinence in nursing homes. Outcome and implications.[see comment].* JAMA, 1989. **261**(18): p. 2656-62.

439. Schnelle, J.F., et al., *A standardized quality assessment system to evaluate incontinence care in the nursing home. [see comment].* Journal of the American Geriatrics Society, 2003. **51**(12): p. 1754-61.

440. Schnelle, J.F., et al., *The use of a computer-based model to implement an incontinence management program.* Gerontologist, 1995. **35**(5): p. 656-65.

441. Fung, C., et al., *Quality indicators for the screening and care of urinary incontinence in vulnerable elders.* J Am Geriatr Soc, 2007. **55 Suppl 2**: p. S443-9.

442. Ostaszkiewicz, J., *A clinical nursing leadership model for enhancing continence care for older adults in a subacute inpatient care setting.* J Wound Ostomy Continence Nurs, 2006. **33**(6): p. 624-9.

443. Palmer, M.H., P.S. German, and J.G. Ouslander, *Risk factors for urinary incontinence one year after nursing home admission.* Research in Nursing & Health, 1991. **14**(6): p. 405-12.

444. Roe, B., et al., *Systematic review of the management of incontinence and promotion of continence in older people in care homes: descriptive studies with urinary incontinence as primary focus.* Journal of Advanced Nursing, 2011. **67**(2): p. 228-250.

445. Bucci, A.T., *Be a continence champion: use the CHAMMP tool to individualize the plan of care.* Geriatr Nurs, 2007. **28**(2): p. 120-4; quiz 125.

446. Jansen, L. and D. Forbes, *The psychometric testing of a urinary incontinence nursing assessment instrument.* J Wound Ostomy Continence Nurs, 2006. **33**(1): p. 69-76.

447. O'Connell, B., J. Ostaszkiewicz, and M. Hawkins, *A suite of evidence-based continence assessment tools for residential aged care.* Australasian journal on ageing, 2011. **30**(1): p. 27-32.

448. Engst, C., et al., *Implementation of a scheduled toileting program in a long term care facility: evaluating the impact on injury risk to caregiving staff.* AAOHN J, 2004. **52**(10): p. 427-35.

449. Tanaka, Y., et al., *Can an individualized and comprehensive care strategy improve urinary incontinence (UI) among nursing home residents?* Arch Gerontol Geriatr, 2009. **49**(2): p. 278-83.

450. Ryden, M., et al., *Value-added outcomes: the use of advanced practice nurses in long-term care facilities.* Gerontologist, 2000. **40**: p. 654-62.

451. Collette, C., G. Bravo, and M. Tu le, *Development of a urinary incontinence educational program using a competency-based approach and case method.* J Nurses Staff Dev, 2009. **25**(4): p. E5-E10.

452. Karlowicz, K.A., *Evaluation of the Urinary Incontinence Scales to measure change after experiential learning: a pilot study.* Urol Nurs, 2009. **29**(1): p. 40-6.

453. Lekan-Rutledge, D., *Diffusion of innovation. A model for implementation of prompted voiding in long-term care settings.* J Gerontol Nurs, 2000. **26**(4): p. 25-33.

454. Palmer, M.H., *Nurses' knowledge and beliefs about continence interventions in long-term care.* J Adv Nurs, 1995. **21**(6): p. 1065-72.

455. Kincade, J.E., et al., *Bladder management in adult care homes. Review of a program in North Carolina.* J Gerontol Nurs, 2003. **29**(10): p. 30-6; quiz 54-5.

456. Stolee, P., et al., *Factors associated with the effectiveness of continuing education in long-term care.* The Gerontologist, 2005. **45**(3): p. 399-405.

457. Popejoy, L.L., et al., *Improving quality of care in nursing facilities. Gerontological clinical nurse specialist as research nurse consultant.* . Journal of Gerontological Nursing, 2000. **26**: p. 6-13.

458. Palmer, M.H. and T.M. Johnson, 2nd, *Quality of incontinence management in U.S. nursing homes: a failing grade.* J Am Geriatr Soc, 2003. **51**(12): p. 1810-2.

459. Roe, B., et al., *Translating research on incontinence into practice.* Nursing Research, 2004. **53**(6S): p. S56-S60.

460. Mason, D.J., D.K. Newman, and M.H. Palmer, *Changing UI practice: this report challenges nurses to lead the way in managing incontinence.* Am J Nurs, 2003. **Suppl**: p. 2-3.

461. Newman, D.K., *Discussion and recommendations: overcoming barriers to nursing care of people with urinary incontinence.* American Journal of Nursing, 2003. **March**(Supplement): p. 47-53.

462. Wyman, J.F., et al., *Shaping future directions for incontinence research in aging adults.* Nursing Research, 2004. **53**(6S): p. S1-S9.

463. Schnelle, J.F., et al., *Translating clinical research into practice: a randomized controlled trial of exercise and incontinence care with nursing home residents.[see comment].* Journal of the American Geriatrics Society, 2002. **50**(9): p. 1476-83.

464. Shaw, B., et al. *Tailored interventions to overcome identified barriers to change: effects on professional practice and health care outcomes*. The Cochrane Database of Systematic Reviews, 2005. ART. No.: CD005470.

465. Remsburg, R.E., et al., *Staff compliance with and ratings of effectiveness of a prompted voiding program in a long-term care facility.* Journal of Wound, Ostomy, & Continence Nursing, 1999. **26**(5): p. 261-9.

466. Lekan-Rutledge, D., M. Palmer, and M. Belyea, *In their own words: Nursing assistants' preceptions of barriers to implementation of prompted voiding in long-term care.* . Gerontologist, 1998. **38**: p. 370-378.

467. Bear, M., et al., *Home-based management of urinary incontinence: a pilot study with both frail and independent elders.[see comment].* Journal of Wound, Ostomy, & Continence Nursing, 1997. **24**(3): p. 163-71.

468. Schnelle, J.F., et al., *The use of a computer-based model to implement an incontinence management program.* Gerontologist, 1995. **35**: p. 656.

469. Schnelle, J.F., et al., *A cost and value analysis of two interventions with incontinent nursing home residents.* Journal of the American Geriatric Society, 1995. **43**: p. 1112-1117.

470. Schnelle, J.F., et al., *Translating clinical research into practice: a randomized controlled trial of exercise and incontinence care with nursing home residents.* J Am Geriatr Soc, 2002. **50**(9): p. 1476-83.

471. Forster, A., et al. *Rehabilitation for older people in long-term care*. Cochrane Database of Systematic Reviews, 2009. Art. No.: CD004294 DOI: 10.1002/14651858.CD004294.pub2.

472. Palese, A. and G. Carniel, *The effects of a multi-intervention incontinence care program on clinical, economic and environmental outcomes.* Journal of Wound, Ostomy & Continence Nursing, 2011. **38**(2): p. 177-183.

473. Beeckman, D., et al., *Pressure ulcers and incontinence-associated dermatitis: effectiveness of the Pressure Ulcer Classification education tool on classification by nurses.* Quality in Safety and Health Care, 2010. **19**(3).

474. Jacobs, D., et al., *Twenty-four-hour sleep-wake patterns in a nursing home population.* Psychology and aging, 1989. **4**(3): p. 352-6.

475. Bliwise, D.L., et al., *Systematic 24-hr behavioral observations of sleep and wakefulness in a skilled-care nursing facility.* Psychology and aging, 1990. **5**(1): p. 16-24.

476. Schnelle, J.F., et al., *The nighttime environment, incontinence care, and sleep disruption in nursing homes.* J Am Geriatr Soc, 1993. **41**(9): p. 910-4.

477. Schnelle, J.F., et al., *Nighttime sleep and bed mobility among incontinent nursing home residents.* J Am Geriatr Soc, 1993. **41**(9): p. 903-9.

478. Cruise, P.A., et al., *The nighttime environment and incontinence care practices in nursing homes.* J Am Geriatr Soc, 1998. **46**(2): p. 181-6.

479. Pat-Horenczyk, R., et al., *Hourly profiles of sleep and wakefulness in severely versus mild-moderately demented nursing home patients.* Aging, 1998. **10**(4): p. 308-15.

480. Alessi, C.A., et al., *Does physical activity improve sleep in impaired nursing home residents?* J Am Geriatr Soc, 1995. **43**(10): p. 1098-102.

481. Alessi, C.A., et al., *A randomized trial of a combined physical activity and environmental intervention in nursing home residents: do sleep and agitation improve?* J Am Geriatr Soc, 1999. **47**(7): p. 784-91.

482. Schnelle, J.F., et al., *Individualizing nighttime incontinence care in nursing home residents.* Nurs Res, 1998. **47**(4): p. 197-204.

483. Schnelle, J.F., et al., *The nursing home at night: effects of an intervention on noise, light, and sleep.* J Am Geriatr Soc, 1999. **47**(4): p. 430-8.

484. Ouslander, J.G., et al., *Implementation of a nursing home urinary incontinence management program with and without tolterodine.* J Am Med Dir Assoc, 2001. **2**(5): p. 207-14.

485. Fader, M., et al., *Management of night-time urinary incontinence in residential settings for older people: an investigation into the effects of different pad changing regimes on skin health.* J Clin Nurs, 2003. **12**(3): p. 374-86.

486. Ouslander, J.G., N. Ai-Samarrai, and J.F. Schnelle, *Prompted voiding for nighttime incontinence in nursing homes: is it effective?* J Am Geriatr Soc, 2001. **49**(6): p. 706-9.

487. Shimanouchi, S., T. Kamei, and M. Hayashi, *Home care for the frail elderly based on urinary incontinence level.* Public Health Nursing, 2000. **17**(6): p. 468-73.

488. Upton, N. and V. Reed, *The meaning of incontinence in dementia care.* Int J Psychiatr Nurs Res, 2005. **11**(1): p. 1200-10.

489. Hutchinson, S., S. Leger-Krall, and H.S. Wilson, *Toileting: a biobehavioral challenge in Alzheimer's dementia care.* Journal of Gerontological Nursing, 1996. **22**(10): p. 18-27.

490. Cassells, C. and E. Watt, *The impact of incontinence on older spousal caregivers.* Journal of Advanced Nursing, 2003. **42**(6): p. 607-16.

491. Engberg, S., et al., *Effectiveness of prompted voiding in treating urinary incontinence in cognitively impaired homebound older adults.* Journal of Wound, Ostomy, & Continence Nursing, 2002. **29**(5): p. 252-65.

492. Du Moulin, M.F., et al., *Urinary incontinence in older adults receiving home care diagnosis and strategies.* Scand J Caring Sci, 2009. **23**(2): p. 222-30.

493. Narayanan, S., et al., *Is drug therapy for urinary incontinence used optimally in long-term care facilities?* J Am Med Dir Assoc, 2007: p. 98-104.

494. Min, L.C., et al., *The vulnerable elders-13 survey predicts 5-year functional decline and mortality outcomes in older ambulatory care patients.* Journal Of The American Geriatrics Society, 2009. **57**(11): p. 2070-2076.

495. Paquette, A., P. Gou, and C. Tannenbaum, *Systematic review and meta-analysis: do clinical trials testing antimuscarinic agents for overactive bladder adequately measure central nervous system adverse events?* Journal of the American Geriatrics Society, 2011. **59**(7): p. 1332-9.

496. Lackner, T., et al., *Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin in cognitively impaired nursing home residents with urge urinary incontinence.* J Am Geriatr Soc, 2008. **56**: p. 862-870.

497. Minassian, V. and et al, *Randomized trial of oxybutynin extended versus immediate release for women aged 65 and older with overactive bladder; lessons learned from conducting a trial.* J Obstet Gynaecol Can, 2007. **29**: p. 726–732.

498. Sand, P. and et al, *Oxybutynin transdermal system improves the quality of life in adults with overactive bladder: a multi-centre community based, randomized study.* BJU Int, 2007. **99**: p. 836-844.

499. Hughes, K.M., et al., *Measurement of oxybutynin and its N-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers.* Xenobiotica, 1992. **22**(7): p. 859-69.

500. Ouslander, J.G., et al., *Pharmacokinetics and clinical effects of oxybutynin in geriatric patients.* Journal of Urology, 1988. **140**(1): p. 47-50.

501. Zobrist, R., et al., *Pharmacokinetics and metabolism of transdermal oxybutynin: in vitro and in vivo performance of a novel delivery system.* Pharmaceut Res, 2003. **20**: p. 103-109.

502. Ouslander, J.G., et al., *Habit training and oxybutynin for incontinence in nursing home patients: a placebo-controlled trial.* Journal of the American Geriatrics Society., 1988. **36**(1): p. 40-6.

503. Ouslander, J.G., et al., *Does oxybutynin add to the effectiveness of prompted voiding for urinary incontinence among nursing home residents? A placebo-controlled trial.* Journal of the American Geriatrics Society., 1995. **43**(6): p. 610-7.

504. Zorzitto, M.L., et al., *Oxybutynin chloride for geriatric urinary dysfunction: a double-blind placebo-controlled study. [see comment].* Age & Ageing., 1989. **18**(3): p. 195-200.

505. Szonyi, G., et al., *Oxybutynin with bladder retraining for detrusor instability in elderly people: a randomized controlled trial.* Age & Ageing, 1995. **24**(4): p. 287-91.

506. Uchibayashi, T., et al., *[Assessment of the use of oxybutynin hydrochloride (Pollakisu tablets) in the elderly].* Hinyokika Kiyo - Acta Urologica Japonica, 1991. **37**(9): p. 1077-85.

507. Mizunaga, M., et al., *[Intravesical oxybutynin hydrochloride in the treatment of urge incontinence in the elderly].* Nippon Hinyokika Gakkai Zasshi - Japanese Journal of Urology, 1996. **87**(6): p. 923-7.

508. Griffiths, D.J., et al., *Urge incontinence in elderly people: factors predicting the severity of urine loss before and after pharmacological treatment.* Neurourology & Urodynamics, 1996. **15**(1): p. 53-7.

509. Sugiyama, T., et al., *[Anticholinergic therapy of urinary incontinence and urinary frequency associated with the elderly--with special reference to dementia].* Nippon Hinyokika Gakkai Zasshi - Japanese Journal of Urology, 1993. **84**(6): p. 1068-73.

510. Zellner, M., et al., *Trospium chloride and oxybutynin hydrochloride in a german study of adults with urinary urge incontinence: results of a 12-week, multicenter, randomized, double-blind, parallel-group, flexible-dose noninferiority trial.* Clin Ther, 2009. **31**(11): p. 2519-39.

511. Donnellan, C., et al., *Oxybutynin and cognitive dysfunction.* BMJ, 1997. **315**(7119): p. 1363-4.

512. Patel, H.R., et al., *Can oxybutynin cause peripheral neuropathy?* Journal of Urology, 2002. **168**(2): p. 646.

513. Adubofour, K.O., et al., *Oxybutynin-induced heatstroke in an elderly patient.* Annals of Pharmacotherapy, 1996. **30**(2): p. 144-7.

514. Hussain, R.M., et al., *Effect of oxybutynin on the QTc interval in elderly patients with urinary incontinence.* British Journal of Clinical Pharmacology, 1996. **41**(1): p. 73-5.

515. Wang, P.S., et al., *Urinary antispasmodic use and the risks of ventricular arrhythmia and sudden death in older patients.* Journal of the American Geriatrics Society, 2002. **50**(1): p. 117-24.

516. Zinner, N.R., A. Mattiasson, and S.L. Stanton, *Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients.* Journal of the American Geriatrics Society, 2002. **50**(5): p. 799-807.

517. Millard, R., et al., *Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity.[see comment].* Journal of Urology, 1999. **161**(5): p. 1551-5.

518. Drutz, H.P., et al., *Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder.* International Urogynecology Journal, 1999. **10**(5): p. 283-9.

519. Michel, M.C., et al., *Does gender or age affect the efficacy and safety of tolterodine?* Journal of Urology, 2002. **168**(3): p. 1027-31.

520. Chung, S.D., et al., *The efficacy of additive tolterodine extended release for 1-year in older men with storage symptoms and clinical benign proastatic hyperplasia.* Neurourology and Urodynamics, 2011. **30**(4): p. 568-71.

521. Tsao, J.W. and K.M. Heilman, *Transient memory impairment and hallucinations associated with tolterodine use.* New England Journal of Medicine, 2003. **349**(23): p. 2274-5.

522. Womack, K.B. and K.M. Heilman, *Tolterodine and memory: dry but forgetful.* Archives of Neurology, 2003. **60**(5): p. 771-3.

523. Salvatore, S., et al., *Cognitive dysfunction with tolterodine use.* Am J Obstet Gynecol, 2007. **197**.

524. Edwards, K.R. and J.T. O'Connor, *Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors.[comment].* Journal of the American Geriatrics Society, 2002. **50**(6): p. 1165-6.

525. Layton, D., G.L. Pearce, and S.A. Shakir, *Safety profile of tolterodine as used in general practice in England: results of prescription-event monitoring.* Drug Safety, 2001. **24**(9): p. 703-13.

526. Malhotra, B.K., N. Wood, and R. Sachse, *Influence of age, gender, and race on pharmacokinetics, pharmacodynamics, and safety of fesoterodine.* International journal of clinical pharmacology and therapeutics, 2009. **47**(9): p. 570-8.

527. Wagg, A., Khullar, V., Marscall-Kehrel, D., Michel, M., Oelke, M., Tincello, D., Darekar, A., Ebel Bitoun, C., Osterloh, I., Weinstein D., *Assessment of fesoterodine treatment in older people with overactive bladder: Results of SOFIA, a double blind, placebo controlled pan -European trial.* Proceedings of the meeting of the Euopean Urology Association, 2010: p. 880.

528. DuBeau, C.E., Ouslander, J.G., Johnson, T.M., Wyman, J.F., Kraus, S.R., Griebling, T.L., Newman, D.K., Sun,F., Catuogno, J., Bavendam, T., *Fesoterodine is effective and well tolerated in vulnerable elderly subjects with urgency incontinence: A double-blind, placebo-controlled study*, in *American Urological Association*2012: Atlanta.

529. Kay, G.G., et al., *Evaluation of cognitive function in healthy older subjects treated with fesoterodine.* Postgraduate medicine, 2012. **124**(3): p. 7-15.

530. Krauwinkel, W., et al., *Effect of age on the pharmacokinetics of solifenacin in men and women.* Int J Clin Pharmacol Ther, 2005. **43**: p. 227-238.

531. Wagg, A., J. Wyndaele, and P. Sieber, *Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: a pooled analysis.* Am J Geriatr Pharmacother, 2006. **4**: p. 14-24.

532. Michel, M., et al., *Cardiovascular safety and overall tolerability of solifenacin in routine clinical use: A 12-week, open-label, post-marketing surveillance study.* Drug Safety, 2008. **31**(6): p. 505-514.

533. Wesnes, K.A., et al., *Exploratory pilot study assessing the risk of cognitive impairment or sedation in the elderly following single doses of solifenacin 10 mg.* Expert Opin Drug Saf, 2009. **8**(6): p. 615-26.

534. Wagg, A., et al., *Solifenacin and cognitive function in elderly people with mild cognitive impairment: The SENIOR study*2011.

535. Chapple, C., et al., *Darifenacin treatment of patients > or = 65 years with overactive bladder: results of a randomized, controlled, 12-week trial.* Curr Med Res Opin, 2007. **23**: p. 2347-2358.

536. Hill, S., et al., *Long-term darifenacin treatment for overactive bladder in patients aged 65 years and older: analysis of results from a 2-year, open-label extension study.* Current medical research and opinion, 2007. **23**(11): p. 2697-704.

537. Lipton, R., K. Kolodner, and K. Wesnes, *Assessment of cognitive function of the elderly population: effects of darifenacin.* J Urol, 2005. **173**: p. 493-498.

538. Kay, G. and et al, *Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects.* Eur Urol, 2006. **50**: p. 317-326.

539. Dmochowski, R., et al., *Trospium 60 mg once daily (QD) for overactive bladder syndrome: results from a placebo-controlled interventional study.* Urology, 2008. **71**: p. 449-454.

540. Staskin, D., et al., *Trospium chloride has no effect on memory testing and is assay undetectable in the central nervous system of older patients with overactive bladder.* Int J Clin Pract. **64**(9): p. 1294-300.

541. Staskin, D., Kay, G., Tannenbaum, C., Goldman, H.B., Bhash,i K., Ling, J., Oefelein, M.G., *Trospium chloride is undetectable in older human central nervous system.* Journal of the American Geriatrics Society, 2010. **58**(8): p. 1618 - 1619.

542. Madersbacher, H. and G. Murtz, *Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic).* World Journal of Urology, 2001. **19**(5): p. 324-35.

543. Mori, S., et al., *[Bladder dysfunction in dementia patients showing urinary incontinence: evaluation with cystometry and treatment with propiverine hydrochloride].* Nippon Ronen Igakkai Zasshi - Japanese Journal of Geriatrics, 1999. **36**(7): p. 489-94.

544. Otomo, E., et al., *Clinical evaluation of propiverine hydrochloride (P-4) on urinary disturbances due to neurological diseases.* Japan J Pharmacol, 1990. **18**: p. 1731-1740.

545. Dorschner, W., et al., *[The elderly patient with urge incontinence or urge-stress incontinence - efficacy and cardiac safety of propiverine].* Aktuelle Urologie, 2003. **34**(2): p. 102-8.

546. Kanayama, N., et al., *Drug-drug interactions in the metabolism of imidafenacin: role of the human cytochrome P450 enzymes and UDP-glucuronic acid transferases, and potential of imidafenacin to inhibit human cytochrome P450 enzymes.* Xenobiotica, 2007. **37**(2): p. 139-54.

547. Ohno, T., et al., *Population pharmacokinetic analysis of a novel muscarinic receptor antagonist, imidafenacin, in healthy volunteers and overactive bladder patients.* Drug Metab Pharmacokinet, 2008. **23**(6): p. 456-63.

548. Nakade, S., et al., *No effect of imidafenacin, a novel antimuscarinic drug, on digoxin pharmacokinetics in healthy subjects.* Drug Metab Pharmacokinet, 2008. **23**(2): p. 95-100.

549. Skinner, M. and et al, *Effect of age on the pharmacokinetics of duloxetine in women.* Br J Clin Pharmacol, 2004. **57**: p. 54-61.

550. van Kerrebroeck, P. and et al, *Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence.* Br J Obstet Gynaecol, 2004. **111**: p. 249-257.

551. Steers, W. and et al, *Duloxetine compared with placebo for treating women with symptoms of overactive bladder.* BJU Int, 2007. **100**: p. 337-345.

552. Bent, A. and et al, *Duloxetine compared with placebo for the treatment of women with mixed urinary incontinence.* Neurourol Urodyn, 2008. **27**: p. 212-221.

553. Teng, E.L. and H.C. Chui, *The Modified Mini-Mental State (3MS) examination.* The Journal of clinical psychiatry, 1987. **48**(8): p. 314-8.

554. Schagen van Leeuwen, J.H., et al., *Efficacy and safety of duloxetine in elderly women with stress urinary incontinence or stress-predominant mixed urinary incontinence.* Maturitas, 2008. **60**(2): p. 138-47.

555. Astellas Pharma Global Development, I.A., *Mirabegron (YM178) for the treatment of overactive bladder: Advisory Committee Briefing Document*, 2012, Astellas Pharma Global Development, Inc (APGD) Deerfield, IL, USA.

556. Judge, T., *The use of quinestrodol in elderly incontinent women, a preliminary report.* Gerontol Clin, 1969. **11**: p. 159-164.

557. Ouslander, J.G., et al., *Effects of oral estrogen and progestin on the lower urinary tract among female nursing home residents.* Journal of the American Geriatrics Society, 2001. **49**(6): p. 803-7.

558. Ouslander, J.G., E. Cooper, and D. Godley, *Estrogen treatment for incontinence in frail older women.* Journal of the American Geriatrics Society, 1999. **47**(11): p. 1383-4.

559. Sink, K.M., et al., *Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes.* J Am Geriatr Soc, 2008. **56**(5): p. 847-53.

560. Ehrt, U., Broich, K., Larsen, J.P., Ballard, C., Aarsland, D., *Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study.* J Neurol Neurosurg Psychiatry, 2010. **81**(2): p. 160 - 165.

561. Whalley, L.J., et al., *Anticholinergic Drugs in Late Life: Adverse Effects on Cognition but not on Progress to Dementia.* Journal of Alzheimer's disease : JAD, 2012.

562. Fox, C., et al., *Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study.* Journal of the American Geriatrics Society, 2011. **59**(8): p. 1477-83.

563. Gomes, T., et al., *Risk of serious falls associated with oxybutynin and tolterodine: a population based study.* The Journal of urology, 2011. **186**(4): p. 1340-4.

564. Carriere, I., et al., *Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study.* Archives of internal medicine, 2009. **169**(14): p. 1317-24.

565. Delancey, J.O., *Why do women have stress urinary incontinence?* Neurourol Urodyn, 2010. **29 Suppl 1**: p. S13-7.

566. DeLancey, J.O., et al., *Stress urinary incontinence: relative importance of urethral support and urethral closure pressure.* J Urol, 2008. **179**(6): p. 2286-90; discussion 2290.

567. Butler, R.N., et al., *Love and sex after 60: how to evaluate and treat the sexually-active woman.* Geriatrics, 1994. **49**(11): p. 33-4, 37-8, 41-2.

568. Carey, J.M. and G.E. Leach, *Transvaginal surgery in the octogenarian using cadaveric fascia for pelvic prolapse and stress incontinence: minimal one-year results compared to younger patients.* Urology, 2004. **63**(4): p. 665-70.

569. Solomon, D.H., LoCicero, J. 3rd, Rosenthal, R.A., *New Frontiers in Geriatrics Research:An Agenda for Surgical and Related Medical Specialties.*2004., New York: American Geriatrics Society.

570. LoCicero, J.L.r., *Cross cutting issues*. New Frontiers in Geriatrics Research: An Agenda for Surgical and Related Medical Specialties, ed. D.H. Solomon, LoCicero, J. 3rd, Rosenthal, R.A.. 2004.2004, New York: American Geriatrics Society.

571. Olsen, A.L., et al., *Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence.* Obstet Gynecol, 1997. **89**(4): p. 501-6.

572. Boyles, S.H., A.M. Weber, and L. Meyn, *Procedures for pelvic organ prolapse in the United States, 1979-1997.* Am J Obstet Gynecol, 2003. **188**(1): p. 108-15.

573. FitzGerald, M.P. and L. Brubaker, *Colpocleisis and urinary incontinence.* Am J Obstet Gynecol, 2003. **189**(5): p. 1241-4.

574. Boyles, S.H., A.M. Weber, and L. Meyn, *Ambulatory procedures for urinary incontinence in the United States, 1994-1996.* Am J Obstet Gynecol, 2004. **190**(1): p. 33-6.

575. Brown, J.S., et al., *Pelvic organ prolapse surgery in the United States, 1997.* Am J Obstet Gynecol, 2002. **186**(4): p. 712-6.

576. Shah, A.D., et al., *The age distribution, rates, and types of surgery for stress urinary incontinence in the USA.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(1): p. 89-96.

577. Toglia, M.R. and T.E. Nolan, *Morbidity and mortality rates of elective gynecologic surgery in the elderly woman.* Am J Obstet Gynecol, 2003. **189**(6): p. 1584-7; discussion 1587-9.

578. Boyles, S.H., et al., *Complications associated with transobturator sling procedures.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(1): p. 19-22.

579. Miller K.S.M., R., H.., Granieri, E., Andrews, W. New York, American Geriatrics Society 2004:225-67. , *New Frontiers in Geriatric Research*, D.H. Solomon, LoCicero, J. 3rd, Rosenthal, R.A., Editor 2004, American Geriatrics Society: New York. p. 225 - 267.

580. Coleman, A.L., Bierman, A.S. , *New Frontiers in Geriatrics Rescarch. An agenda for surgical and related medical speciaties*, in *New Frontiers in Geriatrics Rescarch. An agenda for surgical and related medical speciaties*, D.H. Solomon, LoCicero, J. 3rd, Rosenthal, R.A., Editor 2004, American Geriatrics Society: New York. p. 369-419.

581. Rosow, C.E., et al., *Reversal of opioid-induced bladder dysfunction by intravenous naloxone and methylnaltrexone.* Clinical pharmacology and therapeutics, 2007. **82**(1): p. 48-53.

582. Lo, T.S., et al., *Use of intravenous anesthesia for tension-free vaginal tape therapy in elderly women with genuine stress incontinence.* Urology, 2002. **59**(3): p. 349-53.

583. Sevestre, S., et al., *Results of the tension-free vaginal tape technique in the elderly.* Eur Urol, 2003. **44**(1): p. 128-31.

584. Karantanis, E., M.M. Fynes, and S.L. Stanton, *The tension-free vaginal tape in older women.* BJOG : an international journal of obstetrics and gynaecology, 2004. **111**(8): p. 837-41.

585. Hellberg, D., et al., *The very obese woman and the very old woman: tension-free vaginal tape for the treatment of stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(4): p. 423-9.

586. Ku, J.H., et al., *Age is not a limiting factor for midurethral sling procedures in the elderly with urinary incontinence.* Gynecol Obstet Invest, 2006. **61**(4): p. 194-9.

587. Campeau, L., et al., *A multicenter, prospective, randomized clinical trial comparing tension-free vaginal tape surgery and no treatment for the management of stress urinary incontinence in elderly women.* Neurourol Urodyn, 2007. **26**(7): p. 990-4.

588. Dalpiaz, O., G. Primus, and L. Schips, *SPARC sling system for treatment of female stress urinary incontinence in the elderly.* Eur Urol, 2006. **50**(4): p. 826-30; discussion 830-1.

589. Kim, J., et al., *Worse long-term surgical outcomes in elderly patients undergoing SPARC retropubic midurethral sling placement.* BJU international, 2011. **108**(5): p. 708-12.

590. Groutz, A., et al., *The safety and efficacy of the "inside-out" trans-obturator TVT in elderly versus younger stress-incontinent women: a prospective study of 353 consecutive patients.* Neurourology and Urodynamics, 2011. **30**(3): p. 380-3.

591. Gousse, A.E., et al., *Artificial urinary sphincter for post-radical prostatectomy urinary incontinence: long-term subjective results.* J Urol, 2001. **166**(5): p. 1755-8.

592. Groutz, A., et al., *The pathophysiology of post-radical prostatectomy incontinence: a clinical and video urodynamic study.* The Journal of urology, 2000. **163**(6): p. 1767-70.

593. Martins, F.E., et al., *Adverse prognostic features of collagen injection therapy for urinary incontinence following radical retropubic prostatectomy.* J Urol, 1997. **158**(5): p. 1745-9.

594. Gormley, E.A., et al., *Effect of transurethral resection of the prostate on detrusor instability and urge incontinence in elderly males.* Neurourol Urodyn, 1993. **12**(5): p. 445-53.

595. Brierly, R.D., et al., *Is transurethral resection of the prostate safe and effective in the over 80-year-old?* Annals of the Royal College of Surgeons of England, 2001. **83**(1): p. 50-3.

596. Inouye, S.K., et al., *Burden of illness score for elderly persons: risk adjustment incorporating the cumulative impact of diseases, physiologic abnormalities, and functional impairments.* Medical care, 2003. **41**(1): p. 70-83.

597. Inouye, S.K., et al., *The Hospital Elder Life Program: a model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital Elder Life Program.* Journal of the American Geriatrics Society, 2000. **48**(12): p. 1697-706.

598. Bogardus, S.T., Jr., et al., *The effects of a targeted multicomponent delirium intervention on postdischarge outcomes for hospitalized older adults.* The American journal of medicine, 2003. **114**(5): p. 383-90.

599. Inouye, S.K., et al., *Clarifying confusion: the confusion assessment method. A new method for detection of delirium.* Annals of internal medicine, 1990. **113**(12): p. 941-8.

600. Britton, A. and R. Russell, *Multidisciplinary team interventions for delirium in patients with chronic cognitive impairment.* Cochrane database of systematic reviews, 2001(1): p. CD000395.

601. Herr, K.A. and L. Garand, *Assessment and measurement of pain in older adults.* Clinics in geriatric medicine, 2001. **17**(3): p. 457-78, vi.

602. Allen, C., P. Glasziou, and C. Del Mar, *Bed rest: a potentially harmful treatment needing more careful evaluation.* Lancet, 1999. **354**(9186): p. 1229-33.

603. Sager, M.A., et al., *Hospital admission risk profile (HARP): identifying older patients at risk for functional decline following acute medical illness and hospitalization.* Journal of the American Geriatrics Society, 1996. **44**(3): p. 251-7.

604. Counsell, S.R., et al., *Effects of a multicomponent intervention on functional outcomes and process of care in hospitalized older patients: a randomized controlled trial of Acute Care for Elders (ACE) in a community hospital.* Journal of the American Geriatrics Society, 2000. **48**(12): p. 1572-81.

605. Gould, C.V., et al., *Guideline for Prevention of Catheter-Associated Urinary Tract Infections*, http://ehis.ebscohost.com/ehost/pdfviewer/pdfviewer?vid=5&hid=1&sid=8250e35c-568b-4a4b-9e4f-a2ce10eb4bf0%40sessionmgr11, Editor 2009.

606. Maki, D.G. and P.A. Tambyah, *Engineering out the risk for infection with urinary catheters.* Emerg Infec Dis, 2001. **7**(2): p. 342-7.

607. Jonsson, K., et al., *Urine bladder catheters in nursing home patients: a one-day point prevalence study in a Swedish county.* Scandinavian Journal Of Urology And Nephrology, 2010. **44**: p. 320-323.

608. Landi, F., et al., *Indwelling urethral catheter and mortality in frail elderly women living in community.* Neurourology and Urodynamics, 2004. **23**(7): p. 697-701.

609. Centers for Medicare and Medicaide Services, *Minimum dataset quality indicator and resident reports*, 2010, Centers for Medicare and Medicaid Services

610. Kunin, C.M., Q.F. Chin, and S. Chambers, *Morbidity and mortality associated with indwelling urinary catheters in elderly patients in a nursing home-confounding due to the presence of associated diseases.* J Am Geriatr Soc, 1987. **35**(11): p. 1001-6.

611. Anger, J.T., et al., *True prevalence of urinary incontinence among female nursing home residents.* Urology, 2006. **67**(2): p. 281-287.

612. Tsan, L., et al., *Prevalence of nursing home-associated infections in the Department of Veterans Affairs nursing home care units.* Am J Infect Control, 2008. **36**(3): p. 173-179.

613. Tsan, L., et al., *Nursing home-associated infections in Department of Veterans Affiars community living centers.* Am J Infect Control, 2010. **38**: p. 461-6.

614. Georgiou, A., et al., *Measuring the quality of urinary continence care in long-term care facilities: an analysis of outcome indicators.* Age and Ageing, 2001. **30**(1): p. 63-66.

615. McNulty, C., et al., *Prevalence of urinary catheterization in UK nursing homes.* Journal of Hospital Infection, 2003. **55**: p. 119-123.

616. Lomas, G.M., R. Howell-Jones, and C.A.M. McNulty, *Identifying key factors that affect care home catheterisation rates: changing practice through audit.* Journal of Infection Prevention, 2009. **10**(2): p. 66-69.

617. Nicolle, L.E., *The chronic indwelling catheter and urinary infection in long-term-care facility residents.* Infection Control & Hospital Epidemiology, 2001. **22**(5): p. 316-321.

618. Roe, B., *Long term catheter care in the community.* Nursing Times, 2989. **85**(36): p. 43-44.

619. Sorbye, L.W., et al., *Indwelling catheter use in home care; elderly, aged 65+, in 11 different countries in Europe.* Age and Ageing, 2005. **34**: p. 377-381.

620. Lakhan, P., et al., *A prospective cohort study of geriatric syndromes among older medical patients admitted to acute care hospitals.* Journal of the American Geriatric Society, 2011.

621. Fainsinger, R.L., et al., *The use of urinary catheters in terminally ill cancer patients.* Journal of Pain and Symptom Management, 1992. **7**(6): p. 333-338.

622. Gokula, R.M., J.A. Hickner, and M.A. Smith, *Inappropriate use of urinary catheters in elderly patients at a midwestern community teaching hospital.* Am J Infect Control, 2004. **32**(4): p. 196-199.

623. Apisarnthanarak, A., et al., *Initial inappropriate urinary catheters use in a tertiary-care center: Incidence, risk factors, and outcomes.* Am J Infect Control, 2007. **35**: p. 594-599.

624. McNulty, C., et al., *Exploring reasons for variation in urinary catheterisation prevalence in care homes: a qualitative study. Age and Ageing. 37(6):706-710.* Age and Ageing, 2008. **37**(6): p. 706-710.

625. Kunin, C.M., et al., *The association between the use of urinary catheters and morbidity and mortality among elderly patients in nursing homes.* Am J Epidemiol, 1992. **135**: p. 291-301.

626. Palmer, M.H., *Urinary incontinence in nursing homes.* Journal of Wound, Ostomy & Continence Nursing, 2002. **29**(1): p. 4-5.

627. Pilloni, S., et al., *Intermittent catheterisation in older people: a valuable alternative to an indwelling catheter?* Age and Ageing, 2005. **34**(1): p. 57-60.

628. van Kerrebroeck, P., et al., *The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society.* Neurourology & Urodynamics, 2002. **21**(2): p. 179-83.

629. Tikkinen, K.A., et al., *Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland.* European Urology, 2010. **57**(3): p. 488-96.

630. Chen, F.Y., et al., *Perception of nocturia and medical consulting behavior among community-dwelling women.* International Urogynecology Journal, 2007. **18**(4): p. 431-6.

631. Weiss, J.P., et al., *The evaluation and treatment of nocturia: a consensus statement.* BJU International, 2011. **108**(1): p. 6-21.

632. Vaughan, C., et al., *Self-rated sleep characteristics and bother from nocturia. .* International Journal of Clinical Practice, 2012. **66**(4): p. 369-373.

633. Dubeau, C.E. and J.F. Tsui, *Nocturia in the Elderly*, in *Nocturia: Causes, Consequences, and Clinical Approaches*, J.P. Weiss, et al., Editors. 2012, Springer: New York. p. 147-155.

634. Ouslander, J.G., et al., *Nighttime urinary incontinence and sleep disruption among nursing home residents.* Journal of the American Geriatrics Society, 1998. **46**(4): p. 463-6.

635. Weiss, J.P. and J.G. Blaivas, *Nocturia.* Journal of Urology, 2000. **163**(1): p. 5.

636. Weiss, J., et al., *Nocturia: new directions.* Neurourol Urodyn, 2011. **30**(5): p. 700-3

637. Weatherall, M., *The risk of hyponatremia in older adults using desmopressin for nocturia: a systematic review and meta-analysis.* Neurourol Urodyn, 2004. **23**(4): p. 302-5.

638. Hale, W.E., et al., *Symptom prevalence in the elderly. An evaluation of age, sex, disease, and medication use.* Journal of the American Geriatrics Society, 1986. **34**(5): p. 333-40.

639. Malmsten, U.G., et al., *Urinary incontinence and lower urinary tract symptoms: an epidemiological study of men aged 45 to 99 years.* Journal of Urology, 1997. **158**(5): p. 1733-7.

640. Pinnock, C. and V.R. Marshall, *Troublesome lower urinary tract symptoms in the community: a prevalence study. [see comments.].* Medical Journal of Australia, 1997. **167**(2): p. 72-5.

641. Perry, S., et al., *An epidemiological study to establish the prevalence of urinary symptoms and felt need in the community: the Leicestershire MRC Incontinence Study. Leicestershire MRC Incontinence Study Team.* Journal of Public Health Medicine, 2000. **22**(3): p. 427-34.

642. Schatzl, G., et al., *Cross-sectional study of nocturia in both sexes: analysis of a voluntary health screening project.* Urology, 2000. **56**(1): p. 71-5.

643. Markland, A.D., et al., *Prevalence of nocturia in United States men: results from the National Health and Nutrition Examination Survey.* Journal of Urology, 2011. **185**(3): p. 998-1002.

644. Tikkinen, K.A., et al., *Is nocturia equally common among men and women? A population based study in Finland.* J Urol, 2006. **175**(2): p. 596-600.

645. Wehrberger, C., et al., *Lower urinary tract symptoms and urinary incontinence in a geriatric cohort - a population-based analysis.* BJU Int, 2012.

646. van Doorn, B., et al., *Once nocturia, always nocturia? Natural history of nocturia in older men based on frequency-volume charts: the Krimpen study.* J Urol, 2011. **186**(5): p. 1956-61.

647. Burgio, K.L., et al., *Prevalence and correlates of nocturia in community-dwelling older adults.* J Am Geriatr Soc, 2010. **58**(5): p. 861-6.

648. Gopal, M., et al., *Investigating the associations between nocturia and sleep disorders in perimenopausal women.* J Urol, 2008. **180**(5): p. 2063-7.

649. Kupelian, V., et al., *Are racial/ethnic disparities in the prevalence of nocturia due to socioeconomic status? Results of the BACH survey.* J Urol, 2009. **181**(4): p. 1756-63.

650. Fitzgerald, M.P., et al., *The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey.* Journal of Urology, 2007. **177**(4): p. 1385-9.

651. Johnson, T.M., 2nd, et al., *Evaluating potentially modifiable risk factors for prevalent and incident nocturia in older adults.* J Am Geriatr Soc, 2005. **53**(6): p. 1011-6.

652. Plantinga, L., et al., *Association of sleep-related problems with CKD in the United States, 2005-2008.* Am J Kidney Dis, 2011. **58**(4): p. 554-64.

653. Hillier, P., M.S. Knapp, and R. Cove-Smith, *Circadian variations in urine excretion in chronic renal failure.* Quarterly Journal of Medicine, 1980. **49**(196): p. 461-78.

654. Rembratt, A., J.P. Norgaard, and K.E. Andersson, *Nocturia and associated morbidity in a community-dwelling elderly population.* BJU Int, 2003. **92**(7): p. 726-30.

655. Asplund, R., *Nocturia in relation to sleep, somatic diseases and medical treatment in the elderly.[see comment].* BJU International, 2002. **90**(6): p. 533-6.

656. Parsons, J.K., et al., *Lower urinary tract symptoms increase the risk of falls in older men.* BJU Int, 2009. **104**(1): p. 63-8.

657. Vaughan, C.P., et al., *The association of nocturia with incident falls in an elderly community-dwelling cohort.* International Journal of Clinical Practice, 2010. **64**(5): p. 577-83.

658. Temml, C., et al., *Nocturia is an age-independent risk factor for hip-fractures in men.* Neurourol Urodyn, 2009. **28**(8): p. 949-52.

659. Nakagawa, H., et al., *Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study.* J Urol, 2010. **184**(4): p. 1413-8.

660. Kupelian, V., et al., *Nocturia and quality of life: results from the Boston area community health survey.* Eur Urol, 2012. **61**(1): p. 78-84.

661. Coyne, K.S., et al., *The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA.[see comment].* BJU International, 2003. **92**(9): p. 948-54.

662. Mock, L.L., et al., *Content validation of symptom-specific nocturia quality-of-life instrument developed in men: issues expressed by women, as well as men.* Urology, 2008. **72**(4): p. 736-42.

663. Booth, J.M., et al., *Exploring older peoples' experiences of nocturia: a poorly recognised urinary condition that limits participation.* Disabil Rehabil, 2010. **32**(9): p. 765-74.

664. Yoshimura, K., et al., *Differences and associations between nocturnal voiding/nocturia and sleep disorders.* BJU Int, 2010. **106**(2): p. 232-7.

665. Bliwise, D.L., et al., *Nocturia and disturbed sleep in the elderly.* Sleep Medicine, 2009. **10**(5): p. 540-8.

666. Endeshaw, Y., *Correlates of self-reported nocturia among community-dwelling older adults.* Journals of Gerontology Series A-Biological Sciences & Medical Sciences, 2009. **64**(1): p. 142-8.

667. Helfand, B.T., et al., *The relationship between lower urinary tract symptom severity and sleep disturbance in the CAMUS trial.* J Urol, 2011. **185**(6): p. 2223-8.

668. Abraham, L., et al., *Development and validation of a quality-of-life measure for men with nocturia.* Urology, 2004. **63**(3): p. 481-6.

669. Kupelian, V., et al., *Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey.* Journal of Urology, 2011. **185**(2): p. 571-7.

670. Bursztyn, M., J. Jacob, and J. Stessman, *Usefulness of nocturia as a mortality risk factor for coronary heart disease among persons born in 1920 or 1921.* Am J Cardiol, 2006. **98**(10): p. 1311-5.

671. Lightner, D.J., et al., *Nocturia is associated with an increased risk of coronary heart disease and death.* BJU Int, 2012.

672. van Doorn, B., et al., *Mortality in Older Men With Nocturia. A 15-Year Followup of the Krimpen Study.* J Urol, 2012.

673. Parthasarathy, S., et al., *Nocturia, sleep-disordered breathing, and cardiovascular morbidity in a community-based cohort.* PLoS ONE [Electronic Resource], 2012. **7**(2): p. e30969.

674. Tikkinen, K.A., et al., *A systematic evaluation of factors associated with nocturia--the population-based FINNO study.* American Journal of Epidemiology, 2009. **170**(3): p. 361-8.

675. Abrams, P., et al., *The role of desmopressin in the treatment of adult nocturia.* BJU International, 2002. **90 Suppl 3**: p. 32-6.

676. Shahab, N., et al., *The profiles and patterns of detrusor overactivity and their association with overactive bladder symptoms in men with benign prostatic enlargement associated with detrusor overactivity.* Neurourol Urodyn, 2009. **28**(8): p. 953-8.

677. Huang, A.J., et al., *Clinical significance of postvoid residual volume in older ambulatory women.* J Am Geriatr Soc, 2011. **59**(8): p. 1452-8.

678. Kirkland, J.L., et al., *Patterns of Urine Flow and Electrolyte Excretion in Healthy Elderly People.* Br Med J, 1983. **287**: p. 1665-1667.

679. Blanker, M.H., A.M. Bohnen, and J.L. Ruud Bosch, *Nocturia in relation to sleep, somatic diseases and medical treatment in the elderly.[comment].* BJU International, 2003. **91**(1): p. 125.

680. Miller, M., *Nocturnal polyuria in older people: pathophysiology and clinical implication.* Journal of the American Geriatrics Society, 2000. **48**: p. 1321-29.

681. Rembratt, A., J.P. Norgaard, and K.E. Andersson, *Desmopressin in elderly patients with nocturia: short-term safety and effects on urine output, sleep and voiding patterns.* BJU International, 2003. **91**(7): p. 642-6.

682. Ouslander, J., et al., *The dark side of incontinence: nighttime incontinence in nursing home residents.* Journal of the American Geriatrics Society, 1993. **41**(4): p. 371-6.

683. Kim, S.O., et al., *Age related change of nocturia in women.* Int Neurourol J, 2010. **14**(4): p. 245-9.

684. Weiss, J.P., et al., *Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia.* J Urol, 2011. **186**(4): p. 1358-63.

685. Weiss, J.P., et al., *Age related pathogenesis of nocturia in patients with overactive bladder.[see comment].* Journal of Urology, 2007. **178**(2): p. 548-51; discussion 551.

686. Hall, S.A., et al., *Commonly used antihypertensives and lower urinary tract symptoms: results from the Boston Area Community Health (BACH) Survey.* BJU Int, 2011.

687. Asplund, R. and H. Aberg, *Diurnal variation in the levels of antidiuretic hormone in the elderly.* J Intern Med, 1991. **229**(2): p. 131-4.

688. Ouslander, J.G., et al., *Arginine vasopressin levels in nursing home residents with nighttime urinary incontinence [published erratum appears in J Am Geriatr Soc 1999 Apr;47(4):481].* Journal of the American Geriatrics Society, 1998. **46**(10): p. 1274-9.

689. Johnson, T.M., 2nd, et al., *Changes in nocturia from medical treatment of benign prostatic hyperplasia: secondary analysis of the Department of Veterans Affairs Cooperative Study Trial.* Journal of Urology, 2003. **170**(1): p. 145-8.

690. Umlauf, M.G., et al., *Obstructive sleep apnoea, nocturia and polyuria in older adults.* Sleep, 2004. **27**(1): p. 139-44.

691. Ouslander, J., et al., *Atrial natriuretic peptide levels in geriatric patients with nocturia and nursing home residents with nighttime incontinence.* Journal of the American Geriatrics Society, 1999. **47**(12): p. 1439-44.

692. Dahlstrand, C., et al., *Snoring--a common cause of voiding disturbance in elderly men.* Lancet, 1996. **347**(8996): p. 270-1.

693. Bliwise, D.L., C.L. Adelman, and J.G. Ouslander, *Polysomnographic correlates of spontaneous nocturnal wetness episodes in incontinent geriatric patients.* Sleep, 2004. **27**(1): p. 153-7.

694. Pressman, M.R., et al., *Nocturia. A rarely recognized symptom of sleep apnoea and other occult sleep disorders.* Arch Intern Med, 1996. **156**(5): p. 545-50.

695. Endeshaw, Y.W., et al., *Sleep-disordered breathing and nocturia in older adults.* Journal of the American Geriatrics Society, 2004. **52**(6): p. 957-60.

696. Romero, E., et al., *Nocturia and snoring: predictive symptoms for obstructive sleep apnoea.* Sleep Breath, 2010. **14**(4): p. 337-43.

697. Abrams, P. and B. Klevmark, *Frequency volume charts: an indispensable part of lower urinary tract assessment.* Scand J Urol Nephrol Suppl, 1996. **179**: p. 47-53.

698. Weiss, J.P., et al., *Desmopressin orally disintegrating tablet effectively reduces nocturia: Results of a randomized, double-blind, placebo-controlled trial.* Neurourol Urodyn, 2012.

699. Johnson, T.M., 2nd, et al., *Effects of behavioral and drug therapy on nocturia in older incontinent women.* Journal of the American Geriatrics Society, 2005. **53**(5): p. 846-50.

700. Johnson, T.M., 2nd, et al., *The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia.* J Urol, 2007. **178**(5): p. 2045-50; discussion 2050-1.

701. Lose, G., et al., *Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women.* American Journal of Obstetrics & Gynecology, 2003. **189**(4): p. 1106-1113.

702. Mattiasson, A., et al., *Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men.* BJU International, 2002. **89**(9): p. 855-62.

703. Smith, A.L. and A.J. Wein, *Outcomes of pharmacological management of nocturia with non-antidiuretic agents: does statistically significant equal clinically significant?* BJU International, 2011. **107**(10): p. 1550-4.

704. Vaughan, C.P., et al., *A multicomponent behavioural and drug intervention for nocturia in elderly men: rationale and pilot results.* BJU international, 2009. **104**(1): p. 69-74.

705. Soda, T., et al., *Efficacy of nondrug lifestyle measures for the treatment of nocturia.* J Urol, 2010. **184**(3): p. 1000-4.

706. Fitzgerald, M.P., et al., *Nocturia, nocturnal incontinence prevalence, and response to anticholinergic and behavioral therapy.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(11): p. 1545-50.

707. Burgio, K., et al., *Behavioral versus drug treatment for overactive bladder in men: the male overactive bladder treatment in veterans (MOTIVE) trial.* Journal of the American Geriatrics Society 2011 **59**(12): p. 2209-2216.

708. Wagg, A., J.J. Wyndaele, and P. Sieber, *Efficacy and tolerability of solefenacin in elderly subjects with overactive bladder syndrome: a pooled analysis.* American Journal of Geriatric Pharmacology, 2006. **4**: p. 14-24.

709. Kaplan, S.A., et al., *Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial.* JAMA, 2006. **296**(19): p. 2319-28.

710. Rackley, R., et al., *Nighttime dosing with tolterodine reduces overactive bladder-related nocturnal micturitions in patients with overactive bladder and nocturia.* Urology, 2006. **67**: p. 731.

711. Vardy, M.D., et al., *Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient-reported outcomes: results from VIBRANT - a double-blind, placebo-controlled trial.* Int J Clin Pract, 2009. **63**(12): p. 1702-14.

712. Chapple, C., et al., *A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder.* BJU International, 2005. **95**(7): p. 993-1001.

713. Nitti, V.W., et al., *Efficacy and tolerability of tolterodine extended-release in continent patients with overactive bladder and nocturia.* BJU International, 2006. **97**(6): p. 1262-6.

714. Herschorn, S., et al., *Tolerability of 5 mg solifenacin once daily versus 5 mg oxybutynin immediate release 3 times daily: results of the VECTOR trial.* J Urol, 2010. **183**(5): p. 1892-8.

715. Kaplan, S.A., et al., *Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder.* JAMA, 2006. **296**: p. 2319-2328.

716. Yokoyama, O., et al., *Efficacy of solifenacin on nocturia in Japanese patients with overactive bladder: impact on sleep evaluated by bladder diary.* J Urol, 2011. **186**(1): p. 170-4.

717. Chapple, C.R., et al., *Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe.* Eur Urol, 2011. **59**(3): p. 342-52.

718. Barry, M.J., et al., *Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: a randomized trial.* JAMA, 2011. **306**(12): p. 1344-51.

719. Johnson, T.M., 2nd, et al., *The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia.* Journal of Urology, 2007. **178**(5): p. 2045-50; discussion 2050-1.

720. Kok, A.L., et al., *Micturition complaints in postmenopausal women treated with continuously combined hormone replacement therapy: a prospective study.* Maturitas, 1999. **31**(2): p. 143-9.

721. Fantl, J.A., et al., *Urinary Incontinence in Adults: Acute and Chronic Management. Clinical Practice Guideline No. 2, 1996 Update.*, 1996, U.S. Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 96-0682: Rockville, MD.

722. Drake, M.J., I.W. Mills, and J.G. Noble, *Melatonin pharmacotherapy for nocturia in men with benign prostatic enlargement.[see comment].* Journal of Urology, 2004. **171**(3): p. 1199-202.

723. Sugaya, K., et al., *Effects of melatonin and rilmazafone on nocturia in the elderly.* Journal of International Medical Research, 2007. **35**(5): p. 685-91.

724. Pedersen, P.A. and P.B. Johansen, *Prophylactic treatment of adult nocturia with bumetanide.* British Journal of Urology, 1988. **62**(2): p. 145-7.

725. Reynard, J.M., et al., *A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. [see comments.].* British Journal of Urology, 1998. **81**(2): p. 215-8.

726. Committee for Establishment of the Clinical Guidelines for Nocturia of the Neurogenic Bladder, S., *Clinical guidelines for nocturia.* International Journal of Urology, 2010. **17**(5): p. 397-409.

727. Fitzgerald, M.P., et al., *The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey.* J Urol, 2007. **177**(4): p. 1385-9.

728. Seiler, W., H. Stahelin, and U. Hefti, *Desmopressin reduces night urine volume in elderly: implication for treatment of the nocturnal incontinence.* Clinical Investigator, 1992. **70**: p. 619.

729. Seiler, W.O., H.B. Stahelin, and U. Hefti, *Desmopressin reduces night urine volume in geriatric patients: implication for treatment of the nocturnal incontinence.* Clinical Investigator, 1992. **70**(7): p. 619.

730. Asplund, R. and H. Aberg, *Desmopressin in elderly subjects with increased nocturnal diuresis. A two-month treatment study.* Scand J Urol Nephrol, 1993. **27**(1): p. 77-82.

731. Asplund, R. and H. Aberg, *Desmopressin in elderly women with increased nocturnal diuresis.* Journal of Urology, 1993. **72**: p. 42-43.

732. Asplund, R. and H. Aberg, *Desmopressin in elderly women with increased nocturnal diuresis. A short-term study.* British Journal of Urology, 1993. **72**(1): p. 42-5.

733. Asplund, R., B. Sundberg, and P. Bengtsson, *Oral desmopressin for nocturnal polyuria in elderly subjects: a double-blind, placebo-controlled randomized exploratory study.* BJU International, 1999. **83**(6): p. 591-5.

734. Assassa, R.P., D.E. Osborn, and C.M. Castleden, *Male lower urinary tract symptoms: is surgery always necessary?* Gerontology, 1998. **44**(2): p. 61-6.

735. Cannon, A., et al., *Desmopressin in the treatment of nocturnal polyuria in the male. [see comments.].* BJU International, 1999. **84**(1): p. 20-4.

736. Chancellor, M.B., et al., *Beneficial effect of intranasal desmopressin for men with benign prostatic hyperplasia and nocturia: preliminary results.* Techniques in Urology, 1999. **5**(4): p. 191-4.

737. Kuo, H.C., *Efficacy of desmopressin in treatment of refractory nocturia in patients older than 65 years.* Urology, 2002. **59**(4): p. 485-9.

738. Wang, C.J., et al., *Low dose oral desmopressin for nocturnal polyuria in patients with benign prostatic hyperplasia: a double-blind, placebo controlled, randomized study.* J Urol, 2011. **185**(1): p. 219-23.

739. Rezakhaniha, B., N. Arianpour, and S. Siroosbakhat, *Efficacy of desmopressin in treatment of nocturia in elderly men.* J Res Med Sci, 2011. **16**(4): p. 516-23.

740. Fu, F.G., H.J. Lavery, and D.L. Wu, *Reducing nocturia in the elderly: a randomized placebo-controlled trial of staggered furosemide and desmopressin.* Neurourology & Urodynamics, 2011. **30**(3): p. 312-6.

741. van Kerrebroeck, P., et al., *Desmopressin in the treatment of nocturia: a double-blind, placebo-controlled study.* European Urology, 2007. **52**(1): p. 221-9.

742. Johnson, T.M., et al., *The relationship between the action of arginine vasopressin and responsiveness to oral desmopressin in older men: a pilot study.* Journal of the American Geriatrics Society, 2007. **55**(4): p. 562-9.

743. Bae, J.H., et al., *The effects of long-term administration of oral desmopressin on the baseline secretion of antidiuretic hormone and serum sodium concentration for the treatment of nocturia: a circadian study.* Journal of Urology, 2007. **178**(1): p. 200-3.

744. Johnson, T.M., 2nd, et al., *Oral ddAVP for nighttime urinary incontinence in characterized nursing home residents: a pilot study.* Journal of the American Medical Directors Association, 2006. **7**(1): p. 6-11.

745. Weatherall, M. and T. Arnold, *Nocturia in adults: draft New Zealand guidelines for its assessment and management in primary care.* New Zealand Medical Journal, 2006. **119**: p. U1976.

746. Rembratt, A., A. Riis, and J.P. Norgaard, *Desmopressin treatment in nocturia; an analysis of risk factors for hyponatremia.* Neurourol Urodyn, 2006. **25**(2): p. 105-9.

747. Rembratt, A., et al., *Pharmacokinetics and pharmacodynamics of desmopressin administered orally versus intravenously at daytime versus night-time in healthy men aged 55-70 years.* European Journal of Clinical Pharmacology, 2004. **60**(6): p. 397-402.

748. Juul, K.V., et al., *Gender difference in antidiuretic response to desmopressin.* Am J Physiol Renal Physiol, 2011. **300**(5): p. F1116-22.

749. Peters, K.M., et al., *Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial.* J Urol, 2010. **183**(4): p. 1438-43.

750. MacDiarmid, S.A., et al., *Long-term durability of percutaneous tibial nerve stimulation for the treatment of overactive bladder.* J Urol, 2010. **183**(1): p. 234-40.

751. Hakenberg, O.W., C.B. Pinnock, and V.R. Marshall, *Does evaluation with the International Prostate Symptom Score predict the outcome of transurethral resection of the prostate?* J Urol, 1997. **158**(1): p. 94-9.

752. Meyhoff, H.H. and J. Nordling, *Long term results of transurethral and transvesical prostatectomy. A randomized study.* Scandinavian Journal of Urology & Nephrology, 1986. **20**(1): p. 27-33.

753. Seki, N., et al., *Analysis of the prognostic factors for overactive bladder symptoms following surgical treatment in patients with benign prostatic obstruction.* Neurourol Urodyn, 2009. **28**(3): p. 197-201.

754. Simaioforidis, V., et al., *Tamsulosin versus transurethral resection of the prostate: effect on nocturia as a result of benign prostatic hyperplasia.* Int J Urol, 2011. **18**(3): p. 243-8.

755. Margel, D., et al., *Predictors of nocturia quality of life before and shortly after prostatectomy.* Urology, 2007. **70**(3): p. 493-7.

756. Seki, N., et al., *Association among the symptoms, quality of life and urodynamic parameters in patients with improved lower urinary tract symptoms following a transurethral resection of the prostate.* Neurourol Urodyn, 2008. **27**(3): p. 222-5.

757. Talley, K.M., J.F. Wyman, and T.A. Shamliyan, *State of the science: conservative interventions for urinary incontinence in frail community-dwelling older adults.* Nursing outlook, 2011. **59**(4): p. 215-20, 220 e1.

758. McDowell, B.J., et al., *Effectiveness of behavioral therapy to treat incontinence in homebound older adults.* J Am Geriatr Soc, 1999. **47**(3): p. 309-18.

759. Harari, D. and C. Igbedioh, *Restoring continence in frail older people living in the community: what factors influence successful treatment outcomes?* Age Ageing, 2009. **38**(2): p. 228-33.

760. Gotoh, M., et al., *Impact of urinary incontinence on the psychological burden of family caregivers.* Neurourol Urodyn, 2009. **28**(6): p. 492-6.

761. Black, J.M., et al., *MASD part 2: incontinence-associated dermatitis and intertriginous dermatitis: a consensus.* Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN, 2011. **38**(4): p. 359-70; quiz 371-2.

762. Du Moulin, M.F., et al., *Quality systems to improve care in older patients with urinary incontinence receiving home care: do they work?* Qual Saf Health Care, 2010. **19**(5): p. e18.

763. Borrie, M.J., et al., *Interventions led by nurse continence advisers in the management of urinary incontinence: a randomized controlled trial.* CMAJ, 2002. **166**(10): p. 1267-73.

764. Williams, K.S., et al., *Clinical and cost-effectiveness of a new nurse-led continence service: a randomised controlled trial.* Br J Gen Pract, 2005. **55**(518): p. 696-703.

765. Williams, K.S., et al., *A randomized controlled trial of the effectiveness of pelvic floor therapies for urodynamic stress and mixed incontinence.* BJU Int, 2006. **98**(5): p. 1043-50.

766. Johnson, R.W., Toohey,D.,Wiener,J.M. , *Meeting the long-term care needs of the baby boomers: How changing families will affect paid helpers and institutions.*, 2007 The Urban Institute. : Washington, D.C.

767. Pearson, A., et al., *Systematic review of evidence on the impact of nursing workload and staffing on establishing healthy work environments.* International journal of evidence-based healthcare, 2006. **4**(4): p. 337-84.

768. Rycroft-Malone, J., *The PARIHS framework--a framework for guiding the implementation of evidence-based practice.* Journal of nursing care quality, 2004. **19**(4): p. 297-304.

769. Crooks, V.C., et al., *Use of the Minimum Data Set to rate incontinence severity.* J Am Geriatr Soc, 1995. **43**(12): p. 1363-9.

770. Resnick, N.M., et al., *Evaluating a national assessment strategy for urinary incontinence in nursing home residents: reliability of the minimum data set and validity of the resident assessment protocol.* Neurourol Urodyn, 1996. **15**(6): p. 583-98.

771. Ouslander, J.G. and T.M. Johnson, 2nd, *Continence care for frail older adults: it is time to go beyond assessing quality.* J Am Med Dir Assoc, 2004. **5**(3): p. 213-6.

772. Potter, J., et al., *National audit of continence care for older people: management of faecal incontinence.* Age Ageing, 2007. **36**(3): p. 268-73.

773. Schnelle, J.F., et al., *Total quality management: administrative and clinical applications in nursing homes.* J Am Geriatr Soc, 1993. **41**(11): p. 1259-66.

774. Horn, S.D., et al., *Beyond CMS quality measure adjustments: identifying key resident and nursing home facility factors associated with quality measures.* Journal of the American Medical Directors Association, 2010. **11**(7): p. 500-5.

775. Mezey, M.D., E.L. Mitty, and S.G. Burger, *Rethinking teaching nursing homes: potential for improving long-term care.* The Gerontologist, 2008. **48**(1): p. 8-15.

776. Ostaszkiewicz, J., B. O'Connell, and L. Millar, *Incontinence: managed or mismanaged in hospital settings?* Int J Nurs Pract, 2008. **14**(6): p. 495-502.

777. Weiner, J.M., *An assessment of strategies for improving quality of care in nursing homes.* The Gerontologist, 2003. **43**: p. 19-27.

778. O'Connell, B., et al., *The Tri-focal model of care: advancing the teaching-nursing home concept.* International journal of nursing practice, 2008. **14**(6): p. 411-7.

779. Frantz, R.A., et al., *Implementing an incontinence management protocol in long-term care. Clinical outcomes and costs.* J Gerontol Nurs, 2003. **29**(8): p. 46-53.

780. Krichbaum, K.E., V. Pearson, and J. Hanscom, *Better care in nursing homes: advanced practice nurses' strategies for improving staff use of protocols.* Clinical nurse specialist CNS, 2000. **14**(1): p. 40-6.

781. Watson, N.M., Brink, C. A., Zimmer, J. G., & Mayer, R. D., *Final report: A model for use of the urinary incontinence guideline in US nursing homes.*, 2005, Agency for Health Care Research and Quality. University of Rochester:: Rochester.

782. Lakhan, P., et al., *A prospective cohort study of geriatric syndromes among older medical patients admitted to acute care hospitals.* Journal of the American Geriatrics Society, 2011. **59**(11): p. 2001-8.

783. Palmer, M.H., et al., *Risk factors for hospital-acquired incontinence in elderly female hip fracture patients.* J Gerontol A Biol Sci Med Sci, 2002. **57**(10): p. M672-7.

784. Palese, A., et al., *Incontinence pad use in patients admitted to medical wards: an Italian multicenter prospective cohort study.* J Wound Ostomy Continence Nurs, 2007. **34**(6): p. 649-54.

785. Connor, P.A. and B.M. Kooker, *Nurses' knowledge, attitudes, and practices in managing urinary incontinence in the acute care setting.* Medsurg Nurs, 1996. **5**(2): p. 87-92, 117.

786. Cooper, G. and E. Watt, *An exploration of acute care nurses' approach to assessment and management of people with urinary incontinence.* J Wound Ostomy Continence Nurs, 2003. **30**(6): p. 305-13.

787. Hancock, R., et al., *Factors associated with nursing interventions to reduce incontinence in hospitalized older adults.* Urol Nurs, 1996. **16**(3): p. 79-85.

788. Vinsnes, A.G., et al., *Healthcare personnel's attitudes towards patients with urinary incontinence.* J Clin Nurs, 2001. **10**(4): p. 455-62.

789. Norheim, A., Vinsnes, A. G. , *Staff's attitudes towards hospitalised elderly patients with urinary incontinence.* . Nordic Journal of Nursing Research & Clinical Studies, 2005 **25.** (1): p. 21-25.

790. Miles, T.P., et al., *New-onset incontinence and markers of frailty: data from the Hispanic Established Populations for Epidemiologic Studies of the Elderly.* J Gerontol A Biol Sci Med Sci, 2001. **56**(1): p. M19-24.

791. Jenkins, K.R. and N.H. Fultz, *Functional impairment as a risk factor for urinary incontinence among older Americans.* Neurourol Urodyn, 2005. **24**(1): p. 51-5.

792. Dowling-Castronovo, A. and J.K. Specht, *How to try this: Assessment of transient urinary incontinence in older adults.* The American journal of nursing, 2009. **109**(2): p. 62-71; quiz 72.

793. AlAmeel, T., M.K. Andrew, and C. MacKnight, *The association of fecal incontinence with institutionalization and mortality in older adults.* Am J Gastroenterol, 2010. **105**(8): p. 1830-4.

794. Chassagne, P., et al., *Fecal incontinence in the institutionalized elderly: incidence, risk factors, and prognosis.* Am J Med, 1999. **106**(2): p. 185-90.

795. Nakanishi, N., et al., *Mortality in relation to urinary and faecal incontinence in elderly people living at home.* Age & Ageing, 1999. **28**(3): p. 301-6.

796. Alayne D. Markland, P.S.G.K.L.B.D.T.R.H.E.R.P.S.R.M .A., *Correlates of Urinary, Fecal, and Dual Incontinence in Older African-American and White Men and Women.* Journal of the American Geriatrics Society, 2008. **56**(2): p. 285-290.

797. Quander, C.R., et al., *Prevalence of and factors associated with fecal incontinence in a large community study of older individuals.* American Journal of Gastroenterology, 2005. **100**(4): p. 905-9.

798. Goode, P.S., et al., *Prevalence and correlates of fecal incontinence in community-dwelling older adults.* Journal of the American Geriatrics Society, 2005. **53**(4): p. 629-35.

799. Nelson, R., et al., *Community-based prevalence of anal incontinence.* JAMA, 1995. **274**(7): p. 559-61.

800. Dunivan, G.C., et al., *Fecal incontinence in primary care: prevalence, diagnosis, and health care utilization.* Am J Obstet Gynecol, 2010. **202**(5): p. 493.e1-6.

801. Finne-Soveri, H., et al., *Increased work-load associated with faecal incontinence among home care patients in 11 European countries.* Eur J Public Health, 2008. **18**(3): p. 323-8.

802. Grover, M., et al., *Survey of geriatricians on the effect of fecal incontinence on nursing home referral.* J Am Geriatr Soc, 2010. **58**(6): p. 1058-62.

803. Thekkinkattil, D.K., et al., *Awareness of investigations and treatment of faecal incontinence among the general practitioners: a postal questionnaire survey.* Colorectal Dis, 2008. **10**(3): p. 263-7.

804. Norton, C., et al., *Management of faecal incontinence in adults: summary of NICE guidance.* BMJ, 2007. **334**(7608): p. 1370-1371.

805. Chiang, L., et al., *Dually incontinent nursing home residents: clinical characteristics and treatment differences.* Journal of the American Geriatrics Society, 2000. **48**(6): p. 673-6.

806. Markland, A.D., et al., *Correlates of urinary, fecal, and dual incontinence in older African-American and white men and women.* J Am Geriatr Soc, 2008. **56**(2): p. 285-90.

807. Nakanishi, N., et al., *Urinary and fecal incontinence in a community-residing older population in Japan.* Journal of the American Geriatrics Society, 1997. **45**(2): p. 215-9.

808. Roberts, R.O., et al., *Prevalence of combined fecal and urinary incontinence: a community-based study.* Journal of the American Geriatrics Society, 1999. **47**(7): p. 837-41.

809. Teunissen, T.A., et al., *Prevalence of urinary, fecal and double incontinence in the elderly living at home.* Int Urogynecol J Pelvic Floor Dysfunct, 2004. **15**: p. 10 - 3; discussion 13.

810. Shamliyan, T., et al., *Prevention of urinary and fecal incontinence in adults.* Evid Rep Technol Assess (Full Rep), 2007(161): p. 1-379.

811. William, E.W., et al., *Fecal Incontinence in US Adults: Epidemiology and Risk Factors.* Gastroenterology, 2009. **137**(2): p. 512.

812. Sharma, A., et al., *Determining levels of fecal incontinence in the community: a New Zealand cross-sectional study.* Dis Colon Rectum, 2011. **54**(11): p. 1381-7.

813. Joh, H.K., M.K. Seong, and S.W. Oh, *Fecal incontinence in elderly Koreans.* J Am Geriatr Soc, 2010. **58**(1): p. 116-21.

814. Shamliyan, T.A., et al., *Prevalence and risk factors of fecal incontinence in community-dwelling men.* Rev Gastroenterol Disord, 2009. **9**(4): p. E97-110.

815. Pretlove, S., et al., *Prevalence of anal incontinence according to age and gender: a systematic review and meta-regression analysis.* International Urogynecology Journal, 2006. **17**(4): p. 407.

816. Brubaker, L., et al., *Mixed incontinence: comparing definitions in non-surgical patients.* Neurourol Urodyn, 2011. **30**(1): p. 47-51.

817. Markland, A.D., et al., *Incidence and risk factors for fecal incontinence in black and white older adults: a population-based study.* J Am Geriatr Soc, 2010. **58**(7): p. 1341-6.

818. Rey, E., et al., *Onset and Risk Factors for Fecal Incontinence in a US Community.* Am J Gastroenterol, 2009.

819. Westra, B.L., et al., *Predicting improvement in urinary and bowel incontinence for home health patients using electronic health record data.* J Wound Ostomy Continence Nurs, 2011. **38**(1): p. 77-87.

820. Foxx-Orenstein, A., et al., *Incidence, risk factors, and outcomes of fecal incontinence after acute brain injury: Findings from the traumatic brain injury model systems national database.* Archives of Physical Medicine and Rehabilitation, 2003. **84**(2): p. 231.

821. Rotholtz, N.A., et al., *Long-term assessment of fecal incontinence after lateral internal sphincterotomy.* Tech Coloproctol, 2005. **9**(2): p. 115-8.

822. Bliss, D.Z., et al., *Fecal incontinence in hospitalized patients who are acutely ill.* Nursing Research, 2000. **49**(2): p. 101-8.

823. Junkin, J. and J.L. Selekof, *Prevalence of incontinence and associated skin injury in the acute care inpatient.* J Wound Ostomy Continence Nurs, 2007. **34**(3): p. 260-9.

824. Li, Y., et al., *The "Nursing Home Compare" measure of urinary/fecal incontinence: cross-sectional variation, stability over time, and the impact of case mix.* Health Serv Res, 2010. **45**(1): p. 79-97.

825. Schnelle, J.F., et al., *Prevalence of constipation symptoms in fecally incontinent nursing home residents.* J Am Geriatr Soc, 2009. **57**(4): p. 647-52.

826. Johanson, J.F., F. Irizarry, and A. Doughty, *Risk factors for fecal incontinence in a nursing home population.* Journal of Clinical Gastroenterology, 1997. **24**(3): p. 156-60.

827. Nelson, R.L. and S.E. Furner, *Risk factors for the development of fecal and urinary incontinence in Wisconsin nursing home residents.* Maturitas, 2005. **52**(1): p. 26-31.

828. Peet, S.M., C.M. Castleden, and C.W. McGrother, *Prevalence of urinary and faecal incontinence in hospitals and residential and nursing homes for older people.[comment].* BMJ, 1995. **311**(7012): p. 1063-4.

829. Schnelle, J.F., et al., *A controlled trial of an intervention to improve urinary and fecal incontinence and constipation.* J Am Geriatr Soc, 2010. **58**(8): p. 1504-11.

830. Cotterill, N., et al., *A Patient-Centered Approach to Developing a Comprehensive Symptom and Quality of Life Assessment of Anal Incontinence.* Diseases of the Colon & Rectum, 2008. **51**(1): p. 82.

831. Nyrop, K.A., et al., *Likelihood of Nursing Home Referral for Fecally Incontinent Elderly Patients is Influenced by Physician Views on Nursing Home Care and Outpatient Management of Fecal Incontinence.* J Am Med Dir Assoc, 2011.

832. Nelson, R.L., *Epidemiology of fecal incontinence.* Gastroenterology, 2004. **126**(1 Suppl 1): p. S3-7.

833. Varma, M., et al., *Fecal Incontinence in Females Older Than Aged 40 Years: Who is at Risk?* Diseases of the Colon & Rectum, 2006.

834. Abramov, Y., et al., *Risk factors for female anal incontinence: new insight through the Evanston-Northwestern twin sisters study.* Obstetrics & Gynecology, 2005. **106**(4): p. 726-32.

835. Khullar, V., et al., *Prevalence of faecal incontinence among women with urinary incontinence.[comment].* British Journal of Obstetrics & Gynaecology, 1998. **105**(11): p. 1211-3.

836. Nelson, R., S. Furner, and V. Jesudason, *Fecal incontinence in Wisconsin nursing homes: prevalence and associations.* Diseases of the Colon & Rectum, 1998. **41**(10): p. 1226-9.

837. Bharucha, A.E., et al., *Bowel disturbances are the most important risk factors for late onset fecal incontinence: a population-based case-control study in women.* Gastroenterology, 2010. **139**(5): p. 1559-66.

838. Wald, A., *Systemic diseases causing disorders of defecation and continence.* Seminars in Gastrointestinal Disease, 1995. **6**(4): p. 194-202.

839. Harari, D., et al., *New-Onset Fecal Incontinence After Stroke: Prevalence, Natural History, Risk Factors, and Impact.* Stroke, 2003. **34**(1): p. 144-150.

840. Bytzer, P., et al., *Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults.[see comment].* Archives of Internal Medicine, 2001. **161**(16): p. 1989-96.

841. Wang, J., et al., *Pelvic floor disorders and quality of life in women with self-reported irritable bowel syndrome.* Aliment Pharmacol Ther, 2010. **31**(3): p. 424-31.

842. Thoua, N.M., et al., *Fecal Incontinence in Systemic Sclerosis Is Secondary to Neuropathy.* Am J Gastroenterol, 2011.

843. McHugh, S.M. and N.E. Diamant, *Effect of age, gender and partiy on anal canal pressures.* Digestive Diseases & Sciences, 1987. **32**(7): p. 726-736.

844. Matheson, D.M. and M.R.B. Keighley, *Manometric evaluation of rectal prolapse an dfaecal incontinence.* Gut, 1981. **22**: p. 126-129.

845. Ryhammer, A.M., S. Laurberg, and K.M. Bek, *Age and anorectal sensibility in normal women.* Scandanavian Journal of Gastroenterology, 1997. **32**: p. 278-284.

846. Wang, J.Y., et al., *Fecal incontinence: Does age matter? Characteristics of older vs. younger women presenting for treatment of fcal incontinence.* Dis Colon Rectum 2008. **51**: p. 426-431.

847. Loenig-Baucke, V. and S. Anuras, *Sigmoidal and rectal motility in healthy elderly. .* Journal American Geriatrics Society, 1984. **32**: p. 887-891.

848. Loenig-Baucke, V. and S. Anuras, *Effects of age and sex on anorectal manometry.* Am J Gastroenterol, 1985. **80**(1): p. 50-53.

849. Read, N.W., et al., *Anorectal function in elderly patients with fecal impaction.* Gastroenterology, 1985. **89**: p. 959-966.

850. Barrett, J.A., et al., *Anal function in geriatric patients with faecal incontinence. .* Gut 1989. **30**(1244-1251).

851. Percy, J.P., M.E. Neill, and T.K. Kandiah, *A neurogenic factor in faecal incontinence in the elderly. .* Age and Ageing, 1982. **11**: p. 175-179.

852. Lewicky-Gaupp, C., et al., *Anal sphincter structure and function relationships in aging and fecal incontinence.* Am J Obstet Gynecol, 2009. **200**(559): p. e1-e5.

853. Bannister, J.J., L. Abouzekry, and N.W. Read, *Effect of aging on anorectal function.* Gut, 1987. **28**: p. 353-357.

854. Akervall, S., et al., *The effects of age, gender, and parity on rectoanal function in adults.* Scandanavian Journal of Gastroenterology, 1990. **25**: p. 1247-1256.

855. Gundling, F., et al., *Influence of gender and age on anorectal function:Normal values from anorectal manometry in a large caucasian population.* Digestion, 2010. **81**: p. 207-213.

856. Haadem, K., J.A. Dahlstrom, and L. Ling, *Anal sphincter competence in healthy women: Clinical implications of age and other factors.* Obstetrics & Gynecology, 1991. **78**: p. 823-827.

857. Ryhammer, A.M., S. Laurberg, and F.H. Sorenson, *Effects of age on anal function in normal women.* Int J Colorect Dis, 1997. **12**: p. 225-229.

858. Fox, J.C., et al., *Effect of aging on anorectal and pelvic floor functions in females.* Dis Colon Rectum, 2006. **49**: p. 1726-1735.

859. Loenig-Baucke, V. and S. Anuras, *Anorectal manometry in healthy elderly subjects.* Journal American Geriatrics Society, 1984. **32**(9): p. 636-639.

860. Laurberg, S. and M. Swash, *Effects of aging on the anorectal sphincters and their innervation.* Dis Colon Rectum, 1989. **32**: p. 737-742.

861. Burnett, S.J.D. and C.I. Bartram, *Endosonographic variations in the normal internal anal sphincter.* Int J Colorect Dis, 1991. **6**: p. 2-4.

862. Huebner, M., et al., *Age effects on internal anal sphincter thickness and diameter in nulliparous females.* Dis Colon Rectum, 2007. **50**: p. 1405-1411.

863. Papachrysostomou, M., et al., *Significance of the thickness of the anal sphincters with age and its relevance in fecal incontinence.* Scandanavian Journal of Gastroenterology, 1994. **29**: p. 710-714.

864. Frudinger, A., et al., *Female anal sphincter: Age-related differences in asymptomatic volunteers with high-frequency endoanal US.* Radiology, 2002. **224**: p. 417-423.

865. Rociu, E., et al., *Normal anal sphincter anatomy and age- and sex-related variations at high-spatial-resolution endoanal MR imaging.* Radiology, 2000. **217**: p. 395-401.

866. Gomes, O.A., R.R. de Souza, and E.A. Liberti, *A preliminary investigation in the effects of aging on the nerve cell number in the myenteric ganglia of the human colon.* Gerontology, 1997. **43**(4): p. 210-217.

867. Swash, M., et al., *Ultrastructural changes in internal anal sphincter n neurogenic faecal incontinence.* Gut, 1988. **29**: p. 1692-1698.

868. Klosterhalfen, B., et al., *Sclerosis of the internal anal sphincter- A process of Aging.* Dis Colon Rectum, 1990. **33**: p. 606-609.

869. Jameson, J.S., et al., *Effect of age, sex and parity on anorectal function.* British J Surgery, 1994. **81**: p. 1689-1692.

870. Lagier, E., et al., *Influence of age on rectal tone and sensitivity to distension in healthy subjects.* Neurogastroenterology Motility, 1999. **11**: p. 101-107.

871. Rasmussen, O.O., et al., *Pudendal nerve function in idiopathic fecal incontinence. .* Dis Colon Rectum, 2000. **43**: p. 633-636.

872. Vaccaro, C.A., et al., *Pudendal neuropathy in evacuatory disorders.* Dis Colon Rectum, 1995. **38**: p. 166-171.

873. Barrett, J.A., et al., *Rectal motility studies in geriatric patients with faecal incontinence.* Age and Ageing, 1990. **19**: p. 311-317.

874. Lewicky-Gaupp, C., et al., *Fecal incontinence in older women are levator ani defects a factor?* Am J Obstet Gynecol, 2010. **202**(491): p. e1-e6.

875. Gage, H., et al., *Correlates of constipation in people with Parkinson's.* Parkinsonism Relat Disord, 2011. **17**(2): p. 106-11.

876. Riss, S., et al., *Haemorrhoids, constipation and faecal incontinence: is there any relationship?* Colorectal Dis, 2011. **13**(8): p. e227-33.

877. Burgell, R.E., et al., *Fecal incontinence in men: coexistent constipation and impact of rectal hyposensitivity.* Dis Colon Rectum, 2012. **55**(1): p. 18-25.

878. Akpan, A., M.A. Gosney, and J. Barret, *Factors contributing to fecal incontinence in older people and outcome of routine management in home, hospital and nursing home settings.* Clin Interv Aging, 2007. **2**(1): p. 139-45.

879. Chassagne, P., et al., *Does treatment of constipation improve faecal incontinence in institutionalized elderly patients?* Age & Ageing, 2000. **29**(2): p. 159-64.

880. Bharucha, A.E., et al., *Relation of Bowel Habits to Fecal Incontinence in Women.* Am J Gastroenterol, 2008. **103**(6): p. 1470.

881. Markland, A.D., et al., *Factors impacting quality of life in women with fecal incontinence.* Dis Colon Rectum, 2010. **53**(8): p. 1148-54.

882. Wang, J.Y., et al., *Fecal incontinence: does age matter? Characteristics of older vs. younger women presenting for treatment of fecal incontinence.* Dis Colon Rectum, 2008. **51**(4): p. 426-31.

883. Papathanasopoulos, A.A., et al., *Increased fatigability of external anal sphincter in inflammatory bowel disease: significance in fecal urgency and incontinence.* J Crohns Colitis, 2010. **4**(5): p. 553-60.

884. J, W., et al., *Pelvic floor disorders and quality of life in women with self-reported irritable bowel syndrome.* Alimentary Pharmacology & Therapeutics. **31**(3): p. 424-431.

885. Ritchie, R.D., J.M. Sackier, and J.P. Hodde, *Incontinence rates after cutting seton treatment for anal fistula.* Colorectal Dis, 2009. **11**(6): p. 564-71.

886. Abbas, M.A., C.H. Jackson, and P.I. Haigh, *Predictors of outcome for anal fistula surgery.* Arch Surg, 2011. **146**(9): p. 1011-6.

887. Levack, M.M., et al., *Sigmoidectomy syndrome? Patients' perspectives on the functional outcomes following surgery for diverticulitis.* Dis Colon Rectum, 2012. **55**(1): p. 10-7.

888. Scheer, A.S., et al., *The long-term gastrointestinal functional outcomes following curative anterior resection in adults with rectal cancer: a systematic review and meta-analysis.* Dis Colon Rectum, 2011. **54**(12): p. 1589-97.

889. Nikoletti, S., et al., *Bowel problems, self-care practices, and information needs of colorectal cancer survivors at 6 to 24 months after sphincter-saving surgery.* Cancer Nurs, 2008. **31**(5): p. 389-98.

890. Maeda, Y., et al., *Faecal incontinence following radiotherapy for prostate cancer: a systematic review.* Radiother Oncol, 2011. **98**(2): p. 145-53.

891. Edwards, N.I. and D. Jones, *The prevalence of faecal incontinence in older people living at home.[comment].* Age & Ageing, 2001. **30**(6): p. 503-7.

892. Aslan, E., et al., *The prevalence of and the related factors for urinary and fecal incontinence among older residing in nursing homes.* J Clin Nurs, 2009. **18**(23): p. 3290-8.

893. Brittain, K., et al., *Isolated Urinary, Fecal, and Double Incontinence: Prevalence and Degree of Soiling in Stroke Survivors.* Journal of the American Geriatrics Society, 2006. **54**(12): p. 1915-1919.

894. Nakayama, H., et al., *Prevalence and risk factors of incontinence after stroke. The Copenhagen Stroke Study.* Stroke, 1997. **28**(1): p. 58-62.

895. Leary, S.M., et al., *Incontinence after brain injury: prevalence, outcome and multidisciplinary management on a neurological rehabilitation unit.* Clin Rehabil, 2006. **20**(12): p. 1094-9.

896. Vallès, M. and F. Mearin, *Pathophysiology of bowel dysfunction in patients with motor incomplete spinal cord injury: comparison with patients with motor complete spinal cord injury.* Dis Colon Rectum, 2009. **52**(9): p. 1589-97.

897. Deutekom, M., et al., *Clinical presentation of fecal incontinence and anorectal function: what is the relationship?* The American journal of gastroenterology, 2007. **102**(2): p. 351-61.

898. Bharucha, A.E., et al., *Relationship between symptoms and disordered continence mechanisms in women with idiopathic faecal incontinence.* Gut, 2005. **54**(4): p. 546-55.

899. Osterberg, A., et al., *Evaluation of a questionnaire in the assessment of patients with faecal incontinence and constipation.* Scandinavian journal of gastroenterology, 1996. **31**(6): p. 575-80.

900. O'Keefe, E.A., et al., *A bowel symptom questionnaire for the elderly.* Journal of gerontology, 1992. **47**(4): p. M116-21.

901. Frank, L., J. Flynn, and M. Rothman, *Use of a self-report constipation questionnaire with older adults in long-term care.* The Gerontologist, 2001. **41**(6): p. 778-86.

902. Engel, A.F., et al., *Relationship of symptoms in faecal incontinence to specific sphincter abnormalities.* International journal of colorectal disease, 1995. **10**(3): p. 152-5.

903. Talley, N.J., et al., *Constipation in an elderly community: a study of prevalence and potential risk factors.* The American journal of gastroenterology, 1996. **91**(1): p. 19-25.

904. Harari, D., et al., *How do older persons define constipation? Implications for therapeutic management.* Journal of general internal medicine, 1997. **12**(1): p. 63-6.

905. Potter, J. and A. Wagg, *Management of bowel problems in older people: an update.* Clin Med, 2005. **5**(3): p. 289-95.

906. Ciriza-de-Los-Rios, C., et al., *Differences in the pressures of canal anal and rectal sensitivity in patients with fecal incontinence, chronic constipation and healthy subjects.* Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva, 2010. **102**(12): p. 683-90.

907. Gundling, F., et al., *Influence of gender and age on anorectal function: normal values from anorectal manometry in a large caucasian population.* Digestion, 2010. **81**(4): p. 207-13.

908. McCrea, G.L., et al., *Age differences in patients evaluated for constipation: constipation characteristics, symptoms, and bowel and dietary habits.* Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN, 2010. **37**(6): p. 667-76.

909. Hallan, R.I., et al., *Comparison of digital and manometric assessment of anal sphincter function.* The British journal of surgery, 1989. **76**(9): p. 973-5.

910. Majumdar, S.R., R.H. Fletcher, and A.T. Evans, *How does colorectal cancer present? Symptoms, duration, and clues to location.* The American journal of gastroenterology, 1999. **94**(10): p. 3039-45.

911. Hippisley-Cox, J. and C. Coupland, *Identifying patients with suspected colorectal cancer in primary care: derivation and validation of an algorithm.* The British journal of general practice : the journal of the Royal College of General Practitioners, 2012. **62**(594): p. e29-37.

912. Ness, R.M., et al., *Predictors of inadequate bowel preparation for colonoscopy.* The American journal of gastroenterology, 2001. **96**(6): p. 1797-802.

913. Laghi, A., et al., *Current status on performance of CT colonography and clinical indications.* European journal of radiology, 2012.

914. Sharp, C.A. and M.L. McLaws, *Estimating the risk of pressure ulcer development: is it truly evidence based?* International wound journal, 2006. **3**(4): p. 344-53.

915. Baumgarten, M., et al., *Pressure ulcers and the transition to long-term care.* Adv Skin Wound Care, 2003. **16**(6): p. 299-304.

916. Jackson, S.L., et al., *Fecal incontinence in women with urinary incontinence and pelvic organ prolapse.* Obstet Gynecol, 1997. **89**(3): p. 423-7.

917. Meschia, M., et al., *Prevalence of anal incontinence in women with symptoms of urinary incontinence and genital prolapse.* Obstet Gynecol, 2002. **100**(4): p. 719-23.

918. Norton, C., J.D. Cody, and G. Hosker, *Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults.* Cochrane Database Syst Rev, 2006. **3**: p. CD002111.

919. Heymen, S., et al., *Randomized controlled trial shows biofeedback to be superior to pelvic floor exercises for fecal incontinence.* Dis Colon Rectum, 2009. **52**(10): p. 1730-7.

920. Miner, P.B., T.C. Donnelly, and N.W. Read, *Investigation of mode of action of biofeedback in treatment of fecal incontinence.* Dig Dis Sci, 1990. **35**: p. 1291 - 1298.

921. Heymen, S., et al., *Biofeedback treatment of fecal incontinence: a critical review.* Diseases of the Colon & Rectum, 2001. **44**(5): p. 728-36.

922. Bols, E., et al., *Rectal balloon training as add-on therapy to pelvic floor muscle training in adults with fecal incontinence: A randomized controlled trial.* Neurourol Urodyn, 2012. **31**(1): p. 132-8.

923. Cheetham, M., et al., *Drug treatment for faecal incontinence in adults.* Cochrane Database of Systematic Reviews, 2003(3): p. CD002116.

924. Lauti, M., D. Scott, and M.W. Thompson-Fawcett, *Fibre supplementation in addition to loperamide for faecal incontinence in adults: a randomized trial.* Colorectal Dis, 2008. **10**(6): p. 553-62.

925. Harari, D., et al., *Treatment of constipation and fecal incontinence in stroke patients: randomized controlled trial.* Stroke, 2004. **35**(11): p. 2549-55.

926. Mowatt, G., C. Glazener, and M. Jarrett, *Sacral nerve stimulation for faecal incontinence and constipation in adults.* Cochrane Database Syst Rev, 2007(3): p. CD004464.

927. Wexner, S.D., et al., *Sacral nerve stimulation for fecal incontinence: results of a 120-patient prospective multicenter study.* Ann Surg, 2010. **251**(3): p. 441-9.

928. Mellgren, A., et al., *Long-term efficacy and safety of sacral nerve stimulation for fecal incontinence.* Dis Colon Rectum, 2011. **54**(9): p. 1065-75.

929. Matzel, K.E., et al., *Sacral spinal nerve stimulation for faecal incontinence: multicentre study.* Lancet, 2004. **363**(9417): p. 1270-6.

930. Wallace, P.A., F.L. Lane, and K.L. Noblett, *Sacral nerve neuromodulation in patients with cardiac pacemakers.* Am J Obstet Gynecol, 2007. **197**(1): p. 94.e1-3.

931. Wallace, P.A., F.L. Lane, and K.L. Noblett, *Sacral nerve neuromodulation in patients with underlying neurologic disease.* Am J Obstet Gynecol, 2007. **197**(1): p. 96.e1-5.

932. Maeda, Y., et al., *Postoperative issues of sacral nerve stimulation for fecal incontinence and constipation: a systematic literature review and treatment guideline.* Dis Colon Rectum, 2011. **54**(11): p. 1443-60.

933. Shafik, A., et al., *Percutaneous peripheral neuromodulation in the treatment of fecal incontinence.* Eur Surg Res, 2003. **35**(2): p. 103-7.

934. Queralto, M., et al., *Preliminary results of peripheral transcutaneous neuromodulation in the treatment of idiopathic fecal incontinence.* Int J Colorectal Dis, 2006. **21**(7): p. 670-2.

935. Mentes, B.B., et al., *Posterior tibial nerve stimulation for faecal incontinence after partial spinal injury: preliminary report.* Tech Coloproctol, 2007. **11**(2): p. 115-9.

936. Vitton, V., et al., *Transcutaneous electrical posterior tibial nerve stimulation for faecal incontinence: effects on symptoms and quality of life.* Int J Colorectal Dis, 2010. **25**(8): p. 1017-20.

937. de la Portilla, F., et al., *Evaluation of the use of posterior tibial nerve stimulation for the treatment of fecal incontinence: preliminary results of a prospective study.* Dis Colon Rectum, 2009. **52**(8): p. 1427-33.

938. Govaert, B., et al., *A prospective multicentre study to investigate percutaneous tibial nerve stimulation for the treatment of faecal incontinence.* Colorectal Dis, 2010. **12**(12): p. 1236-41.

939. Boyle, D.J., et al., *Percutaneous tibial nerve stimulation for the treatment of urge fecal incontinence.* Dis Colon Rectum, 2010. **53**(4): p. 432-7.

940. Findlay, J.M., et al., *Peripheral neuromodulation via posterior tibial nerve stimulation - a potential treatment for faecal incontinence?* Ann R Coll Surg Engl, 2010. **92**(5): p. 385-90.

941. Boyle, D.J., et al., *Efficacy of sacral nerve stimulation for the treatment of fecal incontinence.* Dis Colon Rectum, 2011. **54**(10): p. 1271-8.

942. Findlay, J.M. and C. Maxwell-Armstrong, *Posterior tibial nerve stimulation and faecal incontinence: a review.* Int J Colorectal Dis, 2011. **26**(3): p. 265-73.

943. Du Moulin, M.F.M.T., et al., *Urinary incontinence in older adults receiving homecare diagnosis and strategies.* Scandinavian Journal of Caring Sciences, 2009. **23**(2): p. 222-230.

944. Watson, N.M., et al., *Use of the Agency for Health Care Policy and Research Urinary Incontinence Guideline in nursing homes.* Journal of the American Geriatrics Society, 2003. **51**(12): p. 1779-1786.

945. Sampselle, C.M., *Behavioral interventions in young and middle-age women.* American Journal of Nursing, 2003. **March**(Supplement): p. 9-19.

946. Bryant, C.M., C.J. Dowell, and G. Fairbrother, *Caffeine reduction education to improve urinary symptoms.* Br J Nurs, 2002. **11**(8): p. 560-5.

947. Ostaszkiewicz, J., L. Johnston, and B. Roe, *Habit retraining for the management of urinary incontinence in adults.* Cochrane Database Syst Rev, 2004(2): p. CD002801.

948. Nikoletti, S., J. Young, and M. King, *Evaluation of an electronic monitoring device for urinary incontinence in elderly patients in an acute care setting.* J Wound Ostomy Continence Nurs, 2004. **31**(3): p. 138-49.

949. Sand, P., et al., *Oxybutynin transdermal system improves the quality of life in adults with overactive bladder: a multicentre, community-based, randomized study.* BJU Int, 2007. **99**(4): p. 836-44.

950. Lackner, T.E., et al., *Efficacy of oral extended-release oxybutynin in cognitively impaired older nursing home residents with urge urinary incontinence: a randomized placebo-controlled trial.* Journal of the American Medical Directors Association, 2011. **12**(9): p. 639-47.

951. Chapple, C., et al., *Darifenacin treatment of patients >or= 65 years with overactive bladder: results of a randomized, controlled, 12-week trial.* Current medical research and opinion, 2007. **23**(10): p. 2347-58.

952. van Kerrebroeck, P., et al., *Desmopressin in the treatment of nocturia: a double-blind, placebo-controlled study.* Eur Urol, 2007. **52**(1): p. 221-9.

953. Johnson, T.M., et al., *The relationship between the action of arginine vasopressin and responsiveness to oral desmopressin in older men: a pilot study.* J Am Geriatr Soc, 2007. **55**(4): p. 562-9.

Committee 12

Adult Conservative Management

Co-Chair

K. Moore (Canada), C. Dumoulin (Canada)

Members

C. Bradley (USA),

K. Burgio (USA),

T. Chambers (Canada)

S. Hagen (UK),

K. Hunter (Canada),

M. Imamura (UK),

R. Thakar (UK),

K. Williams (UK)

Consultants

L. Vale (UK)

The present chapter would not have been possible without the work of the previous editors, Jean Hay Smith [2008] and Don Wilson [2000, 2004]. They produced the remarkable framework for the present review. Indispensable assistance was also provided by Victoria Mei Lee, Fiona Stewart, Sheila Wallace, and the Cochrane Incontinence Group. Finally, this chapter would not have been possible without the untiring dedication of Mr. Wayne Day.

CONTENTS

I. INTRODUCTION

A.UI IN WOMEN

I. LIFESTYLE INTERVENTIONS

II. PELVIC FLOOR MUSCLE TRAINING (PFMT)

III. WEIGHTED VAGINAL CONES (VCS)

IV. ELECTRICAL STIMULATION (ESTIM)

V. MAGNETIC STIMULATION (MSTIM)

VI. SCHEDULED VOIDING REGIMENS

VII. COMPLEMENTARY AND ALTERNATIVE MEDICINES

VIII. SUMMARY AND RECOMMENDATIONS

IX. FUTURE RESEARCH DIRECTIONS

B. PELVIC ORGAN PROLAPSE (POP)

I. LIFESTYLE INTERVENTIONS

II. PHYSICAL THERAPIES

III. PESSARIES

IV. SUMMARY AND RECOMMENDATIONS

C. URINARY INCONTINENCE IN MEN

I. LIFESTYLE INTERVENTIONS

II. PELVIC FLOOR MUSCLE TRAINING (PFMT)

III. ELECTRICAL STIMULATION (ESTIM)

IV. MAGNETIC STIMULATION (MSTIM)

V. SCHEDULED VOIDING REGIMENS

VI. COMPLEMENTARY AND ALTERNATIVE MEDICINES

VII. SUMMARY

ANNEX

REFERENCES

Adult Conservative Management

K. Moore, C. Dumoulin
C. Bradley, K. Burgio, T. Chambers, S. Hagen, K. Hunter, M. Imamura, R. Thakar, K. Williams
L. Vale

I. INTRODUCTION

Conservative treatment is any therapy not involving surgical treatment of incontinence. In this chapter update, we cover studies that provide some comparison data between therapy and lifestyle interventions (also called lifestyle interventions), physical therapies, scheduled voiding regimens, complementary and alternative medicines, anti-incontinence devices, supportive rings/pessaries for pelvic organ prolapse (POP) and medications with a direct comparison with conservative management.

Conservative therapies are considered relatively low cost, non-invasive approaches, with minimal adverse effects that are typically guided by a healthcare professional and depend on user participation. It is generally accepted that conservative measures are part of the initial counselling at the primary care level of individuals suffering from either UI or POP. Conservative therapy is also indicated for those for whom other treatments are inappropriate, for example, those unwilling to undergo or unfit for surgery and women who plan future pregnancies (as these may adversely affect surgery). Other indications include individuals awaiting surgery or who wish to delay surgery and those whose symptoms are not serious enough for surgical intervention.

The research base on which to judge the effectiveness of conservative management is growing although some aspects such as lifestyle interventions and alternative and complementary medicines in particular, require considerably more well designed trials. In this chapter we add to what was known in the 2009 4th Edition ICI [1] and integrate the evidence since the last search on treatment of urinary incontinence and pelvic organ prolapse (POP). The updated literature search was conducted from 1 January 2008 to August 2011 of randomised controlled trials (RCTs). (Appendix 2 lists the details of the literature search).

Each section concludes with the level of evidence and factors affecting outcome. Separate chapters in this 5th Edition address incontinence in the elderly, children, pharmacological treatment, products for continence, those with neurological conditions and those suffering from faecal incontinence.

Where summary statistics are presented, the raw data from which these are derived can be found in the tables at the end of the chapter, in trial reports and systematic reviews cited in the chapter. The Chapter is intended as a stand alone document and adds to the comprehensive reports from previous ICI editions.

A.UI IN WOMEN

I. LIFESTYLE INTERVENTIONS

A number of lifestyle factors may play a role in either the development or resolution of UI. Few RCTs have been carried out to assess the effect of a specific lifestyle change on UI. This section will examine the evidence for the association and use of lifestyle interventions in the management of female UI. A summary of the search strategy and inclusion/exclusion criteria is given in Appendix 2.

1. PREVENTION

No RCTs assessing the effect of lifestyle interventions on UI prevention were identified.

2. TREATMENT

Where RCTs are available, these are reviewed. Where there are no RCTs for a particular lifestyle intervention, other types of evidence are considered giving priority to good quality cohort studies.

a) Weight loss

Three RCTs were identified on weight loss. Two specifically recruited incontinent women [2-4]. The third focused on the effect of intensive lifestyle intervention in overweight women with diabetes [5]; this intervention mainly comprised weight loss. Four prospective cohort studies [6-9] evaluated the effect of weight loss. Other study designs were

cross-sectional [10-16], retrospective cohort [17], or case-control studies [18]. The non-RCT evidence will not be reviewed here in light of the available RCT evidence.

1. Quality Of Trials

Sample sizes for the three RCTs were 48 [2], 338 [3,4], and 1,957 [5]. Participant blinding was not possible in any of the three RCTs. Of 48 randomised in one trial, 40 remained in the study at the time of assessment [2]. The Subak [2009] study randomised 338 women, six month incontinence outcome data was available for 304 women (290 had diary data – the primary outcome measure). Participants were followed up at 12 and 18 months, at which time 96% provided urinary incontinence outcome data. In the large RCT with diabetes as the primary focus, 2191 women were enrolled and 234 were excluded because data about UI were not available; the number that dropped out before the endpoint is not detailed for this subpopulation of women.

All three trials used subjective and objective measures including urodynamics, urinary diary and 24 hour pad test. Follow-up periods were three months after completion of a very low calorie liquid diet and exercise [2], six months after completing an intensive group weight intervention programme that included lifestyle and behaviour changes [3], and a mean of 2.9 years after beginning the intervention [5]. In addition, the Subak study population [3,4] was followed up at 12 and 18 months, and is reported in a separate paper [19].

Results

In the 2005 RCT [2] involving 48 participants, median baseline weight (95 kg) and number of incontinent episodes (21 per week) were similar between the groups. Compared to controls (wait list) that did not participate in a weight loss programme, women in the weight loss (liquid diet) group lost 15kg (SD 7) (compared to 0kg (SD 4)) and experienced a 60% reduction in weekly incontinent episodes (compared to 15%).

The Programme to Reduce incontinence by Diet and Exercise (PRIDE) [4,19] randomised 338 overweight incontinent women in a 2:1 ratio to an intensive 6-month group weight intervention programme or usual care, consisting of four information sessions. Women in the intervention group lost a mean of 8% of their body weight from baseline compared with 1.6% in the usual care group after 6 months. Forty one percent of women in the intervention group decreased the weekly number of incontinence episodes by at least 70% compared to a 22% reduction in the usual care group. At 12 months weight loss in the intervention group was 7.5% of their body weight from baseline compared to 1.7% with 46% reporting 70% less incontinence in the weight loss group compared with 31% in usual care. By 18 months weight loss was 5.5% in the intervention group compared to 1.6% with 46% reporting 70% less incontinence episodes compared to 40% in the usual care group.

The RCT from the Diabetes Prevention Programme [5] reporting on 1957 participants found that overweight diabetic women assigned to intensive lifestyle therapy (consisting of low-fat diet, moderately intense exercise for at least 150 minutes per week and a behavioural and educational curriculum) were less likely to be incontinent compared to those assigned to placebo drug with standard lifestyle advice or metformin alone (38.3% versus 45.7% and 48.1%, respectively; p=0.001).

Wing et al (2010a) [19] combined data from the Subak 2009 RCT and Wing (2010b) [20] follow-up of the same sample to determine the magnitude of weight loss associated with significant improvement in urinary incontinence. They combined the intervention and control groups into weight loss categories irrespective of randomisation group. Women who lost 5-10% of their body weight were 2-4 times more likely to achieve a 70% reduction in incontinence episodes compared with those who gained weight at 6, 12 or 18 months. Weight losses larger than 10% did not result in greater improvements in incontinence outcomes. It is important to note that individuals were not randomly assigned to weight loss categories therefore groups may have differed in other ways.

2. Summary

Obesity is an important independent risk factor for the prevalence of UI. Massive weight loss (15 to 20 BMI points) significantly decreases UI in morbidly obese women. (Level of Evidence: 2). Moderate weight loss maybe effective in decreasing UI especially if combined with exercise (seeB.1.2b(i)). **(Level of Evidence: 1).**

3. Recommendations

For morbidly and moderately obese women weight loss should be considered a first line treatment to reduce UI prevalence **(Grade of Recommendation: A).** Given the high prevalence of both UI and obesity in women, the dual issues of weight loss and prevention of weight gain (and exercise) should receive high research priority.

b) Physical activity

No RCTs exist in which moderate physical activity and its effect on UI is compared to no activity.

1.Quality of data

Two prospective studies assessed the risk of incident UI according to physical activity level, reported as metabolic equivalent task hours per week, in 2,355 women aged 54 to79 years [21] and 30,135 women 37 to 54 years at risk of incident UI [22]. Both

suggested that low levels of physical activity are predictive for the onset of UI in middle aged women or older. In the prospective study of women aged 37-54 repeated physical activity reports over 12 years were averaged to estimate long term activity levels. Over the subsequent 2 years 4081 incident cases were identified with monthly incontinence.

2. Results

In older women enrolled in the Nurses' Health Study, total physical activity (i.e. top versus bottom quintile of metabolic equivalent task hours per week) was significantly associated with a reduced risk of new UI (OR 0.81) in analyses adjusted for confounders. Walking constituted about half of the total physical activity among the participants and was related to a 26% lower risk of developing UI. Total physical activity was not related to the incidence of UUI [21]. These findings were mirrored in younger women enrolled in the same study [22]: the risk of at least monthly UI decreased with increasing quintiles of moderate physical activity.

3. Summary

There is good prospective cohort information suggesting that moderate exercise decreases the incidence of UI in middle-aged and older women; this effect may be mediated by weight control **(Level of Evidence: 3).**

4. Recommendations

Epidemiological evidence is building for an association between moderate physical activity and a reduction in urinary incontinence. There is a need for randomised controlled trials to confirm causality.

c) Physical Forces (exercise and work)

No RCTs exist in which UI prevalence is compared between subjects assigned to heavy work or high impact activity versus sedentary activities

1. Quality of data

Two trials have evaluated the difference in UI prevalence between 305 and 144 women, respectively, engaged in high versus low impact activities [23,24]. In another trial, Bø (2001a) compared 572 athletes ages 15-39 years with 574 controls [25]. Caylet [2006] compared UI prevalence between 157 elite female athletes and 426 women from the general population between ages 18 and 35 [26]. Kruger [2007] conducted a case-control study exploring mechanisms by which athletes might be more likely to experience SUI and compared pelvic organ descent and pubovisceral muscle volume between 24 elite nulliparous athletes and 22 age and BMI matched controls [27]. Eliasson [2005] compared UI at 36 weeks gestation and one year postpartum between 665 primiparous women participating in high-impact, low-impact or no activity [28].

Several cross-sectional studies compared the prevalence of UI with the self-reported level of physical activity. The Norwegian EPINCONT study compared both any and severe UI in 27,936 women according to three levels of high impact physical activity [13]. Another compared UI prevalence and severity in 3,364 women according to physical activity level as assessed by the International Physical Activity Questionnaire [29].

2. Results

Minimal SUI is common in young exercising women [23]. College athletes participating in high impact activities are more likely to report the symptom of SUI during exercise than those participating in low impact exercise [24]. In one trial no difference in UI prevalence was found between elite athletes and controls [25]. Another found that 28% of elite athletes reported UI compared to 10% of controls [26]. There was no difference in UI prevalence between physically active and sedentary controls. In the prospective study of pregnant and postpartum women, high-impact physical activity before pregnancy was associated with more urinary leakage one year postpartum compared to low-impact activity [28].

There is little available information on whether strenuous exercise or activity causes the condition of UI later in life. In a study of 104 women who were Olympians approximately 25 years prior to data collection, those who competed in gymnastics or track and field were not more likely to currently report daily or weekly UI than Olympians who competed in swimming [30].

The EPICONT study reporting on 27,936 women found no difference in either 'any' UI or severe UI in women that reported high impact physical activity one to two hours per week or three or more hours per week compared to those that reported exercised less than one hour per week (after adjusting for age, BMI, parity, coughing and wheezing) [13]. In contrast, Nygaard [2005] reported that UI with physical activity was more common among highly active than less active women (15.9% versus 11.8%; p=0.01) [29]. Additionally, after adjusting for age, parity, comorbidities and other factors, women with very severe UI were more likely to be less active than continent women. Danish nursing assistants, who are exposed to frequent heavy lifting, were more likely to undergo surgery for genital prolapse and/or UI than women in the general population; parity was not controlled for [31].

3. Summary

Strenuous exercise may unmask the symptom of SUI during provocation. There is currently no evidence that strenuous exercise causes the condition of UI. There are scant uncontrolled data that suggests that women engaged in occupations with heavy lifting may be predisposed to genital prolapse and/or UI **(Level of Evidence: 3).**

4. Recommendations

There is a paucity of data about the association of strenuous exercise and lifting and UI, this association should be investigated further.

d) Smoking

There are no RCTs investigating the effect of smoking on UI. There are no trials of the effect of smoking cessation.

1. Quality of data

One case-control study compared incontinent smokers with non-smokers [32], another compared smoking behaviour between continent and incontinent women [33]. Cross sectional studies have evaluated multiple risk factors for UI, including smoking [10,13,16,34-37]. One case-control study evaluated smoking as a risk factor for failure of SUI surgery [38]. One trial of women planning surgery for SUI assessed the association between smoking and severity of UI, defined by mean number of incontinence episodes per day on a bladder diary [39]. An in vitro study assessed the effects of nicotine on bladder muscle contraction [40]. Sample sizes were 189 [32], 1761 [34], 160 [33], 199 [38], 7949 [10], 7338 [35], 3302 [36], 5,488 [37], 27,936 [13], and 83,355 [16].

2. Results

Smokers were more likely to report UI than non-smokers in some studies [13,16,33,35,36], but not others [10,34,37]. Amongst women with SUI, current smoking was positively associated with UI severity after adjusting for confounders [39]. After adjusting for age, parity, type of delivery, and pre-pregnancy BMI, smokers had a 1.3 fold higher RR (95% CI 1.0 to1.8) of reporting UI at 16 weeks gestation than non-smokers [35]. The adjusted OR for moderate or severe UI among women reporting UI was 1.38 (95% CI 1.04 to 1.82) in current smokers, after adjusting for perimenopausal status, BMI, diabetes and ethnicity [36]. In the large population based study by Hannestad et al [13], smoking increased the odds of severe UI (OR 1.4, 95% CI 1.2 to1.6) but not of mild UI. In the case-control study, after adjusting for confounders, smoking was a protective factor against recurrent UI after anti-incontinence surgery [38]. Incontinent smokers were found to have stronger urethral sphincters and lower overall risk profiles than incontinent non-smokers [32]; therefore, the authors proposed that more violent coughing promotes anatomic defects, which allow UI.

Two studies have reproted that nicotine produces phasic contraction of isolated bladder muscle probes in vitro [40,41]. However, Milsom (1993) reported an apparent paradoxical local estrogenic effect of nicotine on the vagina, resulting in a decrease in vaginal pH and an increase in lactobacilli [42].

3. Summary

Data suggest that smoking increases the risk of more severe UI **(Level of Evidence: 3).** Smokers may have a different mechanism causing their UI than non-smokers.

4. Recommendations

Further prospective studies are needed to determine whether smoking cessation prevents the onset, or promotes the resolution, of UI.

e) Dietary factors

1. Diet

No RCT was identified that addressed dietary changes for urinary incontinence alone.

However, a randomised cross over trial examined the effect of a soy-rich diet on urogenital changes including urge incontinence [43]. The study recruited 36 women to undergo two 12 week diet periods, a soy rich diet and a control diet (soy free).

The recent BACHs study group (Boston Area Community Health Survey) [44] undertook an epidemiological, cross sectional, population based study of 2060 women aged 30-79 and used a validated food frequency questionnaire to collect data on dietary intake as well as collecting data on lower urinary tract symptoms (LUTS). In a prospective questionnaire study, Dallosso (2004a) studied the impact of dietary risk factors on the one-year incidence of SUI in women [45] and OAB symptoms [46,47]. Participants completed a 130-item validated food frequency questionnaire.

2. Caffeine

No new studies on caffeine and incontinence were found. One RCT [48] assessed the effects of a caffeine reduction intervention upon frequency, urgency and UUI for those who consumed more than 100mg caffeine daily. The experimental group received bladder training and a caffeine-fading method to decrease caffeine intake to less than 100mg per day, while the control group also received bladder training but no caffeine reduction information. Another RCT [49] used a crossover design to evaluate the effect of caffeine restriction and of increasing and decreasing fluid intake on urinary symptoms over a four-week period in women with urodynamic SUI or DO.

3. Fluid Intake

In one RCT, women with UI were randomly assigned to one of three groups: increase fluid intake by 500 cc, maintain fluid intake at baseline level, or decrease by 300 cc. Participants kept fluid intake and output diaries for five weeks [50]. Another study [51] recruited 24 people to a crossover trial in which they were asked to increase or decrease their fluid intake. Individuals were randomised into two groups,

the groups amended their fluid intake over 4 day blocks, group 1: drinking 25% more (group 2: 25% less) than baseline for 4 days followed by 2 days of normal drinking, 4 days drinking 50% more (group 2: 50% less) than baseline (2 days normal drinking) followed by 4 days drinking 25% less (group 2:25% more) than baseline (2 days normal drinking) and finally 4 days drinking 50% less (group 2: 50% less) than baseline. Any changes in frequency, urgency, nocturia and incontinence episodes were then recorded according to randomised group and stage. Participants completed a 4 day frequency volume chart and a validated ICIQ-OAB

In a large postal survey, 6037 men and women responded to questions about tea, soft drink and alcohol consumption, as well as whether or not they had UI [52].

4. Quality of data

It was not feasible to blind participants in any of the RCTs. Dropout rates were: 8% [43], 22% [48], 37% [49], and 45% [50].

5. Results

(a) Diet: One RCT found no statistical difference in urinary incontinence following a soy-rich diet [43]. Non-RCT data showed that after adjusting for age, physical functioning, SUI at baseline, obesity, smoking and certain dietary factors, the incidence of SUI at one year was increased in women consuming more total fat, saturated fatty acids and monounsaturated fatty acids, as well as those that consumed more carbonated beverages, zinc or vitamin B12 at baseline [45,46]. The incidence of SUI was reduced in those that ate more vegetables, bread and chicken at baseline [46]. Higher intake of vitamin D, protein and potassium were also associated with decreased risk of onset of OAB in women [47]. The 2011 BACHS study [44] found that greater total energy intake was associated with LUTS. The same data source was used to test the hypothesis that carotenoid, vitamin C and calcium intakes were associated with UI in women, they found that high dose vitamin C and calcium were positively associated with incontinence whilst vitamin C from food and drinks were negatively associated with incontinence.

(b) Caffeine: One RCT found a clinical effect of decreasing caffeine, while the other did not. Bryant (2002) reported that women in the intervention group decreased daily caffeine consumption to a mean of 96.5mg, compared to 238.7mg in the control group. The experimental group had statistically significant reduction in urgency episodes (61% versus 12%); the number of Incontinence episodes decreased as well (55% compared to 26% in the controls) but this was not statistically significant. In contrast, while Swithinbank (2005) found no effect of decreasing fluid intakes (see below)or changing from caffeine containing to decaffeinated drinks.

(c) Fluid intake: In an RCT, 32 women were assigned to one of three groups: increase fluid intake by 500cc over baseline, decrease by same amount, or maintain baseline level [50]. While non-adherence to the protocol made results difficult to interpret, the authors reported that 20 women who had fewer incontinent episodes at the end of the trial attributed this to drinking more fluids. Another RCT that used a cross-over design found that when fluid intake was decreased, 39 women with SUI decreased the number of incontinence episodes; similarly, 30 women with DO significantly decreased voiding frequency, urgency and incontinence episodes [49]. Fluid manipulation [51] with a decrease in normal intake by 25% led to a significant reduction in frequency (23%), urgency (34%) and nocturia (7%) but not urinary incontinence. Increases in fluid consumption led to symptom worsening.

After adjusting for age and gender, no association was found between UI and consumption of alcohol [52]. After adjusting for age and fluid intake, consumption of wine, beer or spirits did not increase the incidence of either SUI or OAB (there was a trend towards less SUI in beer drinkers; OR 0.75 (95% CI 0.56 to1.01) for weekly drinkers versus those that drank beer less than monthly) [46]. Similarly, in a large cross-sectional study, there was no association in either unadjusted or adjusted analyses between alcohol consumption and UI [11].

6. Summary

Indications from epidemiological data suggest diet may play a role in urinary incontinence **(Level of Evidence: 3)**. Evidence is building on the role of macronutrient intake and reduction of UI. Fluid intake may play a minor role in the pathogenesis of UI. Caffeine consumption may play a role in exacerbating UI. Small clinical trials do suggest that decreasing caffeine intake improves continence. **(Level of Evidence: 2).**

7. Recommendations

Minor decrease of fluid intake by 25% may be recommended provided baseline consumption is not less than one litre a day **(Grade of Recommendation: B).** Further RCT's to assess the role of diet in urinary incontinence are warranted.

A reduction in caffeine intake is recommended for those with incontinence symptoms **(Grade of Recommendation: B)**. Larger RCTs to assess the effect of caffeine and other dietary factors are feasible and important.

f) Constipation

No published RCTs were found which assessed the effect in adults of regulating bowel function on UI. An observational study compared the self-report of straining as a child with urogynaecological symptoms as an adult [53]. Population-based studies assessed multiple risk factors for UI [54,55].

1. Quality of data

Sample sizes range from 73 for the observational study [53] to 213 in a study correlating the surrogate measures of perineal descent and pudendal neuropathy [56] to 1154 and 1051 in the population-based studies [54] respectively.

2. Results

In a small observational study, 30% of women with SUI and 61% of women with uterovaginal prolapse reported straining at stool as a young adult, compared to 4% of women without urogynaecological symptoms [53]. In a large population-based study of 1154 women over age 60 years, those with UI were slightly more likely to report constipation than those who were continent of urine (31.6% vs 24.7%) [54]. After adjusting for demographic and obstetric confounders, women who reported straining at stool were more likely to report SUI and urgency [55]. There appears to be an association between straining and pudendal nerve function. The mean pudendal nerve terminal motor latency increased after straining, correlated with the amount of descent, and returned to resting by four minutes after a strain [57]. Others found evidence of pudendal neuropathy in only 25% of women with abnormal perineal descent; in this large group of patients with defecating dysfunction no relationship was seen between neuropathy and pelvic descent, leading to the conclusion that pelvic descent and neuropathy may be two independent findings [56].

3. Summary

There is some evidence to suggest that chronic straining may be a risk factor for the development of UI. **(Level of Evidence: 3).** There are no intervention trials that address the effect of resolving constipation on UI.

4. Recommendations

Further research is needed to define the role of straining in the pathogenesis of UI. If the association holds, public education, particularly of parents and paediatricians, is needed to make an impact on the common problem of straining due to constipation in children.

g) Other

There are many other lifestyle interventions suggested either by healthcare professionals or the lay press for the treatment of UI, including reducing emotional stress, wearing non-restrictive clothing, utilising a bedside commode, decreasing lower extremity oedema and treating allergies and coughs. There is no evidence to support these interventions for UI; support for these interventions is all anecdotal in nature.

3. OTHER LUTS

No data was found.

4. FACTORS AFFECTING OUTCOME

No data was found.

II. PELVIC FLOOR MUSCLE TRAINING (PFMT)

Pelvic floor muscle training (PFMT) remains a key factor in the prevention and treatment of UI. Because pelvic floor muscle (PFM) integrity appears to play an important role in the continence mechanism (see report from Committee 4: Pathophysiology), there is a biological rationale to support the use of PFMT in preventing and treating UI in women [58]. The role of PFMT in the treatment of UUI came later, when it was recognized that PFM contraction can also be used to occlude the urethra to prevent leakage during detrusor contraction, as well as inhibit and suppress detrusor contraction.

1. RATIONALE AND PRINCIPLES

a) Biological rationale for PFMT for SUI

The biological rationale for using PFMT to treat SUI is at least three-fold.

First, in healthy continent women, activation of the PFM before or during physical exertion seems to be an automatic anatomic response [59-61]. This PFM 'reflex' contraction is a feed-forward loop and might precede bladder pressure rise by 200-240 milliseconds [62,63]. An intentional and effective PFM contraction, prior to and during effort or exertion, compresses the urethra and increases the urethral pressure, preventing urine leakage [64]. Supporting this rationale, both ultrasonography and MRI studies have demonstrated the cranial and forward movements of the PFM during an active contraction and the resulting impact on the postion of the urethra [65,66]. This active contraction of PFM during activities that cause SUI leakage has been referred toin various ways including counterbracing, perineal pre-contraction, PFM functional training, stress strategy, and the "knack" [67,68]. Miller assessed effectiveness in an RCT and demonstrated that a voluntary PFM contraction before or during coughing can reduce leakage after only one week of training in middle-aged and older women with SUI and in pregnant women with de novo SUI. Performing a rapid, strong, and well-timed PFM contraction seems to actively prevent urethral descent during an intra-abdominal rise in pressure [69]. Thus, the timing of a PFM contraction could be an important factor in the maintenance of urinary continence. Active, volitional contraction of PFM to occlude the urethra during physical activity is now routinely combined with PFM exercise to improve strength and tone. However, the optimal strength required to compress the urethra and prevent urine leakage has yet to been determined.

Second, the bladder neck is supported by a strong, toned PFM (resistant to stretching), limiting its

downward movement during effort and exertion, thereby preventing urine leakage [64,70]. Intensive strength training may reinforce structural support by permanently elevating the levator plate to a higher position inside the pelvis and enhancing the hypertrophy and stiffness of the connective tissues [70]. Anatomical and dynometic differences of the PFM have been demonstrated between continent and incontinent women [71-73].Women with SUI and MUI demonstrate less PFM passive force (tone), maximal strength, rapidity of contraction and endurance as compared to continent women [74,75]. In a pre and post PFM training study using an MRI reconstruction method, a significant reduction in the internal surface area of the levator ani was observed after PFMT; this suggests an increase in passive tone of the levator ani, which in turn is indicative of the state of PFM tone [76] Increased urethral stability at rest and during effort following 14 weeks of supervised PFMT and behavioural modification has been noted [77]. Thus, a growing body of evidence supports the rationale that PFMT improves PFM tone, facilitates more effective automatic motor-unit-firing of the PFM, and thus prevents PFM descent and urine leakage during increased intra-abdominal pressure [78]. Finally, morphological and functional changes after PFMT indicated a relationship between improved PFM coordination and increased PFM mobility and also to striated urethral sphincter hypertrophy [79]. Therefore, PFMT could also contribute to continence through a direct action on the urethral sphincter. However, more research is needed to confirm these results

Finally, there is some evidence that contraction of the transversus abdominus (TrA) muscle is associated with co-activation of the PFM. This has been demonstrated by US, EMG and MRI studies [80-84]. However, a TrA muscle contraction does not appear to elevate the PFM in all women [85] and when it does, it does not appear to be as effective as a direct PFM contraction [83,84]. More research is needed to better understand the relationship between the TrA and the PFM muscles as well as the effect on incontinence of rehabilitating the interaction between TrA muscle and the PFM.

Given the above biological rationale, in treating SUI the objective behind PFMT is to improve the timing (of contraction), strength and stiffness of the PFMs and perhaps urethral sphincter function.

b) Biological rationale for PFMT for UUI

PFMT can also be used in the management of urgency and urge urinary incontinence (UUI). In 1975 Godec observed that a detrusor muscle contraction can be inhibited by a PFM contraction that has been induced by electrical stimulation (EStim) [86] and Burgio demonstrated that a detrusor contraction can be inhibited by a voluntary PFM contraction [87]. During urine storage, bladder distension produces low-level vesical afferent firing, which in turn stimulates the pudendal nerve outflow to the external urethral sphincter thereby increasing intraurethral pressure, an effect he termed a 'guarding reflex' for continence [88]. It is also posited that Barrington's Micturition Centre's excitatory loop switches on when bladder pressures are between five to 25mmHg, while the inhibitory loop is predominantly active above 25mmHg [89]. Inhibition involves an automatic (unconscious) increase in tone for both the PFMs and the urethral striated muscle.

Thus, voluntary PFM contractions may be used, often as part of a broader urge suppression strategy, to treat UUI. Generally, patients are instructed not to rush to the toilet in response to any urge sensation, because it can trigger detrusor contraction and increase intra-abdominal pressure. The strategy involves remaining still, repeatedly contracting PFMs, and waiting for the urge to pass. After inhibiting the urgency to void and the detrusor contraction, the patient can learn to reach the toilet in time to avoid urine leakage. However, the number, the duration, the intensity and the timing of the PFM contraction required to inhibit a detrusor muscle contraction is not known.

This focus on urge suppression strategies, often combined with PFM exercise, is commonly called behavioural training. Behavioural training also involves teaching the concept of using volitional PFM contraction to occlude the urethra and prevent urine loss during uninhibited detrusor contraction. Further, patients can also be taught to be more vigilant about PFM tone when they begin to sense bladder fullness and consciously maintain resting tone rather than allowing the pelvic floor relaxation that immediately precedes and coordinates with detrusor contraction.

c) Principles of skeletal muscle strengthening

The aim of any strengthening programme is to alter muscle morphology by increasing the cross-sectional area, increasing the number and frequency of motor neuron excitations, and improving tone and stiffness. When muscles engage in intense, repetitive tasks that exceed the normal demands of daily activities this stimulates an increase in the muscle fibre size (hypertrophy), which in turn increases muscle bulk. However, hypertrophy is not immediately evident as a training response. An increase in strength is evident long before visible hypertrophy. Early improvements in strength result from neural adaptation, including a greater number of activated motor units, an increased rate of motor unit excitation, more synchronised motor unit firings and more persistent activation of type II motor units [90-92]. Hypertrophy begins only after a minimum of eight weeks of regular and intense strength training [93]. With increased overload, hypertrophy may continue for some years.

There are four principles of strength training: specificity, overload, progression and maintenance [78].

Strength training is specific to the muscle(s) being trained and requires overload (that is, exposing the muscle(s) being trained to a gradual increase in resistance, repetitions or repetition speed). Progression is the extension, through increased resistance, intensity and volume of training, of the initial exercise programme. Finally, maintenance refers to the extent to which the muscle is able to maintain a continued level of strength. In order to achieve an effective strength training programme, the American College of Sports Medicine recommends that all these elements be addressed [94].

d) Principles of behaviour change

PFMT is a treatment that involves changing an individual's behaviour and teaching new skills. Because its effectiveness depends on the active patient participation, including adherence to instructions, clinicians are faced with the challenges of changing the individual's behaviour. Some are self-motivated, but most require assistance. In general, models of healthcare behaviour change rely on providing information and education. But these are usually inadequate in the case of interventions like PFMT that typically take effect gradually and require several weeks at least to reach optimal efficacy.

Much of human learning follows the principles of operant learning, in which behaviour is a function of antecedents and consequences. Antecedents include education, motivating techniques, as well as daily reminders including cues to exercise PFM or to use them volitionally to prevent urine loss with physical activities or in response to urge. Most learning occurs through the consequences of behaviour, i.e., by trial and error and feedback. Thus, people learn how to contract and relax PFMs not only through instructions, but also through various modes of feedback. This can include visual or auditory feedback loops provided by a therapist verbally or through biofeedback, in which physiological parameters are measured and fed back using various instruments. Operant learning principles include the concept of positive reinforcement: positive results reinforce behaviour and it is more likely to be repeated. Behaviours that do not produce the desired results tend to be abandoned. Herein lies the challenge for clinicians using PFMT, to help the patient sustain their efforts for long enough to achieve a result, whether it is a change in muscle strength or improvement in symptoms. Even when they result in short-term improvements, patients in PFMT tend to have difficulty sustaining regular exercise long-term, partly because discontinuing the exercise regimen does not result in immediate regression.

Learning is mediated by individual characteristics, including disposition, attitudes, beliefs, and experiences. Several models of behaviour change have evolved that are relevant for addressing health behaviours. According to one widely-adopted model, Social Cognitive Theory, people will engage in a new behaviour when they believe it will lead to positive outcomes and they believe they are capable of performing the behaviour (concept known as self-efficacy). Factors that may affect the ability to learn new skills and change daily habits fall into several domains, including social, cognitive, physical, emotional, behavioural, and environmental. Clinicians have the opportunity potentially to influence any of these by making an effort to understand the patient's daily life, assessing barriers to change during treatment, and assisting patients with overcoming the impediments they encounter. It is generally accepted that clinicians should promote realistic expectations of treatment and outcome, individualize treatment protocols, and follow-up with patients to assess adherence, monitor progress, encourage persistence, and facilitate long-term behaviour change.

This section presents the evidence for the use of PFMT in the prevention and treatment of UI in women. Questions addressed are:

a) Is PFMT effective in the prevention of UI?

b) Is PFMT better than no treatment, placebo or control treatments in the treatment of UI?

c) Is one type of PFMT programme better than another in the treatment of UI?

d) Is PFMT better than other treatments in the treatment of UI?

e) Does the addition of PFMT to other treatments add any benefit in the treatment of UI?

f) What factors might affect the outcome of PFMT in the treatment of UI?

g) What is the effect of PFMT on other lower urinary tract symptoms?

In this section, the pre-specified primary outcomes of interest were 1) self-reported UI (for prevention studies), 2) self-reported cure or 3) cure and improvement in UI symptoms (for treatment studies). Secondary outcomes of interest were 1) quality of life (prevention and treatment studies) and 2) leakage episodes and amount (treatment studies) [95].

2. PREVENTION AND TREATMENT (PREGNANT AND POSTNATAL WOMEN ONLY)

This subsection specifically considers PFMT for the prevention and treatment of UI in pregnant and postnatal women (called childbearing women in this section). As the physiological changes of childbearing can affect PFM function, it is possible that the effect of PFMT might differ in this group compared to non-childbearing women.

A 2008 Cochrane review in this area analyzed data from 15 trials in 6,181 participants [96]. An additional 6 randomised trials published between 2008 and 2011 were identified and also reviewed

for this subsection (total 21). Similar to methods used in the Cochrane review, trials in this section have been grouped in 3 areas: 1) trials of PFMT for prevention of UI (performed in women without UI symptoms when randomised); 2) trials of PFMT for treatment of UI; and 3) trials of PFMT for the prevention and treatment of UI (participants with and without UI symptoms enrolled). Trials were further separated into those beginning during pregnancy (antenatal) or postnatal.

As in the recently updated Cochrane review, the primary outcome of interest was self-reported UI [97]. Secondary outcomes included condition specific quality of life (e.g. King's Health Questionnaire (KHQ), Incontinence Impact Questionnaire (IIQ), or any other quality of life or health status measure (for example Short Form-36); symptom severity; number of leakage episodes; measures of pelvic floor muscle function; and economic analyses. Other outcomes of interest included adherence measures.

a) Is PFMT effective in the prevention of UI in childbearing women?

There are three grades of prevention: primary, secondary and tertiary. Primary prevention aims to remove the causes of a disease. Secondary prevention focuses on the detection of asymptomatic dysfunction and provides treatment aimed at stopping its progression. Tertiary prevention focuses on existing symptoms to prevent the progression of the disease through treatment. This subsection addresses the question of PFMT effectiveness for primary and secondary prevention of UI in childbearing women. Clinically it can be difficult to effectively screen trial participants to ensure that a disease process is altogether absent (for primary prevention studies) or present, although asymptomatic (for secondary prevention). Trials investigating prevention of UI usually enroll people purely on the basis of the absence of symptoms. Thus, the trials in this section likely represent a combination of primary and secondary prevention effects.

The 2008 Cochrane review [96] included 5 trials addressing prevention of UI in childbearing women [98-102]. Two of the studies were combined prevention/treatment studies, but published or unpublished data were available for women who were continent at recruitment [98,101]. In the study by Sampselle (1998), 54 of 72 women were continent based on a standing stress test at 20 weeks gestation. After drop outs, unpublished data were available from 37 previously continent women (16 PFMT and 21 controls). Mørkved (2003) [101] published data for 207 of 301 women who were continent before pregnancy and at 20 weeks gestation. After dropouts, data were available from 193 previously continent women (94 PFMT and 99 controls). Neither study was powered to detect differences in the previously continent subgroup and the subgroup sizes were small.

One new prevention trial published in 2010 was found [103] and two combined prevention/treatment trials of antenatal PFMT with UI outcomes were published since 2008, but outcome data specific to the women who were continent at baseline were not presented [104,105]. Thus, these two trials and their results are included in the section below on combined prevention/treatment trials.

Five studies [98,99,101-103] recruited nulliparous or primiparous women during pregnancy, and one recruited "pregnant women" [100]. Reilly (2002) recruited primigravid women without a pre-pregnancy or current history of UI, but with bladder neck hypermobility at 18 to 20 weeks gestation. Primigravidae were recruited at 18 [98], 20 [101,103] and 28 weeks [102] gestation.

In all six trials, PFMT began during pregnancy while controls received the usual antenatal care, which may have included advice on PFMT from their maternity caregivers [98,99,101,103] or were asked not to do PFMT [100,102]. There were some variations in the PFMT parameters (intensity and supervision):

•Eight to 12 near-maximal voluntary PFM contractions, held for six to eight seconds, followed by three to four fast contractions at the end of each contraction, twice daily from 20 weeks gestation [101,103]. Also a weekly [101] or monthly [103] exercise class from weeks 20 to 36.

- Eight to 12 PFM contractions, held for six seconds with a two second rest, three sets twice daily, from 18 weeks gestation. Also individual PFMT with physiotherapist during monthly visit [99].
- Up to 30 near-maximal PFM contractions per day from 20 weeks of gestation [98].
- 10 PFM contractions; held for eight seconds each followed by three fast one second contractions; a six-second rest between contractions; for up to 20 weeks. PFMT taught one-on-one with physiotherapist. Weekly clinic appointments (one hour each) for eight weeks, then weekly phone calls [102].
- PFMT not described. Participants were seen twice monthly throughout pregnancy, and every three months postpartum for one year [100].

Correct voluntary PFM contraction was checked prior to training in four [98,101-103].

1. Quality of data

Allocation concealment appeared adequate in four trials [98,99,101,102] and the outcome assessors were blind in five of the six trials [98-101,103]. Dropout rates varied, including 4% [101,102], 14% [99], 36% [98] and as high as 53% [103]. Stothers (2002) did not report any losses to follow up.

Outcomes were measured at various times: 28 and 35 weeks gestation and six weeks postpartum

[102]; six and 12 months postpartum [100]; 34 to 36 weeks gestation then at three months postpartum [99,101,103]; 35 weeks post partum then postpartum at six weeks and six and 12 months [98] with the primary endpoint being 12 months. Reilly [2002] was the only trial with long-term follow up, at four years and more recently at 8 year follow up [106].

2. Results

Pooled data described in this section are reported from the 2008 Cochrane review [96].

(a) Late pregnancy (34 weeks or later): Pooled data from three trials [98,101,102] showed that women in the antenatal PFMT group were 56% less likely to report UI than the controls. Statistically significant heterogeneity was observed in this comparison. The point estimates in all three studies favoured PFMT but these differed considerably. A possible reason for the more pronounced difference between PFMT women and controls in the study by Gorbea Chavez (2004) is that the comparison group was asked not to do PFMT, whereas in the other two controls had usual care that might have included PFMT. In another trial [103] a lower proportion of women in the PFMT group at 36 weeks gestation reported SUI compared to controls, but the difference was not statistically significant.

(b) Early postpartum (up to 12 weeks): Pooled data from two trials showed that PFMT women were around 50% less likely to report UI, compared to the controls (RR 0.50 95% CI 0.31 to 0.80) [98,102].

(c) Mid postpartum (three to six month postpartum): In the pooled analysis, PFMT women were still statistically significantly less likely than controls to report UI, although the difference in risk had reduced to about 30% (RR 0.71 95% CI 0.52 to 0.97) [98-101]. Similar to their results at 36 weeks of pregnancy, Mason et al [103] found fewer women in the PFMT group compared to controls reported SUI symptoms at three months postpartum, but this difference was not statistically significant. Loss to follow-up was high, and this outcome was assessed in only 47% of those with baseline data.

(d) Late postpartum (up to one year postpartum): Too few participants (n=44) were available in 1 trial [98] to determine if there was a difference in prevalence of UI between PFMT women and controls at 12 months postpartum.

(e) Long term (more than one year): At four year follow up, Reilly (2002) reported seven of 42 PFMT women and 26 of 58 controls had symptoms of SUI. However, this apparent benefit for the PFMT group was not seen in a later 8 year follow up study [106]. In that report, 164 (71%) of the initial 230 participants with postnatal data were analyzed, and SUI was reported by 35.4% in the PFMT group versus 38.8% in the control group; 70% of those assessed had had one or more additional deliveries during the follow-up period.

Regarding secondary outcome measures, five of the six trials reported symptom severity data such as frequency or amount of urine leakage. None of the measures, or the ways in which they were reported, were common to the four trials. In general, the data suggested that PFMT women with symptoms of UI might have demonstrated less severe symptoms than the controls. Only Stothers [2002] noted adverse events; two of the 43 PFMT women withdrew due to pelvic floor pain.

Only three trials reported treatment adherence data. Gorbea Chavez (2004) reported that 84% of PFMT women attended seven or eight of the eight physiotherapy appointments. In another, nearly half the women in the PFMT group exercised for 28 days or more; postpartum similar proportions of women in the intervention and control groups were doing occasional or no PFMT (28% and 34% respectively [99] Mason [2010] reported that just 64% of women assigned to the PFMT group attended at least one class, but women in the intervention group reported performing more exercises in a 3-day diary at both 36 weeks of pregnancy and three months postpartum than did controls.

3. Summary

Pregnancy and birth appear to be important factors associated with the development of UI in women. Therefore, all women who have had a child or children might be considered 'at risk' of developing UI at a later date.

Continent pregnant women having their first baby who participated in a more 'intensive and supervised' PFMT programme than the PFMT provided as part of usual care were less likely to experience UI from late pregnancy up to six months postpartum **(Level of Evidence: 1)**. There was not sufficient evidence available to demonstrate whether this benefit persists at 12 months postpartum; results from a single trial suggest the benefit of PFMT is not maintained eight years after treatment or with subsequent deliveries **(Level of Evidence: 2)**. There was no evidence investigating the preventive effects of PFMT in pregnant, previously continent, multiparous women.

4. Recommendations

Continent, pregnant women having their first baby should be offered a supervised (including regular health professional contact) and intensive strengthening antepartum PFMT programme to prevent postpartum UI **(Grade of Recommendation: A)**. The usual or standard approach to PFMT in pregnancy (which is commonly verbal or written instruction without confirmation of correct contraction or supervision of training) needs to be reviewed.

Additional trials with longer-term follow-up (greater than 12 months postnatal) are needed to determine long-term benefits of antenatal PFMT. Further,

large, good-quality RCTs are needed to investigate the effect of antepartum PFMT on preventing postpartum UI in multiparous women.

b) Is PFMT effective in the treatment of UI in childbearing women?

Four studies which addressed the treatment of existing UI after delivery [107-110] were identified and all were included in the 2008 Cochrane review [96]. One study recruited incontinent women during pregnancy [110], while the other three recruited women three months or more after delivery. All four studies recruited a mix of primiparous and multiparous women.

The control groups in three [107,108,110] received standard care, which included ante and postpartum advice on PFMT, whereas the control group in Dumoulin's (2004) study received, in lieu of training, relaxation massages at the same frequency as the PFMT treatments.

The PFMT interventions varied as follows:

- intervention group received either PFMT, or PFMT with vaginal cones, or vaginal cones (VC). PFMT comprised 80 to100 PFM contractions per day (a mix of fast and slow), with three home visits by a nurse, healthcare visitor or continence advisor. The VC group received 15 minutes per day of cone therapy while the combined PFMT/VC group received both interventions [107].
- as above supplemented by instruction from a physiotherapist on four occasions [108].
- PFMT with biofeedback + electrical stimulation (EStim) with or without deep abdominal training. PFMT comprised weekly sessions supervised by physiotherapists for eight weeks with 15 minutes of Estim and 25 minute of PFM exercice with biofeedback including strenghtening and motor relearning exercices [109]
- four one to one and half hour sessions with a physiotherapist (three antepartum and one at six weeks postpartum) but details of the PFMT programme were not given [110]

1. Quality of data

Random allocation concealment was adequate in three of the four trials [107-109] and outcome assessors were blind in two [108,109].

In one trial losses to follow-up were high in all intervention groups (51% PFMT; 63% PFMT/VC; 41% VC). In two others losses to follow-up were 30% [111] and 38% [110]. In contrast, Dumoulin's (2004) trial (which included weekly contacts with a physiotherapist for eight weeks) reported a 6% loss to follow-up. Outcomes were measured outcome 12 months after delivery [107,108], and then 24 to 44 months post-delivery, and six years after the index delivery [111]. Dumoulin (2004) reported outcome nine weeks after intervention began. However as women were recruited at varying lengths of time following delivery (all more than three months postpartum) the data are presented alongside those from Glazener (2001), and Wilson (1998), as long-term post-natal data.

2. Results

In the one study of antepartum PFMT for treatment of UI, no statistically significant difference was reported in the prevalence of UI between PFMT and control groups at 35 weeks, eight weeks postpartum, six months and 12 months postpartum [110].

Pooled data from the three trials of postpartum PFMT found women were about 20% less likely to have UI after treatment compared to the controls (RR 0.79, 95% CI 0.70 to 0.90) [96]. Statistically significant heterogeneity was observed. The treatment effect in the study by Dumoulin (2004) was much greater than that in the other two studies. Possible reasons are that the controls in the study by Dumoulin (2004) were asked not to do PFMT, whereas controls in the other two studies received usual care and both interventions and control groups were also doing PFMT (a mean of 20 versus five PFM contractions per day in Glazener 2001), and 86 versus 35 in Wilson 1998). Another difference was the intensity and supervision of the PFMT intervention; Dumoulin (2004) used a more intensive PFMT programme with adjunctive EStim and BF and physiotherapy appointments once a week for eight weeks, whereas in the other two studies [107,108] women had three or four appointments with a health professional over approximately six months and were asked to do PFMT on their own.

All four treatment trials reported some data on symptom severity such as frequency or amount of urine leakage. None of the measures, or the ways they were reported, was common to the four trials. The data suggested that PFMT women with symptoms of UI might have less severe symptoms than the controls, but this was not a consistent or clear-cut finding. Dumoulin (2004) stated that none of the women in the PFMT group reported any adverse events.

Three trials reported some data related to treatment adherence, one for antepartum PFMT [110] and two for postpartum PFMT [107,108]. In the antepartum study, at 36 weeks gestation 37% of the PFMT women were exercising intensively compared to 14% of the controls. Mean number of PFM voluntary contractions per day at 12 months postpartum were 20 [108] and 86 [107]per day in PFMT women, and 5 and 35 respectively per day in the controls.

Glazener and colleagues followed up women six years after the index delivery. The effect of PFMT on UI was not sustained. At six years, 100 out of the 263 in the intervention group and 99 out of the 253 in the control group experienced UI at least once

per week [111]. However, the women had had an average of 1.5 deliveries since the index delivery.

3. Summary

To date, only one trial has investigated the effect of PFMT for the treatment of UI in pregnant women [110]. This was a moderate-size study that did not report allocation concealment or blinding of the assessors, and did not describe the type of PFMT programme employed. In the absence of any detail on the PFMT programme it is impossible to judge if the intervention had the potential to be effective.

Postpartum women with UI who were randomised to PFMT taught and supervised by a health professional were less likely to be incontinent than controls (standard care or relaxation massage) six to 12 months following delivery **(Level of Evidence: 1)**. Of the three trials, the one that used an intensively supervised strength training programme demonstrated the greatest treatment effect. It is unclear if the benefit of PFMT is maintained over time or with subsequent deliveries **(Level of Evidence: 2).**

For women who have persistent symptoms of UI at three months postpartum PFMT is a more effective treatment than standard postnatal care or relaxation massage; effects might be greater with supervised and intensive strengthening PFMT (with the addition of EStim). It is not clear if the effect can be sustained over the long-term; there is also no data on the effect of short periodic refresher sessions on long-term effect.

4. Recommendations

PFMT should be offered as first line conservative therapy to women with persistent UI symptoms three months after delivery (Grade of Recommendation: A); an 'intensive' PFMT programme (in terms of supervision and exercise content) is likely to increase the treatment effect (Grade of Recommendation: B).

There is a need for at least one large, pragmatic, well-conducted and explicitly reported trial with long term follow-up (five plus years) of postpartum PFMT that investigates the effect of 'intensive' treatment followed by periodic refresher sessions.

c) Is PFMT effective in the mixed prevention and treatment of UI in childbearing women?

Ten trials are included in this section. Of these trials, some women did and some did not have UI at the time of recruitment, i.e. the effect of PFMT included a mix of prevention and treatment. Eight [98,101,112-117] were included in the 2008 Cochrane systematic review [96] and two were more recently published [104,105].

In six, nulliparous or primiparous women were randomised to either supervised antepartum PFMT or usual antepartum care [98,101,104,105,113,116]. The other four randomised nulliparous women during pregnancy [114] or postpartum [112,115,117] to either postpartum PFMT [112,115,117] or usual postpartum care or no PFMT [114].

(a) Antepartum PFMT versus usual care: The interventions of two trials (98,101] in pregnant women have been described in section B.2.1a.

Two new studies were added [104,105]. Ko (2011) recruited nulliparous women at 16-24 weeks gestation. Women in the PFMT group met individually with a physical therapist for instruction, and correct contraction was assessed by observing inward movement of the perineum during contraction. The individual therapy was similar to that used by Reilly (2002) described above, including three sets of eight contractions repeated twice daily. Additional group therapy occurred weekly in 45 minute sessions over a 12 week period. Controls were excluded if they reported previous use of PFMT, but were not specifically discouraged to do PFMT during pregnancy; otherwise they received usual prenatal care. Bø's study (2011) differed in that the primary aim was to assess the effect of regular exercise on weight gain in pregnancy. Primiparous, sedentary women within the first 24 weeks of pregnancy were recruited and randomised to aerobic fitness classes including group instruction and practice of PFMT or usual care (not described). Women in the exercise group were asked to attend two to three 1-hour aerobic fitness classes weekly for at least 12 weeks. The PFMT included verbal instruction and group performance of three sets of eight to twelve contractions, holding six to eight seconds each in sitting, kneeling and standing positions. No individual assessment of the ability to perform a correct contraction was included. In addition, the exercise group was given a PFMT pamphlet that recommended a regimen of three sets of eight to twelve PFM contractions daily.

Hughes (2001) recruited nulliparous women at 20 weeks gestation and women randomised to PFMT attended one individual appointment then, between 22 and 25 weeks gestation, a group PFMT session (maximum six women) with a physiotherapist. No details of the training parameters were reported. Women with no palpable voluntary PFM contraction or a flicker of contraction were randomised. Controls received the usual community antepartum care. In another trial [116], women in the PFMT group were trained to use an Epi-No device (an inflatable vaginal balloon connected to a pressure gauge for visual feedback), 15 minutes daily; for three to six weeks. Controls received no device. The authors' primary interest was in improving the elasticity of the PFM for delivery rather than continence outcomes.

(b) Postpartum PFMT versus usual care or no PFMT: Chiarelli (2002) only included women who had had forceps or ventouse deliveries, or had delivered a baby weighing 4000g or more. Ewings (2005) only included women who had already experienced UI and who were at high risk of UI following childbirth

in accordance with the SIFCRAFT risk scale. The control groups received the usual postpartum care, which included: an invitation to postpartum classes taught by physiotherapists [115], standard ante and postpartum care [112], no PFM re-education from two to 10 months postpartum [114] and verbal promotion of PFM exercises supplemented by a leaflet [117]. In PFMT groups, women were visited by a midwife or physiotherapist on the postnatal ward and were advised to train as follows:

- PFMT exercises as often as remembered and contractions integrated with daily living activities, plus midstream urine stop. Correct PFM contraction was checked on a second visit at eight weeks postpartum [112].
- PFMT exercises with three to six-second holds, three times a day. A variety of adherence strategies were employed (e.g. red stick-up dots, home or hospital visit after eight weeks).
- PFMT programme including 12 visits with a physiotherapist between two and 10 months postpartum, including a 20 minute BF training session and a 15 minute EStim session [114].
- PFMT taught one to one with physiotherapist in hospital in addition to an invitation to attend PFMT class at two and four months postpartum; 21 of 284 women participated in the first class (18%) and only 5 (4%) attended both [117].

1. Quality of data

(a) Antepartum PFMT versus usual care: Three of the six trials had adequate random allocation concealment [98,101,105]. In the others women were allocated at random but it was not clear if allocation was adequately concealed [104,113,116]. Assessors were blinded in four of the six trials [98,101,104,105]. Sample sizes varied: 72 [98], 105 [104], 144 [116], 300 [105], 301 [101], and 1169 [113]. Dropout rates were 14% at 6 weeks postpartum [104], 4% [101] at three months postpartum and ranged from 0% [105] to 34% [113] at six to seven months post-partum. At 12 months, the drop-out rate was 36% [98].

(b) Postpartum PFMT versus usual care or no PFMT: Random allocation concealment was adequate in three trials [112,115,117] but inadequate in Meyer (2001) where alternate assignment was used. Blinding of outcome assessment was adequate in one [115]. Sample sizes were large and varied: 1,800 women [112]; 720 [115]; 234 [117], and 107 [114]. Outcomes were measured at Both the Sleep (1987) and Chiarelli (2005) trials measured outcomes at three months [112,115]; 6 months [117], or 10 months [114]. Lost to follow up ranged from 6% to 19%.

2. Results

(a) Antepartum PFMT versus usual care: As reported by Hay-Smith and colleagues in 2008 [96] pooled data from three trials [98,101,113] showed that women who were randomised to antepartum PFMT had about 10% less risk of UI in late pregnancy. Statistically significant heterogeneity was observed in this comparison. While the point estimates in all three studies favoured PFMT these differed considerably between the trials ; the study by Hughes (2001) carried considerable weight in the pooled analysis, most likely because it was the largest study. One of the differences between the studies by Mørkved (2003) and the other two in this analysis was the PFMT intensity and supervision as reported previously, being more 'intense' in the former. Ko (2011), used a similarly more intense PFMT programme, and also found significantly less UI in the PMFT women at 36 weeks gestation compared to controls (34% vs. 51%, $p< 0.01$). Bø (2011) found no difference in the prevalence of UI in the exercise and control groups in late pregnancy.

In the pooled analyses from Hay-Smith (2008), the prevalence of UI was not statistically significant between PFMT and control groups in the early, [98] mid, [98,101,113] or late postpartum period [98,116]. At 6 weeks and 6 months postpartum, Ko (2011) found less UI in the PFMT compared to control group (25% vs. 35% and 16% vs. 27%, respectively); this difference was of borderline significance ($p=0.06$ at 6 weeks and $p=0.04$ at 6 months postpartum). Bø (2011) found no difference in the prevalence of UI in the exercise and control groups in the early postpartum period.

Symptom severity such as frequency or amount of urine leakage was reported in three trials, but PFMT was not found to be superior to control or vice versa at the primary endpoint for each study [98,112,113]. In another, statistically significant lower Urogenital Distress Inventory Short Form (UDI-6) and IIQ Short Form (IIQ-7) scores in the PFMT group were noted compared to controls at all end-points (late pregnancy and three days, six weeks and six months after delivery, suggesting less bother related to urinary symptoms and less functional impact from UI in the treatment group [105].

Some adherence outcomes were included for four of the six trials: 81% of the PFMT women attended more than half of the weekly classes [101]; 85% and 62-90% of the PFMT women reported performing PFMT at least 75% of the time at 35 weeks gestation and at 1 year postpartum [98]; >80% of the PFMT women attended every group session, and at 36 gestational weeks, 87% reported PFMT practice at least 75% of the time [105]; or 40% of the exercise group attended >80% of the weekly exercise classes [104].

(b) Postpartum PFMT versus usual care or no PFMT: There was no statistically significant difference in the prevalence of UI in women randomised to postpartum PFMT or control in the mid [112,115,117] or late postpartum period [114,115]. Statistically significant heterogeneity was observed in the combined

data for the mid postpartum period, with one study favouring PFMT [115], one neither PFMT nor control and one favouring the control condition [117]. Some potentially important clinical differences were noted between the studies. Firstly, Chiarelli (2002) recommended a PFM strength training programme; neither of the other two studies described their PFMT programme, so it is not possible to determine whether the latter studies could have had an effect or how different the PFMT and control conditions were. Further, Sleep (1987) noted only a moderate difference in the proportion of PFMT women and controls doing some PFMT at three months postpartum while at three months postpartum Chiarelli reported that about half the controls were doing PFMT and an even greater proportion of the PFMT group were exercising. A second difference was that Chiarellirecruited women at potentially increased risk of postnatal UI, such as those who had a large baby or a forceps delivery.

3. Summary

The effect of antepartum PFMT or postpartum PFMT, in groups of women where some did and some did not have prior UI symptoms, varied by study with some showing a benefit on UI prevalence whereas others did not **(Level of Evidence: 2)**. The characteristics of the three trials, all methodologically robust, that demonstrated some effect were:

(a) For antepartum PFMT: pregnant women having their first baby and used intensively supervised strengthening PFMT programmes; PFMT reduced UI prevalence in late pregnancy and three to six months postpartum [101,105], but this was not evident six years after the index delivery [101].

(b) For postpartum PFMT: primiparous and multiparous women at potentially greater risk of postpartum UI after a large baby or forceps delivery, and used a strengthening PFMT programme; PFMT reduced UI prevalence at three months postpartum but not at one year [115].

4. Recommendations

Health providers should carefully consider the cost/benefit of population based approaches to health professional taught antepartum or postpartum PFMT, that is, health professional instruction to all pregnant or postpartum women regardless of their current or prior continence status **(Grade of Recommendation: B).**

Where a population approach is used, the 'best' evidence to date suggests the following: (a) an intervention comprising of a daily home PFMT and weekly physiotherapist-led exercise classes for 12 weeks, starting at 20-24 weeks gestation for pregnant women having their first baby, and (b) an individually taught strengthening PFMT programme that incorporates adherence strategies for postpartum women who have had a forceps delivery or a vaginal delivery of a large baby (4000g or more) **(Grade of Recommendation: C)**

3. PREVENTION (OTHER WOMEN)

Hay-Smith and colleagues [96] have previously reviewed trials of PFMT for the prevention of UI in pregnant, postnatal or childbearing women. No trials investigating the primary/secondary prevention effects of PFMT for UI in non-childbearing women were found. These results were considered in section B.2.1. Prevention of post prostatectomy UI is considered in Section D.2.1.

a) Is PFMT effective in the prevention of UI?

No trials investigating the prevention effects of PFMT for UI in non-childbearing women were found.

4. TREATMENT (WOMEN)

a) Is PFMT better than no treatment, a placebo or a control group treatment?

The recommendations in this section are based on the updated 2011 Cochrane Review [97]. Primary outcomes were 1) patient-reported cure or improvement in symptoms and 2) symptom bother (level of distress) and an incontinence-specific quality-of-life assessment. Secondary outcomes of interest included the number of leakage episodes and pad and paper towel testing. For a comprehensive background to the rationale for treatment of urinary incontinence with PFMT see Dumoulin 2010 [118].

There were 25 RCTs comparing PFMT with no treatment for women with UI identified, of which 7 were excluded: one included women with symptoms of geriatric syndrome that could have influenced the results [119], three compared supervised with unsupervised PFMT [120-122], one abstract that did not clearly state "RCT" [123] and two due to the sham PFMT consisting of strong isometric hip abductor contractions [124,125]. According to EMG, dynamometric and MRI studies, both hip abductions and external rotations result in a synergic contraction of the PFMs [61,74,126,127]. Thus, in all likelihood, these two trials probably compared a direct versus an indirect approach to PFMT.

1. Studies included in the analysis

Among the 18 RCTs, three were not considered in the final analysis because they lacked adequate data [68,128,129].

Of the remaining 16, 12 recruited women with SUI exclusively [67,130-140] and one included women with SUI, with or without UUI. However, only one trial was found for women with mixed urinary incontinence (MUI) and it was thus analysed with the SUI studies [141]. One included older women with UUI with or without SUI (with urge as the predominant type) [142].The remaining two recruited women with a range of diagnoses [119,143].

2. PFMT details

Twelve of the 16 studies provided adequate detail about the type of PFMT program used. In all 12, PFMT was taught by a health professional and in eight, a correct voluntary PFM contraction was confirmed prior to training [67,119,130,134,136,139,140,142,143]. Based on the description of the programmes, two trials had PFMT programmes that clearly targeted coordination [67] or strength training [134]. It was more difficult to categorise the other PFMT programmes, because they were either a mixed (i.e. strength and endurance or strength and coordination) programme or did not provide enough information on the exercise parameters. All PFM exercise programs are presented in **Table 1**.

3. Control group details

Among the 15 studies, the 'control' groups received no treatment in eight [67,130,131,135,136,139,141,143], a placebo drug [142], sham EStim, [132], sham PFMT with placebo drug in one [137], a non-active control intervention such as the use of an anti-incontinence device [134], advice on incontinence pads [132] and general education on healthy aging [119,138,140].

Our ability to consider the combined results from individual studies was limited by: 1) lack of consistency in the choice of outcome measures chosen by the researchers; and in the older studies 2) poor reporting of outcome data (i.e. mean reported without a measure of dispersion) hence some data could not be used in the pooled analysis.

4. Quality of data

In three trials published as conference abstracts, the brevity of the reporting made it difficult to assess data quality [131,135,137]. Only three trials reported adequate random allocation concealment [119,134,140]; 9 reported using blinded outcome assessors [67,119,128,133-135,140-142].

5. Results

There were 16 RCTs comparing PFMT with no treatment, placebo, sham or other non-active control treatments. Two reported data on subjective cure and both found that women in a PFMT group were statistically and significantly more likely to report cure [134,142]. However, the effect size was quite different in the two trials. In the trial exclusive to women with SUI, the PFMT group were about 17 times more likely to report a cure compared to the controls [134], whereas in the study of PFMT women with urge-predominant UI, the women were only about two-and-half times as likely to report a cure [142].

With regard to an individual-perceived cure or improvement, two trials in women with urodynamic SUI [132,134] suggested a greater likelihood of cure or improvement than the single study in women with UUI with or without urodynamic SUI [142].

In five, psychometrically robust questionnaires were used to assess symptom impact. Bø (1999) used the Bristol Female Lower Urinary Tract Symptoms (B-FLUTS) questionnaire, but only reported the lifestyle and sex-life results. Women in the PFMT group were less likely to report that UI symptoms interfered with activities or were problematic post-PFMT. Schagen van Leeuwen (2004) reported a mean change in the Incontinence Quality of Life (I-QoL) score, but it was not clear if the difference, which favoured the PFMT group, was important as the reported means lacked a measure of dispersion. Two used QOL in Persons with Urinary Incontinence I-QoL score and reported a mean change in the QOL favouring PFMT over control [140,143]. Another found a significant difference favouring the PFMT group when the scores for incontinence-related limitations and impact on daily life were compared [139].

Six studies used urinary diaries to count leakage episodes: three days [134,143], seven days [140,144]; and 14 days [141,142]. Effect size was greatest in the Lagro-Janssen's (1991) trial; however, the treatment effect may have been overestimated due to inadequate concealment of random allocation. The point estimates in the other trials were similar and all were statistically significant [134,141-143]. Ultimately, PFMT women experienced approximately 1 to 1.5 less leakage episode per 24 hours as compared to the controls.

Three other studies measured incontinence frequency [119,136,138] with either a four-point ordinal scale (1 =urine loss once a day to 4 urine loss once a month) [136] or a six-point leakage scale to document cure (0 = no urine leakage to 5 = every day) [119,138]. Kim's 2007 study, the post-treatment scores were significantly better for the PFMT group post-treatment compared to the control, while in the 2011 trial 44.1% reported a cure in the PFMT group versus 1.6% in the control group immediately after intervention, a statistically significant difference.

One new trial was added to the section [143] making a total of 9 trials reported on pad and paper towel tests. Eight used "short office-based pad tests" and one used a paper towel test [67] Five involving women with SUI [130,131,134,136,140] dichotomised the short pad test data as either "cured"/ "not cured" [134,136,140]; or "cured and improved"/ "not improved" [130,131,136]. Four of the five found that "cured" or "cured and improved" was statistically and significantly more likely in the PFMT group. One older trial was small and did not find a statistically significant difference (fewer than 10 participants per group) [130,131]. Four reported data as mean and SD [128,134,140,143], and two others as a mean change in pad weight from baseline [135,143]. The two trials in women with urodynamic SUI, found that PFMT women had, on average, about 30g [134] and 12g [140] less urine loss than the controls. In a study of women with unspecified urinary incontinence,

Table 1: Characteristics of studies comparing PFM training to a control.

Study ID	PFM Training Type	Training Program	Training Duration	Notes
Aksac, 2003 [136]	Strength training (20) vs control (10)	VPFMC confirmed by palpation. Set: 10 VPFMC, with 5-second hold and 10-second rest. Progressed at 2 weeks to 10-second hold and 20 second rest. Sets per day: 3	8 weeks	Supervision: Weekly visit Drop out: not stated
Bø, 1999 [134]	Strength training (29) vs control (32)	VPFMC confirmed by palpation. Set: 8 to 12 high-intensity maximal VPFMC with a 6-to-8-second hold followed by 3 to 4 fast contractions at the end of each, and a 6-second rest between maximal contractions. Sets per day: 3. Exercises done in different body positions included supine, kneeling, sitting and standing - all with the legs apart.	6 months	Supervision: Weekly 45 minute exercise class Monthly clinic visit with Physiotherapist Drop out: 4/29 PFMT, 2/32 controls
Burgio 1998 [142]	Combined training (65) vs control (65)	VPFMC taught by trained nurse practitioner. Visit 1: anorectal biofeedback for teaching VPFMC with abdominal muscle relaxation. Visit 2: teaching urge strategies (adaptive response to sensation of urge) such as pause, sit, relaxation but repeated VPFMC to decrease detrusor contraction, urgency and urge incontinence. Visit 3: bladder-sphincter biofeedback for those with < 50% reduction in incontinence episodes to teach VPFMC against increasing fluid volume and increasing urgency. Visit 4: review progress, adapt home programme, Home programme 15 VPFMC 3x day in lying, sitting, standing. Also VPFMC with activities that precipitate incontinence episodes. Slow or interrupt urine stream 1x day	8 weeks	Supervision: 4 clinic visit at 2 weeks intervals Drop out: 4/65: PFMT, 8/65 Control
Burns, 1993 [141]	Endurance training (43) vs control (40)	10 VPFMC with 3-second hold, and 10 VPFMC with 10-second hold. Progressed by 10 per set to daily maximum of 200. Sets per day: 4	8 weeks	Supervision: Weekly exercise reminder cards mailed between visits Weekly clinic visits with nurse Drop out: 10 group not specified
Carneiro 2010 [139]	Combined training (25) vs control (25)	VPFMC taught by a trained physical therapist 1 serie of 8-12 repetitions of 5 VPFMC in the recumbent, sitting, and standing positions, with contractions sustained for 6 to 10 seconds	8 weeks	Supervision: 30 minutes twice weekly Drop out: not reported

Table 1: Characteristics of studies comparing PFM training to a control (continued).

Study ID	PFM Training Type	Training Program	Training Duration	Notes
Castro, 2008 [140]	Combined training (26) vs control (24)	VPFMC taught by trained physiotherapist Sets: 5 VPFMC with 10-second hold, 10 VPFMC with 5-second hold, 20 PFMC with 2-second hold, 20 VPFMC with 1-sec hold, 5 contractions with cough Sets per day: Once, three times per week	6 months	Supervision: 3 group session per week for 6 Months Drop out: 3/26 PFMT, 5/24 controls
Henalla 1989 [130]	Endurance training (26) vs control (25)	Correct VPFMC taught by physiotherapist Sets: 5 VPFMC with 5-second hold. Sets per day: 1 set per hour	12 weeks	Supervision: Weekly clinic visit Drop out: None
Kim 2007 [138]	Combined training (35) vs control (35)	VPFMC taught by trained physiotherapist Sets:10 VPFMC with 3-second hold, 10 VPFMC with 10-second hold in sitting, lying, and standing positions with the legs apart Sets per day: 2 times per week	12 weeks	Supervision: Exercise class twice a week Drop out: 2/35: PFMT, 3/35 Control
Kim, 2011 [119]	Combined training (63) vs control (64)	VPFMC taught by trained physiotherapist Sets:10 VPFMC with 3-second hold, 10 VPFMC with 10-second hold in sitting, lying, and standing positions with the legs apart Sets per day: 2 times per week	3 months	Supervision: Exercise class twice a week Drop out: 2/63: PFMT, 1/63 Control
Lagro Jensen 1991 [133]	Endurance training (54) vs control (56)	VPFMC : 5 to 10 daily sessions of 10 exercises of 6 sec each to be done during usual daily activities.	3 months	Drop out: 1/54: PFMT, 3/56 Control
Miller, 1998 [67]	Coordination training (13) vs control (14)	Voluntary PFM contraction (VPFMC) instructed and confirmed by palpation. Short programme aimed at improving coordination between a VPFMC and a rise in intra-abdominal pressure.	1 week	Dropouts: none
Sari, 2009 [143]	PFMT training (22) vs control (19)	VPMC taught by a nurse Sets : 30 contractions in 1 set (fast and slow contractions in supine, sit- ting, and standing positions progressing up to 10 seconds knack	6 weeks	Supervision: Telephone weekly to insure adherence to PFMT program Drop out: 17/22: PFMT, 17/19 Control

PFMT women had about 5g less urine loss compared to the controls; however, the wide confidence intervals included the possibility of no difference [128]. Sari (2009), evaluating women with SUI and MUI, reported PFMT women had about 14g less urine loss compared to the control. Finally, Bidmead (2002) found women with SUI in PFMT group reported a pad weight change of 13g more than controls, based on a baseline comparison.

The only trial indicating a 24-hour home-based pad test [134] reported data as mean and SD. PFMT women reported about 28g less leakage than the controls but with wide confidence intervals that included the possibility of no difference. The only trial reporting a paper towel test [68,145] for either a moderate or a deep cough reported data as mean wet area with SD: the wet area for PFMT women as compared to the controls was approximately 20cm2 less on a medium cough and 21cm2 less on a deep cough. However, in both cases, the wide confidence intervals included the possibility of no difference.

Five trials have published long-term follow-up results ranging from three and six [141], seven [119], nine [130], 12 months [138], and one and five years [144]. Burns (1993) found that those experiencing mild leakages were more likely to have a return of symptoms in contrast with those experiencing moderate to severe leakages and were more likely to continue execising in order to continue to improve. Henalla (1989) reported 18% who returned the nine-month questionnaire had recurrent symptoms. Five years post-trial, Lagro-Janssen (1991) contacted 101 of the 110 women included in their original trial. Data from the 88 consenting women showed that the proportion of continent women (about 25%) was similar after five years, but the number with severe incontinence and those reporting leakage episodes increased from 3% to 18%. Two thirds of women (67%) remained satisfied with the outcome and did not want further treatment. Kim documented cure at 10 months (2011) and 12 months (2007) post-treatment, according to bladder diary. In the 2007 trial, 55% in the treatment group were cured at 12 months compared to 9.3% in the control; this suggests a greater likelihood of continence after one year in the PFMT group; at 10 months, 39.3% were cured at 7 month in the treatment group compared to 1.6% in the control group [119].

6. Summary

PFMT is better than no treatment, a placebo drug or an inactive control treatment for women with SUI, UUI, or MUI (Level of Evidence: 1). Women treated with PFMT were more likely to report a cure or improvement and a better quality of life; they also indicated fewer daily leakage episodes and had less urine leakage on the pad and paper towel test than those in the control group in immediately after treatment and in the long term. The effect of PFMT in Women with SUI does not seem to decrease with increased age: in trials with older Women with SUI it appeared both primary and secondary outcome measures were comparable to those in trials focused on younger women. Moreover, the treatment effect appears to be enhanced where PFMT is based on sound muscle training principles such as specificity, overload progression, correct contraction confirmed prior to training, and use of the Knack **(Level of Evidence: 4).**

7. Recommendations

Supervised PFMT should be offered as a first-line conservative therapy for women of all ages with SUI, urge or MUI **(Grade of Recommendation: A).**

b) Is one type of PFMT programme better than another?

As discussed in the last section, PFMT is more effective than no treatment, placebo or inactive control treatments for women with urinary incontinence, which leads to another question: What is the most effective PFMT programme? A number of factors can influence the outcome of a PFMT programme such as the way in which it is taught and/or supervised, the parameters of the actual exercises, and adherence to the training regime. In this section, different approaches to PFMT were considered based on a Cochrane systematic review [97]. The review compared the effects of different approaches to PFMT on the management of female SUI, urge, and MUI. From 34 potentially eligible trials thirteen were excluded: 2 because they were still on going and 11 due to inadequate information. The interventions from the 21 included trials are described in detail in **Table 2**.

Among the included trials the following variables were compared:

1. *Supervision of training:* amount of contact with health professional [146-151].
2. *Supervision of training:* individual versus group supervision [146,147,149,152-154].
3. *Exercise programme:* direct versus indirect exercises [124,125,150,152,153,155].
4. *Exercise programme:* generic versus individualised exercises [154].
5. *Exercise programme:* submaximal versus near maximal contractions [156].
6. *Exercise programme:* daily versus 3 times per week [157].
7. *Exercise programme:* addition of upright exercise position [158].
8. *Exercise programme:* addition of strength training to motor learning [159].

9. Exercise programme: addition of abdominal muscle exercises [157].

Table 2 Characteristics of studies comparing different PFMT programs

Study ID	Training Type	Training Program	Training Duration	Notes
Bø, 1990 [146]	Intensive PFMT (23) vs Home PFMT (29)	Intensive PFMT: Home PFMT + 45-minute PFMT exercise course in groups, once a week for 6 months. Course: sets of 8-12 VPFMC with 6-8 second holds in standing, sitting, lying, and kneeling with legs apart; 3-4 fast contractions added after held contraction. Home PFMT: 8-12 maximal VPFMC per set, 3 times a day	6 months	Drop out: Intensive PFMT: 3 Home PFMT:2
Borello-France, 2006 [158]	Supine PFMT (22) vs Different position PFMT (22)	Twice daily VPFMC in a supine position Twice daily VPFMC in a combination of positions: supine, sitting and standing	12 weeks	Drop out: 18%
Delgado, 2009 [161]	PFMT (20) PFMT + resistance (20)	PFMT : As below without device PFMT +resistance ; 5 quick and 5 slow (sustained), high-intensity contractions daily. Advised to hold contractions as long as possible, relaxing their PFM for an equivalent time before repeating the process. Intravaginal resistance: instructions to use the Pelvic-Toner Device concurrently whilst exer- cising.Two clinic visits and one phone call	16 weeks	Drop outs : Total 12/52 Dropouts by group: not stated.
de Oliveira, 2009 [154]	Individual supervised individual PFMT (30) Group supervised PFMT (30)	Individualised programme based on PERFECT scheme. 10 slow and 10 fast contractions with 10-sec rest; 10 alternating fast and slow contractions and 5 slow contractions with a cough VPFMC confirmed by DVP, in 'ortho- static' position. 10 contractions/5-sec hold/5-sec rest; and 20 contractions/1- sec hold/1-sec rest; and 5x strong con- tractions with stimulated cough. 1-minute interval between sets	12 weeks	Drop out: Total : 1 Dropouts by group :: not stated
Felicissimo, 2010 [149]	Unsupervised home PFMT (31) Group supervised and home PFMT (31)	Individual : Correct VPFMC con- firmed. PFMT: 10 contractions with 6- sec hold and 12-sec rest in different positions 9 times per day. Start with 90 contractions in first week, then 180 a day for remaining 7 weeks Group : As above, with addition of twice-weekly 50-min group exercise session	8 weeks	Dropouts: 1/31 unsuper- vised PFMT 2/31 super- vised PFMT

Table 2 Characteristics of studies comparing different PFMT programs (continued)

Study ID	Training Type	Training Program	Training Duration	Notes
Ferguson 1990 [160]	PFMT (10): home training PFMT+ resistance (10):	PFMT : same as below without resistance PFMT + resistance: exercises at home for strength and endurance, using audio-tape to guide exercises at home. Intrav- aginal resistance: use of intravaginal balloon. Weekly phone call	6 weeks	Dropouts: none
Gallo 1997 [162]	PFMT (43) PFMT+ audiotape (43)	Adherence strategy: audiocassette tape for use twice a day (contained verbal instruction and counted aloud 25 consecutive PFM contractions, with 10-sec hold and 10-sec relaxation) Encouraged to exercise 10 minutes twice a day, potential times suggested depending on lifestyle	4 to 6 weeks	Dropouts by group: 9/43 PFMT, 2/43 PFMT + audiotape
Ghoneim, 2005 [125]	PFMT (47) vs Imitation PFMT (50)	PFMT: 3 sets of 10 long VPFMC with 6-8 seconds hold, and 2 sets of 10 rapid VPFMC with 1-2 seconds hold, 4 days weekly + Knack. Imitation PFMT: Hip abductor muscle contraction for 6-8 seconds with feet crossed at the ankles. 3 sets of long and 2 sets of rapid contractions, 4 times weekly.	12 weeks	Drop out: PFMT: 9 Imitation PFMT : 9
Hay-Smith, 2002 [159]	Motor relearning PFMT(62) vs strength training PFMT (61)	Motor relearning: VPFMC in different body positions, preceding and sustained during different provocative activities. Strength training: 10-12 near maximal VPFMC, 6-to-8-second hold with equivalent rest, three times a day, at least three days a week	18 to 20 weeks	Drop out: Less than 5%
Hung, 2010 [150]	Unsupervised home PFMT (35) Supervised “Sapsford” PFMT (35)	Correct VPFMC confirmed. Oral in- struction in PFMT. No other detail given Correct VPFMC confirmed. ’Indirect’ + Participants in this group were ”asked not to perform iso- late voluntary pelvic floor muscle contraction exercise during the intervention period“	18 to 20 weeks	Drop out: Less than 5%
Johnson, 2001 [156]	Maximal PFMT(16) vs Sub-maximal PFMT (16)	Maximal PFMT: 10 minutes, three times a day, at 90% of maximal VPFMC intensity Sub-maximal PFMT: 15 minutes, three times a day, at 60% of maximum VPFMC intensity	6 weeks	Drop out: 14%

Table 2 Characteristics of studies comparing different PFMT programs (continued)

Study ID	Training Type	Training Program	Training Duration	Notes
Konstantinidou, 2007 [147]	PFMT individual (10) vs PFMT + group sessions (12)	PFMT individual: At home, 3 sets of fast contractions and 3-4 sets of slow contractions daily in lying, sitting and standing positions readjusted according to subject's progress. PFMT with group sessions: As above + weekly session in a group of 5	12 weeks	Drop out: PFMT: 5 PFMT + group session: 3
Liebergall 2005 [152]	PFMT (29) Paula method PFMT (30)	Weekly 30-minute lesson for 4 weeks in groups of 5. Encouraged to practise at home 15 min/day. Fortnightly phone call from physiotherapist Taught 'Paula' method of sphincter contraction. Weekly individual 45-min training for 12 weeks. Encouraged to practise daily 15 to 45 min	12 weeks	2/29 PFMT versus 2/ 30 Paula PFMT
Liebergall 2009 [153]	Individually supervised PFMT (117) Individually supervised Paula method PFMT (123):	Weekly individual sessions of 45 minutes and daily home exer- cises for 45 minutes for 12 weeks. Paula method was taught; first 2 steps were 'rhythmically' contracting the PFM 'with gradual intensity'. Last 3 steps in- volved contraction and relaxation of eyelids, movement of the mouth and fingers. VPFMC confirmed, based on ob- servation. 6 group classes (1 to 10 women) of 30 minutes each. Once weekly for first 4 weeks, 2 more classes in last 2 months. Exercises in different positions. Separate contractions of levator ani and anal sphincter. Prolonged, rapid and gradual contractions. 1 to 2 minutes between exercises	12 weeks	36/123 PFMT versus 21/117 Paula PFMT
Ng, 2008 [151]	PFMT (34) PFMT with phone call follow-up (n34)	Not clear if correct VPFMC con- firmed. Home PFMT progressing to 50 to 75 contractions three times a day. Taught urgency strategies. One-hour clinic visits twice a week for 4 weeks with nurse As above, then phone calls twice a week from the nurse after cessation of clinic visits to encourage exercise	6 months	10/44 PFMT versus 10/44 PFMT with phone calls
Ramsay, 1990 [124]	Direct PFMT (22) vs Indirect PFMT (22)	Direct PFMT: 4 maximum VPFMC with 4 second hold and 10 second rest, 1 set every waking hour. Indirect PFMT: As direct PFMT but comprising of hip abductor muscle contrac- tion with feet crossed at the ankles.	3 months	Drop out: None

Table 2 Characteristics of studies comparing different PFMT programs (continued)

Study ID	Training Type	Training Program	Training Duration	Notes
Savage, 2005 [155]	PFMT (4) vs Modified Pilates (6)	PFMT: 6 individual physiotherapy sessions of 30-45 minutes over a 12-weeks + home v PFMC Modified Pilates: Lumbopelvic stability training exercises taught using the modified Pilates method.	12 weeks	Drop out: PFMT: 1 Modified Pilate: 0
Sriboonreung, 2011 [157]	Daily home PFMT (23) Thrice-weekly home PFMT (22)	Eight to 12 maximal contractions with 6 to 8-sec hold with 6 to 8 fast contractions, with 6 to 8-sec rest, daily, 3 times a day As above except 3 sets a day, 3 days a week.	12 weeks	3/23 daily PFMT versus 3/22 thrice weekly PFMT
Sugaya, 2003 [163]	PFMT (23) PFMT + chime device (23)	1 minute of rapid contractions every 2 sec, followed by 1 minute of slow 10-sec contractions with 10-sec rests, performed 3 times a day. Adherence strategy: pocket size device with chime or blinking light to indicate time to exer- cise (3 times a day) and when activated leads person through PFMT programme, and kept record of exercise. Fortnightly follow-up As above with device	8 weeks	3/23 PFMT versus 2/ 23 PFMT with device
Wells, 1999 [129]	PFMT (71) PFMT with intravaginal resistance device (71)	PFMT: minimum of 80 VPFMC with 10- sec hold and 10- sec rest per day distributed in individual pattern throughout the day. Intravaginal resistance: Fitted with vaginal dilator to use as resistive device. Monthly clinic visits As above without device	5 months	30/71 PFMT versus 32/71 PFMT + device
Zanetti, 2007 [148]	PFMT HP unsupervised (21) vs PFMT HP supervised (23)	PFMT unsupervised: 10 VPFMC of 5-second hold and 5-second rest, 20 VPFMC of 2-second hold and 2-second rest, 20 VPFMC of 1 second hold and 1 second rest, and 5 VPFMC of 10-second hold and 10-second rest, followed by 5 strong contractions together with a cough, with one-minute intervals with each set. PFMT supervised: As above + VPFMC performed under guidance from a physiotherapist, twice a week, for 45 minutes.	3 months	Drop out: Not reported

Footnotes PFM = Pelvic floor muscle, VPFMC = voluntary PFM contraction, PFMT = PFM training, HP= Health professional Set = one episode or sequence of PFM contractions or training, including length of time of holding contraction, positions while performing contractions and number of repetitions of contractions.

10. *Exercise programme:* addition of intravaginal resistance device [129,160,161].

11. *Exercise programme:* addition of adherence strategy [162,163].

12. *Exercise programme:* addition of biofeedback: clinic biofeedback [120,141,164-166]; home biofeedback [136,167-169].

1. Quality of data

Of the 21 trials, one was a conference abstract [124] rendering it difficult to assess. Ten of the remaining 20 trials provided sufficient detail of the methods to generate a randomisation to ensure they were genuinely random [134, 148 - 150, 152 - 154, 156, 157, 170]. Of the remaining 10 trials, 3 were clearly not random [147,162,163]. The final 6 provided sufficient detail to ensure that allocation was concealed [125, 134, 150, 153, 159, 161].

Overall, in regard to random allocation and concealment, 6 trials were considered to have a low risk of bias [125, 146, 150, 153, 159, 161] and 4 had a high risk; in the remaining 11, the risk of bias was unclear.

Only three trials clearly stated that the outcome assessment was blinded for one or more of the outcomes of interest [150, 155, 159] and 2 stated that a lack of blind outcome assessment was a limitation [129,157].

None of the included trials was large and nearly two-thirds (13/21) were mid-sized, with only 20 to 50 participants per group. Four had fewer than 20 participants per comparison group [147,155,156,160]; one of which was reported as a pilot study [155]. The largest trial randomised 120 women to each of two trial arms: 240 participants in all [153].

2. Results:

Comparison 1. Supervision of training: amount of contact with health professional

Subgroup 1.1: additional group supervision

Four trials shared similarities in terms of the amount of time and frequency of the extra health professional contact: [146-149]. All four recruited women with urodynamic SUI. Three provided the same home-based PFMT programme and individual supervision to both trial arms, then investigated the effect of adding an additional supervised group exercise session (a 45-minute weekly exercise class [146]; a 50-minute twice-weekly exercise class [149]; a weekly group session [147]. The fourth also added a 45-minute twice-weekly exercise session [148]; however, it was unclear if this was offered individually or as a supervised group exercise session.

Subgroup 1.2: additional phone calls

Ng (2008) recruited women with MUI, offered the same home-based PFMT programme in both trial arms, and investigated the effect of adding twice-weekly phone call subsequent to the initial face-to-face contact with a health professional [151]. This was the only trial included in the second subgroup.

Subgroup 1.3: individual supervision versus no supervision (different PFMT)

In the trial of women with SUI or MUI, both arms differed in the amount of health professional contact and the type of PFMT programme used [150]. This was the only trial in the third subgroup.

- *Cure/no cure*: There was no statistically significant difference in the number of women reporting "no cure" comparing PMFT with and without additional group supervision, subgroup 1 [23,149]. As well, for subgroup 1.3, no difference was found between the supervised and unsupervised groups [150]. Ng [151], subgroup 1.2, reported the odds ratio (95% confidence interval) for the difference between the groups for their responses to 2 items from the BFLUTS (i.e., whether they did or did not have symptoms of SUI or urgency incontinence). For both items, the participants in the 'phone call group' (subgroup 1.2) had lower odds of reporting either SUI or urgency incontinence, suggesting that more women in the phone call group were asymptomatic.

- *No improvement/Improvement:* Women receiving additional group supervision (subgroup 1.1) were less likely to report incontinence [23,147-149]. Hung (2010) found women in the supervised group (subgroup 1.3) were less likely to report no improvement [150].

- *Leakage episodes:* Only one of the 4 trials investigating the effect of 'additional group supervision' (subgroup 1.1) measured leakage episodes [147]; similarly those receiving additional supervision reported fewer leakage episodes per day. Based on the Leakage Index [23,146], leakage was less in the group receiving additional supervision. Hung (2010), subgroup 1.3, also measured leakage episodes and found no differences between the supervised and non-supervised groups.

- *Pad and paper towel tests:* All 4 trials investigating the addition of group supervision used pad tests (90-second [146]; 20 minute [150] one-hour [148]; 24-hour [149]). Due to missing data, it was not possible to estimate differences between the treatment groups; where it was possible to calculate differences, these were not statistically significant.

Comparison 2. Supervision of training: individual versus group

Six trials were included in this comparison; however, each had at least one other difference between

trial arms (i.e., between the subjects and the controls within each trial), hence caution is required in interpreting the data.

Subgroup 2.1: individual versus individual+group supervision

The 3 trials in this subgroup (which were also included in Comparison 1, subgroup 1.1) used the same PFMT programme in both trial arms, supplemented with group supervision in one (in terms of frequency and total time) and individual supervision in the other [146,147,149]. Trials included women with SUI only.

Subgroup 2.2: individual versus group supervision (different PFMT)

The 3 trials in this subgroup differed in both supervision and the PFMT programmes [152-154]. Women with SUI [153,154] or mixed incontinence were included [152].

- *No cure/Cure:* There was no statistically significant difference in the number of women reporting 'no cure' between the group and individual supervision arms [146,149] in subgroup 2.1.
- *No improvement /Improvement:* In subgroup 2.1, women who received group supervision were more likely to report 'improvement' in their incontinence [146,147,149]. In subgroup 2.2, difference between group and individual supervision was found [154].
- *Leakage episodes:* In addition to the group versus individual supervision comparison, two trials measured leakage episodes; one used a different PFMT programme between the trial arms [154] and the other used the same programme for both [147]. De Oliveira [2009] indicated no difference between groups while Konstantinidou [2007] reported that the women who had received group supervision indicated fewer leakage episodes per day.
- *Pad and Paper towel test:* All 3 trials in subgroup 2.1 used pad tests (90-second [146]; and 24-hour [147, 149]). The differences, where they could be calculated, were not statistically significant. All 3 trials in the subgroup 2.2 used a 1-hour pad test; and one used a standardised bladder volume rather than maximum bladder capacity [154]. The overall pattern was one of no difference between the groups.

Comparison 3. Exercise programme: direct versus indirect exercises

This comparison encompassed four subgroups.

Subgroup 3.1: PFMT versus sham/imitation

The first comprised 2 trials in women with SUI that compared PFMT versus sham or imitation PFMT treatments [124,125].

Subgroup 3.2: PFMT versus the 'Paula method'

The second subgroup included 2 trials comparing PFMT versus the 'Paula method' in women with SUI [153] or SUI and mixed incontinence [152].

Subgroup 3.3: PFMT versus the 'Sapsford' approach

The third subgroup contained a single trial that compared PFMT with the 'Sapsford' approach in women with SUI or mixed incontinence [150].

Subgroup 3.4: PFMT versus Pilates

The fourth subgroup also comprised a single trial; a pilot study that compared PFMT versus Pilates in women with SUI [155].

- *No cure/Cure:* No difference between 'direct' PFMT and the 'Sapsford' approach was found in the single trial in subgroup 3.3 [150].
- *No improvement/Improvement:* The pooled data from the two trials in subgroup 3.1 (PFMT versus sham/imitation) did not show a statistically significant difference in favour of either trial arm [124, 125]. In contrast, Hung [2010] in subgroup 3.3 found that women in the 'Sapsford' approach group (with more health professional contact) were more likely to report improvement. Savage [2005], subgroup 3.4, did not report on improvement but, instead indicated there was no difference between the groups in terms of satisfaction.
- *Leakage episodes:* Hung [2010], subgroup 3.3, found no difference between the trial arms (median 0 leaks per day, IQR 0 to 0.3, in both groups). In terms of a less than 50% reduction in leakage frequency, neither Ghoniem [2005], subgroup 3.1, nor Liebergall [2009], subgroup 3.2, found differences between groups in weekly or more frequent incontinence episodes.
- *Pad and paper towel test:* Four trials reported pad test data: 20 minute [150]; 1 hour [152,153]; or type not known [124]. The data of two [150] subgroup 3.3, and subgroup 3.2 [124], could not be used to calculate an estimate of effect. Neither of Liebergall's studies [152,153] found a difference in the mean change from baseline.

Comparison 4. Exercise programme: generic versus individualised exercise

This comparison included one study [154] in which women were randomised to either individualised PFMT provided on a 30-minute twice-weekly clinical visit or to a generic PFMT programme offered through a 45-minute twice-weekly group exercise class.

- *No cure/ Cure:* No data was reported.
- *No improvement/ Improvement:* No difference between the generic and individualised exercise trial arms was reported [154].
- *Leakage episodes:* There were no differences in the number of leakages between the generic and individualised exercise trial arms in a 24-hour trial period [154].
- *Pad and paper towel test*: There was no difference in a 1-hour pad and cough test between the trial arms [154].

Comparison 5. Exercise programme: submaximal versus near maximal contractions

One study assigned women with SUI to PFMT programmes that were the same in all aspects with one arm adding either near maximal PFM contractions or submaximal contractions [156]. Both groups received the same amount of contact from health professionals.

- *Not cured/ Cured:* No data was reported for this outcome.
- *No improvement/ Improvement:* No data was reported for this outcome.
- *Leakage episodes:* No statistically significant differences reported between the exercise groups for leakage episodes in a 24-hour period [156].
- *Pad and paper towel test:* Pad weight (10-hour pad test) did not differ between the groups.

Comparison 6. Exercise programme: daily versus 3 times per week.

A new trial [157] compared PFMT programmes that were the same in all aspects except one group was asked to do daily exercise and the other 3 times a week. Both groups had the same amount of contact with health professionals.

- *Not cured/ Cure:* There was no statistically significant difference between the groups in terms of the number of women who reported 'no cure'.
- *No improvement/ Improvement:* None of the women in either group indicated any significant difference in improvement..
- *Leakage episodes:* No data was reported.
- *Pad and paper towel test:* There was no difference between the groups on a 1-hour pad test.

Comparison 7. Exercise programme: addition of upright exercise position

Two PFMT programmes were compared that were the same in all aspects except one group was asked to exercise only in the supine position while the other alternated exercise sets between the supine, sitting and standing positions [158]. Both groups had the same amount of contact with health professionals.

- *No cure/ Cure:* No data was reported for this outcome.
- *No improvement/ Improvement:* No data was reported for this outcome.
- *Leakage episodes:* There was no statistically significant difference between the exercise groups for leakage episodes in a 24-hour period.
- *Pad and paper towel tests:* There was no difference between the groups for the mean change in pad weight gain on a 1-hour pad test.

Comparison 8. Exercise programme: addition of strength training to motor learning.

Women with SUI or MUI took part in two motor-learning PFMT programmes that were the same in all aspects except one group undetook additional strengthening in PFMT. Both groups had the same amount of contact with health professionals..

- *No cure/ Cure:* There was no difference between the groups in terms of the number of women who reported 'no cure'.
- *No improvement/ Improvement:* There was no difference between the groups in number who reported 'no improvement'. There were no differences in other self-reported improvement outcomes: satisfaction with treatment, comfort with continuing the training and desire for further treatment although in this last, the women in the motor learning PFMT group were less likely to want to continue.
- *Leakage episodes:* There was no statistically significant difference between the groups for the number of leakage episodes per day.
- *Pad and paper towel tests:* There was no difference between the groups on either a paper towel test or a 24-hour pad test.

Comparison 9. Exercise programme: addition of abdominal muscle exercise Sriboonreung (2011) compared two PFMT programmes that were the same in all aspects except one group was asked to undertake additional abdominal muscle exercises (these were not described in further detail) [157]. Both groups had the same amount of contact with health professionals.

- No cure/ Cure: There was no statistically significant difference between the groups in terms of the number who indicated 'no cure'.
- *No improvement/Improvement:* There was no statistically significant difference between the groups.

- *Leakage episodes:* No data were reported.
- *Pad and paper towel tests:* There was no difference between the groups on a 1-hour pad test.

Comparison 10. Exercise programme: addition of intravaginal resistance device One new trial was added to this section [161] for a total of three which compared two PFMT programmes that were the same in all aspects except one group used an intravaginal device design to increase the resistance to the PFM contraction [129,160,161]. The resistance devices included a spring-loaded device with two limbs [161] an intravaginal balloon [160], and a vaginal dilator [129]. In all three, each arm had the same amount of contact with health professionals. The women in one study had SUI [Ferguson 1990] and in the others SUI or MUI [Delgado, 2009; Wells, 1999].

- *No cure/ Cure:* There was no statistically significant difference between the groups in terms of the number of women who indicated 'no cure' [129,161].
- *Not improved/ Improvement:* There was no statistically significant difference between the groups in terms of the number of women who indicated 'no improvement' (129,161].
- *Leakage episodes:* No statistically significant difference between the two treatment groups was found [129].
- *Pad and paper towel tests:* All three reported pad test data (30-minute and 24 hour [160,161] or unspecified duration [129]. None of these found statistically significant differences between the treatment groups.

Comparison 11. Exercise programme: addition of adherence strategy

Adherence strategies such as audiotape [162] or small chiming (alarm) device [163] have been tried. The PFMT programmes were [163] or appeared to be [162] the same for both trial arms. Both trial arms in each study had the same amount of contact with health professionals.

- No cure/Cure: No data was reported for this outcome.
- No improvement/Improvement: The group using the devices was less likely to report 'no improvement' post treatment.
- Leakage episodes: No statistically significant difference was found between the groups for the number of leakage episodes in 24 hours [163].
- Pad and paper towel tests: The average amount of leakage on a 1-hour pad test was less in the groups using the devices post treatment.

Comparison 12 Teaching programme: Addition of biofeedback

No new studies were found that compared biofeedback alone to PFMT plus biofeedback in either the home or clinic. Three studies were excluded based on the BF group differing from the no BF group in terms of treatment intensity (e.g., number of clinic visits) [122,171,172] or supervision (i.e., group versus individual teaching) and absence of between group analyses [173].

Five trials used clinic based BF in the treatment of predominantly SUI symptoms [141,164,165], predominantly UUI [120], or OAB with UUI [166]. In four, the home PFMT programme was the same in both groups, with the addition in one arm of clinic BF once every two weeks [120], once a week [141,165], twice a week [166] or three times a week [164].

Treatment durations in both arms were four [164,165], eight [120,141] and 12 weeks [166]. In one, there was more supervisory HP contact with the BF group than with the PFMT alone group [165].

Of the five clinic based BF trials, three had adequate random allocation concealment [120,141,164,166] and three had blinded outcome assessors [120,164]. Three randomised between 25 and 74 women to each group [120,141,165,166], while others randomised less than 25 women per group [164,165]. Withdrawals or losses to follow up were none [164,165], less than 10% [141], less than 15% [120,165,166]. All women were assessed post-treatment; further follow up was conducted at three and six months [141] or at three months and two to three years [165].

There were no new home based trials added to this section so there remains a total of four. Random allocation concealment was adequate in just one [167], and outcome assessors were blind for some or all of the outcomes in two [167,168]. The number of women allocated to the comparison groups was 20 or less [136,168], 40 women in the BF group and 20 in the PFMT [169] or 50 or more per group [167]. Two had complete data sets on trial completion [136,168], one reported 9% withdrawal [167], and 33% dropped out of another [169].

With regard to clinic BF, two of the five trials reported significantly better outcomes with the addition of BF to PFMT. Based on pad weight in women with urodynamic SUI at one to two years after treatment, five of 19 women in the BF group and none of the 14 women in PFMT reported cure [165]. However, the BF group had 4 treatment sessions whereas the PFMT group had 2-3 sessions. In women with OAB there were changes in the total score on the KHQ with the addition of BF, but no statistically significant differences between the groups on any of the nine subscales [166]. Patient-reported cure or improvement was 50% for the BF

group and 38% for PFMT alone; a statistical comparison was not reported [166].

Three trials, including the two largest trials, reported significant improvements in incontinence with PFMT with or without BF, but no significant differences between groups [120,141,164].

For the home BF trials, only one reported a significant effect for the addition of BF [168]. In the others, including the largest trial [167]both groups had significant improvements, but no differences between groups.

A 2011 Cochrane review on feedback or biofeedback to augment PFMT [174] included 24 trials involving 1,583 women and concluded that women who received PFMT with BF were significantly more likely to report that their UI was cured or improved compared to those who received PFMT alone. However, this review included trials in which the treatment groups differed on parameters other than BF, and the authors caution that women in the BF groups commonly had more contact with the health provider. Thus, more research is needed to determine whether differences are due to BF or other differences such as intensity, approach, or contact with the health professionals.

With regard to clinic based BF, studies were inconsistent. The larger trials indicated no statistically significant differences between BF assisted and non-BF groups for self-reported cure, cure/improvement, or leakage episodes per day or quality of life **(Level of Evidence: 1)**. This pattern appeared to be consistent across trials that recruited women with SUI, UUI, or MUI. There were a similar number of trials addressing the effect of home BF, but fewer data. In a single robust trial there were no statistically significant differences between home BF and non-BF groups for self-reported cure, cure/improvement, or quality of life for women with urodynamic SUI **(Level of Evidence: 2).**

3. Recommendations

Clinicians should provide the most intensive HP led PFMT programme possible within service constraints because HP taught and supervised programmes are better than self-directed programmes, and more HP contact is better than less **(Grade of Recommendation: A).** Although studies are inconsistent, there does not appear to be a clear benefit of adding clinic **(Grade of Recommendation: A)** or home based BF **(Grade of Recommendation: B)** to a PFMT programme.

4. Conclusion

Based on the limited available data it appears that PFMT with regular (e.g. weekly) supervision is better than PFMT with little or no supervision. However, the data were unclear if supervision is more effective in individual or group settings.

Cautiously, we conclude that voluntary PFM contractions are better than exercises that facilitate co-contraction of the PFM muscles (e.g. crossing the ankles and pulling the legs apart). Further, 'indirect' methods (e.g. the 'Paula method' or 'Sapsford' approach) did not appear to be better than direct PFM contractions, noting that some study data were confounded by differences in the amount of contact time with health professionals. Moreover, and tentatively, we found there was no benefit from adding intravaginal devices to increase resistance in PFMT.

This review underlines the fact that existing evidence is insufficient to make any robust recommendations about the best approaches to PFMT, beyond the fact that the amount of health professional contact may influence women's perceptions of their improvement.

5. Implications for research

Comparisons of PFMT approaches are, de facto, comparisons of two active treatments. Therefore, it is difficult to determine which approach is best, unless (a) the differences in outcome are large or (b) the trials are powered to find small to moderate differences in outcomes that would be indicative of the need for larger trials. Although finding the best approach to PFMT has been identified as a high priority research area, large, costly trials may not be the best use of research funds, particularly where the difference in outcomes between two active treatments is expected to be small. Therefore, the highest research priority should be to investigate the effect of supervision on PFMT. In addition to clinical effectiveness, this is an important question because of resource implications, both financial and human, for health-service delivery.

6. Recommendations

Clinicians should provide the most intensive supervision-led PFMT programme possible within service constraints because supervised PFMT programmes are better than those with little or no supervision. (Grade of Recommendation: A).

c) Is PFMT better than other treatments?

Trials were considered for inclusion in this section if they compared PFMT with another stand-alone intervention, e.g. vaginal cones, bladder training, drug therapy. Of note is that there are 37 RCTs comparing PFMT with another stand-alone treatment but few recent studies since the last update. For this review, four were excluded, two as conference abstracts [175,176], one reported in two conference abstracts with inconsistent data [177], and one compared PFMT and vaginal cones versus EStim [178].

The 33 trials addressed the following comparisons:

- PFMT versus vaginal cones (VC) [107, 122, 134, 140, 169, 175, 179-183]

- PFMT versus EStim (EStim) [130, 132, 134, 140, 166, 184-188]
- PFMT versus bladder training (BT) [128,189,190]
- PFMT versus drug [125, 130, 131, 142, 188, 191-193]
- PFMT versus surgery [194]

(a) PFMT versus VC: Eleven trials compared PFMT with VC [107,122,134,140,169,175,179-183,185]. The details of the VC and PFMT programmes for each trial are presented in **Table 4**.

(b) PFMT versus EStim: 10 trials compared PFMT with EStim in women with UI [186] SUI [134, 184, 185], urodynamic SUI [130, 132, 140], mixed UI [187] or OAB [166, 188]. There were different PFMT and EStim protocols in each study.

Two trials used interferential current, two to three times weekly, 30 minutes, 10-50Hz to PFMT (weekly PFM exercise courses and daily home exercises), for four to six weeks [185] or 20 minutes weekly for 10 weeks, 0-100Hz, at maximal tolerated intensity to PFMT (five PFM contractions with five second holds, hourly, every day for 12 weeks) [130]. Another applied external (extra-vaginal and lumbar) electrodes to deliver an unknown type of current (10 minutes, three times weekly, intensity increased until noticeable PFM contraction and patient added voluntary PFM contraction) versus PFMT (no details given), for six weeks [132].

The remaining trials all delivered the stimulation using a vaginal electrode. The comparisons were, in approximately ascending order of duration of EStim:

- 20 minutes, twice weekly, biphasic symmetric intermittent current at 10Hz, pulse duration 400 microseconds, duty cycle 10 seconds on and five off, maximum tolerated intensity, versus PFMT (no details given), for 12 weeks [166]
- 20 minutes, twice per week, biphasic intermittent current at 10Hz, pulse duration 1 millisecond, unidentified number of seconds of contraction and, duty cycle, at maximal tolerated intensity up to 100 mA [188]
- 20 minutes, three times weekly, biphasic intermittent current at 50Hz, pulse duration 0.5 millisecond, 5 second contraction, duty cycle one to two, at maximal tolerated intensity up to 100 mA [140]
- 30 minutes, three times weekly, biphasic intermittent current at 50Hz, pulse duration one millisecond, two second contraction, duty cycle one to two, at maximal tolerated intensity up to 100 mA (for predominant SUI) or the same stimulation at 20Hz (for predominant UUI), versus PFMT (no details given), for eight weeks [186]
- 30 minutes daily, biphasic intermittent current at 50Hz, pulse duration 0.2 milliseconds, individualised duty cycle depending on ability to hold PFM contraction, at maximal tolerated intensity up to120mA, versus PFMT (three times daily, eight to 12 near-maximal PFM contractions with six second hold and six to eight second rest, with three to four fast contractions at the end of every contraction in addition to weekly exercise class), for six months [134]
- up to 60 minutes, twice daily, asymmetric balance biphasic intermittent current at 12.5 and 50Hz, pulse duration 300 microseconds, five second contraction time with two second ramp up and one second ramp down, duty cycle one to two, intensity to 80mA, versus PFMT (daily, 60 slow and quick PFM contractions), for four months [187]
- six to eight hours per night, intermittent current at 12, 20 or 50Hz, versus PFMT (six to eight times daily, five to 10 maximal PFM contractions with five second hold and five seconds rest, and one sub-maximal contraction with 30 to 40 second hold), for six months [184].

Amount of HP contact was the same for both groups in two trials [130,140], greater for EStim in two [132,185], and greater for PFMT in another [134,188]. Any differences were not clear in the other four trials.

(c) PFMT versus BT: Three trials compared PFMT with BT in women with SUI [190], SUI and/or DO [189] or UI [128]. BT comprised a voiding schedule with weekly progression [128,189,190]. Wyman (1998) also included urge inhibition techniques (affirmations, distraction and relaxation). Sherburn trial added to voiding schedule, education on normal bladder control and voiding parameters, skin care, pad usage, fluids and fluid intake, optimal toileting position, voiding dynamics, and relaxation, distraction and breath control as part of the deferral strategies.

In the three trials BT was compared with:

- PFMT with clinic based BF, and a twice daily home PFMT programme of five fast (three second holds) and 20 sustained (10 second holds with 10 second rests) PFM contractions, PFM contraction for urge suppression and with increases in intra-abdominal pressure [Wyman, 1998].
- PFMT with clinic based BF, and daily home PFMT of 30 PFM contractions for strength and endurance (12 second holds) [Yoon, 2003].
- PFMT with weekly group class, and daily home PFMT prgram. The PFMT execise class included intensive PFMT, combining motor control, strength, endurance, power and functional training in a variety of different body positions [Sherburn, 2011].

Treatment duration, and amount of HP contact, was the same in both arms of all three trials, with treatment duration ranging from eight (Yoon, 2003), 12 (Wyman, 1998), and 20 weeks (Sherburn, 2011).

(d) PFMT versus drug therapy: Eight trials compared PFMT to drug therapy in women with SUI [125, 130, 131, 191, 192] or UUI [142, 188, 193, 195, 196].

The trials for SUI used several different drugs. In two, premarin (conjugated equine oestrogens) 2g per night for six or 12 weeks was compared to PFMT [130, 131]. In one of these [130], the PFMT was comprised of a daily home programme of five PFM contractions with five second holds per hour; in the other [131] PFMT was not described. Another trial compared phenylpropanolamine hydrochloride for four weeks versus six months of PFMT (90 to 160 PFM contractions with 10 second hold and 10 second rest distributed throughout the day) [192]. Ishiko [2000] compared clenbuterol (20mg bid) versus PFMT (10 minutes daily), for 12 weeks [191]. One study compared duloxetine (4mg bid, plus sham PFMT) versus PFMT (four times weekly, three sets of 10 six to eight second contractions and two sets of 10 one to two second contractions) for 12 weeks [125].

Three trials on UUI used oxybutynin(193) [142,188,193]. Doses and PFMT programs varied: oxybutynin chloride (2.5mg tid, progressed to maximum 5mg tid) versus PFMT with urge suppression strategies for eight weeks [142]; extended-release oxybutynin (5mg/day) versus PFMT (plus lengthening voiding intervals and urge strategies) for 3 months [193]; and oxybutynin chloride (5mg bid, progressed to maximum 5mg tid) to PFMT (and to functional electrostimulation) for 12 weeks [188].

Four trials had approximately the same amount of HP contact in drug and PFMT groups [125,130,142,191]; in one, this was not clear [130]. Wells [1991] assessed treatment effect after four weeks in the drug group, and six months in the PFMT group. Kafri [2007] provided 5 sessions for the PFMT group, but not for the drug group. Arruda [2008] provided two sessions per week with physiotherapist for the PFMT group and visits every 4 weeks for the drug group.

(e) PFMT versus surgery: Only one trial, published, in 1986, has compared PFMT to surgery [197]. The surgical technique was based on the type of defect identified: Burch colposuspension for anterior suspension defects and vaginal repair for posterior bladder descent. Women with both defects had a combined Burch and vaginal repair procedure. No details on the PFMT parameters were provided; women had five or more group sessions with a physiotherapist.

1. Quality of data

(a) PFMT versus VC: Adequate allocation concealment was reported by five: [107,122,134,140,180]. Three indicated that outcome assessors were blinded [134,140,183]; only some of the outcome assessments were blinded in two [107,122]. Sample sizes ranged from fewer than 40 women [107, 134,140,169,175,179,180,182,183], 50 [181] to 79 per group [122]. There were dropouts in both the PFMT and VC groups in all trials except Gameiro's (2010) [181] where no details were provided or in Cammu's (1998), in which all of the dropouts were from the VC group. Dropout rates were higher in the VC groups for several [169,175,179,180,183]; conversely, they were higher in the PFMT group for others [107,122,134,140,182]. Only one trial reported any follow-up beyond the post-treatment evaluation, and this, at 6 and 12 months post treatment [181].

(b) PFMT versus EStim: Of the eight trials, three reported adequate random allocation concealment and blinding of outcome assessors; samples sizes ranged from 10 to 20 and 35 women per group. Four trials appeared to have no dropouts [130,132,184,187]. Others reported 5% [186], 10% [140], 12% [134,188], 13% [166] and 19% [169]. All women were assessed post treatment; follow up was at nine months and one year [130] and four years [184].

(c) PFMT versus BT: Adequate random allocation concealment was reported in one trial [190]; outcome assessors were blinded in two [128,190]. Samples sizes ranged from 15 to 20 women [128], 43 to PFMT and 41 to BT [190] to 70 women per group. Dropouts were approximately 4% for Wyman (1998) and 12% for Yoon (2003) and 8% for Sherburn (2011). All women were assessed post treatment, and Wyman (1998) followed-up three months later (i.e. six months after treatment began).

(d) PFMT versus drug therapy: Random allocation was concealed in two of the eight trials [125,196]. Outcome assessors were blinded in two [125,142]. Five trials randomised 25 or fewer participants per group [130,131,188,191,193]; one randomised approximately 50 per group [125]. The two largest randomised about 80 [192] or 85 women per group [142]. Dropout rates were: 0% [130], 14% [142], 15.9% [193], 16% [191], 16.9% [196], 25% [192] and 36% [125]. Drop out rates were not reported in two [131,193]. Most trials assessed outcomes immediately post-treatment and three had longer follow up of nine months [130], one year [188], and 21-month [193] although in this last trial most participants had discontinued drug therapy after active intervention.

(e) PFMT versus surgery: It was not clear if allocation was adequately concealed, or if the outcome assessors were blinded. Approximately 25 women were in each comparison group with no dropouts at four months (post treatment assessment). There was further long-term follow-up at one year, then four to eight years [197].

2. Results

(a) PFMT versus VC: The comparative results in seven of the 11 studies were inconsistent. For cure,

one trial favoured PFMT [134]. Six favoured neither PFMT nor VCs [107, 122, 140, 179, 182, 183]. Pooled data from these eight trials showed statistically significant heterogeneity.

For *cure/improvement*, pooled data in six of the 11 trials showed no statistically significant differences. In four, PFMT was better than VCs in terms of daily leakage episodes. And, two others [140,181] no significant differences in terms of incontinence-specific quality of life measures (I-QoL) and the number of incontinence episodes were found.

Three reported adverse effects associated with cones such as the inability to use then, pain, vaginitis, bleeding, a sense of unpleasantness [134,180] or inconvenience [183].

[b) PFMT versus EStim: Pooled data from three trials of women with SUI found self-reported cure was more likely with PFMT [134, 184, 187], although only one found a statistically significant difference when data from the trials was considered individually [134]. It was not clear if the cure data reported by Hofbauer (1990) were derived from a symptom scale or a voiding diary; these data were therefore excluded. Pooled data from three trials in women with also found self-reported cure/improvement was more likely in PFMT women [134,184,185]; again only Bø (1999) found a statistically significant difference when trial data were considered individually. At 6 months, QOL (as measured with I-QoL Questionnaire) increased significantly both in the PFMT group 28.4% and in the EStim group 32.4% but there was no significant difference between the groups [140]. Leakage episodes and quality of life (Social Activity Index) were not statistically significant in one study [134]. At nine months post treatment, Henalla (1989) found that three out of 17 PFMT women and one out of eight in the EStim group reported recurrent symptoms. Side effects related to EStim included vaginal irritation and/or bleeding [134,184,187].

Spruijt [2003] [186] recruited women with SUI, UUI or MUI and Wang (2004) [166] women with UUI. Neither found a statistically significant difference between the groups for self-reported cure/improvement' although Wang indicated women in the PFMT group had statistically significantly fewer leakage episodes per day. EStim produced "physical and emotional stress" in the elderly women in the Spruijit trial. On the KHQ there were no statistically significant differences in general health perception, incontinence impact, role limitation, physical limitation, social limitation, and personal relationship, but the EStim group had statistically significant better scores for emotions, sleep/energy and severity measures. In the Arruda (188) study [188], 52% and 76% of the women randomised to the EStim and PFMT groups, respectively, claimed to be satisfied after 12 weeks of the study treatment period. Further, there was a significant decrease in the urge-incontinence episodes, the daily number of urinary pads. However, there was no significant difference in any of these measures between the groups.

(c) PFMT versus BT: Wyman [1998] [189] recruited women with SUI, UUI or MUI. While more women in the PFMT group reported symptomatic improvement or fewer leakage episodes the difference was not statistically significant post-treatment or three months later. Sherbrun recruited women with SUI. Women in the PFMT group reported significantly lower amounts of leakage on the stress test , improved symptoms and bother and greater perception of change after 5 months than the BT group (Sherburn, 2011). No adverse event data were reported in either trial. Yoon (2003) [128] did not report any data for the outcomes of interest.

(d) PFMT versus drug: Neither of the two trials comparing vaginal oestrogens versus PFMT in women with urodynamic SUI reported data for the outcomes of interest [130,131]. Of those that responded to a follow-up questionnaire at nine months, three out of 17 PFMT women and three women using oestrogens reported recurrent symptoms. Adverse events were not reported in either trial.

Two older trials that compared an adrenergic agonist and PFMT in women with SUI or MUI were previously reported in ICI 2009. No significant differences between groups were reported [129,191].

Duloxetine had a significantly greater impact in decreasing incontinence episodes than PFMT (57% versus 35% median decrease between drug and PFMT respectively) [125]. However post-treatment data collection began immediately after treatment initiation, before the effects of PFMT could be expected to occur. There were no significant differences between the treatments with respect to Incontinence Quality of Life (I-QoL).

In the three trials that compared PFMT to oxybutynin, PFMT groups had similar or better outcomes on most parameters. In the largest of these, a comparison of PFMT and oxybutynin in older women with DO or DO with urodynamic SUI, women in the PFMT group had significantly greater reduction in incontinence episodes compared to those in drug treatment and fewer incontinence episodes per day [142]. Women in PFMT were more likely to report that they were "much better" but cure rates did not differ significantly. Side-effects were common among women in the drug group, particularly dry mouth.

One trial reported that the PFMT group had better outcomes for voiding frequency, but not for incontinence episodes [193]. Follow-up at 21 months showed that the PFMT group maintained or improved their voiding frequency, whereas the drug group regressed to baseline levels. However, most participants had discontinued the drug. Similarly, another trial reported that subjective symptom improvement was almost identical in the PFMT and

drug groups *(77%, 76%, respectively)* [188]. Changes in incontinence episode frequency favored the PFMT group, but were not significantly different.

(e) PFMT versus surgery: At four months PFMT women with urodynamic SUI were less likely to report cure than women who had surgery, although there was no statistically significant difference in the proportions reporting cure/improvement. At 12 months, 10/24 from the PFMT group were satisfied with initial therapy, versus 19/26 randomised to surgery. Long-term data (four to eight years) were not presented by group allocation. Adverse events were associated with surgery: new UUI, retropubic or pelvic pain, or dyspareunia [197].

3. Summary

In the 11 trials that compared PFMT with VCs in women with SUI, no consistent pattern emerged in the data. Further, data on self-reported cure in eight of the trials were inconsistent and there was no difference in the pooled data from six trials for self-reported cure/improvement. Notably, there were in fact fewer daily leakage episodes with PFMT in the pooled data from three trials **(Level of Evidence: 1)**.

PFMT with EStim in women with SUI was compared in six trials. Pooled data demonstrated that self-reported cure and cure/improvement were more likely in PFMT than in EStim groups **(Level of Evidence: 1)**. It is worth noting that only one trial individually demonstrated a statistically significant difference in these outcomes and there was more health professional contact in the PFMT arm. There were no statistically significant differences between PFMT and EStim groups for leakage episodes or quality of life, based on a single trial on MUI **(Level of Evidence: 2)**. In the one trial that recruited women with SUI, UUI or MUI self-reported cure/improvement rates were not statistically significantly different **(Level of Evidence: 2).** Self-reported cure and cure/improvement rates and satisfaction were not statistically significantly different in the 2 trials in women with UUI, although PFMT women had fewer leakage episodes per day, and women in the EStim group had better quality of life in three of the nine domains measured on the KHQ (166). **(Level of Evidence: 2)**. Some women reported adverse events attributable to ES.

PFMT and BT was reported in three but only two included data of interest. In women with SUI, symptomatic improvement, leakage episodes and quality of life were statistically significantly better in the PFMT group **(Level of Evidence: 2)**. In contrast the study that recruited women with SUI, UUI and MUI did not find statistically significant differences between the groups **(Level of Evidence: 2)** .

There is insufficient evidence to determine if PFMT is better than vaginal oestrogens. Neither trial that compared an adrenergic agonist with PFMT in women with SUI or MUI found a difference in self-reported cure/improvement and adrenergic side effects were bothersome **(Level of Evidence: 2)**. One trial of PFMT versus oxybutynin in women with DO or DO with urodynamic SUI found women doing PFMT were more likely to report improvement and have fewer leakage episodes per day after treatment **(Level of Evidence: 2)**. Many women taking oxybutynin reported drug-related side effects. One trial compared a serotonin-norepinephrine reuptake inhibitor (duloxetine) with PFMT and while women who took the drug had fewer leakage episodes, there was no difference in terms of quality of life between the two groups and drug side effects were sufficient to discontinue treatment in some women. **(Level of Evidence: 2)**.

Based on one trial it seemed self-reported cure was more likely after surgery than PFMT for women with urodynamic SUI, but no statistically significant difference in the proportion of women reporting cure/improvement **(Level of Evidence: 2)**. There was insufficient detail about the PFMT programme to make a judgment about how effective it might have been.

4. Recommendations

For women with SUI:

- PFMT is better than EStim as first line conservative therapy, particularly if PFMT is intensively supervised **(Grade of Recommendation: B)**.
- PFMT is better than BT as first line conservative therapy **(Grade of Recommendation: B)**.
- PFMT and duloxetine are both effective in first line therapy, although PFMT is better because of the side effects experienced with the drug **(Grade of Recommendation: C).**
- PFMT and surgery are both effective therapies, although PFMT is better as first line therapy because it is less invasive **(Grade of Recommendation: C)**.

For women with SUI or MUI:

- PFMT is better than VC as first line conservative therapy **(Grade of Recommendation: B)**.

For women with UUI or MUI:

- PFMT,and BT are effective first line conservative therapy **(Grade of Recommendation: B)**.
- PFMT is better than oxybutynin as first line therapy **(Grade of Recommendation: B)**.

For women with UUI:

- PFMT,and BT are effective first line conservative therapy **(Grade of Recommendation: B)**.

Larger, good quality trials are needed to address each of the above comparisons if these are of interest to women. In planning comparisons researchers should consider carefully the potential impact of dif-

ferent levels of supervisory intensity between groups, particularly in comparisons of conservative therapies. A comparison of surgery and PFMT might be least useful, because PFMT is usually first-line therapy with surgery reserved for those in whom PFMT was unsuccessful or is not the treatment of choice.

d) Does the addition of PFMT to other treatments add benefit?

In this section, the effects of PFMT combined with therapy A versus therapy A alone, are compared to address the additive benefit of PFMT. Nine RCTs were found, and three were excluded: no useable data [198]; men and women and the data were not reported separately [199] and a combination BT/PFMT programme [200].

(a) PFMT⁄VC versus VC: Two trials, in women with urodynamic SUI [201]or SUI [107], compared combined PFMT⁄ VC versus VC. In both arms of each study the recommended VC regime was twice daily for 15 minutes, with cone weight progressing from 20g to 70g [201] or 100g [107]. Both PFMT programmes asked women to do 100 PFM contractions per day with 10 contractions 10 times a day [201], or a combination of fast and slow contractions [107]. Treatment duration was 12 weeks in both arms of both studies.

(b) PFMT⁄EStim versus EStim: No new trials have been published on the topic since the last review. In women with urodynamic SUI, EStim (10 minutes, three times weekly, sufficient intensity to provoke a visible contraction to which the patient added their own PFM contraction, extravaginal and lumbar electrodes) was compared to PFMT⁄ES (daily PFMT home programme (not specified) and a twice weekly exercise class plus the same ES programme) [132]. Treatment duration was six weeks in both arms.

(c) PFMT⁄BT versus BT: No new studies were found. In women with urodynamic SUI, or urodynamic SUI with DO, Wyman (1998) compared BT (progressive voiding schedule, advice on urge inhibition techniques such as affirmations, distraction and relaxation) to PFMT⁄BT (twice daily PFMT, maximum of 10 fast contraction with three second holds and 40 sustained contractions with 10 second holds in addition to bladder training as above). The combined PFMT⁄BT group began with BT and added PFMT in the 3rd week of the intervention. Women in both groups received the same preliminary education programme and treatment duration was 12 weeks in both arms [189].

(d) PFMT⁄drug versus drug: Two previously reported trials compared PFMT⁄drug (beta(2)-adrenergic agonist (clenbuterol); duloxetine) [125,191].

Two new trials compared PFMT⁄drug to drug alone in women with UUI [202,203]. One was a two-stage, multi-site RCTI [203]. In Stage 1, women received tolterodine (4 mg/day) versus tolterodine plus PFMT with urge suppression strategies (behavioural training) for 4 visits over 10 weeks. Stage 2 involved drug discontinuation. PFMT included 3 sessions of 15 exercises daily, starting at 2-seconds duration and progressed to 10 seconds. The other trial [202] was a single-site study of individually-titrated, extended-release oxybutynin (initiated at 5 mg/day and escalated as tolerated to a maximum of 30mg/day) with proactive management of side effects versus oxybutynin plus PFMT with urge suppression strategies for 4 visits across approximately 8 weeks. PFMT was also 3 sessions of 15 exercises daily, starting at an individualized duration and progressed to a maximum of 10 seconds.

1. Quality of data

(a) PFM⁄VC versus VC: Adequate allocation concealment and some outcome assessment was blind in one [107]. Neither of these was clearly reported in the study by another [201]. Sample sizes were approximately 20 women in each comparison group. Dropouts ranged from 63% of the women in the PFM/VC group compared to 41% in the VC group [107] to 30% of the PFM/VC group versus 9% in the VC only group [201].

(b) PFMT⁄ES versus ES: It was not clear if random allocation concealment was adequate or whether assessors were blind [132]. There were only 11 women in each comparison group. There did not appear to be any dropouts.

(c) PFMT⁄BT versus BT: In one, it was not clear if random allocation concealment was adequate; outcome assessors were not blinded [189]. There were 68 women in the BT group and 67 in combination therapy with fewer than 10% dropouts after 12 weeks of treatment. Further follow-up was reported at six months and approximately three years after study entry.

(d) PFMT⁄drug versus drug: Although adequate allocation concealment and blinded assessors where used in three trials [125,202,203] it was not clear in another [191]. Sample sizes varied from 18 women in the drug group and 23 in the combination therapy group [191] with 27% and 17% dropouts respectively, principally because of drug-related side effects. In another, approximately 50 women with SUI were assigned to each group, 30% of whom dropped out of both treatment groups. Burgio (2008) randomised 307 women with urge-predominant UI and had a drop out rate of 8.8% at the end of active treatment (10 weeks). Burgio (2010) randomised 64 women with urge-predominant UI before being stopped for futility and had a drop out rate of 9.4%.

2. Results

(a) PFM⁄VC versus VC: In this comparison, neither of the two trials identified any statistically significant differences between the groups (for patient reported cure, improvement as measured by a Visual Analogue Scale or pad test) and all of the confidence intervals were wide [107,201].

(b) PFMT/ES versus ES: Although Hofbauer (1990) [132] reported cure/improvement, it was not clear whether this was based on data from a symptom scale or a urinary diary. There were no data reported for the other outcomes of interest.

(c) PFMT/BT versus BT: No statistically significant difference was found in one early study [189] between combination versus single therapy in the number of women reporting they were much better or in the number of leakage episodes per day; however more in the combination group reported they were much better at six months post treatment. With regard to quality of life the combination therapy group had statistically significantly better scores on UDI and IIQ after treatment, but there was no statistically significant difference in either measure six months after treatment had begun. Approximately three years later, a similar number in each group had sought further treatment for UI (19 of 48 BT, 18 of 48 PFMT/BT). Of the women who had not sought further treatment, fewer were free of leakage episodes in the BT group (four of 22 in BT group versus eight of 16 in the combination group). Adverse events are not mentioned.

(d) PFMT/drug versus drug:. Ghoniem [2005] [125] reported that the combined treatment was not significantly different from the drug-only-treatment in terms of frequency of incontinence episodes, quality of life (IQOL) and Patient Global Impression of Improvement Scale. Ishiko (2000) [191] did not report data for any of the primary outcomes of interest; 10/13 in the drug group, and 17/19 in the combination therapy group had no leakage episodes per week post treatment, and some reported drug-related side effects sufficient enough to withdraw from treatment

A higher proportion of women in the combined therapy group had a successful outcome, defined as at least 70% reduction in frequency of UI episodes [203]. The combined therapy group also had greater subjective improvement, greater patient satisfaction and greater reductions in symptom distress on validated questionnaires. In another study [202], the groups were so similar on an interim analysis and power calculation that recruitment was stopped early for futility. With the individualized, escalating dose titration and proactive management of side-effects, the drug alone group achieved an 88.5% reduction of incontinence episodes, leaving little room for added benefit.

3. Summary

There were few trials addressing the effect of adding PFMT to another therapy, and only five of the eight studies reported useful data. There appears to be no benefit of adding PFMT to VC or duloxetine respectively in women with SUI [107,125] **(Level of Evidence: 2)**. There may be benefit to adding PFMT to BT for women with urodynamic SUI or SUI with DO in the short term (three months), but it is not clear if this benefit persists at six months or more [189] **(Level of Evidence: 2)**. There is not sufficient evidence to be sure if there is any benefit in adding PFMT to ES. There is a single trial indicating added benefit of PFMT when drug therapy is administered with the usual intensity.

4. Recommendations

For women with SUI or MUI a combination of PFMT/BT may be better than BT alone in the short-term **(Grade of Recommendation: C)**, and a combination of PFMT/drug may be better than drug alone. If a woman is taking duloxetine or using VC, it may not help to add PFMT **(Grade of Recommendation: C)**. However, these recommendations are based on single trials of variable quality and larger, good quality trials are needed to address each of the above comparisons if these are of interest to women. Further, these studies examine the effects of combining therapies as an initial approach. Less is known about the effects of combining therapies in a stepped fashion when women do not achieve the desired outcomes with a single therapy.

5. OTHER LUTS

Seven trials included above reported data for other LUTS, e.g. frequency, nocturia, bladder pain but no new trials were added to this section for the update.

The effect of a PFMT programme on frequency, nocturia and urgency in women with MUI improved self report of symptom bother both frequency and nocturia significantly more in the PFMT group, while urgency persisted [204].

Three trials investigating different type of PFMT programs reported whether women had nocturia [147,150,152,153]. There were few data and some missing, making it difficult to observe a difference between PFMT programs.

A secondary analysis looked at the effect of PFMT versus drug therapy on nocturia in older women with UUI or MUI [142]. The PFMT group reduced nocturia by a median of 0.5 episodes per night; this was significantly more effective than drug treatment.

One trial addressed PFMT versus EStim on urgency symptoms and nocturia in women with DO. There was a significant decrease in urge incontinence episodes in both groups, but no difference between groups. Further, there was a reduction in nocturia frequencies in the EStim group [188].

Finally, one new trial [202] studied the effect of drug therapy alone and combined with PFMT on urgency and 24-voiding frequency in women with urgency – predominant incontinence. Urgency decreased significantly although there was no difference between the two groups.

6. FACTORS AFFECTING OUTCOME

Apart from differences in effect attributed to PFMT or comparison interventions, other factors may affect outcomes. Of particular interest is the effect of older age; this and other factors are considered here.

a) Age

Firstly we looked for trials included above that specifically recruited older woman; there were six. The average age of women in these trials was between 60 and 70 years [120,141,142,192], or over 70 years [186,190] compared with a mean age of 40 to 55 in most other included studies. It was not possible to compare the data from older women with data from younger women for the following comparisons: PFMT versus EStim [186], PFMT versus drug [142,192] and PFMT versus BT [190].

For three comparisons (PFMT versus no treatment [141], PFMT versus placebo/sham/control [120,142], BF assisted PFMT versus PFMT alone [141], there were no clear differences in the size or direction of effect when the data from the trials in older women were compared with data from other trials. The recommendations arising from these comparisons appear to apply to older women. Namely, that PFMT should be offered, as first-line therapy, to all women with SUI, UUI, or MUI.

Secondly, the methods of included trials were checked for use of regression or other methods to investigate association between baseline characteristics (specifically age) and outcome. The literature search also located some papers that reported secondary analysis of data from the included trials. Papers that reported an association between age and outcome, but did not describe the methods of testing association are not discussed here.

Two reports detailed the testing of independent associations between patient characteristics (including age) and outcome [126,205]. In one data was used from PFMT groups in three RCTs [120,121,142]. The individual trials restricted entry to women 55 years and older [120,142] or 40 years and over [121]. In multivariate analysis, age was not a significant predictor of reduction in leakage episodes for PFMT women with SUI, UUI or MUI. In another trial, Hay Smith (2006) investigated the associations between leakage on paper towel test and patient characteristics using data from a trial that compared two approaches to PFMT for Women with SUI [126]. Older age was associated with more leakage in univariate models, but was not significant in multivariate analysis.

One further trial [189] used correlation methods, and one [206] categorised women as successes or failures, to investigate the association between age and outcome. In a secondary analysis [207] of the trial by Wyman [1998] there were no statistically significant correlations between age and reduction in leakage episodes or change in PFM activity after PFMT or BT in women with SUI, UUI or MUI. Bø (1992) characterised participants in the intensive PFMT group as treatment responders or non-responders. Treatment responders were statistically significantly older than borderline responders; there were no non-responders.

Considering the number of included trials, there were few that restricted entry to older women and/or investigated the association between age and treatment outcome. Only two studies have used the most appropriate methods to test independent associations. More research is needed to investigate the association between age and treatment outcome. Neither study using multivariate models found an association between age and outcome, nor was there a reported correlation in another. The two studies that categorised women as treatment successes or failures had conflicting results.

Summary

There is no good evidence to date to suggest that 'healthy' older women with UI do benefit less from PFMT compared to younger women.

b) Other

Aside from age, other factors have the potential to mediate treatment outcome, e.g. baseline UI severity, duration of symptoms and co-morbid conditions. All reports were checked for the methods used to address association between baseline characteristics and treatment outcome. Some appeared to be based on researcher observation; these data are not discussed here. Seven reports of interest were found [118,126,141,171,192,205-208]. A wide range of patient characteristics were considered in these papers; it is not clear whether it is more important to know which baseline characteristics might be predictors of outcome, or which ones might not. To eliminate long lists of non-significant associations, a pragmatic choice was made to report only significant associations although this creates a false impression of some consistent associations. None of the variables discussed here has demonstrated a consistent association with outcome, and all are worthy of further investigation.

Two reports addressed independent associations between patient characteristics and outcome [126,205]. Burgio (2003) used data from PFMT groups in three RCTs [120,121,142]. In multivariate analysis of data from PFMT women with UUI or urge predominant MUI, a 75% reduction in leakage episodes was more likely if women did not use protection (e.g. pads) prior to treatment. Continence (100% reduction in leakage episodes) was more likely if women had fewer Incontinence episodes at baseline and had a lower educational level, but less likely if they had prior UI surgery. For PFMT women with SUI or stress predominant MUI a 75% reduction in leakage episodes was less likely if women had previously been evaluated for UI or had

more than 10 leakage episodes per week pre-treatment. Hay-Smith (2003) investigated the associations between patient characteristics and two outcomes (leakage on paper towel test, self-reported improvement) using data from a trial that compared two approaches to PFMT for Women with SUI. In multivariate models increasing parity was associated with less improvement in leakage symptoms and more risk of leakage on a paper towel test. Shorter symptom duration and higher body mass index were both associated with more improvement in symptoms. Leakage once or more per day was associated with greater risk of leakage on a paper towel test; the reverse was true for women with a history of constipation.

There was no statistically significant correlation between any of the baseline characteristics listed and the two outcomes (reduction in leakage episodes or change in PFM activity) in a secondary analysis [207].

Treatment responders had statistically significantly longer symptom duration, higher body mass index, stronger PFM, and were more motivated (clinician judgement) than borderline responders; there were no non-responders [206].

Two studies examined PFM characteristics as possible predictors of successful response to PFMT [118, 208]. Yoo [2011] reported on biofeedback assisted PFMT. In multivariable regression, the only factor predictive of successful treatment response was change in mean amplitude of tonic contraction after the 8th treatment session. Dumoulin [2010] studied PFM function variables measured by dynamometer in women with postpartum SUI. Treatment success (20-minute pad test volume < 2g) was associated with lower pre-treatment passive force and greater pre-treatment PFM endurance.

Few studies investigated the association between patient characteristics and treatment outcome and no consistent pattern emerged from the available data. Even fewer studies used appropriate methods. More research is needed to test for independent associations between patient characteristics and outcome. Given the few data available, and the methodological limitations of some papers, any patient characteristic described above that was associated with outcome should be considered as a possible rather than established prognostic factor.

Summary

It is not clear if there are any reliable predictors of PFMT outcome. Too few trials have appropriately investigated the association between patient characteristics and outcome to be sure.

III. WEIGHTED VAGINAL CONES (VCS)

Weighted vaginal cones (VCs) were developed as a method for testing PFM function and to provide progressive muscular overload during PFM strengthening exercises [182,209]. In theory, when a cone is inserted into the vagina, the sensation of 'losing the cone' provides strong sensory feedback that prompts the PFMs to contract to prevent the cone from slipping out. Women start in a standing position with a weighted cone held inside the vagina for at least one minute, incrementally adding time and increased cone weight whilst standing or walking. The goal is to walk around for 20 minutes without losing the cone; the gradual increase in cone weight maintains muscle overload over the course of the exercise programme.

There are varous cone weights and sizes (**Figure 1**). However, the effectiveness of the VC training method is unclear. Of note is that the PFM contraction is not the only reason the cone is retained and because orientation of the vagina is not completely vertical, some women can retain the cone without actually contracting the pelvic floor. Radiology has also demonstrated that the cones can rest in a transverse position [210,211]. Depending on the axis of the vagina, women need to produce different force intensities to retain the cone. Thus, using VCs as a measure of PFM function does not appear to be a valid method. Finally, some women may find it impossible to insert the cones due to a narrowed vaginal opening or, conversely, to retain it due to an enlarged vaginal opening, prolapse, or an insufficient PFM contraction, one incapable of holding even the lightest cone.

This section examines the evidence for VCs in the prevention and treatment of UI in women. Questions addressed:

- Are VCs better than no treatment, placebo or control for the prevention of UI?
- Are VCs better than no treatment, placebo or control for the treatment of UI?
- Are VCs as effective as other treatments for the treatment of UI?
- Are VCs combined with PFMT better than PFMT alone for the treatment of UI?

1.PREVENTION

No trials investigating either the primary or secondary prevention effects of training with VCs for women with UI were found. The literature search revealed two reviews on the prevention of UI [159,212]. Of these, only Hay-Smith (2002) considered VC prevention trials; however, none of the trials measured the effect on UI, only PFM activity. Because no continence-related outcomes were measured, these trials are not reviewed here. Further, the most recent Cochrane review of VCs did not address prevention [213], and our search did not revealed any new RCTs on VCs as a preventive treatment.

Figure 1: Weighted vaginal cones

2.TREATMENT

The literature search revealed one systematic review that specifically addressed the effects of VCs in the treatment of UI in women [213]. One new trial [181], the review and three RCTs from ICI 2009 form the basis of this subsection [122,140,181,183].

a) Are VCs better than no treatment, placebo or control treatments?

Four RCTs compared VCs with control treatments for women with UI [107,122,134,140]. Details of the VC programmes for each trial are presented in **Table 3**.

1. Quality of data

All four reported adequate allocation concealment, randomisation and blinding of outcome assessors. Dropout rates were 3% [122], 12% [134], 14% [140], and 40% [107]. In one, the VC group experienced more dropouts (42%) than the control group (22%) [107]. In another, participants in the VC group reported abdominal pain, vaginitis or bleeding and 14 reported problems with self-motivation and difficulty in using the cones [134]. Williams did not report any side effects for either treatment group other than the fact that 2.5% of the women in each of the trial arms reported urinary tract infections (UTI). Wilson [1998] and Castro [2008] did not report any side effects in either group.

2. Results

Women in the VC groups were more likely to report they were cured than the controls (RR 1.98, 95% CI 1.21 to 3.23). The pooled data for self-reported improvement/cure from two trials [122,134] showed statistically significant heterogeneity. Individually, one trial favoured the VC group [134] while the other favoured neither group [122]. VC participants scored better than the controls on the Leakage Index but showed no statistical differences on the Social Activity Index [134]. Further, Castro (2008) [140] reported better incontinence-related QOL in VC participants as compared to the controls on the IQoL questionnaire.

3. Summary

The evidence from these four RCTs suggests that VCs are better than control treatments for subjective reporting of cure or cure/improvement and QoL impact in the treatment of SUI **(Level of Evidence: 1)**. However, VC treatment may be inappropriate in some cases due to potential reported side effects.

4. Recommendations

For women with SUI, VCs with supervised training sessions by a trained health professional can be offered as a first-line conservative therapy to those who can and are prepared to use them **(Grade of Recommendation: B)**; VCs may be inappropriate in some cases due to inability to insert or retain the the cone or because of side effects and discomfort. Trained health professional assessment is recommended **(Grade of Recommendation: D)**

b) Are VCs as effective as other treatments?

VCs have been compared with PFMT and EStim, but not with other therapies such as drug treatment, BT or surgery.

(a) VCs versus PFMT

This comparison has been addressed in Section B2.3c. The details of the VC and PFMT programmes for each trial are presented in **Table 4**.

(b) VCs versus EStim

Five trials compared VCs with EStim [134, 140, 201, 214, 215]. The details of the VC and EStim programmes for each trial are presented in **Table 5**.

1. Quality of data

(a) VCs versus PFMT: See Section B2.3c.

(b) VCs versus EStim

Among the five trials, two [134,140] reported adequate randomisation, allocation concealment and blinding of outcome assessors; blinding was unclear in the other three [201,214,215]. Dropout rates were higher in the VC groups for [201,214,215] but higher in the EStim groups for three [134,140,201].

2. Results

(a) VCs versus PFMT See Section BII4c.

(b)VCs versus EStim

There was no statistically significant difference between VCs and EStim in the pooled data between two trials [134,140] in terms of self-reported cure nor in the pooled data [134,215] for cure/improvement.

Table 3: Characteristics of studies comparing vaginal cones (VCs) and no treatment, placebo or control treatments

Study ID, population	Training Type	Training Program	Training Duration	Effectiveness	Notes
Bø, 1999 [134] Women with urodynamically proven SUI	VCs (29) vs Control treatment (32)	VCs: One daily 20-minute consultation with physiotherapist, 20 min/day; three cylindrical weights: 20, 40 and 70 grams. Control: Used a continence guard (Coloplast AS).	6 months	Subjective Cure: VCs 5/27 vs Control 1/30 RR 5.56 (0.69-44.61) Cure & improvement: VCs 17/27 vs Control 1/30 RR 18.89 (2.69-132.58)	Dropouts: VCs: 2/29 Control: 3/32
Castro, 2008 [140] Women with urodynamically proven stress or mix UI	VCs (27) vs Control treatment (30)	VCs: One training session with a physiotherapist and 3 days/week under a physiotherapist's supervision. Held the heaviest cone 45 minutes. Cylindrical weights 20-100 grams. Control: Untreated, but received motivational once-monthly phone calls.	6 months	Subjective Cure: VC 13/24 vs Control 5/24 RR: 2.6 (1.10-6.16)	Dropouts: VCs: 3/27, 93% compliance Control: 6/30
Williams, 2006 [122] Women with urodynamically proven stress or mix UI	VCs (80) vs Standard care (79)	VCs: One training session with a nurse. Holding heaviest cone they could retain (10-60g) 15 minutes, 2x /day, 7 days/week. Standard care: leaflet detailing PFM anatomy and exercises.	3 months	Cure : VCs 7/80 vs Control 6/79 RR 1.15 (0.41-2.38) Subjective cure or improvement : VCs 30/80 vs Control 34/79 RR 0.87, 95% CI 0.60 to 1.27	Dropouts: VCs: 1/80 Controls: 3/79
Wilson, 1998 [107] Women with symptoms of UI three months postpartum	VCs (36) vs Control treatment (117)	VCs: One training session and 3 follow-up visits with a physiotherapist. Cone held for two 15-min home exercises sessions per day.Nine conical weights: 20-100 grams. Control: Standard post-natal care	9 months	Subjective Cure: VCs 11/21 vs Control 22/91 RR 2.17 (1.25- 3.74)	Dropouts: VCs: 15/36 Control: 26/117

Footnotes: VCs = vaginal cones

Table 4: Characteristics of studies comparing vaginal Cones (VCs) and PFMT

Study ID, population	Training Type	Training Program	Training Duration	Effectiveness	Notes
Arvonen, 2001 [179] Women with symptoms of SUI	PFMT (20) vs VCs (20)	PFMT: Under supervision of a physiotherapist or nurse. PFM contraction in sitting and in standing position twice daily: one daily set of 10 PFM contractions (5 sec on / 5 sec off) and one daily set of 15 (3 sec) submaximal contractions. VCs: Under supervision of a physiotherapist or nurse. Starting with the 65-gram VC, 10 contractions (20 sec on/ 20 sec off); plus a 50-gram VC x15 min while walking, 2x/day; both progressing to 100- and 80-gram VCs, respectively.	4 months	Cure: VCs 4/18 vs PFMT 0/19 RR 9.47(0.55-164.35) Cure or improvement: VCs 11/18 vs PFMT 11/19 RR 1.06 (0.62-1.80)	Dropouts: PFMT: 1/20 VCs: 2/20
Arvonen, 2002 [183] Women with symptoms of SUI	PFMT (12) vs VCs (12)	PFMT: Supervision with physiotherapist, 2 visits. Progressive PFMT in sitting and standing position. PFM contractions of short and long duration or with cough. VCs: Supervision with physiotherapist, 2 visits. Starting with the 65-gram VC, 10 contractions (20 sec on/ 20 sec off), plus a 50-gram VC x15 min while walking, 2x/day; both progressing to 100- and 80-gram VCs, respectively.	4 months	Cure: VCs 2/7 vs PFMT 0/10 RR 6.88 (0.38-124.52) Cure & improvement: VCs 6/7 vs PFMT 9/10 RR 0.95 (0.66-1.37)	Dropouts: PFMT: 2/12 VCs: 5/12
Bø, 1999 [134] Women with urodynamically proven SUI	PFMT (29) vs VCs (27)	PFMT: One consultation with physiotherapist.8-12 PFM contractions, 3x per day, plus 1 group-session/week. VCs: One consultation with physiotherapist. 20 min per day, three cylindrical weights: 20, 40, and 70 grams.	6 months	Subjective Cure: VCs 5/27 vs PFMT 12/25 RR 0.39 (0.16-0.94) Cure & improvement: VCs 17/27 vs PFMT 23/25 RR 0.68 (0.50-0.93)	Dropouts: VCs 2/29 PFMT: 4/29
Cammu, 1998 [180] Women with urodynamically proven stress or SUI	PFMT (30) vs VCs (30)	PFMT: Once weekly, 30-min PFM-training sessions with a physiotherapist, plus individualised home-based PFM exercises. VCs: Initial training plus twice-weekly visit with physiotherapist, in addition to holding the heaviest cone 15 min, 2x daily Five VCs 20-70 grams.	12 weeks	Cure & improvement VCs 17/30 vs PFMT 16/30 RR 1.06 (0.67-1.68)	Dropouts: VCs: 14/30 PFMT: 0/30

Table 4: Characteristics of studies comparing vaginal Cones (VCs) and PFMT (continued)

Study ID, population	Training Type	Training Program	Training Duration	Effectiveness	Notes
Castro, 2008 [140] Women with urodynamically proven stress or mix UI	PFMT (31) vs VCs (27)	PFMT: One training session with physiotherapist plus 3 days/week with physiotherapist supervision. PFM contractions: • 10x, 5sec on/5 sec off • 20 x, 2sec on/2 sec off • 20 x, 1sec on/1 sec off • 5 x, 10sec on/10 sec off • 5 contractions with cough VCs: One training session with physiotherapist plus 3 days/week with physiotherapist supervision.Held the heaviest cone, 45 min. Cylindrical weights: 20-100 grams	6 months	Subjective Cure: VCs 13/24 vs PFMT 15/26 RR 0.94 (0.57-1.54)	Dropouts: VCs: 3/27 & 93% compliance PFMT: 5/31
Gameiro, 2010 [181] Women with predominent symptoms of SUI	PFMT (52) vs VCs (51)	PFMT: Once weekly, 45-min session of PFMT2 series of 10 PFM contractions (short and long) VCs:Once weekly, 45min session of VCs. Walked 1 minute, coughed 3 times and ascended and descended a 2-step stair 10 times. Cylindrical weights: 20-70 grams	12 weeks	Cure: VCs 36/51 vs PFMT 26/52 RR 1.41 (1.02-1.95) Cure & improvement: VCs 27/51vs PFMT 22/52 RR 1.25 (0.83-1.88)	Dropouts: No details provided
Haken, 1991 [175] Women with urodynamically proven stress UI	PFMT (31) vs VCs (33)	PFMT: 5 contractions, 10 times per day VCs: Hold for 15 min, 2x/day 5 cylindrical weights: 20-70 grams	10 weeks	Cure: details not reported	Dropouts: VCs: 8/31 PFMT: 3/33
Laycock, 2001 [185] Women with urodynamically proven stress UI	PFMT (20) vs cones (41)	PFMT: Supervision with physiotherapist. PFM exercises lying, sitting and standing, 10 min/day VCs: 10 minutes per day with VC	3 months	No data reported on subjective cure or improvement	Dropouts: VCs: 11/41 PFMT: 4/20

Table 4: Characteristics of studies comparing vaginal Cones (VCs) and PFMT (continued)

Study ID, population	Training Type	Training Program	Training Duration	Effectiveness	Notes
Peattie, 1988 [182] Women with urodynamically proven stress UI	PFMT (22) vs VCs (22)	PFMT: 3 PFM training sessions. VCs: twice/day held cone for 15 min. Weekly phone calls Nine conical weights: 20-100 grams	4 weeks	Cure: VCs 12/17 vs PFMT 10/16 RR 1.13 (0.69-1.84)	Dropouts: VCs: 5/22 PFMT: 6/22
Williams, 2006 [122] Women with urodynamically proven stress or mix UI	PFMT (77) vs VCs (80)	PFMT: initial +bi-weekly training session with nurse 4 sets/day, PFM exercise program progressed according to Oxford scale VC: One training session with nurse. Held heaviest cone (10-60g) 15 minutes, 2x /day.	3 months	Cure: VCs 7/80 vs PFMT 4/79 RR 1.73 (0.53-5.67) Cure or improvement: VCs 51/80 vs PFMT 47/79 RR 1.07 (0.84-1.37)	Dropouts: VCs: 1/80 PFMT: 2/79
Wilson, 1998 [107] Women with symptoms of UI three months postpartum	PFMT (39) vs VCs (36)	PFMT: One training session with 3 follow-up sessions, fast and slow contractions (100 per day) VCs: One training session and 3 follow-up visits with physiotherapist. Held the cone for two 15-min sessions /day. Nine cone weights: 20-100 grams	9 months	Cure: VCs 11/21 vs PFMT 10/19 RR 1.00 (0.55-1.80)	Dropouts: VCs: 15/36 PFMT: 20/39

Footnotes: PFM = Pelvic floor muscle, PFMT= Pelvic floor muscle training, VCs = vaginal cones

Table: 5 Characteristics of studies comparing vaginal cones and electrical stimulation (Estim)

Study ID, population	Training Type	Training Program	Training Duration	Effectiveness	Notes
Bø, 1999 [134] Women with urodynamically proven SUI	VCs (29) vs EStim (32)	VCs: One consultation with physiotherapist. 20 min/day, three cylindrical weights: 20, 40 & 70 grams EStim: One consultation with physiotherapist; 30 min of transvaginal EStim per day: biphasic intermittent current, 50Hz, pulse width of 0.2ms, current intensity 0-120mA, on/off time in line with each woman's ability	6 months	Subjective Cure: VCs 5/27 vs EStim3/25 RR: 1.54 (0.41-5.80) Cure & improvement: 17/27 cone vs 16/25 EStim RR: 0.98 (0.65-1.49) Cure & improvement, on pad test: VCs18/27 vs EStim 19/25 RR: 0.88 (0.62-1.24)	Dropouts: VCs: 2/29 EStim: 7/32
Castro, 2008 [140] Women with urodynamically proven stress or mix UI	VCs (27) vs EStim(30)	VCs: One training session with physiotherapist plus 3 days/week with physiotherapist supervision. Held the heaviest cone 45 min. Cylindrical weights: 20-100 grams EStim: 20 min of transvaginal EStim, 3 times/ week: biphasic square current 50Hz, pulse width of 0.5ms, current intensity 0-100mA, and cycle of 5 sec. on/10 sec off.	6 months	Subjective Cure: VCs 13/24 vs Estim 15/27 RR: 0.97 (0.59-1.61)	Dropouts: VCs: 3/27 plus 93% compliance EStim: 3/30
Delneri, 2000 [214] Women with signs and symptoms of SUI	VCs (10) vs EStim (10)	VCs: Initial training Used VCs 25-35 min/day, increasing cone weight progressively. 5 plastic cones: 20-70 grams EStim: Two15-min transvaginal EStim sessions daily, 5x per week: biphasic square current 20Hz and 50Hz, duty cycle 4/8, at maximum tolerated intensity.	VCs: 4 weeks EStim: 12 sessions in 16 days	No outcome of interest	Dropouts: VCs: 2/10 EStim: 0/10
Olah, 1990 [215] Women with symptoms of SUI	VCs (24) vs EStim (30)	VCs: Instructed by a physiotherapist once per week for 4 weeks plus15 min, 2x/day home exercises; Nine cones: 20-100 grams EStim: Instructed by a physiotherapist 3x per week for 4 weeks. Interferential current with 4 external vacuum electrodes. Frequency 0-100Hz, maximal tolerated intensity for 15 min.	4 weeks	Cure and improvement: VCs 6/24 vs EStim21/30 RR: 0.36 (.17-0.74) Cure & improvement, on pad test: VCs 12/24 vs EStim 23/30 RR: 0.65 (0.42-1.02)	Dropouts: VCs: 5/24 EStim: 2/30
Wise, 1993 [201] Women with urody-namically proven stress and genuine stress incontinence	VCs (21) vs EStim (20)	VCs: Used VCs, 15 min, 2x/day,increasing cone weight progressively. EStim: 20 min of transvaginal EStim, daily: biphasic square current 20Hz, pulse width of 0.75ms, current intensity 0-90mA	12 weeks	Cure & improvement, on pad test: VCs 14/21 vs EStim 12/20 RR 1.11 (0.70-1.78)	Dropouts: VCs: 2/21 EStim: 4/20

Footnotes: VCs = vaginal cones, Estim = Electrical stimulation

No differences were reported on the I-QoL questionnaire or in the number of leakage episodes on a 7-day bladder diary evaluation (mean and standard deviations: cones 1.5 ±1.8 vs. EStim 2.3 ±5.5) [140]. Bø [1999] also found no differences in daily leakage episodes on a 7-day bladder diary.

Discomfort or side effects between EStim and VC are reported to be similar [140,214] . One study described women who were unable to use the VCs because of vaginal size [215] and another reported tenderness and bleeding, discomfort or motivational and other difficulties in using the EStim [134]. In the VC group, one participant reported abdominal pain, two vaginitis and one bleeding; 14 reported motivational problems and difficulty using the cones.

3. Summary

Overall, the pooled data for VCs and EStim demonstrated no statistically significant differences between the groups in terms of a self-reported cure, a cure/improvement, incontinence-specific QOL measures or the number of leakage episodes **(Level of Evidence: 1)**. Additionally, both the VC and EStim groups reported adverse events.

4. Recommendations

VCs and EStim seem equally effective in the treatment of SUI and MUI, but the side effects and discomfort caused by the VCs and EStim limit their utility in clinical practice **(Grade of Recommendation: B)**.

c) Are VCs combined with PFMT better than PFMT alone?

Two trials compared a combined PFMT/VCs to PFMT alone (107,216] Details of the PFMT/VCs and PFMT are presented in **Table 6**. None of the outcomes used in the two trials overlapped.

1. Quality of data

Allocation concealment was clear in one and some outcomes had blinded assessors [107,216], but neither of these variables was clearly reported the other [216].

2. Results

No statistically significant differences were detected for either cure or cure/improvement after 12 weeks in either study. Dropout rates in both trials were higher in the combined PFMT/VCs group.

3. Summary

The limited available evidence suggested no benefit from adding VCs to PFMT for women with SUI **(Level of Evidence: 2)**.

4. Recommendations

If this combined intervention proves to be of interest to women, then more research is needed to confirm or refute the advantages of adding VCs to PFMT.

3. OTHER LOWER URINARY TRACT SYMPTOMS (LUTS)

Two trials included in the VC section reported data on other LUTS: urgency and nocturia [122], nocturia [181]. In the Williams [2006] study, there were no differences between VC, control and PFMT group after intervention for urgency or nocturia. Gameiro [2010] however, noted a significant reduction in nocturia after treatment in both VC and PFMT groups, but no significant difference between groups.

4. FACTORS AFFECTING OUTCOME

None of the trials above addressed the effect of age or other factors on the outcome of VC training. Nonetheless, it is worth noting that in the 22 trials included in this section, on average, 24% of the women being treated with VCs (range 0 to 63%) withdrew or dropped out. Although few trials examined the causes of attrition, among those that reported causal factors low compliance, motivational problems, unpleasantness, aesthetic dislike, discomfort, and bleeding were indicated although no one reason predominated.

IV. ELECTRICAL STIMULATION (ESTIM)

The literature concerning EStim in the management of UI remains difficult to interpret, due to the lack of a well-substantiated biological rationale underpinning the use of EStim[217]. However, the theoretical basis of stimulation interventions is emerging with increasing understanding of the neuroanatomy and physiology of the central and peripheral nervous systems. The mechanisms of action may vary depending on the cause(s) of UI and the structure(s) being targeted e.g. PFM or detrusor, peripheral or central nervous system. In general, the aim of EStim for women with SUI appears to be to improve the function of the PFM, while for women with UUI the objective seems to be to inhibit detrusor overactivity (DO).

EStim is provided by clinic-based mains powered machines or portable battery powered stimulators (Figure 2) with a seemingly infinite combination of current types, waveforms, frequencies, intensities, electrode types and placements (Figure 3). Without a clear biological rationale it is difficult to make rationale choices about different ways of delivering EStim. Additional confusion is created by the relatively rapid developments in the area of EStim, and a wide variety of stimulation devices and protocols have been developed even for the same condition. For example, in the last 30 years or so women with SUI have been treated with a wide variety of EStim ranging from general anaesthetic for 20 minutes [168], to six months of low intensity stimulation at 10 Hz using a vaginal electrode [1,218].

Finally, the nomenclature used to describe EStim remains inconsistent. EStim has not only been described based on the type of current being used

Table 6: Characteristics of studies comparing PFMT + vaginal cones vs PFMT

Study ID, population	Training Type	Training Program	Training Duration	Effectiveness	Notes
Pieber, 1995 [216] Women with urodynamically proven SUI, premenauposal	PFMT+ VCs (21) Vs PFMT (25)	PFMT+VCs: Instruction on PFMT by physiotherapist plus visits with physiotherapist every 2-4 weeks; 100 PFM contractions plus Knack, daily Held the VCs for 15 min/day. Five cone weights: 20-70 grams PFMT: Instruction on PFMT by physiotherapist. 100 PFM contractions/day + Knack; visits with physiotherapist every 2-4 weeks	3 months	Subjective Cure: PFMT+VCs 5/21 vs PFMT 3/25 RR: 1.98 (0.54-7.34) Cure and improvement: PFMT+VCs 11/21 vs PFMT 12/25 RR 1.09 (0.61-1.94)	Dropouts: PFMT+VCs : 8/21 PFMT: 9/25
Wilson, 1998 [107] Women with symptoms of UI three months postpartum	PFMT+VCs (38) vs PFMT (39)	PFMT+VCs: One training session with a physiotherapist plus 3 follow-up visits. 100 fast and slow contractions per day PFMT: One training session with 3 follow-up sessions, fast and slow contractions (100 per day)	9 months	Subjective Cure: PFMT+VCs 6/14 vs PFMT 10/19 RR: 0.81 (0.39-1.71)	Dropouts: PFMT+VC: 24/38 PFMT: 20/39

Footnotes: PFMT= pelvic floor muscle training, VCs = vaginal cones, Estim = Electrical stimulation

(e.g. faradic, interferential), but also on the structures targeted (e.g. neuromuscular), the current intensity (e.g. low-intensity, or maximal stimulation), and the proposed mechanism of action (e.g. neuromodulation). In the absence of agreement of how best to classify EStim, no attempts were made to classify different types of EStim.

This section presents the evidence for the use of EStim in the prevention and treatment of UI in women. Questions addressed are:

- Is EStim effective in the prevention of UI?
- Is EStim better than no active treatment (placebo, sham, control or no treatment) for treatment of UI?
- Is one type of EStim better than another in the treatment of UI?
- Is EStim better than other treatments in the treatment of UI?
- Does the addition of EStim to other treatments add any benefit in the treatment of UI?
- What is the effect of EStim on other LUTS?
- What factors might affect the outcome of EStim in the treatment of UI?

Eligible interventions were non-invasive EStim without implanted electrodes. (Magnetic stimulation is described in Section B.5.0.) Other criteria for inclusion were (1) randomised or quasi-randomised (lternate allocation) trial design, (2) women with UI or other LUTS, (3) no participants with incontinence due to neurological or cognitive impairment and (4) no pregnant or postpartum women (within 12 months of childbirth). Trial data reported in conference abstracts as well as full-text papers were included. EStim compared with PFMT and vaginal cones are covered in previous sections (sections B.2 and B.3). This section focuses on EStim compared with other conservative treatments or no active treatment.

Figure 2: EStim machine

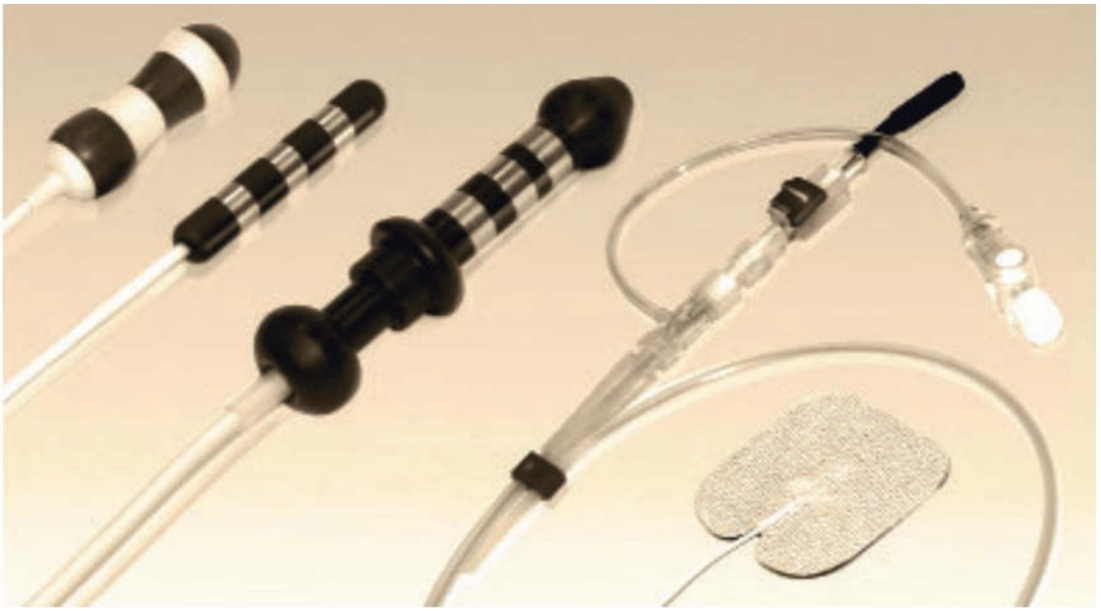


Figure 3 : Vaginal, rectal (anal), and skin electrodes for electrical stimulation

The primary outcomes were cure rates (the number of women cured), and improvement rates (the number of women improved, including cure). There was considerable variability in the way these outcomes were measured. Women's self-report was given priority but for studies in which it was not reported, the rate based on diaries was used as a proxy; where diary data were also not reported, the rate based on pad tests or any other definitions chosen by the trialists was used [219]. Data on health-related quality of life and adverse effects were also extracted. Data at the end of the prescribed treatment phase, or at the first outcome measurement, if later, were used in the analysis. Any treatment effects shown are likely to reflect maximum effect of each intervention. Data from further follow-ups were also recorded.

Due to the small number of available studies per intervention, data were sub-grouped by dominant type or pattern of incontinence: (1) studies with all or at least 50% of participants having SUI alone or a predominant symptom of SUI (as defined by trialists), (2) studies with all or >50% of participants having UUI alone or a predominant symptom of UUI (as defined by trialists), (3) other studies of UI in which neither stress- or urge-UI represented a predominant symptom in the study population, and (4) studies of OAB or DO in which it was unclear whether all participants had UI.

Single estimates with 95% confidence intervals (CI) were derived for each study comparison using odds ratios (OR) for dichotomous variables or mean difference (MD) for continuous variables. Summary estimates were calculated using random effects models if there was more than one study reporting the same outcome (meta-analysis).

'Risk of bias' in the included studies was assessed for allocation concealment (selection bias) and completeness of outcome data (attrition bias), using relevant items in a standard tool developed by the Cochrane Urinary Incontinence Group [220]. Risk of bias regarding blinding to the allocated intervention should be considered to be high in most included studies: blinding of participants and care providers is not always feasible (other than the use of sham EStim), and blinding of outcome assessors is equally difficult for self-reported outcomes such as cure, improvement and quality of life.

Description of intervention in included studies of EStim

A total of 33 trials were eligible. The electrical stimulation parameters and protocols in this section are summarised in **Table 7**. Some approaches to treatment are now rare, such as the use of faradic current or external electrodes. There was considerable variation in the intervention protocol. Although the biological rationale and purpose of EStim might be different depending on diagnosis, there was no consistency in the EStim protocols used for women with SUI, UUI, MUI, or DO.

In addition, there were three trials that recruited both men and women. These include comparing: EStim (transcutaneous electrical nerve stimulation) with oxybutynin for 13 men and 30 women with idiopathic DO [221]; EStim with sham EStim for 29 men and 39 women with UI due to either idiopathic or neurogenic DO [222]; and EStim and MStim for 15 men and 17 women with UI due to either idiopathic or neurogenic DO [223]. These trials did not differentiate the effects of treatment by gender or by diagnosis and therefore did not contribute to the analysis.

Table 7: Electrical stimulation parameters and protocols in the electrical stimulation (Estim) trials

Study	Current	Current Intensity	Pulse Shape & Duration	Frequency (Hz)	Duty Cycle	Electrodes	Treatment Duration/ Supervision	Target UI
Abel 1997 [232]		Vaginal: 110mA ; anal: 50mA	Duration: 1.0 msec	Single freq: 5Hz	Constant	Anal and vaginal electrode	20min sessions, 1/week: 12wks	UUI
Amaro 2006 [231]		According to tolerance (range 0-100mA)	Duration: 0.1 µsec	Single freq: 4Hz	Single ratio: 1:2 (2s on, 4s off)	Single vaginal electrode	20min sessions, 3/week on alternate days, by nursing staff: 7wks	MUI/UUI
Arruda 2008 [188]	Intermittent biphasic	According to tolerance (range 10-100mA)	Duration: 1.0 msec	Single freq: 10Hz		Single vaginal electrode	20min sessions, 2/week, by physiotherapist: 12wks	DO
Barroso 2004 [229]	Biphasic	Max tolerable intensity (range 0-100mA)	Shape: asymmetric Duration: 300 µsec;	UUI or MUI: 20Hz ; SUI: 50Hz	Single ratio: 1:1 (5s on, 5s off) + 1s rise time	Single vaginal electrode	20min sessions, 2/day, home treatment: 12wks	Any UI
Berghmans 2001* [436]	Biphasic	Max tolerable intensity (range 0-100mA)	Shape: rectangular; Duration: 200 µsec	Freq. stochastic range: 4 - 10Hz		Single vaginal electrode	1/week, office-based and home treatment: 9wks	UUI/DO
Bergmans 2002 [224]	Biphasic	Max tolerable intensity (range 0-100mA)	Shape: rectangular; Duration: 200 µsec	Freq. stochastic range: 4 - 10Hz		Single vaginal electrode	30min sessions, 1x a week, office-based: 9wks ; 20min sessions, 2/day, home treatment: 9wks	DO
Bidmead 2002 [135]						Single vaginal electrode	2/day, home treatment: 9wks	SUI
Blowman 1991 [234]		Until patient is aware of some electrical sensation (not enough to cause PFM contraction, and comfortable enough to be ignored)	Duration: 80µsec	Two freq: 10Hz and 35Hz	Single ratio: 1:1 (4s on, 4s off)	Transcutaneous: cathode over perineum, anode over buttock	lower freq (10Hz): 60min sessions, 1/day, home treatment: 4wks; higher freq (35Hz): 15min sessions, 1/day, home treatment: 2wks	SUI

Table 7: Electrical stimulation parameters and protocols in the electrical stimulation (Estim) trials (continued)

Study	Current	Current Intensity	Pulse Shape & Duration	Frequency (Hz)	Duty Cycle	Electrodes	Treatment Duration/ Supervision	Target UI
Bø 1999 [134]	Intermittent biphasic	Max tolerable intensity to get a contraction (range 0-120mA)	Duration: 0.2msec	Single freq: 50Hz	Individually adapted cycles dependent on voluntary contraction time (On between 0.5-10s, Off between 0-30s)	Single vaginal electrode	30min sessions, 1/day, home treatment (monthy clinic visits): 6mths	SUI
Bower 1998 (226]		Max tolerable intensity	Duration: 200µsec	Suprapubic: 150Hz or sacral: 10Hz		Transcutaneous suprapubic or transcutaneous sacral	Single session?	DO
Brubaker 1997 [227]		Max tolerable intensity (range 0-100mA)	Shape: bipolar square; Duration: 0.1µsec	Single freq: 20Hz	Single ratio: 1:2 (2s on, 4s off)	Single vaginal electrode	20min sessions, 2/day, home treatment: 8wks	SUI/DO
Castro 2008 [140]		Max tolerable intensity (range 0-100mA)	Shape: bipolar square; Duration: 0.5msec	Single freq: 50Hz	Single ratio: 1:2 (5s on, 10s off)	Single vaginal electrode	20min sessions, 3/week, by physiotherapist: 6mths	SUI
Eyjolfsdottir 2009 [235]	Intermittent						15min sessions, 2/day: 9wks	SUI
Goode 2003 [121]	Biphasic	Max tolerable intensity (range 0-100mA)	Duration: 1.0msec	Single freq: 20Hz	Single ratio: 1:1	Single vaginal electrode	15min sessions, every alternate day, home treatment (fortnightly clinic visits): 8wks	SUI/MUI
Haig 1995 [236]	Interferential			Single freq: Freq range: 10-40Hz		Single vaginal electrode	20min sessions, 3x weekly, clinic-based treatment: 1mth (total study period 3mths, Estim done in 2nd month only)	SUI

Table 7: Electrical stimulation parameters and protocols in the electrical stimulation (Estim) trials (continued)

Study	Current	Current Intensity	Pulse Shape & Duration	Frequency (Hz)	Duty Cycle	Electrodes	Treatment Duration/ Supervision	Target UI
Henalla 1989 [130]	Interferential	According to tolerance		Freq range: 0-100Hz			20min sessions, 1/week, clinic-based treatment: 10wks	SUI
Hofbauer 1990 [132]	Faradic (low freqency interrupted direct)	Noticable muscle contraciton (with voluntary PFM contraction				Vaginal, perineal electrodes (active), lumbar electrodes (inactive)	10min sessions, 3/week: 6wks	SUI
Jeyaseelan 2000 [198]				Two freq: low & intermedi-ate		Single vaginal electrode	1hr session, 1/day: 8wks	SUI
Knight 1998 [218] (study arm 1)		Barely perceptible tingling sensation	Duration: 200µsec	Two freq: 10Hz and 35Hz	Single ratio: 1:1 (5s on, 5s off)	Single vaginal electrode	Home treatment : overnight (1/day), 6 months	SUI
Knight 1998 {{78 Knight,S. 1998}} (study arm 2)		Max tolerable intensity + voluntary PFMC	Duration: 250µsec	Two freq: 10Hz and 35Hz	Single ratio: 1:1 (5s on, 5s off)	Single vaginal electrode	Clinic-based treatment: 30min session, 1/day: 6mths (total 16 sessions)	SUI
Laycock 1993 [178]	Interferential (bipolar)	Max tolerable intensity		Freq range: 10-40Hz; and 1Hz to 40Hz		Transcutane-ous electrodes	15mins (first session), 30mins (subsequent sessions): 10 sessions, clinic-based treatment	SUI
Lin 2004 [204]		Range 8-70mA	Duration: 200-500µsec	Freq range: 5-50Hz		Vaginal or anal electrode	20min sessions, 1/day, 5x a week: 4-6 weeks	DO
Lo 2003 [237]		Max tolerable intensity		Freq range: 0-100Hz		Transcutane-ous: 2 anterior, 2 posterior	First session 15 mins; other sessions 30mins, 3/week, by physiothera-pist: 4wks	SUI/UUI

Table 7: Electrical stimulation parameters and protocols in the electrical stimulation (Estim) trials (continued)

Study	Current	Current Intensity	Pulse Shape & Duration	Frequency (Hz)	Duty Cycle	Electrodes	Treatment Duration/ Supervision	Target UI
Lobel 1998* [233]				Freq range: 0-100Hz		Anal and vaginal electrodes	5 wks. Additional 5 wks if any cure or improvement was noted.	DO
Luber 1997 [228]		Adjustable (10-100mA)	Duration: 2msec	Single freq: 50Hz	Single ratio: 1:2 (2s on, 4s off)	Single vaginal electrode	15min sessions, 2/day, home treatment: 12wks	SUI
Sand 1995 [230]		Max tolerable intensity		Two freq: 12.5Hz and 50Hz	Alternating ratio: 1:1 and 1:2	Single vaginal electrode	7 sessions, clinic-based treatment: 15wks (12wks treatment, 2wks before, 1wk after) ; 70hrs total planned	SUI
Schmidt 2009 [173]	Biphasic	Max tolerable intensity without discomfort	Shape: asym-metric; Duration: 300µsec	Single freq: 50Hz		Vaginal (ring electrodes x 2)	12wks	SUI/MUI
Shepherd 1984 [168]	Monophasic	Noticable PFMC	Shape: square	Freq range: 10-50Hz		Anal and vaginal electrodes	A single 20min session under anaesthesia	Any UI
Smith 1996 [187]	Biphasic pulsed	Progressive: 5-25mA	Shape: asymmetric; Duration: 0.3msec	Two freq: 12.5Hz and 50Hz	Single ratio: 1:2	Single vaginal electrode	2/day, home treatment: 4mths	UUI/DO
Tapp 1987* [238]	Faradic low frequency interrupted direct)					Single vaginal electrode	2/week: 1mth	SUI
Tapp 1989 [177]	Faradic (low frequency interrupted direct)							SUI

Table 7: Electrical stimulation parameters and protocols in the electrical stimulation (Estim) trials (continued)

Study	Current	Current Intensity	Pulse Shape & Duration	Frequency (Hz)	Duty Cycle	Electrodes	Treatment Duration/ Supervision	Target UI
Wang 2006 [225]	Biphasic	Max tolerable intensity	Shape: symmetric; Duration: 400µsec	Single freq: 10Hz	Single ratio: 2:1 (10s on, 5s off)	Single vaginal electrode	20min sessions, 2/week, by physiotherapist: 12wks	DO
Wilson 1987 [171] (study arm 1)	Faradic (low frequency interrupted direct)	Max tolerable intensity + PFMC		Low frequency	12 surges, 2 min rest (repeated 3x)	Transcutane-ous sacral; Transcutane-ous perineal	12 sessions, clinic-based treatment: 6wks	SUI
Wilson 1987 [171] (study arm 2)	Interferential (range20-25mA)	Pressure peak 0.25-0.30Pa/cm2 for 15pulses (range20-25mA)		Medium frequency	4000cycles/sec	transcutane-oussuction electrodes (x4)	12 sessions (first session 10min; other sessions 15mins), clinic based treatment: 6wks	SUI
Wise 1993* [201]	Variable	Just below level of discomfort (range= 0-90mA)		Single freq: 20Hz		Single vaginal electrode	20min sessions, daily home treatment: 6wks	DO

*Footnotes: * abstract only; Estim = electrical stimulation, freq= current frequency, PFM = Pelvic floor muscle, PFMC= Pelvic floor muscle contraction, VPFMC= voluntary Pelvic floor muscle contraction*

1. PREVENTION

No published trials were found that investigated either the primary or secondary prevention of UI or LUTS.

2. TREATMENT

a) Is EStim better than no active treatment (placebo, sham, control or no treatment) for treatment of UI?

Seventeen studies compared EStim with no active treatment. Characteristics of studies comparing EStim with no active treatment are presented in **Table 8**. No active treatment consisted of sham EStim in the majority (11 of 17) of the studies. In others, the 'no active treatment' groups received no treatment [130,224], placebo drugs [225], non-active control intervention such as instruction in the use of an anti-incontinence device [134] or motivational phone calls [140].

One study [226] was a three-arm trial: two of the arms using EStim with either sacral or suprapubic electrodes were combined (N = 32) and compared with the sham ES arm (N = 16). The trial by Brubaker and colleagues [227] included women with SUI or DO with women with SUI comprising the majority of the study sample. Data from this trial therefore contributed to the analysis for SUI.

1. Quality of data (risk of bias)

Three studies [134,225,228] reported adequate methods of allocation concealment, namely opaque (and sealed) envelopes with third party involvement in the allocation procedure. Allocation concealment was assessed as suboptimal in two [168,224] that used opaque or sealed envelopes but with no indication of third party involvement. The remainder did not describe methods used for allocation concealment. Trial results were reported for everyone who entered the trial in three studies [132,224,229] but this was not done in the others.

2. Results

(a) SUI or predominant SUI. Pooled data suggest that cure rates were on average higher for EStim compared with no active treatment but the difference was not statistically significant [132,134,140,178,227,228,230]. Improvement rates were statistically significantly higher for EStim compared with no active treatment [134] [130,132,134,178,227,228,230] although there was some evidence of statistical heterogeneity for the improvement rate (I-squared = 59%).

Adverse effects appeared uncommon. One study reported tenderness and bleeding in 10 of 32 participants using the active EStim device, of which seven withdrew from treatment due to adverse effects [134]. Another study reported that 14 of 35 participants using the active EStim device and seven of 17 participants using the sham device experienced vaginal irritation, pain or infection [230].

Quality of life was reported using diverse measures in three studies. Two of these studies reported statistically significant differences favouring EStim compared with no active treatment: the first [134] used the Social Activity Index, and the second [140] used the I-QoL questionnaire. However, the third study [198] found no significant differences between the groups based on either the Urogenital Distress Inventory or the IIQ.

(b) UUI or predominant UUI. One small study in which all participants had MUI with UUI as a predominant pattern found no significant difference between the groups in cure rates [231] although the confidence interval was wide. Improvement rates were significantly higher for EStim compared with no active treatment based on another small study in which all participants had UUI alone [232]. However, these differences are not informative, because the confidence interval is very wide and the OR is clinically implausible. No information was available on adverse effects and quality of life.

(c) SUI, UUI or MUI. One study [168] that provided information on cure and improvement found no difference between the groups. No information was available on adverse effects and quality of life.

(d) DO (wet or dry). Cure and improvement rates were reported only in one study [225]. There was a statistically significant difference in the improvement rate in favour of the EStim group compared with no active treatment but no difference was found for the cure rate. Caution is required, as the OR is clinically implausible and may be a statistical artefact. Two studies with data on quality of life outcomes reported inconsistent results [224,225]. One study using the KHQ (total score] reported a statistically significant difference favouring EStim compared with no active treatment [225], whereas the other study using the IIQ found no significant difference between the groups [224]. No information was available on adverse effects.

3. Summary

Included studies were generally assessed as having a high risk of bias. EStim might be more effective than no treatment in improving (not necessarily curing) symptoms in women with SUI, UUI or DO, although this may not result in cure **(Level of Evidence: 2**). Information on quality of life was sparsely reported and the limited data that were available were not consistent. Adverse effects appear uncommon but some women experienced discomfort with the treatment device. Few data were available on long-term performance.

4. Recommendations

EStim might be better than no treatment in improving symptoms **(Grade of Recommendation: B)**. However, the recommendation should be viewed with caution until the findings are supported or refuted in

Table 8: Characteristics of studies comparing Electrical stimulation with no active treatment

Author	Comparator	N	Study population	Duration (months)	Source of outcome**	
					Cure	Improvement
SUI or predominantly SUI						
Bø 1999 [134]	No treatment	64	SUI	6	Patient-reported	Patient-reported
Brubaker 1997 [227]	Sham Estim	148	50% of study sample had SUI only	2	Quantified	Patient-reported
Castro 2008 [140]	No treatment	60	SUI	6	Patient-reported	NR
Henalla 1989 [130]	No treatment	50	SUI	3	NR	Quantified
Hofbauer 1990 [132]	Sham Estim	21	SUI	1.5	Patient-reported	Patient-reported
Jeyaseelan 2000 [198]	Sham Estim	27	SUI	2	NR	NR
Laycock 1993 [178]	Sham Estim	30	SUI	2 to 3	Patient-reported	Patient-reported
Luber 1997 [228)	Sham Estim	54	SUI	3	Patient-reported	Patient-reported
Sand 1995 [230]	Sham Estim	52	SUI	3	Quantified	Quantified
UUI or predominantly UUI						
Abel 1997† [232]	Sham Estim	28	UUI only	3	Patient-reported	Patient-reported
Amaro 2006 [231]	Sham Estim	40	Urgency-predominant MUI	1.75	Patient-reported	NR
Berghmans 2001* [436]	No treatment	NR‡	OAB with UI	2.25	NR	NR
Any UI						
Barroso 2004 [229]	Sham Estim	36	SUI, UUI or MUI	3	NR	NR
Shepherd 1984 [168]	Sham Estim	107	SUI, UUI or MUI	3	Patient-reported	Patient-reported
DO/OAB (wet or dry)						
Berghmans 2002 [224]	No treatment	31	OAB	2.25	NR	NR
Bower 1998 [226]	Sham Estim	48	DI or sensory urgency	NR	NR	NR
Wang 2006 [225]	Placebo drug	48	OAB	3	Quantified	Quantified

*Footnote: * abstract only; **Source of outcome: women's self-report was given priority but for studies in which it was not reported, quantification of outcomes based on diaries, pad tests or any other definitions chosen by trialists was used as a proxy. † Publication in Danish with English abstract. English translation of the main text was not available at the time of writing. ‡ Part of 4-arm trial which randomised 83 women with OAB. The number in each arm was not reported; Estim = electrical stimulation, OAB= overactive bladder, DI = detrusor instability, SUI = stress urinary incontinence, UUI = urge urinary incontinence, MUI mixte urinary incontinence, NR = not reported*

further trials; it would be particularly useful if further trials used a validated and reliable quality life measure as a primary outcome.

b) Is one type of EStim better than another in the treatment of UI?

Four studies compared one approach to EStim versus another; two in women with SUI [171,218] and two in women with DO and sensory urge [226,233]. The characteristics of studies comparing one type of Electrical stimulation with another are presented in **Table 9**. No study focusing on UUI or predominant UUI was identified.

1. Quality of data (risk of bias)

Allocation concealment was inadequate in one study that used consecutive (alternative) assignment (quasi-randomisation) [171]. Allocation concealment was also suboptimal in another study in which sealed consecutively numbered envelopes were used but it was unclear if they were opaque and whether a third party was involved in the allocation procedure [218]. The other two studies did not mention allocation concealment [226,233]. In Lobel (1998) data were reported only for those who completed the trial (37 of 43 randomised). It was unclear in the other three studies if trial results were reported for everyone who entered the trial.

2. Results

(a) SUI. Two studies assessed different variants of EStim performed as an adjunct to PFMT and biofeedback. The first compared faradism with interferential therapy: no difference was found between the groups in improvement rates, both after the supervised treatment phase and at six months after the end of the supervised phase [171]. The second study compared maximal EStim with low intensity EStim with higher improvement rates for maximum EStim either at the end of supervised phase or at 6 months after the supervised phase [218]. No information was available on cure rates, adverse effects or quality of life.

(b) DO (wet or dry). Data were available from one study comparing two groups receiving EStim either once or twice a week (for 10 weeks) [233]. The most common adverse effects reported were discomfort and leg tremor during treatment, and UTI, although it was unclear in which group these adverse effects occurred. No difference was found between the groups on a quality of life questionnaire (not specified). No information was available on cure and improvement rates.

3. Summary

Included studies were generally assessed as having a high risk of bias. There were four small trials comparing different EStim protocols; the clinical heterogeneity between studies meant it was not appropriate to pool the data. Based on a single trial for women with SUI, maximal clinic-based stimulation may be more effective than low-intensity home-based stimulation in improving symptoms, although no data were available on cure rates, quality of life and adverse effects **(Level of Evidence: 2)**. The other studies did not find clinically important differences between stimulation groups; the studies were small and may have been underpowered. Further comparisons of EStim protocols are needed.

4. Recommendations

For women with SUI maximal clinic-based EStim might be better than daily low-intensity home-based EStim in improving symptoms **(Grade of Recommendation: B)**. There is a need for studies to elucidate the purpose and biological rationale for EStim in different diagnostic groups, so these can then be tested and compared in clinical trials.

c) Is EStim better than other treatments for UI?

EStim has been compared with PFMT, VC, magnetic stimulation (MStim), and drugs. The comparisons of EStim versus PFMT, and EStim versus VC, have been addressed in Sections B.2.3c and B.3.2b, respectively. For the comparison of EStim and MStim, one trial by Yamanishi and colleagues included both men and women with UI due to either idiopathic or urogenital DO [223]. Because data were not reported separately for women with idiopathic DO it is not clear from this trial whether there was any difference in the effect of MStim compared with EStim.

The remainder of this section focuses on studies that compared EStim with medications: vaginal oestrogen (Premarin) for women with SUI [130]; propantheline bromide 7.5 to 45 mg (various dose) two to three times per day for women with UI due to DO (assumed to be predominant UUI) [187]; oxybutynin 5 mg twice [188,201] or 2.5 mg three times per day [225] and tolterodine 2 mg twice per day [204]. Four studies recruited women with DO [201] or OAB [204,225], or both DO and OAB [188] where some but not all had UI. (**See Table 10.**)

1. Quality of data (risk of bias)

Methods used for allocation concealment were adequate in one [225] but unclear in the other five. Trial results were reported for everyone who entered the trial in one study [187] but this was not done in four [130,188,201] and unclear in one [204].

2. Results

(a) SUI. In one small study of 25 women, 32% in the EStim group and 13% in the oestrogen group reported improvement and the difference was statistically significant [130]. At 9 month follow-up, one of the eight women in the EStim group and all three in the oestrogen group who had reported improvement post-treatment had recurrent symptoms. There was no report of adverse effects. No information was available on cure rates or quality of life.

Table 9: Characteristics of studies comparing one type of electrical stimulation with another

Author	Comparator		N	Study population	Duration (months)	Source of outcome	
						Cure	Improvement
SUI							
Knight 1998 [218]	PFMT+BF +EStim (max)	PFMT+BF+ EStim (low)	49	SUI	6	NR	Patient-reported
Wilson 1987 [171]	PFMT + BF + EStim(faradism)	PFMT + BF + EStim (interferential)	30	SUI	1.5	NR	Patient-reported
DO (wet or dry)							
Bower 1998 [226]	EStim (sacral 150Hz)	EStim (supra-pubic 10Hz)	32	DO or sensory urgency	NR	NR	NR
Lobel 1998* [233]	EStim (once a week)	EStim (twice a week)	37	DO	2.5	NR	NR

*Foot note: * abstract only; **Source of outcome: women's self-report was given priority but for studies in which it was not reported, quantification of outcomes based on diaries, pad tests or any other definitions chosen by trialists was used as a proxy. Estim = electrical stimulation, OAB= overactive bladder, DO = detrusor ioveractivity, SUI = stress urinary incontinence, UUI = urge urinary incontinence, MUI mixte urinary incontinence, NR = not reported*

Table 10: Characteristics of studies comparing electrical stimulation (EStim) with another treatment

Author	Comparator	N	Study population	Duration (months)	Source of outcome**	
					Cure	Improvement
SUI						
Henalla 1989 [130]	Oestrogen cream	49	SUI	3	NR	Quantified
Predominant UUI						
Smith 1996 [187]	Propantheline bromide	38	DI with UI	4	Quantified	Quantified
DO/OAB (wet or dry)						
Arruda 2008 [188]	Oxybutynin	51	OAB and DO (some had urge-predominant MUI)	3	Patient reported	Patient reported
Lin 2004† [204]	Tolterodine	60	OAB	EStim 1-1.5; Drug 0.5-1.	Quantified	Quantified
Wang 2006 [225]	Oxybutynin	51	OAB	3	Quantified	Quantified
Wise 1993* [201]	Oxybutynin	60	DO (some had UI)	1.5	NR	NR

*Foot note: *Abstract only; **Source of outcome: women's self-report was given priority but for studies in which it was not reported, quantification of outcomes based on diaries, pad tests or any other definitions chosen by trialists was used as a proxy.*
† Publication in Chinese with English abstract. English translation of the main text was not available at the time of writing. Estim = electrical stimulation, OAB= overactive bladder, DO = detrusor overactivity, DI = detrusor instability; SUI = stress urinary incontinence, MUI = mixed urinary incontinence, NR = not reported

(b) Predominant UUI. Based on one older small study that recruited women with UI due to DO (UUI was assumed to be the predominant symptom), there was no evidence of a difference between EStim and propantheline bromide both in terms of cure and improvement [187]. No data were available for adverse effects or quality of life.

(c) DO (wet or dry). In three studies with data on cure or improvement, there was no evidence of a difference in cure or improvement between EStim and oxybutynin [225], or between EStim and tolterodine [188]. In two of these studies cure and improvement were defined in terms of resolution or reduction of urgency symptoms rather than UUI [188,225] whereas the outcomes were not defined in the other [204]. Follow-up data based on one study found that treatment effects persisted over time (one year) in four of the 11 (36%) participants in the EStim group and 10 of the 17 (59%) participants in the oxybutynin group who had reported improvement in the initial treatment phase (three months) but the difference between the groups was not statistically significant [188] .

More women with DO who received drugs, experienced adverse effects than those who did not. The most commonly reported adverse effect in both oxybutynin or tolterodine treatment group was a high percentage of dry mouth [188,204] which was "intolerable" [225] or "unacceptable" [201] in a smaller number. Other drug side effects were constipation, indigestion, nausea, headache, dizziness and blurred vision. There was no report of adverse effects or adverse effects resulting in treatment withdrawal in the EStim group. Quality of life outcomes were reported only in one study using the KHQ (total score) [225]. The study reported a statistically significant difference in favour of EStim over oxybutynin; no further data was provided).

3. Summary

Included studies were generally assessed as having a high risk of bias. With small numbers per comparison group available, there is insufficient evidence to determine if EStim is better than vaginal oestrogens in women with SUI, propantheline bromide in women with UUI, or oxybutynin and tolterodine for DO **(Level of Evidence: 2)**.

4. Recommendation

Based on current evidence medical treatments appear to be no more effective than EStim **(Grade of Recommendation: B)**. This hypothesis needs to be investigated further with high quality trials, if it is a clinical question of interest to women.

d) Does the addition of EStim to other treatments add any benefit in the treatment of UI?

A total of 12 studies assessed the effect of EStim as an adjunct to another treatment, compared with the other treatment alone (**Table 11**). Of these, 10 [121,132,135,173,177,234-238] combined EStim with PFMT (EStim + PFMT vs. PFMT), while the other two studies [171, 218] combined EStim with PFMT and biofeedback (EStim + PFMT + BF vs. PFMT + BF).

Two studies were three-arm trials that included both PFMT and PFMT plus sham EStim as two of the study arms [135,236]. These arms were classified as being equivalent to PFMT and combined in the analysis. In two other three-arm trials two of the study arms involving EStim were also combined [107,218]. In one, ESim arms included faradism and interferential therapy [218]; in another, maximal and low intensity EStim were included [171].

1. Quality of data (risk of bias)

Allocation concealment was inadequate in two studies that used consecutive (alternative) assignment (quasi-randomisation) [171,236]. Allocation concealment was also suboptimal in another two in which sealed consecutively numbered envelopes were used but it was unclear whether they were opaque and whether a third party was involved in the allocation procedure [218,237]. The remainder (66%) did not mention allocation concealment. In six (50%) studies, results were reported for everyone who entered the trial [121,132,173,235,237,238], but this was not done in one [234] and unclear in three others [135,171,218].

2. Results

A. EStim + PFMT vs. PFMT

(a) SUI or predominant SUI. Pooled data found no evidence of a difference between the groups in terms of cure [121,132,177,234,235] or improvement [121,132,177]. Adverse effects were reported in one study [121]; the group randomised to EStim with PFMT recorded four occurrences (6%) of vaginal irritation due to application of EStim devices, compared with none in the PFMT only group. Quality of life was also reported only in one study [121]; the results based on the IIQ found no difference between the groups (no further data was provided).

(b) SUI, UUI and MUI. Data available from one study found no significant difference between the groups for either cure or improvement [237]. One small study using the KHQ reported that quality of life was on average better after EStim compared with no EStim during the treatment and at three-month follow-up [173]. The differences reached statistical significance at three-month follow-up. No adverse effects were reported.

B. EStim + PFMT with biofeedback vs. PFMT with biofeedback

SUI. Pooled data from two studies found no difference between the groups in terms of the improvement rate [171,218]. Improvement rates at six

Table 11. Characteristics of studies comparing a combination of electrical stimulation (Estim) and other treatment with the other treatment

Author	Comparator		N	Study population	Duration (months)	Source of outcome**	
						Cure	Improvement
SUI or predominantly SUI							
Bidmead 2002 [135]	EStim+ PFMT	PFMT	164?	SUI	3.5	NR	NR
Blowman 1991 [234]	EStim + PFMT	PFMT	14	SUI	1?	Quantified	NR
Eyjolfsdottir 2009 [235]	EStim+ PFMT	PFMT	24	SUI	2.25	Patient -reported	NR
Goode 2003 [121]	EStim+ PFMT	PFMT	133	≥50% of study sample had SUI-predominant MUI	2	Quantified	Patient-reported
Haig 1995 [236]	EStim+ PFMT	PFMT	58	SUI	3	NR	NR
Hofbauer 1990 [132]	EStim+ PFMT	PFMT	22	SUI	1.5	Patient -reported	Patient-reported
Tapp 1987 [238]	EStim+ PFMT	PFMT	29	SUI	3	NR	NR
Tapp 1989 [177]	EStim+ PFMT	PFMT	53	SUI	3	Quantified	Quantified
Knight 1998 [218]	EStim+ PFMT+BF	PFMT+BF	70	SUI	6	NR	Patient-reported
Wilson 1987 [171]	EStim+ PFMT + BF	PFMT+BF	45	SUI	1.5	NR	Patient-reported
Any UI							
Lo 2003 [237]	EStim+ PFMT	PFMT	24	SUI or UUI	1	Quantified	Quantified
Schmidt 2009 [173]	EStim+ PFMT	PFMT	22	SUI or MUI	3	NR	NR

*Foot note: **Source of outcome: women's self-report was given priority but for studies in which it was not reported, quantification of outcomes based on diaries, pad tests or any other definitions chosen by trialists was used as a proxy. Estim = electrical stimulation, SUI = stress urinary incontinence, MUI = mixed urinary incontinence, UUI urge urinary incontinence, NR = not reported*

months after the end of the initial treatment phase did not differ between the groups in either study. No data were available on cure rates, adverse effects and quality of life.

3. Summary

For comparisons of EStim with PFMT versus PFMT alone, there was no evidence of a difference between the groups in women with SUI or MUI (in which SUI was the predominant symptom) **(Level of Evidence: 2)**. There was also no evidence to suggest that the addition of EStim to a BF-assisted PFMT was more effective than BF-assisted PFMT in women with SUI **(Level of Evidence: 2)**. A few women experienced side effects with EStim. There is no evidence to draw any conclusion about the effect of adding EStim to PFMT for women with UUI.

4. Recommendations

The addition of EStim to PFMT or BF-assisted PFMT programmes does not appear to add benefit **(Grade of Recommendation:B)**; this hypothesis needs to be investigated further with high quality trials if it is a clinical/research question of interest to women.

3. OTHER LUTS

No trials were identified that analysed the effect of EStim in women with other LUTS alone, i.e., frequency of voiding, urgency and/or nocturia.

4. FACTORS AFFECTING OUTCOME

None of the included trials addressed the effect of age, or any other factor, on outcomes of EStim. Regarding age, there was no clear indication from the included trials that EStim could not be tolerated by elderly. On this basis there is no reason to exclude older women from studies of EStim, or not to offer EStim as part of a conservative management programme, except where recognised contraindications such as a cardiac pacemaker are present. However, it should be noted that this section considered the effect of EStim from studies recruiting independent, community dwelling women; the frail elderly are considered in the chapter on the elderly.

Of note, in a prospective cohort of 3,198 women treated with home-managed EStim in Norway during 1992-1994, there was no association between self-reported improvement and age [239]. In the same cohort, success rates defined by clinicians were higher in younger individuals but this effect was no longer significant after controlling for other factors.

Aside from age, other factors may have the potential to mediate treatment outcome. On the basis of trial reports to date, it appeared that there was considerable variation in EStim protocols with no consistent pattern emerging. EStim protocols are also often poorly reported, lacking detail of stimulation parameters, devices and methods of delivery. The wide range of protocols that have been tested may have impacted on the effect estimates reported in this section.

It is not clear whether one diagnostic group may benefit more than another from EStim. It has been hypothesised that, in women with SUI who cannot voluntarily contract the PFM to begin a PFMT programme, EStim might help initiate or substitute for a voluntary contraction. However, most studies focusing on the efficacy of EStim do use EStim to initiate or substitute for a voluntary PFM contraction [240]. To date, there has been no trial addressing this hypothesis.

EStim is reported to be unsuccessful in women with major descent of the vagina and prolapse of the uterus [228]. Additionally, denervated PFM muscles might not respond to EStim [241]. This means that in women with reduced or no integrity of the relevant nerve pathways EStim provides no or little chance of cure/improvement [217]. It has also been reported that treatment will fail if EStim does not increase urethral pressure profile, although age, oestrogenisation, and urethral mobility may also affect urethral pressure profile and may influence therapeutic outcome [242]. It is unfortunate that it is difficult to assess individuals easily in the clinical setting with regard to integrity of the sacral arc, and other factors, to determine the suitability of EStim as a treatment modality.

As with all conservative therapy modalities, one of the key factors to the success or failure of EStim is treatment adherence. Some authors commented on adherence or reported adherence data. However, adherence measures were highly variable, making comparison across studies difficult. Adherence to EStim was satisfactory and could be attributed to the physician motivating individuals to continue with EStim if they considered stopping prematurely [229]. 'Excellent' or 'good' adherence was observed in 45% of the study participants in one study and this did not differ between EStim and sham [234]. However, another [243] reported that the proportion of women achieving 80% adherence was lower in the active EStim group (61%) compared with the sham group (89%). Bø [134] reported a 75% adherence rate, although it is not clear how this compares with the non-active control group (instruction in the use of an anti-incontinence device). Nevertheless, adherence to EStim was less than that for PFMT (93%) in the same trial, and the reasons for non-adherence to EStim were a lack of motivation and discomfort. Knight [218] reported adherence to home-based low intensity EStim (72.5%) was somewhat higher than that for clinic-based maximal intensity EStim (percentage not reported).

V. MAGNETIC STIMULATION (MSTIM)

MStim has been developed for noninvasive stimulation of both central and peripheral nervous systems [244]. MStim for the treatment of UI was reported

for the first time in 1999 by Galloway [245]. In contrast to EStim, extracorporeal magnetic innervation (more commonly called magnetic stimulation) stimulates the PFM and sacral nerve roots without insertion of an anal or vaginal probe [246] For treatment, the individual is positioned in a chair. Within the seat is a magnetic field generator (therapy head) that is powered and controlled by an external power unit (**Figure 4**). A concentrated steep gradient magnetic field is directed vertically through the seat of the chair. When seated, the individual's perineum is centred in the middle of the seat, which places the PFM and sphincters directly on the primary axis of the pulsing magnetic field (**Figure 5**). Because of this, all tissues of the perineum can be penetrated by the magnetic field. According to Galloway [1999] no electricity, but only magnetic flux enters the body from the device. Goldberg [2000] has suggested that, in contrast to electrical current, the conduction of magnetic energy is unaffected by tissue impedance, creating a theoretical advantage in its clinical application compared to EStim as structures such as sacral roots or pudendal nerves can be magnetically stimulated without discomfort or the inconvenience of a vaginal or rectal probe. Conventional magnetic stimulators deliver, at frequencies of 10 to 50 Hz, repetitive pulses of current lasting less than 100 μsec [246] and 275 Φs [245] in duration. Size and strength of the magnetic field is determined by adjustments of this amplitude by the therapist [245].

Possible advantages of MStim are that it is performed through full clothing, needs no probes, skin preparation, or physical or electrical contact with the skin surface. On the other hand, the need for repeated clinic based treatment sessions is a potential disadvantage. In contrast to EStim, MStim lacks portability, although in 2003 [247] reported the development of a portable small electromagnetic device (Pulsegen) for home use that fit into the underwear and was designed for continuous use for up to 8 weeks. Furthermore, because both the depth and width of magnetic field penetration is proportional to coil diameter, the present technology is still best suited for stimulation of a field, rather than a narrowly focused target as the sacral roots or the pudendal nerve [246].

MStim of the sacral nerve roots and pelvic floor is said to be effective for both UUI and SUI [246] , although the mechanism of action is not fully understood [248]. Some authors have suggested that in SUI stimulation of the PFM causes external sphincter contraction [249], acts as a passive PFMT exercise [250], and increases maximal urethral closure pressure [247]. In UUI, MStim might suppress DO through activation of pudendal nerve afferents blocking parasympathetic detrusor motor fibres at the spinal reflex arc, activation of inhibitory hypogastric sympathetic neurons, or a combination of both mechanisms [251]. Stimulation of sympathetic fibres maintaining smooth muscle tone within the intrinsic urethral sphincter and modulation of pudendal nerve afferent branches stimulating an inhibitory spinal reflex at the S3 nerve root, are also suggested to play a role in this mechanism of action [251].

Figure 4 : Magnetic stimulation chair with external power unit (Courtesy of Professor Kate Moore and Dr Alastair Morris, University of Sydney, Australia)

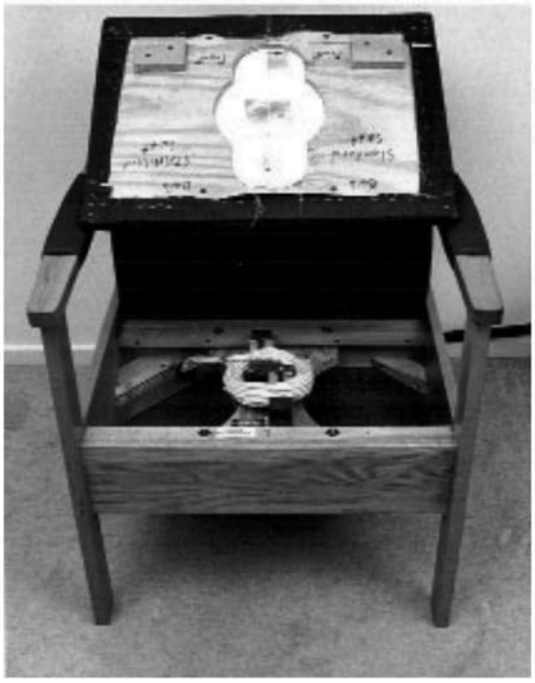


Figure 5: Magnetic stimulation chair with seat lifted to show magnetic field generator (Courtesy of Professor Kate Moore and Dr Alastair Morris, University of Sydney, Australia)

In this section the evidence is considere for the use of MStim for the prevention and treatment of UI in women. Questions addressed are:

- Is MStim effective in the prevention of UI?
- Is MStim better than no active treatment (placebo, sham, control or no treatment) for the treatment of UI?

- Is one type of MStim better than another in the treatment of UI?
- Is MStim better than other treatments in the treatment of UI?
- Does the addition of MStim to other treatments add any benefit in the treatment of UI?
- What is the effect of MStim on other LUTS?
- What factors might affect the outcome of MStim in the treatment of UI?

Description of intervention

Ten trials were identified. Characteristics of the MStim intervention in the included studies are summarised in **Table 12**. Two further trials that did not specify the gender of the participants were found: a cross-over trial comparing MStim plus PFMT with sham MStim plus PFMT for 56 individuals with UUI (due to DO) or SUI [252]; and a comparison of MStim with sham MStim for 87 participants with UUI (due to DO) or SUI [253]. These trials did not contribute to the analysis. **Table 12** illustrates the intervention characteristics.

1. PREVENTION

No trials investigating the primary or secondary prevention effects of MStim for women with UI were found.

2. TREATMENT

a) Is MStim better than no active treatment (placebo, control or no treatment)?

Nine RCTs comparing MStim with sham for women with UI were found. Characteristics of studies comparing magnetic stimulation with no active treatment are presented in **table 13**. One report by Gilling [2002] [254] was an abstract. The trial, which has not yet been fully published, appears to be related to Gilling [2001] [255] of which a full report was published in 2009 [256] (comparing MStim plus PFMT with PFMT alone), but there was insufficient information to verify this. No data were available for any of the pre-specified outcomes. Of the nine included trials, three assessed the efficacy of a magnetic stimulator developed for home use, whereas in others treatment was provided in the clinic setting [247, 257, 258].

1. Quality of data (risk of bias)

Allocation concealment was considered to be adequate in three (33%) trials that used numbered devices of identical appearance [247, 257, 259], or involved a randomisation list in a locked drawer only accessible to a member who had no other involvement in the trial. Allocation concealment was assessed as being suboptimal in one study [258] that used sealed envelopes but did not mention whether envelopes were opaque nor any involvement of a third party in the allocation process. Another five (56%) did not describe methods used for allocation concealment [254, 260-263]. Two studies reported data for all participants randomised [260, 261]. In three, data were reported only for those participants who completed the study [247, 259, 263]. In particular, in the study by Morris [2007] only 29 of 44 (66%) women randomised completed the study, including 10 women deemed ineligible after randomisation. The number of women lost to follow-up was not clearly reported in the other four (45%) trials [247, 254].

2. Results

(a) SUI. Data on cure and improvement rates were reported in one study [Fujishiro, 2000]: on average active treatment (single session) was better than sham treatment both in terms of cure and improvement but the difference was statistically significant only for improvement. One other study that provided stimulation for three days a week for two weeks (six sessions in all) that also measured cure and improvement did not provide any data but reported no statistically significant differences [262].

Information on quality of life was provided in two studies using different measures [261,262]. One study using the KHQ did not report a total score but scores on all questionnaire items were similar between the groups either at one week or one month after the intervention [262]. The second study did not describe how quality of life was ascertained but reported that mean scores did not differ significantly between the groups [261]. No adverse effects were observed in one of these studies [261].

(b) UUI. Suzuki and colleagues (2007)[263] conducted a cross-over trial including 16 men and 23 women with UUI refractory to PFMT [263]. Participants were randomised to either 10-week active treatment, four-week no treatment and 10-week sham treatment (A-S group) or 10-week sham treatment, four-week no treatment and 10-week active treatment (S-A group). Only quality of life outcomes were reported separately for women, based on the International Consultation on Incontinence-Questionnaire: Short Form (ICIQ-SF), in which lower scores indicate better quality of life. In women in the A-S group, ICIQ-SF scores (mean, SD) decreased from baseline by 4.6 (3.9) at 10 weeks and 3.5 (3.5) at 24 weeks. The corresponding scores in women in the S-A group were 1.3 (2.9) at 10 weeks and 4.5 (4.2) points at 24 weeks. These results were interpreted by the study authors to mean that active MStim was more effective than sham MStim. There was no report of adverse effects.

(c) MUI. In one small study, active treatment resulted in statistically significantly higher improvement rates compared with sham treatment [257]. There were no adverse effects in either group. Information on cure and quality of life was not available.

(d) SUI, UUI, or MUI. One small study reported statistically significant differences in favour of active treatment for cure or improvement [247]. In

Table 12: Characteristics of magnetic stimulation (MStim) in the included studies

Study	Intervention description
But 2003 [247]	Pilsegen device for home use, worn in specially designed underwear day and night for 2 months. Magnetic field intensity B max = 230 µT ±10%. Pulse frequency 10 Hz.
But 2005 [257]	Pilsegen device for home use, worn in specially designed underwear day and night for 2 months. Pulse frequency 18.5 Hz.
Fujishiro 2000 [261)	In prone position, using a rapid rate stimulator with a rapid 90 mm circular coil. Coil fixed over the sacrum to cover the bilateral third sacral foramina. A 15 Hz repetitive magnetic stimulation on the sacral roots with 50% intensity output for 5 seconds per minute for 30 minutes.
Fujishiro 2002[260]	In prone position, using a rapid rate stimulator with a rapid 90 mm cicular coil. Coil fixed over the sacrum to cover the bilateral third sacral foramina. A 15 Hz repetitive magnetic stimulation on the sacral roots with 50% intensity output for 5 seconds per minute for 30 minutes.
Gilling 2001 [255)	NeoContol chair with an inbuilt magnetic coil for 10 minutes at 10 Hz followed by 3-minute rest, and 10 minutes at 50 Hz. Intensity adjusted to the maximum level tolerated. Total: 16 treatments (3 per week) over 6 weeks.
Gilling 2002* [254]	16 treatments
Lee 2004† [264]	Fully clothed and seated on a special chair, 20 minutes, 2-3 times a week for 12 weeks.
Manganotti 2007 [262]	Chair using a rapid rate stimulator with a 90 mm circular coil. Repetitive 15 Hz magnetic stimulation over the distal cauda at 60% intensity for 15 minutes, 3 days/week for 2 weeks.
Morris 2007 [259]	Neocontrol device for two 10-minute periods of stimulation at 10 Hz, at individual maximum tolerance, separated by 2 minutes rest. 20 treatment sessions over 6 weeks, with at least 36-72 hours between sessions.
O'Reilly 2008 [258]	Trans-sacral magnetic stimulator for home use, applied using a small belt device over the S3 and S4 sacral foramina for 20 min each day for 12 weeks. Pulse rate between 5 and 20 Hz with pulse width of 1 ms producing a magnetic field of 200 G.
Suzuki 2007 [263]	Armchair type stimulator. 10Hz continuously with 300 µsec for 20 minutes, 1/week for 10 weeks.

*Foot notes: * Abstract only. † Publication in Korean with abstract and tables. English translation of the main text was not available at the time of writing.*

Table 13. Characteristics of studies comparing magnetic stimulation (MStim) with no active treatment

Author	Comparator	N	Study population	Treatment duration (months of treatment or when outcome was measured)	Source of outcome**	
					Cure	Improve-ment
SUI						
Fujishiro 2000 [261]	Sham MStim	62	SUI	1 session (outcome measured at 1 week]	Quantified	Quantified
Gilling 2002 [254]* (ongoing)	Sham MStim	43	SUI	NR	NR	NR
Manganotti 2007 [262] (preliminary investigation)	Sham MStim	20	SUI	0.5(outcome measured at 1 month)	Quantified	Quantified
UUI						
Suzuki 2007 [263] (cross-over trial)	Sham MStim	23	DO with UUI	1.25	NR	NR
MUI						
But 2005 [257]	Sham MStim	39	MUI	2	NR	Patient reported
Any UI						
But 2003 [247]	Sham MStim	55	SUI, UUI or MUI	2	Patient reported	Patient reported
DI/OAB (wet or dry)						
Fujishiro 2002 [260]	Sham MStim	37	DI (UUI or urinary frequency)	1 session (outcome measured at 1 week)	NR	NR
Morris 2007 [259]	Sham MStim	44	Idiopathic DO (some had UUI)	0.75	NR	NR
O'Reilly 2008 [258]	Sham MStim	63	OAB (some had UUI)	3	NR	Patient reported

*Foot notes: NR = not reported; * abstract only; **Source of outcome: women's self-report was given priority but for studies in which it was not reported, quantification of outcomes based on diaries, pad tests or any other definitions chosen by trialists was used as a proxy.*

this study, one of 31 women in the active treatment group had lumbar-ischial pain in the right leg and withdrew from treatment, whereas none of 24 women in the sham group experienced any adverse effects. Information on quality of life was not provided.

(e) DO (wet or dry). One small study reported that improvement rates did not differ significantly between active and sham treatments [258]. No information was available regarding cure rates. Quality of life outcomes were reported in three studies using different measures [258-260]. There was no difference between the groups in terms of the IIQ or the Urogenital Distress Inventory [259] or between KHQ or the Australian Quality of Life questionnaire [258]. There was one report of statistically significant better qualify of life scores for treatment than sham, although it was unclear how this was ascertained [260]. No adverse effects were noted.

3. Summary

Since there was little duplication of MStim interventions, or sample populations, in the nine small trials, it was not thought appropriate to combine study findings. For women with SUI a single trial showed that one session of sacral root MStim might be more effective than sham in improving symptoms **(Level of Evidence: 2)**, but another trial suggested that six sessions of a chair-based MStim might be no better than sham **(Level of Evidence: 2)**. For women with UUI, evidence from a small trial suggests that active MStim might result in better quality of life than sham **(Level of Evidence: 2)**, although there is some uncertainty surrounding this. Active MStim was associated with higher cure rates than sham in a small trial with women with MUI **(Level of Evidence: 2)**, and also higher cure and improvement rates in another small trial with women with SUI, UUI or MUI **(Level of Evidence: 2)** but no such difference was observed for women with DO (wet or dry) **(Level of Evidence: 2)**. In general, adverse effects appear uncommon.

4. Recommendations

Of the MStim protocols investigated to date, it seems that both sacral root MStim and home-based MStim, are worthy of further investigation in women with UI. No recommendation is possible based on current evidence **(Level of recommendation: D)**.

b) Is one approach to MStim better than another?

One study from Korea [264] compared the effect of pelvic floor MStim with BIOCON compared with stimulation via NEOCONTROL for females with SUI (**Table 14**). This report was published in Korean. Data were extracted only from the abstract and main data tables that were reported in English.

1. Quality of data (risk of bias)

Risk of bias could not be assessed, because the trial was published in the Korean language and English translation was not available at the time of writing.

2. Results

Any UI. No statistical difference was found between the groups in terms of cure of UUI or cure of SUI. Quality of life scores based on the Bristol Female Urinary Tract Symptoms were also similar between the groups.

3. Summary

There is insufficient evidence to determine if one type of MStim is better than another **(Level of Evidence: 2)**. No recommendation is possible **(Level of Recommendation: D)**.

c) Is MStim better than other treatments?

There was a single trial by Yamanishi and colleagues that addressed this comparison [223]. In this trial, MStim was compared with intravaginal EStim in 17 women and 15 men with either idiopathic or neurogenic DO. As data were not reported separately by gender and by diagnosis, it is not clear whether there is any difference in effect of MStim compared to EStim for women with idiopathic DO.

d) Does the addition of MStim to other treatments add any benefit in the treatment of UI?

One trial [255] was identified for this comparison. This report was initially available only as an abstract published in 2001. Subsequently, a full-text publication became available in 2009 [256], although participants were followed up for six months post-intervention and no further follow-up was reported. It should be noted that the aim of the trial was to compare active and sham MStim treatments, rather than to examine the effect of MStim as an adjunct to PFMT. Because trial participants had varying degrees of pre-existing knowledge about their condition and available treatments such as PFMT, low-intensity PFMT supervised by a uro-physiotherapist was added to both groups in order to minimise a potential bias. Characteristics of studies comparing MStim combined with another treatment with the other treatment are presented in **table 15**.

1. Results

SUI. The trial found no statistically significant difference for any outcome between the active and sham groups at eight weeks or 6 months (cure; Incontinence Quality of Life questionnaire, KHQ) [255].

The study authors postulate that PFMT performed in each arm of the trial might have concealed any small additional benefit from MStim. This was supported by a post hoc subgroup analysis which suggested that the women with poor PFM tone at baseline (and therefore unlikely to have performed PFMT properly) did better with active treatment than sham treatment.

2. Recommendation

Based on current evidence **(Level of Evidence: 2)** the addition of MStim to PFMT does not appear

Table 14: Characteristics of studies comparing one type of magnetic stimulation (MStim) with another

Author	Comparator		N	Study population	Treatment duration (months)	Source of outcome**	
						Cure	Improve-ment
Any UI							
Lee 2004† [264]	BIOCON MStim	NEO-CONTROL MStim	49	Any UI	3	Patient reported	NR

*Foot notes: NR = not reported; **Source of outcome: women's self-report was given priority but for studies in which it was not reported, quantification of outcomes based on diaries, pad tests or any other definitions chosen by trialists was used as a proxy. † Publication in Korean with abstract and tables. English translation of the main text was not available at the time of writing.*

Table 15: Characteristics of studies comparing magnetic stimulation (MStim)S combined with another treatment with the other treatment

Author	Comparator		N	Study population	Treatment duration (months)	Source of outcome	
						Cure	Improvement
Gilling 2001 [255]	MStim + low-intensity PFMT	Sham MStim + low-intensity PFMT	70	SUI	0.75 (outcome measured at 2 and 6 months after treatment)	Quantified	NR

*Foot notes: NR = not reported; **Source of outcome: women's self-report was given priority but for studies in which it was not reported, quantification of outcomes based on diaries, pad tests or any other definitions chosen by trialists was used as a proxy.*

to be beneficial **(Grade of Recommendation: C)**. This hypothesis needs to be investigated further with high quality trials, if it is a clinical question of interest to women.

3. Other LUTS

No trials were identified that analysed the effect of MStim in women with other LUTS alone, i.e., frequency of voiding, urgency and/or nocturia.

4. Factors affecting outcome

None of the included trials addressed the effect of age, or any other factor, on outcome of MStim. In one early prospective multi-centre study, factors predicting success of MStim were included [243]. Treatment success was associated with no prior hysterectomy, no prior anti-incontinence operations, UI symptoms for less than 10 years, and no use of medications known to cause UI. Brodak has suggested that detrusor response to stimulation might be better in 'thin' individuals (presumably due to a shorter distance between the stimulating coil and the sacral nerve roots) and at low bladder volumes [265]. Overall, little is known about the factors affecting the outcome of MStim.

VI. SCHEDULED VOIDING REGIMENS

This section examines the evidence on use of scheduled voiding regimes in cognitively intact, non-institutionalised women with UUI, SUI, and MUI and provides recommendations for their use in clinical practice. A summary of the search strategy and inclusion/exclusion criteria for selecting studies for review is provided (See appendix). The chapters on the Frail Elderly and Neurogenic Incontinence provide detailed review of scheduled voiding regimens that are used in those with cognitive impairment, or UI secondary to central nervous system or spinal cord disease.

Scheduled Voiding Regimens

Bladder training is a broad term often used to describe any type of a scheduled toileting intervention. This has created conceptual confusion in interpreting research reports where few details are provided other than the statement that bladder training was used. The types of scheduled voiding regimens can be categorised as: bladder training, timed voiding, habit training, and prompted voiding [266]. Although these regimens share a common feature of a toileting schedule, they differ on the basis of adjustments to the voiding schedule, the active or passive involvement of the patient, the nature of patient education including the teaching of strategies to control urgency and prevent stress leakage, the use of reinforcement techniques, and the nature of the interactions between clinicians and patients. In practice, however, scheduled voiding regimens may share aspects of one or more of these features.

Bladder training

Bladder training (also referred to as bladder drill, bladder discipline, bladder re-education, and bladder re-training) involves a programme of patient education along with a scheduled voiding regimen with gradually progressive voiding intervals. Specific goals of bladder training are to correct faulty habit patterns of frequent urination (if present), improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes, and restore patient confidence in controlling bladder function. The underlying mechanism of how bladder training achieves its effect is poorly understood. Several hypotheses have been proposed including improved cortical inhibition over detrusor contractions; improved

cortical facilitation over urethral closure during bladder filling; improved central modulation of afferent sensory impulses; altered behaviour resulting from better individual awareness of the lower urinary tract function and circumstances that cause UI, and increasing the "reserve capacity" of the lower urinary tract system [189,267,268]. A Cochrane review of bladder training was last updated in 2010 [269].

Timed voiding

Timed voiding is a fixed voiding schedule that remains unchanged over the course of treatment [266]. The goal is to prevent UI by providing regular opportunities for bladder emptying prior to exceeding bladder capacity. Timed voiding has been recommended for patients who cannot participate in independent toileting [270]. It also has applicability for use in outpatient settings with incontinent women who have infrequent or irregular voiding patterns [271] and men who are independent in their voiding function [272]. A Cochrane review of timed voiding was last updated in 2009 (published 2010) [273].

Habit training

Habit training is a toileting schedule matched to the individual's voiding pattern based on an their voiding diary. The toileting schedule is assigned to fit a time interval that is shorter than the person's normal voiding pattern and precedes the time period when incontinent episodes are expected. Thus, the voiding interval may be lengthened or shortened throughout the day depending on the patient's voiding pattern with the goal to pre-empt UI. Habit training is usually implemented by caregivers, in institutional settings with cognitively and/or physically impaired adults, but it has also been tested in homebound older adults [274]. It is potentially useful for adults without cognitive or physical impairment, who have a consistent pattern of UI [271].

A Cochrane review on habit training was updated in 2009 and published in 2010 [275] following first publication in 2004. Prior to this, the last literature review was published in 1986 [266]. The Cochrane review identified three trials that described the effects of habit training combined with other treatment components compared to usual care on the frequency and severity of UI [274, 276, 277]. A fourth trial compared habit training alone with habit training and an electronic monitoring device [278]. Participants from the first three trials were primarily care-dependent women with cognitive and/or mobility impairment, and the fourth trial comprised men and women with a mean age of 83 years and thus, did not meet the criteria for this chapter. No studies were located that investigated habit retraining in independent-living women.

Prompted voiding

Prompted voiding refers to a caregiver education programme in combination with a scheduled voiding regimen, typically every two hours. It is used to teach people with or without cognitive impairment to initiate their own toileting through requests for help and positive reinforcement from caregivers when they do so [279]. It has been used primarily in institutionalized settings with cognitively and physically impaired older adults. In a 2009 Cochrane review of prompted voiding [279], nine trials were identified involving 674 elderly people, mainly women. These trials did not meet the criteria for this chapter as the samples were drawn from care home settings and comprised elderly individuals with impaired cognitive and/or functional ability.

This section will examine the evidence for the use of timed voiding and bladder training for the prevention and treatment of UI in non-institutionalised women of all ages without cognitive or mobility impairments. However, the majority of evidence available pertains to bladder training thus the effects of bladder training are the focus of this section.

Questions addressed are:

- Can scheduled voiding regimes prevent UI?
- What is the most appropriate bladder training protocol?
- Is bladder training better than no treatment, placebo or control treatments?
- Is bladder training better than other treatments?
- Can any other treatment be added to bladder training to add benefit?
- Does the addition of bladder training to other treatments add any benefit?
- What is the effect of bladder training on other LUTS?
- What factors might affect the outcome of bladder training?

This section is based on previously published systematic reviews, including Cochrane reviews, and additional searches of the literature. Studies that were excluded from prior systematic reviews, due to the inclusion criteria for the review or restriction to RCTs or quasi-RCTs, were also considered. Conference abstracts were considered where adequate information was available.

1. PREVENTION

No trials were identified that examined scheduled voiding regimens as a sole intervention in the prevention of UI.

2. TREATMENT

Three systematic reviews on bladder training were located that provided descriptive synthesis with evidence grading [269, 270, 280]. The third is a published Cochrane review that has been updated in 1999, 2004, 2007, and 2010 [269].

a) What is the most appropriate bladder training (BT) protocol?

No trials were identified that compared two or more methods of bladder training (BT). In the absence of trials comparing two or more approaches, a content analysis of the protocols used in trials investigating the effects of BT was performed. Seventeen trials on BT involving a total of 2462 women were identified. Six of the trials provided no or minimal details regarding the specific BT protocol used [128,269,281-285]. In trials that did provide some description, BT protocols were implemented in several ways.

All protocols involved some type of patient education, namely:

- Brief verbal [282,283] or written instructions [286, 287]
- Verbal, written, and audiovisual instruction [189, 268, 288]
- Introduction to an individual who successfully completed BT [284]

If specified, the education was provided by nurses [128,189,268,281,289,290], or general practitioners [291].

Scheduling of voids varied in the following ways:

- Assignment of the initial voiding interval varied from 30 minutes to two hours, with one hour being the most common interval based upon the participant's voiding pattern or 30 minutes beyond the participant's average voiding interval [287,292].
- Adjustments to the voiding interval varied from 15 to 30 minutes, with 30 minutes the most common interval. Increases were made daily for inpatient regimens [284], after 48 hours of dryness [293], every four to five days [292], or weekly if schedule was well-tolerated [189,268].
- Goals for optimal voiding interval varied from three to four hours.
- Voiding was 'mandatory' with restriction of voiding in between assigned toileting times even if UI occurred [284], a scheduled voiding regimen that allowed interruptions in the schedule if urgency became unbearable [189,268,289], or self-scheduling of voiding with a target goal to reach [286].
- Voids were not scheduled (allowed) during sleeping hours [284]; none of the other protocols identified how voids were handled during sleeping hours.

In some protocols the scheduled voiding regimen was supplemented by specific strategies to control urgency and/or stress leakage, including distraction and relaxation [189, 268, 286, 287, 289], and pelvic floor muscle contraction [189, 281, 287]. In other studies there was encouragement to suppress urge but it was not clear what strategies were used [48, 283, 291]. Feedback techniques included self-monitoring [189, 268, 282, 285, 289], goal setting with feedback of progress [290], and positive reinforcement [189, 268, 292].

Several protocols included use of adjunctive treatments:

- Fluid and caffeine adjustments [48,288,289]
- Fluids allowed up to a certain level (1,500 ml) [293]
- No fluid modifications [189,268,286,291]
- Advice on constipation prevention [289].

Both in and outpatient BT programmes have been used. Early inpatient BT programmes involved five to13 days of hospitalisation to ensure strict protocol adherence [284]. Outpatient programmes are more commonly described and the amount of health professional contact had ranged from weekly visits for six weeks with fortnightly telephone calls for six additional weeks [189], to weekly visits [128,268], fortnightly visits [292], and monthly visits [293].

Overall, there is a lack of consistency in BT protocols. Based on the protocols described, a reasonable outpatient BT protocol is shown in **Figure 6.**

Box: Typical Bladder Training Regimen

- an initial voiding interval typically beginning at one hour during waking hours, which is increased by 15 to 30 minutes per week depending on tolerance of the schedule (such as fewer incontinent episodes than the previous week, minimal interruptions to the schedule, and the woman's feeling of control over urgency and confidence to expand the voiding interval), until a two to three hour voiding interval is achieved. A shorter initial voiding interval, e.g. 30 minutes or less, may be necessary for women whose baseline micturition patterns reveal an average daytime voiding interval of less than one hour.
- education about normal bladder control and methods to control urgency such as distraction and relaxation techniques and PFM contraction.
- self- monitoring of voiding behaviour using diaries or logs in order to determine adherence to the schedule, enhance self-awareness, evaluate progress, and determine whether the voiding interval should be changed. **FIGURE 6** from 2009
- a supervising health care professional to monitor progress, suggest adjustments to the voiding interval, and provide positive reinforcement to women undergoing BT at least weekly during the training period.

If there is no improvement after three weeks of BT, re-evaluation is warranted and other treatment

Figure 6: Self-monitoring of voiding behaviour (Courtesy of Dr Jean Wyman, University of Minnesota, USA)

options would be considered. Inpatient BT programmes may follow a more rigid scheduling regimen with progression of the voiding interval on a daily basis.

1. Summary

There is no trial evidence to suggest the most effective method or specific parameters of BT. For those undertaking BT it is likely that more health professional contact will be better than less, based on the developing evidence for PFMT, which like BT, requires behavioural change. The literature suggests several variables that could be investigated in future trials including the instructional approach, supervisory intensity, strategies for controlling urgency, scheduling parameters, frequency of schedule adjustments, length of treatment, and use of adjunctive treatments.

2. Recommendations

It is not clear what the most effective BT parameters are. Clinicians and researchers are advised to refer to the operant conditioning and educational literature to provide a rationale for their choice of BT parameters or approach **(Grade of Recommendation: D).** Clinicians should provide the most intensive BT supervision that is possible within service constraints **(Grade of Recommendation: D)**. More research is needed to investigate which BT parameters, supervisory intensity, and adjunctive treatments are most effective. Future trials should include outcomes that matter to patients including the length and frequency of supervisory contact.

b) Is BT better than no treatment, placebo or control treatments?

BT as the sole therapy has been used in the treatment of DO, urodynamic SUI, MUI, UUI, UUI with a stable bladder, and OAB syndrome (also called urgency-frequency syndrome). Individual RCTs that met inclusion criteria and the Cochrane review [269] were used to address the question of whether BT is better than no treatment, placebo, or control treatments for UI.

Five RCTs reporting on 515 women were identified that compared the effect of BT to no treatment or control [128,268,285,289,291]. In one trial, it was not possible to identify the effect of BT alone, because results of participants in the treatment group who received BT (those with UUI or MUI) were combined with those who also received PFMT (SUI participants) [291]. However, in the Cochrane review, additional data were provided by the lead author to describe the women with DO who were randomised to BT versus control. In another trial with three consecutive treatments (self-monitoring, BT, and PFMT; with the decision for which treatments to implement based on participants' goals), it was difficult to discern the effect of BT alone as compared to a control group, because some participants had already undergone lifestyle modifications (caffeine and fluid modifications and constipation advice) and diary keeping in a prior self-monitoring condition [289]. Thus, this trial is not discussed further in this section. A recent trial by Diokno et al 2010 [288] compares group session teaching of a behavioural modification program (BMP) includes both bladder training and pelvic floor muscle training, thus it was not possible to determine the effect of BT alone in this study and it is not included in subsequent discussion.

There were four older trials with analysable data: Jarvis (1980) investigated the effect of an in-patient BT programme in 60 women aged 27 to 79 years with a diagnosis of DO or coexisting SUI, whereas three [128,268,291] examined the effect of an outpatient programme. Fantl (1991) studied the effect of a six week outpatient programme in 123 women aged 55 to 90 years with urodynamic SUI, DO, or both who reported an effect of an eight week outpatient programme in 50 women aged 35 to 55 years with UI (type not identified) who had pad test weights at least 1g or more and 14 or more voids during a two day diary. Lagro-Jansen (1992) studied the effect of an outpatient programme in 18 women aged 20 to 65 years who reported UUI twice or more per month and had urodynamically confirmed DO.

1. Quality of data

In one trial random allocation concealment was inadequate [291]; in the remainder it was not clear if allocation was concealed. One used stratification based on urodynamic diagnosis of urodynamic SUI and/or DO [268]. Blinding of outcome assessors was described in only one trial [128].

Sample sizes in the four analysable trials were 18 [291], 50 [128], 60 [285], and 123 [268]. Fantl (1991) reported a power calculation although details were not described. Losses to follow up were none in one trial, although it was not clear if this was due to having no dropouts or due to lack of reporting [285]. In the other two analysable RCTs, loss to follow up was 6% [268] and 14% [128]. Dropout rates at the immediate follow-up time point seemed similar between the BT and the control groups, ranging from 8% vs. 5%, respectively [268], to 10% versus 14%, respectively [128]. No trials reported whether analyses were based on intent-to-treat principles. Follow-up periods ranged from six [268], eight [128] and 12 weeks [285,291], with an additional evaluation six months [285] and nine months [268], after initiation of treatment. Two trials noted whether there were adverse events with BT [268,285]. No trial reported on adherence.

All of these RCTs, with the exception of the one by Jarvis (1980), were considered in the Cochrane review [269]. The Cochrane reviewers based their conclusions on data available from 172 women in the other three trials.

2. Results

Three of the four RCTs reported statistically significant improvements in the BT group compared to the control group incontinent episodes [268,285,291]; the fourth did not report data on incontinent episodes [128].

Jarvis (1980) reported that 90% of the participants in the treatment group were continent and 83% were symptom free at six months (method for determination of continence and symptom status was not specified but probably self-report) compared to 23% of the control group who were both continent and symptom free. All women who were symptom free after treatment reverted to a normal cystometrogram.

Twelve percent of participants in the treatment group were continent and 75% had reduced their incontinent episodes by at least 50% or more at six weeks, measured by a seven day voiding diary, compared to 3% of controls with no incontinent episodes and 24% with at least 50% reduction in their incontinent episodes [268]. These results were maintained at six months. Women with DO and those with urodynamic SUI with and without DO had similar improvement rates. Participants in the treatment group also significantly decreased the grams of fluid lost on a retrograde pad filling test by 54% with results maintained six months later; this was more pronounced in those who had DO with or without urodynamic stress UI. While some women did revert back to normal bladder function following BT, no relationship was found between changes in urodynamic variables and the number of incontinent episodes [294].

Lagro-Jansen [1992] reported that eight or nine patients in BT perceived improvement of UI compared to none of nine in the control group. Yoon (2003) reported that there was no difference between the BT and control groups in the amount of leaked urine at an immediate follow-up; however, it was not clear if this referred to pad test weights solely or a UI severity score. Conclusions from this trial are uninterpretable because of insufficient power.

The Cochrane review [269] noted that the few data available tend to favour BT; however, the scarcity of data implies that they should be interpreted cautiously.

3. Summary

The few trials available were small and of variable quality, there is minimal Level 1 evidence that BT may be an effective treatment for women with UUI, SUI, and MUI **(Level of Evidence: 1).**

4. Recommendations

BT is an appropriate first line conservative therapy for UI in women **(Grade of Recommendation: A).** Additional high quality studies are needed that examine the effect of BT versus no treatment in treatment of women with UUI, SUI, and MUI.

c) Is BT better than other treatments?

To be included in this section, trials needed to compare BT alone versus another active therapy. For the comparison of BT versus PFMT see B.2.3d. The only other comparison for which trials were found was BT versus drug therapy. Individual trial reports that met inclusion criteria and the Cochrane review [269] were used as the basis of the review of BT versus drug therapy.

Three RCTs were located that compared BT to drug therapy in 322 women [281, 284, 292]. The study by Park and colleagues [281] compared a 12-week BT programme to 2mg tolterodine twice daily in women (ages unknown) with OAB (unclear if UI was present); because there were no findings reported on UI, this trial is discussed in the section on Other LUTS (B.6.3). The two trials included in this section used a combination of flavoxate hydrochloride and imipramine [284], or used immediate-release oxybutynin chloride [292].

1. Quality of data

One trial reported adequate random allocation concealment [292]. Sample sizes were 50 [284] and 79 [292]. Neither trial reported a power calculation;

Follow up periods varied from four [284], six [292], and 12 weeks [284], and six months [292]. Both RCTs evaluated drug tolerability and adverse events. Dropouts were none in one trial; however, it is not clear whether this was a reporting issue [284]. In the other trial loss to follow up was 7% [292]. Neither trial identified whether intent-to-treat principles were followed. The conclusions of the Cochrane review [269] were based on the same trials.

2. Results

One RCT published in 1981 suggested that BT may be superior to drug therapy in women with DO [284]. Inpatient BT was compared to outpatient treatment of 200mg of flavoxate hydrochloride (three times a day) and 25mg of imipramine (three times per day) in 50 women aged 17 to 78 years with DO, and concluded that BT was more effective. In the BT group, significantly more patients (84%) became continent and symptom free (76%) assessed by self-report, as compared to the drug group where 56% became continent and 48% were symptom free at four weeks. Patients who were symptom free at four weeks were able to maintain their outcomes at 12 weeks and more in the BT group perceived that they were cured at the end of the treatment phase and approximately two month after treatment ended. Adverse events included dry mouth, dizziness, headache, nausea, vomiting, and drowsiness in participants who received drug therapy; there were none with BT.

A similar clinical cure rate (i.e. self-reported total disappearance of UUI, no protective pads or further treatment) was reported in outpatient BT women aged 24 to 65 years with DO [292]. 'Clinical cure' was observed in 93% and 62% of patients with DO, 67% and 75% of those with low compliance bladder, and 60% and 81% of those with urgency-frequency syndrome in those randomised to oxybutynin and BT respectively. The relapse rate at six months was higher for the drug group. In the analysis by the Cochrane Group (2010) participants' perception of cure was not statistically significant at the end of the treatment phase but favoured BT six months after the treatment ended. Perceptions of improvement were also higher in the BT group at the end of the treatment phase but this difference was not statistically significant. Adverse events included dry mouth, constipation, nausea and tachycardia in patients who received drug therapy, with none in those who received BT.

3. Summary

It is not clear whether BT is more effective than drug therapy for women with DO or UUI **(Level of Evidence: 1)**. This is consistent with the findings of the Cochrane review [269], which concluded that there was not enough evidence to determine whether first line therapy should be BT or anticholinergic drugs.

4. Recommendations

In a choice between BT and anticholinergic drug for women with DO or UUI, either may be effective **(Grade of Recommendation: B)**. BT may be preferred by some clinicians and women because it does not produce the side effects and adverse events associated with drug therapy **(Grade of Recommendation: D).**

d) Can any other treatment be added to BT to add benefit?

To be included, trials needed to investigate the effects of BT versus BT plus therapy A to address the additive benefit of therapy A. Trials addressing the additional benefit of three other treatments were found: caffeine reduction, PFMT, and drug therapy. The trial addressing the added benefit of caffeine reduction [48] is considered in the section on Lifestyle Interventions (A.I.2d), and the trial addressing the added benefit of PFMT [189] is considered in the section on PFMT (A.II.3e). The trials addressing the added benefit of drug therapy are considered below.

One RCT was found that compared BT alone versus BT with tolterodine (2mg, twice daily) in women with OAB [281]. However, incontinence status of the participants was unknown, and details regarding the study methodology were limited (abstract only). Therefore this trial was not considered further in this section.

A further three RCTs compared BT with placebo drug versus BT with drug therapy in patients with DO. One of these used terodoline (a drug that was withdrawn from the market) [283]. Therefore, this trial was not considered further in this section. In the other two trials the drugs used were imipramine [293] and immediate release oxybutynin [282].

Castleden [1986] studied 34 patients with DO (28 women aged 30 to 91 years and six men). Szonyi [1995} recruited 60 patients aged 70 years and over (56 women, four men). While it is possible that the placebo drug could augment BT, and both these trials included a small number of men in addition to women (and data for women were not reported

separately), a pragmatic decision was made to review these two trials in this section.

1. Quality of data

Adequate random allocation concealment, or blinding was not reported in either study [282,293]. Study size was based on a power calculation in one [282]. Post-treatment follow up periods were variable. One trial evaluated participants at six weeks [282]; 16 were lost to follow up. The other did not have a clear endpoint but followed participants for one to 11 months; one participant was lost to follow-up [293].

2. Results

It was not possible to discern the treatment effects in only women in these two trials, and the findings were inconsistent. More participatents became dry on BT plus imipramine 25mg or more per day (14 of 19) compared to those in the BT plus placebo group (six of 14), but the authors reported that there was no statistically significant difference in outcome between the two groups [293]. One patient in the imipramine group became confused and another complained that the drug made him feel ill. Several patients taking imipramine reported dry mouth and constipation (data not reported), but none on placebo.

No difference was found in a comparison of BT plus 2.5mg of immediate release oxybutynin (twice daily) compared to BT and placebo for reducing incontinent episodes [282]. The authors concluded, however, that the combined therapy group was superior to the BT and placebo group, because it had greater subjective benefit (86% versus 55%), and adverse events were similar in the two groups at 50%.

3. Summary

In two small trials comparing BT plus placebo drug versus BT plus drug in DO, there was a suggestion that the effect of BT might be enhanced by active drug **(Level of Evidence: 2)**. However both trials were small, placebo controlled, conducted in gender mixed sample populations, and the outcomes were not common to both trials. Thus, there is insufficient evidence to derive a conclusion related to the effectiveness of augmenting BT with drug therapy.

4. Recommendations

Direct comparisons of BT versus BT with drug are needed to address the question of whether the effect of BT can be augmented by drug therapy.

e) Does the addition of BT to any other treatment add benefit?

To be included, trials needed to investigate the effects of Therapy A versus Therapy A plus BT to assess the added benefit of BT over Therapy A alone. Trials were located that investigated the effects of PFMT alone versus PFMT plus BT, and drug therapy alone versus BT plus drug therapy.

A new trial compared Solifenacin (5/10mg) alone with Solifenacin and bladder training [287]. One older study (Wyman 1998) compared BT, PFMT, and combination therapy in 204 community dwelling women aged 45 years and older with SUI and/or DO [189]. Two RCTs were identified that compared BT plus tolterodine (2mg twice daily) [281,286] to drug therapy alone. In one three arm trial [281], women with OAB were enrolled but it was unclear if UI was present. Therefore this trial was not considered further.

1. Quality of data

(a) BT plus PFMT versus PFMT alone: In an early, three arm RCT women were ransomised to PFMT (n=69) or PFMT with BT (n=67) [189]. Outcomes were assessed after the 12 week intervention and three months later. It was not clear if random allocation was adequate or outcome assessors were blind. Study size was based on a power calculation. Losses to follow-up were six at 12 weeks, and 16 three months later.

(b) BT plus drug therapy versus drug therapy alone: Mattiasson [2003] evaluated “simplified” BT (consisting of a one page instruction sheet) in a single blind study of 501 participants (378 women and 123 men) aged 18 years and over with OAB with or without UUI. Allocation concealment, blinding of assessors, and a prior power calculation were not described. Post-treatment follow-up was 12 weeks, and then 24 weeks. Seven participants were lost to follow-up: five in drug therapy and two in combination therapy. Analyses were based on intent-to-treat principles. However, because of reporting issues, it was not possible to discern the effect of treatment in women alone. In 2010, Mattiasson compared solifenacin alone with solifenacin and bladder training in a prospective, parallel group, open label study of 643 men and women with OAB, it was not possible to identify the treatment effect in women alone (85% of sample were women).

2. Results

(a) BT plus PFMT versus PFMT alone: Post-treatment the combination therapy group had significantly fewer incontinence episodes compared to PFMT alone. More women in the combination therapy group than PFMT group reported cure (31% versus 13% respectively), or 50% improvement or more (70% versus 50%). The combination therapy group also reported greater perception of improvement and more satisfaction with treatment than PFMT alone. However, three months later between group differences were not statistically significantly different for cure (27% versus 20%), improvement (59% versus 56%), perception of improvement, or satisfaction with treatment.

(b) BT plus drug therapy versus drug therapy alone: Mattiasson (2003) reported no difference between participants who received brief written BT instructions plus tolterodine versus tolterodine alone with

respect to reducing incontinent episodes (median reduction 87% vs. 81%, respectively). Data were combined for men and women and most data were not presented separately for those who had UI versus those who did not. Mattiasson [2010] reported solifenacin was effective in improving OAB at 8 weeks reducing mean number of micturitions by 2.09, when BT was added there was a further significant improvement reducing episodes by 2.78. Again this study did not present data which enabled analysis of men and women separately.

3. Summary

A single trial found that combining BT with PFMT improves short-term outcomes compared to PFMT alone, but the added benefit did not persist three months later.

There is no evidence for an added benefit of combining brief written BT instructions with tolterodine (2mg twice daily) compared to tolterodine alone for urge incontinence (**Level of Evidence: 2**), although this trial included men and women and it is not known if one gender did better than the other with respect to outcome. The use of BT with solifenacin (5/10mg) adds benefit to symptom reduction at 8 weeks compared to solifenacin alone, mainly to symptoms of frequency (**Level of Evidence 2** – NOTE: This evidence related to men and women)

4. Recommendations

The current evidence is conflicting for the addition of written information on bladder training for women taking an antimuscarinic drug. One trial states no clinical benefit in adding brief written instruction in BT (**Grade of Recommendation: B**), whilst another suggests no significant improvements to urgency and urge incontinence but significant improvements in frequency (**Grade of recommendation: B**). More research is needed using an appropriately supervised BT programme (see B.6.2a) combined with anticholinergic or antimuscarinic drug therapies versus drug alone.

f) Timed voiding

A 2010 Cochrane review on timed voiding for management of UI in adults was recently published [273]. Ostaszkiewicz (2010) considered randomised and quasi-randomised trials only and identified two trials that compared timed voiding combined with additional interventions (including medications) to usual care. Both trials were conducted in nursing facilities and most participants were elderly women with cognitive impairment, therefore neither study recruited participants that met the criteria of interest for this chapter.

Two non-randomised studies that were not included in the Cochrane review reported findings related to the effects of timed voiding in women with UUI, stable bladders with UUI, and MUI [194,295]. Klarskov [1986] reported a consecutive series of 20 women aged 27 to 75 years with a double-blind crossover to compare timed voiding plus anticholinergic drug therapy (terodoline) to timed voiding plus placebo. As terodoline has been withdrawn from the market, this study is not considered further.

1. Quality of data

A 1984 case series report involved 20 women aged 24 to 94 years in women with a mild degree of UI, irregular voiding patterns, and normal urodynamic parameters (UI type not clearly reported) [295]. The voiding schedule consisted of a two hour voiding interval. Follow-up periods ranged from six weeks to eight months after treatment [295].

2. Results

A 79% success rate (not objectively quantified) was reported in the case series. Fifteen patients became totally continent, one had less leakage, three (with neurogenic diseases) remained unchanged, and one patient was lost to follow-up

3. Summary

There are no RCTs, or high quality observational studies, providing evidence on the effects of timed voiding for UI in women. Based upon the data from one small uncontrolled study, it seems a two hour timed voiding schedule may be beneficial in treating women with mild UI, infrequent voiding patterns, and stable bladder function **(Level of Evidence: 3)**.

4. Recommendations

Timed voiding with a two hour voiding interval may be beneficial as a sole intervention for women with mild UI infrequent voiding patterns (**Grade of Recommendation: C**). It may also be helpful as an adjunct to other treatment.

3. OTHER LUTS

One trial recruited participants with OAB but the continence status was unclear [281]. BT was compared to tolterodine (2mg, twice daily) or combined BT and tolterodine in women with OAB [281]; this study was reported as a conference abstract. Tolterodine/BT group had greater reductions in diurnal micturition (32.6%), nocturnal micturition (63.2%), urgency scores (63.2%), and bladder symptom improvement rates (69.3%) than those in BT alone or tolterodine alone. However, only the bladder symptom improvement scores were statistically significantly better in the combination therapy group. Thus, it is not clear if BT alone, tolterodine alone, or the combination, is better for LUTS other than UI in women with OAB symptoms.

The most common LUTS, aside from UI, are urgency, daytime (or diurnal) frequency and nocturia. Some trials that contributed to the sections above reported data specifically for these symptoms.

(a) Urgency: Jarvis [1981] compared BT and drug therapy (flavoxate and imipramine), and 16% versus 44% of participants reported they continued to experience urgency post-treatment. Mattiasson [2003] compared BT with tolterodine versus tolterodine alone and patient rating of urgency was somewhat less in the combination therapy group.

(b) Daytime (diurnal) frequency: Data on frequency are more commonly collected that data on urgency. Three trials reported diurnal frequency in comparisons of BT with no treatment. Jarvis [1980] reported a small controlled trial of inpatient bladder drill for DO [285]. After BT 17% in the treatment group and 77% in the control group continued to have symptoms of diurnal frequency. Fantl [1991], in subgroup analyses, found a significant reduction in diurnal frequency in participants with urodynamic SUI who had a baseline diurnal micturition frequency of at least 61 per week, and also in participants with DO with or without urodynamic SUI who had at least 57 diurnal micturitions per week [268]. Finally, Yoon (2003) reported that the BT group significantly reduced diurnal micturitions, whereas the control group deteriorated slightly [128].

Three trials compared BT with drug therapy. Jarvis [1981] reported that 24% of the BT group continued to experience frequency as compared to 48% of the drug group (flavoxate and imipramine) [284]. Columbo (1995) found that diurnal frequency was resolved in 18 (56%) of 32 patients taking oxybutynin versus 20 (69%) of 29 BT patients [292]. Kim SW et al [2008] found improvement in daytime frequency in 15 (65%) cases using bladder training alone and 21 (84%) using BT and propiverine combined.

Another trial compared BT plus placebo versus BT plus drug [282]. Szonyi [1995] found that there was a greater reduction in diurnal micturition frequencies in participants taking oxybutynin alongside BT compared to those on placebo and BT. Similarly, in a trial of BT plus drug versus drug alone Mattiasson (2003) found that “simplified” BT significantly augmented the effect of tolterodine compared to drug alone for voiding frequency (33% versus 25% improvement, respectively; $p<0.001$).

(c) Nocturia: Three trials reported data on nocturia in comparisons of BT with no treatment. Jarvis (1980) reported a small controlled trial of inpatient bladder drill for DO. After bladder training, there were 11% in the treatment group and 80% in the control group who continued to have symptoms of nocturnal frequency [285]. Fantl [1991] also found significant reductions in nocturnal frequency [268]. In subgroup analyses, nocturnal micturitions were only significantly decreased in women with urodynamic SUI alone, who experienced at least five episodes of nocturia per week, and not in those who had DO. Yoon [2003] reported that the BT group significantly reduced nocturnal micturitions, whereas the control group deteriorated slightly [128].

Two trials compared BT with drug therapy. Jarvis [1981] reported that the 19% of the BT group continued to experience nocturia compared to 68% of the drug group (flavoxate and imipramine) [284]. Columbo [1995] found that nocturia disappeared in three (27%) of 11 patients taking oxybutynin and 11 (61%) of 18 BT patients [292]. Another trial compared BT plus placebo versus BT plus drug [282]. Szonyi [1995] found no difference in nocturnal micturition frequencies.

1. Summary

Scheduled voiding regimens have been implemented in many forms and with a variety of intensities, ranging from strict in-patient regimens to simple instruction sheets. Most research has examined BT, and most of these trials have recruited women with symptoms of UUI or OAB. It is therefore disappointing that there is so little data about LUTS other than UI. The indications so far are that BT is effective for reducing UI, as well as frequency of micturition. The scant research comparing BT to drug therapy is inconsistent with some evidence for the superiority of each. It is not yet clear whether drug therapy can enhance BT, or whether BT can enhance UI outcomes from drug therapy, although it appears that reductions in frequency of micturition may be greater with the addition of BT.

4. FACTORS AFFECTING OUTCOME

a) Age

With the exception of two RCTs [128, 291] all trials included older women in their study populations. Three specifically recruited elderly women aged 65 to70 years and over [282, 283, 293]; and two recruited women aged 55 years and over [268, 289]. In conducting analyses of factors predicting success, two trials reported that age was not a factor in treatment outcome [189,289].

b) Other

Few trials on BT examined other predictors of treatment response. Several discussed the effect of diagnosis on treatment outcome; two reported that urodynamic diagnosis did not have an effect on treatment outcome as measured by incontinent episodes and the IIQ [189,268]. These RCTs included women with urodynamic SUI, DO, or both diagnoses. BT also led to more clinical cures in one small drug trial. BT in women with sensory urgency (81%) and low compliance bladders (75%) produced better outcomes than in those on oxybutynin immediate release (60%, 67%, respectively); however, oxybutynin led to greater cure rates in patients with DO (93% versus 62%).

VII. COMPLEMENTARY AND ALTERNATIVE MEDICINES

There is minimal evidence that complementary and alternative medicines (CAMs) may influence physiologic function and/or health outcomes. CAMs include

those therapies that are not part of the traditional biomedical model, such as meditation, imagery, hypnosis, acupuncture and naturopathic and herbal remedies. While some consider biofeedback (BF) part of complementary therapy, we have included BF in this chapter as an adjunct to physical therapies.

A search of AMED (Allied and Complementary Medicine) using the key words randomised controlled trials, and urinary incontinence, retrieved 32 records in 2012. One reported a randomised controlled trial investigating the effect of hand acupuncture for female SUI on 52 women randomly assigned to either experimental hand acupuncture or control, assessment was made at 12 weeks and 37% less incontinence was reported in the experiental group. The reporting of this trial did not conform to traditional standards and should be treated with caution, however the undertaking of an RCT in the CAMs literature indicates a move towards the gathering of robust 'main-stream' evidence in this area.

There is a need for well conducted RCT's in the area of CAMs before recommendations can be made.

VIII. SUMMARY AND RECOMMENDATIONS

1. SUMMARY

Whislt the effect of PFMT has received considerable research attention, the effect of lifestyle interventions or prevention trials have not. However even with the number of reasonable trials on conservative management of UI in women, the standards of trial conduct and reporting varied considerably and it is strongly recommended that future randomised trials account for sample size, heterogenity, risk of bias, and followup.

2. RECOMMENDATIONS FOR PRACTICE

- While some recommendations are underpinned by good and consistent evidence of effect,

there are also many recommendations that need further testing because there is insufficient **Level 1 or 2 evidence**. For this update, the recommendations from ICI 2009 remain. These are not based on robust reserach and require further study:

a) Lifestyle Intervention

- Weight loss in obese and morbidly should be considered a first line treatment to reduce UI prevalence **(Grade of Recommendation: A)**.
- Caffeine reduction may help in improving incontinence symptoms **(Grade of Recommendation: B)**
- Minor decrease of fluid intake by 25% may be recommended provided baseline consumption is not less than 30 ml/kg a day **(Grade of Recommendation: B)** Moderate exercise may help in decreasing the incidence of UI; this effect may be mediated by weight control **(Grade of Recommendation: C)**

b) PFMT (principal recommendation)

- Supervised PFMT should be offered as first line conservative therapy to women with stress, urge, or mixed urinary incontinence **(Grade of Recommendation: A)**
- The most intensive PFMT programme possible should be provided (in terms of exercise dose, health professional teaching, and supervision) within service constraints ; health professional taught and supervised programmes are better than self-directed programmes ; more health professional contact is better than less **(Grade of Recommendation: A)**.
- There does not appear to be a clear benefit of adding clinic **(Grade of Recommendation: B)** or home based BF **(Grade of Recommendation: B)** to a PFMT programme.

c) PFMT (other recommendation)

Pregnant women expecting their first baby:

- Intensive strengthening antepartum PFMT, with regular health professional contact to teach and supervise training, to prevent postpartum urinary incontinence **(Grades of Recommendation: A)** (for women continent at 18 weeks) and B (for population approaches, that is intervention offered whether women are continent or not at 20 weeks gestation)

Postnatal women, immediately after delivery:

- Individually taught PFMT programme that incorporates adherence strategies for women who had a vaginal delivery of a large baby (4000g or more) or a forceps delivery **(Grade of Recommendation: C)**

For postnatal women with persistent symptoms of UI three months after delivery:

- PFMT is offered as first line conservative therapy **(Grade of Recommendation: A)**
- The 'best' PFMT programmes are 'intensive' with regard to supervision and exercise content **(Grade of Recommendation: B)**

For women with SUI:

- PFMT is better than EStim as first line conservative therapy, particularly if PFMT is intensively supervised **(Grade of Recommendation: B).**
- PFMT is better than BT as first line conservative therapy **(Grade of Recommendation: B).**

- PFMT and duloxetine are both effective in first line therapy, although PFMT is better because of the side effects experienced with the drug **(Grade of Recommendation: C).**
- PFMT and surgery are both effective therapies, although PFMT is better as first line therapy because it is less invasive **(Grade of Recommendation: C).**

For women with SUI or MUI:

- PFMT is better than VC as first line conservative therapy **(Grade of Recommendation: B)**.

For women with UUI or MUI:

- PFMT and BT are effective first line conservative therapy **(Grade of Recommendation: B).**
- PFMT is better than oxybutynin as first line therapy **(Grade of Recommendation: B).**

For women with UUI:

- PFMT and BT are effective first line conservative therapy **(Grade of Recommendation: B).**

Vaginal cones:

- For women with SUI, VCs with supervised training sessions by a trained health professional can a first-line therapy to women able and prepared to use them **(Grade of Recommendation: B)**; some women cannot insert or retain the the cone or have side effects and discomfort. Trained health professional assessment is recommended **(Grade of Recommendation: D)**

Electrical stimulation (EStim)

While the usefulness of EStim in practice might be limited because some women cannot use it (due to contraindications), have difficulty using it, or dislike it:

- EStim might be better than no treatment in improving symptoms **(Grade of Recommendation: B).**
- EStim may be equal to other medical treatments **(Grade of Recommendation: B).**
- EStim plus PFMT or BF-assisted PFMT programmes does not appear to add benefit **(Grade of Recommendation: B)**

Magnetic stimulation (MStim)

- Of the MStim protocols investigated to date, it seems that both sacral root MStim and home-based MStim, are worthy of further investigation in women with UI. No recommendation is possible based on current evidence **(Level of recommendation: D).**

Bladder training (BT)

With regard to **Grade A** recommendations for BT:

- BT is an appropriate first line treatment for UI in women (Unchanged).

Grade B recommendations (all unchanged from ICI 2009):

- Either BT or antimuscarinic drug may be effective, although BT may be preferred by some because it does not produce side effects and adverse events associated with drug therapy.
- There may be no benefit in adding brief written instruction in BT to drug therapy for incontinence but it mayimprove episodes of frequency.
- A combination of PFMT/BT may be better than PFMT alone in the short-term for women with symptoms of SUI or MUI.

There are two **Grade D recommendations** (unchanged from (C(2009):

- Clinicians and researchers should refer to the operant conditioning and educational literature to provide a rationale for their choice of training parameters or approach.
- Health Professionals should provide the most intensive BT supervision that is possible within service constraints.

Timed voiding (unchanged)

- Timed voiding with a two hour voiding interval may be beneficial as a sole intervention for women with mild UI infrequent voiding patterns **(Grade of Recommendation: C).**

IX. FUTURE RESEARCH DIRECTIONS

Conservative management of incontinence is ripe for future research directions. Research that is urgently needed, in the opinion of the committee members, is highlighted with the use of *italics*. There are a few recommendations that apply to all further studies:

- All future trials must be designed, implemented and reported in ways that maximise their usefulness in practice; this includes being well powered, with longer term follow up, with evaluation of cost- effectiveness and planned secondary analysis of trial data to investigate factors affecting outcome. Readers are referred to the revised CONSORT statement for guidance (http://www.consort-statement.org/)

a) Lifestyle Intervention:

- Given the high prevalence of both UI and obesity in women, the dual issues of weight loss and prevention of weight gain (and exercise) should receive high research priority.

- Larger RCTs to assess the effect of caffeine and other dietary factors are feasible and important.
- Further research is needed to define the role of straining in the pathogenesis of UI.
- Studies to establish whether heavy exertion is an etiologic factor in the pathogenesis of UI and whether changing exertions can alleviate established UI.
- Prospective studies on the effect of smoking cessation on the prevention or resolution of UI.
- Separate investigations of the impact of lifestyle interventions on nocturia, diurnal frequency, urgency and UUI to delineate whether certain interventions preferentially affect different areas of OAB.

b) Pelvic floor muscle training (PFMT)

In antenatal and postnatal women, trials are needed to investigate the effects of:

- Antepartum PFMT on preventing postpartum UI in multiparous women.
- Postpartum PFMT programme (suitable exercise dose and supervision) in the long term (five plus years).
- Periodic refresher sessions after an initial supervised postpartum PFMT programme, in the long term (five plus years).

In all women, trials are needed to investigate:

- The effect of different supervisory intensity in PFMT program. In addition to clinical effectiveness, this is an important question because of resource implications, both financial and human, for health-service delivery.
- Whether clinic BF may benefit certain women, such as those with a weak PFM or with difficulty contracting the PFM in isolation.
- Whether the addition of bladder training or medication adds benefit to PFMT.

c) Vaginal cones (VC)

- If the combination of VC with PFMT is an intervention of interest for women then this combination of therapies could be explored further. VC could be used as an overload progression to active PFM strengthening exercises. Thus, a VC programme could be offered to women with a demonstrated minimum PFM strength level and could be aimed at either additional strength training by pulling on the cone for three series of eight to12 contractions daily, or endurance training, using a low-load over a sustained period of time.

d) Electrical stimulation (EStim) and magnetic stimulation (MStim)

- Studies to elucidate the purpose and biological rationale for EStim in different diagnostic groups, so these can then be tested and compared in clinical trials.
- Comparisons of EStim with other treatments such as PFMT, vaginal cones, and bladder training are more important than comparison of EStim with sham.
- EStim as an adjunct to treatments that seem to be effective such as PFMT, vaginal cones, and bladder training.
- MStim protocols, both sacral root MStim and home-based MStim, are worthy of further investigation. Well powered RCT are needed to study the clinical effect of Mstim in different diagnostic group.

e) Scheduled voiding regimes, especially bladder training (BT)

- BT variables to be investigated include the instructional approach, supervisory intensity, strategies for controlling urgency, scheduling parameters, frequency of schedule adjustments, length of treatment, and use of adjunctive treatments.
- BT versus another active treatment such as PFMT or drug therapy.
- The potential benefits of combining BT and anticholinergic/antimuscarinic drug need further investigation, including comparisons of BT plus drug versus drug alone, and BT plus drug versus BT alone, or BT vs no treatment.
- Habit training in women with a consistent pattern of UI who are ambulatory and cognitively intact.

B. PELVIC ORGAN PROLAPSE (POP)

Pelvic organ prolapse is characterised by a variety of pelvic floor symptoms. Treatment depends on the severity of the prolapse and its symptoms, and the woman's general health. Conservative treatment is generally considered for those with a mild degree of prolapse, those who wish to have more children, the frail or those unwilling to undergo surgery. Conservative treatment is defined here as lifestyle interventions, physical therapies and pessaries.

The aims of conservative treatment in the management of POP include:

- to prevent the prolapse becoming worse;
- to help decrease the frequency or severity of symptoms caused by prolapse (pelvic heaviness, vaginal symptoms, backache, urinary, bowel and sexual symptoms);
- to avert or delay the need for surgery.

In this section the evidence is applied for the use of conservative treatments in the management of

POP, utilising information from two Cochrane systematic reviews [296,297], and literature identified via a search strategy summarised in Appendix 2.

I. LIFESTYLE INTERVENTIONS

Lifestyle interventions include weight loss, reducing exacerbating activities (e.g. lifting, coughing) and treating constipation and are intended to avoid exacerbation of the prolapse by decreasing intra-abdominal pressure. The extent to which any of these lifestyle interventions are effective in managing prolapse is largely unknown [195].

1. PREVENTION

a) Quality of data

No new intervention studies were identified in this update, however further observational studies have been published and these are reported here and summarised in **Table 16**. In ICI 4th edition, no literature was found relating to the effects of lifestyle change interventions for the prevention of POP. Observational studies were identified that examined the association between factors such as occupation (involving heavy lifting/strenuous physical activity), bodyweight and constipation, and POP.

(a) Association between POP and occupation:

Three new studies investigated the association between occupation and prolapse.

Miedel [298] undertook an assessment of non-obstetric risk factors, including heavy lifting at work, in a population-based, cross-sectional study derived from a sample of 5489 Stockholm women, 30 to 79 years old, who answered a validated questionnaire for the identification of symptomatic prolapse. 69% responded and of those, women who had symptomatic prolapse (n=454) and randomly selected controls (n=405) were given a detailed questionnaire regarding their risk factors, including current or previous occupations that involved heavy lifting (up to 10 kg daily, more than 10 kg) or exposure to vibrations, and participation in low- and high-impact exercise. Only women with intact uteri and no history of surgery for prolapse or incontinence were included (n=273 cases, n=285 controls). Odds ratios and confidence intervals were estimated from multiple logistic regression analysis.

Slieker-ten Hove undertook a cross-sectional study of all female residents between 45 and 85 years old in one Dutch city (n=2979), the results of which were reported in four articles [299-302]. Women received a validated questionnaires via which they were classified as symptomatic (if they reported feeling and/or seeing a vaginal bulge) or non-symptomatic. A response rate of 63% was achieved. Finally 1224 women were included in the analysis (n=142 symptomatic; n=1082 asymptomatic). Multiple logistic regression was used to estimate the odds ratios and confidence intervals for the potential risk factors including current and past heavy physical work [299].

Braekken [303] carried out a one-to-one age and parity matched case-control study (n=49 women with prolapse >=stage II with or without symptoms, and n=49 controls with prolapse stage 0 or I) with recruitment via community gynaecologists and newspaper advertisements. Women had clinical examination, pelvic floor muscle (PFM) function assessment (strength, endurance and vaginal resting pressure in cmH2O) and completed questionnaires including risk factor assessment. The study primarily looked at the association between PFM function and POP, but also measured occupational heavy lifting and BMI as potential risk factors for POP. Heavy occupational work was defined by a positive response to three questions: self-report of physically heavy occupational work; >20 heavy lifts per week; >50% of working time in standing position. One or two positive responses was classified as moderate occupational work. Multivariate logistic regression was used to estimate odds ratios for risk factors.

(b) Association between POP and bodyweight:

Four new studies have addressed the relationship between obesity and prolapse [298, 303-305].

Whitcomb [2009] published a secondary analysis of the data from 1155 obese women from the Kaiser Permanente Continence-Associated Risk Epidemiology Study. Prolapse was identified from responses to a question regarding the sensation of a bulge or something falling out of the vagina. Women were asked to report bother on a visual analogue scale. Multivariable logistic regression was used to assess severity of obesity (obese, severely obese, morbidly obese) as a risk factor for various pelvic floor disorders including prolapse. Models were adjusted for age, parity and mode of delivery.

Washington [2010] reported on a cross-sectional study of all women with pelvic floor disorders (n=971) attending a tertiary urogynaecology centre over one year. Data on POP-Q, PFDI-20, and PFIQ-7 were gathered. Women with POP-Q >=stage II were classed as having prolapse; women with BMI>=30 were classed as obese.

In addition, two studies [298,306] (described above) assessed body mass index as one of several risk factor for prolapse.

(c) Association between POP and bowel function:

Four new studies, one relating to irritable bowel and prolapse [307] and three looking more generally at defecatory problems [298,301,308] were found.

Wang [2010] analysed data from the Reproductive Risks for Incontinence Study addressing the relationship between irritable bowel syndrome and pelvic

Table 16: Characteristics of lifestyle and pelvic organ prolapse studies

Author/ year	Study design	Comparison group	Participants	Risk factors assessed	Subjective and Objective assessment	Objective assessment	Length of follow-up	Results
Badalian 2010 [310]	Cross-sectional, analysis of US National Health and Nutrition Examination Study. Analysis adjusted for age, parity, education, race		Non-pregnant women aged 20 and over, n=1881	Level of vitamin D	Experience of bulge or something falling out		N/A	Vitamin D level was not associated with vaginal bulge
Braekken 2009 [303]	Age and parity matched case-control study		Community and routine Gynae. Population, n=98	PFM function, occupational heavy lifting, BMI		POP-Q		• Heavy occupational work was associated with greater risk of prolapse (>=stage II) • BMI • Weaker PFMs, poorer endurance and lower vaginal resting pressure significantly associated with prolapse >=stage II. Significant interaction between muscle strength and vaginal resting pressure
Braekken 2010 [306]	RCT	PFMT vs control	N=109	N/A	Mouritsen questionnaire PFM function	POP-Q	6 months	PFMT group compared to control group were significantly more likely to have reduced symptom frequency and bother, less likely to have no improvement in POP-Q stage. Change in resting position of the bladder and rectum, were significantly greater in PFMT group; changes in muscles and hiatal area were significantly in favour of the PFMT group.
Miedel 2009 [298]	Cross-sectional, case-control. Analysis adjusted for factors including age, parity and family history of prolapse	Those with vs those without symptomatic prolapse	Population-based, n=359	N/A Occupational heavy lifting BMI bowel	72-item questionnaire		N/A	• Compared to women who did no heavy lifting at work, those lifting weights up to 10kg and over 10 kg had increased risks of symptomatic prolapse • Compared to women of normal weight (BMI 19-25), overweight (BMI 26-30) and obese women (BMI >30) had increased odds of symptomatic prolapse • lack of a normal bowel habit was associated with increased risk of symptomatic prolapse
Moen 2009 [316]	Observational. unadjusted analysis		Women presenting with PFM disorders, n=325	PFM strength (Oxford)		Prolapse stage	N/A	PFM contraction strength was significantly lower in women with prolapse >= stage 2

Table 16: Characteristics of lifestyle and pelvic organ prolapse studies (continued)

Author/ year	Study design	Comparison group	Participants	Risk factors assessed	Subjective and Objective assessment	Objective assessment	Length of follow-up	Results
Saks 2010 [308]	Cross-sectional. Analysis adjusted for age, BMI, presence of apical or anterior prolapse	Those with vs those without obstructive bowel symptoms	Tertiary urogynaecology service, n=331	Obstructive bowel symptoms	PFDI-20	Baden-Walker	N/A	Women with posterior wall prolapse more likely to report obstructive bowel symptoms than those without. Grade of prolapse not significantly associated with obstructive bowel symptoms.
Slieker-ten Hove 2009	Cross-sectional, case-control. Adjusted analysis of occupational lifting only	Symptomatic vs non-symptomatic	Population-based, n=1224, n=469 had POP-Q	Heavy physical work PFM function bowel		POP-Q	N/A	• 24.5% of cases versus 18.9% of controls currently engaged in heavy work (OR 1.48, 95% CI 0.98-2.23). Past heavy work was not a significant risk factor. • Higher stages of prolapse associated with less ability to attain levator closure, and lack of effective involuntary contraction during coughing, but better ability to perform proper straining technique. No association between stage of prolapse and voluntary muscle contraction strength or endurance • no significant association between constipation or straining to defaecate and POP-Q stage
Stupp 2011 [318]	RCT (pilot)	PFMT vs control	N=37	N/A	P-QoL PFM function	POP-Q	14 weeks	PFMT group had significantly greater anatomic improvements in the anterior and posterior vaginal wall prolapses than did the control group and a decrease of symptoms. Also greater improvements in PFM strength, endurance and electromyography parameters
Wang 2010 [307]	Cohort, analysis of RR survey data. Analysis adjusted for age, race, medical history, urinary urgency, UI	Those with vs those without irritable bowel syndrome (IBS)	Racially diverse women, aged 40-69 years, n=2109	IBS	Feeling or seeing a bulge or protrusion		N/A	Risk of symptomatic prolapse significantly greater in group with IBS. Risk of bother with prolapse was also significantly greater in the IBS group.
Washington 2010 [305]	Cross-sectional. Unadjusted analysis of comparable groups	Obese vs non-obese	Tertiary urogynaecology centre, women with pelvic floor disorders, n=971	Obesity (BMI>=30)	PFDI-20, PFIQ-7	POP-Q	N/A	Obese compare to non-obese women were more likely to have prolapse. Significant difference in PFDI-20 but not the prolapse subscale.
Whitcomb 2009 [304]	Cross-sectional, secondary analysis of survey data. Analysis adjusted for age, parity, mode of delivery	Obese vs severely obese vs morbidly obese	Population-based,n=1155 obese women	Obesity	Sensation of bulge or something falling out		N/A	Morbidly obese (but not severely obese) women are at greater risk of bulge than obese women. No difference between obesity groups in terms of bother.

Foot notes: N/A non applicable; PFM= Pelvic floor muscle, PFMT = pelvic floor muscle training,

floor disorders, and the effects of such symptoms on quality of life. RRISK is a racially-diverse cohort of women aged between 40 and 69 years (n=2109). Data were collected by self-administered questionnaires and interviews. IBS status was determined by asking a single question regarding whether a woman had ever been told by a medical doctor that she had IBS. Prolapse was identified by asking about feeling or seeing a bulge or protrusion. Multivariate logistic regression was used to assess factors associated with having IBS including prolapse.

Saks [2010] in a cross-sectional study examined whether there was an association between obstructive defaecatory symptoms and prolapse. Women presenting with prolapse of grade 2 or greater (Baden-Walker system) of any compartment (anterior, posterior, apical) to one tertiary urogynaecology service completed a questionnaire (PFDI-20) that reported pelvic floor symptoms. A multivariate regression analysis was performed, adjusting for confounding variables, the dependent variable being presence of obstructive bowel symptoms (defined as at least moderate bother with one or more of: splinting, straining, incomplete emptying).

Both Miedel [2009] and Slieker-ten Hove [2009] assessed the presence of constipation (<3 bowel movements per week), hard stools and difficult evacuation as risk factors for symptomatic prolapse and changes in POP-Q stage.

(d) Association between POP and nutrition:

Previously one study of women in rural Gambia had been published on the association between prolapse severity and anaemia [309]. A new study by Badalian [310] adressed the association between Vitamin D deficiency and pelvic floor disorders. The authors hypothesised that there is a plausible link between vitamin D deficiency and poor muscle strength since vitamin D receptors are found in human muscle tissue. Over three thousand women aged 20 years or above from the US National Health and Nutrition Examination Study 2005-2006 were selected by probability sampling. Analysis was based on the 1881 non-pregnant women who participated, and who had data on both vitamin D levels and pelvic floor disorders. Prolapse was identified from a positive response to a question on the experience of a bulge or something falling out that is seen or felt in the vaginal area. Level of vitamin D was analysed both as a continuous variable and as a dichotomous variable (>= 30 ng/mL, <30 ng/mL). Analysis included both univariate and multivariate regression models. Models adjusted for age, BMI, parity, education and race.

b) Results

(a) Association between POP and occupation:

In the Miedel study [2009] a total of 655 (76.2%) women returned completed risk factor questionnaires with 558 women included in the analysis (n=273 symptomatic; n=285 controls). Heavy lifting at work was found to be positively linked to symptomatic prolapse in a simple age- and parity-adjusted model. Compared to women who did no heavy lifting at work, those lifting weights up to 10kg had an increased risk of symptomatic prolapse (OR 1.81, 95% CI 1.11–2.95). There was a similar increased risk for those women lifting 10kg or more at work: OR 1.67, 95% CI 1.07–2.61. This finding was confirmed in the multiple logistic regression analysis which indicated eight variables that were significantly associated with symptomatic prolapse. Age, parity, family history of prolapse, increased BMI, the presence of any condition suggestive of deficient connective tissue, fewer years smoking, heavy lifting at work, and abnormal bowel habit were all risk factors for symptomatic prolapse. From this model the results for heavy lifting compared to no heavy lifting were: <10kg OR 1.98, 95% CI 1.10–3.59; >=10kg OR 1.94, 95% CI 1.15–3.27. Thus no clear dose response was confirmed.

Slieker-ten Hove [299] found that current heavy physical work was an independently significant risk factor for symptomatic prolapse; 24.5% of cases versus 18.9% of controls were currently engaged in heavy work. The odds ratio was 1.48 (95% confidence interval 0.98-2.23) and the population attributable risk (PAR) was 8.5%. Other independent risk factors were having POP symptoms during pregnancy and mother having prolapse. Past heavy work was not a significant risk factor.

Braekken [2009] also reported that heavy occupational work, compared to moderate or light occupational work, was associated with greater risk of prolapse >= stage II. BMI and pelvic floor muscle function variables were also significantly associated with risk of prolapse as described in later sections.

Previously the majority of studies (5 out of 6) reported a positive association between occupations associated with lifting and the presence of prolapse. The additional three studies were supportive of an association between current heavy occupational lifting and prolapse, however the odds ratio in one study was only marginally significant.

(b) Association between POP and bodyweight:

Morbidly obese women had significantly increased odds of having prolapse (reported bulge) compared to obese women (Whitcomb, 2009). The odds for severely obese women compared to obese women were not significantly increased. The visual analogue scores for bother with prolapse did not differ significantly between obesity groups. There may be a trend towards increasing prevalence of prolapse with increasing severity of obesity. However this was not reflected in the bother reported.

In the Washington [2010] study of 971 women, 721 met the inclusion criteria and had sufficient data

to be included in the analysis. Mean age was 56.5 years (SD 16.2) and 65.2% were post-menopausal. 35.8% were obese and 62.2% non-obese. The mean BMI was 35.8 (SD 5.4). Stage >=II prolapse was present in 52% of women. No difference in presence of prolapse of stage II or greater was found between obese and non-obese women and similarly for stage 3 or greater prolapse: obese 16.2% vs non-obese 18.4%. Being obese was however associated with more pelvic floor symptom distress: the mean score on the PFDI-20 was significantly higher for obese women compared to non-obese women, due to higher mean scores on subscales for colorectal-anal distress and urinary distress. There was no significant difference between obese and non-obese women in the prolapse-specific subscale of the PFDI-20. The analysis performed was unadjusted, but it was reported that there were no significant differences in age, parity, race, prior pelvic surgery or co-morbidities between the obese and non-obese group.

Miedel [2009] found that although age, parity, and family history of prolapse were the dominating risk factors for symptomatic prolapse, increased BMI was also an independent significant risk factor in the final fully adjusted model (p=0.038). Compared to women of normal weight (BMI 19 to 25), overweight (BMI 26 to 30) and obese women (BMI >30) had increased odds of symptomatic prolapse (OR 1.88 95% CI 1.15 to 3.08 and OR 2.07 95% CI 0.95 to 4.50, respectively).

Braekken [2009] reported that having a BMI of >25 (compared to <=25) was significantly associated with having prolapse >= stage II (OR 5.0, 95% CI 1.1 to 23.0).

In ICI 4th edition the majority of studies (4 out of 6) indicated an association between being overweight and having prolapse. There are now four additional studies to draw on. Each study supported the previous finding.

(c) Association between POP and bowel function:

Symptomatic prolapse in the last 12 months was associated with having inflammatory bowel symptoms (IBS) after adjusting for age, race, medical history, urinary urgency and urinary incontinence: 5% in the no IBS group had symptomatic prolapse compared to 12% in the IBS group. Bother due to prolapse was also significantly associated with IBS. The authors suggest that women with IBS have cycles of constipation which makes them prone to having a weak pelvic floor and prolapse [Wang, 2010].

In the study by Saks [2010], 311 women met the inclusion criteria: mean age 60.5 years (SD 12.5), BMI 27.1 (SD 5.5), and parity 2.6 (SD 1.3). Most women were white (69%) and post-menopausal (79%). Apical prolapse was the most common type (86%), followed by anterior (77%) and posterior (23%). Most had prolapse involving more than one compartment. Nine bowel symptoms were examined and in all cases the prevalence of the symptom was not associated with grade of prolapse. Some obstructive symptoms (splinting, straining, anal incontinence, bulging of rectal tissue) were associated with the presence of a posterior prolapse, but none were associated with the grade of posterior prolapse. In a multivariate regression analysis adjusting for age, BMI and presence of apical or anterior prolapse it was confirmed that women with posterior wall prolapse were more likely to report obstructive bowel symptoms than those who did not have posterior wall prolapse (OR 3.46, 95% CI 1.69 to 7.01). Grade of prolapse (either overall or specifically for the posterior wall) was not significantly associated with obstructive bowel symptoms. The authors concluded that obstructive bowel symptoms often co-exist with posterior vaginal wall prolapse but probably do not cause the symptoms.

Miedel [2009] found all bowel variables were significantly associated with risk of symptomatic prolapse in an age- and parity-adjusted model. In the final multivariable logistic model, one variable remained significant: lack of a normal bowel habit was associated with a two-fold risk of symptomatic prolapse (OR 2.13, 95% CI 1.37 to 3.31).

Slieker-ten Hove [2009] found, in an unadjusted analysis, no significant association between constipation and POP-Q stage, nor straining to defaecate and POP-Q stage.

Previously the evidence was inconclusive with regards to the relationship between constipation and prolapse. There tended to be positive associations with symptoms of prolapse but not anatomical prolapse measures (e.g. POP-Q). Four new studies add some information in this area. The conclusions from these are similar however: significant associations with prolapse symptoms, but no significant associations with prolapse stage.

(d) Association between POP and nutrition:

In the ICI 4th Edition, only one study was found that suggested anaemia was associated with increased odds of having prolapse. A new study by Badalian (2010), looking at the effects on prolapse of vitamin D, found in a univariate analysis that women reporting bulge had higher levels of vitamin D: in women over 50 years old 8.6% reported bulge in the >=30 ng/mL group compared to 3.3% in the <30 ng/mL group. However the model findings suggested that vitamin D level was not associated with vaginal bulge (prolapse): a vitamin D level of 30 ng/mL or more (normal) compared to lower levels had an odds ratio for prolapse of 1.66 (95% CI 0.61 to 4.49). The authors suggest that the small numbers of women reporting prolapse may have been an underestimate due to self-reporting. A significant association between low level of vitamin D and presence of urinary incontinence was reported.

c) Summary

Overall there are still no prospective studies of lifestyle interventions to prevent prolapse.

Some new observational studies were located adding to our knowledge of potentially helpful ways to modify lifestyle risk factors. There is now further evidence that occupations involving heavy lifting/hard physical labour or being overweight may play a role in the development of POP **(Level of Evidence: 3)**.

Constipation is a modifiable risk factor which perhaps has potential to impact on development of prolapse symptoms. However, evidence regarding the association between constipation or straining at stool and prolapse remains conflicting. New studies were reasonably sized and adjusted for covariates.

No further studies on anaemia were found. A study of vitamin D found no association with self-reported bulge.

2. TREATMENT

Previously no studies had been identified that evaluated the effectiveness of lifestyle interventions in the treatment of women with POP. Currently this is still the case.

II. PHYSICAL THERAPIES

The primary physical therapy for POP is PFMT, with or without other adjuncts. PFMT may include PFM assessment and education, PFM exercise instruction, and PFM bracing against increased intra-abdominal pressure, for example when coughing and sneezing (termed “The Knack” [145]). Adjuncts (such as biofeedback) or other physical therapies (such as neuromuscular EStim) may be used. These therapies aim to improve PFM strength, endurance, coordination and function.

The promotion of PFMT for prolapse varies between treatment centres with some providing only a patient information leaflet and others giving individual instruction from a physiotherapist [311]. Research shows that verbal teaching of pelvic floor exercises alone is insufficient [312]. It is suggested that 15% of women are incorrectly ‘bearing down’ when trying to carry out these exercises. In women with prolapse, this could further add to the strain on the area and worsen the condition.

A Cochrane systematic review has indicated that PFMT should be offered as first-line conservative management for urinary stress, urge and mixed incontinence [126]. However, its role in managing prolapse is less well-established [313]. The importance of clarifying the place of PFMT in the prevention and management of prolapse has been highlighted [314,315].

1. PREVENTION

a) Quality of data

No studies have been identified to date that evaluate the role of PFMT in prevention of POP. This lack of evidence was noted by Harvey (2003) in a systematic review of PFMT during and after pregnancy [212].

However, one trial is now underway [http://clinicaltrials.gov/ct2/show/NCT01171846]. Four hundred women originally enrolled in a longitudinal follow-up of post-natal incontinence (including a subgroup involved in a trial of post-natal PFMT), who have not sought treatment for prolapse, have been randomised to receive either a programme of PFMT (individualised physiotherapy appointments, maintenance via Pilates-based classes and annual one-to-one check-ups) or a prolapse prevention advice leaflet. Women are being followed up at 2 years. This trial is due to report in late 2013.

In addition, three more cross-sectional studies have examined the relationship between pelvic floor muscle function and prolapse.

Braekken [2009] conducted a case-control study, in which they examined the association between PFM function and POP, but also measured occupational heavy lifting and BMI as risk factors for POP as reported above.

Moen [2009] [316] undertook an observational study in women presenting with pelvic floor disorders. Women were questioned about their performance of pelvic floor muscle exercises and then were examined to measure pelvic floor muscle contraction strength (Oxford grading scale). Prolapse stage was also recorded. Univariate analysis was performed to assess associations between prolapse stage and muscle strength.

Slieker-ten Hove, as described above, performed a cross-sectional study of women aged 45-85 (n=2979) in one town in the Netherlands [302]. Women completed a validated questionnaire and indicated if they would consent to a vaginal examination. A random sample of consenting women were examined to assess prolapse stage (POP-Q) and pelvic floor muscle function (voluntary muscle contraction and effective involuntary muscle contraction during coughing, relaxation and straining were scored by visual inspection and digital palpation). The chi squared test for trend or ANOVA was used in an unadjusted analysis to assess associations between prolapse stage and pelvic floor muscle variables.

b) Results

In one study [303] weaker pelvic floor muscles, poorer endurance and lower vaginal resting pressure were each significantly associated with greater risk of prolapse >=stage II. There was a significant interaction between muscle strength and vaginal

resting pressure: weak pelvic floor muscles and low vaginal resting pressure giving a higher odds ratio than other combinations. The authors concluded that women with poor PFM function were more likely to experience POP compared with women with good PFM function, and that this supports the hypothesis that PFMT may be important in the prevention and treatment of POP.

In another study [316] of 325 women with a mean age of 57.8 years, 48.9% (159) had prolapse (stage II, III or IV) and 23.4% (76) were able to perform a contraction with strength rated 3, 4 or 5 on the Oxford scale. Pelvic floor muscle contraction strength was significantly lower in women with prolapse >=II compared to women with stage 0 or I prolapse (1.52 versus 1.87, p=0.007).

Slieker-ten Hove [2010] achieved a 62.7% response rate with 1140 women both completing the questionnaire and consenting to a vaginal examination. Of these 1140 women, 800 were randomly selected and 649 then underwent vaginal examination. Fifty four (8.3%) had prolapse. Higher stages of prolapse compared to lower stages were associated with less ability to attain levator closure. Higher stages of prolapse were also associated with lack of effective involuntary contraction during coughing, but better ability to perform proper straining technique. There was no association between stage of prolapse and voluntary muscle contraction strength or endurance. The authors suggest tentatively that strong pelvic floor muscles alone do not prevent the development of prolapse.

c) Summary

Previously one study had reported women with stage II prolapse were better able to elevate their pelvic floor than those with stage III or IV, and hypothesised that poor PFMs may contribute to the development of prolapse. Now additionally three other studies have examined the association between pelvic floor muscle function and prolapse. Two studies had large sample sizes but unadjusted analyses; the third study was smaller but used an adjusted analysis. Two studies suggested the strength of voluntary pelvic floor muscle contractions was negatively associated with prolapse stage, whilst the third did not, but instead found an association between higher stages of prolapse and lack of an effective involuntary contraction.

Currently, there is no evidence from intervention studies regarding the role of PFMT or other physical therapies in the prevention of POP; better PFM function may be associated with less risk of prolapse **(Level of Evidence: 3)**.

2. TREATMENT

a) Quality of data

An evidence-base is now emerging regarding the role of PFMT in the treatment of prolapse, both as a treatment in itself and as an adjunct to surgery. A Cochrane review specifically addressing this question was first published in 2004 and its second update was published in November 2011 [296].

(a) PFMT alone:

Six trials now exist in this area **(Table 17)**, three of which were included in the 4th edition. The three new trials are reported in detail below.

Braekken [2010] undertook a single-centre trial where they randomised 109 women (59 PFMT, 50 control), the results of which were reported in two articles [306,317]. Women had stage I, II or III prolapse of any type (determined by POP-Q), and 63% were reporting symptoms of prolapse. Randomisation was stated as stratified by severity of prolapse. The intervention group women were instructed in PFMT for 6 months (weekly physiotherapy appointments for three months then fortnightly appointments) with home exercise (3 sets of 8-12 close to maximal contractions daily). Both groups were given lifestyle advice and taught “the Knack”. Prolapse stage, prolapse, bladder and bowel symptoms, pelvic floor muscle manometry and ultrasound measurements were taken at 6 months.

The risk of bias was judged to be low. A statistician generated and stored the allocation envelopes. The participant opened the opaque sealed envelope herself. Random permuted blocks were not used which resulted in unequal group sizes. There was a significant difference at baseline between the randomised groups in the prevalence of prolapse symptoms (43/59 PFMT group, 26/50 control group). Pelvic floor ultrasounds were taken and assessed blinded to women’s group in the trial, but pelvic floor assessments were not blinded. Dropouts were adequately reported and the rate was low (2%).

Stupp [2011] randomised women with untreated stage II anterior or posterior prolapse attending a urogynaecology service in Sao Paulo, Brazil [318]. POP symptoms were the women’s main clinical presentation. The PFMT group (n=21) received 6 appointments over 14 weeks with a specialist women’s health physiotherapist at weeks 0, 1, 2, 6, 10 and 14. The first 3 sessions aimed to achieve sensory awareness. A 12-week home exercise program was prescribed and women were encouraged to perform 3 sets of exercises daily. One set was 8-12 MVCs, held for 6-10 secs, double rest times between contractions, followed by 3-5 fast contractions in a row. Fortnightly the same physiotherapist phoned the woman. A standardised lifestyle advice sheet was given to both groups containing global stretching exercises and advice on weight loss, fluid intake, constipation, and avoidance of heavy lifting. No detail was provided of who delivered the intervention e.g. how many physiotherapists. Control group (n=16) received instructions on performing a PFM contraction without a protocol, and a lifestyle advice

Table 17: Characteristics of studies comparing PFMT versus no active treatment for pelvic organ prolapse

Study ID, population	Training Type	Training Program	Training Duration	Effectiveness	Notes
Braekken [306,317]	PFMTvs control (given lifestyle a, taught the Knack)	Weekly physiotherapy appointments for three months then fortnightly visits, with home exercise (3 sets of 8-12 close to maximal contractions daily)	6 months	Reduced frequency of symptoms: PFMT 74% vs control 31%, RR 0.37, 95% CI 0.21 to 0.65) Reduced symptom bother: PFMT 67% vs control 42%, RR 0.56, CI 0.33 to 0.97 POP-Q stage not improved: 47/58 PFMT vs 46/50 control, RR 0.88, CI 0.76 to 1.02	Stage I, II and III prolapse included. Dropout rate 2%
Ghroubi 2008 [437]	PFMT+ healthy living advice vs control	Taught PFMEs (stretch reflex technique) + electrical stimulation + digital biofeedback. 24 sessions, 30 minutes per session. From 10th session 20 contractions per day at home. Lifestyle advice.	unknown	Post-Rx no. with pelvic heaviness; 5/27 PFMT vs 14/20 control, RR 0.26, CI 0.11 to 0.61	Stage I or II cystocele, with or without stage I rectocele. No detail of dropouts.
Hagen 2009 [438]	PFMT vs control (given lifestyle advice leaflet)	5 physiotherapy sessions (weeks 0, 2, 6, 11 and 16). Individualised advice and home exercise programme - 6 sets per day recommended, 1 set = up to 10 max. voluntary contractions, held for up to 10 secs, with 4 secs rest in between, 1 min rest, then 10 or more fast contractions.	16 weeks	Pelvic Organ Prolapse Symptom Score, mean diff. btwn groups in change from baseline: 3.37, CI 0.51 to 6.23 Self-report of no improvement: 7/19 PFMT vs 16/21 control, RR 0.48, CI 0.26 to 0.91 POP-Q stage not improved: 6/11 PFMT vs 9/9, RR 0.57, CI 0.33 to 0.98	Stage I and II prolapse included. Dropouts: PFMT 4, control 3.
Hagen 2011 [296]	PFMT vs control (given lifestyle advice leaflet)	5 physiotherapy sessions (weeks 0, 2, 6, 11 and 16). Individualised advice and home exercise programme – at least 3 sets per day recommended, 1 set = up to 10 max. voluntary contractions, held for up to 10 secs, with 4 secs rest in between, 1 min rest, then 10 or more fast contractions.	16 weeks	Pelvic Organ Prolapse Symptom Score, mean diff. btwn groups in change from baseline at 12 months: 2.37, CI 1.30 to 3.44 (results of statistical modelling subsequent to ICS abstract) POP-Q stage not improved: 135/168 PFMT vs 150/171 control, RR 0.92, CI 0.83 to 1.01	Stage 1, II and III prolapse included. Questionnaire response at 12 months: 67% PFMT, 65% control. 6-month POP-Q attendance: 81% PFMT; 82% control

Table 17: Characteristics of studies comparing PFMT versus no active treatment for pelvic organ prolapse (continued)

Study ID, population	Training Type	Training Program	Training Duration	Effectiveness	Notes
Piya-anant 2003 [439]	PFMT vs control	PFMEs taught on one occasion. If woman unable to perform, attended monthly until could do so. 30 exercises "after one meal every day". Advice on diet and fluid intake.	unknown	PFMT group less likely to have worse prolapse at 24 months follow-up (28%) than those in the control group (72%) (P < 0.05).	These two percentages were the only numeric outcome data reported. Women over 60 years of age, with or without anterior wall prolapse. 88/330 PFMT and 91/324 control did not attend for follow-up.
Stupp 2011 [318]	PFMT vs control (given lifestyle advice sheet)	7 appointments with women's health physiotherapist (weeks 0, 1, 2, 6, 10, 14). 12-week home exercise program was prescribed - 3 sets of exercises daily encouraged: 8-12 MVCs, held for 6-10 secs, double rest times btwn contractions, 3-5 fast contractions in a row. Fortnightly the same physio phoned the woman. Lifestyle advice sheet given to both groups.	14 weeks	POP-Q stage not improved: anterior 6/19 PFMT vs 11/14 control, RR 0.40, CI 0.20 to 0.82; posterior 6/12 PFMT vs 4/5 control, RR 0.63, CI 0.31 to 1.28 Strength (Oxford), mean diff btwn groups post-Rx: 1.5, CI 101 to 1.99 Endurance, mean diff btwn groups post-Rx: 4.4, CI 3.37 to 5.43 MVC, mean diff btwn groups post-Rx: 4.4, CI 1.63 to 7.17	Stage II anterior or posterior prolapse. Stated compliance 100% PFMT and 76.2% control.

Foot notes: MVC = maximum voluntary contraction, PFMT = pelvic floor muscle training, PFME = pelvic floor muscle exercises,

sheet as above. The primary outcome measure was POP-Q performed by one gynaecologist who was blinded to group allocation. Secondary outcomes were: pelvic floor muscle function (strength – Oxford grading, endurance – PERFECT assessment); electrical activity (sEMG); symptom severity. It was stated that compliance in the PFM group was 100% and in the control group 76.2%. 91% in the PFM group adhered to the home exercise programme.

Risk of bias in this study was potentially high: no detail of the randomisation process was given, nor blinding of the outcomes measures, other than POP-Q.

A multicentre trial of PFMT for stage I, II or III prolapse which randomised 477 women has recently been completed [296]. This was a parallel group randomised controlled trial. Women in the intervention group were randomised to PFMT, delivered by a physiotherapist at 5 appointments over 16 weeks, and lifestyle advice. Women in the control group received a Lifestyle Advice Sheet by post only. Women had their prolapse assessed by a gynaecologist (POP-Q system) at baseline and (blinded) 6 months, and completed postal questionnaires at baseline (prior to randomisation) and 6 and 12 months. The primary outcome was prolapse symptom severity (Pelvic Organ Prolapse Symptom Score – POP-SS) at 12 months. Other key outcomes were prolapse severity (POP-Q), women's perceived change in prolapse, uptake of further treatment and cost-effectiveness. Analysis was by intention-to-treat.

The risk of bias was judged to be low. Randomisation was by computer allocation using a remote randomisation service, and groups were comparable at baseline. Outcomes were measured mainly via questionnaire thus avoiding measurement bias. Gynaecologists were blinded to women's trial group when undertaking the follow-up POP-Q assessments. Questionnaire response rates were high at 6 month follow-up (84% intervention; 86% control), but lower at 12 months (67% intervention; 65% control). Rates of attendance for 6-month prolapse assessment and POP-Q were good (81% intervention; 82% control). Compliance with the intervention was high: 80% of women attended 4 or 5 physiotherapy sessions.

(b) PFMT and surgery:

No new evidence to report.

(c) PFMT and pessary:

A feasibility study (the PEPPY study) looking at the possible effects of PFMT with a vaginal pessary in situ has been completed but full results have not yet been published.

(d) Ongoing trials:

There is currently one ongoing RCT (of PFMT as an adjunct to vault prolapse surgery – OPTIMAL) under the direction of the NIH-sponsored Pelvic Floor Disorders Network [319]. This trial compares two methods of suspending the vaginal vault in women undergoing vaginal surgery for POP and additionally will randomise half of the participants to adjunctive post-operative PFM exercises and behavioural therapy and half to routine care. The analysis will assess whether such adjunct therapy improves both anatomic and symptomatic outcomes two years after surgery. The study is expected to be complete by 2012 (the OPTIMAL trial, ClinicalTrials.gov Identifier: NCT00597935).

A further feasibility study of pre- and post-operative PFMT for women undergoing prolapse repair is underway (the SUPER study: ISRCTN 08203457). This study aims to recruit 30 participants over 3 sites. Participants are randomised to either the intervention group (n=15) or the control group (n=15). Prior to surgery all patients who have agreed to take part are seen by a physiotherapist to complete baseline outcome measures. Those in the intervention group are also seen once pre-operatively by another physiotherapist to be taught pelvic floor muscle exercises. After 6 weeks those in the intervention group are seen for a total of 5 visits over a 16 week period for further instruction in pelvic floor muscle exercises and advice. Both groups complete outcome measures at 6 and 12 months post-surgery.

b) Results

(a) PFMT alone:

In the Braekken trial [306,317], in women with prolapse symptoms at baseline (69/109), those in the PFMT group compared to the control group were significantly more likely to have reduced symptom frequency (74% vs 31%) and bother (67% vs 42%). Fewer women in the PFMT group than the control group had no improvement in POP-Q stage (81% versus 92%). In contrast, no significant difference was noted in the subgroup of women with prolapse beyond the hymen (80% versus 80%). The authors also used ultrasound to measure the position of the bladder and rectum within the pelvis, and the dimensions of the muscles and hiatal area, to indicate the severity of prolapse. They found the change in resting position in standing of the bladder and rectum, compared to baseline, were significantly greater (both were higher) in the intervention group than the control group; and changes in measures of the muscles and hiatal area were also significantly different in favour of the intervention group. Manometry (unblinded) was used to measure contraction strength and endurance and found improvement in strength and endurance were significantly greater in the intervention group compared to the control group. Braekken also reported better urinary outcomes for women in the intervention group in their trial.

Stupp [2011] showed that the intervention group had significantly greater anatomic improvements in anterior and posterior vaginal wall prolapse than did the

control group, and a decrease in symptoms [318]. In addition, the intervention group had greater improvements in muscle strength, endurance, and electromyography parameters compared to the control group.

Hagen [2011] found prolapse symptoms were reduced significantly more in the intervention group compared to the control group at 6 months and 12 months. Change in prolapse stage from baseline to 6-month follow-up showed a marginally significant difference between trial groups: 20% in the intervention group had an improved stage versus 12% in the control group. The majority of women in both groups had no change in their prolapse stage. By 12 months, a significantly greater proportion of control women (55%) reported they had received further treatment for prolapse compared to the intervention women (30%). Control women were significantly more likely than intervention women to report subsequent referral to physiotherapy. Rates for receiving other treatments were similar. When analysis of the primary outcome measure was adjusted for additional treatment received, the estimate of the effect of PFMT at 12 months was greater and comparable with that at 6 months.

ICI 4th edition reported on three trials of PFMT versus control for prolapse that found a positive effect, however two of the trials were small (<25 per arm) and the remaining trial had serious methodological limitations. Results from an additional three trials are now available [296,306,317,318] indicating a benefit on both anatomical and symptom measures of prolapse. Stupp (2011) was a pilot study; the remaining two trials were rigorously conducted trials with large sample sizes which provide level 1 evidence of the effectiveness of PFMT for women with stage I to III prolapse.

c) Summary

Based on previous studies and new evidence from two rigorously conducted trials and a smaller pilot trial, we conclude that PFMT can improve the symptoms of prolapse and the anatomical defects. **(Level of Evidence: 1)**

No further evidence is available regarding the role of PFMT as an adjuct to surgery and thus conclusions are unchanged: pre- and post-operative PFMT may help to improve quality of life and urinary symptoms in women undergoing surgery for POP, but the findings regarding its effects on PFM strength are contradictory. The evidence available however is based on two small trials, one of which included women undergoing surgery for UI and/or prolapse. **(Level of Evidence: 2)**

d) Recommendations

PFMT can improve prolapse symptoms and severity **(Grade of Recommendation: A)**.

Preoperative PFMT may help improve quality of life and urinary symptoms in women undergoing surgery for prolapse **(Grade of Recommendation: C).** Larger trials are needed, and prolapse-specific measures should be primary outcomes in such trials

Future studies of PFMT for POP should aim to reach a consensus on the optimal intervention programme prescribed and might also consider comparisons of individualised training with group training.

III. PESSARIES

Pessaries offer a non-surgical option for the treatment of urinary incontinence and pelvic organ prolapse (POP). Pessary use dates back prior to the days of Hippocrates, and innumerable varieties such as half a pomegranate, a linen tampon soaked with astringent vinegar or a piece of beef have been used. It was only in the 16th century that a device was made specifically to be used as a pessary, as opposed to using naturally occurring objects. Since the 20th century, considerable refinements have occurred and modern pessaries are made from a variety of materials including rubber, clear plastic, soft plastic with metal reinforcements and silicone [320].

A range of vaginal pessaries (**Figure 7**) exist which can be broadly divided into two types: support and space-filling pessaries. Support pessaries lie along the vaginal axis, with the posterior component sitting in the posterior fornix and the anterior component coming to rest just under the symphysis pubis, thus providing a supportive shelf for the descending pelvic organs [321]. As there is no evidence to support the use of a specific type of pessary, choice is based on experience and trial and error. It is generally accepted that the ring pessary should be tried first because of ease of insertion and removal, and if this fails, other pessaries can be used [322]. Clemons [323,324] found that the ring pessary was successful in grades II and III prolapse, but for higher grades, a Gellhorn pessary was more effective. By contrast, a randomised crossover trial of the ring versus the Gellhorn pessary, did not demonstrate any difference in effectiveness between the two types of pessaries [325].

While it is not possible to establish a global perspective of the full extent of pessary use, a survey of the members of the American Urogynecologic Society showed that 75% of members used pessaries as first-line therapy for POP. Ninety two percent of physicians believed that pessaries relieve symptoms associated with POP, while 48% felt that pessaries also had therapeutic benefit in addition to relieving symptoms. No clear consensus emerged regarding the type of pessary or their indications for use [326]. Similarly there are no clear prevailing removal regimes [Cundiff, 2000]. In the United Kingdom, a recent postal survey demonstrated that 87% of consultants use vaginal pessaries for management of POP [327]. Many physicians receive little or no

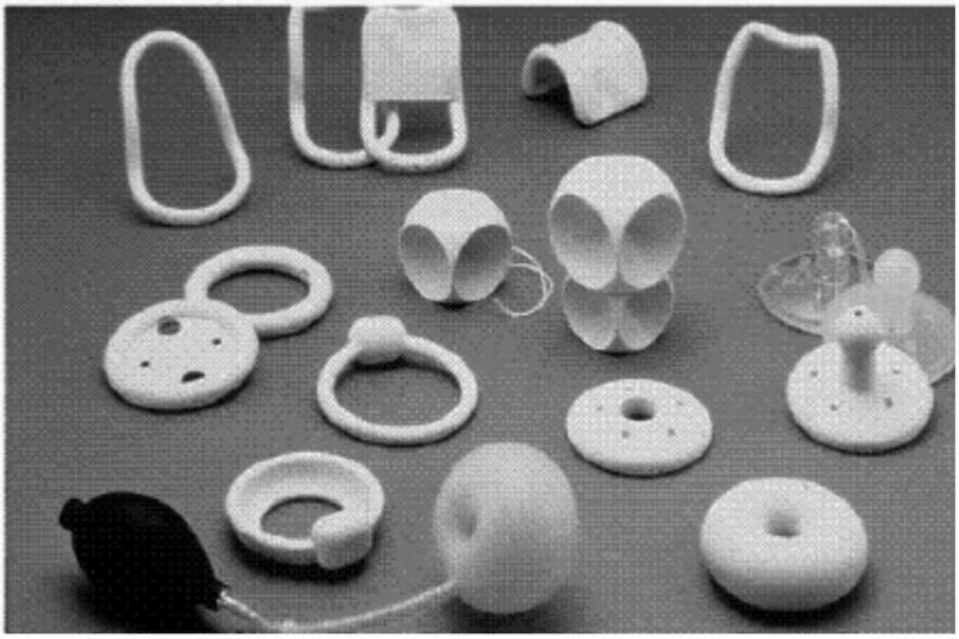


Figure 7 : Range of pessaries (Courtesy of Mediplus Ltd, UK)

training in the use of pessaries [328] and have limited experience with pessary selection and fitting.

Likely candidates for vaginal pessaries are those with co-morbid medical conditions, those who still wish to bear children, as interim relief prior to surgery and for those who prefer non-surgical treatment [314]. Kapoor (2009) demonstrated that when pessaries are offered to patients with symptomatic pelvic organ prolapse, nearly two thirds of women choose a pessary rather than surgery as initial management [329]. Furthermore, a case-control study comparing women who chose pessaries to those who underwent surgery one year after their respective treatment found no difference in prolapse symptoms, bladder, bowel or sexual dysfunction between groups [330]. Thus, although traditionally thought of as treatment only for women deemed unfit for surgery or infirm, pessaries should be considered a viable treatment option for the majority of women in the initial management of POP. Other indications include vaginal laxity, neonatal prolapse mainly seen in association with neural tube defects such as spina bifida and prolapse during pregnancy [322].

Factors that predict the type of treatment chosen for POP have been evaluated in various studies. Powers [2004] [331) noted that patients who refused a pessary were significantly younger and had a higher incidence of urodynamic stress urinary incontinence (SUI). More patients with stage III prolapse refused while more patients with stage IV accepted pessary trial. Heit [2003] [332) found that the probability of choosing a pessary over surgery increased as age increased and decreased as the prolapse severity increased. Clemons 2004 [324] evaluated characteristics that were predictive for pessary usage for up to one year. Age greater than 65 years at the time of pessary insertion and more severe prolapse (Stage III-IV) were more predictive for pessary discontinuation. Brincat [2004] [333] found that women who were sexually active and those with POP were more likely to continue wearing a pessary than women with urinary incontinence. In keeping with this, Ko [2011] [334] found that substantially older women or menopausal women opted for a pessary rather than surgery, and significantly more sexually active women preferred surgery.

Evidence of the effectiveness of pessary use for prolapse can be obtained from a large number of observational studies (prospective and retrospective) and two RCTs (**Table 18 and Table 19**).

1. QUALITY OF DATA

(a) Randomised controlled studies:

One new randomised intervention was found [335] in which the Colpexin Sphere was compared to PFMT in women with stage I and II pelvic organ prolapse on improving pelvic floor muscle strength and reducing symptoms. The device is a spherical

intravaginal device, similar to a pessary, which is placed above the levator musculature and requires active PFM contractions to keep it in place. Its purpose is to reduce the prolapse while facilitating PFM strengthening. Group 1 used Colpexin Sphere with PFMT and the other group did PFMT only for a 16 week period. Outcomes were evaluated at baseline and at 16 weeks for comparison of pelvic floor muscle strength. A total of 50 women were enrolled and 48 women completed the full 16 week assessment which consisted of Colpexin pull through test and a digital test. All assessments were performed by only one investigator who was blinded to the group assigned. The small sample size and the short period of treatment are limitations. In addition, the authors did not report a power calculation. The participants were stratified into two groups by using computer-generated random numbers. Participants within each stratum were randomised by using opaque sealed envelopes to one of two study groups.

No other new randomised contolled trials were found on the use of a pessary compared to another device or treatment protocol. Cundiff [325] conducted the largest multi-centre crossover trial, comparing a ring with support and a gellhorn pessary for the treatment of symptomatic stage II or greater symptomatic prolapse. There were no significant differences between groups in baseline characteristics. Participants were fitted with one of the pessaries for three months, and with the second for a further three months. During each three-month period, data were collected at one, six and twelve weeks from women who had a successful fit. Outcomes were measured at enrolment and three and 12 months, and included objective assessment using POP-Q and subjective assessment using Pelvic Floor Distress Inventory (PFDI), Pelvic Floor Impact Questionnaire (PFIQ), and a sexual function questionnaire. Random allocation was by computer-generated random numbers using permuted blocks of variable size. Opaque, sealed envelopes were used to store the random allocation. Participants and clinicians were not blind to the allocation, but data were coded such that analysis was conducted blind.

(b) Prospective observational cohort studies

Wu [1997] [336] conducted a prospective study of 110 women with symptomatic POP to evaluate a protocol for pessary treatment. After intitial fitting, they were seen at two weeks for re-examination and thereafter at 3-6 month intervals. Handa (2002) [337] described the course of POP amongst 56 women who used a supportive vaginal pessary for at least one year.

In 100 women with prolapse, Clemons [2004] [323], analysed the factors that contributed to successful pessary use. Two publications resulted: one on the symptoms and patient satisfaction at two months on 73 out of the original 100 study women who had a successful pessary fit and the other on the continuation with pessary at one year of the sub-group who were satisfied users [324].

Lukban [2006] [338] described a study of the effectiveness and safety of the Colpexin Sphere device in women (n=39) with prolapse beyond the hymenal ring; all women had grade three or greater prolapse of at least one vaginal compartment (69% cystocele, 44% rectocele, 31% enterocele, 8% vault prolapse, 21% uterine prolapse). Women were instructed to use the Colpexin Sphere only whilst in bed for the first week, and to use continuously thereafter, and were taught PFM exercises to be performed twice daily (PFMT and knee squeezes). The intervention period was 16 weeks. Outcome measures included prolapse stage (modified Baden and Walker classification system), PFM assessment (Brink Scale score), and a Pull Test to measure PFM tone and strength (a tensiometer is used to measure the force required to remove a 35mm sphere from above the levator plate). The small sample size, lack of control group and short follow-up were limitations of the study.

Using the Sheffield Pelvic Organ Prolapse quality of life questionnaire, Fernando [2006] [339] addressed the effectiveness of pessaries in alleviating symptoms associated with POP in a prospective study of 203 consecutive women attending a specialist urogynaecology unit four months after pessary insertion. Abdool [2011] [330] evaluated and compared the effectiveness of pessaries and surgery in patients with pelvic organ prolapse in 554 women one year after treatment. Of these 359 were treated with a vaginal pessary and 195 had surgery. Lone [2011] [340] prospectively evaluated the use of pessaries in 246 women over a 5 year period and identified complication rates and reasons for discontinuing use over the 5 year period. There was an overlap of patients in these studies as they are from one institute. Kuhn [2009] [341] used the same Sheffield Pelvic Organ Prolapse quality of life questionnaire and Female Sexual Function Index questionnaire to evaluate quality of life and pelvic organ and sexual function before and during pessary use in 73 women of whom 31 were sexually active.

Komesu [2007] [342] compared pelvic floor symptom changes in 36 who continued pessary use to 28 who discontinued using the Pelvic Floor Distress Inventory-20 (PFDI-20) before and after pessary use. In the same group of women, they further explored whether patient determined goal achievement was associated with pessary continuation.

Barber [343] undertook a study to evaluate the responsiveness PFDI and PFIQ in women with pop undergoing surgical and non-surgical management. The pessary group consisted of 42 women with stage II or greater prolapse enrolled in an multicentre randomised trial comparing two different pessaries and 64 women with Stage III or greater prolapse who underwent vaginal reconstructive surgery. All subjects completed the questionnaires at baseline and again

either three months (pessary group) or six months (surgery group) after initiation of treatment.

Jones [344] evaluated 90 women who had a pessary inserted for POP at baseline and 3 months after pessary use. Pelvic Floor symptoms were assessed using PDFI scores. In addition they assessed the change in genital hiatus measurements. Logistic regression analysis was used to assess baseline characteristics predictive of continued pessary use.

Patel [345] sought to evaluate whether use of a vaginal pessary would change body image, bother symptoms, and quality of life in women with pelvic organ prolapse. Seventy five women presenting for pessary insertion completed the short forms of Pelvic Floor Distress Inventory-20, Pelvic Floor Impact Questionnaire, and Body Image Scale. After successful pessary insertion and use for at least 3 months, 54 subjects repeated the surveys.

(c) Retrospective studies:

There are several retrospective studies on pessary benefits and outcomes but these are limited by the retrospective study design [334,346-351]. Thus we have chosen not to evaluate them in this review as there are several prospective cohort studies that allow a better assessment of effect.

2. OUTCOME

a) Patient reported outcomes

As can be seen in Table 18, follow-up periods evaluating patient reported quality of life varied from three to 12 months. In most studies a recognised measure of prolapse was used i.e. POP-Q examination, to objectively assess and evaluate the prolapse. One study [342] included patients with prolapse and/or incontinence. Various types of pessaries were used. Validated questionnaires to assess patient related outcome were used in eight studies. Commonly used questionnaires were the Sheffield POP symptom questionnaire, and the Pelvic Floor Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ). Other questionnaires used were Female Sexual Function Index, Body Image Scale and Kings Health Questionnaire.

A direct comparison between studies is difficult as different outcome measures have been used. When pessary insertion was successful, there appears to be a significant improvement in prolapse symptoms. Cundiff [2007] found significant and clinically significant improvements in majority of the PFDI scales and many PDIQ scales with both pessaries but no difference between the ring or gellhorn pessary. Two prospective studies [343,344] found a significant improvement in the urinary and prolapse scales of the PFDI but not in the colorectal scale 3 months after insertion of pessary compared to baseline. Others [342,345] demonstrated a significant improvement of the PFDI-20 scale 3 months after pessary use.

However data on the questionnaire that measures impact i.e. PFIQ varies as Barber (2006) demonstrated no significant changes in the 3 scales while Patel (2010) showed significant decrease in PFIQ scores and prolapse/vaginal subscale of the PFIQ. Fernando (2006) and Abdool (2011) administered the Sheffield Pelvic Organ Prolapse Quality of Life questionnaire (SPS-Q) at before, 4 monthsand one year after pessary insertion. Two hundred and three patients from the previous study (Fernando) were included in the later paper (Abdool). A significant improvement was seen in prolapse symptoms, bladder and bowel function as seen in Table 18. Contrary to Fernando 's study, Abdool did not demonstrate improvement in bowel evacuation at one year probably as this was only marginally significant (p=0.045) at 4 months.

Women who were sexually active and wore a pessary showed significant improvement in satisfaction of sexual activity at 4 months [339] and at 12 months [330]. Kuhn [341] found a significant improvements in desire, orgasm, lubrication and satisfaction after pessary use. This suggests that a vaginal pessary does not negatively interfere with sexual activity but may even improve sexual function. However, sexual activity is only possible with a ring pessary insitu [330,339]. The other pessaries need to be removed prior to sexual intercourse.

Self-perception of body image is reduced in women with advanced POP [352]. A significant decrease in body image scale scores has been reported indicating an improvement in women's perception of themselves in addition to improvement in PFDI-20 and PFIQ scores at 3 months [345]. However, majority of subjects in this study had stage 3 prolapse, so it is possible that improvements might not be the same for women with less advanced prolapse (i.e., stage 2) and those with urinary incontinence alone.

Two studies [330,343] compared patient related outcome after pessary and surgery use. Abdool demonstrated a significant improvement in prolapse, urinary, bowel and sexual function in both treatment arms but no difference between the two groups. However, Barber (2006) found that subjects in the surgery group had significantly greater improvement in each of the scales of the PFDI and the prolapse and urinary scales of the PFIQ than did the pessary group.

The placebo effect of treatment for prolapse needs further exploration. Komesu [2007] found an improvement in the PFDI-20 total, bladder and prolapse scores in women who discontinued and those who continued pessary use although this was more modest [342]. This could be because of placebo effect or because of conservative interventions such as dietary change and pelvic floor exercises. In the same group they further studied the association between patient determined goal achievement and pessary continuation. Goals commonly listed were

bladder (36%), activity (20%), and general health (13%) and prolapse related (11%). Although goals were found to be variable, women who continued pessary use were more likely to meet one to two goals. Women who attained self-determined goals were more likely to continue pessary use.

1. Success Rates

There is no agreement in the literature on what is considered successful fitting of a pessary. Some consider success if a pessary was perceived comfortable by a patient when retained during valsalva and voiding at the initial visit, while others consider it success if a patient continued to use the pessary until the following visit to the doctor. Therefore, the rates of successful fitting vary between 89% to 8% with the follow-up time to define success ranging from initial fit to 7 years. (**Table 19**). Five studies [333,342,347,349,351] included patients with prolapse and/or incontinence.

Higher success rates for specific types of prolapse (83% for uterine prolapse and 82% for cystocele) are recorded [349]. Comparison of success rates by pessary type was difficult due to use of differing protocols for pessary selection within studies (**Table 19**). Wu [1997] [336] used ring pessaries in 96% of women who were successfully fitted. Similarly, ring pessaries were the primary choice of treatment in other studies [337,339,353]. The fitting protocol used by Mutone [348] specified the ring pessary with support diaphragm in the first instance. Of women who had a successful pessary fitting, ring pessaries were used more often in women with stage II (100%) and stage III (71%) prolapse whereas Gellhorn pessaries were used more often with stage IV (64%) prolapsed [353]. Hanson [2006] found significantly greater success with the ring, ring with support and Gellhorn pessaries than other type of pessaries ($p<0.05$), however only 54% of women in this study had prolapse (the remainder had UI).

Parameters reported as associated with a successful pessary fitting were often contradictory. Hanson [2006], Clemons [2004], and Mutone [2005] reported that patient age was not significantly related to the success of pessary fitting whereas Wu [1997] and Friedman [2010] reported that women who were fitted successfully tended to be older. Mutone [2005] found that women classed as obese were significantly less likely to have a successful fit, whereas Maito [2006] [347] indicated that weight was not a predictor of successful pessary fit.

Clemons 2004 [353] reported no effect on fitting success of previous surgical intervention while others found a significant relationship between unsuccessful fit and previous hysterectomy or prolapse repair [346-348]. Wu [1997] reported that a history of pelvic surgery reduced the probability of a successful pessary fitting from 79% to 67%, although this result was not significant ($p=0.2$). Hanson [2006] found a higher fitting success rate in women with previous abdominal genitourinary surgery (71%) compared to those with a history of genitourinary surgery via the vaginal route (60%). Fernando [2006] found 75% retained the pessary at two weeks, and that failure to retain was associated both with increasing parity and hysterectomy in a multivariate logistic regression analysis; site and type of prolapse did not affect success.

Current hormone use did not predict greater likelihood of fitting success [336,353] whereas use of local oestrogen (with or without systemic HRT) was felt to play an important role in successful pessary fitting [349]. Sexually active women were more likely to continue wearing a pessary for a longer period of time [333,343].

Women with SUI before pessary fitting are reported to have a significantly lower success rate in two trials [336,346] but not in one [324]. Maito [2006] found no significant difference in success rates between women with SUI (94%), POP (89%), or both (81%).

Increasing severity of prolapse did not affect the success of pessary fit [336, 348, 353]. Neither was large genital hiatus [324,348,350], severe vaginal atrophy nor a foreshortened vagina affected success nor was the location of the prolapsed an issue [348]. However, a shorter vaginal length and wider vaginal introitus were associated with an unsuccessful fitting [324,350]. On the other hand, Maito [2006] [347] found mild posterior prolapse to be a significant predictor of successful fit. Clearly, differing techniques, follow up, support and skills affect how well pessaries are tolerated and maintained.

Comparison of long term pessary usage rates was difficult due to differing follow-up periods used in the studies reported. Maito [2006] reported continued pessary use of on average six months (range one to 17 months); discontinuation of pessary use was significantly associated with severe posterior prolapse after adjustment for age. Wu [1997] found that 66% of those who used a pessary for more than one month were still users after 12 months and 53% were still users after 36 months. Lone [2011] prospectively evaluated 246 women who opted to use a vaginal pessary (ring, cube, gellhorn, donut) [340]. One hundred and eighty seven (76%) successfully retained the pessary four weeks after pessary insertion. Over a five year period, 19% of the 187 women were lost too follow-up. Of the 151 women included in the analysis, 13.9% discontinued use at some point after four weeks, whereas 86.1% used the pessary successfully over 5 years. The authors concluded that if the treatment for pessary is successful at four weeks, most women will continue to use the pessary over 5 years without a concomitant increase in complications.

Reasons for failure range from expulsion to complications such as vaginal discharge, erosion, de novo SUI, pain, voiding difficulty and constipation (**Table 19**).

2. Complications

Minor complications after pessary insertion range from vaginal discharge, erosion, de novo SUI, bleeding pain and constipation as can be seen in Table 19. Sarma [2009] [351] reported a complication rate of 56% after pessary use. Rarely major complications may occur. Neglected pessaries present with more serious complications namely fistula formation and peritonitis. Erosion into the bowel or bladder and dense adhesions to other pelvic structures has been reported. Unusual complications of cervical entrapment, small bowel incarceration, and hydronephrosis [354] have been reported.

3. Pelvic Floor Muscle Strength

In a randomised study on the use of Colpexin Sphere [335] a statistically significant improvement in pelvic floor muscle strength was noted as compared with baseline values and at 16 weeks was shown in both groups, with mean difference pull test contraction values of 2.25 + 3.28 N ($P < 0.05$) in the study group and 1.38 + 2.17 N ($P < 0.05$) in the control group. There was no statistically significant difference in improving pelvic floor muscle strength between the study and the control groups. The authors concluded that even though Colpexin Sphere plus pelvic floor exercise improved pelvic floor muscle strength, the improvement was not statistically different from exercise alone

4. Financial implications:

Hullfish [355], developed a Markov decision analysis model to assess and compare the relative cost effectiveness of treatment decision alternatives for post-hysterectomy pelvic organ prolapse e.g. expectant management, use of a pessary and surgery obtaining months of quality-adjusted life over one year. Sensitivity analysis was conducted to determine whether the results depended on specific estimates of patient utilities for pessary use, probablitites for complications and other events and estimated costs. Only two treatments i.e. initial pessary use and vaginal reconstructive surgery were found to be efficient choices. Pessary use (including patients that eventually transitioned to surgery) achieved 10.4 quality-adjusted months at a cost of $10,000 per patient, while vaginal reconstructive surgery obtained 11.4 quality adjusted months at a cost of $15,000 per patient. The authors concluded that research is needed to standardise POP outcomes and complication, so that healthcare providers best utilise cost information in balancing the risks and benefits of their treatment decisions.

IV. SUMMARY AND RECOMMENDATIONS

There is growing attention being paid to the effectiveness of conservative interventions for the condition. There are encouraging signs of more rigorous research in this area, with the publication of 4 RCTs [296,306,318,335] in this field since the 4th ICI and 3 more trials awaited.

C.4.1 Recommendations for practice

There is limited Level 1 and Level 2 evidence on which to base recommendations for practice, and most recommendations are, in effect, hypotheses that need further testing in RCTs.

Pelvic floor muscle training (PFMT)

•PFMT can help improve prolapse symptoms and severity **(Grade of Recommendation: A)** (New).

•Preoperative PFMT may help improve quality of life and urinary symptoms in women undergoing surgery for prolapse **(Grade of Recommendation: C)** (Unchanged).

Pessaries

•In a choice between the Gellhorn pessary and a ring with support, either may improve prolapse symptoms and reduce their impact **(Grade of Recommendation: B).**

2. FUTURE RESEARCH DIRECTIONS

a) Lifestyle interventions

- Studies are needed to fully investigate the association between occupation/heavy lifting, bodyweight, constipation and POP. These studies should ensure that:
    - o Occupation, physical activity, bowel function and diet are assessed rigorously, using instruments with sound psychometric properties.
    - o Potential confounding variables are considered.
    - o Attempts are made to overcome some of the obstacles in research in this area such as recall bias inherent in assessing lifetime occupational history, or healthy worker bias which is a problem when attempting to compare POP in women currently employed in heavy labour type jobs versus others.
- Only when the links between various lifestyle factors and POP have been more clearly established can good RCTs be set up to investigate the effects that changes in these lifestyle factors can have on preventing POP.
- Anaemia is a treatable condition, either through diet or medication, and further research on its role in prevention of prolapse is warranted.

b) Pelvic floor muscle training (PFMT)

- Studies are needed to fully investigate the role of physical therapies in the prevention of POP. Such studies should:

Table 18: Characteristics of studies on symptomatic prolapse and pessary

Author/ year	Study design	Comparison group	Partici-pants	Type of pessary	Subjective and Objective assessment	Objective assessment	Length of follow-up	Improvement in symptoms
Abdool et al 2011 [330]	Prospective observational cohort case controlled	Pessary treatment compared to surgery	359	Ring, Gellhorn, Cube, Donut	Sheffield prolapse questionnaire	Baden-Walker	12 months	Awareness of lump, prolapse coming out of vagina, dragging pain in lower abdomen, low back pain, voiding difficulty, need to push prolapse to void, urinary urgency, fecal urgency, improvement in sexual satisfaction, interference with physical activity and quality of life
Barber et al 2006 [343]	Prospective observational cohort case controlled	Pessary treatment (3 months) compared to surgery (6 months) for pelvic organ prolapse	Pessary (n= 42) Surgery (n=64)	Ring and Gellhorn	PFDI and PFIQ	POP-Q	3 months for pessary	Significant improvement in prolapse and urinary scales of the PFDI. No change in the colorectal scale. No change in the PFIQ scales
Clemons et al 2004 [323]	Prospective observational cohort	N/A	100	Ring and Gellhorn	Not validated	POP-Q	2 months	Bulge (90% to 3%) Pressure (49% to 3%) Discharge (12% to 0%) Splinting (14% to 0%) SUI 45% UI 46% Voiding difficulty 53%
Cundiff et al 2007 [325]	Randomised cross-over	Ring with support to Gellhorn	134	Ring with support to Gellhorn	PFDI,PFIQ, Sexual Function Question-naire	POP-Q	6 months	Statistically and clinically significant improvements in majority of the PFDI and many PFIQ scales in both pessaries, but no clinically significant differences between the two pessaries
Fernando et al 2006 [339]	Prospective observa-tional cohort	N/A	203	Ring, Gellhorn, Cube, Donut	Sheffield prolapse questionnaire	Baden Walker	4 months	Awareness of lump (71%), Prolapse coming out of vagina (52%), Vaginal soreness (21%), Dragging sesation in lower abdomen 24%), Lower back ache (30%), Difficulty emptying bladder (40%), Push prolapse to void (29%), urinary urgency (38%), Urge urinary incontinence (29%), Stress urinary incontinence (40%), Incomplete emptying of bowels (28%), Rectal digitation to empty bowels (12%), Vaginal digitation to empty bowel (7%), Faecal urgency (30%), Urge faecal incontinence (20%), Frequency of sexual intercourse (16%),Improvement in sexual satisfaction (11%)

Table 18: Characteristics of studies on symptomatic prolapse and pessary (continued)

Author/ year	Study design	Comparison group	Partici-pants	Type of pessary	Subjective and Objective assessment	Objective assessment	Length of follow-up	Improvement in symptoms
Jones et al 2008 [344]	Prospective observa-tional cohort	N/A	90	Ring, Inconti-nence ring, Gellhorn, Oval	PFDI	POP-Q	3 months	Improvement in the overall PFDI scale and all subscales with the exception of colorectal distress inventory
Komesu et al 2007* [342]	Prospective observa-tional cohort	Compare PF symptoms in patients who continue and discon-tinue pessary use	64	Choice of pessary left to discretion of the provider	PFDI-20	POP-Q	6-12 months	In the continuation group final PFDI-20 total, bladder and prolapse scale scores were better than the discontinuation group.
Kuhn et al 2009 [341,344]	Prospective observa-tional cohort	N/A	73	Cube	Female Sexual Function Index, Sheffield question-naire, Kings Health Questionnaire	POP-Q	3 months	Improvement in feeling of bulge, improvement in stool outlet problems, overactive bladder symptoms. Improve-ment in sexual desire, orgasm, lubrica-tion, satisfaction after therapy
Patel et al 2010 [345]	Prospective observa-tional cohort	N/A	75	Ring, Ring with support, Gellhorn	Body Image Scale (BIS) and PFDI-20, PFIQ, Prolapse subscale of PFIQ	POP-Q	3 months	Improvement in body image scale scores, PFDI-20 scores, PFIQ scores

Foot notes: N/A-Not applicable, SUI- Stress Urinary Incontinence, UUI-Urge urinary incontinence, RCT- Randomised Controlled study, P- Prospective Observational study, PFDI- Pelvic Floor Distress Inventory, UDI -Urinary Distress Inventory

Table 19: Success rates after pessary insertion and risk factors for failure

Author/ year	Number	Types of pessaries	Study design	Follow-up period	Success rate n (%)	Reason for failure	Risk factors
Abdool et al 2011 [330]	554	Ring, Gellhorn, Cube, Donut	Prospective observational cohort	12 months	243 (68%)	N/A	N/A
Clemons et al 2004 (c) [323]	100	Ring, Gellhorn	Prospective observational cohort	2 weeks	73 (73%)	De novo voiding difficulty, occult stress incontinence, de novo voiding difficulty**	Desire for surgery and stage III-IV posterior vaginal wall prolapse***
Fernando et al 2006 [339]	203	Ring, Gellhorn, Cube, Donut	Prospective observational cohort	2 weeks	153 (75%)	Failure to retain pessary, Pain/ Bleeding/Discomfort, Worsening symptoms	Increasing parity, previous hysterectomy
Handa et al 2002 [337]	56	Ring, Donut, Gellhorn, Cube	Prospective observational cohort	3 months	36 (64.3%)	Discomfort, expulsion	-
Jones et al 2008 [344]	90	Ring, Incontinence ring, Gellhorn, Oval	Prospective observational cohort	3 months	42 (47%)	Failure to retain, Inadequate relief of symptoms	Large baseline measurement of the perineal body at rest Large LA hiatus width?
Komesu et al 2007 [342]	64*	Choice of pessary left to discretion of the provider	Prospective observational cohort	6-12 months	64 (56%)	failure to retain, uncomfortable	Prolapse score decrease to 77% of baseline
Kuhn et al 2009 [341]	73	cube	Prospective observational cohort	12 months	32 (44%)	Pessary expulsion, desire for surgery, bothersome de novo SUI, inability to remove or insert pessary, pain or feeling of discomfort, uspecified	N/A
Lone et al 2011 [340]	246	Ring, Gellhorn, Cube, Donut	Prospective observational cohort	5 years	53 (28.3%)	Expulsion, excoriation/bleeding, Pain/discomfort, Constipation	N/A same comment
Lukban et al 2006 [338]	39	Colpexin	Prospective observational cohort	4 months	27 (69%)	Device displacement, Subject noncompliance , Lost to follow-up , Subject choice	N/A
Patel et al 2010 [345]	75	Ring, Ring with support, Gellhorn	Prospective observational cohort	3 months	54 (79%)	Failure to retain, ineffective	N/A
Wu et al 1997 [336]	110	Ring with and without diaphragm, Cube	Prospective observational cohort	Initial visit	81 (74%)	Failure to sustain support of the prolapse, intolerable urinary incontinence, vaginal discharge, pelvic pain, vaginal abrasions and erosions	Younger women, previous pelvic surgery, history of stress incontinence prior to pessary insertion

*Foot notes: N\A = not applicable; N/R = not reported,*Includes patients with incontinence and/or prolapse; ** women who discontinued pessary usage after two weeks and within the first two 2 months; ***Predictors identified at one year*

- Consider the exact nature and timing of any physical therapies.
- Ensure that the effects of lifestyle factors and other potential confounding variables are taken into account.

• Further trials are needed to add to the evidence regarding:

- The effectiveness of PFMT for different stages and types of prolapse.
- The role of PFMT as an adjunct to prolapse surgery.

• There are no trials that address the following comparisons of interest:

- Low versus high intensity supervision of PFMT
- Individual versus group PFMT.
- PFMT versus surgery.
- PFMT versus pessary.

c) Pessaries

• There remains a pressing need for well-designed RCTs to examine the effects of using the wide variety of different pessaries in the treatment of POP. Such studies need to:

- Address optimal pessary effectiveness, including the symptomatic and therapeutic benefits of pessaries as well as the indications for use, pessary fit, replacement and care.
- Adopt consistent protocols regarding choice of pessary.
- Allow sufficient follow-up periods.

• Randomisation may not be appropriate but efforts should be made to match the characteristics of the treatment groups being compared. Comparisons of interest are:

- Pessaries versus surgery.
- Pessaries versus physical therapies.
- Pessary in conjunction with PFMT.

The assessment and measurement of POP and the assessment of prolapse symptoms need to be made in a standardised fashion using a validated outcome measure (such as the POP-Q examination). The choice of a single validated symptom tool is problematic at the present time.

C. URINARY INCONTINENCE IN MEN

UI in men remains under-reported and under-studied in comparison to studies including women. The report from the 4th ICI indicated that the prevalence of UI and LUTS in men ranged from eight to 23% depending on the method of data collection, population accessed, and location [1,356). As for previous consultations, despite the prevalence of UI and LUTS in older men, the only aspect which continues to receive systematic consideration with respect to conservative management are post-prostatectomy urinary symptoms. Thus, the major focus of this section is UI after prostatectomy for benign or malignant disease. All prostatectomy types and approaches were considered including radical prostatectomy (open radical retropubic or perineal, laparoscopic, and robotic) or endoscopic procedures (such as transurethral prostatic resection, high intensity microwave therapy).

The PMFT, EStim and MStim interventions in the current review were reorganized to reflect the evolving evidence and emerging directions of research on post-prostatectomy urinary incontinence. Studies of EStim and MStim in men post prostectomy all included PFMT as an intervention as well, so these were combined under PFMT. EStim and MStim studies of non prostatectomy related incontinence or other LUTS were kept in separate sections. As preoperative studies may represent the only truly preventative studies, and studies that only included incontinent men the true treatment studies, the categories of prevention and treatment were changed in the PFMT section. Instead, studies in these sections have been grouped into three types: preoperative interventions, mixed pre and post operatives studies of all men undergoing prostatectomy and studies of post operative interventionsfor men with established incontinence. Studies in the pre and post operative study category are heterogenous in timing of recruitment and intervention, an ongoing concern in this research area.

Aetiology of UI after prostatectomy

For purposes of the current review, the reader is directed to the report from the 3rd and 4th ICI (1,356) in which the aetiology of UI after prostatectomy is covered in detail (see report from Committee 13: Surgery for urinary incontinence in men). In brief, risk factors which have been repeatedly identified for UI after radical prostatectomy and transurethral resection of prostate (TURP) are abnormalities of detrusor contractility [357] and age [358]. Other related factors include neurovascular injury during surgery, previous TURP [359], preoperative radiotherapy, trauma, spinal cord lesion, new obstruction such as prostatic regrowth, bladder neck contracture, urethral stricture, Parkinson's disease [360,361], dementia, and medications [356].

Treatment

The primary conservative treatment for UI after prostatectomy remains physical therapies with or without some form of Biofeedback (BF). PFMT, along with

anal EStim, BF or transcutaneous electrical nerve stimulation (TENS), MStim, and even pharmaceuticals have all been utilised and reported as modestly successful in some trials and not in others.

A literature search of relevant systematic reviews and reports of RCTs and quasi-RCTs was performed. No other types of study design were considered. The report of the 4th ICI (1) identified 14 relevant RCTs on conservative management of UI post radical prostatectomy (n= 12) or TURP (n=2) [362-375). For this review, nine new published trials [376-384], and seven abstracts [385-391] were found, 14 in men undergoing radical prostatectomy, two in men undergoing TURP. One was excluded as it was a study in progress [388], and one [386] was found to be the same study as one of the published trials [384]. Thus, 14 trials were added to the current evidence base for a total of 32 RCTs on some aspect of continence treatment after radical prostatectomy and four on treatment after TURP. **Table 20** provides summary information on the trials.

I. LIFESTYLE INTERVENTIONS

Lifestyle recommendations such as smoking cessation, healthy eating, appropriate body weight, avoiding excessive caffeine or alcohol are all part of a primary care approach and are intended to be preventative in the onset of obesity, cardiovascular disease, diabetes. Whether these factors have a direct impact on continence is suggested but not known. To date, no trials have addressed the topic of lifestyle interventions alone for men with UI. Nevertheless, in practice, it seems reasonable to offer advice on healthy lifestyle choices that may reduce or delay the onset of continence problems.

II. PELVIC FLOOR MUSCLE TRAINING (PFMT)

The quality of trials included in this update of PFMT has improved from earlier ICI reports although heterogeneity and varying outcome measures continue affect the ability to compare trial findings.

1. PREOPERATIVE RP PFMT

Trials in this section compared preoperative interventions. Two new studies were identified as focusing on preoperative PFMT [385,389].

Delmastro [2010] report a trial in which men undergoing radical prostatectomy were randomised preoperatively to PFMT plus proprioceptive training (n=60) vs PFMT alone (n=57). The authors present a novel arguement that proprioceptive training of the agonist and antagonist muscle activity preoperatively may affect acute adaptive responsiveness, enhancing the effectiveness of PFMT in men undergoing radical prostatectomy. Outcomes were measured at baseline (preop) and 4,8, and 24 weeks post surgery; Although the authors report significant differences in outcomes favouring the intervention group (PFMT plus proprioceptive training) the report of the study was available in abstract form only, and details of the randomization technique and data were not available. This study represents an innovative theoretical perspective, but further investigation and testing is needed to establish efficacy of the treatment approach.

Tobia [2008] (article translated from Spanish) randomised 38 men to to preoperative kinesic perineal exercises (n=19) or no preoperative treatment (n=19). Using DRE and perinemeter plus 'low to medium frequency EStim', participants undertook 'kinestetic exercises', practiced daily at home 7-10 times. No futher details of the intervention were provided such as the number of times the participants visisted the therapist, how participants were randomised, assessors blinded. Nor was continence defined. The authors reported no difference between groups in continence at 14, 30 or 60 days post catheter removal.

2. PREOPERATIVE AND/OR POSTOPERATIVE RP PFMT, POST RP CONTINENCE STATUS NOT ESTABLISHED PRIOR TO INTERVENTION

Trials in this section addressed the effect of PFMT initiated preoperatively and/or postoperatively but before post op continence/incontinence was established. In these studies, men were recruited preoperatively or immediately postoperatively and the investigators compared a treatment group that received the intervention preoperatively and/or postoperatively RP to a group receiving an intervention only post operatively. Post operative interventions were often described as usual care. Nine trials from the previous review [210,362,369,370,372,375,392-394] and one new study [382] are included for a total of 10 trials in this category. One study in abstract form [388] was not included as it described a study in progress with no findings presented.

a) Preoperative PFMT instruction with postoperative home PFMT versus control

No new trials were added to this section. Three were all addressed in the ICI 2009 chapter [1,362,392,393]. Two utilised preoperative BF assisted instruction in PFMT followed by postoperative self-PFMT at home, compared to postoperative verbal instruction [362] or usual postoperative exercise advice [392]. The other study (abstract only), assigned participants to PFMT plus BF (method/type not described) or PFMT alone plus home exercises. Primary outcomes were pads or bladder diary.

1. Quality of data

Of the three trials in this subsection, only one [392] reported adequate random allocation concealment. With regard to blinding of outcome assessment, Bales [2000] attempted to control for bias in outcome

Table 20: Characteristics of male urinary incontinence studies

Primary Author	Timing of interven-tion	Open/lap/robotic	Design	Intervention	Randomization	Blinding	Findings	Definition of Incontinence
Centemero, 2010 [382]	Pre Op Post Op	RRP open	Pre Op/post PFME vs Post Op only; Enrolled > 4 weeks Pre Op. RP.	N=118 T: (n=59 no dropouts) Pre/post BF PFMT 2x/wk 30 min intensive PFMT with PT + 30 min at home; 48 hr post catheter removal 2x/wk x 4 wks + home PFMT until dry; Focussed on "tonic fibres of the superficial perineal musculature". C Group: (n=59 no dropouts) Post Op PFMT (method not described)	block randomisation in blocks of 10 in sequentially numbered sealed envelopes; power analysis SS 118.	surgeons blinded.	At 1 & 3 months T group more likely to be continent (44%, 59% vs 20%, 37%); on pad test: 25%, 17% vs 34%, 32% > 150 gm. Nb no other pad test data provided. Conclude that Pre Op PFMT self reported continence higher in treatment group.	Self report Continence = 0 leakage on bladder diary & negative stress test; ICS male SF; PGI-I .
Delmastro, 2010 [385] (abstract only SIUD)	Pre Op		Intensive Pre Op PFMT + proprioceptive training vs two groups Pre OP PFMT vs N=112. Enrolled Pre Op or actively (time Pre Op not given).	T group (n=60; 10 dropouts); 10 hr individual PFMT sessions + 3 1 hr group sessions + home training; control (n=57; 13 dropouts) PFMT and "no proprioceptive training" (but this is not described); Post Op both groups received verbal info.	not described	PT blinded.	At baseline (Pre Op) & 4,8,24 wks post surgery; reports significant difference favouring treatment but no data provided.	Continence: 1 or less pads per day; pF strength, endurance & function; Post Op patient global impression of improvement (PGI-I).
Dubbelman, 2010 [379]	Post Op	RRP open	Post Op RP two groups 1 day Pre OP all men received verbal instruction from a PT plus written materials 1 wk after catheter removal; PFME with PT + home exercises/written materials vs written materials alone. Enrolled men with > 1 gram urine loss on 1 hour pad test 1 week after catheter removal.	N=79 T group (n=44;33 complete) C group (n=35; 33 complete)	1:1 randomisation 1 wk post catheter removal; sealed envelope open by trial nurse after pad test result.	trial nurse not involved in intervention; PT unaware of outcome data of either group; power analysis done - needed 96 per arm.	At 1,4,8,12,26 wks; at 26 wks on 1 and 24 hr pad test 30% vs 27% were continent; no significant difference in time to continence; amt of urine lost at baseline a significant predictor of continence at 6/12.	Continence < 4 gm on 24 hr pad test; < 1 gm on 1 hr pad test; 1 hr pad test dry (<1g), mild (< 10 g), moderate (10-50 g), severe (>50 g).

Table 20: Characteristics of male urinary incontinence studies (continued)

Primary Author	Timing of interven-tion	Open/lap/robotic	Design	Intervention	Randomization	Blinding	Findings	Definition of Incontinence
Glazener, 2011 [377]	Post Op	TURP	Post Op: TURP two groups 6 weeks post surgery: PFMT vs written material. Enrolled men reporting incontinence on screening questions 6 weeks postop.	N=442 T group (n=220; 194 complete); C group (n=222; 203 complete)	Remote computed randomization independent of clinical collaborators.	Intervention could not be masked from participants and therapists. Clerk entering data blind to allocation.	At 12 months T group 65% incontinent vs 62% C group (RR1.06; CI 0.91 - 1.23).	Any positive response to either of 2 screening questions from the ICIQ-UI SF questionnaire.
Glazener, 2011 [376]	Post Op	Open & lap RP	Post Op: RP two group 6 wks post surgery; Post Op PFMT +/-BF or written material. Enrolled men reporting incontinence on screening questions 6 weeks Post Op.	N=411 T group (n=205; 196 complete) = PT sessions over 3 month period + home exercises; C group (n=206; 195 complete)	Remote computed randomization independent of clinical collaborators.	Intervention could not be masked from participants and therapists. Clerk entering data blind to allocation.	At 12 months T group 76% incontinent vs 77% C group (RR0.97; CI 0.87 - 1.09).	Any positive response to either of 2 screening questions from the ICIQ-UI SF questionnaire.
Goode, 2011 [380]	Post Op	RP open	Post Op (1-17 yrs post surgery) Three groups: PFMT + behavioural therapy (BT); BT + ES + BF; no intervention.	N=208 --T group 1 (n=70; 47 completed) 4 sessions PFMT + BT x 8 wks plus home management; T group 2 (n=70; 40 completed) BT + ES + BF office + home; C group (n=68; 64 completed): no intervention (on wait list)	3 sites; stratified by site; computer generated list; group assignment in sealed envelope opened at randomisation.	Staff scoring of bladder diaries were blinded.	At 2, 6, 12 months 8 wks UI recorded on 7 day bladder diary; both T groups improved: incontinence episodes per wk at baseline and 8 wks: 28, 26, 24 vs 13, 12, 21;also improved % UI episodes no difference between treatment groups; no benefit of adding ES to PFMT. Full data provided for 2 months only, not 6 and 12 months. QOL results modest changes.	Continence: % reduction of UI on 7 day bladder diary; IIQ-7; SF-36; AUA Symptom score
Marchiori, 2010 [387]	Post Op	RP open or lap	one month post catheter removal intensive PFMT with BF + ES vs oral & written info + home exercises.	N=332 Both groups received written and DRE teaching of PFMT on day of catheter removal. Control group continued with home exercises; T group did home exercises plus received daily BF + ES x 15 mins at the hospital clinic x 2-3 wks.	not described	not described	FUp at 1 yr; self report of UI at 3, 6, 12 mon; median continence achievement 44+/-2 days vs 76 +/-4 days in favour of intensive treatment; all subjects were 'dry' by 12/12..	Continence = < 2 mini pads per day; ICI-Q; RAND 36 (only 10% of subjects completed Questionnaires).

Table 20: Characteristics of male urinary incontinence studies (continued)

Primary Author	Timing of interven-tion	Open/lap/robotic	Design	Intervention	Randomization	Blinding	Findings	Definition of Incontinence
Mariotti, 2009 [384]	Post Op	RP Open	Post Op RP PFMT + ES + BF vs verbal & written info from Urologist. Enrolled 7 days post catheter removal.	N=60 (all completed) T Group (n=30) PFME + ES + BF 2x/wk x 6/52; BF x 15 mins then ES x 20 mins (anal) @ 30 Hz x 10 min; 50 Hz x 10 min; µs 300 pulse duration; max current 24 MA; BF 1 channel perineal; 1 channel abd. C group (n=30): verbal and written info from urologist.	not described	not described	Mean time to continence: 8 +/-6.49 wks vs 13.88 +/-8.32 wks in favour of treatment; at 6/12 3.3% vs 33% had UI in favour of treatment. By 12/12 no difference.	Continence 24 hr pad test < 2 gm; no. of pads; ICS-male Q; voiding diary. Eval at baseline, 2, 4 wks; 2.3.4.5.6 months post enrolment.
Park, 2011 [390] (abstract only)	Post Op	RP tech-nique not stated	Active overall exercise vs PFMT alone N=49 Enrolled Pre OP, interventions postop.	T group: (n=24) with ball, elastic bands + PFMT; C group: (n=23) PFMT alone (method not described)	not described	not described	improvement in exercise group overall function, pad test and ICI-Q (no data provided)	Pad test; ICI-Q; Beck depression inventory; SF 36.
Sciarra, 2009 [386] (abstract only) Same paper as Mariotti.	Post Op		Post RP FES + BF vs written and verbal information	N=60 T group: FES + BF 7 days post catheter removal 2x/wk x 6 wks; C group: written & verbal info	not described	not described	Mean time to continence	Continence = 0 pads; Eval at 2,4 wks and 2,3,4,5,6 months; 24 hr pad test; ICS-UI questionnaire; bladder diary.
Tibaek, 2007 [381]	Pre Op Post op	TURP	Pre/post Op two group PFMT Pre Op + home exercises or post Op verbal instructions. Pre Op enrollment of men scheduled for TURP.	N=58 T group (n=26; 26 completed): Pre Op PFMT 1:1 x 1 hr; 3 hr group session; home exercises and verbal Post Op; C group (n=23; 23 completed) received verbal instructions post op.	not described	PT assessing;	At 2, 4, 12 wks post op; increased PF strength but no differences in Symptom scores, pad test or pd use. Incontinence per se not measured.	Danish Prostate Sx score; 3 day diary; pad test.
Tobia 2008 [389] (English abstract only; Spanish translated)	Pre Op	RP not described	Pre Op kinesthetic perineal exercises treatment vs no kinesthetic training. Pre Op enrollment of men scheduled for RP.	T group: N=19 kinesthetic training C: group (n=19) no training. Method not described.	not described	not described	At 14, 30 & 60 days post op no difference between groups.	% continent.

Table 20: Characteristics of male urinary incontinence studies (continued)

Primary Author	Timing of interven-tion	Open/lap/robotic	Design	Intervention	Randomization	Blinding	Findings	Definition of Incontinence
Voorham-vander Zalm, 2010 [388] (abstract only) Not included - study in progress.	Pre Op Post Op		Pre Op PFMT vs control (standard care not described). Pre Op enrollment of men scheduled laparoscopic RP.	T group: not described	not described	not described	Pre Op; 6 wks, 3, 6, 9, 12 mons post op; findings not presented - study in progress (author contacted for more information).	Pelvic Floor Inventories (PelFIs); pelvic floor exam; KHQ, IPSS, voiding diary; 24 hr pad test
Yamanishi, 2010 [378]	Post Op	RRP open	two group Post Op PFMT + ES or control (sham ES) enrolled 1 week post catheter removal. Only included subjects with UI > 200 gm on 24 hr pad test 1 week after catheter removal.	N=56; T group (n=26 22 completed): Estim 2x/day x 15 mins by anal electrode 50 Hz with 300 µs pulse duration; max output 70 mA (5 secs on/off) -- does not state if this was home based or clinic; C group: sham ES (n=30; 25 completed) .	By computer connected to stimulation device; power calculation 22/group.	Subjects and Physicians blinded.	At 1, 3, 6 mon significant difference favouring treatment: 36%, 63%, 81%, 86% vs 4%, 16%,44%, 86% were continent. No difference at 12 months Post Op.	PFMT
Zellner, 2011 [383] (in German, translation available)	Post Op	RRP open	Three groups Whole body vibration; PFMT with BF + ES; PFMT alone enrolled on day 22 post surgery	N=75 C group: n= 25 PFMT from physio with individual & group therapy (not described); T Group (1) n=25 Standard care plus ES + BF via recall probe 420-N=75 unit Myo daily x 20 mins (not stated if at home or in the clinic); T Group (2) n=25 whole body vibration: vibration plate with vertical sinusoidal oscillations, Hz 20 to stimulate all body muscles including pelvic floor.	not described	not described	No differences between Standard group & PF/ES group (both improved); not stated if all completed. Not clear when outcomes were assessed - appears to be at end of 3 wk intervention period. Subjects mildly incontinent based on pad test (not clear if 24 or 1 hr).	IPSS; pad test; uroflow and voided volume; PFM strength
Zhang, 2008 [391] (abstract only)	Post Op		Post Op combined PFMT and social support in group. Enrolled men incontinent post prostatectomy.	T group: (n=14) 6 biweekly group sessions + PFMT + BF; C Group (n=15): PFMT at home.	not described	not described	at 3 months post treatment less UI and fewer pads favouring Treatment (50% vs 84%); decreased urge (71% vs 38%); improved depression and Sx distress.	VAS 0-10; pad count.

assessment by having a nurse not directly involved in the study interview the subjects. It is not clear whether he/she was blinded to allocation group. Burgio [2006] had outcomes assessors blinded to group assignment and described dropouts.

2. Results

Burgio [2006] reported a statistically significant difference in favour of PFMT in time to regain continence and proportion of men with severe or continual leakage measured by voiding diary at six months, PFMT (59%) versus controls (78%); additional data provided by the authors on the 24 hour pad test did not indicate a difference between groups. Bales [2000] found no significant group difference on participant report of number of pads used or time to return to continence. Lilli [2006] did not find a difference between participants who received BF in addition to PFMT at any of the time points; at six months, 71% and 67% respectively dry and no use of pads. In the Lilli trial both groups received intervention and it is not clear how intensive the pre-operative PFMT instruction was.

D.2.2b Pre-operative PFMT instruction followed by supervised post-operative PFMT versus post-operative PFMT

One new trial was added to this subsection, making a total of four studies included [369,370,372,382]. Centemero (2010) randomised 118 men more than four weeks preoperatively, with the treatment group receiving twice weekly BF (anal probe) intensive PFMT with a physical therapist plus home exercise and repeated the twice weekly sessions for four weeks post operatively with home exercise until dry. The control group received only post operative PFMT. Outcomes were self report of leakage on bladder diary and provocative (stress) pad test. As reported in ICI 2009 [1], one trial compared active pre- and post-operative PFMT programme to no PFMT instruction [372] and two others pre- and post-operative instruction versus post-operative instruction [369,370]. Participants in one trial [372] had two pre-operative and four post-operative sessions of anal probe BF plus post-operative home PFMT using an exercise ball, or no intervention (similar to Burgio (2006) above). Continence was assessed by pads report and continence questionnaires at six, 12, 16, 20, 28 and 52 weeks post surgery. Sueppel (2001) randomised 16 men (no dropouts) to two pre-operative and five post-operative sessions of anal probe BF or five post-operative sessions plus home PFMT. Continence and quality of life were assessed by AUA symptom score and quality of life questionnaire, pad count, 45 minute standardised pad test, and a leakage questionnaire at six weeks and one year post surgery In another [369] all participants had one session of pre-operative instruction using BF and verbal coaching and were then randomised to intervention or control groups. The intervention group (n=26) practised PFMT daily with a home BF unit (anal probe) from week 3 to 12 after surgery, whereas the control group (n=24) only followed written instructions. Both groups completed questionnaires, pad counts, and 24 hour pad tests at two, five and 12 weeks post-operatively.

Quality of data

Centemero [2010] had surgeons blinded to group allocation and reported no dropouts. Sueppel [2001] indicated incomplete data but did not describe dropouts. Two did not provide any information [372].

Results

Treatment group was more likely to be continent at one and three months post operatively measured by leakage recorded on a bladder diary (44%, 59% vs 20%, 37%) and on pad test (25%, 17% vs 34%, 32% > 150 gm) [382]. More men were continent in the pre and post treatment group at 12 weeks but there was no statistically significant difference at any other time point to 12 months [372] . Sueppel [2001] reported that at one year the pre and post treatment group had less leakage on a standardised 45 minute pad test compared to the postoperative group (mean 2.8g (range 0.0-13.0g) versus 33.3g (range 0 to 194g) and Mathewson-Chapman [1997] found no statistically significant differences between groups at any of the time points.

c) Post-operative PFMT immediately after catheter removal (no pre-operative instruction)

No new trials were found comparing post operative PFMT immediately post catheter removal. Three previously reported trials in ICI 2009 commenced post-operative PFMT immediately after catheter removal [210, 375, 394]. A total of 524 men were randomised to PFMT programme or no formal instruction Filocamo [2005], weekly 45 minute PFMT guided by a physiotherapist or one PFMT training session then home exercises [210] or PFMT with verbal and written instructions intensive postoperative physiotherapy for three days, a post-discharge rehabilitation programme for three weeks, and a three month home PFMT programme with twice daily with EStim or PFMT with EStim and BF [375]. Outcomes in the studies varied from ICS Male Questionnaire (ICS MaleQ), pad count, and pad test (one and 24 hours), self-report of no pads, and PFM strength.

1. Quality of data

In one study, surgeons were blinded to group allocation [210]. Another had data analysed by a professional statistician [375]. Dropouts were described by two [210] and number of dropouts was provided by one [375] but reasons were not described. ITT analysis was decribed by two [394].

2. Results

One trial [394] favoured treatment at three and 6 months for self-reported ‘completely dry’. Differences between treatment and control were 96% versus 65%

at six months and at one year 99% and 88% (not significant). There were no significant differences between groups on 24 hour pad test (Filocamo, personal communication). Overgård (2008) reported no difference between groups for proportion dry (no pads) or 24 hour pad test at three months; however, at 12 months, the proportion of continent men was statistically significantly greater in the treatment group (33/36; 96%) versus the control (28/39; 72%). PFM strength and 24 hour pad test results did not differ between groups at any of the time points. Of note is that 20 participants in the treatment group did not receive face to face instruction due to distance from facility but rather followed detailed instructions provided on a DVD. Wille (2003) found more men in the PFMT/EStim group reported recovery compared to PFMT alone, but the difference was not statistically significantly different (OR 0.48, 95% CI 0.21 to 1.09).

3. Summary

A total of 10 trials were found applying a variety of pre- or post-operative PFMT based interventions (or a combination of both). Any differences between experimental and control groups were modest and short term; differences did not appear to be sustained up to 12 months post surgery. A particular challenge in evaluating the trials was that participant reported outcomes in three of the studies [210, 392, 394] all indicate some level of improvement in the treatment groups; however, there were no clear differences in pad test results in any of the trials. Because all the studies reviewed were generally small, varied in design, and had different outcome measures, it is difficult to interpret them as a whole. Whilst the evidence that therapist delivered PFMT with or without BF before or after surgery improves continence recovery after radical prostatectomy remains inconsistent, there is some suggestion that men who undergo some sort of conservative management including PFMT will achieve continence in a shorter time frame than non-treated men but that this difference is not significant at 12 months post surgery **(Level of Evidence: 2)**.

Further discussion is needed on the outcomes of most importance. It is possible that the emphasis on quantitative outcomes is not meaningful to participants; men appear to find therapy personally helpful and value the direction provided by a therapist.

4. Recommendations

Some preoperative or immediate post-operative instruction in PFMT for men undergoing radical prostatectomy may be helpful **(Grade of Recommendation: B)**; whether this is in the form of 'hands on' therapy of verbal instruction and support remains unclear. Studies comparing the effectiveness of pre- versus post-operative PFMT, and the number of sessions required, are needed so that practitioners may advise men about pre-operative preparation and budget conscious health boards can make informed decisions on programme funding. In designing such studies, the natural history of UI after radical prostatectomy must be taken into account because the spontaneous recovery rate means that sample sizes must be large to detect any differences between protocols.

3. POSTOPERATIVE RP PFMT FOR INCONTINENT MEN

a) PFMT with digital rectal feedback (DRE) after radical prostatectomy

Two additional trials were identified for this update [376,379] resulting in a total of five trials as Dubbelman [2004] is considered a duplicate [367, 368, 376, 379, 395, 396] in which PFMT was taught using digital rectal feedback (DRE) in at least one arm.

In the largest RCT to date, 411 men who had undergone open or laproscopic RP and who reported incontinence 6 weeks after surgery were randomised to lifestyle information leaflet or leaflet plus 4 sessions of PFMT with a continence physiotherapist or nurse and home exercises (2,376]. PFMT regime was three maximum strength contractions with 10 second break between each lying, sitting and standing twice daily plus submaximal contractions when walking. DRE was used to assess strength of contraction during training sessions. Dubbelman [2010] randomised 79 men who were incontinent one week after catheter removal to physiotherapist guided PFMT using DRE to to written material only. Treatment group received nine 30 minute sessions plus daily home exercises and written material provided one day prior to surgery; the control group received only the written material. This trial appears to be the same as the 2004 report by the authors which was a poster at the ICS [395].

Joseph [2000] randomised a mixed group of 10 men (four radical retropubic prostatectomy and six radical perineal prostatectomy) to weekly verbal teaching plus DRE or BF assisted PFMT over a four week period. Manassero [2007] randomised 107 (94 completed) men to urologist taught PFMT using DRE (unclear how often) plus daily home exercises for up to a year; the control group did not receive any instruction. Participants were assessed at one, three, six and 12 months with a home pad test, VAS and DRE. In Moore [1999] 63 men (58 completed) were randomised to one of three groups: control (written materials only and no therapist contact), PFMT using DRE, or PFMT augmented with EStim via anal probe. Both treatment groups met with the therapist twice a week for up to 12 weeks.

1. Quality of data

Three trials [368, 376, 379] reported adequate random allocation concealment. Data were collected by blinded assessors in two [379,396]. In another, data were collected and outcomes as-

sessed by the primary investigator who had a direct involvement in the trial, although treatment was provided by a therapist blinded to the control group outcomes [368]. Three trials described reasons for dropout [368, 376, 396] but only Glazener [2011] indicated how withdrawals/dropouts were dealt with in the analysis and provided intention to treat analysis. Dubbelman [2010] conducted a power analysis for sample size, but fell short of recruiting the target number.

There was considerable variation in the type and intensity of interventions, follow-up ranged from six and a half months to 12 months, and primary outcomes varied from pad test, pad count or subject report.

2. Results

Between them, the five trials,considering Dubbelman [2004] as a duplicate, had over 600 participants with complete data. Four of the five studies did not find statistically significant differences between the groups. Outcomes included one and 24 hour pad tests, voiding diary or quality of life (IIQ-7). No differences were reported between groups at 1, 4, 8, 12 and 26 weeks on one and 24 hour pad test as well as no difference in time to continence [379]; between treatment and control groups in participant reports of any incontinence or severe incontinence at 12 months [376]; or in pad test between PFMT and PFMT with EStim groups [368]. In a small study of 10 participants no differences between treatment and control groups were found [367].

One research group reported a difference between groups [396]. There was a statistically significant difference in proportion of continent subjects (<2g on 24 hour pad test) in the PFMT group at three, six and 12 months (54%, 33%, 17% compared to 78%, 60%, and 53% for the controls), with 9/54 versus 21/40 incontinent at 12 months.

3. Summary

The most recent and largest trials [376, 379, 396], which compared PFMT taught by DRE or no instruction used different approaches to defining and measuring continence and showed conflicting results. Whereas Mannasero [2007] reported a statistically significant difference in the proportion of continent men (based on 24 hour pad test) in the treatment group at three, six and 12 months the other two found no differences in continence status between groups based on participant report using standardized questionnaires or 24 hour pad test respectively [376, 379]. In the three other smaller and earlier trials, in which the control groups had written or verbal instruction on PFMT, there were no statistically significant differences between groups on pad test. **(Level of Evidence: 2).** Clinical heterogeneity meant that it was difficult to consider the findings from the studies as a whole.

4. Recommendations

Some instruction in PFMT may be helpful; it remains unclear on the objective benefit of the PFMT. Whether PFMT taught by DRE offers any benefit over and above verbal or written instruction **(Grade of Recommendation: B)** is not clear. Further well designed studies using standardized outcome measures and participant input are needed to test this hypothesis.

b) PFMT with BF after radical prostatectomy

No new trials were found under this category although reference Riberio [2008] [397] was a conference abstract and is replaced by Ribeiro [2010] [398]. Thus to date, there are six trials evaluating PFMT with BF compared to a non active or alternate treatment commencing after radical prostatectomy [365, 366, 371, 374, 397-399].

Three compared PFMT with BF versus no treatment, placebo treatment, or usual care [366,374,398] and three compared PFMT with BF versus verbal instruction and home PFMT [365,371,399]. Continence was measured variously by 1 hour, 24, and 48 hour pad test.

1. Quality of data

Two trials appeared to have adequate random allocation and concealment [374,398], although in the latter treatment was provided by the primary investigator who was aware of group assignment. In another [399], therapists were blinded to the results of the control group; pads were weighed by a person unaware of group assignment; data was entered by a data manager. Van Kampen (2000) had pad weights done directly by the individual at home. Dropouts were accounted for and described fully in two [374,399], partially in one [371]. There was a high dropout rate in Franke (2000) and these data were not accounted for in the analysis. There were no reported dropouts two others [365,398]. ITT analysis was described by three [365,374,399].

Continence evaluation was different for each study as well as timing of recruitment and intervention, content of intervention and control treatments. Outcomes varied widely: percentage of participants pad free [366]; one hour pad test [365]; 24 hour pad test (<2g=continent) [374,398]; <8g=continent [399]; and pad test not described [371]. Follow up ranged from 12 weeks to one year.

2. Results

Three trials compared PFMT and BF to a control condition [366,374,398]. At 12 weeks, Ribeiro [2010] reported statistically significant difference in 24 hour pad tests (51g, SD 119 versus 197g, SD 269, p=0.026), but there was no statistically significant difference at six months post surgery. In another study [374] at 8 weeks, there was a statistically significant difference in mean urine loss (30g treatment; 82g control). By 12 weeks this difference

was no longer statistically significant but the proportion of treatment group participants reporting continence compared to control (88% versus 56%) was statistically significant ; no differences were found beyond three months. One other trial reported no difference between groups on 24 hour pad test or pad-free rates but sample was small and dropout rate nearly 50% [366].

None of the three trials that utilised PFMT and BF versus verbal or written instruction on home PFMT showed statistically significant differences between the groups. Outcomes were measured using one hour pad test or number of pads [365], 24 hour pad test, International Prostate Symptom Score (IPSS), or subjective report of continence at eight, 12, 16, 18, or 52 weeks [399], and pad test at 12 weeks [371].

3. Summary

Health professional instruction in PFMT with BF when compared with control conditions seemed to reduce the amount of leakage in the early weeks of recovery (up to three months). However, comparisons of PFMT with clinic BF versus PFMT at home did not find similar differences. Based on the current evidence the addition of EStim or BF does not appear to improve continence outcomes over and above PFMT. **(Level of Evidence: 2).** However, BF may be less difficult for the therapist than DRE.

It seems men who participate in PFMT compared to no active treatment might have less leakage in the first three months postoperatively. To the individual, this early improvement may be important in activity, well-being, and socialising. Such concepts require further investigation.

4. Recommendations

The use of BF in clinic, over and above home PFMT, is currently a therapist/individual decision based on economics and preference. **(Grade of Recommendation: B)**.

c) PFMT plus or minus BF with EStim or MStim after radical prostatectomy

The most notable addition to the evidence base in this section is five new trials which combined EStim with PFMT for men incontinent post radical prostatectomy [378, 380, 383, 384, 387] with four of these including BF as part of the intervention. These five trials were added to two RCTs previously included in the EStim section [400]. Opsomer [1994] compared intensive PFMT plus EStim (once a week) plus BF versus simple PFMT in 43 men. As it was not possible to differentiate the effects of additive EStim (method not described) from adjunctive BF this study was not further considered for this section.

Two studies [400] previously reported and one new [378] reported comparisons of PFMT to PFMT plus EStim and recruited men with severe post prostatectomy UI one week after catheter removal (more than 200 gm of urine lost daily on pad test). In the Yamanishi trial, men were randomised into active EStim group (n=26) or sham EStim (n=30) by computerized random assessment through a connection to the stimulation device. All men had PFMT by nurses (verbal and written information) and were coached to continue this though the study period. Active EStim was 50 Hz with a 300 µsecond pulse duration, 5 seconds on/5 seconds off duty cycle and maximum output of 70 mA. Men receiving sham EStim received limited stimulation at 3 mA with a 2 seconds on/13 seconds off duty cycle. Treatment continued until the incontinence was cured or the 12 month study period ended.

Moore [1999] compared standard treatment (verbal and written instructions about PFMT) versus intensive PFMT, versus intensive PFMT plus rectal EStim in 63 men with UI median of 8 weeks (range 4-241) post radical prostatectomy. EStim was provided by a surface anal electrode, with intensity to induce visual lifting of the levator ani. Stimulation parameters were 50Hz, biphasic pulse shape with one second burst, a one second pulse width and one second pulse trains. All therapy was performed by one experienced physiotherapist. Hoffmann [2004] compared percutaneous EStim plus PFMT versus anal EStim plus PFMT versus PFMT alone in men with post-prostatectomy incontinence; this trial allocated 60 men per group, the intervention was for four weeks, and each individual was followed up for three months. PFMT consisted of a “specialized program” of “continence training”, lifestyle changes, osteopathy and “Feldenkrais Lehre” three times/week in the clinic and three times/day at home, with a daily maintenance home programme after finishing the therapy. In comparing PFMT with BF plus EStim, three trials [383,384,387] included men one to four weeks after catheter removal and one [380] enrolled men at least one year after surgery. Mariotti [2009] compared PFMT with BF plus EStim to a control group which received only verbal and written information from a urologist. Randomisation occurred one week after catheter removal, and severity of incontinence among participants at enrolment varied from 20-1500 gm of urine lost on 24 hour pad test. Men in the intervention group received 12 treatment sessions (twice weekly for 6 weeks) of PFMT with BF and EStim from a single clinician. EStim was delivered by anal surface electrode at 30 Hz for 10 minutes and 50 Hz for the following 10 minutes, 300 µsecond pulse duration and a maximum output of 24 mA. BF was via perineal and abdominal surface electrodes. The frequency details of home PFMT were not provided. Marchiori [2010] randomised 332 men one month after catheter removal to intensive PFMT with BF plus EStim or a control group that received only verbal and written instruction and home exercises. This study was available only as an abstract, and the intervention was not fully described.

Zellner [2011] [383] used a three group design in which men on Day 22 post surgery were randomised to PFMT, PFMT plus EStim and Biofeedback (Myo-420 unitR via rectal probe) or whole body vibration daily at 20 Hz on a vibration plate (Fitvibe MedicalR) plus exercises (not described). Each group was in contact with the therapist over a 3-4 week period and had home exercises prescribed (protocols not described). Outcomes were testosterone, blood sugar, IPSS, pad count, and pad test. This trial was translated from German for this review.

Goode [2011] recruited 208 men with post radical prostatectomy incontinence persisting at least one year after surgery (range 1-17 years) and conducted a three group comparison of behaviour therapy BT that included PFMT, bladder control techniques and fluid management, BT/PFMT plus EStim and control (delayed treatment) [380]. Four visits two weeks apart to teach PFMT were provided for instruction from physician investigators or nurse practitioners. Anal palpation was used during instruction. The second group (BT plus) received BT with added in office dual channel biofeedback with either perianal surface or anal probe and 15 minutes of daily home EStim via anal probe with setting at 20 Hz, pulse width 1 millesecond, duty cycle of 5 seconds on and 15 seconds off and current up to 100 mA (adjusted by participant). The control group received office visits only for 8 weeks to monitor bladder diaries, and were provided with a choice of treatment after 8 weeks.

In a three arm trial [401] electrical stimulation (EStim), magnetic stimulation (MStim) and verbal/written instruction in PFMT were compared in 36 men with post RP incontinence. Home EStim comprised 15 minutes of twice daily stimulation for one month, at maximum tolerable level of intensity. For MStim, treatment sessions were 20 minutes, twice a week for two months, with stimulating intensity gradually increased up to the tolerable level. PFMT consisted of PFM exercises in supine position with instructions how to contract the anal muscles selectively. Verbal and written instructions for home practice were given to the men. Participants were followed up for six months.

1. Quality of data

Blinding, dropouts and continence evaluation

Three studies had adequate concealment of randomisation [368,378,380]; one included a power calculation, and adherence to protocol was monitored using patient-recorded diaries. Five participants dropped out, three in PFMT/EStim and two in the PFMT group. In one participant dropout was related to the use of EStim (rectal pain) [368]. Goode (2011) included a power calculation and stratified participants by site, incontinence type and severity. Randomization was conducted via a computer generated random assignment schedule. Sealed envelopes with group assignments were opened sequentially at the time of randomization. There were 23/70 dropouts in the BT group, 30/70 dropout in the BT plus EStim plus BF group and 4/68 in the group that received no intervention. Dropouts were explained and analysis was by intention to treat. Interventions were not concealed as physician investigators were involved in delivery of interventions. Yamanishi [2010] used a computer generated random assignment that connected to the EStim devices, thereby blinding participants, physicians and staff to assignment. Dropouts included 4/26 in the active EStim group and 5/30 in the sham EStim group.

Randomisation details were not provided in two trials [384,401]. In the Mariotti trial , intervention was directed by the lead author, therefore there was no blinding of the researcher to the intervention group. A power analysis was performed to determine sample size. All participants completed the study. Another [400] did not make clear if allocation was concealed or if observers were blinded. Dropouts were 22/60 in the anal EStim/PFMT group, 4/60 in the percutaneous EStim/PFMT group and 0/60 in the PFMT group. Marchiori [2010] data was available only in abstract form and details of randomization and blinding are not described. In theYokoyama trial, the number of treatments, duration and intensity seemed to be different between groups.

2. Results

In comparisons of PFMT +/- EStim, 9/60 men in the anal EStim/PFMT group reported recovery, versus 11/60 in the percutaneous EStim/PFMT group; data were not reported for the PFMT only group [400]. For comparisons of PFMT to PFMT plus EStim and BF, Goode [2011] found that both treatment groups (BT/PFMTand BT/PFMT plus EStim and BF) reported a statistically significant reduction in incontinence episodes at 8 weeks compared to the control group as recorded on bladder diaries. Both treatment groups maintained improvement at six and twelve months, although there were no statistically significant differences between treatment groups. No comparison to the control group was made after 8 weeks.

Pad test results were not consistent. Using a 24 hour pad test [368] one reported a decrease of urine loss favouring PFMT over EStim/PFMT; another found that at three months 77% in EStim/PFMT group were continent versus 65% in the PFMT group, with 82% and 77% continent respectively after 12 months [375]. None of these differences at any of the time points were statistically significant. Yamamishi [2010] reported more men in the active EStim group were continent (less than 8 gm urine lost on 24 hour pad test) at 1, 3 and 6 months than those in the sham EStim group (4%, 16%, 44% versus 36%, 63%, 81% respectively), although there was no difference at 12 months (86% continent in both groups).

For comparisons of PFMT plus EStim and BF, men in the treatment group who received PFMT plus EStim

and BF had a shorter mean time to continence (urine loss less than 2 gm on 24 hour pad test) than those in the control group (8 weeks versus 13.88 weeks) [384]. At six months, 3.3% of the intervention group and 33.3% of the control group were still incontinent, at 12 months there was no difference between the groups. A shorter time to continence favouring intervention group receiving PFMT with EStim and BF (44 days intervention group vs 76 days control group), was reported with all participants continent (2 mini pads or less per day) at 12 months [384].

EStim was associated with adverse events. Discomfort [378,400], urethral stricture [378], or bladder neck contractures [368]. Whether the EStim caused the strictures or contractures is debatable.

Yokoyama (2004) reported that at one month, urine loss on 24 hour pad test was 72g, 83g and 175g (FES, ExMI, and control groups respectively (EStim versus PFMT, $p<0.05$), and was 54g, 18g and 92g respectively at two months (MStim versus PFMT $p<0.05$). At six months mean loss was less than 10g in all groups. No complications were noted in any of the groups. The authors concluded that both MStim and EStim offered earlier continence compared with PFMT after radical prostatectomy.

Zellner [2011] (translated from German) reported no difference between control and the PFMT/BF/EStim groups based on IPSS, pad test, and pad count but the whole body vibration group (FitVibe medicalTM) had a statistically significant decrease in pad test results from 41 g pre therapy to 11g post relative to the other two groups. Whole body vibration was not described in detail.

3. Summary

Seven RCTs investigated the addition of EStim to PFMT plus or minus BF for men with post-prostatectomy incontinence. Data suggested no further benefit of EStim when added to PFMT over PFMT alone, although EStim may help achieve continence earlier in men with severe incontinence post prostatectomy; the numbers in each trial were relatively small. **(Level of Evidence: 2)**

4. Recommendations

For men with post-prostatectomy incontinence there does not appear to be any benefit of adding EStim to a PFMT programme **(Grade of Recommendation: B).**

d) PFMT compared to other interventions after radical prostatectomy

Two new trials were identified that combined PFMT postoperatively with other novel interventions in men with post prostatectomy incontinence [390,391]. Park [2011] compared PFMT to an overall 12 week exercise program plus PFMT in 49 men over 65 years after RP, reporting that the exercise (treatment) group had an earlier return to continence on pad test and self report. Zhang [2008] randomised 29 men to PFMT + BF plus six biweekly meetings of a support group (n=14) or to a control group which had only the PFMT +BF. The treatment group reported less UI on VAS rating scale (3.2 vs 4.7), less pad use (50% vs 84.6%), and had better adherence to the PFMT regime. Both trials were available only in abstract form, and details on baseline incontinence, randomisation, blinding and data were not provided.

4. PREOPERATIVE TURP PFMT

Little study has been dedicated to UI after TURP. In fact, the issue has been largely ignored, perhaps because the incidence of UI after TURP is reported to be very low.

5. PREOPERATIVE AND/OR POSTOPERATIVE TURP PFMT

In previous consultations, two trials were potentially eligible for inclusion [367], but the latter trial was grouped with studies of PFMT after radical prostatectomy because the 11 participants comprised one following TURP and 10 following radical prostatectomy.

One new trial on TURP pre and post operatively was added [381].

Men undergoing TURP were randomised preoperatively to a treatment group (n=26) which involved preoperative PFMT of 1 hour individual and a 3 hour group session along with home exercises compared to control group (n=23) which received verbal information only post operatively. Outcome was symptoms as measured by the Danish Prostate Score. Three day bladder diaries and a pad test were also identified as measurements in the study but data from these were not included in the published report, therefore the effect on incontinence is not clear. An earlier trial included men booked for TURP [373]. At the baseline preoperative visit, PFM strength, tone and grading were established with a DRE. There were weekly follow up sessions for four weeks post TURP. It was unclear what information, if any, the control group received.

Quality of data

It was unclear if random allocation was concealed or outcome assessment blinded, and the proportion of dropouts was not stated.

Results

While there were statistically significant differences in UI and post micturition dribble as measured by voiding diary and IPSS, there was no statistically significant difference at four weeks.

Summary

In the absence of sufficient data from rigorous and well-reported trials it is not known if PFMT reduces

UI following TURP. More systematic investigation of the the natural history of UI after TURP is probably needed, to establish the potential cost/benefit of intervention, before further trials are initiated.

6. POSTOPERATIVE TURP PFMT FOR INCONTINENT MEN

Only one study was identified which included men incontinent after TURP. Glazener [376] randomised 442 men post TURP who reported incontinence 6 weeks after surgery. All men received a lifestyle information leaflet; those assigned to the invention group had four 1:1 sessions with specialist continence physiotherapist or nurse. PFMT regime was three maximum strength contractions with 10 second break between each practiced lying, sitting, and standing twice daily plus submaximal contractions when walking plus home exercises. DRE was used to assess strength of contraction during training sessions.

7. PFMT FOR OTHER LUTS

Post micturition dribble (PMD) is an annoying problem experienced by many men of all ages likely due to a failure of the bulbocavernosus muscle to evacuate the bulbar portion of the urethra, causing pooling of urine in the bulbar urethra which then dribbles with movement.

The 4rd ICI identified two RCTs on conservative management of PMD [364,402] and no further trials were found for the past two updates. No trials were found on prevention of PMD and it is unlikely that such studies would be undertaken because of the longitudinal nature of such an exploration.

a) PFMT for post micturition dribble (PMD)

Two RCTs totalling 85 participants who had not undergone prostatectomy have been reported in which PFMT and/or urethral milking were compared to verbal instruction and lifestyle changes [364,402]. In one men were assigned: daily PFMT, urethral milking, or lifestyle changes using four hour pad test at five, nine, and 13 weeks. In another study on erectile dysfunction [403], over 65% of participants also complained of PMD and were randomised to PFMT using BF (5 weekly treatments plus home exercises) or lifestyle advice. Outcome was patient report using a standardised questionnaire administered by an interviewer unaware of group assignment.

1. Quality of data

It was not clear if allocation was adequately concealed in either study. In both studies data collection was done by the researchers but data analysis was done by a separate party.

2. Results

Paterson [1997] found both PFMT and urethral milking were equally effective and better than lifestyle changes. Dorey [2004] found that the PFMT group not only reported a significant improvement in erectile function measured by International Index of Erectile Function ($p=0.001$) but also a significant improvement in PMD measured by standardised questionnaire (67% improved in treatment group compared to 7% of controls; $p<0.002$).

3. Summary

Based on two small studies, it seems that PFMT and urethral milking might both be effective in the control of the annoying symptom of PMD **(Level of Evidence: 2).**

4. Recommendations

Men can be offered instruction to do a strong PFM contraction immediately after voiding, or urethral massage to empty the urethra, to improve symptoms of PMD **(Grade of Recommendation: C)**.

8. FACTORS AFFECTING OUTCOME

Based on the current evidence, it appears that time from surgery to implementation of exercises does affect outcome and that by three months after surgery less improvement is noted. Future trials could consider analysis to evaluate the effect of length of time from prostatectomy surgery, co-morbid conditions, prior pelvic surgery, and medications (including smoking and alcohol use) on treatment outcome.

III. ELECTRICAL STIMULATION (ESTIM)

EStim (EStim) is reported to be effective in the treatment of UUI but no better than PFMT alone for men with SUI [242,404,405].

Symptoms of DO and UUI can be associated with neurogenic disorders and to bladder outlet obstruction such as benign prostatic hyperplasia; in some men the cause is unknown. It is believed that EStim for UUI acts through reflex inhibition of pelvic efferents or activation of hypogastric efferents through stimulation of the afferent input in the sacral route [223,405].

SUI is rare unless iatrogenic with radical prostatectomy, pelvic surgery or radiation, or TURP [368,406-408]. DO, poor compliance and decreased contractility may also be factors related to post-prostatectomy incontinence [368, 409]. For male SUI, EStim could be used to enhance sensory response to contraction of the PFMs in the same way as female SUI [410,411]. As a stand alone therapy it is unclear whether EStim enhances continence recovery [375,412]. It has been postulated that continence is regained more rapidly [413] and the duration of the application of EStim is reduced when PFMT is augmented with EStim [413,414]. EStim is also believed to be more effective in participants who are initially unable to identify and contract the correct PFMs [415]. Interestingly, it is generally agreed amongst those using

EStim that it should be avoided for those with carcinoma of the bladder for fear that EStim may increase abnormal cell activity [403]. Although there are no data to confirm or refute this, many physiotherapists are unwilling to use EStim for individuals with cancer and, therefore, post radical prostatectomy. Further research is needed to clarify this risk.

This section will examine evidence for the use of EStim for the prevention and treatment of UI in men. Questions addressed are:

- What is the most appropriate EStim protocol?
- Can EStim prevent UI?
- Is EStim better than no treatment, placebo or control treatments for UI?
- Is EStim better than other treatments?
- Does the addition of EStim to other treatments add any benefit?
- What is the effect of EStim on LUTS other than UI?
- What factors might affect the outcome of EStim?

A literature search for reports of relevant systematic reviews and reports of RCTs and quasi-RCTs was performed (see Appendix 2). No other types of study design were considered. Since the 3rd ICI only one new RCT [400] was identified and included in this chapter. A previous relevant Cochrane systematic [412] was updated and contributed to this section [416].

1. PREVENTION OF UI

There have been no studies on the effect of EStim for prevention of non postprostatectomy UUI or SUI in men.

2. TREATMENT OF UI

In the 4th ICI, one systematic review was identified [412], along with nine RCTs [221-223,368,371,375,400,401,404]. An abstract of a trial [417] reported data for men, but the separate effects of EStim could not be assessed and the study was excluded.

a) Is EStim better than no treatment, placebo or control treatments?

No new studies were identified that compared EStim with no treatment or a control. Two earlier placebo controlled trials both included men and women. One included 29 men and 39 women with UUI [222,404]and the other 30 women and five men with SUI [404]. In the latter trial, four men had post-prostatectomy incontinence and one had sphincter deficiency due to sacral cord tumour.

1. Quality of data

Both trials blinded participants and doctors to treatment allocation [222,404]. For EStim in UUI, three participants (8%) in the active group and one (3%) in the sham group dropped out, and two in each group discontinued the treatment due to adverse events (5.4% and 6.5% respectively). For EStim in SUI, two of 35 participants (6%) dropped out and none had adverse events.

2. Results

(a) Men with UUI: The authors reported statistically significant differences in cure (22% active and 4% sham) and improvement rates (81% active and 35% sham) between the groups; data were not differentiated for men and women [222].

(b) Men with SUI: None of the participants in the sham group were cured or improved. One man in the active EStim group was cured and a second was improved; five men participated in the study but it was not clear how many were allocated to sham and how many to active EStim.

3. Summary

In the absence of sufficient data from rigorous and well-reported trials it is not known if EStim, as a stand alone treatment for male UUI or SUI, is better than no treatment, placebo or control treatments.

b) Is one approach to EStim better than another?

EStim protocols for men are similar to those for women and like protocols in women vary widely. Intermittent, short-term stimulation (or maximal EStim) using a portable stimulation device at home or in clinic is most common [368,375,401]. Rectal or surface electrodes are most common; surface electrodes are positioned over the perineal region.

For the treatment of SUI (and post-prostatectomy incontinence) EStim amy be combined with PFMT or monotherapy. Usually a rectal electrode is used, and the stimulation artificially stimulates the pudendal nerve and its branches to cause direct reflex responses of the urethral and periurethral striated muscles [368,400,401].

Frequencies of 14Hz have been used for UUI [400], while 20Hz [401], 27Hz [375] and 50Hz [368] have been used for SUI. Pulse form is mostly biphasic; pulse width varies and includes 300 microseconds [401], 250 milliseconds [400][401], one [368] and five seconds [375]. Duration of the stimulation varies as well, from 15 minutes [375] to 30 minutes [368], and from twice daily [375] to twice weekly [368]. Duration of treatment has ranged from one month [401], to three months [375].

1. Summary

So far, no studies comparing EStim protocols have been identified. The most appropriate EStim protocol for different types of symptoms is unknown. EStim protocols for men have been developed from studies in women. The variability in the findings of

the trials included in the remainder of this section may in part be due to differences in the effectiveness of the wide range of protocols that have been tested. There are many differences in clinical application that have not yet been investigated. Some populations or subgroups of men may benefit from EStim more than others, but this observation has not yet been investigated.

c) Is EStim better than other treatments?

No new trials were found comparing EStim with other treatments making a total of two comparing EStim with MStim [223] or medication [221] in men and women with UUI. One evaluated EStim with MStim for inhibition of DO in a urodynamic study of 32 participants (15 males, 17 females) [223]. The other compared EStim (TENS) with medication (oxybutynin) for UUI in 43 participants (13 men, 30 women) with DO [221]. Results were not reported by gender. Oxybutynin was started at a dose of 2.5mg orally twice daily and titrated to 5mg orally three times daily by day seven. Dual channel TENS with two self-adhesive pads connected to the stimulator and applied bilaterally over the perianal region (S2 to S3 dermatome) was used. Stimulation parameters were set at a frequency of 20Hz and a pulse width of 0.2msecs on a continuous mode. TENS duration was up to six hours daily.

1. Quality of data

Random allocation concealment was adequate; results were not reported by gender [222]; another did not provide information about randomisation procedure, random allocation concealment, blinding of observers, or drop-outs [221].

2. Results

In the urodynamic study of EStim versus MStim in men with DO, bladder capacity at first desire to void and maximum cystometric capacity increased significantly in both groups compared to baseline; the increase in maximum cystometric capacity was statistically significantly greater in the MStim (106%, SD 130) than the EStim group (16%, SD 34).

EStim and medication improved subjective parameters but only oxybutynin showed statistically significant improvements in objective urodynamic parameters such as bladder volume at first desire to void and at first overactive detrusor contraction [221].

3. Summary

There were few men in either of the two trials comparing EStim and MStim, the single trial comparing EStim with verbal/written instruction in PFMT, or single crossover trial comparing EStim with oxybutynin. In the absence of sufficient data it is not known if EStim is better than MStim or written/verbal instruction in PFMT or oxybutynin for UI in men.

d) Does the addition of EStim to other treatments add benefit?

Four RCTs have been identified investigating the addition of EStim to other treatments for men with post-prostatectomy incontinence [368,371,375,400] and are discussed under the PFMT section on post-prostatectomy incontinence. No studies of EStim being added to other treatments for UUI and SUI were identified.

3. OTHER LUTS

No studies were identified which addressed this comparison in men.

4. FACTORS AFFECTING OUTCOME

a) Age

There are no comparisons of the effects of EStim for UI between younger and older men. While many EStim studies include participants over 50 years most studies don't include those over about 80 years [418]. In the studies of EStim for post-prostatectomy incontinence in this chapter the mean age of men is about 66 years. Although post-prostatectomy studies have included older men it may be unwise to extrapolate the effects of EStim in older men with SUI to older men with UUI, because in the former UI is usually as a result of sphincter incompetence whereas in the latter the symptoms are those of an OAB.

b) Other

Many other factors, such as types of electrodes, intensity, frequency and duration of stimulation, electrode positioning, the number of treatment sessions, diagnosis and underlying cause, participant selection, and treatment adherence are plausible factors affecting outcome. Little is known about the effect of any of these and there are no trials investigating these factors in males.

IV. MAGNETIC STIMULATION (MSTIM)

Background information about extra corporeal magnetic innervation, more commonly called magnetic stimulatio n (MStim), has been given in the section on MStim for women (see B5). MStim has also been used in men; it is unclear whether the mode of action and effects of MStim are similar in men and women. In men, MStim is used to treat UI after radical prostatectomy [401,419] and for the inhibition of DO [223].

The questions to be addressed are the same as those for women (see B5). Since the 4th ICI no further RCTs were found. Suzuki [2007] compared the effect of MStim versus sham MStim for UUI in 39 individuals (23 females and 16 males). The study was not included in the review below because both groups also received PFMT, and data were not reported separately for men and women [263].

1. PREVENTION OF UI

No trials investigating the primary or secondary prevention effects of MStim for men with UI were found.

2. TREATMENT OF UI

Three treatment RCTs were identified; two published articles [223,401] and one abstract of an ongoing study without data [419]. The first trial [223] included both men and women with UI; because the effects of MStim might be different between sexes (due to differences in the underlying aetiology of symptoms) this study has only contributed to the analysis where the researchers' differentiated the effects of treatment in men and women.

a) Is MStim better than no treatment, placebo or control treatment?

No studies were found addressing this question.

b) Is one approach to MStim better than another?

No studies were found addressing this question.

c) Is MStim better than other treatments?

Two studies were identified [223]. Both compared MStim with EStim; the latter also compared MStim and PFMT. Readers are referred to section D.3.2c for a description of these studies, findings, and summary.

3. OTHER LUTS

No studies were found.

4. FACTORS AFFECTING OUTCOME

None of the included trials addressed the effect of age, or any other factor, on outcome of MStim. The relationship between age (or any other factor, such as treatment parameters, treatment adherence, or diagnosis) and the outcome of MStim has yet to be determined.

V. SCHEDULED VOIDING REGIMENS

Scheduled voiding regimens include bladder training , timed voiding, habit training and prompted voiding. They are frequently combined to achieve maximum benefits. Although there is evidence to indicate that scheduled voiding regimens, especially bladder training and timed voiding, are commonly used in the treatment of men with UI and other LUTS, there has been substantially less research that addresses their use in men compared to the literature on their use in women.

1. PREVENTION OF UI

No trials investigating the preventive effects of scheduled voiding regimens for men with UI were found.

2. TREATMENT OF UI

Since the 4th ICI in 2009, there have been no new reports of bladder training that have included men. Of the five that have included men, most had only a small number of men in the sample [48,282,283,286,293]. Two observational studies, but no RCTs, were found regarding timed voiding. No studies were located that addressed habit training or prompted voiding in men.

a) Bladder training

A total of five RCTs involving 142 men met the criteria for inclusion in this review. All trials (previously described in section B6) had predominantly female participants; one RCT compared bladder training (BT) to BT plus caffeine reduction (seven men, 86 women) [48]; and three RCTs compared BT plus placebo drug versus anticholinergic drug therapy (six men, 28 women [293]; four men, 30 women [283]; two men, 58 women [282]. The largest RCT compared drug therapy alone (tolterodine) to drug therapy plus BT (123 men, 378 women) [286]. A sixth study was located that compared BT supplemented with drug therapy after three months, but it was excluded from review because the full length report was in Japanese and an English translation was not available [420].

As none of the trials reported outcome data separately for men, and with the proportion of male participants being so small (3%, [282]; 8%, [48]; 12%, [283]; 8%, [293]; 25%, [286], there is insufficient evidence available to comment on the effectiveness of BT in men.

b) Timed voiding

No new trials were found on timed voiding. There are two clinical series that investigated timed voiding in men only [272,421]. In the first, timed voiding was initiatied in incontinent men in a geriatric hospital [421] and in the other men with persistent post-prostatectomy incontinence [272]. Outcomes were measured by a two week voiding diary kept at baseline and during two weeks of timed voiding by patients diagnosed with SUI, UUI, and/or continual leakage.

1. Quality of data

Both studies used a clinical series design and patients in both subsequently received other treatment if they were not adequately improved. In the Sogbein study, nurses checked the patients' clothing for wetness at each two-hour voiding interval and recorded the results. Data in the Burgio study were based on bladder diaries completed by the patients. Reasons for drop-out [421]and non-adherence [272]were provided.

2. Results

In one study an 85% improvement rate in UI was reported [421]. In the second, the two hour timed voiding schedule was used with only 12 out of 20 men, because they were either already on a voiding schedule, unwilling to go on a voiding schedule, or were noncompliant [272]. In five men with SUI,

there was a 29% decrease of incontinent episodes; in three men with UUI, two improved and one dramatically regressed producing a 33% increase in incontinent episodes. In four patients with continual leakage, there was no reduction in percentage of wet intervals.

3. Summary

With limited **Level 3** evidence (and no higher order evidence), there is insufficient evidence available to comment on the effectiveness of TV in men.

3. OTHER LUTS

No studies were identified in men.

4. FACTORS AFFECTING OUTCOME

a) Age

No new trials were found addressing outcome. The five RCTs involving bladder training included older men, as well as women. Three specifically recruited adults aged over 65 years [282, 283, 293]. The largest trial recruited men with a median age of 62 years. There was no subgroup analysis related to age and gender effects, so it is not possible to draw conclusions regarding the effect of BT in older men [286]. Voiding regimens are of particular interest for the elderly, but some are effective in younger patients with UI [266].

b) Other

No studies were identified on other factors affecting outcome of BT or prompted voiding in men.

Individuals who appear to benefit most from scheduled voiding regimens are highly motivated without cognitive deficits. Men and women with SUI and UUI have benefited, whereas patients with severe sphincter damage (e.g. after radical prostatectomy) generally do not [Hadley, 1986].

VI. COMPLEMENTARY AND ALTERNATIVE MEDICINES

Therapies include acupuncture, relaxation, meditation, imagery, hypnosis, naturopathic and herbal remedies, but only trials of acupuncture therapy have been found in men with UI. Therefore, only acupuncture will be considered in the remainder of this section.

Acupuncture is a traditional Chinese modality and has been used for the treatment of urinary disturbances. Acupuncture has been reported to relieve OAB symptoms including UI due to spinal cord injury [422], and idiopathic DO or MUI [423,424].

1. PREVENTION OF UI

No studies were identified on the preventative role of complementary therapies in men.

2. TREATMENT UI

Acupuncture may improve urodynamic parameters such as sphincter function [425,426] or bladder capacity in men with UUI (Honjo, 2000; Kitakoji, 1995). It is a form of somatic sensory stimulation [Bergstrom, 2000]. The mechanism by which acupuncture inhibits DO remains unclear, but suppression of the spinal and supraspinal reflexes that lead to detrusor contractions is considered one of the most important mechanisms [427,428] or release of endorphins [Bergstrom, 2000]. There has been no report on the effects of acupuncture for male SUI or post-prostatectomy incontinence.

a) What is the most effective acupuncture protocol?

Acupuncture has been carried out with disposable stainless steel needles (0.3mm in diameter, 60mm in length) inserted into the bilateral BL-33 points on the skin of the third posterior sacral foramina [422,423,429] or several other points (BL-31,32, 21, 23, SP-6, KI-3, LI-11,CV-1,2,4,5) [430], and usually performed once or twice weekly [422-424,429,431]. Acupuncture protocols vary and there is no apparent consensus between investigators. It is not known if any acupuncture protocol is more effective than another.

b) Acupuncture versus no treatment, sham acupuncture or any other treatment

No new studies were identifified. Only one RCT has been identified including both men and women [432], but there is no study exclusively for men. In a randomised, placebo-controlled, single-blind study among 20 elderly patients (three males, 17 females) Ellis (1990) showed that the frequency of voiding at night was reduced after acupuncture. Uncontrolled studies suggest improved symptoms post acupuncture [422,423].

The evidence of the effectiveness of acupuncture for men with UI is limited by the lacked of controlled studies. To date, the studies are small, objective measures of UI are not included and long-term follow-up is lacking. Uncontrolled studies suggest that RCTs of acupuncture in the treatment of UI in men are warranted.

3. OTHER LUTS

No new trials were found in this category. In the one trial in men with sensory urgency after TURP [431]a significant improvement was reported by acupuncture reflexotherapy (EStim of somatic and auricular points) in terms of IPSS, QOL scores, decrease of daytime frequency and nocturia, but no improvements with the use of placebo or oxybutynin.

4. FACTORS AFFECTING OUTCOME

Aside from Ellis [1990], reported above, who specifically recruited elderly participants there is a lack of

evidence about the effect of any prognostic factor for the outcome of complementary therapies in men.

VII. SUMMARY

Despite the prevalence of UI and LUTS in older men, the only group that has received much attention in research is men following radical prostatectomy. Overall, the effect of conservative treatment (lifestyle interventions, physical therapies, schedule voiding regimes, complementary therapies) for men has received much less research attention compared to women.

1. RECOMMENDATIONS FOR PRACTICE

There is generally insufficient Level 1 or 2 evidence on which to base recommendations for practice, and most recommendations are, in effect hypotheses, that need further testing in research.

Lifestyle interventions

- It seems reasonable for health professionals to offer men advice on healthy lifestyle choices that may reduce or delay the onset co-morbid conditions that are risk factors for incontinence **(Grade of Recommendation: D)** (Unchanged).

Pelvic floor muscle training (PFMT)

- Some preoperative or immediate post-operative instruction in PFMT for men undergoing radical prostatectomy may be helpful **(Grade of Recommendation: B)** (Unchanged).
- It is not clear whether PFMT taught by digital rectal examination (DRE) offers any benefit over and above verbal or written instruction in PFMT **(Grade of Recommendation: B)** (Unchanged).
- The use of BF to assist PFMT is currently a therapist/patient decision based on economics and preference **(Grade of Recommendation: B)** (Unchanged).
- Use of a strong pelvic floor muscle contraction immediately after voiding, or urethral massage to empty the urethra, can improve symptoms of post micturition dribble **(Grade of Recommendation: C)** (Unchanged).

EStim (EStim)

- For men with post-prostatectomy incontinence there does not appear to be any benefit of adding EStim to a PFMT programme **(Grade of Recommendation: B)** (Unchanged).

2. FUTURE RESEARCH DIRECTIONS

There is much scope for research on the effects of conservative therapies for UI and LUTS in men. Research that is urgently needed, in the opinion of committee members, is highlighted with the use of italics. There are a few recommendations that apply to all future studies in men, namely:

- All future intervention studies must be designed to allow standardised and comprehensive reporting of results based on the ICS and CONSORT recommendations.
- The natural history of UI after radical prostatectomy must be taken into account in study design as the spontaneous recovery rate means that sample sizes must be large to detect any differences between protocols.
- More research is needed to find out what are the most important outcomes for men with UI, so such measures can be incorporated as the primary outcome measures in further trials.
- Data are needed to establish to the cost, and cost effectiveness, of conservative therapies in men with UI.
- Surgical approaches with laparoscopy or robotics offer promising improvements in visualisation for nerve-sparing procedures; further research should address continence and erectile function after these newer surgical procedures.

a) Lifestyle interventions

- To date, no trials have addressed the topic of lifestyle interventions for men with UI.
- The effects of interventions such as weight and caffeine reduction, both of which show some evidence of benefit in women, are priorities for future research.

b) Pelvic floor muscle training (PFMT)

- Further studies to test the hypothesis that preoperative proprioceptive training plus PFMT is more effective than PFMT alone to prevent UI in men undergoing radial prostatectomy.
- A comparison of preoperative versus postoperative PFMT verbal and written feedback to reduce prevalence and severity of UI following radical prostatectomy is needed.
- Methods of PFMT instruction and supervision require further investigation. Two areas of research interest are:
    - Whether PFMT taught by DRE offers any benefit over and above verbal or written instruction.
    - The effect of group exercise. Because of the peer support that men may receive from participating in a group (433] this might be useful after radical prostatectomy; three reported that support in the post operative period may be important to healthy recovery [368,371,391].

- More systematic investigation of the the natural history of UI after TURP is needed, to establish the potential cost/benefit of intervention, before further trials are initiated.

- The relationship between age, or any other factor, and the outcome of PFMT for UI in men has yet to be determined.

c) Electrical stimulation (EStim) and magnetic stimulation (MStim)

- It is not known if pre or postoperative EStim or MStim has a role in reducing UI after radical prostatectomy.

- RCTs in larger samples, with long-term follow up, are needed to investigate all aspects of the effectiveness of EStim and MStim as a treatment for UI in men, including:

    - o Either type of stimulation versus no treatment, sham stimulation or other control conditions.

    - o Comparisons of both EStim and MStim protocols.

    - o EStim versus MStim.

    - o Either type of stimulation versus medication.

    - o Whether the addition of either type of stimulation to other treatments adds benefit, in particular the addition of stimulation to PFMT.

- The effect of age, and other factors, on outcome of stimulation. Elderly men may have more comorbid conditions than young men and a more pragmatic approach to inclusion in EStim studies is needed.

d) Scheduled voiding regimens

In the absence of trials exclusively in men, or trials that report data separately for men and women, there is a pressing need for high quality RCTs with an appropriate sample size and long-term follow up to address the effects of BT, Timed voiding, habit training and prompted voiding in men suffering from UI.

APPENDIX 1

TERMINOLOGY

Pelvic Floor Muscle Therapy (PFMT): any programme of repetitious, voluntary PFM contractions taught by a healthcare professional. It is the PFMs, not pelvic muscles in general, which are the target of the intervention. This broad definition accommodates variations in the PFMT end-goal, type of supervision (e.g. individual or group sessions) and the exercise programme (e.g. variations in frequency, intensity, number of contractions and duration of training). It may include the use of PFM contractions for urge suppression and to prevent stress leakage, under the term "the knack".

PFMT is used in preference to other previously-used terms such as Kegel's Exercises, pelvic floor exercises and PFM exercises. The term 'Kegel's Exercises' is no longer appropriate because it refers to Kegel's original exercise programme of 500 contractions per day (58). Current PFM programmes are very different from the one originally prescribed by Kegel (1948).

"Training" is also viewed as a more appropriate word than "exercise". The term "exercise" is commonly interpreted as one training episode or a single muscle action, whereas, "training" encompasses repeated exercises over a sustained period of time.

APPENDIX 2

REVIEW OF THE LITERATURE/SEARCH TERMS

A systematic search of studies up to the end of August 2011 was conducted. Only papers published in English or in a language for which a translator could be found were included. Relevant systematic reviews and reports of RCTs and quasi-RCTs were included. Therefore, only Level 1 evidence is considered in this section and recommendations are based on the findings of existing up-to-date systematic reviews and more recent RCTs.

Several Cochrane reviews were critical to the rigour of the present chapter: UI prevention (96,170); management of urinary continence in women (97,126,213); management of urinary incontinence in men (412,416); management of pelvic organ prolapse (296,297); habit training and timed voiding (273,275); and bladder training (269). Pre-specified outcomes of interest were urinary continence (for prevention studies), urinary continence, patient symptoms, quality-of-life measures and pad tests (for treatment studies).

Data for SUI were taken from a recent UK Health Technology Assessment (HTA) on non-surgical interventions for stress urinary incontinence in women (219). This was supplemented with additional studies for SUI completed after publication of this HTA, and studies for UUI and other LUTS, located through additional literature searching conducted in the Cochrane Incontinence Group Specialised Register as part of an ongoing Cochrane review. The same methods used in the HTA for data collection and analysis for SUI were applied to the studies on UUI and LUTS.

Criteria for inclusion were (1) randomised or quasi-randomised (alternate allocation) trial study design, (2) women with UI or other LUTS, (3) no participants with incontinence due to neurological or cognitive impairment and (4) no pregnant or postpartum women. Retrospective data was not included. 'Risk of bias' in the included studies was assessed for allocation concealment (selection bias) and completeness of outcome data (attrition bias), using relevant items in a standard tool developed by the Cochrane Urinary Incontinence Group (220). Risk of bias due to blinding to the allocated intervention should be considered to be high in most included studies: blinding of participants and care providers is not always feasible (other than the use of sham EStim), and blinding of outcome assessors is equally difficult for self-reported outcomes such as cure, improvement and quality of life.

The Consort Statement Checklist was used to determine the quality each study (434). Empirical evidence indicates that two elements of trial quality, allocation concealment and double blinding, are important for estimating treatment effect with precision. Trials with inadequate or unclear concealment of allocation appear to overestimate treatment effect by about 30% and trials that are not double-blinded overestimate effect by about 15% (435). Therefore, trials that reported adequate allocation concealment have been noted. Although it is often difficult or impossible to blind patients to PFMT, trials that reported blinding of the outcome assessment have also been noted. Readers may wish to consider these factors in their interpretation of the data.

The search terms may be seen at http://hdl.handle.net/10402/era.26262. (Click on the "download" link, top right.)

REFERENCES

1. Hay-Smith EJ, Berghmans B, Burgio KL, Dumoulin C, Hagen S, Moore KN, et al. Adult Conservative Management. In: Abrams P, Cardoza L, Khoury S, Wein A, editors. Incontinence. Proceedings of the 4th International Consultation on Incontinence. Paris. July 5-8, 2008 Paris: Health Publications Ltd. 2009. Editions 21; 2009. p. 1025-1120.
2. Subak LL, Whitcomb E, Shen H, Saxton J, Vittinghoff E, Brown JS. Weight loss: a novel and effective treatment for urinary incontinence. J Urol 2005 Jul;174(1):190-195.
3. Subak LL, Wing R, Smith West D, Franklin F, Vittinghoff E, Creasman J, et al. A behavioral weight loss program significantly reduces urinary incontinence episodes in overweight and obese women (Abstract number 1). Journal of Pelvic Medicine & Surgery 2007;13(5):223-224.
4. Subak LL, Wing R, West DS, Franklin F, Vittinghoff E, Creasman JM, et al. Weight loss to treat urinary incontinence in overweight and obese women. N Engl J Med 2009 29 Jan 2009;360(5):481-490.
5. Brown JS, Wing R, Barrett-Connor E, Nyberg LM, Kusek JW, Orchard TJ, et al. Lifestyle intervention is associated with lower prevalence of urinary incontinence: the Diabetes Prevention Program. Diabetes Care 2006 Feb;29(2):385-390.
6. Subak LL, Johnson C, Whitcomb E, Boban D, Saxton J, Brown JS. Does weight loss improve incontinence in moderately obese women? Int Urogynecol J Pelvic Floor Dysfunct 2002;13(1):40-43.
7. Bump RC, Sugerman HJ, Fantl JA, McClish DK. Obesity and lower urinary tract function in women: effect of surgically induced weight loss. Am J Obstet Gynecol 1992 Aug;167(2):392-7; discussion 397-9.
8. Deitel M, Stone E, Kassam HA, Wilk EJ, Sutherland DJ. Gynecologic-obstetric changes after loss of massive excess weight following bariatric surgery. J Am Coll Nutr 1988 Apr;7(2):147-153.
9. Burgio KL, Richter HE, Clements RH, Redden DT, Goode PS. Changes in urinary and fecal incontinence symptoms with weight loss surgery in morbidly obese women. Obstet Gynecol 2007 Nov;110(5):1034-1040.
10. Brown JS, Seeley DG, Fong J, Black DM, Ensrud KE, Grady D. Urinary incontinence in older women: who is at risk? Study of Osteoporotic Fractures Research Group. Obstet Gynecol 1996 May;87(5 Pt 1):715-721.
11. Brown JS, Grady D, Ouslander JG, Herzog AR, Varner RE, Posner SF. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estrogen/Progestin Replacement Study (HERS) Research Group. Obstet Gynecol 1999 Jul;94(1):66-70.
12. Thom DH, van den Eeden SK, Brown JS. Evaluation of parturition and other reproductive variables as risk factors for urinary incontinence in later life. Obstet Gynecol 1997 Dec;90(6):983-989.
13. Hannestad YS, Rortveit G, Daltveit AK, Hunskaar S. Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. BJOG 2003 Mar;110(3):247-254.
14. Samsioe G, Heraib F, Lidfeldt J, Nerbrand C, Lindholm L, Agardh C, et al. Urogenital symptoms in women aged 50-59 years. Women's Health in Lund Area (WHILSA) Study Group. Gynecol Endocrinol 1999 Apr;13(2):113-117.
15. Melville JL, Katon W, Delaney K, Newton K. Urinary incontinence in US women: a population-based study. Arch Intern Med 2005 Mar 14;165(5):537-542.
16. Danforth KN, Townsend MK, Lifford K, Curhan GC, Resnick NM, Grodstein F. Risk factors for urinary incontinence among middle-aged women. Am J Obstet Gynecol 2006 Feb 2006;194(2):339-345.
17. Kölbi H, Riss P. Obesity and stress urinary incontinence: significance of indices of relative weight. Urol Int 1988;43(1):7-10.
18. Rasmussen KL, Krue S, Johansson LE, Knudsen HJ, Agger AO. Obesity as a predictor of postpartum urinary symptoms. Acta Obstet Gynecol Scand 1997 Apr;76(4):359-362.
19. Wing RR, Creasman JM, West DS, Richter HE, Myers D, Burgio KL, et al. Improving urinary incontinence in overweight and obese women through modest weight loss. Obstet Gynecol 2010 Aug;116(2 Pt 1):284-292.
20. Wing RR, West DS, Grady D, Creasman JM, Richter HE, Myers D, et al. Effect of weight loss on urinary incontinence in overweight and obese women: results at 12 and 18 months. J Urol 2010 Sep;184(3):1005-1010.
21. Danforth KN, Shah AD, Townsend MK, Lifford KL, Curhan GC, Resnick NM, et al. Physical activity and urinary incontinence among healthy, older women. Obstet Gynecol 2007 Mar;109(3):721-727.
22. Townsend MK, Danforth KN, Rosner B, Curhan GC, Resnick NM, Grodstein F. Physical activity and incident urinary incontinence in middle-aged women. J Urol 2008 discussion 1016-7; Mar;179(3):1012-1016.
23. Bø K, Maehlum S, Oseid S, Larsen S. Prevalence of stress urinary incontinence among physically active and sedentary female students. Scandinavian Journal of Sports Sciences 1989 1989;11(3):113-116.
24. Nygaard IE, Thompson FL, Svengalis SL, Albright JP. Urinary incontinence in elite nulliparous athletes. Obstet Gynecol 1994 Aug;84(2):183-187.
25. Bø K, Borgen JS. Prevalence of stress and urge urinary incontinence in elite athletes and controls. Med Sci Sports Exerc 2001 Nov;33(11):1797-1802.
26. Caylet N, Fabbro-Peray P, Mares P, Dauzat M, Prat-Pradal D, Corcos J. Prevalence and occurrence of stress urinary incontinence in elite women athletes. Can J Urol 2006 Aug;13(4):3174-3179.
27. Kruger JA, Dietz HP, Murphy BA. Pelvic floor function in elite nulliparous athletes. Ultrasound Obstet Gynecol 2007 Jul;30(1):81-85.
28. Eliasson K, Nordlander I, Larson B, Hammarstrom M, Mattsson E. Influence of physical activity on urinary leakage in primiparous women. Scand J Med Sci Sports 2005 Apr;15(2):87-94.
29. Nygaard I, Girts T, Fultz NH, Kinchen K, Pohl G, Sternfeld B. Is urinary incontinence a barrier to exercise in women? Obstet Gynecol 2005 Aug;106(2):307-314.
30. Nygaard IE. Does prolonged high-impact activity contribute to later urinary incontinence? A retrospective cohort study of female Olympians. Obstet Gynecol 1997 Nov;90(5):718-722.
31. Jörgensen S, Hein HO, Gyntelberg F. Heavy lifting at work and risk of genital prolapse and herniated lumbar disc in assistant nurses. Occup Med (Lond) 1994 Feb;44(1):47-49.
32. Bump RC, McClish DM. Cigarette smoking and pure genuine stress incontinence of urine: a comparison of risk factors and determinants between smokers and nonsmokers. Am J Obstet Gynecol 1994 Feb;170(2):579-582.
33. Tampakoudis P, Tantanassis T, Grimbizis G, Papaletsos M, Mantalenakis S. Cigarette smoking and urinary incontinence in women--a new calculative method of estimating the exposure to smoke. Eur J Obstet Gynecol Reprod Biol 1995 Nov;63(1):27-30.
34. van Geelen JM, van de Weijer PH, Arnolds HT. Urogenital symptoms and resulting discomfort in non-institutionalized Dutch women aged 50-75 years. Int Urogynecol J Pelvic Floor Dysfunct 2000;11(1):9-14.
35. Højberg KE, Salvig JD, Winslow NA, Lose G, Secher NJ. Urinary incontinence: prevalence and risk factors at 16 weeks of gestation. Br J Obstet Gynaecol 1999 Aug;106(8):842-850.

36. Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. Obstet Gynecol 2002 Dec;100(6):1230-1238.

37. Bortolotti A, Bernardini B, Colli E, Di Benedetto P, Giocoli Nacci G, Landoni M, et al. Prevalence and risk factors for urinary incontinence in Italy. Eur Urol 2000 Jan;37(1):30-35.

38. Daneshgari F, Moore C, Frinjari H, Babineau D. Patient related risk factors for recurrent stress urinary incontinence surgery in women treated at a tertiary care center. J Urol 2006 Oct;176(4 Pt 1):1493-1499.

39. Richter HE, Burgio KL, Brubaker L, Moalli PA, Markland AD, Mallet V, et al. Factors associated with incontinence frequency in a surgical cohort of stress incontinent women. Am J Obstet Gynecol 2005 Dec;193(6):2088-2093.

40. Hisayama T, Shinkai M, Takayanagi I, Toyoda T. Mechanism of action of nicotine in isolated urinary bladder of guinea-pig. Br J Pharmacol 1988 Oct;95(2):465-472.

41. Koley B, Koley J, Saha JK. The effects of nicotine on spontaneous contractions of cat urinary bladder in situ. Br J Pharmacol 1984 Oct;83(2):347-355.

42. Milsom I, Arvidsson L, Ekelund P, Molander U, Eriksson O. Factors influencing vaginal cytology, pH and bacterial flora in elderly women. Acta Obstet Gynecol Scand 1993 May;72(4):286-291.

43. Manonai J, Songchitsomboon S, Chanda K, Hong JH, Komindr S. The effect of a soy-rich diet on urogenital atrophy: a randomized, cross-over trial. Maturitas 2006 May 20;54(2):135-140.

44. Maserejian NN, Giovannucci EL, McVary KT, McGrother C, McKinlay JB. Dietary Macronutrient and Energy Intake and Urinary Incontinence in Women. American Journal of Epidemiology 2010 May 15;171(10):1116-1125.

45. Dallosso H, Matthews R, McGrother C, Donaldson M. Diet as a risk factor for the development of stress urinary incontinence: a longitudinal study in women. Eur J Clin Nutr 2004 Jun;58(6):920-926.

46. Dallosso HM, McGrother CW, Matthews RJ, Donaldson MM, Leicestershire MRC Incontinence Study Group. The association of diet and other lifestyle factors with overactive bladder and stress incontinence: a longitudinal study in women. BJU Int 2003 Jul;92(1):69-77.

47. Dallosso HM, McGrother CW, Matthews RJ, Donaldson MM, Leicestershire MRC Incontinence Study Group. Nutrient composition of the diet and the development of overactive bladder: a longitudinal study in women. Neurourol Urodyn 2004;23(3):204-210.

48. Bryant CM, Dowell CJ, Fairbrother G. Caffeine reduction education to improve urinary symptoms. Br J Nurs 2002 Apr 25-May 8;11(8):560-565.

49. Swithinbank L, Hashim H, Abrams P. The effect of fluid intake on urinary symptoms in women. J Urol 2005 Jul;174(1):187-189.

50. Dowd TT, Campbell JM, Jones JA. Fluid intake and urinary incontinence in older community-dwelling women. J Community Health Nurs 1996;13(3):179-186.

51. Hashim H, Abrams P. How should patients with an overactive bladder manipulate their fluid intake?. BJU Int 2008 Jul;102(1):62-66.

52. Roe B, Doll H. Lifestyle factors and continence status: comparison of self-report data from a postal survey in England. J Wound Ostomy Continence Nurs 1999 Nov;26(6):312-3, 315-9.

53. Spence-Jones C, Kamm MA, Henry MM, Hudson CN. Bowel dysfunction: a pathogenic factor in uterovaginal prolapse and urinary stress incontinence. Br J Obstet Gynaecol 1994 Feb;101(2):147-152.

54. Diokno AC, Brock BM, Herzog AR, Bromberg J. Medical correlates of urinary incontinence in the elderly. Urology 1990 Aug;36(2):129-138.

55. Alling Møller L, Lose G, Jørgensen T. Risk factors for lower urinary tract symptoms in women 40 to 60 years of age. Obstet Gynecol 2000 Sep;96(3):446-451.

56. Jorge JM, Wexner SD, Ehrenpreis ED, Nogueras JJ, Jagelman DG. Does perineal descent correlate with pudendal neuropathy? Dis Colon Rectum 1993 May;36(5):475-483.

57. Lubowski DZ, Swash M, Nicholls RJ, Henry MM. Increase in pudendal nerve terminal motor latency with defaecation straining. Br J Surg 1988 Nov;75(11):1095-1097.

58. Kegel AH. Progressive resistance exercise in the functional restoration of the perineal muscles. Am J Obstet Gynecol 1948 Aug;56(2):238-248.

59. Deindl FM, Vodusek DB, Hesse U, Schussler B. Activity patterns of pubococcygeal muscles in nulliparous continent women. Br J Urol 1993 Jul;72(1):46-51.

60. Peschers UM, Vodusek DB, Fanger G, Schaer GN, DeLancey JO, Schuessler B. Pelvic muscle activity in nulliparous volunteers. Neurourol Urodyn 2001;20(3):269-275.

61. Bø K, Stien R, Kulseng-Hanssen S, Kristofferson M. Clinical and urodynamic assessment of nulliparous young women with and without stress incontinence symptoms: a case-control study. Obstet Gynecol 1994 Dec;84(6):1028-1032.

62. Constantinou CE, Govan DE. Spatial distribution and timing of transmitted and reflexly generated urethral pressures in healthy women. J Urol 1982 May;127(5):964-969.

63. Thind P, Lose G, Jorgensen L, Colstrup H. Variations in urethral and bladder pressure during stress episodes in healthy women. Br J Urol 1990 Oct;66(4):389-392.

64. DeLancey JOL. Structural aspects of urethrovesical function in the female. Neurourol Urodyn 1988 1988;7(6):509-519.

65. Thompson JA, O'Sullivan PB. Levator plate movement during voluntary pelvic floor muscle contraction in subjects with incontinence and prolapse: a cross-sectional study and review. Int Urogynecol J Pelvic Floor Dysfunct 2003 Jun;14(2):84-88.

66. Bø K, Lilleas F, Talseth T, Hedland H. Dynamic MRI of the pelvic floor muscles in an upright sitting position. Neurourol Urodyn 2001;20(2):167-174.

67. Miller JM, Ashton-Miller JA, DeLancey JO. A pelvic muscle precontraction can reduce cough-related urine loss in selected women with mild SUI. J Am Geriatr Soc 1998 Jul;46(7):870-874.

68. Miller JM, Sampselle C, Ashton-Miller J, Hong GR, DeLancey JO. Clarification and confirmation of the Knack maneuver: the effect of volitional pelvic floor muscle contraction to preempt expected stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008 Jun;19(6):773-782.

69. Bø K. Pelvic floor muscle exercise for the treatment of stress urinary incontinence: An exercise physiology perspective. Int Urogynecol J Pelvic Floor Dysfunct 1995 1995;6(5):282-291.

70. Bø K. Pelvic floor muscle training is effective in treatment of female stress urinary incontinence, but how does it work? Int Urogynecol J Pelvic Floor Dysfunct 2004 Mar-Apr;15(2):76-84.

71. Peschers UM, Schaer GN, DeLancey JO, Schuessler B. Levator ani function before and after childbirth. Br J Obstet Gynaecol 1997 Sep;104(9):1004-1008.

72. Hoyte L, Schierlitz L, Zou K, Flesh G, Fielding JR. Two- and 3-dimensional MRI comparison of levator ani structure, volume, and integrity in women with stress incontinence and prolapse. Am J Obstet Gynecol 2001 Jul;185(1):11-19.

73. Pontbriand-Drolet S, Madill S, Tang A, Dumoulin C. Pelvic floor morphology in older continent and urinary incontinent women: An MRI study.. Oral and poster presentation, Joint ICS-IUGA Annual Meeting, Toronto, Canada. Aug. 2010. Neurourol Urodyn 2010;29(6):141.

74. Morin M, Bourbonnais D, Gravel D, Dumoulin C, Lemieux MC. Pelvic floor muscle function in continent and stress urinary incontinent women using dynamometric measurements. Neurourol Urodyn 2004;23(7):668-674.

75. Verelst M, Leivseth G. Are fatigue and disturbances in preprogrammed activity of pelvic floor muscles associated with female stress urinary incontinence? Neurourol Urodyn 2004;23(2):143-147.

76. Dumoulin C, Peng Q, Stodkilde-Jorgensen H, Shishido K, Constantinou C. Changes in levator ani anatomical configuration following physiotherapy in women with stress urinary incontinence. J Urol 2007 Sep;178(3 Pt 1):970-7; quiz 1129.

77. Balmforth J, Bidmead J, Cardozo L, Hextall A, Kelvin B, Mantle J. Raising the tone: a prospective observational study evaluating the effect of pelvic floor muscle training on bladder neck mobility and associated improvement in stress urinary incontinence. Neurourol Urodyn 2004;23(5-6):553-554.

78. Bø K, Berghmans B, Mørkved S, Van Kampen M. Evidence-based physical therapy for the pelvic floor : bridging science and clinical practice. Edinburgh: Churchill Livingstone; 2007.

79. Madill S, Tang A, Pontbriand-Drolet S, Dumoulin C. Comparison of two methods for measuring the pubococcygeal line from sagittal-plane magnetic resonance imaging. Neurourol Urodyn 2011 Nov;30(8):1613-1619.

80. Sapsford RR, Hodges PW. Contraction of the pelvic floor muscles during abdominal maneuvers. Arch Phys Med Rehabil 2001 Aug;82(8):1081-1088.

81. Sapsford RR, Hodges PW, Richardson CA, Cooper DH, Markwell SJ, Jull GA. Co-activation of the abdominal and pelvic floor muscles during voluntary exercises. Neurourol Urodyn 2001;20(1):31-42.

82. Neumann P, Gill V. Pelvic floor and abdominal muscle interaction: EMG activity and intra-abdominal pressure. Int Urogynecol J Pelvic Floor Dysfunct 2002;13(2):125-132.

83. Bladder neck elevation during different pelvic floor activation techniques: An MRI study. Proceedings of the 36th ASnnual Meeting of the International Continence Society, 2006; 2006.

84. Jones RC, Peng Q, Shishido K, Perkash I, Constantinou CE. 2D ultrasound imaging and motion tracking of the pelvic floor muscle (PFM) activity during abdominal manoeuvres in stress urinary incontinent (SUI) women. Neurourol Urodyn 2006;25(6):596-597.

85. Bø K, Sherburn M, Allen T. Transabdominal ultrasound measurement of pelvic floor muscle activity when activated directly or via a transversus abdominis muscle contraction. Neurourol Urodyn 2003;22(6):582-588.

86. Godec C, Cass AS, Ayala GF. Bladder inhibition with functional electrical stimulation. Urology 1975 Dec;6(6):663-666.

87. Burgio KL, Whitehead WE, Engel BT. Urinary incontinence in the elderly. Bladder-sphincter biofeedback and toileting skills training. Ann Intern Med 1985 Oct;103(4):507-515.

88. de Groat WC. A neurologic basis for the overactive bladder. Urology 1997 Dec;50(6A Suppl):36-52; discussion 53-6.

89. Morrison JFB. The excitability of the micturition reflex. Scandinavian Journal of Urology and Nephrology, Supplement 1995 1995(175):21-25.

90. Jones K, Barker K. Human movement explained. Oxford: Butterworth-Heineman; 1996.

91. Kisner C, Colby LA. Therapeutic exercise : foundations and techniques. 5th ed. Philadelphia: F. A. Davis Company; 2007.

92. McComas AJ. Skeletal muscle. Form and function. Champaign, IL: Human Kinetics; 1996.

93. DiNubile NA. Strength training. Clin Sports Med 1991 Jan;10(1):33-62.

94. Kraemer WJ, Adams K, Cafarelli E, Dudley GA, Dooly C, Feigenbaum MS, et al. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc 2002 Feb;34(2):364-380.

95. Hilton P, Robinson D. Defining cure. Neurourol Urodyn 2011 June 2011;30(5):741-745.

96. Hay-Smith J, Mørkved S, Fairbrother KA, Herbison GP. Pelvic floor muscle training for prevention and treatment of urinary and faecal incontinence in antenatal and postnatal women. Cochrane Database Syst Rev 2008 Oct 8;(4)(4):CD007471.

97. Hay-Smith JE, Herderschee R, Dumoulin C, Herbison PG. Comparisons of approaches to pelvic floor muscle training for urinary incontinence in women. Cochrane Database of Systematic Reviews 2011;8.

98. Sampselle CM, Miller JM, Mims BL, Delancey JO, Ashton-Miller JA, Antonakos CL. Effect of pelvic muscle exercise on transient incontinence during pregnancy and after birth. Obstet Gynecol 1998 Mar;91(3):406-412.

99. Reilly ET, Freeman RM, Waterfield MR, Waterfield AE, Steggles P, Pedlar F. Prevention of postpartum stress incontinence in primigravidae with increased bladder neck mobility: a randomised controlled trial of antenatal pelvic floor exercises. BJOG 2002 Jan;109(1):68-76.

100. Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. Can J Urol 2002 Jun;9(3):1558-1562.

101. Mørkved S, Bø K, Schei B, Salvesen KA. Pelvic floor muscle training during pregnancy to prevent urinary incontinence: a single-blind randomized controlled trial. Obstet Gynecol 2003 Feb;101(2):313-319.

102. Gorbea Chavez V, Velazquez Sanchez Mdel P, Kunhardt Rasch JR. Effect of pelvic floor exercise during pregnancy and puerperium on prevention of urinary stress incontinence. Ginecol Obstet Mex 2004 Dec;72(12):628-636.

103. Mason L, Roe B, Wong H, Davies J, Bamber J. The role of antenatal pelvic floor muscle exercises in prevention of postpartum stress incontinence: A randomised controlled trial. J Clin Nurs 2010;19(19-20) (pp 2777-2786):ate of Pubaton: Otober 2010.

104. Bø K, Haakstad LA. Is pelvic floor muscle training effective when taught in a general fitness class in pregnancy? A randomised controlled trial. Physiotherapy 2011 Sep;97(3):190-195.

105. Ko PC, Liang CC, Chang SD, Lee JT, Chao AS, Cheng PJ. A randomized controlled trial of antenatal pelvic floor exercises to prevent and treat urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2011 Jan;22(1):17-22.

106. (106) Agur WI, Steggles P, Waterfield M, Freeman RM. The long-term effectiveness of antenatal pelvic floor muscle training: eight-year follow up of a randomised controlled trial. BJOG 2008 Jul;115(8):985-990.

107. Wilson PD, Herbison GP. A randomized controlled trial of pelvic floor muscle exercises to treat postnatal urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1998;9(5):257-264.

108. Glazener CM, Herbison GP, Wilson PD, MacArthur C, Lang GD, Gee H, et al. Conservative management of persistent postnatal urinary and faecal incontinence: randomised controlled trial. BMJ 2001 Sep 15;323(7313):593-596.

109. Dumoulin C, Lemieux MC, Bourbonnais D, Gravel D, Bravo G, Morin M. Physiotherapy for persistent postnatal stress urinary incontinence: a randomized controlled trial. Obstet Gynecol 2004 Sep;104(3):504-510.

110. Woldringh C, van den Wijngaart M, Albers-Heitner P, Lycklama a Nijeholt AA, Lagro-Janssen T. Pelvic floor muscle training is not effective in women with UI in pregnancy: a randomised controlled trial. Int Urogynecol J Pelvic Floor Dysfunct 2007 Apr;18(4):383-390.

111. Glazener CM, Herbison GP, MacArthur C, Grant A, Wilson PD. Randomised controlled trial of conservative management of postnatal urinary and faecal incontinence: six year follow up. BMJ 2005 Feb 12;330(7487):337.

112. Sleep J, Grant A. Pelvic floor exercises in postnatal care. Midwifery 1987 Dec;3(4):158-164.

113. Hughes P, Jackson S, Smith P, Abrams P. Can antenatal pelvic floor exercises prevent postnatal incontinence. Neurourol Urodyn 2001;20(4):447-448.

114. Meyer S, Hohlfeld P, Achtari C, De Grandi P. Pelvic floor education after vaginal delivery. Obstet Gynecol 2001 May;97(5 Pt 1):673-677.

115. Chiarelli P, Cockburn J. Promoting urinary continence in women after delivery: randomised controlled trial. BMJ 2002 May 25;324(7348):1241.

116. Dannecker C, Baur C, Ruckhaberle E, Peschers U, Jundt K, Reich A, et al. The effect of the pelvic floor training device Epi-No on the maternal pelvic floor function six months after childbirth - Follow-up study of a randomised controlled trial. Geburtshilfe Frauenheilkd 2004 Nov 2004;64(11):1192-1198.

117. Ewings P, Spencer S, Marsh H, O'Sullivan M. Obstetric risk factors for urinary incontinence and preventative pelvic floor exercises: cohort study and nested randomized controlled trial. J Obstet Gynaecol 2005 Aug;25(6):558-564.

118. Dumoulin C, Bourbonnais D, Morin M, Gravel D, Lemieux MC. Predictors of success for physiotherapy treatment in women with persistent postpartum stress urinary incontinence. Arch Phys Med Rehabil 2010 Jul;91(7):1059-1063.

119. Kim H, Yoshida H, Suzuki T. The effects of multidimensional exercise on functional decline, urinary incontinence, and fear of falling in community-dwelling elderly women with multiple symptoms of geriatric syndrome: A randomized controlled and 6-month follow-up trial. Arch Gerontol Geriatr 2011 January-February 2011;52(1):99-105.

120. Burgio KL, Goode PS, Locher JL, Umlauf MG, Roth DL, Richter HE, et al. Behavioral training with and without biofeedback in the treatment of urge incontinence in older women: a randomized controlled trial. JAMA 2002 Nov 13;288(18):2293-2299.

121. Goode PS, Burgio KL, Locher JL, Roth DL, Umlauf MG, Richter HE, et al. Effect of behavioral training with or without pelvic floor electrical stimulation on stress incontinence in women: a randomized controlled trial. JAMA 2003 Jul 16;290(3):345-352.

122. Williams KS, Assassa RP, Gillies CL, Abrams KR, Turner DA, Shaw C, et al. A randomized controlled trial of the effectiveness of pelvic floor therapies for urodynamic stress and mixed incontinence. BJU Int 2006 Nov;98(5):1043-1050.

123. Yoon HS, Hong J, Choi Y, Back S. The effect of pelvic floor muscle exercises on genuine stress incontinence among Korean Women: focusing on it's effects on the quality of life. Proceedings of the 29th Annual Meeting of the International Continence Society 1999.

124. Ramsay I, Tchou M. **A** randomized, double blind, placebo controlled trial of pelvic floor exercises in **the** treatment of genuine stress incontinence. Neurourol Urodyn 1990;9(4):398-399.

125. Ghoniem GM, Van Leeuwen JS, Elser DM, Freeman RM, Zhao YD, Yalcin I, et al. A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. J Urol 2005;173(5):1647–1653.

126. Hay-Smith EJ, Dumoulin C. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev 2006 Jan 25;(1)(1):CD005654.

127. Dumoulin C. Postnatal pelvic floor muscle training for preventing and treating urinary incontinence: where do we stand? Curr Opin Obstet Gynecol 2006 Oct;18(5):538-543.

128. Yoon HS, Song HH, Ro YJ. A comparison of effectiveness of bladder training and pelvic muscle exercise on female urinary incontinence. Int J Nurs Stud 2003 Jan;40(1):45-50.

129. Wells JA, Ouslander JG, Meadows E, Johnson VY. Urinary incontinence in a geriatric patient with a complex neurologic history. J Wound Ostomy Continence Nurs 1999 Sep;26(5):270-4; discussion 274-5.

130. Henalla SM, Hutchins CJ, Robinson P, MacVicar J. Non-operative methods in the treatment of female genuine stress incontinence of urine. Journal of Obstetrics and Gynaecology 1989 1989;9(3):222-225.

131. Henalla SM, Millar DR, Wallace KJ. Surgical versus conservative management for post-menopausal genuine stress incontinence of urine. Neurourol Urodyn 1990;9(4):436-437.

132. Hofbauer J, Preisinger F, Nurnberger N. The value of physical therapy in genuine female stress incontinence. Z Urol Nephrol 1990 May;83(5):249-254.

133. Lagro-Janssen TL, Debruyne FM, Smits AJ, van Weel C. Controlled trial of pelvic floor exercises in the treatment of urinary stress incontinence in general practice. Br J Gen Pract 1991 Nov;41(352):445-449.

134. Bø K, Talseth T, Holme I. Single blind, randomised controlled trial of pelvic floor exercises, electrical stimulation, vaginal cones, and no treatment in management of genuine stress incontinence in women. BMJ 1999 Feb 20;318(7182):487-493.

135. Bidmead J, Mantle J, Cardozo L, Hextall A, Boos K. Home electrical stimulation in addition to conventional pelvic floor exercises: a useful adjunct or expensive distraction? Neurourol Urodyn 2002;21(4):372-373.

136. Aksac B, Aki S, Karan A, Yalcin O, Isikoglu M, Eskiyurt N. Biofeedback and pelvic floor exercises for the rehabilitation of urinary stress incontinence. Gynecol Obstet Invest 2003;56(1):23-27.

137. Schagen van Leeuwen JH, Elser D, Freeman R, Ghonien G, Zhao Y, Yalcin I, et al. 197 Controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment, and no treatment in women with stress urinary incontinence (SUI). European Urology Supplements 2004 2;3(2):52-52.

138. Kim H, Suzuki T, Yoshida Y, Yoshida H. Effectiveness of multidimensional exercises for the treatment of stress urinary incontinence in elderly community-dwelling Japanese women: a randomized, controlled, crossover trial. J Am Geriatr Soc 2007 Dec;55(12):1932-1939.

139. Carneiro EF, Araujo Ndos S, Beuttenmull L, Vieira PC, Cader SA, Cader SA, et al. [The anatomical-functional characteristics of the pelvic floor and quality of life of women with stress urinary incontinence subjected to perineal exercises]. Actas Urol Esp 2010 Oct;34(9):788-793.

140. Castro RA, Arruda RM, Zanetti MR, Santos PD, Sartori MG, Girao MJ. Single-blind, randomized, controlled trial of pelvic floor muscle training, electrical stimulation, vaginal cones, and no active treatment in the management of stress urinary incontinence. Clinics 2008 Aug;63(4):465-472.

141. Burns PA, Pranikoff K, Nochajski TH, Hadley EC, Levy KJ, Ory MG. A comparison of effectiveness of biofeedback and pelvic muscle exercise treatment of stress incontinence in older community-dwelling women. J Gerontol 1993;48(4Using Smart Source Parsing (pp English):M167-M174.

142. Burgio KL, Locher JL, Goode PS, Hardin JM, McDowell BJ, Dombrowski M, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. JAMA 1998;280(23):1995-2000.

143. Sari D, Khorshid L. The effects of pelvic floor muscle training on stress and mixed urinary incontinence and quality of life. Journal of Wound, Ostomy and Continence Nursing 2009 July-August 2009;36(4):429-435.

144. Lagro-Janssen AL, van Weel C. Long-term effect of treat-

ment of female incontinence in general practice. Br J Gen Pract 1998;48(436):1735-1738.

145. Miller J, Aston-Miller JA, DeLancey JOL. The Knack: use of precisely-timed pelvic muscle contraction can reduce leakage in SUI. Neurourology and Urodynamics 1996;15(4):392-393.

146. Bø K, Hagen RH, Kvarstein B, Jorgensen J, Larsen S. Pelvic floor muscle exercise for the treatment of female stress urinary incontinence: III. Effects of two different degrees of pelvic floor muscle exercises. Neurourol Urodyn 1990 1990;9(5):489-502.

147. Konstantinidou E, Apostolidis A, Kondelidis N, Tsimtsiou Z, Hatzichristou D, Ioannides E. Short-term efficacy of group pelvic floor training under intensive supervision versus unsupervised home training for female stress urinary incontinence: a randomized pilot study. Neurourol Urodyn 2007;26(4):486-491.

148. Zanetti MR, Castro Rde A, Rotta AL, Santos PD, Sartori M, Girao MJ. Impact of supervised physiotherapeutic pelvic floor exercises for treating female stress urinary incontinence. Sao Paulo Med J 2007 Sep 6;125(5):265-269.

149. Felicissimo MF, Carneiro MM, Saleme CS, Pinto RZ, da Fonseca AM, da Silva-Filho AL. Intensive supervised versus unsupervised pelvic floor muscle training for the treatment of stress urinary incontinence: a randomized comparative trial. Int Urogynecol J 2010 Jul;21(7):835-840.

150. Hung HC, Hsiao SM, Chih SY, Lin HH, Tsauo JY. An alternative intervention for urinary incontinence: retraining diaphragmatic, deep abdominal and pelvic floor muscle coordinated function. Manual Ther 2010 Jun;15(3):273-279.

151. Ng SC, Lin TL, Chang SJ, Tai HL, Hu SW, Chen GD. Nursing intervention to enhance efficacy of home practice of pelvic floor muscle exercises in treating mixed urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008 May;19(5):637-642.

152. Liebergall-Wischnitzer M, Hochner-Celnikier D, Lavy Y, Manor O, Arbel R, Paltiel O. Paula method of circular muscle exercises for urinary stress incontinence--a clinical trial. Int Urogynecol J Pelvic Floor Dysfunct 2005 Sep-Oct;16(5):345-351.

153. Liebergall-Wischnitzer M, Hochner-Celnikier D, Lavy Y, Manor O, Shveiky D, Paltiel O. Randomized trial of circular muscle versus pelvic floor training for stress urinary incontinence in women. J Womens Health (Larchmt) 2009 Mar;18(3):377-385.

154. de Oliveira Camargo F, Rodrigues AM, Arruda RM, Ferreira Sartori MG, Girao MJ, Castro RA. Pelvic floor muscle training in female stress urinary incontinence: comparison between group training and individual treatment using PERFECT assessment scheme. Int Urogynecol J Pelvic Floor Dysfunct 2009 Dec;20(12):1455-1462.

155. Savage A. Is lumbopelvic stability training (using the Pilates model) an effective treatment strategy for women with stress urinary incontinence? A review of the literature and report of a pilot study. Journal of the Association of CharteredPhysiotherapists in Women's health 2005;97:33-48.

156. Johnson VY. Effects of a submaximal exercise protocol to recondition the pelvic floor musculature. Nurs Res 2001 Jan-Feb;50(1):33-41.

157. Sriboonreung T, Wongtra-ngan S, Eungpinichpong W, Laopaiboon M. Effectiveness of pelvic floor muscle training in incontinent women at Maharaj Nakorn Chiang Mai Hospital: a randomized controlled trial. J Med Assoc Thai 2011 Jan;94(1):1-7.

158. Borello-France DF, Zyczynski HM, Downey PA, Rause CR, Wister JA. Effect of pelvic-floor muscle exercise position on continence and quality-of-life outcomes in women with stress urinary incontinence. Phys Ther 2006 Jul;86(7):974-986.

159. Hay-Smith EJC, Herbison GP, Wilson PD. Pelvic floor muscle training for women with symptoms of stress urinary incontinence: a randomised trial comparing strengthening and motor relearning approaches. Neurourol Urodyn 2002;21(4):371-372.

160. Ferguson KL, McKey PL, Bishop KR, Kloen P, Verheul JB, Dougherty MC. Stress urinary incontinence: effect of pelvic muscle exercise. Obstet Gynecol 1990 Apr;75(4):671-675.

161. Delgado D, Drake M. A randomised study to compare the PelvicToner device against standard pelvic floor exercises in the treatment of stress urinary incontinence in women (Abstract number 486). Proceedings of the 39th Annual Meeting of the International Continence Society (ICS), Sep 29 - Oct 3, San Francisco, CA.2009 2009.

162. Gallo ML, Staskin DR. Cues to action: pelvic floor muscle exercise compliance in women with stress urinary incontinence. Neurourol Urodyn 1997;16(3):167-177.

163. Sugaya K, Owan T, Hatano T, Nishijima S, Miyazato M, Mukouyama H, et al. Device to promote pelvic floor muscle training for stress incontinence. Int J Urol 2003 Aug;10(8):416-422.

164. Berghmans LC, Frederiks CM, de Bie RA, Weil EH, Smeets LW, van Waalwijk van Doorn ES, et al. Efficacy of biofeedback, when included with pelvic floor muscle exercise treatment, for genuine stress incontinence. Neurourol Urodyn 1996;15(1):37-52.

165. Glavind K, Nohr SB, Walter S. Biofeedback and physiotherapy versus physiotherapy alone in the treatment of genuine stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1996;7(6):339-343.

166. Wang AC, Wang YY, Chen MC. Single-blind, randomized trial of pelvic floor muscle training, biofeedback-assisted pelvic floor muscle training, and electrical stimulation in the management of overactive bladder. Urology 2004 Jan;63(1):61-66.

167. Mørkved S, Bo K, Fjortoft T. Effect of adding biofeedback to pelvic floor muscle training to treat urodynamic stress incontinence. Obstet Gynecol 2002 Oct;100(4):730-739.

168. Shepherd AM, Tribe E, Bainton D. Maximum perineal stimulation. A controlled study. Br J Urol 1984 Dec;56(6):644-646.

169. Laycock J, Brown J, Cusack C, Green S, Jerwood D, Mann K, et al. Pelvic floor reeducation for stress incontinence: comparing three methods. Br J Community Nurs 2001 May;6(5):230-237.

170. Hay-Smith J, Herbison P, Mørkved S. Physical therapies for prevention of urinary and faecal incontinence in adults. Cochrane Database Syst Rev 2002;(2)(2):CD003191.

171. Wilson PD, Al Samarrai T, Deakin M, Kolbe E, Brown AD. An objective assessment of physiotherapy for female genuine stress incontinence. Br J Obstet Gynaecol 1987 Jun;94(6):575-582.

172. Tejero Sanchez M, Marco E, Boza R, Selva F, Piqueras M, Guillen A, et al. Stress urinary incontinence and pelvic floor muscle exercises: Effectiveness two different training intensive versus home instruccitions. Trauma 2008 July/September 2008;19(3):171-177.

173. Schmidt AP, Sanches PR, Silva DP,Jr, Ramos JG, Nohama P. A new pelvic muscle trainer for the treatment of urinary incontinence. Int J Gynaecol Obstet 2009 Jun;105(3):218-222.

174. Herderschee R, Hay-Smith EJ, Herbison GP, Roovers JP, Heineman MJ. Feedback or biofeedback to augment pelvic floor muscle training for urinary incontinence in women. Cochrane Database Syst Rev 2011 Jul 6;(7)(7):CD009252.

175. Haken J, Benness C, Cardozo L, Cutner A. A randomised trial of vaginal cones and pelvic floor exercises in the management of genuine stress incontinence. Neurourol Urodyn 1991;10(4):393-394.

176. Jeyaseelan SM, Haslam J, Oldham JA. Can the effects of pelvic floor muscle exercises be enhanced with a new pattern of electrical stimulation in women with stress incontinence? Pilot data. [Abstract 135]. Neurourol Urodyn 2002;21:66-67.

177. Tapp AJS, Hills B, Cardozo LD. Randomised study com-

paring pelvic floor physiotherapy with the burch colposuspension. Neurourol Urodyn 1989;8(4):356-357.

178. Laycock J, Jerwood D. Does pre-modulated interferential therapy cure genuine stress incontinence?. Physiotherapy 1993 1993;79(8):553-560.

179. Arvonen T, Fianu-Jonasson A, Tyni-Lenne R. Effectiveness of two conservative modes of physical therapy in women with urinary stress incontinence. Neurourol Urodyn 2001;20(5):591-599.

180. Cammu H, Van Nylen M. Pelvic floor exercises versus vaginal weight cones in genuine stress incontinence. Eur J Obstet Gynecol Reprod Biol 1998 Mar;77(1):89-93.

181. Gameiro MO, Moreira EH, Gameiro FO, Moreno JC, Padovani CR, Amaro JL. Vaginal weight cone versus assisted pelvic floor muscle training in the treatment of female urinary incontinence. A prospective, single-blind, randomized trial. Int Urogynecol J Pelvic Floor Dysfunct 2010 April 2010;21(4):395-399.

182. Peattie AB, Plevnick S. Cones versus physiotherapy as conservative management of genuine stress incontinence [Abstract 72]. Neurourol Urodyn 1988;7(3):255-256.

183. Arvonen T, Fianu-Jonasson A, Tyni-Lenne R. A clinical trial comparing conventional PF training and training with vaginal balls in women with stress urinary incontinence- a pilot study. Nordisk fysioterapi 2002;6:41-46.

184. Hahn I, Sommar S, Fall M. A comparative study of pelvic floor training and electrical stimulation for the treatment of genuine female stress urinary incontinence. Neurourol Urodyn 1991 1991;10(6):545-554.

185. Laycock J. Interferential therapy in the treatment of genuine stress incontinence. Neurourol Urodyn 1988;7(3):268-269.

186. (186) Sprujit J, Vierhout M, Verstraeten R, Janssens J, Burger C. Vaginal electrical stimulation of the pelvic floor: A randomized feasibility study in urinary incontinent elderly women. Acta Obstet Gynecol Scand 2003;82(11):1043-1048.

187. Smith JJ,3rd. Intravaginal stimulation randomized trial. J Urol 1996 Jan;155(1):127-130.

188. Arruda RM, Castro RA, Sousa GC, Sartori MG, Baracat EC, Girao MJ. Prospective randomized comparison of oxybutynin, functional electrostimulation, and pelvic floor training for treatment of detrusor overactivity in women. Int Urogynecol J Pelvic Floor Dysfunct 2008 Aug;19(8):1055-1061.

189. Wyman JF, Fantl JA, McClish DK, Bump RC. Comparative efficacy of behavioral interventions in the management of female urinary incontinence. Continence Program for Women Research Group. Am J Obstet Gynecol 1998 Oct;179(4):999-1007.

190. Sherburn M, Bird M, Carey M, Bo K, Galea MP. Incontinence improves in older women after intensive pelvic floor muscle training: an assessor-blinded randomized controlled trial. Neurourol Urodyn 2011 Mar;30(3):317-324.

191. Ishiko O, Ushiroyama T, Saji F, Mitsuhashi Y, Tamura T, Yamamoto K, et al. beta2-Adrenergic agonists and pelvic floor exercises for female stress incontinence. International Journal of Gynecology and Obstetrics 2000 2000;71(1):39-44.

192. Wells TJ, Brink CA, Diokno AC, Wolfe R, Gillis GL. Pelvic muscle exercise for stress urinary incontinence in elderly women. J Am Geriatr Soc 1991 Aug;39(8):785-791.

193. Kafri R, Langer R, Dvir Z, Katz-Leurer M. Rehabilitation vs drug therapy for urge urinary incontinence: short-term outcome. Int Urogynecol J Pelvic Floor Dysfunct 2007 Apr;18(4):407-411.

194. Klarskov P, Gerstenberg TC, Hald T. Bladder training and terodiline in females with idiopathic urge incontinence and stable detrusor function. Scand J Urol Nephrol 1986;20(1):41-46.

195. Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. Obstet Gynecol Clin North Am 1998 Dec;25(4):723-746.

196. Oldham JA, inventor. AnonymousInternational patent. WO97/47357. 1997 .

197. Klarskov P, Belving D, Bischoff N, Dorph S, Gerstenberg T, Okholm B, et al. Pelvic floor exercise versus surgery for female urinary stress incontinence. Urol Int 1986;41(2):129-132.

198. Jeyaseelan SM, Haslam EJ, Winstanley J, Roe BH, Oldham JA. An evaluation of a new pattern of electrical stimulation as a treatment for urinary stress incontinence: a randomized, double-blind, controlled trial. Clin Rehabil 2000 Dec;14(6):631-640.

199. Millard RJ, Asia Pacific Tolterodine Study Group. Clinical efficacy of tolterodine with or without a simplified pelvic floor exercise regimen. Neurourol Urodyn 2004;23(1):48-53.

200. The efficacy and user friendliness of the urethral occlusive device. International Continence Society; 1997.

201. Wise BG, Haken J, Cardozo LD, Plevnick S. A comparative study of vaginal cone therapy, cones and Kegel exercises and maximal electrical stimulation in the treatment of female genuine stress incontinence. Neurourol Urodyn 1993;12(4):436-437.

202. Burgio KL, Goode PS, Richter HE, Markland AD, Johnson II TM, Redden DT. Combined behavioral and individualized drug therapy versus individualized drug therapy alone for urge urinary incontinence in women. J Urol 2010 2010;184(2):598-603.

203. Burgio KL, Kraus SR, Menefee S, Borello-France D, Corton M, Johnson HW, et al. Behavioral therapy to enable women with urge incontinence to discontinue drug treatment: A randomized trial. Ann Intern Med 2008 05 Aug 2008;149(3):161-169.

204. Lin LS, Song YF, Song J, Chen MF. A clinical study of pelvic floor electrical stimulation in treatment of overactive bladder. Zhonghua Fu Chan Ke Za Zhi 2004 Dec;39(12):801-803.

205. Burgio KL, Goode PS, Locher JL, Richter HE, Roth DL, Wright KC, et al. Predictors of outcome in the behavioral treatment of urinary incontinence in women. Obstet Gynecol 2003 Nov;102(5 Pt 1):940-947.

206. Bø K, Larsen S. Pelvic floor muscle exercise for the treatment of female stress urinary incontinence: Classification and characterization of responders. Neurourol Urodyn 1992;11(5):497-507.

207. Theofrastous JP, Wyman JF, Bump RC, McClish DK, Elser DM, Bland DR, et al. Effects of pelvic floor muscle training on strength and predictors of response in the treatment of urinary incontinence. Neurourol Urodyn 2002;21(5):486-490.

208. Yoo EH, Kim YM, Kim D. Factors predicting the response to biofeedback-assisted pelvic floor muscle training for urinary incontinence. Int J Gynaecol Obstet 2011 Mar;112(3):179-181.

209. Plevnik S. New method for testing and strengthening of pelvic floor muscles. In proceedings of 15th Annual General Meeting. International Continence Society; London, England 1985:267-268.

210. Overgård M, Angelsen A, Lydersen S, Morkved S. Does Physiotherapist-Guided Pelvic Floor Muscle Training Reduce Urinary Incontinence After Radical Prostatectomy?. A Randomised Controlled Trial. Eur Urol 2008 August 2008;54(2):438-448.

211. Hahn I, Milsom I, Ohlsson BL, Ekelund P, Uhlemann C, Fall M. Comparative assessment of pelvic floor function using vaginal cones, vaginal digital palpation and vaginal pressure measurements. Gynecol Obstet Invest 1996;41(4):269-274.

212. Harvey MA. Pelvic floor exercises during and after pregnancy: a systematic review of their role in preventing

pelvic floor dysfunction. J Obstet Gynaecol Can 2003 Jun;25(6):487-498.

213. Herbison GP, Dean N. Weighted vaginal cones for urinary incontinence. Cochrane Database of Systematic Reviews 2009;1.

214. Delneri C, Di Benedetto P. Pelvic floor rehabilitation. A comparison of two methods of treatment: Vaginal cones versus functional electrical stimulation. Europa Medicophysica 2000 2000;36(1):45-48.

215. Olah KS, Bridges N, Denning J, Farrar DJ. The conservative management of patients with symptoms of stress incontinence: a randomized, prospective study comparing weighted vaginal cones and interferential therapy. Am J Obstet Gynecol 1990 Jan;162(1):87-92.

216. Pieber D, Zivkovic F, Tamussino K, Ralph G, Lippitt G, Fauland B. Pelvic floor exercise alone or with vaginal cones for the treatment of mild to moderate stress urinary incontinence in premenopausal women. Int Urogynecol J Pelvic Floor Dysfunct 1995 1995;6(1):14-17.

217. Brubaker L. Electrical stimulation in overactive bladder. Urology 2000 May;55(5A Suppl):17-23; discussion 31-2.

218. Knight S, Laycock J, Naylor D. Evaluation of neuromuscular electrical stimulation in the treatment of genuine stress incontinence. Physiotherapy 1998 Feb 1998;84(2):61-71.

219. Imamura M, Abrams P, Bain C, Buckley B, Cardozo L, Cody J, et al. Systematic review and economic modelling of the effectiveness and cost-effectiveness of non-surgical treatments for women with stress urinary incontinence. Health Technol Assess 2010;14(40):1-506.

220. Grant AM, Cody DJ, Glazener CMA, Hay-Smith J, Herbison P, Lapitan MC, et al. Cochrane Incontinence Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2007;Issue 4:Art. No.: INCONT.

221. Soomro NA, Khadra MH, Robson W, Neal DE. A crossover randomized trial of transcutaneous electrical nerve stimulation and oxybutynin in patients with detrusor instability. J Urol 2001 Jul;166(1):146-149.

222. Yamanishi T, Yasuda K, Sakakibara R, Hattori T, Suda S. Randomized, double-blind study of electrical stimulation for urinary incontinence due to detrusor overactivity. Urology 2000 Mar;55(3):353-357.

223. Yamanishi T, Sakakibara R, Uchiyama T, Suda S, Hattori T, Ito H, et al. Comparative study of the effects of magnetic versus electrical stimulation on inhibition of detrusor overactivity. Urology 2000 Nov 1;56(5):777-781.

224. Berghmans B, van Waalwijk van Doorn E, Nieman F, de Bie R, van den Brandt P, Van Kerrebroeck P. Efficacy of physical therapeutic modalities in women with proven bladder overactivity. Eur Urol 2002 Jun;41(6):581-587.

225. Wang AC, Chih SY, Chen MC. Comparison of electric stimulation and oxybutynin chloride in management of overactive bladder with special reference to urinary urgency: a randomized placebo-controlled trial. Urology 2006 Nov;68(5):999-1004.

226. Bower WF, Moore KH, Adams RD, Shepherd R. A urodynamic study of surface neuromodulation versus sham in detrusor instability and sensory urgency. J Urol 1998 Dec;160(6 Pt 1):2133-2136.

227. Brubaker L, Benson JT, Bent A, Clark A, Shott S. Transvaginal electrical stimulation for female urinary incontinence. Am J Obstet Gynecol 1997 Sep;177(3):536-540.

228. Luber KM, Wolde-Tsadik G. Efficacy of functional electrical stimulation in treating genuine stress incontinence: a randomized clinical trial. Neurourol Urodyn 1997;16(6):543-551.

229. Barroso JC, Ramos JG, Martins-Costa S, Sanches PR, Muller AF. Transvaginal electrical stimulation in the treatment of urinary incontinence. BJU Int 2004 Feb;93(3):319-323.

230. Sand PK, Richardson DA, Staskin DR, Swift SE, Appell RA, Whitmore KE, et al. Pelvic floor electrical stimulation in the treatment of genuine stress incontinence: a multicenter, placebo-controlled trial. Am J Obstet Gynecol 1995 Jul;173(1):72-79.

231. Amaro JL, Gameiro MO, Kawano PR, Padovani CR. Intravaginal electrical stimulation: a randomized, double-blind study on the treatment of mixed urinary incontinence. Acta Obstet Gynecol Scand 2006;85(5):619-622.

232. Abel I. Elektrostimulation og lokal ostrogenterapi til behandling af urininkontinens hos postmenopausale kvinder. 1997.

233. Lobel RW, Sasso KM, Sand PK. Prospective, randomized trial of maximal electrical stimulation for treatment of detrusor instability. Neurourol Urodyn 1998;17(4):abstract 185.

234. Blowman C, Pickles C, Emery S, Creates V, Towell L, Blackburn N, et al. Prospective double blind controlled trial of intensive physiotherapy with and without stimulation of the pelvic floor in treatment of genuine stress incontinence. Physiotherapy 1991 1991;77(10):661-664.

235. Eyjolfsdottir H, Ragnarsdottir M, Geirsson G. Pelvic floor muscle training with and without functional electrical stimulation as treatment for stress urinary incontinence. Laeknabladid 2009 Sep 2009;95(9):575-580; quiz 581.

236. Haig L, Mantle J, Vergi E. Does interferential therapy (IFT) confer added benefit over a pelvic floor muscle exercise programme (PFMEP) for genuine stress incontinence (GSI)? Proceedings of the International Continence Society 1995;17-20 October:abstract 111.

237. Lo SK, Naidu J, Cao Y. Additive effect of interferential therapy over pelvic floor exercise alone in the treatment of female urinary stress and urge incontinence: a randomized controlled trial. Hong Kong Physiotherapy Journal 2003;21(1):37-42.

238. The role of physiotherapy in the treatment of genuine stress incontinence. ; 2-5 September; ; 1987.

239. Indrekvam S, Sandvik H, Hunskaar S. A Norwegian national cohort of 3198 women treated with home-managed electrical stimulation for urinary incontinence--effectiveness and treatment results. Scand J Urol Nephrol 2001 Feb;35(1):32-39.

240. Moore KN. Treatment of urinary incontinence in men with electrical stimulation: is practice evidence-based? Journal of Wound, Ostomy, & Continence Nursing. 2000;27(1Review):20-31.

241. Godec C, Cass AS, Ayala GF. Electrical stimulation for incontinence. Technique, selection, and results. Urology 1976 Apr;7(4):388-397.

242. Yamanishi T, Yasuda K. Electrical stimulation for stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1998;9(5):281-290.

243. Sand P, Appell R, Bavendam T, Whitmore K, Carlan S. Factors influencing success with extracorporeal magnetic innervation (ExMI) treatment of mixed urinary incontinence. International Bladder Symposium 1999;Washington, D.C.

244. Barker AT, Freeston IL, Jalinous R, Jarratt JA. Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation. Neurosurgery 1987 Jan;20(1):100-109.

245. Galloway NT, El-Galley RE, Sand PK, Appell RA, Russell HW, Carlan SJ. Extracorporeal magnetic innervation therapy for stress urinary incontinence. Urology 1999 Jun;53(6):1108-1111.

246. Goldberg RP, Sand PK. Electromagnetic pelvic floor stimulation: applications for the gynecologist. Obstet Gynecol Surv 2000 Nov;55(11):715-720.

247. But I. Conservative treatment of female urinary incontinence with functional magnetic stimulation. Urology 2003 Mar;61(3):558-561.

248. Quek P. A critical review on magnetic stimulation: what is its role in the management of pelvic floor disorders? Curr Opin Urol 2005 Jul;15(4):231-235.

249. Craggs MD, Sheriff MKM, Shah PJR, Fowler CJ, Petersen T. Response to multi-pulse magnetic stimulation of spinal nerve roots mapped over the sacrum in man. J Physiol 1995;483:127.

250. Kralj B. Conservative treatment of female stress urinary incontinence with functional electrical stimulation. Eur J Obstet Gynecol Reprod Biol 1999 Jul;85(1):53-56.

251. Lindstrom S, Fall M, Carlsson CA, Erlandson BE. The neurophysiological basis of bladder inhibition in response to intravaginal electrical stimulation. J Urol 1983 Feb;129(2):405-410.

252. Suzuki T, Yasuda K, Yamanishi T, Kitahara S, Nakai H, Yamashita T, et al. A cross-over study for evaluation of functional continuous magnetic stimulation (FCMS) in patients with urinary incontinence on pelvic floor muscle exercise (PFME). Neurourol Urodyn 2004;23(5-6):574-575.

253. Yamanishi T, Suzuki T, Yasuda K, Kitahara S, Yoshida KI. Randomised sham-controlled evaluation of functional continuous magnetic stimulation with pelvic floor muscle training in patients with urinary incontinence. European Urology Supplements 2006;5(2):156.

254. Gilling PJ, Kennett KM, Bell D, Fraundorfer M. Extracorporeal magnetic stimulation versus sham treatment for female genuine stress urinary incontinence: randomised trial. Aus 2002;72:A143.

255. Gilling P, Kennett K, Bell D, Wrigley T, Fraundorfer M. A double blind randomised trial comparing magnetic stimulation of the pelvic floor to sham treatment for women with stress urinary incontinence. Proceedings of the International Continence Society 2001:18-21 September.

256. Gilling PJ, Wilson LC, Westenberg AM, McAllister WJ, Kennett KM, Frampton CM, et al. A double-blind randomized controlled trial of electromagnetic stimulation of the pelvic floor vs sham therapy in the treatment of women with stress urinary incontinence. BJU Int 2009 May;103(10):1386-1390.

257. But I, Faganelj M, Sostaric A. Functional magnetic stimulation for mixed urinary incontinence. J Urol 2005 May;173(5):1644-1646.

258. O'Reilly BA, Fynes M, Achtari C, Hiscock R, Thomas E, Murray C, et al. A prospective randomised double-blind controlled trial evaluating the effect of trans-sacral magnetic stimulation in women with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct 2008 Apr 2008;19(4):497-502.

259. Morris AR, O'Sullivan R, Dunkley P, Moore KH. Extracorporeal magnetic stimulation is of limited clinical benefit to women with idiopathic detrusor overactivity: a randomized sham controlled trial. Eur Urol 2007 Sep;52(3):876-881.

260. Fujishiro T, Takahashi S, Enomoto H, Ugawa Y, Ueno S, Kitamura T. Magnetic stimulation of the sacral roots for the treatment of urinary frequency and urge incontinence: an investigational study and placebo controlled trial. J Urol 2002 Sep;168(3):1036-1039.

261. Fujishiro T, Enomoto H, Ugawa Y, Takahashi S, Ueno S, Kitamura T. Magnetic stimulation of the sacral roots for the treatment of stress incontinence: an investigational study and placebo controlled trial. J Urol 2000 Oct;164(4):1277-1279.

262. Manganotti P, Zaina F, Vedovi E, Pistoia L, Rubilotta E, D'Amico A, et al. Repetitive magnetic stimulation of the sacral roots for the treatment of stress incontinence: a brief report. Europa medicophysica 2007 Sep;43(3):339-344.

263. Suzuki T, Yasuda K, Yamanishi T, Kitahara S, Nakai H, Suda S, et al. Randomized, double-blind, sham-controlled evaluation of the effect of functional continuous magnetic stimulation in patients with urgency incontinence. Neurourol Urodyn 2007;26(6):767-772.

264. Lee JS, Hong JY, Kim MH, Seo JT. Comparative study of the pelvic floor magnetic stimulation with Biocon-2000 in female urinary incontinence patients. Korean Journal of Urology 2004;45(5):438-443.

265. Brodak PP, Bidair M, Joseph A, Szollar S, Juma S. Magnetic stimulation of the sacral roots. Neurourol Urodyn 1993;12(6):533-540.

266. Hadley EC. Bladder training and related therapies for urinary incontinence in older people. JAMA 1986 Jul 18;256(3):372-379.

267. Wyman JF, Fantl JA. Bladder training in ambulatory care management of urinary incontinence. Urologic Nursing 1991;11(3Sep Journal Article Forms Tables/Charts Teaching Materials):11-17.

268. Fantl JA, Wyman JF, McClish DK, Harkins SW, Elswick RK, Taylor JR, et al. Efficacy of bladder training in older women with urinary incontinence. JAMA 1991 Feb 6;265(5):609-613.

269. Wallace SA, Roe B, Williams K, Palmer M. Bladder training for urinary incontinence in adults. Cochrane Database of Systematic Reviews 2010;10.

270. Fantl JA, Newman DK, Colling JC, DeLancey JO, Kees C, Loughery R. Urinary incontinence in adults: acute and chronic management. Clinical Practice Guideline, no.2, 1996 Update. 1996.

271. Wyman JF. Treatment of urinary incontinence in men and older women: the evidence shows the efficacy of a variety of techniques. AJN, American Journal of Nursing 2003;Suppl33-5 2003 Mar Journal Article Ceu Exam Questions Review Tables/Charts:26-31.

272. Burgio KL, Stutzman RE, Engel BT. Behavioral training for post-prostatectomy urinary incontinence. J Urol 1989 Feb;141(2):303-306.

273. Ostaszkiewicz J, Johnston L, Roe B. Timed voiding for the management of urinary incontinence in adults. Cochrane Database of Systematic Reviews 2010;11.

274. Colling J, Owen TR, McCreedy M, Newman D. The effects of a continence program on frail community-dwelling elderly persons. Urol Nurs 2003 Apr;23(2):117-22, 127-31.

275. Ostaszkiewicz J, Chestney T, Roe B. Habit retraining for the management of urinary incontinence in adults. Cochrane Database of Systematic Reviews 2009;1.

276. Colling J, Ouslander J, Hadley BJ, Eisch J, Campbell E. The effects of patterned urge-response toileting (PURT) on urinary incontinence among nursing home residents. J Am Geriatr Soc 1992 Feb;40(2):135-141.

277. Jirovec MM, Templin T. Predicting success using individualized scheduled toileting for memory-impaired elders at home. Res Nurs Health 2001 Feb;24(1):1-8.

278. Nikoletti S, Young J, King M. Evaluation of an electronic monitoring device for urinary incontinence in elderly patients in an acute care setting. J Wound Ostomy Continence Nurs 2004 May-Jun;31(3):138-149.

279. Eustice S, Roe B, Paterson J. Prompted voiding for the management of urinary incontinence in adults. Cochrane Database of Systematic Reviews 2009;1.

280. Berghmans LC, Hendriks HJ, De Bie RA, van Waalwijk van Doorn ES, Bo K, van Kerrebroeck PE. Conservative treatment of urge urinary incontinence in women: a systematic review of randomized clinical trials. BJU Int 2000 Feb;85(3):254-263.

281. Park JT, Song C, Choo M. The effects of bladder training, tolterodine, and bladder training with tolterodine in female patients with overactive bladddder: prospective, randomized study. Neurourol Urodyn 2002;21(4):434-435.

282. Szonyi G, Collas DM, Ding YY, Malone-Lee JG. Oxybutynin with bladder retraining for detrusor instability in elderly people: A randomized controlled trial. Age & Ageing 1995;24(4Using Smart Source Parsing (pp English):287-291.

283. Wiseman PA, Malone-Lee J, Rai GS. Terodiline with bladder retraining for treating detrusor instability in elderly people. BMJ 1991 Apr 27;302(6783):994-996.

284. Jarvis GJ. A controlled trial of bladder drill and drug therapy in the management of detrusor instability. Br J Urol 1981 Dec;53(6):565-566.

285. Jarvis GJ, Millar DR. Controlled trial of bladder drill for detrusor instability. Br Med J 1980 Nov 15;281(6251):1322-1323.

286. Mattiasson A, Blaakaer J, Hoye K, Wein AJ, Tolterodine Scandinavian Study Group. Simplified bladder training augments the effectiveness of tolterodine in patients with an overactive bladder. BJU Int 2003 Jan;91(1):54-60.

287. Mattiasson A, Masala A, Morton R, Bolodeoku J. Efficacy of simplified bladder training in patients with overactive bladder receiving a solifenacin flexible-dose regimen: Results from a randomized study. BJU Int 2010 April 2010;105(8):1126-1135.

288. Diokno AC, Ocampo MS,Jr, Ibrahim IA, Karl CR, Lajiness MJ, Hall SA. Group session teaching of behavioral modification program (BMP) for urinary incontinence: a randomized controlled trial among incontinent women. Int Urol Nephrol 2010 Jun;42(2):375-381.

289. Dougherty MC, Dwyer JW, Pendergast JF, Boyington AR, Tomlinson BU, Coward RT, et al. A randomized trial of behavioral management for continence with older rural women. Res Nurs Health 2002 Feb;25(1):3-13.

290. Dougherty MC, Dwyer JW, Pendergast JF, Tomlinson BU, Boyington AR, Vogel WB, et al. Community-based nursing: continence care for older rural women. Nurs Outlook 1998 Sep-Oct;46(5):233-244.

291. Lagro-Janssen AL, Debruyne FM, Smits AJ, van Weel C. The effects of treatment of urinary incontinence in general practice. Family Practice. 1992;9(3):284-289.

292. Colombo M, Zanetta G, Scalambrino S, Milani R. Oxybutynin and bladder training in the management of female urinary urge incontinence: A randomized study. Int Urogynecol J Pelvic Floor Dysfunct 1995 1995;6(2):63-67.

293. Castleden CM, Duffin HM, Gulati RS. Double-blind study of imipramine and placebo for incontinence due to bladder instability. Age Ageing 1986 Sep;15(5):299-303.

294. McClish DK, Fantl JA, Wyman JF, Pisani G, Bump RC. Bladder training in older women with urinary incontinence: relationship between outcome and changes in urodynamic observations. Obstet Gynecol 1991 Feb;77(2):281-286.

295. Godec CJ. «Timed voiding»--a useful tool in the treatment of urinary incontinence. Urology 1984 Jan;23(1):97-100.

296. Hagen S, Stark D. Conservative prevention and management of pelvic organ prolapse in women. Cochrane Database Syst Rev 2011 Dec 7;12:CD003882.

297. Adams E, Thomson A, Maher C, Hagen S. Mechanical devices for pelvic organ prolapse in women. Cochrane Database Syst Rev 2004;(2)(2):CD004010.

298. Miedel A, Tegerstedt G, Maehle-Schmidt M, Nyren O, Hammarstrom M. Nonobstetric risk factors for symptomatic pelvic organ prolapse. Obstet Gynecol 2009 May;113(5):1089-1097.

299. Slieker-ten Hove MC, Pool-Goudzwaard AL, Eijkemans MJ, Steegers-Theunissen RP, Burger CW, Vierhout ME. Symptomatic pelvic organ prolapse and possible risk factors in a general population. Am J Obstet Gynecol 2009 Feb;200(2):184.e1-184.e7.

300. Slieker-ten Hove MC, Pool-Goudzwaard AL, Eijkemans MJ, Steegers-Theunissen RP, Burger CW, Vierhout ME. Prediction model and prognostic index to estimate clinically relevant pelvic organ prolapse in a general female population. Int Urogynecol J Pelvic Floor Dysfunct 2009 Sep;20(9):1013-1021.

301. Slieker-ten Hove MC, Pool-Goudzwaard AL, Eijkemans MJ, Steegers-Theunissen RP, Burger CW, Vierhout ME. The prevalence of pelvic organ prolapse symptoms and signs and their relation with bladder and bowel disorders in a general female population. Int Urogynecol J Pelvic Floor Dysfunct 2009 Sep;20(9):1037-1045.

302. Slieker-ten Hove M, Pool-Goudzwaard A, Eijkemans M, Steegers-Theunissen R, Burger C, Vierhout M. Pelvic floor muscle function in a general population of women with and without pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2010 Mar;21(3):311-319.

303. Braekken IH, Majida M, Ellström Engh M, Holme IM, Bø K. Pelvic floor function is independently associated with pelvic organ prolapse. BJOG 2009 12;116(13):1706-1714.

304. Whitcomb EL, Lukacz ES, Lawrence JM, Nager CW, Luber KM. Prevalence and degree of bother from pelvic floor disorders in obese women. Int Urogynecol J Pelvic Floor Dysfunct 2009 03;20(3):289-294.

305. Washington BB, Erekson EA, Kassis NC, Myers DL. The association between obesity and stage II or greater prolapse. Am J Obstet Gynecol 2010 May;202(5):503.e1-503.e4.

306. Braekken IH, Majida M, Engh ME, Bø K. Can pelvic floor muscle training reverse pelvic organ prolapse and reduce prolapse symptoms? An assessor-blinded, randomized, controlled trial. Am J Obstet Gynecol 2010 Aug;203(2):170.e1-170.e7.

307. Wang J, Varma MG, Creasman JM, Subak LL, Brown JS, Thom DH, et al. Pelvic floor disorders and quality of life in women with self-reported irritable bowel syndrome. Aliment Pharmacol Ther 2010 Feb 1;31(3):424-431.

308. Saks EK, Harvie HS, Asfaw TS, Arya LA. Clinical significance of obstructive defecatory symptoms in women with pelvic organ prolapse. Int J Gynaecol Obstet 2010 Dec;111(3):237-240.

309. Scherf C, Morison L, Fiander A, Ekpo G, Walraven G. Epidemiology of pelvic organ prolapse in rural Gambia, West Africa. BJOG 2002 Apr;109(4):431-436.

310. Badalian SS, Rosenbaum PF. Vitamin D and pelvic floor disorders in women: results from the National Health and Nutrition Examination Survey. Obstet Gynecol 2010 Apr;115(4):795-803.

311. Hagen S, Stark D, Cattermole D. A United Kingdom-wide survey of physiotherapy practice in the treatment of pelvic organ prolapse. Physiotherapy 2004 3;90(1):19-26.

312. Bump RC, Hurt WG, Fantl JA, Wyman JF. Assessment of Kegel pelvic muscle exercise performance after brief verbal instruction. Am J Obstet Gynecol 1991 Aug;165(2):322-7; discussion 327-9.

313. Poma PA. Nonsurgical management of genital prolapse. A review and recommendations for clinical practice. Journal of Reproductive Medicine. 2000;45(10Review):789-797.

314. Thakar R, Stanton S. Management of genital prolapse. BMJ 2002 May 25;324(7348):1258-1262.

315. Doshani A, Teo RE, Mayne CJ, Tincello DG. Uterine prolapse. BMJ 2007 Oct 20;335(7624):819-823.

316. Moen MD, Noone MB, Vassallo BJ, Elser DM, Urogynecology N. Pelvic floor muscle function in women presenting with pelvic floor disorders. Int Urogynecol J Pelvic Floor Dysfunct 2009 Jul;20(7):843-846.

317. Braekken IH, Majida M, Engh ME, Bø K. Morphological changes after pelvic floor muscle training measured by 3-dimensional ultrasonography: A randomized controlled trial. Obstet Gynecol 2010;115(2 PART 1) (pp 317-324):ate of Pubaton: February 2010.

318. Stupp L, Resende AP, Oliveira E, Castro RA, Girao MJ, Sartori MG. Pelvic floor muscle training for treatment of pelvic organ prolapse: an assessor-blinded randomized controlled trial. Int Urogynecol J 2011 Oct;22(10):1233-1239.

319. Barber MD, Brubaker L, Menefee S, Norton P, Borello-France D, Varner E, et al. Operations and pelvic muscle training in the management of apical support loss (OPTIMAL) trial: design and methods. Contemporary clinical trials 2009 Mar;30(2):178-189.

320. Zeitlin MP, Lebherz TB. Pessaries in the geriatric patient. J Am Geriatr Soc 1992 Jun;40(6):635-639.

321. Baydock SA, Farrell SA. Selection of pessaries for pelvic organ prolapse. In: Farrell SA, editor. Pessaries in clinical practice London: Springer-Verlag; 2006. p. 32-45.

322. Oliver R, Thakar R, Sultan AH. The history and usage of the vaginal pessary: a review. Eur J Obstet Gynecol Reprod Biol 2011 Jun;156(2):125-130.

323. Clemons JL, Aguilar VC, Tillinghast TA, Jackson ND, Myers DL. Patient satisfaction and changes in prolapse and urinary symptoms in women who were fitted successfully with a pessary for pelvic organ prolapse. Am J Obstet Gynecol 2004 Apr;190(4):1025-1029.

324. Clemons JL, Aguilar VC, Sokol ER, Jackson ND, Myers DL. Patient characteristics that are associated with continued pessary use versus surgery after 1 year. Am J Obstet Gynecol 2004 Jul;191(1):159-164.

325. Cundiff GW, Amundsen CL, Bent AE, Coates KW, Schaffer JI, Strohbehn K, et al. The PESSRI study: symptom relief outcomes of a randomized crossover trial of the ring and Gellhorn pessaries. Am J Obstet Gynecol 2007 Apr;196(4):405.e1-405.e8.

326. Cundiff GW, Weidner AC, Visco AG, Bump RC, Addison WA. A survey of pessary use by members of the American urogynecologic society. Obstet Gynecol 2000 Jun;95(6 Pt 1):931-935.

327. Gorti M, Hudelist G, Simons A. Evaluation of vaginal pessary management: a UK-based survey. J Obstet Gynaecol 2009 Feb;29(2):129-131.

328. Pott-Grinstein E, Newcomer JR. Gynecologists' patterns of prescribing pessaries. J Reprod Med 2001 Mar;46(3):205-208.

329. Kapoor DS, Thakar R, Sultan AH, Oliver R. Conservative versus surgical management of prolapse: what dictates patient choice?. Int Urogynecol J Pelvic Floor Dysfunct 2009 Oct;20(10):1157-1161.

330. Abdool Z, Thakar R, Sultan AH, Oliver RS. Prospective evaluation of outcome of vaginal pessaries versus surgery in women with symptomatic pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2011 Mar;22(3):273-278.

331. Powers K, Lazarou G, Wang A, LaCombe J, Bensinger G, Greston WM, et al. Pessary use in advanced pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2006 Feb 2006;17(2):160-164.

332. Heit M, Rosenquist C, Culligan P, Graham C, Murphy M, Shott S. Predicting treatment choice for patients with pelvic organ prolapse. Obstet Gynecol 2003 01 Jun 2003;101(6):1279-1284.

333. Brincat C, Kenton K, Pat Fitzgerald M, Brubaker L. Sexual activity predicts continued pessary use. Am J Obstet Gynecol 2004 Jul;191(1):198-200.

334. Ko PC, Lo TS, Tseng LH, Lin YH, Liang CC, Lee SJ. Use of a pessary in treatment of pelvic organ prolapse: quality of life, compliance, and failure at 1-year follow-up. J Minim Invasive Gynecol 2011 Jan-Feb;18(1):68-74.

335. Harnsomboon T, Manonai J, Sarit-Apirak S, Wattanayingcharoenchai R, Chittacharoen A, Sututvoravut S. Effect of colpexin sphere on pelvic floor muscle strength in women with pelvic organ prolapse: a randomized controlled trial (a preliminary report). Arch Gynecol Obstet 2011 Mar;283(3):575-579.

336. Wu V, Farrell SA, Baskett TF, Flowerdew G. A simplified protocol for pessary management. Obstet Gynecol 1997 Dec;90(6):990-994.

337. Handa VL, Jones M. Do pessaries prevent the progression of pelvic organ prolapse? Int Urogynecol J Pelvic Floor Dysfunct 2002 Nov;13(6):349-51; discussion 352.

338. Lukban JC, Aguirre OA, Davila GW, Sand PK. Safety and effectiveness of Colpexin Sphere in the treatment of pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2006 Sep;17(5):449-454.

339. Fernando RJ, Thakar R, Sultan AH, Shah SM, Jones PW. Effect of vaginal pessaries on symptoms associated with pelvic organ prolapse. Obstet Gynecol 2006 Jul;108(1):93-99.

340. Lone F, Thakar R, Sultan AH, Karamalis G. A 5-year prospective study of vaginal pessary use for pelvic organ prolapse. Int J Gynaecol Obstet 2011 Jul;114(1):56-59.

341. Kuhn A, Bapst D, Stadlmayr W, Vits K, Mueller MD. Sexual and organ function in patients with symptomatic prolapse: are pessaries helpful?. Fertil Steril 2009 May;91(5):1914-1918.

342. Komesu YM, Rogers RG, Rode MA, Craig EC, Gallegos KA, Montoya AR, et al. Pelvic floor symptom changes in pessary users. Am J Obstet Gynecol 2007 Dec;197(6):620.e1-620.e6.

343. Barber MD, Walters MD, Cundiff GW, PESSRI Trial Group. Responsiveness of the Pelvic Floor Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ) in women undergoing vaginal surgery and pessary treatment for pelvic organ prolapse. Am J Obstet Gynecol 2006 May;194(5):1492-1498.

344. Jones K, Yang L, Lowder JL, Meyn L, Ellison R, Zyczynski HM, et al. Effect of pessary use on genital hiatus measurements in women with pelvic organ prolapse. Obstet Gynecol 2008 Sep;112(3):630-636.

345. Patel M, Mellen C, O'Sullivan D, LaSala CA. Impact of pessary use on prolapse symptoms, quality of life, and body image. Am J Obstet Gynecol 2010 05;202(5):499.e1-4.

346. Friedman S, Sandhu KS, Wang C, Mikhail MS, Banks E. Factors influencing long-term pessary use. Int Urogynecol J Pelvic Floor Dysfunct 2010 Jun;21(6):673-678.

347. Maito JM, Quam ZA, Craig E, Danner KA, Rogers RG. Predictors of successful pessary fitting and continued use in a nurse-midwifery pessary clinic. J Midwifery Womens Health 2006 Mar-Apr;51(2):78-84.

348. Mutone MF, Terry C, Hale DS, Benson JT. Factors which influence the short-term success of pessary management of pelvic organ prolapse. Am J Obstet Gynecol 2005 Jul;193(1):89-94.

349. Hanson LA, Schulz JA, Flood CG, Cooley B, Tam F. Vaginal pessaries in managing women with pelvic organ prolapse and urinary incontinence: patient characteristics and factors contributing to success. Int Urogynecol J Pelvic Floor Dysfunct 2006 Feb;17(2):155-159.

350. Manchana T. Ring pessary for all pelvic organ prolapse. Arch Gynecol Obstet 2011 Aug;284(2):391-395.

351. Sarma S, Ying T, Moore KH. Long-term vaginal ring pessary use: discontinuation rates and adverse events. BJOG 2009 Dec;116(13):1715-1721.

352. Jelovsek JE, Barber MD, Paraiso MF, Walters MD. Functional bowel and anorectal disorders in patients with pelvic organ prolapse and incontinence. Am J Obstet Gynecol 2005 Dec;193(6):2105-2111.

353. Clemons JL, Aguilar VC, Tillinghast TA, Jackson ND, Myers DL. Risk factors associated with an unsuccessful pessary fitting trial in women with pelvic organ prolapse. Am J Obstet Gynecol 2004 Feb;190(2):345-350.

354. Vierhout ME. The use of pessaries in vaginal prolapse. Eur J Obstet Gynecol Reprod Biol 2004 Nov 10;117(1):4-9.

355. Hullfish KL, Trowbridge ER, Stukenborg GJ. Treatment strategies for pelvic organ prolapse: a cost-effectiveness analysis. Int Urogynecol J 2011 May;22(5):507-515.

356. Wilson D, Hay-Smith EJ, Berghmans LC, Moore KN, Wyman JF, Yamada T. Adult Conservative Management. In: Abrams P, Cardoza L, Khoury S, Wein A, editors. Incontinence. Proceedings of the 3rd International Consultation on Incontinence. Monaco. June 26-29, 2004. Paris: Health Publication Ltd, Editions 21; 2005. p. 855-964.

357. Leach GE. Post-prostatectomy incontinence: the importance of bladder dysfunction. Journal of Urology. 1995;153(3 Pt 2):1038.

358. Post prostatectomy urinary incontinence. Proceedings of

the First International Conference for the Prevention of Incontinence, June. Marlowe, UK: Simon Foundation, USA and The Continence Foundation, UK; 1997.

359. Moore KN, Truong V, Estey E, Voaklander DC. Urinary Incontinence After Radical Prostatectomy: Can Men at Risk Be Identified Preoperatively? J Wound Ostomy Continence Nurs 2007 May/June;34(3):270-279.

360. Kondo A, Lin TL, Nordling J, Siroky M, Tammela T. Conservative management in men. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. Proceedings of 2nd International Consultation on Incontinence. Paris. July 1-3, 2001 Plymouth, UK: Health Publications Ltd 2002, Plymbrige Distribution Ltd; 2002. p. 553-569.

361. Staskin DS, Vardi Y, Siroky MB. Post-prostatectomy continence in the parkinsonian patient: The significant of poor voluntary sphincter control. J Urol 1988;140(1Using Smart Source Parsing (pp English):117-118.

362. Bales GT, Gerber GS, Minor TX, Mhoon DA, McFarland JM, Kim HL, et al. Effect of preoperative biofeedback/pelvic floor training on continence in men undergoing radical prostatectomy. Urology 2000;56(4):627-630.

363. Chang PL, Tsai LH, Huang ST, Wang TM, Hsieh ML, Tsui KH. The early effect of pelvic floor muscle exercise after transurethral prostatectomy. Journal of Urology. 1998;160(2):402-405.

364. Dorey G, Speakman M, Feneley R, Swinkels A, Dunn C, Ewings P. Pelvic floor exercises for treating post-micturition dribble in men with erectile dysfunction: a randomized controlled trial. Urol Nurs 2004 Dec;24(6):490-7, 512.

365. Floratos DL, Sonke GS, Rapidou CA, Alivizatos GJ, Deliveliotis C, Constantinides CA, et al. Biofeedback vs verbal feedback as learning tools for pelvic muscle exercises in the early management of urinary incontinence after radical prostatectomy. BJU Int 2002;89(7):714-719.

366. Franke JJ, Gilbert WB, Grier J, Koch MO, Shyr Y, Smith JA,Jr. Early post-prostatectomy pelvic floor biofeedback. J Urol 2000;163(1):191-193.

367. Joseph AC, Chang MK. Comparison of behavior therapy methods for urinary incontinence following prostate surgery: a pilot study. Urologic Nursing 2000;20(3Jun Journal Article Research):203-204.

368. Moore KN, Griffiths D, Hughton A. Urinary incontinence after radical prostatectomy: a randomized controlled trial comparing pelvic muscle exercises with or without electrical stimulation. BJU International. 1999;83(1):57-65.

369. Mathewson-Chapman M. Pelvic muscle exercise/biofeedback for urinary incontinence after prostatectomy: an education program. J Cancer Educ 1997;12(4Winter Journal Article Clinical Trial Research Tables/Charts):218-223.

370. Sueppel C, Kreder K, See W. Improved continence outcomes with preoperative pelvic floor muscle strengthening exercises. Urologic Nursing 2001;21(3Jun Journal Article Forms Research Tables/Charts):201-210.

371. Opsomer RJ, Castille Y, Abi-Add AS, Van Cangh PJ. Urinary incontinence after radical prostatectomy: is professional pelvic floor training necessary? Neurourol Urodyn 1994;13(4):382-384.

372. Parekh AR, Feng MI, Kirages D, Bremner H, Kaswick J, Aboseif S. The role of pelvic floor exercises on post-prostatectomy incontinence. J Urol 2003;170(1Using Smart Source Parsing (pp Date of Publication: 01 JUL 2003 English):130-133.

373. Porru D, Campus G, Caria A, Madeddu G, Cucchi A, Rovereto B, et al. Impact of early pelvic floor rehabilitation after transurethral resection of the prostate. Neurourology & Urodynamics 2001;20(1Using Smart Source Parsing (pp English):53-59.

374. Van Kampen M, De Weerdt W, Van Poppel H, De Ridder D, Feys H, Baert L. Effect of pelvic-floor re-education on duration and degree of incontinence after radical prostatectomy: A randomised controlled trial. Lancet 2000;355(9198):98-102.

375. Wille S, Sobottka A, Heidenreich A, Hofmann R. Pelvic floor exercises, electrical stimulation and biofeedback after radical prostatectomy: results of a prospective randomized trial. J Urol 2003;170(2 Pt 1):490-493.

376. Glazener C, Boachie C, Buckley B, Cochran C, Dorey G, Grant A, et al. Conservative treatment for urinary incontinence in Men After Prostate Surgery (MAPS): two parallel randomised controlled trials. Health Technol Assess 2011 Jun;15(24):1-296.

377. Glazener C, Boachie C, Buckley B, Cochran C, Dorey G, Grant A, et al. A randomised controlled trial of conservative treatment (pelvic floor muscle training and bladder training) for urinary incontinence in men after prostate surgery (maps). Neurourology and Urodynamics.Conference: Joint Annual Meeting of the International Continence Society, ICS and International Urogynecological Association, IUGA Toronto, ON Canada.Conference Start: 20100823 Conference End: 20100827.Conference Pub(TRUNCATED) 2010 August 2010;29(6):1093-1094.

378. Yamanishi T, Mizuno T, Watanabe M, Honda M, Yoshida K. Randomized, placebo controlled study of electrical stimulation with pelvic floor muscle training for severe urinary incontinence after radical prostatectomy. J Urol 2010 Nov;184(5):2007-2012.

379. Dubbelman Y, Groen J, Wildhagen M, Rikken B, Bosch R. The recovery of urinary continence after radical retropubic prostatectomy: a randomized trial comparing the effect of physiotherapist-guided pelvic floor muscle exercises with guidance by an instruction folder only. BJU Int 2010 Aug;106(4):515-522.

380. Goode PS, Burgio KL, Johnson TM,2nd, Clay OJ, Roth DL, Markland AD, et al. Behavioral therapy with or without biofeedback and pelvic floor electrical stimulation for persistent postprostatectomy incontinence: a randomized controlled trial. JAMA 2011 Jan 12;305(2):151-159.

381. Tibaek S, Klarskov P, Lund Hansen B, Thomsen H, Andresen H, Schmidt Jensen C, et al. Pelvic floor muscle training before transurethral resection of the prostate: a randomized, controlled, blinded study. Scand J Urol Nephrol 2007;41(4):329-334.

382. Centemero A, Rigatti L, Giraudo D, Lazzeri M, Lughezzani G, Zugna D, et al. Preoperative pelvic floor muscle exercise for early continence after radical prostatectomy: a randomised controlled study. Eur Urol 2010 Jun;57(6):1039-1043.

383. Zellner M. Incontinence after radical prostatectomy and cystectomy : Are combined training with mechanical devices and whole body vibration effective?. Urologe - Ausgabe A 2011 April 2011;50(4):433-444.

384. Mariotti G, Sciarra A, Gentilucci A, Salciccia S, Alfarone A, Di Pierro G, et al. Early recovery of urinary continence after radical prostatectomy using early pelvic floor electrical stimulation and biofeedback associated treatment. J Urol 2009 Apr;181(4):1788-1793.

385. Delmastro F, Marchisio C, Lamberti G, Giraudo D. Urinary incontinence after radical prostatectomy: a randomized controlled trial comparing preoperative intensive pelvic muscle exercises with or without proprioceptive training (Abstract). Neurourol Urodyn 2010;29(2S):62-63.

386. Sciarra A, Salciccia S, Gentilucci A, Alfarone A, Di Pierro GB, Mariotti G, et al. Early recovery of urinary continence after radical prostatectomy using early pelvic floor electric stimulation and biofeedback associated treatment. Journal of Urology.Conference: 2009 American Urological Association (AUA) Annual Meeting Chicago, IL United States.Conference Start: 20090425 Conference End: 20090430.Conference Publication: (var.pagings) 2009 April 2009;181(4 SUPPL. 1):680.

387. Marchiori D, Bertaccini A, Manferrari F, Ferri C, Martorana G. Pelvic floor rehabilitation for continence recovery after radical prostatectomy: role of a personal training re-educational program. Anticancer Res 2010 Feb;30(2):553-556.

388. Voorham - van der Zalm,P.J., Stoetman AM, Putter H, Bevers RFM, Pelger RCM. Effect of preoperative pelvic

floor physiotherapy versus standard care on incontinence in men undergoing radical laparoscopic prostatectomy: an ongoing study. (Abstract number 590). Proceedings of the Joint Meeting of the International Continence Society (ICS) and the International Urogynecological Association, August 23-27, 2010. Toronto, Canada 2010.

389. Tobia I, Gonzalez MS, Martinez P, Tejerizo JC, Gueglio G, Damia O, et al. Randomized study on urinary continence after radical prostatectomy with previous kinesic perineal physiotherapy. Arch Esp Urol 2008 Sep 2008;61(7):793-798.

390. Park S-, Park C-, Kim T-, Lee W, Nam J-, Lee S-, et al. The effects of a 12-week's combined exercise intervention on physical function and mental health after radical prostatectomy in elderly patients with prostate cancer: A prospective, randomized controlled study. Journal of Urology.Conference: 2011 Annual Meeting of the American Urological Association, AUA Washington, DC United States.Conference Start: 20110514 Conference End: 20110519.Conference Publication: (var.pagings) 2011 April 2011;185(4 SUPPL. 1):e524.

391. Zhang Z, Strauss G, Siminoff L. Effects of combined pelvic floor muscle exercises and support group on urinary incontinence and quality of life of patients with prostatectomy. Oncol Nurs Forum 2008 05;35(3):552-552.

392. Burgio KL, Goode PS, Urban DA, Umlauf MG, Locher JL, Bueschen A, et al. Preoperative biofeedback assisted behavioral training to decrease post-prostatectomy incontinence: a randomized, controlled trial. J Urol 2006 Jan;175(1):196-201; discussion 201.

393. Lilli P, Mercuriali M, Fiori M, Hanitzsch H, Gunelli R, Bercovich E. Impact of preoperative biofeedback on incontinence in cancer patients undergoing radical prostatectomy. Archivio Italiano di Urologia e Andrologia 2006 Sep;78(3):92-96.

394. Filocamo MT, Li Marzi V, Del Popolo G, Cecconi F, Marzocco M, Tosto A, et al. Effectiveness of early pelvic floor rehabilitation treatment for post-prostatectomy incontinence. Eur Urol 2005 Nov;48(5):734-738.

395. Dubbelman YD, Groen J, Bosch R. Postprostatectomy incontinence: significance of pre-operative urethral pressure profile and the role of physiotherapy. International Continence Society Annual Meeting (Abstract 52). Neurourol Urodyn 2004 August;23(5):471-472.

396. Manassero F, Traversi C, Ales V, Pistolesi D, Panicucci E, Valent F, et al. Contribution of early intensive prolonged pelvic floor exercises on urinary continence recovery after bladder neck-sparing radical prostatectomy: results of a prospective controlled randomized trial. Neurourol Urodyn 2007;26(7):985-989.

397. Ribeiro LS, Prota C, Gomes CM, Dall'Oglio MF, Bruschini H, Srougi M. Effect of early postoperative pelvic-floor biofeedback on continence on men undergoing radical prostatectomy: a randomized, controlled trial. J Urol 2008 4;179(4, Supplement 1):483-483.

398. Ribeiro LH, Prota C, Gomes CM, de Bessa J,Jr, Boldarine MP, Dall'Oglio MF, et al. Long-term effect of early postoperative pelvic floor biofeedback on continence in men undergoing radical prostatectomy: a prospective, randomized, controlled trial. J Urol 2010 Sep;184(3):1034-1039.

399. Moore KN, Valiquette L, Chetner MP, Byrniak S, Herbison GP. Return to continence after radical retropubic prostatectomy: a randomized trial of verbal and written instructions versus therapist-directed pelvic floor muscle therapy. Urology 2008 Dec;72(6):1280-1286.

400. Hoffmann W, Liedke S, Dombo O, Otto U. Die Electrostimulation in der Therapie der posopertiven Harninkontinenz. Therapeutischer Nutzen unter Berucksichtigung der Lebensqualitat [Electrical stimulation to treat postoperative incontinence: Therapeutic benefit in regard to quality of life]. Urologe 2004;44(1):33-40.

401. Yokoyama T, Nishiguchi J, Watanabe T, Nose H, Nozaki K, Fujita O, et al. Comparative study of effects of extracorporeal magnetic innervation versus electrical stimulation for urinary incontinence after radical prostatectomy. Urology 2004;63(2):264-267.

402. Paterson J, Pinnock CB, Marshall VR. Pelvic floor exercises as a treatment for post-micturition dribble. Br J Urol 1997;79(6Using Smart Source Parsing (pp English):892-897.

403. Dorey G. Conservative treatment of male urinary incontinence and erectile dysfunction : a textbook for physiotherapists, nurses and doctors. London: Whurr Publishers Ltd; 2001.

404. Yamanishi T, Yasuda K, Sakakibara R, Hattori T, Ito H, Murakami S. Pelvic floor electrical stimulation in the treatment of stress incontinence: an investigational study and a placebo controlled double-blind trial. J Urol 1997 Dec;158(6):2127-2131.

405. Yasuda K, Yamanishi T. Critical evaluation of electrostimulation for management of female urinary incontinence. Curr Opin Obstet Gynecol 1999 Oct;11(5):503-507.

406. Hu JC, Gold KF, Pashos CL, Mehta SS, Litwin MS. Temporal trends in radical prostatectomy complications from 1991 to 1998. J Urol 2003 Apr;169(4):1443-1448.

407. Palmer MH, Fogarty LA, Somerfield MR, Powel LL. Incontinence after prostatectomy: coping with incontinence after prostate cancer surgery. Oncol Nurs Forum 2003;30(2 part 1Mar-Apr Journal Article Research Tables/Charts):229-238.

408. Gacci M, Bartoletti R, Figlioli S, Sarti E, Eisner B, Boddi V, et al. Urinary symptoms, quality of life and sexual function in patients with benign prostatic hypertrophy before and after prostatectomy: a prospective study. BJU Int 2003 Feb;91(3):196-200.

409. Carlson KV, Nitti VW. Prevention and management of incontinence following radical prostatectomy. Urol Clin North Am 2001 Aug;28(3):595-612.

410. de Nunzio C, Franco G, Rocchegiani A, Iori F, Leonardo C, Laurenti C. The evolution of detrusor overactivity after watchful waiting, medical therapy and surgery in patients with bladder outlet obstruction. J Urol 2003 Feb;169(2):535-539.

411. Krauss DJ, Lilien OM. Transcutaneous electrical nerve stimulator for stress incontinence. J Urol 1981 Jun;125(6):790-793.

412. Hunter KF, Glazener CM, Moore KN. Conservative management for postprostatectomy urinary incontinence. Cochrane Database Syst Rev 2007(2):001843.

413. Salinas Casado J, Virseda Chamorro M, Salomon Mohamed S, Bravo de Rueda C, Aristizabal JM, Resel Estevez L. Results of electric stimulation in the treatment of post-prostatectomy urinary incontinence. Actas Urol Esp 1996 Jun;20(6):544-550.

414. Walsh IK, Johnston RS, Keane PF. Transcutaneous sacral neurostimulation for irritative voiding dysfunction. Eur Urol 1999;35(3):192-196.

415. Berghmans LC, Hendriks HJ, Bø K, Hay-Smith EJ, de Bie RA, van Waalwijk van Doorn ES. Conservative treatment of stress urinary incontinence in women: a systematic review of randomized clinical trials. Br J Urol 1998 Aug;82(2):181-191.

416. Campbell S, Glazener C, Hunter K, Moore KN. Conservative management for postprostatectomy urinary incontinence. Cochrane Database of Systematic Reviews 2011.

417. Ceresoli A, Kartalas Goumas J, Colombo F, Barbetti E, Dell'Aglio F, Bonacina P, et al. Daily transcutaneous electrical nerve stimulation (DTENS) after radical perineal prostatectomy: A free cost effective biofeedback technique in the treatment of post operative urinary incontinence (abstract). Proceedings of the 32nd Annual Meeting of the International Continence Society, Heidelberg, Germany 2002.

418. Primus G, Kramer G. Maximal external electrical stimu-

lation for treatment of neurogenic or non-neurogenic urgency and/or urge incontinence. Neurourol Urodyn 1996;15(3):187-194.

419. Nehra A, Rovner E, Wein A, Lange P, Ellis W, Keane T, et al. Interim analysis of a multi-center study of extracorporeal magnetic innervation (ExMI) for the treatment of urinary incontinence following radical prostatectomy. Neurourol Urodyn 2001;20(4):430-431.

420. Yamanishi T, Igarashi T, Murakami S, Murayama N, Kamura K, Yasuda K, et al. A comparative study of the effects of drug therapy and bladder training therapy. Hinyokika Kiyo 1988 Jan;34(1):102-106.

421. Sogbein SK, Awad SA. Behavioural treatment of urinary incontinence in geriatric patients. Can Med Assoc J 1982 Nov 1;127(9):863-864.

422. Honjo H, Naya Y, Ukimura O, Kojima M, Miki T. Acupuncture on clinical symptoms and urodynamic measurements in spinal-cord-injured patients with detrusor hyperreflexia. Urol Int 2000;65(4):190-195.

423. Kitakoji H, Terasaki T, Honjo H, Odahara Y, Ukimura O, Kojima M, et al. Effect of acupuncture on the overactive bladder. Nippon Hinyokika Gakkai Zasshi 1995 Oct;86(10):1514-1519.

424. Bergstrom K, Carlsson CP, Lindholm C, Widengren R. Improvement of urge- and mixed-type incontinence after acupuncture treatment among elderly women - a pilot study. J Auton Nerv Syst 2000 Mar 15;79(2-3):173-180.

425. Kubista E, Altmann P, Kucera H, Rudelstorfer B. Electroacupuncture's influence on the closure mechanism of the female urethra in incontinence. Am J Chin Med (Gard City N Y) 1976 Summer;4(2):177-181.

426. Morrison JF, Sato A, Sato Y, Suzuki A. Long-lasting facilitation and depression of periurethral skeletal muscle following acupuncture-like stimulation in anesthetized rats. Neurosci Res 1995 Sep;23(2):159-169.

427. Sato A, Sato Y, Suzuki A. Mechanism of the reflex inhibition of micturition contractions of the urinary bladder elicited by acupuncture-like stimulation in anesthetized rats. Neurosci Res 1992 Nov;15(3):189-198.

428. Akiba Y, Kashiwagi H, Sato A, Uchida S. Effects of acupuncture-like stimulation on function of the urinary bladder in anesthetized rats. J Auton Nerv Syst 1993 12;45(3):262-263.

429. Philp T, Shah PJ, Worth PH. Acupuncture in the treatment of bladder instability. Br J Urol 1988 Jun;61(6):490-493.

430. W. H. O. scientific group on international acupuncture nomenclature: Report of a WHO scientific group. 1991:10.

431. Ricci L, Minardi D, Romoli M, Galosi AB, Muzzonigro G. Acupuncture reflexotherapy in the treatment of sensory urgency that persists after transurethral resection of the prostate: a preliminary report. Neurourol Urodyn 2004;23(1):58-62.

432. Ellis N, Briggs R, Dowson D. The effect of acupuncture on nocturnal urinary frequency and incontinence in the elderly. Complementary Medical Research 1990 1990;4(1):16-17.

433. Crevenna R, Zoch C, Keilani M, Quittan M, Fialka-Moser V. Implementation of a physical rehabilitation group for post-prostatectomy urinary incontinence patients and its effects on quality of life. Physikalische Medizin Rehabilitationsmedizin Kurortmedizin 2003;13(6Using Smart Source Parsing (pp English):339-344.

434. Moher D, Schulz KF, Altman DG, Group ftC. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001;357(9263)(April 14):1191-1194.

435. Egger M, Ebrahim S, Smith GD. Where now for meta-analysis? Int J Epidemiol 2002 Feb;31(1):1-5.

436. Berghmans LCM, Nieman FHM, van Waalwijkvan ESC, van Doorn LWH, Smeets LWH, ten Haaf WMM. Effects of phsyiotherapy, using the adapted Dutch I-QoL in women with urge incontinence. Neurourology & Urodynamics 2001;20(4):509-510.

437. Ghroubi S, Kharrat O, Chaari M, Ben Ayed B, Guermazi M, Elleuch MH. [Effect of conservative treatment in the management of low-degree urogenital prolapse]. Ann Readapt Med Phys 2008 Mar;51(2):96-102.

438. Hagen S, Stark D, Glazener C, Sinclair L, Ramsay I. A randomized controlled trial of pelvic floor muscle training for stages I and II pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2009 Jan;20(1):45-51.

439. Piya-Anant M, Therasakvichya S, Leelaphatanadit C, Techatrisak K. Integrated health research program for the Thai elderly: Prevalence of genital prolapse and effectiveness of pelvic floor exercise to prevent worsening of genital prolapse in elderly women. Journal of the Medical Association of Thailand 2003 01 Jun;86(6):509-515.

Committee 13

Surgical Treatment of Urinary Incontinence in Men

Chair

Sender Herschorn, (Canada)

Members

Homero Bruschini (Brazil)

Craig Comiter (USA)

Howard B. Goldman (USA)

Philippe Grise (France)

Tomas Hanus (Czech Republic)

Christopher Woodhouse (U.K.)

CONTENTS

I. INTRODUCTION

II. EVALUATION PRIOR TO SURGICAL THERAPY

III. INCONTINENCE AFTER RADICAL PROSTATECTOMY FOR PROSTATE CANCER

1. INCIDENCE AND PREVALENCE
2. RISK FACTORS
3. PATHOPHYSIOLOGY
4. SURGICAL AND MINIMALLY INVASIVE TREATMENTS
5. TIMING OF SURGICAL INTERVENTION

IV. INCONTINENCE AFTER PROSTATECTOMY FOR BENIGN DISEASE

1. INCIDENCE AND RISK FACTORS
2. TIMING OF SURGICAL INTERVENTION
3. SURGICAL TREATMENT OPTIONS

V. INCONTINENCE AFTER EXTERNAL BEAM RADIOTHERAPY ALONE AND IN COMBINATION WITH SURGERY FOR PROSTATE CANCER

1. SURGICAL TREATMENT

VI. INCONTINENCE AFTER OTHER TREATMENT FOR PROSTATE CANCER AND NEOBLADDER FOR BLADDER CANCER

1. BRACHYTHERAPY
2. CRYOSURGICAL ABLATION OF THE PROSTATE
3. HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU)
4. INCONTINENCE AFTER NEOBLADDER CONSTRUCTION

VII. TRAUMATIC INJURIES OF THE URETHRA AND PELVIC FLOOR

VIII. CONTINUING PEDIATRIC PROBLEMS INTO ADULTHOOD: THE EXSTROPHY-EPISPADIAS COMPLEX AND OTHER CONGENITAL ANOMALIES

1. EARLY MANAGEMENT OF EXSTROPHY AND EPISPADIAS
2. LATE BLADDER FUNCTION
3. MANAGEMENT OF INCONTINENCE
4. RECOMMENDATIONS

IX. DETRUSOR OVERACTIVITY AND REDUCED BLADDER CAPACITY

1. REFRACTORY URGENCY INCONTINENCE AND IDIOPATHIC DETRUSOR OVERACTIVITY
2. REDUCED BLADDER CAPACITY

X. URETHROCUTANEOUS AND RECTOURETHRAL FISTULAE

1. URETHROCUTANEOUS FISTULA (UCF)
2. RECTOURETHRAL FISTULAS (RUF)

XI. THE ARTIFICIAL URINARY SPHINCTER (AUS)

1. AVAILABILITY AND COST
2. INDICATIONS
3. SURGICAL TECHNIQUES
4. COMPLICATIONS
5. DURABILITY OF AUS COMPONENTS
6. DIAGNOSTIC PROCEDURES RELATED TO ARTIFICIAL SPHINCTER FAILURE
7. TREATMENT OF COMPLICATIONS
8. CONSENSUS PROTOCOL FOR FOLLOW-UP OF PATIENTS WITH AUS

XII. SUMMARY AND RECOMMENDATIONS

REFERENCES

Surgical Treatment of Urinary Incontinence in Men

Sender Herschorn

Homero Bruschini, Craig Comiter, Howard B. Goldman, Philippe Grise
Tomas Hanus, Christopher Woodhouse

I. INTRODUCTION

Surgery for male incontinence is an important aspect of treatment with the changing demographics of society and the continuing large numbers of men undergoing surgery and other treatments for prostate cancer.

Basic evaluation of the patient is similar to other areas of incontinence and includes primarily a clinical approach with history, pad testing, frequency-volume chart or bladder diary, and physical examination. Since most of the surgeries apply to patients with incontinence after other operations or trauma, other investigations such as radiographic imaging of the lower urinary tract, cystoscopy, and urodynamic studies may provide important information for the treating clinician.

Although prostatectomy for benign disease has become less frequent in many countries, the complication of incontinence is a rare but unfortunate occurrence that merits treatment. After a period of conservative therapy has been tried, surgical treatment is indicated following similar strategies applied in post-prostate cancer treatment incontinence i.e. slings and artificial urinary sphincter (AUS).

Radical prostatectomy for prostate cancer is performed far more frequently now than 15 to 20 years ago, with nearly two-thirds of surgical cases being performed via the robotic-assisted laparoscopic approach in the United States [1]. Approximately 5-25% of patients will experience incontinence that fails to improve with conservative management, and a substantial minority will ultimately undergo surgical treatment [2]. The AUS has provided a satisfactory result in most cases, regardless of the degree of urinary incontinence, with a positive impact on quality of life. Sling procedures have emerged as an efficacious treatment in the majority of men with mild to moderate stress urinary incontinence, however, they have not proven predictably successful in men with higher degrees of incontinence. Injectable agents have not shown durable long-term results. Volume adjustable balloons have been limited in their utility due to a high complication rate. Newer techniques involving adjustable urethral slings have demonstrated efficacy similar to that of non-adjustable slings, with the potential advantage of postoperative alterations in sling tensioning (tightening) but a higher complication rate.

Stratification of treatment based on the degree of stress incontinence is now feasible. Men with milder degrees of incontinence and normal bladder function are candidates for either artificial urinary sphincter placement or sling surgery, each with similar success rates. Sling surgery appears to have a lower risk of surgical complications in this population. Patient preference may be for a sling versus a mechanical device [3]. On the other hand, with more severe incontinence, AUS surgery has a more predictable success profile than does sling surgery.

Incontinence following radiation therapy, cryosurgery, high-intensity focused ultrasound, other pelvic operations and trauma is a particularly challenging problem because of tissue damage inside and outside the lower urinary tract. In such instances, periurethral bulking, sling procedures, and inflatable periurethral balloons have generally proven inefficacious and worsening of incontinence may happen after such surgery. The AUS is the most successful surgical procedure in this setting, but is associated with a higher rate of complications compared to implantation following surgery in the absence of adjuvant cancer therapy. With tissue damage beyond the urinary sphincter, other surgical approaches may be necessary. Patients with unresolved problems from pediatric age and with associated incontinence from detrusor overactivity may benefit from a variety of complex reconstructive surgical procedures. Other complicated problems encountered include urethrocutaneous fistulae, and fistulae between the prostate, bladder neck, or urethra and rectum. Surgical reconstruction, in experienced hands, often in a staged manner, is usually successful.

With decades of worldwide use of the AUS in the surgical management of male incontinence, its complications and their management are well known. Durability of the device is an important aspect that impacts on outcome and cost of treatment. A growing body of literature regarding male sling surgery, its indications, factors affecting outcome, and complications and their management,

has changed the landscape of incontinence surgery over the past 5 years.

Although the literature is replete with well-done cohort studies, there is a continuing need for prospective randomized clinical trials, especially needed for adequate comparisons among surgical techniques.

MATERIALS AND METHODS

The committee was charged with the responsibility of assessing and reviewing the outcomes of surgical therapy that have been published since the Third Consultation [4] for non-neurogenic male incontinence. Articles from peer-reviewed journals, abstracts from scientific meetings, and literature searches by hand and electronically formed the basis of this review. The outcomes were analyzed, discussed among the members of the committee and included in the chapter.

The incontinence problems were classified according to their etiology, i.e. either primarily sphincter or bladder related, and are listed in **Table 1**. Treatment of fistulae is covered separately.

Specific recommendations are made on the basis of published results and determined by the levels of evidence. Consensus of the committee determined the recommendations, which are found at the end of the chapter. Recommendations for future research are also included.

II. EVALUATION PRIOR TO SURGICAL THERAPY

Recommendations for evaluation prior surgery have not changed substantially from the last edition in 2009 [5]. A basic history and physical is the cornerstone of this evaluation. The history should focus on the precipitating events (surgery, trauma, etc) that led to the incontinence, the evolution over time of the leakage symptoms (has there been improvement, etc), what precipitates the leakage (straining, cough, exercise, etc – suggestive of stress urinary incontinence (SUI) or the sudden onset of urgency, the sense of needing to void immediately, particularly in the absence of any physical activity – suggestive of urgency incontinence) as well as other potential comorbidities. A general sense of the degree of bother of these symptoms, sexual function and pad use is important as well. The physical examination should note any gross urine leakage per meatus with patient straining or coughing as well as general characteristics of the lower abdomen, perineal area and penis and scrotum. Assessment of hand function is important to assess manual dexterity for manipulation of an implanted device. A brief neuro-urological examination (perineal sensation, anal tone, voluntary contraction and relaxation of the anal sphincter, bulbocavernosus reflex [6]) should be performed. A urinalysis to rule out infection or signs of inflammation or hematuria should be obtained.

A frequency-volume chart [7], or bladder diary (indicating daytime and nighttime frequency of micturition, incontinence episodes, voided volumes, 24-hour urinary output, etc.) is also helpful. According to Wyman et al. [8] the 7-day diary can be considered as the gold standard for voiding diaries. Schick et al. [9] demonstrated that a 4 day frequency-volume chart gives a reliable snapshot of the patient's situation. A pad test quantifies the severity of incontinence and may be the most objective measure of the incontinence. The 24-hour home test is the most accurate pad test for quantification and diagnosis of urinary incontinence because it is the most reproducible. [10] The 1-hour pad test may be used because it is easily done and standardized, however there is no strict

Table 1. Classification of surgically correctable problems.

Sphincter related	
	Postoperative
	Post-prostatectomy for prostate cancer
	Post-prostatectomy for benign disease
	TURP and radiation for prostate cancer
	Post-cystectomy and neobladder for bladder cancer
	Post-traumatic
	After prostato-membanous urethral reconstruction
	Pelvic floor trauma
	Unresolved pediatric urologic incontinence
	Exstrophy and epispadias
Bladder related	
	Refractory urgency incontinence due to detrusor overactivity
	Small fibrotic bladder
Fistulae	
	Prostatorectal (urethrorectal)
	Urethrocutaneous

parallel with the 24-hour pad test and it may underestimate the weakness of the sphincter in the later part of the day. A pad test may be helpful in quantifying leak in AUS failures.

The ICIQ-SF (short form) questionnaire (www.iciq.net) can be recommended for the assessment of the man's incontinence, and has been used in RCTs of treatment for post prostatectomy incontinence.

Postvoid residual urine measurement is a good estimation of voiding efficiency [11,12]. These basic investigations are recommended in incontinent males prior to surgical therapy.

Blood testing (BUN, creatinine, glucose) is recommended only if compromised renal function is suspected or if polyuria (in the absence of diuretics) is documented by the frequency-volume chart [13].

Further evaluation should be adapted to the particular patient. Cysto¬urethroscopy will verify the integrity of the urethral wall (anterior aspect of the distal sphincteric mechanism in post-TURP incontinence [14], erosion by the cuff of the artificial sphincter), and the status of the bladder (trabeculation, stone, diverticula, etc). It will allow observation of the urethral sphincter and voluntary contraction on the part of the patient, if done under local anaesthesia. The presence or absence of urethral, prostatic, or bladder neck stenosis is also necessary to ascertain prior to incontinence surgery, especially in patients who have undergone treatment for prostate cancer.

Imaging techniques include plain film of the abdomen (KUB or Kidneys, Ureters, Bladder), in cases of incontinence following artificial sphincter implantation when during the original procedure the hydraulic system was filled with contrast medium. A KUB immediately following sphincter implantation serves as a reference point for subsequent comparisons [15]. **Figure 1** illustrates the case of a young spina bifida patient in whom an artificial sphincter has been implanted with the cuff around the bladder neck. After more than 10 years, he became suddenly incontinent. Second KUB compared to previous one clearly demonstrated fluid loss from the system. Contrast studies include cystography which may demonstrate an open bladder neck when bladder denervation is suspected [16], e.g.: following abdominoperineal resection of the rectum. Cystourethrography may be used to demonstrate a fistula, stricture or urethral diverticulum e.g., following healing of the urethral wall erosion caused by the cuff of the artificial urinary sphincter (**Figure 2**). Ultrasound is widely used not only to evaluate the upper urinary tract, but also to evaluate postvoid residual urine. The sensitivity of 66.7% and specificity of 96.5% when post-void residual is 100 ml or more is adequate for routine clinical use [17]. It has been shown to be cost-effective when compared to catheterization [18]. Other modalities, for example transurethral ultrasound [19] and magnetic resonance imaging of the external sphincter are still under development.

URODYNAMIC TESTING

Urodynamic studies (UDS) have traditionally been performed in men under consideration for invasive treatment in order to assess Valsalva Leak Point Pressure (VLPP), detrusor overactivity and bladder compliance. However, there are now several studies, which call into question the use of routine UDS in men with pure SUI. These studies will be commented on at the end of this section.

When performing UDS there are specific issues that must be considered. In patients with incontinence secondary to radical prostatectomy who developed bladder neck stenosis, the urethral catheter can create obstruction giving false values for Valsalva leak

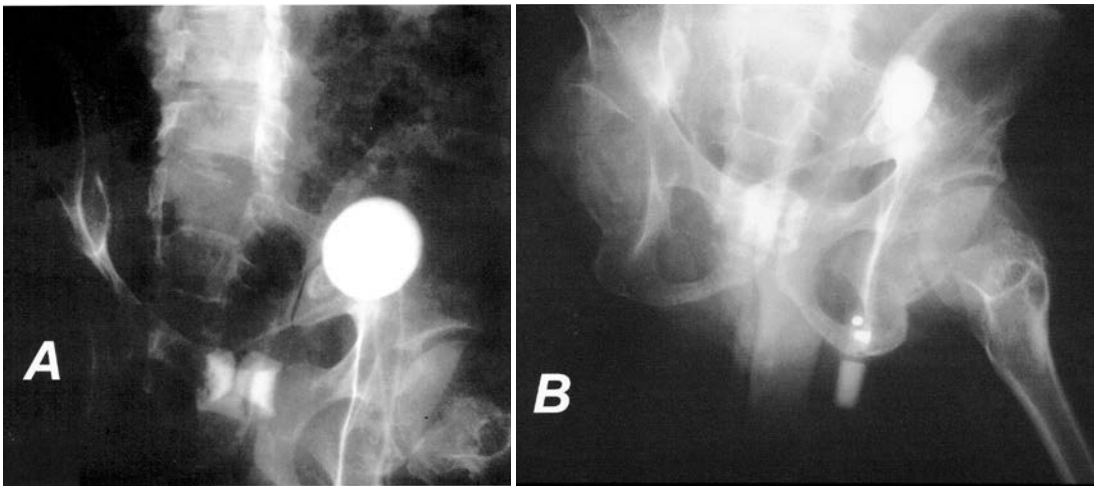


Figure 1. Young spina bifida patient who had a bladder neck artificial sphincter implanted. After more than 10 years, he became incontinent. Early abdominal plain film, A, shows a full reservoir. After leakage started abdominal plain film, B, demonstrates loss of fluid from the reservoir.

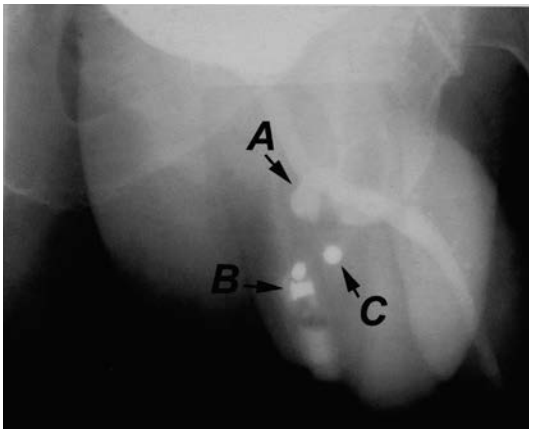


Figure 2. Urethrogram of patient who underwent cuff removal for erosion into the urethra.
A. Site of urethral diverticulum
B. Tubing plug over tube from pump
C. Scrotal pump

point pressure (VLPP). Sphincter weakness can be documented by the Valsalva [20] or cough or abdominal leak point pressure [21]. Catheter size seems to have a significant influence even with a small size 7-F urethral catheter [22], and the correlation is extremely high between the test-retest leak point pressure when the same size of catheter is used [23,24]. In male patients, abdominal leak point pressure may be evaluated via a rectal catheter because a urethral catheter is much more likely to invalidate VLPP measurements than it does in female [25]. It has become evident that bladder volume influences VLPP, i.e. it decreases with bladder filling [26-28]. However, this observation is not consistent [29]. Unfortunately, there is no agreed standardization of the technique at the present time which somewhat limits its usefulness [30]. Measurement of leak point volume may also provide information on the functional capacity of the bladder [31].

Retrograde leak point pressure has been used to study incontinence following placement of an artificial sphincter [32,33]. It correlates with the lowest abdominal leak point pressure [34]. The intraoperative use of this technique has been proposed and this allows early recognition of intraoperative urethral injury and mechanical malfunction [35]. Intraoperative retrograde perfusion sphincterometry may be helpful to determine the appropriate tension on male slings [36]. Similarly, others have utilized repeated intraoperative abdominal leak point pressure (ALPP) measurements to adjust the tension for male slings [37]. Electrophysiologic studies, mainly sphincter electromyography, may be useful to document denervation of the pelvic floor when nerve injury or neuropathology is suspected [38].

Detrusor function is best evaluated by multichannel urodynamics. Its main purpose is to detect detrusor overactivity and/or decreased compliance during bladder filling. It can be coupled with fluoroscopic imaging, video-urodynamics. It has also been proposed by some that fluoroscopy be replaced by transrectal ultrasound [39,40]. Ultrasound measurement of bladder wall thickness was proposed as a better predictor of bladder outlet obstruction than uroflowmetry [41] but at present its use is controversial [42].

Non-invasive pressure-flow urodynamic evaluation based on Doppler ultrasound seems to have potential for diagnosing bladder outlet obstruction [43]. However invasive pressure-flow studies are still the gold standard in the incontinent male to rule out bladder outlet obstruction accompanied by detrusor overactivity [44] which in turn can cause incontinence.

In most recently published studies, urodynamic testing has been done prior to surgery [45-49]. Cystoscopy is frequently done as well [48,50-54]. However, as noted above, there are some reports that question the value of urodynamics studies in predicting outcomes after surgery. Thiel et al. [55] found no evidence that patients with detrusor overactivity, early first sensation of filling, decreased compliance or low bladder capacity had worse outcomes after artificial sphincter placement in 86 men. Trigo Rocha et al. [56] also found that preoperative urodynamic findings such as detrusor overactivity, impaired detrusor contraction, low Valsalva leak pressure, bladder outlet obstruction, and mildly reduced compliance did not lead to a poor outcome after artificial sphincter implantation. Ballert et al. [57] studied the association between preoperative detrusor overactivit and postoperative outcome after male sling surgery and found no difference in the number of pads used postoperatively. Preoperative detrusor overactivity was not associated with worse postoperative outcomes. Finally, Lai et al. [58] reviewed 129 patients with post-prostatectomy incontinence, all of whom had multichannel videourodynamics, and noted that the presence of adverse preoperative urodynamic features (such as detrusor overactivity, early sensation of desire to void, reduced cystometric capacity of <200cc, low abdominal LPP <30 cm H2O, low maximum flow <10cm H2O and poor bladder contractility) did not negatively affect the continence results after AUS implantation.

The proposed evaluation of the incontinent male is summarized in **Table 2**.

III. INCONTINENCE AFTER RADICAL PROSTATECTOMY FOR PROSTATE CANCER

1. INCIDENCE AND PREVALENCE

Urinary incontinence occurring after radical prostatectomy (RP) is a substantial problem. Despite improvements in continence preservation [59] during the 1990's and 2000's primarily due to a better

Table 2: Evaluation prior to surgical therapy

- History
- Physical examination
- Urinalysis
- Urine culture
- Post-void residual (by ultrasound)
- Voiding diary (2-7 days)
    - o polyuria without diuretics: BUN, Creatinine, Glucose
- Pad-test
- Cystourethroscopy
- Urodynamics :
    - Multichannel urodynamics:
        - to characterize the incontinence and to detect detrusor overactivity, decreased compliance, and/or outflow obstruction

understanding of the pathophysiology and improvements in surgical technique, continence rates have generally plateaued over the past decade. As RP has continued to increase in popularity as a treatment for prostate cancer, especially with the advent of robotic-assisted surgery, the prevalence of post prostatectomy incontinence (PPI) has increased in developed countries, which has led to an overall increase in the number of patients affected.

Data from large multicenter studies and prostate cancer databases suggest that following RP, 1% to 40% of patients complain of persistent urinary incontinence. The incidence of post prostatectomy incontinence (PPI) depends on the definition of urinary incontinence and the length of follow-up. [60-62] In addition to numerous definitions of incontinence, the tools used to evaluate incontinence vary from self-administered validated and non-validated questionnaires, to interviews from a data manager, to response to the surgeon's inquiry, to insurance data base inquiries regarding secondary surgical procedures. It should be noted that SUI also affects men who have not had surgery for prostate cancer, occurring at a baseline prevalence of 1.3%-4.8% [63,64]. In addition, men with prostate cancer who choose radiation therapy, androgen ablation, or even watchful waiting also develop urinary incontinence, recently reported at rates of up to 12%, 11%, and 3%, respectively [65,66]. In addition to urinary incontinence, bothersome lower urinary tract symptoms may affect patients following any treatment (or even watchful waiting) for prostate cancer.

Typically, reports of large cohorts use definitions that include "total control/perfect continence/dry", "occasional leakage but no pad", and "less than one pad". Because 1/3 to 1/2 of men who do not wear pads will have occasional leakage of urine [60,67] it is important to distinguish among those men who leak enough to require pad use versus those who do not, as it has been demonstrated that health related quality of life (QOL) is strongly correlated with the level of incontinence. Wearing one pad, even if this pad is considered "a security pad", more significantly affects the quality of life than wearing no pad at all [68,69]. In addition, not all men who leak will elect to have further treatment. Most large cohort studies indicate that between 6% and 9% of patients undergo subsequent surgical treatment for PPI following prostate cancer surgery. [70-73] Several large cohort studies are listed in **Table 3** [62,67,69,74-92].

Another bothersome type of incontinence occurring during orgasm in men post-prostatectomy has been termed 'climacturia' and may significantly affect the quality of men with post-prostatectomy potency [93].

2. RISK FACTORS

Reported risk factors for incontinence following radical prostatectomy include patient age at surgery, socio-economic status, preoperative continence status, obesity, pre-surgical bladder dysfunction, stage of disease, surgical technique (including nerve sparing, bladder neck preservation, and posterior reconstruction of Denonvilliers' musculofascial plate, anterior periurethral suspension sutures [94,95], prior radiation therapy, preoperative length and intraoperative preservation of the membranous urethra, prior transurethral resection of the prostate (TURP), postoperative radiation or cryotherapy, and vascular comorbidities. However, various studies have come to conflicting conclusions regarding the importance of specific risk factors. Predisposing factors contributing to incontinence after TURP have been less clearly defined, probably because the incidence is so low, (and the plethora of minimally invasive therapies is reducing the popularity of TURP surgery), making the accumulation of large prospective series of this type of incontinence difficult. However, previous external beam radiation and prior brachytherapy does predispose to post-TURP incontinence (Section VII in this chapter).

Pre-operative urinary incontinence has been reported as a risk factor for post-operative SUI. While preoperative lower urinary tract symptoms, including

Table 3: Continence rates after radical prostatectomy according definition of continence, Definition 1: total control without any pad or leakage,

Definition 2: no pad use but loses a few drops of urine,

Definition 3: use no or one pad per day.

Author	No. pts.	Mean age (years)	Continence follow-up at 12 months def 1	def 2	def 3	Type of surgery
Kielb, et al [74]	90	59.6	76%		99%	RRP
Sebesta, et al [75]	675	<65	43.7%	69.2%	82.2%	RRP
Lepor and Kaci [76]	92	58.7	44.6%		94.6%	RRP
Olsson, et al [62]	115	65.2	56.8%	78.4%	100%	LRP
Madalinska, et al [77]	107	62.6	33%	65%		RRP
Deliveliotis , et al [78]	149	66.5		92.6%		RPP
Harris, et al [79]	508	65.8		96%		RPP
Maffezzini, et al [80]	300	65.5		88.8%		RRP
Hofmann, et al [81]	83			74.7%	88%	RRP+/-Rx
Ruiz-Deya, et al [82]	200	63			93%	RPP
Augustin, et al [83]	368	63.3			87.5%	RRP
Anastasidis, et al[86]	70 230	65 64			67 72	RRP LRP
Sacco, et al[87]	985	65	83	92	93	RRP
Jacobsen, et al[85]	172 67	64 61	87 83		88 50	RRP LRP
Rassweiler, et al [84]	219 219	65 64			89.9% 90.3%	RRP LRP
Krambeck, et al[88]	588 294	61 61		94 92		RRP RALP
Rocco, et al[89]	240 120	63 63			88 97	RRP RALP
Boris, et al[90]	50 50	64 64			96 96	RRP RALP
Di Pierro, et al[91]	75 75	64 63	80 89			RRP RALP
Liss, et al[69]	420	61	54	67	82	RALP
Wallerstedt, et al[67]	1163	63	67	78	90	RRP or RALP
Reynolds, et al[92]	1005	60	28	68	90	RALP

RRP: radical retropubic prostatectomy; RPP: radical perineal prostatectomy; LRP: Laparoscopic radical prostatectomy; Rx: radiotherapy; RALP:robotic assisted laparoscopic prostatectomy)

urgency incontinence and "overflow incontinence" may improve with de-obstruction secondary to extirpative surgery [96], pre-operative SUI does not improve following RP. Several recent cohort studies have demonstrated that pre-operative sphincteric insufficiency (demonstrated either the pre-existing clinical sign of SUI or the urodynamic finding of lower maximal urethral closure pressure) predicts post-operative SUI. [97,98] Pre-operative bladder dysfunction can also contribute to post-operative incontinence. Pre-existing abnormalities of detrusor function may predispose to leakage following surgery, especially in the setting of neurogenic detrusor overactivity due to Parkinson's disease, dementia or spinal cord injury. [99]

Advancing age as a risk factor is supported by several studies [73,96,100-106]. Steiner, et al found no correlation between age and continence status, but only 21 of the 593 patients were 70 years or older [107]. Others have found advancing age and the number of co-morbidities to have a negative impact on the recovering time for continence during the first year after radical prostatectomy [108] although the rate at one and two years did not seem to be significantly affected [109]. Mohamad and colleagues reviewed 16,524 patients who underwent RRP in public hospitals, covering 95% of all procedures in Austria between 1992 and 2003. They found that increasing age was associated with an increased risk of future AUS implantation. In those aged 45-49, 0.5% were bothered enough by PPI to merit AUS placement, while those age 70-74 were five times as likely to undergo AUS placement for PPI.[110] Similarly, Rogers et al. demonstrated that age affected post-operative continence status following laparoscopic RRP. In those < 50 years old, 100% achieved 0-1 pad per day continence at 1 year, which decreased to 91% and 81% for those age 50-59 and > 60 yrs, respectively ($p<0.01$). [111] Nilsson et al. [112] reported that age at surgery predicted in an exponential manner the long-term risk for urinary incontinence, with an estimated relative increase of 6% per year.

In addition to age, overall well-being has also been related to the risk of PPI. For example, a recent study out of Italy demonstrated that both age and Charlson comorbidity index were independent predictors of return to urinary continence [105]. It is especially interesting to note that in this particular cohort study, there were no variables related to the prostate cancer itself that were significantly correlated with urinary continence. A large study from Sweden recently demonstrated that in addition to age as a risk factor (relative risk of 2.4 between the oldest and youngest quartiles), educational level also impacted incontinence, with low educational level, as compared with high education level, being associated with a 2.5 time risk of incontinence[112].

Obesity, especially when coupled with physical inactivity, appears to be a risk factor for PPI in men undergoing RRP. Obesity with a BMI >30 was reported as a risk factor with an incontinence rate of 25.8% versus 8.7% in BMI <30 in a series of 252 men after RRP [113].

Wolin, et al. demonstrated that greater than one year after surgery, obese men were markedly more likely to have urinary incontinence (defined as any pad use) than were non obese men, while this risk was exacerbated by sedentary lifestyle, and ameliorated by at least 1 hour of physical activity per day (preoperatively). Nonobese active men were 26% less likely to have urinary incontinence than obese inactive men. In obese men who were physically active, the relative risk of urinary incontinence was 15% less than in the inactive obese men [114].

Most large series have found no correlation between the stage of disease and incontinence rates [101,102,115-117] Loeb and colleagues specifically demonstrated excellent continence rates even in high risk (high local stage) patients. [118] However, in certain cases, the stage of disease may affect the surgical technique (i.e. nerve sparing) and incontinence rates may be higher, but this appears to be a reflection on surgical technique and not disease stage [103]. Yang et al reported that neoadjuvant hormonal ablation was associated with a lower risk of urinary incontinence, and while patients with higher stage disease may have been more likely to receive hormonal ablation pre-operatively, it is not clear that stage of disease was an important risk factor [106].

Regarding surgical technique, the many parameters involved in continence may explain difficulties in understanding the benefit of certain technical points. Bladder neck preservation has been reported to improve continence at 1 month [119] and at 3 months [116] but no difference was found at 6 and 12 months [120,121]. Nerve sparing has no significant impact according to Steiner et al. [107] and Lepor and Kaci [76]. Recently Pick et al. reported that nerve sparing, whether unilateral or bilateral, did not affect continence rates following RALP [122]. Others did find benefit [97]. In particular, Nandipati and colleagues reported that in a cohort of 152 patients followed prospectively, bilateral nerve sparing surgery was associated with a shorter time to regain continence as well as improved long-term continence rates compared to non-nerve sparing surgery. They additionally found that increased age was a risk factor for post-prostatectomy incontinence [123]. Burkhard, et al. similarly demonstrated a positive effect of nerve-sparing surgery on post-operative continence. In a prospective cohort study of 536 patients, PPI developed in 1/75 (1.3%), 11/322 (3.4%), and 19/139 (13.7%) with attempted bilateral, attempted unilateral and without attempted nerve sparing, respectively. Attempted nerve sparing was in fact the only statistically significant factor influencing urinary continence after RRP in this cohort [124]. Two recent reports have linked pre-operative sexual function with post-operative continence. While those who are sexually active pre-operatively may be more likely to have

their cavernosal nerves spared during surgery, it appears that the pre-operative status has a significant effect on post-operative continence rather than the nerve sparing technique [119,122,125].

Within the last decade, laparoscopic and robotic-assisted laparoscopic radical prostatectomy have become standard treatments for men with prostate cancer. Over the past 4 years, the body of available data on post-operative continence has generally demonstrated no obvious differences in continence rates between open and laparoscopic/robotic approaches. Several studies have compared the techniques either prospectively in non-randomized fashion, [85,86,88-91,126,127] or via limited meta-analysis [84,128] and similar continence rates were found. Further prospective comparative studies with open surgery are needed. Currently, a multicenter prospective comparative study of robot assisted laparoscopic and retropubic open radical prostatectomy is underway, with an accrual goal of 2100 patient, with the primary objective of comparing rates of urinary incontinence at 1 year post-operatively [126].

Perineal prostatectomy is done by only a limited number of urologists but is still advocated for markedly obese patients and the continence rate was reported as similar to the retropubic route [79,90,129,130].

3. PATHOPHYSIOLOGY

Post-prostatectomy incontinence, like any urinary incontinence, may be caused by bladder dysfunction, sphincter dysfunction or a combination of both. Urodynamic investigations are helpful to rule out bladder outlet obstruction or significant bladder dysfunction. In addition to incontinence symptoms, storage and voiding symptoms may be associated [129,131]. Urodynamics demonstrated that the sphincter incompetence occurs as the sole cause in more than two thirds of patients, while isolated bladder dysfunction (detrusor overactivity, poor compliance, detrusor underactivity during voiding) is uncommon, occurring in less than 10% [132-135].

Sphincter and bladder dysfunction can coexist in at least one third of incontinent patients. Bladder dysfunction may occur de novo after prostatectomy perhaps induced by bladder denervation; may be caused by outlet obstruction, or may be related to pre-existing factors such as age. Impaired detrusor contractility, which occurs in 29% - 61% of patients (de novo in approximately 47%), and poor compliance, which occurs in 8%-39% of patients (de novo in approximately half), have traditionally been thought to resolve in the majority of patients within 8 months [135,136]. However, two recent prospective urodynamic studies have demonstrated that decreased bladder compliance can occur in up to one-third of patients following RP, and persist in 28% at 36 months, while detrusor underactivity can occur in half of the patients, and persist in 25% at 36 months [136,137]. Decreased sphincter resistance may be due to tissue scarring in some cases and reflected by a low urethral compliance, however this parameter is difficult to measure [132]. Scarring may lead to an anastomotic stricture evidenced by endoscopy or urethrography, and is clinically suspected when both incontinence and decreased force of stream coexist.

The pre-operative length of the membranous urethra determined on MRI has been shown to be significantly related to time to post-operative continence. When urethral length was greater than 12 mm, 89% of the patients were continent at one year, versus 77% with or less than this length [138]. Urodynamic studies revealed that a reduced functional urethral length was a predictive parameter of incontinence [97,139,140]. A recent elegant study of intraoperative stretched urethral length (from the urogenital diaphragm to the prostatic apex with cephalad retraction) and cut urethral length (length of preserved urethral stump) during RALP revealed that although in this cohort, MRI urethral length did not correlate well with continence, the intraoperative measurements correlated significantly with time to continence [141]. Different components of the urethra may also be involved. The urethral intrinsic component responsible for passive continence as well as the extrinsic component responsible for active continence may be involved as has been demonstrated in a urodynamic alpha blockade test [142]. This may explain passive incontinence despite a high voluntary urethral pressure or that measured during an active squeeze by the patient. Post-operative disruption of the innervation of the posterior urethra may also be involved and can affect both motor and sensory functions [143,144]. In clinical practice, urodynamic evaluation of a urethral weakness may be assessed by resistance to antegrade leakage (ALPP or VLPP), retrograde leakage, or profilometric measurement (MUCP) [145]. However no such parameters have been correlated to outcomes of treatments for the correction of post-prostatectomy incontinence.

The state of a patient's pelvic floor may also influence continence or return to continence after RP. Physiotherapy and pelvic floor rehabilitation have been shown to improve or enhance continence (decreased time to final continence level) in the post operative period in two randomized studies, but only if such measures are instituted before or immediately after catheter removal [146,147]. Maximum difference between physiotherapy and no treatment is achieved at 3 months, with almost no difference at 12 months. Another study showed that providing patients with instructions for pelvic floor muscle exercise alone was equivalent to biofeedback or electrical stimulation [148]. A randomized study in which randomization occurred 6 weeks after surgery showed no difference in continence at 6 months [149]. On the other hand, a recent trial from Brazil did demonstrate significant difference in 12-month continence rates, quality of life, and lower urinary tract symptoms in general when randomizing patients to biofeedback-

pelvic floor muscle training versus verbal instructions alone [150]. Studies in which physiotherapy was used as a treatment modality for established incontinence have shown more variable results [151-154]. A recent randomized trial of formal one-to-one pelvic-floor muscle training versus advice alone for incontinent men 6 weeks after RP failed to demonstrated any difference in continence rates at 12 months. Nor did the physiotherapy improve SUI after TURP [155].

No medical treatment is available to cure post-prostatectomy incontinence. Duloxetine at 60 mg per day could improve mild or moderate incontinence but half of the patients had some side effects and 25% stopped the treatment because of adverse effects in two short non-randomized series. This treatment is not approved in many countries and could be only a treatment option to improve symptoms in selected patients informed of side effects [156].

4. SURGICAL AND MINIMALLY INVASIVE TREATMENTS

a) Urethral Bulking Agents

Urethral bulking is a minimally invasive treatment proposed for post prostatectomy incontinence, and theoretically works by adding bulk and increasing coaptation at the level of the bladder neck and distal sphincter. It can be done in an office or outpatient setting in a retrograde or antegrade fashion. Several different agents have been used for urethral bulking in men including bovine collagen (Contigen®), silicone macroparticles (Macroplastique®), ethylene vinyl alcohol copolymer (Tegress®), Dextranomer hyaluronic acid (Deflux®), and carbon-coated zirconium beads (Durasphere®). All agents share the similar problems including the need for multiple injections, deterioration of effect over time, and very low cure rates.

For collagen, “success rates” for post-prostatectomy incontinence ranged from 36-69%, with 4-20% of patients reporting being dry [157-164]. Unfortunately, the end points in most of these studies are subjectively based, making comparisons difficult; however, it is clear that cure rates (total dryness) are low, and multiple injections were required to achieve modest rates of subjective improvement. There was no advantage of delivery technique (retrograde vs. antegrade). Several authors identified factors which negatively affect results include extensive scarring or stricture formation, previous radiation, and high grade stress incontinence and low ALPP [158,160,161,164]. One study reported more favorable results for collagen in treating incontinence after transurethral prostatectomy as opposed to radical prostatectomy (35.2% ‘social continence’ versus 62.5%) [161]. It appears that collagen injection did not adversely affect outcomes of artificial sphincter implantation and did not increase the complication rate [165]. Nor did collagen injection adversely affect the outcome of the bone-anchored male sling (BAMS). [166,167] The cost efficacy of injections remains to be determined. Collagen is no longer available as an injectable agent.

Other bulking agents such as polydimethylsiloxane (Macroplastique®) have shown some initial success, but results also deteriorate over time. Bugel and co-workers treated 15 patients. They noted rapid deterioration after initial improvements with success rates of 40%, 71%, 33%, and 26% at 1,3,6, and 12 months respectively [168]. They also noted that a urethral closure pressure of at least 30 cmH2O was essential for success. Kylmala et al. prospectively studied 50 patients with mild to moderate SUI (average 48 cc on 1 hour pad test), with 12% achieving short-term continence following 1 injection, and an additional 20%, 18%, and 10% achieving continence with 2, 3, and 4 injections respectively. Follow-up, however, was limited to 3 months.[169] In a randomized trial of AUS versus Macroplastique injection in patients with minimal SUI (the majority had SUI following BPH surgery, with more than1/3 of the cohort suffering from SUI following RRP), Imamoglu and colleagues demonstrated no difference in success with AUS versus Macroplastique. However, in patients with more severe incontinence, AUS was superior, with minimal improvement following transurethral Macroplastique. [52]

With regard to the newer (not FDA approved for male SUI) injectable bulking agents, dextranomer hyaluronic acid has been reported in men with PPI and in men with neurogenic ISD. Four of four patients with PPI failed to improve, and 1 of 2 neurogenic patients (both with detrusor areflexia, wet between catheterizations) failed [170]. With ethylene vinyl alcohol copolymer (Tegress ®) in a report by Hurtado et al., not only was the failure rate high, but also the complication rate was unacceptable. In 17 men, who averaged 1.4 injection sessions followed at a mean of 4 months, 10 had complications, with erosion of injected material in 41.1%, and with only a minority of patients achieving a 50% decrease in leakage [171]. Tegress ®has been withdrawn. Carbon-coated zirconium beads have been similarly reported to be inefficacious, with a recent report of 8 men with mild to moderate incontinence receiving a relatively large average injected volume (23.8 ml), none of whom achieved subjective or objective cure [172].

There has been interest in the use of autologous muscle cells, stem cells, and fibroblasts as an injectable sphincter-restorative agent for PPI. Transurethral injection of living muscle stem cells to reconstitute the deficient urethral sphincter has been reported. Mitterberger and colleagues demonstrated a 67% continence rate at an average of 1 year follow-up in a cohort of men suffering from PPI who were treated with transurethral ultrasound

guided injections of autologous fibroblasts and myoblasts obtained from skeletal muscle biopsies. 173 An earlier report from the same group demonstrated that men with PPI achieved a 52% dry rate with injection of adult autologous stem cells, which was superior to a similar cohort of men treated with collagen injection.174 However, it must be pointed out that there was a retraction issued by the editors of The Lancet175 for a previous article on the treatment of female SUI with autologous cells published by the same group176. The project was investigated by the AGES PharmMed, a department of the Austrian Government's Agency for Health and Food Safety. The editors stated that in their view "the conclusions of the official investigation pinpoint so many irregularities in the conduct of their work that, taken together, the paper should be retracted from the published record." Current research has focused on the relatively abundant adipose derived stem cells, which are believed to be easier to harvest (higher yield) than are autologous bone-marrow derived stem cells [177].

Conclusion: Bulking agents remain the most minimally invasive treatment for post RP incontinence after conservative measures. All agents for which there is peer-reviewed data available, show only modest success rates with very low cure rates. Effects tend to deteriorate over time. It remains to be seen if improvements in outcomes can be achieved with alternative agents, or if the concept of urethral bulking has achieved its maximal benefit with the agents available now. (Level of evidence 3; Grade of recommendation C)

b) Male Sling

The male sling procedure is based upon the concept of urethral support and external urethral compression, and has established itself as an accepted and efficacious treatment for PPI. The male sling is actually based on the concept similar to that described by Kaufman and associates in the early 1970's [178-180]. At that time a high rate of failure, septic complications and pelvic pain as well as the advent of the mechanical artificial urinary sphincter (AUS) led to the abandonment of the Kaufman prosthesis. Now with the higher prevalence of PPI and patient desire for less invasive surgery and a non-mechanical device the concept has been revisited. Procedures have been developed based on principles used to treat female stress urinary incontinence. These procedures rely on compression from the ventral side of the urethra rather than the circular compression caused by a natural or artificial sphincter. Therefore, most successful sling surgeries rely on a device that is placed under tension, occluding the urethra at rest, and during stress manoeuvres.[181-183]

Schaeffer and Stamey described the bulbourethral sling which uses Dacron bolsters placed under the urethra, which are suspended to the anterior rectus fascia by sutures [184]. Data on this procedure are limited to retrospective analyses from the two authors who described the procedure: it did not gain widespread popularity. In the initial report from 2 centers, 64 patients were included and 56% were "dry" and 8% "improved" at a mean follow up of 22.4 months [184]. Almost one-third needed secondary retightening procedures and patients with radiation fared poorly. Subsequently, Clemens, et al reported a questionnaire-based study of 66 men from a single institution and 41% were cured and 51% improved but mean follow up was only 9.6 months [185]. They also reported that the bulbourethral sling did not cause significant outlet obstruction [186].

The long-term efficacy of the bulbourethral sling was evaluated in 2005, where 95 patients were followed retrospectively at an average of 4 years post-operatively. With follow-up questionnaires returned by 71 patients, the authors found that patients who had undergone radiation, had worse outcomes with only 14% dry and 43% requiring 1 or 2 or fewer pads daily. Moderate to severe pain was reported by 12% of patients after 4 years. Patients who had not had radiation treatment had a cure rate of 42% and 72% used only 0-2 pads per day for mild leakage.[187] Others have described a bulbourethral sling using a polypropylene mesh graft with or without a porcine dermis backing (presumably to reduce the risk of erosion) 53. In two small studies of 9188 and 1653 patients cure rates range from 56-69% and failure rates from 22-25% at a mean follow up of 14 months. John described the bulbourethral composite suspension where porcine dermis is secured to the bulbospongiosus muscle and a 1 cm wide polypropylene sling is placed over this and passed through the retropubic space to emerge from two suprapubic incisions (similar to the tension free vaginal tape procedure in women) 53. He reported a 69% cure and additional 6% improvement in 19 patients, with a mean follow up of 14 months. Eight intraoperative bladder perforations healed without complication.

Xu and colleagues described a bulbourethral composite suspension utilizing a suburethral polyester patch plus a narrow polypropylene tape passed from a perineal incision to a suprapubic incision. At an average of 28 months, 22 (85%) of 26 patients were successfully treated. [189]

A common method of sling fixation involved use of bone anchors. The bone anchored male sling (BAMS) obviated the need for any suprapubic incision for suture passage and fixation. In 2001, Madjar, et al reported on 14 patients with post RP incontinence that underwent the procedure with a synthetic or cadaveric fascial sling 190. At a mean follow up of 12.2 months, 86% were "cured" wearing none or 1 pad. Comiter reported a 76% cure and 14% "substantially improved" rate in 21

men with post prostatectomy incontinence using polypropylene mesh with a mean follow up of 12 months 166. In a 2005 update, the same author reported that with a median of 48 months follow-up, 65% of patients remained pad free and 15% required 1 pad per day. [191] Urodynamic follow up in 22 men, revealed that the sling had no substantial effects on voiding function and no one was obstructed postoperatively [192]. Onur and colleagues reported on 46 men with a mean follow-up of 17 months (6-26) [193]. They used different materials for the sling (allograft dermis, allograft fascia lata, porcine small intestine submucosal (SIS) graft, synthetic mesh, and a composite of synthetic and dermis). Overall they reported 41% of patients dry and 35% improved (50% reduction in the number of pads). All patients in whom allograft or xenograft alone was used failed. A 24-month update revealed a patient satisfaction rate of 70% and a 74% improvement in leakage at a median of 24 months.194 Giberti et al195 reported that in 36 men followed for an average of 41 months, 62% were cured and 70% were satisfactorily improved. In the subset who had a synthetic sling implanted, a higher success rate was experienced, with 77% achieving cure. Complications included sling infection in 4.8%, and de novo detrusor overactivity in 7.1%. Carmel et al196 reported that at an average follow up of 36 months, in a cohort of 45 men with moderate to severe PPI, 78% were improved by pad use, 76% had dry ICS 1-hour pad tests, and 72% were satisfied or very satisfied. Infection occurred in 1 patient, and pain resolved in all patients by 12 weeks postoperatively.

However, the morbidity (infection, pubic bone osteitis, perineal pain) related to bone screws coupled with the emergence of effective alternatives has decreased the popularity of the InVance sling.

The transobturator (TO) male sling technique was introduced in 2004 [197] and has since become the most common type implanted for PPI, since the early reports of 2007, [49,197,198]. This approach relies more on rotation of the dorsal surface of the proximal bulbous urethra and indirect support of the sphincteric urethra, rather than on direct compression of the urethral lumen.[199] Over the past few years, there have been several large case series reporting favorable outcomes. Cornu et al [200] followed 136 men with mild to moderate (< 5 pads per day) PPI for an average of 21 months following implantation of the TO sling. A 78% success rate (based on pad test) was achieved. Rehder et al201 reported their cohort of 118 men with mild to moderate SUI, with a 1-year success rate of 91% at 12 months. Bauer et al202 achieved a success rate of 76%, at a median of 27 months follow-up in 137 men with PPI. In contrast, Gill et al203 reported a subjective success rate of only 51% (PGI-I scale) and objective success rate of 60% (pad use) at a mean follow up of 9 months, and Cornel et al204 reported only 9% of men achieving total dryness at 1 year post-operatively, with a 46% improvement rate.

Membranous rather than bulbar placement of the sling was introduced with the Advance sling with the aim of relocating the urethra in a more proximal direction. However, the concept is controversial as patient anatomy and pathophysiologic modifications are complex. This type of sling surgery close to the membranous urethra requires a deeper dissection compared to bulbar or perineal compression slings.

The I-Stop TOMS sling with four arms and a large surface over the bulbar urethra involves tensioning each corner of the sling. A prospective multicenter study [205] was recently published with 122 patients after minimum follow-up of 12 months for 84% of them, and showed a cure rate of 60% and improvement with only one pad per day in 20%. There were no erosions or acute urinary retention. Wound infection was reported in 2% and all resolved. An “inside-out” TO sling also positioned over the bulbar urethra206 was implanted in 173 men, of whom 49% were cured and an additional 35% improved at a median follow-up of 24 months [207].

In case of failure after sling surgery, no clear guidelines yet exist. Surgical options include repeat sling and balloon or artificial sphincter implant. More studies are needed to document results and predictive factors. With respect to “repeat” TO sling following previous sling failure, Soljanik et al208 reported a cohort of 35 men undergoing a second TO sling. Success rate at 6 months was 79% (46% dry, 33% improved), and was maintained at 76% at a average of 16.6 months, demonstrating that the TO sling may be an effective treatment for managing SUI after a prior failed sling surgery.

Two adjustable retropubic slings have been introduced, with the objective of overcoming potential problems of overcorrection or under correction of continence - the “Argus” [209] and the REMEEX210 slings. In a multicenter trial of the Argus sling in 48 patients211, a 73% continence rate and additional 10% improvement rate was reported after an average of 7.5 months. Erosion and infection necessitated sling removal in 10% of patients. Adjustments were indicated for persistent incontinence as well as for urinary retention [211]. In an update reported of 47 patients after a mean follow up of 45 months, 66% were dry and 79% used < 1 pad per day [212]. Hubner’s group [213] reported similarly favorable results, with 79% of 101 men achieving dryness at an average of 2.2 years post-operatively. Thirty-nine per cent required adjustment (10% loosening, 29% tightening) at a mean of 104 days after surgery. Erosion or infection necessitated explantation in 16% at a mean of 1 year. A report from the Netherlands [214] revealed a 72% success rate for the Argus at a median follow up of 27 months. Outcome was

dependent on the degree of pre-operative incontinence, with surgical success in 92% of men with mild leakage (1-2 pads per day), 67% in men with moderate leakage (3-5 pads per day) and 67% in those with severe (> 5 pads per day) incontinence. Explantation was required in 11%, due to infection, erosion, sling rupture or pain. Bladder perforation occurred in 16%, and de novo urethral stricture requiring treatment in 12%. Dalpiaz et al. [215] reported less favorable results, with 79% of 29 patients achieving dryness and 76% satisfaction in the short term, but the dry rate and satisfaction rates deteriorated to 17% and 28% respectively at 35 months. Complications occurred in >80% of cases, with a 35% explanation rate, 14% de novo urgency rate, and a single instance each of urethral stricture and ureteral injury. In a retrospective cohort study of 16 men status post AUS explantation for erosion [216], who were treated with an Argus sling or repeat AUS, men receiving the AUS had a better outcome. Of those who underwent repeat AUS implantation, 63% were cured, and an additional 25% were improved, with only 12% failing. Notably 75% of the Agus patients failed to improve.

In a prospective multicenter Phase II trial of the REMEEX adjustable sling, 51 patients were followed for an average of 32 months (range: 16-50). With 90% of patients requiring at least 2 adjustments, a continence rate of 64.7% was achieved, with an additional 19.6% reporting improvement over baseline158. More recent, but smaller studies have also shown promising results. Navalon Verdejo et al217 reported that 3 of 5 men were dry at an average of 1.4 months, with the other 2 patients experiencing marked improvement. Four of 5 patients experienced recurrent SUI, which was resolved after surgical re-adjustment via the varitensor. A study with lower success rates was reported from Spain with a cohort of 14 men at an average of 18.6 months postoperatively, 42% are dry and 33% are improved218. However, bladder perforation occurred intraoperatively in 29%, sling explantation was required in 21%, urinary retention occurred in 36%, and readjustment was necessary in 83%.

The newest iteration of the male sling is the VIRTUE® Male Sling (Coloplast, Humlebaek, Denmark) an implantable, sub-urethral, permanent, non-absorbable support sling. The sling is a synthetic suburethral mesh of knitted, monofilament polypropylene that measures 5.5 cm x 7 cm, with superior and inferior extension arms. Quadratic fixation is achieved with both transobturator and suprapubic components198. This hybrid sling is based upon the mechanisms of action of the TO sling and the BAMS, providing a broad area of urethral compression and achieving proximal relocation of the membranous urethra. The sling has been shown to increase the retrograde leak pressure in 22 patients from 33.4 to 68.8 cm water after tensioning intraoperatively [36].

Sling results are shown in **Table 4** [45,46,53,184,187-195,209-211,219-222].

1. Sling Complications

Due to the small size of most reported cohort series of BAMS patients, the precise complication rate is 221 not known. However, reports from the largest cohorts of patients reveal an infection rate ranging from 0-6%, and a urethral erosion rate of 0-2%. [46,191,221] Bothersome scrotal pain or numbness affects 16%-72% of patients post-operatively, but has been reported to resolve in nearly all patients by 3 months.[191,195] Postoperative urinary retention was reported in 2-12% of patients. In most cases, it was self-limited and resolved in within 2 weeks [50,194,196,222,223] or rarely required loosening after one month [46].

Infection of the perineal incision/mesh occurred in 3-12%. These infections usually required removal of the implanted sling. Some superficial infections were successfully treated with antibiotics. In men with postoperative mesh infections, 76% (19/25) required surgical explantation of sling [50,191,195,196,221,223,224]. The majority of infections occurred early, however late infections at 3 months and 1 year have been reported [50,196].

Urethral erosion is a well-defined complication in the female SUI population. It has not been frequently reported with BAMS, although theoretically it may be associated with infection necessitating sling removal in some patients [46].

Abnormal postoperative pain or paresthesia is thought to be from compression or intraoperative disruption of the perineal nerves, or from healing around the newly placed bone screws. This complication is difficult to characterize because there is no standard level of pain that is considered abnormal. While some series acknowledged that the majority of patients experience mild pain for 1-3 months after surgery [221], others reported only those with severe pain that required explantation of the sling [222]. The pain generally resolves within 3 months [191,193,196,221,223] although persistent pain beyond 3 months has been reported46,50. Sling removal has been reported in two patients for persistent pain [46,50].

De novo detrusor overactivity or urinary urgency has been reported at 1-14% of patients, and can be treated with oral anticholinergics when necessary. One patient required sling explantation due to this complication [50].

There is a report of early loosening of one of the bone screws [223]. This caused recurrent incontinence and required a second operation to replace the bone screw. Bone screw dislodgement can happen as a late complication and has been reported in 3 patients [191,225].

Table 4. Results of sling procedures in males with stress urinary incontinence

Authors	No. Patients	Mean Follow-up (months)	Sling type	Cured (%)	Improved (%)	Failed (%)
Thüroff [219]	22	10.3	Fascial sling with suprapubic and perineal approaches	63.6	9	27.3
Madjar, et al[190]	16	12	Synthetic BAMS	86	14	0
Dikranian et al[45]	36 20	12 12	Organic Synthetic BAMS	56 87	31 13	13 0
Ullrich & Comiter[192]	36	25	Perineal Synthetic BAMS	67	25	8
Onur et al[193]	46	18	Synthetic or organic BAMS	41	35	24
John [53]	16	14	Polypropylene suspended suprapubically plus porcine skin collagen	69	6	25
Stern et al[187]	75	48	Bulbourethral suspension	36	32	32
Rajpurkar et al[194]	46	24	Synthetic or organic BAMS	37	37	26
Comiter[191]	48	48	Synthetic BAMS	65	20	15
Castle et al[221]	42	18	Synthetic BAMS	16	24	60
Migliari et al. [188]	9	14	Polypropylene needle suspension	55.6	22.2	22.2
Cespedes & Jacoby [220]	9	13	Perineal BAMS	66.7	11.1	22.2
Schaeffer et al. [184]	64	18	Vascular graft bolsters with needle suspension	56	8	36
Gallagher et al[222]	24	15	Synthetic BAMS	38	37	25
Fischer et al.[46]	62	15	Synthetic BAMS	34	24	42
Xu et al.[189]	26	28.3	Bulbourethral composite suspension	73	19	8
Giberti et al[195]	36	41	Synthetic or organic BAMS	62	8	30
Guimaraes et al.[223]	62	28	Synthetic or organic BAMS	65	23	12
Claudon et al[779]	106	12	Synthetic BAMS	61	14.5	24
Carmel et al [196]	45	36	Synthetic BAMS	36	40	24
Athanasoploulos et al[224]	43	24	Synthetic BAMS	51	30	19
Cornu et al[200]	136	21	AdVance	62	16	22
Cornel et al[204]	36	12	AdVance	9	46	46
Bauer et al[202]	126	27	AdVance	52	23	25
Rehder et al[201]	118	12	AdVance	74	17	9
Leruth et al[207]	173	24	TO inside-out	49	25	16
Grise et al[205]	122	12	I-Stop TOMS	60	27	13
Sousa-Escandon et al [210]	6	18	REMEEX- adjustable	83.3	17	-
Moreno-Sierra et al.[209]	48	7.5	Argus –adjustable	73	10	17
Romano et al[211]	51	32	Argus - adjustable	64.7	19.6	15.7
Romano et al[212]	47	45	Argus - adjustable	66	13	21
Hubner et al[213]	101	27	Argus –adjustable	79	0	21
Bochove-Overgaauw et al [214]	100	27	Argus-adjustable	40	32	28
Dalpiaz et al[215] 2011	29	35	Argus – adjustable	17	11	72
Jimenez et al[218]	14	19	REEMEX –adjustable	42	33	25
Sousa-Escandon et al.[210]	6	18	REMEEX- adjustable	83.3	16.7	-

The most common complications reported with the TO sling are perineal pain and urinary retention and studies are needed to establish the best rate between success and side effects among different slings.

Pain beyond the normal perioperative period has been reported to affect 0-20% of patients, and urinary retention has been reported in 3-21% of cases. While incision or explantation for retention is rare, the need for catheterization can persist for up to 12 weeks [200, 201, 226], with rare instances of retention lasting longer than 3 months203. Less commonly experienced is wound infection, with only rare sling infection or erosion requiring explantation [204, 226, 227]. Unlike the BAMS, however, there are occasional instances of worsening incontinence following TO sling placement, which likely occur if the sling is not adequately fixed in position, and allowed to migrate proximally and posterior to the urethra, thereby exerting a pulling tension that opens the dysfunctional urethral sphincter [204,228].

Reported rates of recurrent incontinence following sling surgery are generally low [46,191,194, 208], and it is unclear which patients are amenable to revision surgery. In theory, the adjustable slings are designed to allow increased sling tensioning via a simple adjustment of the tensioning mechanism silicone washer adjustment for the Argus [212], and varitensor adjustment for the REMEEX [229]. But the small sizes of the cohorts, and the limited follow-up of less than 5 years prevent meaningful comparisons of male slings and to the AUS at this time.

Permanent urinary retention is uncommon with male sling surgery, and may be avoided by excluding those patients with detrusor underactivity on preoperative urodynamics.[195,230,231]. However, a recent report from Han et al. [232] found no difference in postoperative residual or urinary retention when comparing 2 groups of men after sling surgery, one with preoperative normal contractility and one with impaired contractility.

2. Predictors Of Success

Several cohort studies have demonstrated that prior radiation therapy is associated with diminished efficacy of the male sling, probably due to urethral fibrosis and inadequate urethral coaptation.[49,187,193,195,207,233-235] Bauer et al [236] recently published their results of a cohort of men undergoing TO sling placement, all of whom had adjuvant radiotherapy following RP. They reported that success was only achieved in 50% of the cohort (cure in 25%), and that only 46% of men reported they were satisfied with the surgical outcome. With respect to the BAMS, Giberti et al. [195] recently reported a markedly lower rate of success in men who had had previous pelvic radiation, with only 15% cure in those patients. The adjustable REMEEX sling also appears to have inferior success in radiated men (60%) compared to patients without radiotherapy (90.2%) [229]. Worsening of incontinence may also occur and patients must be informed of this, especially those with mild incontinence.

The use of organic (resorbable) material is less efficacious than synthetic (permanent) sling material.[193, 195, 221, 237]. The treatment of male SUI with a suburethral sling requires tension that can only be maintained with the use of synthetic material. Pre-treatment severity of incontinence measured by the degree of leakage also appears to influence sling results. Several reports indicate that those with more severe leakage do not achieve similar continence rates when compared to those with milder leakage. [193, 195, 221, 224]. Fischer and colleagues were able to quantify, in prospective fashion, that leakage greater than 423gm on pre-operative pad weight predicted an inferior outcome, compared to those men with less leakage on pre-operative pad weight test. [46] In their report, 62 patients with SUI were followed prospectively. All patients were rigorously evaluated with 24-hour pad test, urodynamics and validated incontinence questionnaires. Success was determined by the Patient Global Impression of Improvement. Overall, 36/62 (58%) of surgeries were successful at a mean follow-up of 15 months. The only preoperative predictive factor was 24-hour pad weight. If pad weight was less than 423 gm, there was a 6-fold greater success rate compared to those with a pre-operative pad weight of greater than 423 gm.

Finally, previous AUS placement and explantation predicts sling failure.[192,216,221]. However, it is not clear if this is directly due to the urethral fibrosis and poor urethral coaptability, and/or if those patients simply suffer from more severe incontinence, which interferes with successful sling surgery.

3. Conclusion

In the intermediate term, the male sling appears to perform well. Slings have surpassed the artificial sphincter as the most common surgical treatment for PPI. The European Association of Urology Guidelines has concluded that there is limited short- term evidence that fixed slings cure PPI, that men with severe incontinence, previous radiotherapy or urethral stricture surgery have poor outcomes and no sling is superior to other slings. Adjustable slings have limited evidence of efficacy. [238] However, in the UK, the National Clinical Guidelines Centre in The Management of Lower Urinary Tract Symptoms in Men has stated that implanted compression devices and slings can be

offered to men with SUI only within the context of a randomized clinical trial [239].

The best candidates appear to be those with lower and moderate degrees of incontinence, who have neither had previous radiation nor AUS placement. With non-circumferential urethral compression, the male sling appears to have a lower risk of urethral erosion and atrophy than does the AUS in the intermediate term. In men with mild to moderate degrees of SUI, or for patients demanding a less invasive procedure or non-mechanical device, the male sling has established itself as a viable alternative to artificial sphincter. When given a choice of surgery, patients have been reported to overwhelmingly choose the male sling over an artificial urinary sphincter. Kumar et al [3] reported that in men with moderate PPI (pad weight 100 to 400 gm/24 hours) who were recommended to receive an AUS or a male sling, 92% opted for the sling. Interestingly, even when the surgeon recommended an AUS for severe leakage (> 400 gm/24 hours), 25% still opted for the sling. While intermediate and long-term data support the BAMS as a durable treatment for PPI, longer term outcomes of the TO sling, pubourethral sling, and quadratic sling are unknown. **(Level of evidence 3; Grade of recommendation C)**

c) Adjustable Balloons

The adjustable balloon procedure is based upon the concept of passive compression of the urethra utilizing two balloons located on either side of the urethra. Balloons may be progressively inflated until there is optimal coaptation, thereby achieving continence. The biomaterial name ACTTM (Adjustable Continence Therapy) was originally conceived and developed for female stress urinary incontinence, and subsequently was applied to male incontinence. The proACT™ device was developed and reported in 2000 [240].

The device consists of a silicone elastomer balloon attached to an injectable titanium port via a silicone tube. A balloon is implanted on either side of the urethra, either under the bladder neck for post-radical prostatectomy incontinence, or under the veru montanum for post TURP-incontinence. The ports are located subcutaneously in the scrotum, allowing simple access for percutaneous adjustment of the balloon volume. The implantation is performed under general or spinal anesthesia through a short perineal incision. A trocar covered with a U-shaped sheath is inserted up to the site of implantation, and then the balloon is pushed along inside the sheath. Fluoroscopic and urethroscopic guidance are used for the procedure. Transrectal ultrasound guided implantation [241] is a possible option. An isotonic medium with sterile water and contrast medium is prepared to fill the balloons with 2 ml during the initial procedure. Then, after a period of time, approximately one month, the balloons are topped up with 1 ml of this solution at each period (maximum filling is 8 ml) until continence is achieved. The adjustment of the filling are volume limited and are carried out step by step in order to obtain a pseudo-capsule surrounding the balloons and therefore to minimize the risk of urethral erosion or migration. Results from 8 prospective studies [48, 51, 242 - 247] reported are shown in **Table 5**. Of 170 patients reported by Hubner [242] and Lebret [51], one-third became pad free. In other studies

Table 5. Results and complications of six prospective series of Adjustable Balloons (proACT) in post-prostatectomy urinary incontinence

Authors	Number of patients	Follow- up (mo)	Number of adjustments (balloon refilling)	Postoperative Complications with explantation (uni or bilateral)	Continence 0 or 1 pad/day	Complete Continence
Hubner[242]	117	13 (3-54)	3 (1-15)	46 %	68 % (46/63)	35 % (22/63) (idem at 1 and 2 years)
Trigo-Rocha[243]	23	22 (6-48)	5 (1-6)	17 %	65 % (15:23)	
Hubner[48]	50 versus 50 (first pts/last pts)	20 vs 23	5 vs 4	58 % vs 24 %	52% vs 60 %	
Cansino Alcaide[244]	69	22 (3-48)	2	12 %	70 %	14 %
Kocjancic[245]	64	20 (12- 62)	3 (0–8)	17 %		67 %
Lebret[51]	62	6	4	31 %	71 %	30 %
Roupret[247]	128	56		18%	68%	66%
Gregori[246]	79	25	3.6	8%		66%

70% of patients utilized 0-1 pads daily [51,242-244]. Mean procedure time of 35 minutes was reported. Along with this improvement in pad use, there were parallel improvements in I-Qol quality of life score [51,242,243]. Based upon these trials, the mean number of post-operative adjustments of the balloon was 3 to 5, with some patients requiring 6 to 8 refillings. In an interesting comparison of the BAMS and ProACT, Crivellaro et al reported their experience of 84 consecutive patients assigned non-randomly to either surgery. Results were similar with respect to success (1 pad or less) with 68% and 64% achieving social continence respectively. However, the explantation rate for the ProACT was more than double that for the BAMS (14% vs. 6%) [248]. Gregori et al [246] recently reported that previous radiotherapy and severe incontinence were associated with higher ProACT failure rates. According to the degree of incontinence, dry rates achieved in patients with mild, moderate, and severe leakage were 85%, 64% and 33%, respectively. Whereas 66% of patients overall realized dryness on a 24-hour pad test, in those patients previously irradiated, the dry rate was only 36%. They therefore considered these pre-operative factors as relative contraindications to ProACT placement. Roupret et al [247] also recently reported a lower success rate in irradiated patients, with continence rates of 46% in radiated patients versus 68% overall. The only reported risk factor for failure or adverse events was prior external beam radiotherapy. Similarly, Kocjanic et al. [245] demonstrated a continence rate of 67% in non-radiated patients, compared to 36% in radiated patients.

1. Complications

The most common peri-operative complications are urethral or bladder perforation, necessitating removal of the implant on the perforated side. However, contralateral implantation was not adversely affected, and repeat ipsilateral implantation was invariably achieved after healing of the urethral or bladder wall. Lebret et al. [51] reported a perforation rate of 10% and Hubner [48] reported a rate of 18% early in their series, but a lower urethral perforation rate in the most recent cases illustrating a relatively short learning curve for optimal balloon placement near the urethral/bladder wall. Temporary urinary retention from presumed obstruction was reported at 5% [48]; removing fluid from the balloon restored voiding.

Device explantation was related to balloon failure, infection, erosion, or migration. The explantation rate ranged from 6 to 58% [48,51,242-247], but decreased with experience [48]. Device removal is straightforward, as a deflated balloon can be explanted transperineally.

As balloon deflation and migration may occur, a long follow-up is required to appreciate this technique over the time.

2. Conclusion

The proACT™ balloon technique appears to be a feasible procedure to improve the continence in short and median term, with better results occurring with more operator experience. Similar to the male sling procedure, appropriate candidates include those with mild to moderate leakage due to intrinsic sphincter deficiency, and no previous radiation. The benefit of an adjustable system should be weighed against the need for multiple sessions of refilling the balloon, and with reported rate of peri-operative and post-operative complications. Longer follow-up is needed before definitive comparison to male sling or artificial sphincter can be made. No recommendation is possible due to variable data on complication rates (12-58%). (**Level of evidence 3, Grade of recommendation D**).

d) Artificial Urinary Sphincter

The artificial urinary sphincter remains the most effective long-term surgical treatment for post RP incontinence due to sphincteric insufficiency. However, due to the cost, the perceived cumbersomeness of the device with resultant patient reluctance to have or inability to use a mechanical implant, and the fear of complications, it is not suitable for all patients. In addition, the development of less invasive techniques (as described above) potentially gives patients new options for treatment. Ultimately the choice of AUS will be based upon patient dexterity, economics, degree of incontinence, previous incontinence surgery, and expectations from surgery. Patient preference was tested in a study by Kumar et al.[3]. Based on the magnitude of their incontinence patients either had an AUS (high grade incontinence) or sling (low grade incontinence) or a choice between the two (moderated grade incontinence) recommended. Outcomes, length of experience and complications were reviewed with the patients. Of interest, all recommended to have a sling chose a sling, 75% recommended to have an AUS had an AUS while of those given a choice 92% chose a sling. This sheds some light on patient preferences in this area.

The AUS has the longest track record of success in the treatment of PPI. Two older studies have reported that about half of the patients with severe incontinence will undergo AUS implantation [249,250]. However, these studies were conducted before male slings and bulking agents became popular, and sling surgery has since surpassed the AUS in number of procedures performed annually. To this end, it is likely that the advent of the male slings has increased the rate of surgery in men with milder incontinence who may not otherwise have opted for an artificially sphincter. The success rates for AUS as defined by a continence status of zero to one pad per day range from 59% to 90% [251, 252], as shown in **Table 6** [56, 251, 253 - 262]. Just as with

Table 6. Results of the artificial urinary sphincter in post-radical prostatectomy incontinence.

Author	No. pts.	Follow-up (yrs.)	0-1 pad/day
Montague [253]	66	3.2	75%
Perez and Webster [251]	49	3.7	85%
Martins and Boyd [254]	28	2	85%
Fleshner and Herschorn [255]	30	3	87%
Mottet, et al [256]	96	1	86%
Madjar, et al [257]	71	7.7	59%
Klijn, et al [258]	27	3	81%
Haab, et al [259]	36	7.2	80%
Trigo Rocha, et al[56]	40	4.5	90%
Kim, et al.[261]	124	6.8	82%
Lai, et al.[262]	218	3.1	69%
Goldwasser [260]	42	1.2	82%

reported rates of incontinence following prostate cancer surgery depend on the definition of incontinence, continence rates with the AUS can vary with the definition of continence, the method of evaluation, and the length of follow-up. The lowest rates are from patient administered questionnaires when pad free rates range from 10-72% [254, 263 - 267]. Nevertheless, high satisfaction rates of 87% to 90% are consistently reported, even without total continence [255, 259, 263].

One potential downside of the AUS is the need for periodic revisions in a number of patients. Revision and explantation rates due to mechanical failure, urethral atrophy, infection and erosion vary considerably among studies with respectively reports of 8-45% and 7-17% [267]. In a large cohort reported by Lai and colleagues [262], non-mechanical failure has decreased from 17% to 9% and mechanical failure decreased from 21% to 8% following introduction of the narrow back cuff and mean time to reoperation was 26.2 months (mean 2-68 months). With a Kaplan-Meier analysis, the overall 5-year expected product survival was 75%. Only 6% of devices failed mechanically, at an average of 68.1 months, with 75% of patients requiring no revisions at 5 years. Actuarial freedom from revision at 5 years was estimated at 50%-75%. Interestingly, there do not appear to be any urodynamic factors that predict AUS failure in men with ISD. Whereas the male sling has been shown to have inferior success rates in patients with severe leakage, the AUS has been reported to have predictable success regardless of the degree of incontinence and regardless of detrusor underactivity, detrusor overactivity, low abdominal leak point pressure, or diminished compliance [58]. And while the success of the AUS in treating incontinence is not adversely affected by preoperative detrusor overactivity, the rate of persistent overactive bladder symptoms may be high (71%), and patients must be counselled accordingly [268].

The long term efficacy of the AUS was demonstrated by Fulford et al who reported that at 10-15 year followup,269 75% of patients with an implanted AUS either still had or died with a functioning device. Revisions include replacement of the malfunctioning part, cuff replacement, repositioning or downsizing due to urethral atrophy, a second or tandem cuff [270,271] or transcorporal cuff placement [272]. Transcorporal cuff placement, which involves inserting the cuff through the corporal bodies to avoid perforating the dorsal aspect of the urethra, can be particularly useful for patients with prior radiation or urethral erosion; however potency if present may be compromised. Some have advocated tandem cuffs not only as a salvage procedure, but also as a primary procedure for men with severe incontinence [273, 274]. However, O'Connor et al. reported no difference in continence outcome and a higher revision rate in patients undergoing double-cuff implant versus single-cuff after longer follow up [275].

An increased revision rate has been reported for patients who received pelvic radiation [254,27] but was not found in a recent series [252]. The results for continence for radiated patients are variable with some studies showing lower success rates [251,276] while others do not [266]. It has been recommended that such patients have a lower pressure reservoir and/or longer period of deactivation time [254].

CONCLUSION

The AUS remains the gold standard for the treatment of PPI secondary to sphincteric insufficiency in patients with severe incontinence, in those who

have had external beam radiation treatment and in those who have had prior AUS placement. It has the largest body of literature reporting long-term success. The long term success rates and high patient satisfaction seem to outweigh the need for periodic revisions in some patients. Intermediate term data with the male sling demonstrates that the sling is an alternative to the AUS in patients with mild-moderate SUI, provided that those patients have not failed previous AUS surgery, have not had radiation treatment, and have normal bladder contractility. Overall, the AUS remains the reference standard to which all other treatments must be compared. **(Level of evidence 2; Grade of recommendation B)**

5. TIMING OF SURGICAL INTERVENTION

There are no clear data on timing of a surgical intervention for the treatment of PPI, either with benign or malignant disease. Therefore, at present guidelines as to timing of the surgery cannot be formulated. A certain period of watchful waiting supplemented with conservative measures, particularly pelvic floor physiotherapy, seems to be a reasonable option. Thus, conservative management may be tried for periods of up to 6-12 months depending on whether there is any progress noted by the patient. Observational studies of men following prostate cancer surgery typically demonstrate improvement in continence from the early post-operative period until the end of the first year [114]. In addition, it is common for clinical trials of nonoperative management to follow patients for up to 12 months post-operatively, usually with improvement in both the intervention and the control groups during that year of follow up150. In a prospective cohort study of men undergoing RRP, Lepor and Kaci [76] demonstrated continued recovery of continence up to 24 months post-operatively, from 80.6% at 3 months to 95.2% at 12 months, reaching a plateau at 98.5% at 24 months. Other cohort studies have demonstrated a plateau in continence rates at 12 months [277, 278]. Since continence may improve up to 12 months post-operatively, and possibly even until 24 months, it is generally recommended that behavioral/conservative management be utilized during the first year after prostate cancer surgery.

There have been some studies evaluating the effect of early interventional treatment for incontinence. Schneider and colleagues [279] demonstrated a beneficial effect on the earlier return to continence with early injection of periurethral bulking agent. Results were better in the subgroup of 34 patients that were injected early (mean 23 days post-operatively) compared to 10 patients treated at a mean of 26 months post-operatively. It could not be demonstrated, however, that long-term continence is improved by early injection of bulking agent. Similarly, Jones and colleagues [280] demonstrated in a comparative cohort study of RRP patients treated either with or without a simultaneous suburethral sling, that sling placement at the time of RRP resulted in an earlier return to continence. There was no difference after 24 months.

(Level of evidence 3-4; Grade of recommendation C)

IV. INCONTINENCE AFTER PROSTATECTOMY FOR BENIGN DISEASE

1. INCIDENCE AND RISK FACTORS

The incidence of urinary incontinence after prostatectomy for benign disease has been reviewed and described in the AHCPR “Benign Prostatic Hyperplasia” linical Practice Guidelines [281]. The following percentages for stress incontinence and total incontinence, respectively, were reported:

Open surgery (retropubic or transvesical prostatectomy): 1.9% and 0.5%.

TUIP (transurethral incision of the prostate): 1.8% and 0.1%.

TURP (transurethral resection of the prostate): 2.2% and 1.0%.

These figures were based on studies reported before 1990. Several other series were published after 1990. These series were reviewed for the 1st, 2nd, and 3rd International Consultations on Incontinence [4, 282, 283]. A clear description of the method of follow-up and assessment of the continence status was indicated in only about one third of these studies. The incidence of incontinence after open surgery, TURP, TUIP and HoLEP is low: the reported percentages ranged between 0 and 8.4%. Since the method of assessment of the continence status and the definition of incontinence is rarely stated it is actually not possible to make a distinction between simple stress incontinence and total incontinence. There is generally no clear indication that the incidence is affected by patient age or (resected) prostatic volume. [282] However, a recent study out of Brazil did demonstrate that the rate of urinary incontinence following BPH surgery is higher in older patients. However, most of the increased incidence in incontinence was due to bladder dysfunction rather than to sphincter insufficiency. In a retrospective chart review from Wendt-Nordahl and colleagues [284], the incidence of incontinence following TURP was reported to have decrease over 17 years, from 3.3% in 399 patients operated on between 1987 and 1997, compared to 1.3% in 550 patients operated on from 1997-2004. It is not clear whether this statistically significant ($p< 0.05$) difference was due to improvement in surgical technique or patient characteristics. However both the earlier and later incontinence rates are consistent with those in the AHCPR and AUA guidelines reports.

In 2003, the AUA published guidelines for the management of "benign prostatic hyperplasia" [285]. The estimated frequency of incontinence following TURP was 3% (from 19 trials that included > 5000 patients). However, the Veterans Affairs Cooperative Study, reported an incontinence rate of only 1% in TURP patients, which was not different from the watchful waiting arm [286]. The AUA conducted meta-analysis of RCTs comparing TURP with TUIP or transurethral electrovaporization did not reveal any statistically significant differences in incontinence rates. [285, 287-291] The 2010 AUA updated guideline provided no additional information [292].

Over the past decade, transurethral holmium laser enucleation of the prostate (HoLEP) has become a standard treatment for BPO. Review of RCTs by the AUA as well as a meta-anlaysis of RCTs comparing TURP with HoLEP did not reveal any significant differences in incontinence rates [285,291,293-299]. While incontinence did not increase with age in men undergoing HOLEP with morcelation, it was noted that the overall complication rate - including bladder mucosal injury, urethral stricture disease, and bladder neck stenosis = was higher in patients with prostate volumes > 50 g [300]. Moreover, it does not appear that either bipolar resection of the prostate or photovaporization of the prostate are associated with a substantially different rate of urinary incontinence than are other BPO surgeries [301]. While incontinence following PVP is comparable to that of other BPO surgeries, and more often than not improves over 12-36 months postoperatively with conservative management, the rate of post-operative dysuria is higher than that of TURP, recently reported at a rate of 10.1% [302].

In summary, the incidence of urinary incontinence after open surgery, transurethral resection of the prostate, transurethral incision of the prostate, and holmium laser enucleation of the prostate is low, and does not differ appreciably among the various techniques.

2. TIMING OF SURGICAL INTERVENTION

There are no clear data on timing of a surgical intervention for the treatment of incontinence, as mentioned above in the section on post-radical prostatectomy. Therefore, at present guidelines as to the timing of surgery cannot be formulated. A certain period of watchful waiting supplemented with conservative measures, particularly pelvic floor physiotherapy, seems to be a reasonable option. Thus, conservative management may be tried for periods of up to 6-12 months depending on whether there is any progress noted by the patient. (Level of evidence 3-4; Grade of recommendation C)

3. SURGICAL TREATMENT OPTIONS

a) Artificial Sphincter

The literature on this subject was reviewed for the 1st, 2nd, and 3rd International Consultations on Incontinence [4, 282, 283]. Candidates for treatment with the artificial urinary sphincter (AUS) are patients with incontinence due to intrinsic sphincter deficiency that have normal bladder compliance [303]. Detrusor overactivity is not a contraindication [268]. The AUS has been placed around the bulbar urethra via a perineal route or transverse scrotal routes [304] or around the bladder neck [4, 282, 283]. The above mentioned review of the results obtained with the AUS indicated that more than 70% of the men treated with the AUS for this indication are dry or almost dry after a follow-up of more than 2-3 years. However, most series on the AUS include both post-prostatectomy incontinence for benign and malignant disease [282].

In summary, the AUS is a successful surgical treatment option for post-prostatectomy incontinence. It is the most commonly performed surgery for post-prostatectomy incontinence, with the longest follow-up and therefore longest record of success. (**Level of evidence 2; Grade of recommendation B**)

b) Injectable Agents

Most series include post-prostatectomy incontinence after treatment for benign and malignant disease, with the majority after prostate cancer surgery. For collagen, "success rates" range from 36-69%, with 4-20% of patients reporting being dry. [157-164] Study results are inconsistent with both TURP [305] and radical prostatectomy [306] showing better outcomes.

Other bulking agents such as polydimethylsiloxane PDMS (Macroplastique®) have shown some initial success, but results also deteriorate over time. Bugel and co-workers treated 15 patients. They noted rapid deterioration of initial improvements with success rates of 40%, 71%, 33%, and 26% at 1,3,6, and 12 months respectively [168]. As mentioned previously in the section on post-radical prostatectomy incontinence Kylmala et al. prospectively studied 50 patients with mild to moderate SUI (average 48 cc on 1 hour pad test), with 12% achieving continence following 1 injection, and an additional 20%, 18%, and 10% achieving continence with 2, 3, and 4 injections respectively [169]. Follow-up, however, was only 3 months. In a randomized trial of AUS versus Macroplastique injection in patients with minimal SUI (the vast majority had SUI following BPO surgery, with less than1/3 of the cohort suffering from SUI following RP), Imamoglu and colleagues demonstrated no difference in success with AUS versus Macroplastique. However, in patients with more severe incontinence, AUS was superior, with minimal improvement following transurethral Macroplastique. [52] There has also been some initial work with sphincteric injections of muscle stem cells.[173,174]

Bulking therapy fails in up to 75% of men. Of those who are improved only a minority actually becomes

dry with short-term follow-up. Although bulking therapy may be slightly more efficacious in treating SUI following TURP compared to SUI following prostate cancer surgery, bulking is of limited value in those men with all but minimal SUI. **(Level of evidence 3; Grade of recommendation C)**

c) Male Sling Procedures

Since Frangenheim described his first successful urethral sling suspension for post-traumatic stress urinary incontinence in 1914, various sling materials and surgical methods have been reported [307]. Rectus fascia, as described by Frangenheim, has distinct advantages over alloplastic materials with respect to erosion and infection risks. Allograft off-the-shelf-materials like lyophilized fascia lata have a higher infection risk than does autologous fascia, whereas the use of synthetic materials like polypropylene mesh or polytetrafluoroethylene slings are associated with a higher incidence of urethral erosion [308]. According to various published techniques, the sling can be placed either underneath the bladder neck, the urethral bulb or the membranous portion of the urethra. The principle of continence support is similar for all sling procedures and comprises passive compression of the urethra, which is dependent on the applied sling tension [219]. This mode of action favours sling procedures as a treatment option for intrinsic sphincter deficiency. However, the sling tension needed for restoration of continence has not been standardized, with tensioning techniques ranging from perfusion sphincterometry, to a cough test, to visual approximation, [193, 309] and therefore the success of the procedure probably depends heavily to the surgeon's experience and the degree of sphincteric incompetence. Overcorrection with consequent urinary retention (especially in the setting of detrusor underactivity) and undercorrection with persistent or recurrent incontinence are certainly possible, which may adversely affect continence, bladder emptying, and patient satisfaction. Most series of sling surgeries deal with a preponderance of men following prostate cancer surgery. Therefore, it is difficult to draw conclusions about any differences in sling efficacy between those with SUI following BPH surgery versus those with SUI following RP due to small numbers of BPH patients most the cohort series.

V. INCONTINENCE AFTER EXTERNAL BEAM RADIOTHERAPY ALONE AND IN COMBINATION WITH SURGERY FOR PROSTATE CANCER

The risk of incontinence after external beam radiotherapy (EBRT) for prostate cancer is variable and ranges from 0 to 18.8%. Lawton et al. [310] reported a risk of urinary complications of 7.7% in more than 100 patients, proportional to dose. Perez et al. [311] found incontinence in only 5 of 738 patients. Shipley et al. [312] reviewed more than 2500 cases with an incontinence rate of 0.5%. Similar incidences have been reported in more recent series. Madalinska et al. [77] reported an incidence of 6-7%. With three-dimensional conformal radiotherapy, Weil and colleagues [313] reported no incontinence in 168 consecutive patients and Hanlon et al. [314], in a series of 195 men, found that post treatment urinary symptoms were no different from a control group without cancer. With conformal radiotherapy, Sandhu et al. [315] reported a 9% incidence of stress incontinence in 110 patients. the impact of EBRT followed by prostatic boost, for a total of 66-70 Gy, was evaluated. Scalliet and coworkers [316] reported urinary incontinence in 16% of 230 patients, however, Fransson and colleagues [317] reported an increase in urinary incontinence on a patient-administered symptom bother scale 3 years after treatment in 153 men compared to pretreatment status. The increase was from a mean of 0, at the start to 2 out of 10 at 3 years. Ponholzer et al. [318] reported incontinence in 18.8% of a group of 82 men who were surveyed 4.4 year after EBRT for prostate cancer. Furthermore urinary incontinence worsened from year 2 to year 6 in a cohort of 147 men treated with 3D conformal RT. [319] Budaus et al. [320] conducted a review of radiation series published from 1999-2010 and concluded that early storage symproms are commonly reported but long-term incontinence is not.

Pre-radiotherapy transurethral prostatectomy may be a risk factor for incontinence. Jonler et al. [321] reported an incontinence rate of 11% with pretreatment TURP. Green et al. [322] and Lee et al. [323] also reported a higher risk of incontinence with pretreatment TURP versus those without with 5.4% and 2% respectively. There are no series reported on the treatment of patients who only have incontinence after EBRT.

Salvage or adjuvant radiotherapy is frequently given after radical prostatectomy and the impact on continence is controversial. Petrovich et al. [324] reported no difference in incontinence in 2 cohorts of patients, one with and one without adjuvant radiation. In a follow-up study the same group reported no late toxicity. [325] Fontaine et al. also reported no change in continence status in 16 of 17 men after salvage radiation. [326] However, Petroski et al. reported that postoperative radiotherapy worsened continence in 26% of 129 patients followed for a median of 5 years. [327] On the other hand salvage radical prostatectomy following external beam radiotherapy has been generally reported to have a high incidence of urinary incontinence [328-330] possibly because of radiation induced fibrosis of the external sphincter. [329] Cozzarini et al. demonstrated that older age and greater radiation dose in the salvage setting and younger age and hypertension in the adjuvant setting resulted in worse urinary toxicity. [331]

1. SURGICAL TREATMENT

Results of surgical treatment of incontinence in this setting are based on retrospective clinical series. In the past the most commonly published treatment modality was the artificial urinary sphincter as therapy for sphincter damage. As discussed and referenced in the following paragraphs, the series published contain both patients who had and had not received radiotherapy and collagen injections have also been reported in case series.

There has been a higher reported revision rate for the artificial sphincter following radiotherapy (**Table 7)** [251, 252, 254, 262, 265, 276, 332, 333] compared to low risk patients, 38% versus 22%. Although recent reports dispute the higher rate [252, 262]. However, generally this is due to a higher incidence of erosion and infection as well as urethral atrophy, possibly secondary to radiation induced vasculitic fibrosis of the urethra.254 Radiation may also induce detrusor overactivity or poor compliance leading to urgency incontinence. Recurrence of bladder neck contracture may be more common. [262] Radiation was also identified as a co-morbidity associated with erosion [334] and infection. [335] However, good results are reported, and it is generally recommended that the cuff be inserted outside the radiated field. [336]

Collagen injection has also been reported for incontinence after radical prostatectomy and adjuvant radiation [159,163,305,337-339] or after salvage radical prostatectomy following radiotherapy [166.340] Continence results are poorer compared to those without radiation. [306] Very few patients have been reported on with the use of Macroplastique following radical prostatectomy and adjuvant radiotherapy.

The male perineal bone-anchored sling has been reported in patients following adjuvant RT. In Comiter's group with the perineal compression sling 3/21 with radiation had no adverse sequelae.166 Similarly in the series of Onur et al. radiation did not cause a worse outcome.[193] However, Schaeffer et al. reported that prior irradiation was the only identified factor that predisposed to failure. Their success rate following a single sling procedure was only 29% (2 of 7) for irradiated patients, and the corresponding rate for nonirradiated patients was 68% (39 of 57). [184] They postulated that the sling acts by compressing and elevating the urethra, thereby increasing urethral resistance to abdominal pressures. Theoretically, radiation-induced fibrosis of the urethral and periurethral tissues would make compression and elevation more difficult by reducing tissue compliance and mobility. As mentioned above, the results of AdVance slings, adjustable slings, and adjustable balloons are adversely affected by radiation.

In summary, despite the frequently reported higher incidence of complications of the artificial sphincter in post-prostatectomy patients after adjuvant radiation, it has provided acceptable treatment benefits. Injectable agents have yielded poor results. Other techniques are adversely affected by radiation. (**Level of evidence 3; Grade of recommendation C**)

VI. INCONTINENCE AFTER OTHER TREATMENT FOR PROSTATE CANCER AND NEOBLADDER FOR BLADDER CANCER

1. BRACHYTHERAPY

Brachytherapy is a form of radiation therapy in which radioactive materials are placed directly into the prostate gland. The incidence of incontinence following this modality is given in **Table 8** [341-353] and was previously related to the treatment of post-brachytherapy retention of urine. Numerous series have reported retention to be associated with larger initial prostate volumes. [354] In a systematic review of brachytherapy series, Crook et al. [350] reported the incidence of retention to be 1-14%. Many patients require prolonged or permanent alpha blocker or TURP. The main risk factor for incontinence after brachytherapy is TURP. Hu and Wallner [347] reported on the incidence of urinary incontinence after TURP/TUIP following prostate bracytherapy for prostate cancer. Of the 10 patients who underwent the outlet relaxing procedures for refractory urinary obstruction, 7 developed some degree of permanent urinary incontinence. They surmised that the cause may be multifactorial and may include physical damage to the urinary sphincters and the radiation dose to the urethral region. Surgical therapy when required has included the artificial sphincter. [348] High dose brachytherapy that is administered over a short period of time may have reduced toxicity. [355] Urethrorectal fistula is another complication that has been reported in 1.8% of patients in a large U.S. medicare retrospective review. [348] Salvage brachytherapy leads to a higher rate of urinary tract complications. [330]

2. CRYOSURGICAL ABLATION OF THE PROSTATE

Cryosurgical ablation of the prostate is used for clinically localized prostate cancer either as primary treatment or after unsuccessful external beam radiation therapy. The frequency of the main lower urinary tract complications are listed in **Table 9** [356-369]. The artificial sphincter has been mentioned as one of the treatments for incontinence. [367] Cryotherapy is an adverse factor for collagen injections. Urethrorectal fistulae can also occur in up to 5% of treated patients. Severe incontinence and fistulae that occasionally results may have to be treated with extirpative surgery and diversion. [370]

3. HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU)

Transrectal high-intensity focused ultrasound is another minimally invasive treatment for prostate

Table 7. The artificial sphincter for incontinence after radiotherapy

Study	Numberof patients	Revision rate after radiotherapy	Continence
Martins and Boyd [254]	34/81	38% for whole group	88%
Wang and Hadley [332]	16	25% (Infection and Erosion - 12.5%)	87%
Perez and Webster [251]	11/75	55%	63%
Gundian et al. [333]	15/56	22%	90%
Elliott and Barrett [265]	46/313	22%	–
Manunta et al. [276]	15/72	53% (Infection and Erosion – 20%)	73%
Gomha and Boone [252]	28/86	25% (Similar to a non - Radiated control group)	64%
Lai et al.[262]	60/176	20% versus 32% for non - radiated group)	69%

Table 8. Incontinence after brachytherapy for prostate cancer

Author	% Incontinence	% Post TURP	% No TURP
Beyer et al. [341]	1	-	-
Blasko et al. [342]	6	17	0
Stock et al. [343]	0	-	-
Wallner et al. [344]	0	-	-
*Kaye et al. [345]	4	11	1
*Blasko et al. [346]	13	-	-
Hu and Wallner [347]	6	70	-
Merrick et al. [349]	0	-	-
Crook et al.[350]	5.6	13	-
*Talcott et al. [351]	45**	83	39
Bottomley et al. [352]	1.5	-	-
Barkati et al. [353]	0	-	-

** Implant plus external beam radiation*
*** Any incontinence*

Table 9. Lower urinary tract complications after cryosurgery for prostate cancer

Author	N	% Incontinent	% Bladder outlet obstruction
Shinohara et al. 356	102	15	23
Bahn et al. 357	210	3	9
Cox and Crawford 358	63	27	29
Wieder et al. 359	83	2.5	13
Cohen et al. 360	239	4	2.2
Coogan and McKiel 361	95	3.5	6
Sosa et al. 362	1467	11	6.8
Long et al. 363	145	83/2.0*	17.2
Pisters et al. 364	150	60	43
Derakhshani et al. 365	48	10.4	22.9
Long et al. 366	975	7.5	13
De la Taille et al. 367	43	9	4
Robinson et al. 368	46	29 (urinary bother)	
Dhar et al. 369	860	0.9 (8/460)	6

**Previously radiated/not previously radiated*

cancer. HIFU destroys prostate cells by coagulative necrosis of the tissue without damaging the structures intervening between the transrectal probe and the target tissue [371]. Reports of efficacy also include morbidity. In a systematic review involving 37 articles/abstracts Rebillard et al. [372] reported that stress incontinence occurs in 6-28%, urethra/bladder neck stenosis in 1-31%, and rectourethral fistula in 0-3% of treated patients. With improvements in techniques the risk of complications is decreasing [372]. In a recent sytematic review from 2000-2011, Cordeiro et al. noted that the rate of incontinence ranged from <1-34.3% [373].

4. INCONTINENCE AFTER NEOBLADDER CONSTRUCTION

The incidence of continence after neobladder construction following radical cystectomy for bladder cancer ranges from 85 to 100% during the day and 55 to 100% at night **Table 10** [374-386]. Most patients achieve daytime continence after one year and nighttime continence after 2 years. Most of the published reports do not comment on specific surgical management and imipramine is mentioned as treatment only occasionally. Martins and Boyd [254] reported on 8 patients treated with the AUS for persistent sphincter weakness incontinence. Six of these underwent revisions, 3 for infection and/or erosion and 3 for inadequate cuff compression. They cautioned against the use of the AUS and suggested alternatives such as intermittent catheterization at night. However, O'Connor and colleagues [387] reported a successful outcome, after AUS, with no complications in 5/5 men with incontinence after neobladder, with a mean follow-up of 22 months and Simma-Chiang et al. [388] reported success in 11/12 men 22 months after AUS implant. The bone-anchored sling has been reported for one case [389] and the AdVance sling for 2 cases [226] Collagen has only been reported in women following neobladder construction.[390]

In summary there are not enough data upon which to recommend definitive surgical therapy, although the artificial sphincter is reasonable. **(Level of evidence 3; Grade of recommendation C-D)**

VII. TRAUMATIC INJURIES OF THE URETHRA AND PELVIC FLOOR

Incontinence following posterior urethral injuries occurs in 0-20% of patients [391,392] and is thought to be due to the extent of injury rather than to the method of management.

The data on surgical treatment are all retrospective case series and the most commonly published surgical therapy is the AUS. The series published contain both patients with and without traumatic injuries. Perez and Webster [251] reported on 27 patients after urethral or bladder neck strictures. The revision rate was 41% and the continence rate was 85%. In a subsequent report from this centre on reoperations the patients with traumatic injuries were not discussed separately. [393] In Montague's [253] series 22 out of 166 patients had incontinence after trauma. He did not separate the results of this group from those of the other patients. Martins and

Table 10. Continence after neobladder construction for bladder cancer

Author	Number of patients	Follow-up (mo)	Continence (%) Day	Night
Alcini et al. [374]	34	12	100	83
Cancrini et al. [375]	89	24 (22% with SUI)	97	83
Elmajian et al. [376]	266	24	85	85
Studer et al. [377]	100	24	92	80
Benson et al. [378]	32	25	94	74
Abol-Enein and Ghoneim [379]	60	24	90	80
Rogers and Scardino [380]	20	24	90	55
Hautmann et al. [381]	211	36	85	85
Hautmann et al. [382]	363	57	95	95
Steven and Poulsen [383]	166	32.4	100	100 (After 5 years)
Abol-Enein [384]	353	38	93.3	80
Carrion et al. [385]	56 ileum	41	91	68
	57 colon	41	86	68
Nieuwenhuijzen [386]	62	>12	90	67
	50 (sexuality preserving)	>12	96	67

Boyd [254] reported on only one patient out of 81 with a traumatic urethral injury. This patient was dry and required no revisions. Venn at el. [336] reported on 2 with pelvic trauma out of a total of 70. Mundy and Andrich reported successful AUS implant in 7 out of 8 patients after reconstruction for pelvic fracture-related injuries. [394] **(Level of evidence 3; Grade of recommendation C)**

Bladder neck reconstruction by excising the scar and narrowing the calibre was reported by Iselin and Webster [395] in 6 patients who had incontinence with an open bladder neck on cystourethrography, following urethroplasty for traumatic strictures. Bladder neck closure with a Mitrofanoff catheterizable abdominal stoma has also been reported as treatment following severe urethral or bladder trauma. [396] **(Level of evidence 3; Grade of recommendation C)**

For patients with severe bladder neck strictures and incontinence after prostate surgery Meulen et al. [397] and the group from Baylor [262, 398] reported on the use of a Urolume stent with a bulbar artificial sphincter. Alternative management with perineal urethroplasty and subsequent artificial sphincter placement in 6 patients was reported by Simonato et al. [399] **(Level of evidence 3; Grade of recommendation C)**

In summary, the AUS provides a reasonable outcome in appropriate cases. Since there are so few reports of alternative therapies the C recommendations were based primarily on expert opinion as to what is reasonable surgical therapy in very difficult cases.

VIII. CONTINUING PEDIATRIC PROBLEMS INTO ADULTHOOD: THE EXSTROPHY-EPISPADIAS COMPLEX AND OTHER CONGENITAL ANOMALIES

In exstrophy, the bladder plate at birth is smaller than a normal bladder. It is uncertain whether that which does exist is normal. It has been shown that the muscarinic cholinergic and other neuropeptide receptors in exstrophy detrusor muscle are the same as in controls [400, 401]. Microarray analysis shows that the bladders are developmentally immature [402]. The number of number of myelinated nerve fibers in the detrusor is reduced in new born exstrophy bladders compared to that of neonates who had died from cardiac causes (controls) [403]. It seems probable that the spectrum of neurological and morphological changes seen in exstrophy bladders beyond the neonatal period, are largely secondary to the medical management [404].

Control of the bladder outlet depends on proper function of the pelvic floor musculature and of the urethral sphincters. In exstrophy infants who have not had an osteotomy, the pelvic floor muscles have normal bulk, but abnormal orientation, especially in their relationship to the urethra. They are unable, therefore, to contribute very much to urethral continence [405]. The prostate is a flat plate of normal size, lying behind the urethra. It is not wrapped around the urethra [406]. Growth of the prostate at puberty will not improve continence.

The existence of the urethral sphincters is also uncertain. There is no histological study to show their presence or innervation. However, electromyographic studies of continent children have shown normal electrical traces [407].

Epispadias is a very rare condition. There are very few data on the bladder and sphincters for this diagnosis alone. In general the bladder is of better volume and there may be some active sphincter function in those at the better end of the spectrum.

Storage of urine in children with exstrophy depends on creating sufficient bladder outflow resistance that there is a leak point pressure great enough to stretch up the bladder volume. Voiding depends on the ability, either by detrusor or by abdominal wall contraction, to generate enough pressure to overcome a fixed outlet obstruction.

The pediatric literature often refers to patients with exstrophy having a ‘dry interval’ of so many hours. The implication of this is that the bladder has a fixed capacity beyond which the pressure becomes higher than that of the fixed outflow resistance. Providing the child recognizes this point, a visit to the lavatory will avoid incontinence. Patients in many clinical situations to avoid a ‘social or hygienic problem’ use this technique of timed voiding but it does not constitute continence as would be understood by a ‘normal’ person. It is a means of managing poor bladder control. It is rare to find literature on the long-term follow-up of patients with this complex describing ‘normal’ continence. The evidence base is level 3 at best.

1. EARLY MANAGEMENT OF EXSTROPHY AND EPISPADIAS

The early reconstruction of bladder exstrophy is clearly important but not a subject for this chapter. Only an outline will be considered as a basis for discussing problems of continuing incontinence in adolescence and adulthood. Techniques have gradually evolved over the last 100 years since the first (transiently) successful closure described by Trendelenberg in 1906 [408]. The most important development, at least in Western countries, is the concentration of cases in a small number of centers. In the United Kingdom, for example, it is estimated that 12 babies a year are born with exstrophy and all are cared for in two centers.

Broadly, there are three approaches to early reconstruction –

- Staged repair, originally described by Jeffs [409]. Here the principle is to close the bladder in the first operation. The bladder neck and epispadias repair are then done as a second stage.
- Complete primary repair of bladder exstrophy (CPRE) often attributed to Mitchell [410]. The objective is to close the bladder and bladder neck and to repair the epispadias in one operation. Although more than one operation is often needed, the important principle is to create bladder outflow resistance as early as possible. This should allow proper development of bladder volume and compliance. A subsequent bladder neck reconstruction may be needed in up to 40% of children [411].
- Single stage radical soft tissue mobilization (RSTM), usually called the Kelly operation [412]. The entire anterior pelvic contents with blood and nerve supply are mobilized from the pelvic sidewall, reconstructed and repositioned more posteriorly in the pelvis. There is no osteotomy, but the radical mobilization allows abdominal wall closure without osteotomy.

Each of these is subject to many modifications by different surgeons, which makes comparison of results difficult. Not surprisingly, there are no controlled trials. Outcomes have been described from specialist centers with good results and from generalists with, usually less good results.

At the longest follow-up available, the results of these three approaches are very difficult to determine, at least as far as bladder function is concerned. Data beyond the age of 18 are limited, especially for RSTM. Definitive reports in peer-reviewed journals of long-term outcomes from the centers that specifically champion these techniques are lacking. There are reports from other centers of small numbers of patients, but often without the use of a consistent technique.

Approximate figures are given in **Table 11**. Sadly, the results in the world at large are much worse. There are also differences in outcomes in relation to the condition of the kidneys, genitalia, cosmetic appearance and sexual function that are beyond the scope of this chapter.

2. LATE BLADDER FUNCTION

If the figures for continence shown in the table are maintained into adult life and 'partial continence' is not acceptable, no more than 70% of patients will have a native bladder and normal voiding. In reality, this figure is rather optimistic and may be as low as 7% [413].

For the children who have done well, there is some evidence that continence may not be maintained into adulthood. In a follow-up of 56 patients for a minimum of 20 years, 13 were found who where continent and voiding naturally at 10 years old. However, by 20 years old, only three were still in this situation. The remainder were augmented or on CIC or both. The patients had been operated in the 1960s and early 1970s by older techniques than are currently used [414].

Late failure has several possible causes. Possibly the most important is that the outflow resistance generated by bladder neck reconstruction is not sphincteric, but fixed. Voiding is, therefore, always against obstruction. Deterioration in bladder function would come either from detrusor failure or from overactivity. Borer et al found detrusor overactivity in six of 13 children (46%) who had had a staged repair but in none of 19 who had had CPRE [407].

Another problem was identified by Yerkes et al. [415] In an investigation of 18 children who were said by themselves and their parents to be 'continent and voiding well', none were, in fact, voiding normally. Apart from infections, stones and a dry

Table 11. Outcomes of childhood surgery for exstrophy with special reference to continence. Data are best estimates from recent literature from specialist centers. Approximations have been taken as reporting systems are not consistent between papers [412,780,781].
CPRE - Complete primary repair of bladder exstrophy

	Continent, voiding, native bladder	Partial continence, voiding, native bladder	Continent, CIC, native bladder	Continent, CIC, augmented bladder	All other outcomes
Staged repair	70%	10%			20%
CPRE	76%			3%	21%
RSTM	10%	29%	10%		51%

RSTM - Single stage radical soft tissue mobilization

interval of two hours, there were major objective bladder dysfunctions in all patients. Seventy two percent had a residual urine of at least a third of bladder capacity; 70% had a flow rate below 10ml/sec; 30% had staccato stream; and 36% voided by Credé's maneuver.

Finally, there is the problem of the definition of continence. The disciplined life of a closely supervised child may well make a three-hour dry interval seem like continence. It fits in well with the school routine. It does not lie well with the life style of an adolescent. It quickly becomes apparent that the coffee, sodas and alcohol that soon become a part of an adolescent's life expose the fact that they have to make far more visits to the lavatory than their peers or risk being wet. It has been shown that one of the prime desires of exstrophy adolescents is to be 'normal'. This includes being treated as normal and having normal lavatorial habits [416]. This difference from normality may drive some young adults to seek continence surgery even though, by pediatric criteria, they had been classed as continent.

3. MANAGEMENT OF INCONTINENCE

a) Investigation

Standard investigations for incontinence are appropriate for patients with exstrophy. Urodynamic studies have been use to clarify the etiology and have clinical value in management [407,415]. Dave et al. [417] investigated 31 children one year after a modified bladder neck reconstruction. Fifteen had satisfactory continence defined as a dry interval of two hours or more, no stress incontinence and no more than two episodes of nocturnal enuresis per week. The continent children had a better bladder capacity at 162 ml compared to 113ml for those with poor continence or 55ml for the totally incontinent. End filling pressure was around 31cm H_2O for the continent children versus 48 or 41cm for the other two groups. However, involuntary detrusor contractions were seen in a third of the continent group and were associated with a lower than average bladder capacity and less good compliance than the other continent children.

It has been pointed out by Hollowell et al. [418] that even in severely incontinent children who appear to drip continuously, leakage is often due to detrusor overactivity. They found that a leak point pressure (LPP) of at least 10 cmH2O was necessary to allow bladder expansion. However, in some children with a higher LPP than 10, bladder expansion did not occur because detrusor contractions were constantly emptying it.

As in other conditions of bladder abnormality, end filling pressures over 40cmH2O were associated with hydronephrosis (two thirds of patients) [417].

The role of electromyography (EMG) of the sphincters has been reported but not correlated with management or outcomes [407]. In Dave et al's [417] patients only 12 children voided with sustained detrusor contractions and only five voided effectively. Ten children had persistent EMG activity during voiding but no other detectable neurological abnormality. Eight of them had significant residual urine volumes.

Some authors stress the importance of examination under anesthetic. In the assessment of incontinence, the volume of the bladder has some predictive value and is most accurately measured under general anesthesia. Although not statistically significant, children with a bladder capacity before bladder neck reconstruction of less than 25ml do less well than those with larger bladders [407]. Secondly, a transverse oval appearance of the bladder neck is associated with its incompetence and hence incontinence [411].

Complete objective evaluation of bladder function in this manner is particularly important in exstrophy as the description by patients and parents is unreliable [415].

b) Medical Management

The apparent normality of the detrusor muscle at least in infants born with exstrophy, suggests that standard anti-muscarinic drugs should be effective in detrusor overactivity [400]. There have been no disease specific controlled trials, least of all in adults. In children, there has been an uncontrolled trial of imipramine using both clinical and urodynamic criteria to assess response [419]. All of 17 children (mean age 7.9 years) had urodynamically proven detrusor overactivity, small poorly compliant bladders and incontinence. Imipramine 1.5 – 2.0mg/kg was given for a mean of 9.5 months. There was a 40% increase in bladder capacity and a 25% reduction in end filling pressure. Eleven of 17 children had a clinically significant improvement in continence; all of eight children with partial continence (1-2 hr dry interval by day but enuretic) became dry day and night with a dry interval of more than 2hours. Three of nine children with severe incontinence improved. Hydronephrosis improved in three of nine patients. In an editorial comment on this paper, Gearhart stated that he used oxybutynin 0.5mg/kg in combination with imipramine, which 'gave even better results'. No further data were given.

c) Bulking Agents For The Bladder Outflow

In patients with exstrophy who have bladder outflow weakness, there is logic in using injectable bulking agents to increase resistance. Although not mentioned in the literature on this subject, the obvious drawback is that there will be even greater fixed outflow resistance that may limit the opportunity for the action of any active sphincter.

Burki et al. [420] reported the use of polydimethylsiloxane (macroplastique™) in 34 children with exstrophy and 18 with primary epispadias. Apart from bladder neck reconstructions eight had had augmentations. In addition, 14 relied on a Mitrofanoff for self-catheterization. There was no standard technique of injection and the objective seems to have been to put in enough of the bulking agent to produce visual occlusion of the bladder neck area using 2.5 to 7.5 ml. Twenty patients had one injection and the rest had an increasing number up to seven. The follow-up assessment was entirely clinical and there were no urodynamic data. Only 17% were completely dry at a mean of 4.6 years; 33% were reported to be significantly improved. The milder the initial incontinence the better the result, however four of 36 patients who were totally wet did become totally dry. The continence rate was improved by up to four injections but only one patient became dry after more than four (he became dry after six injections). Other bulking agents have been reported including Teflon and collagen but in series of patients with different diagnoses including exstrophy and epispadias.

d) Surgical Management

Adults with exstrophy who have failed to become dry after initial reconstruction and the relatively conservative management of medication and bladder neck bulking have a difficult decision to make. The most elusive outcome is to create a bladder that is continent and from which there is spontaneous voiding. It will be seen that the choice to achieve this result is a second bladder neck reconstruction or insertion of an artificial sphincter. Both of these require a natural bladder of adequate capacity and which retains normal detrusor function. If the bladder is small or of high pressure, there may be some improvement when outflow resistance is increased with a successful bladder neck procedure, though, again, the data come from studies in children and may not be applicable to adults [407]. Otherwise, augmentation will be necessary. The options for augmentation, with or without a Mitrofanoff, are considered elsewhere in this chapter.

A more realistic objective if the urethra is to be used for urinary drainage would be to accept CIC for bladder emptying. If the bladder is inadequate, it can be augmented. However, this option does depend on having a urethra that can be catheterized. This may be difficult after repair of the epispadias and bladder neck initially; after a second bladder neck reconstruction, it may be more difficult.

a) Bladder neck reconstruction: In children who have had a bladder neck reconstruction and failed to become dry, the results of further reconstruction are poor. In adults, data are very limited. In a group of older children (3.2y – 15.5y) the group at the Hospital for Children, Great Ormond Street reported very modest results. There were 20 boys and ten girls most of whom had had several operations apart from the initial bladder neck reconstruction, including injection of bulking agents, augmentation and Mitrofanoff procedures and yet still remained wet. Sixty percent became dry by day (80% of girls but only 50% of boys), but only 50% by night. None could void urethrally and only five performed CIC urethrally. Urethral catheterization was difficult in eight. The authors acknowledged that the outcomes were not good and suggested that closure of the bladder neck might be a better option [421]. In an earlier series from Johns Hopkins all of eight patients achieved a dry interval of three hours or better with a re-do Young-Dees operation but all required CIC [422]. Although these data cannot directly be extrapolated to adults, it seems likely that they are representative of patients with failure of the initial bladder neck reconstruction.

b) Artificial urinary sphincter (AUS): The patient with exstrophy has, by definition, a reconstructed bladder neck and urethra. Such structures are not well suited to the support of an AUS cuff. It is also common for incontinent patients to carry a residual urine and so, with an AUS, would need to use CIC. Even in the earliest reports of the AMS 800 AUS, the results in patients with exstrophy were poor [423]. Again, data on this procedure in adults with exstrophy are limited and often included in series of patients with different diagnoses. In one series of 112 patients without spina bifida, there were 12 with exstrophy and four with epispadias aged four to 17 years old. The AMS 880 AUS was used with 5.5 to 7.5 cm cuffs and 61–70 cm water balloons. The cuff eroded in three of 12 exstrophy patients. Only four were dry and able to void spontaneously all of the time [424]. Herndon et al reported a 20% erosion rate in patients of any diagnosis who had had a bladder neck repair [425].

e) Diversion:

It is beyond the remit of this section to consider urinary diversion for exstrophy in detail. There is a school of thought that the results of exstrophy reconstruction in the long run are so poor that early diversion should be the initial management [426]. The original diversion of choice was a ureterosigmoidostomy, however the results before antibiotics and an understanding of hyperchloremic acidosis were very poor with 50% of children dying before ten years old [427]. With modern management and the use of a de-tubularized rectal pouch, such as the Mainz II, the results are very good and continence rates of 95% day and night are reported [428, 429]. This would certainly be the

management of choice in countries with limited facilities for reconstruction [430]. Surveillance for the development of anastomotic neoplasms from the tenth year after construction is mandatory [431].

Even in exstrophy patients who are continent, very many will have had an intestinal augmentation procedure. If the urethra is continent it may be used for self catheterization. When the urethral reconstruction has failed, either because it is wet or impossible to catheterize, a supra-pubic catheterizable channel, such as a Mitrofanoff, should be formed. The wet urethra is closed at bladder neck level to allow continued seminal ejaculation. If the bladder is too small or of too high pressure, it is augmented with intestine.

In the large series from Baltimore, 91 of 704 (13%) of exstrophy children required such procedures [432]. Of the reconstructed patients, 65% had a bladder neck closure. At a mean follow-up of six years, 93% were continent.

There are no data on the use of these techniques in adults specifically with exstrophy. However, as there are no other alternatives, a reconstruction based on the bladder is the recommended option. Long-term follow-up of intestinal diversions in other situations suggests that stone formation, stomal stenosis, hyperchloremic acidosis are common. Spontaneous rupture, an acute and life-threatening complication is rare. Renal function is preserved at least to ten years [433].

A long-term problem unique to exstrophy patients with a retained bladder is the risk of cancer. At the age of 40, exstrophy patients have a 640 fold increased risk over the normal population of that age. The reported tumors are aggressive and frequently fatal. Histologically, they are a mixture of transitional, squamous and adenomatous, most commonly arising on the bladder neck [434]. To date, the reported cases have been in those whose bladder reconstructions were done in early childhood; it remains to be seen whether those with reconstructions done in the first few days of life will have the same risk. It is important to pay urgent attention to the standard symptoms suggestive of bladder cancer even in young adults with exstrophy.

If the bladder is too small to be useful, or has been removed, one of the standard supra-pubic diversions such as a colonic reservoir can be used. The Mainz II rectal reservoir is an alternative. Ileal conduit is almost never indicated. However, the risk of bladder cancer remains, even if the only remaining part is the bladder neck.

4. RECOMMENDATIONS

The published studies to date are retrospective case series with levels of evidence at best 3 with a **Grade of Recommendation of C and Level of Evidence 3**. The expert opinion of the Committee has resulted in the following recommendations regarding the evaluation and treatment of persisting incontinence in adulthood. **(C)**

- Anti-muscarinic drugs are the first option for detrusor overactivity although there are no data specifically related to exstrophy patients.
- Standard techniques for enlargement of a small or high-pressure bladder are appropriate.
- Bladder neck bulking agents may be effective but continence is unlikely to be achieved if 4 injections have failed
- Re-do bladder neck reconstruction has a high failure rate, and is very unlikely to allow complete, spontaneous voiding. Urethral CIC may be difficult or impossible.
- AUS also has a poor outcome because of erosion, chronic retention and CIC difficulties.
- Supra-pubic continent diversion with or without augmentation and with or without bladder neck closure is the best choice for exstrophy patients with urethral failure. Rectal diversion (eg a Mainz II pouch) should be considered especially in countries with limited medical facilities.
- Patients with exstrophy-epispadias complex should be evaluated and managed in specialized centers
- A universal definition of continence should be established
- Persisting incontinence should be evaluated with urodynamics and its treatment should be individualized based on urodynamic findings
- Life-long follow-up is mandatory in terms of continence, voiding efficiency, upper tract status and other urological complications
- Comparative studies, including quality of life and psychological assessment, should be undertaken if possible.

IX. DETRUSOR OVERACTIVITY AND REDUCED BLADDER CAPACITY

1. REFRACTORY URGENCY INCONTINENCE AND IDIOPATHIC DETRUSOR OVERACTIVITY

The overactive bladder (OAB) syndrome refers to the symptoms of urgency, with or without urge incontinence, usually with frequency and nocturia [435]. Detrusor overactivity (DO) indicates the urodynamic observation characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked. Idiopathic Detrusor Overactivity (IDO) exists when there is no defined cause. Neurogenic Detrusor Overactivity (NDO) is seen when there is a relevant neurological condition. Ahlberg et al found that 82% of patients initially considered idiopathic on careful searching actually had pathology potentially leading to the problem [436].

Idiopathic detrusor overactivity is a normal situation early in life. Children have urgency incontinence as a stage in acquiring bladder control. The incidence of detrusor overactivity during mid-life years (20 to 60) has been estimated as 10% [437]. In the asymptomatic elderly, detrusor overactivity once again becomes common, occurring in 50% of men over 70 [438]. In the symptomatic elderly, over 75 years old, it can reach 90% in men [439]. Detrusor overactivity may be a cause of severe storage symptoms such as frequency, nocturia, urgency and urgency incontinence. Conservative treatment of these symptoms such as bladder training and pharmacotherapy is discussed in other sections.

Magnetic stimulation has been reported as a non-invasive treatment of DO [440,441]. Bradshaw et al. demonstrated an effect on cystometry with magnetic stimulation and found an improvement in urodynamic parameters but no consistent change in OAB symptoms [442]. Almeida et al.[443] in a prospective urodynamic controlled study of 91 women with UI, found an improvement on DO only in patients with initial bladder contractions greater than 15 cm H2O. There are no other specific data available [444].

The use of intravesical neuromodulatory drugs such as capsaicin and resiniferatoxin was extended to DO of non-neurologic origin after the suggestion that its etiology involved the enhancement of the C-fiber mediated spinal micturition reflex [445] and emerged as a minimally invasive procedure: the results are shown in **Table 12** [446-453]. In spite of promising and controversial results, it is still

Table 12. Intravesical capsaicin and resiniferatoxin for detrusor overactivity (males and females)

Author	No.	Improvement	Duration of effect	Drug and dose	Side effects
Cruz et al.[446]	3 IDO (total of 16, including 3 males)	71% continence (overall total of 14) and 21% improvement	Up to 18 months	Capsaicin 125 ml of 30% alcohol in saline containing 1mM	Intense burning sensation
Kuo [447]	13 IDO (41 total)	5 (38,5%)	2 to 9 months	RTX 10 ml of 100 nM RTX in 10% ethanol for 40 min	
	18 previous TURP	11 (61,1%)	Average 5 months		
Kuo [451]	(23) (19 ended)	(11 of 19) (58%)		10nM RTX weekly 3 to 4 times	4 withdrew due to side effects. Significant worsening of emptying
Kuo et al.[452]	17 IDO	Vehicle 2(9) 22% RTX 5 (8) 63%	6 months	Vehicle or 4 weekly 10 nM RTX	Randomized double blind placebo controlled 6 withdrew after first instillation
Liu and Kuo[457]	28	14 (50%)		10 nM RTX weakly for 4 weeks	Transient receptor potential vanilloid subfamily 1 overexpressed in the responders
Palma et al [448]	25 females with idiopathic urgency incontinence	10 (40%) disappearance of urgency incontinence	1 month evaluation only	50 nM RTX	No mention of retention
Rios et al. [453]	58 females With IDO	43% RTX 35 % PlaceboVehicle Improvement -equal (p=0.439)	1 month first evaluation	50nM RTX or 10% ethanol saline solution	Randomized double-blind placebo controlled
Silva et al. [450]	13 IDO (2 men 11 women) (12 incont.)	11 improved (91%) in incontinence 3 (25%) dry	3 months follow up	100 ml 50nM RTX solution 10% ethanol in saline for 30 min	No retention or other problems
Silva et al.[458]	17 IDO (out of 23)	Vehicle 9 (39%) RTX 14 (60%)	Pre-test with vehicle only followed by RTX	Vehicle followed by 100 ml 50nM RTX (patients enrolled in 2005)	No separation of NDO and IDO
Yokoyama et al. 455.[458]	10 (4 men)	5 (2 dry) 50%	3 months follow up	100 ml 50nM RTX for 30 min	Neurometer before and at 30 days

considered experimental and more clinical studies are necessary for it to be licensed [454].

The mechanism of action is still under study. The mean bladder perception threshold is increased only in patients with clinical improvement [455]. The complexity of the mechanism is demonstrated by the presence of vanilloid receptors not only on sensory fibers but also in bladder urothelium and smooth muscle cells [452] and by ineffectiveness in treating an overactive bladder from idiopathic causes or suprapontine lesions with no vanilloid-sensitive fiber-mediated reflex [456]. It has been suggested that over expression of transient receptor potential vanilloid subfamily 1 in the bladder predicts the response [457]. A well designed double-blind placebo-controlled study revealed no difference between placebo ethanol 10% saline solution and 50 nM resiniferatoxin, nevertheless both treatments showed improvement in symptoms of women with IDO [453]. Some placebo-controlled studies either did a quasi randomization458 or did not explain how it was done [452]. Patients with increased bladder sensation without DO presented some improvement in symptoms in a small non placebo controlled series [459]. There are no recent clinical series published and at present time, the use of resiniferatoxin has been restricted to animal studies [460,461].**(levels of evidence 1 – 4; Grade of recommendation D, two level 1 studies have contradictory conclusions**. [452,457])

For symptoms that are refractory to conventional means, 3 interventional treatments have been reported: botulinun-A toxin detrusor injections, neuromodulation, and bladder augmentation.

a) Botulinum toxin A injection in the bladder

The minimal invasiveness of this method makes it very attractive but long-term results in IDO are lacking **Table 13** [462-478]. The effects of its use are still not fully recognized [479], with possible systemic consequences [480-482], such as generalized muscle weakness in a number of patients treated for neurogenic bladder overactivity, and the development of resistance to the drug [483-485]. The FDA conducted a safety review of botulinum toxin products and issued a report that included a “Boxed Warning” highlighting the possibility of life-threatening distant spread of the toxin, a Risk Evaluation and Mitigation Strategy (REMS) with a medication guide to help patients understand the risks and benefits, and changes to the established drug names to reinforce individual potency and lack of interchangeability of the different products and to prevent medication error [486].

Most of the initial experience comes from its use in neurogenic bladders [487-490]. In 2011, OnbotulinumtoxinA was approved by countries in North and South America and Europe for treatment of urinary incontinence in people with neurologic conditions as spinal cord injury or multiple sclerosis. Information about its use in children is scarce [491]. DasGupta et al. [492] published a systematic review on its use in children. They found 225 children in 10 peer-reviewed publications with 165 pediatric patients with neurogenic overactivity (6 studies), 21 patients with idiopathic overactivity (1 study) and 39 patients with voiding dysfunction (3 studies). Only 11 male children with idiopathic OAB were included, limiting conclusions on this subject.

A randomized study comparing the results of botulinum toxin A injections to intravesical resiniferatoxin in NDO showed superior clinical and urodynamic benefit with the use of botulinum toxin [490]. The need for reinjections seems to be overcome by the significant improvement in quality of life of these patients [493-495]. Cost-effectiveness with botulinum toxin A in patients with detrusor overactivity is becoming an important issue with its increasingly widespread use [496]. The number of BTx treatments in the UK has increased dramatically from around 50 in 2000 to 4088 in 2010, making costs an important matter to be considered [497-499]. A 3-year cumulative cost analysis of BTx versus augmentation cystoplasty favoured botulinum toxin injections [500], but longer follow up may change this.

The use of botulinum toxin B (Myobloc – RimabotulinumtoxinB) is less efficient, with duration of action of about 10 weeks [501].

The optimal site of injections, including or not including the trigone, is still under debate [502]. In 2007, Kuo [474], published a study comparing the injections into the detrusor, suburothelial area, and bladder base, with the last location improving urgency but not increasing capacity. Recently Kuo did a single blind, randomized, parallel, actively controlled trial testing 100 U of OnabotulinumtoxinA with patients assigned to receive injection into one of the three following sites: bladder body, 100 U; bladder body, 75 U plus trigone, 25 U; and bladder base, 50 U and trigone, 50 U. He concluded that the injections are a safe and effective treatment for IDO regardless of the injection sites [503]. Manecksha et al [504] performed a study with 500 U of AbobotulinumtoxinA in 22 patients randomized to trigone-included or trigone-sparing detrusor injections. Benefits of trigone included injections were superior to trigone sparing injections for the treatment of refractory IDO and did not cause VUR in this study. A case series of 56 women with IDO underwent submucosa-only injection of 200 U of OnabotulinumtoxinA at 30 sites, showed success in 85.7% at 2 months and 54.3% at 12 months [505]. Initial results of bladder instillation of 300 units of OnabotulinumtoxinA and 50 mL of 50% DMSO in aqueous solution in women with IDO, showed safety and some efficacy that merit further research [506].

Many studies on idiopathic overactive bladder have been done in women [468, 469]. Data are still lacking on dose, concentration, site(s), numbers of injections, long-term efficacy and side effects. Attempts

Table 13. Botulinum Toxin A detrusor injection results

Author	No.	Type of patients	Dose	No. punctures	Results	Comments
Harper et al.[462] Level 3	39 (13 men and 26 women)	Neurogenic and idiopathic origin (not described separately)	200 idiopath 300 neurog	20 to 30 sparing the trigone Flex. cysto.	Increase max bladder volume 174 to 589 ml	
Loch et al.[463] Level 3	30	Neurogenic and idiopathic	200 U	20 injections sparing the trigone	Significant improvement in 67% of the patients - > residual urge	No description of gender or whether NDO
Radziszewski et al. [464] Level 3	12 (6 female and 6 male)	Only idiopathic	Up to 300 U	10-15 injections sparing the trigone	1 months follow up 100% success no residual	Short follow up Inexact criterion of success
Rackley et al.[477] Level 3	18 women	IDO	200-300 U (Botox)	Each 100 U in 1 cc saline, 0.1 cc injections	Improvement 40% frequency 30% urgency	6 months follow up
Rapp et al. [465] Level 3	35 (29 females and 6 males)	6 neurogenic	300 U	30 injections including trigone	34% resolution 26% improvement	40% failure
Kuo, [466] Level 3	30 (12 females and 18 males)	12 neurogenic	200 U	40 injections sparing the trigone	26% resolution 46% improvement	26% failure
Chancellor et al.[467] Level 2/3	10 (2 males and 8 females)	Only idiopathic	100-300 U	20-30 injections only in bladder base and trigone	80% improvement	Control group - 11 neurogenic with 73% improvement
Rajkumar et al.[473] Level 3	15 women	IDO	300 U (Botox)	30 ml – 30 injections	93% improvement	Not randomized prospective study 6 patients with PRV >130 ml
Popat et al.[472] Level 3	31 (18 women and 13 men)	IDO	200 U (Botox)	20 ml – 20 injections	57 % dry at 4 months	19 % needed CISC
Kessler et al.[478] Level 3	11 patients (no gender information – 8 men in total of 22 patients)	IDO	300 U (Botox)	30 ml – 30 injections sparing the trigone	91% dry 5 months duration	Prospective study comparing IDO with NDO 4 high PVR with CSIC (36%)
Werner et al.[782] Level 3	26 women	Only IDO	100 U (Botox)	30 ml- 30 injections	65 % dry at 12 weeks 60% dry at 36 weeks	36 weeks follow up
Schmid et al.[470] Level 3	23 men 77 women	Only IDO	100 U (Botox)	30 ml- 30 injections	88% improved 8% poor results	12 weeks follow-up 4% urinary retention
Kuschel et al.[469] Level 3	26 (only women)	Only idiopathic DO with incontinence	100 U (Botox)	30 ml- 30 injections	11/26 improved (42%) 4 no need further treatment	2-year follow-up 3 complications (1 no response and 2 high PVR)
Jeffery et al. [468] Level 3	25 (only women)	Only idiopathic DO	500 U (Dysport)	20 ml- 20 injections	63% dry – 1 week 32% dry- 3 months	Prospective First study with Dysport
Lee et al. [471] Level 3	13 men 5 women	10 IDO and 8 NDO	50-200 U (NTX component of purified Type A neurotoxin	20-40 injections including trigone Indigocarmine together to check leak	89 % improved	3 months follow-up 6% retention with IC for 12 months
Sahai et al.[476] Level 2	34 patients (16 BTX and 18 placebo) Do not discriminate gender	Only IDO	200 U (Botox) or saline (as placebo)	20 ml – 20 injections	Normalization- Frequency 36% BTX 11% Placebo Urgency No difference Incontinence	12 weeks follow-up Randomized placebo controlled double blind trial Difficult voiding 75% IC 38%

Table 13. Botulinum Toxin A detrusor injection results (continued)

Author	No.	Type of patients	Dose	No. punctures	Results	Comments
Sahai et al. [476] Level 2	34 patients (16 BTX and 18 placebo) Do not discriminate gender	Only IDO	200 U (Botox) or saline (as placebo)	20 ml – 20 injections	Normalization-Frequency 36% BTX 11% Placebo Urgency No difference Incontinence 50% BTX 0% Placebo	12 weeks follow-up Randomized placebo controlled double blind trial Difficult voiding 75% IC 38%
Kuo H-C [474] Level 2	45 patients (gender not specified)	Only IDO	100 U (Botox)	Injections in Detrusor, suburothelial or bladder base	Success 93% Detrusor 80% suburothelial 67% bladder base	Prospective randomized 3 months 4 retentions 14 difficult void
Ghalayini and Al-Ghazo,[475] Level 3	16 patients	IDO	500 U (Dysport)	500 U diluted in 30 ml saline 30 injections	80% of patients satisfied	Prospective study 9 months follow up 1 retention and 4 with PRV >120 ml – 5 ICath
Mohanty et al[783] Level 3	35 women	IDO	200 U Botox	20 ml, 20 injections sparing trigone	85.7% improvement, no adverse effects	Case series No retentions
Kuschel et al[469] Level 3	26 patients (women)	IDO	100 U Botox	30 ml 30 injections	11 re-injections	Case series
Brubaker et al[539] Level 1	43 women (28 Btx and 15 placebo)	IDO	200 U Botox	20-30 injections, sparing trigone	Study stopped – 43% (12 pat.) with large PVR	Randomized double blind placebo controlled
Flynn et al[784] Level 2	22 women (7 placebo and 15, 2 doses of Botox)	IDO	200 or 300 U Botox	10 injections, sparing trigone	6 weeks results only - (improvement) 26% PVR >200 ml 18% infection	Randomized double blind placebo controlled (immediate results)
Sahai et al[536] Level 1	34 patients both sexes	IDO	200U Botox (16 pat) or placebo (18 pat)	20 ml with 20 injections	QoL improved with Botox	Randomized double-blind placebo controlled
Lie et al[785]	19 patients (10 males)	IDO	200 U (onabotulinumtoxi	20 ml, 20 sites sparing trigone	More efficacious in female	Case series 5.2% retention

to determine whether poor responders could be predicted from preoperative urodynamic parameters showed only a very high maximal detrusor pressure over 110 cm H2O as an unfavorable predictor when using 200 units [476]. Studies in women suggest a longer duration of action than its mere motor-nerve blocking potency can explain [469]. Therefore, a dual mechanism of action has been proposed: in addition to binding to cholinergic terminals, it might also affect afferent nerve transmisson, thereby decreasing urgency [507,508]. Kuo evaluated retrospectively the results of 100 U OnabotulinumtoxinA injection in 174 patients (89 males) [509]. Patients who had sensory effects had significantly greater long-term success rates compared to those with motor effects alone. He concluded that improvement of urgency severity seems to be significantly associated with the long-term success of BoNT-A treatment for IDO.

There are two commonly marketed forms of botulinum toxin-A: Botox (Allergan Pharmaceuticals, Irvine, CA, USA), now referred to as OnabotulinumtoxinA, and Dysport (Ipsen Biopharm Ltd., Wrexham, UK), referred to as AbobotulinumtoxinA, as recommended by the US Food and Drug Administration. They require different doses to achieve similar results, in a proportion of approximately 1:3 [510,511]. Other forms of botulinum toxinA do not have enough data in urology to be considered for this report, includng Xeomin (IncobotulinumtoxinA) (Merz, Germany), Prosigne (Lanzhou Institute of Biological Products, China) [512], and Neuronox (Medy-tox, South Korea).

AbobotulinumtoxinA for refractory IDO was published in 2007 with similar results to OnabotulinumtoxinA [468]. Recently, a series of 22 patients with IDO underwent injection of 500 U of AbobotulinumtonA and were randomized to injections including or excluding the trigone [504]. Similar results were obtained regarding side effects (18% retention and no reflux) with the trigone-included group showing better results. Another large case series of 234 patients either with various types of neurogenic bladder dysfunction (NBD) or IDO underwent respectively 500 U and 250 U of AbobotulinumtoxinA including 57 men with IDO. Success was 91% for NBD and 93% for IDO, with 12% retention only in the male patients [513]. In a study using a type A neurotoxin, produced in a medical school laboratory and purified by a procedure using a lactose gel column, Lee at al. [471] reported improvements in 89% of patients treated for incontinence due to IDO and NDO. Mangera et al. [514] did a systematic review on management of lower urinary tract diseases comparing OnbotulinumtoxinA and AbobotulinumtoxinA. They identified good-quality

studies for OnabotulinumtoxinA in adults and lack of such studies for Abobotulinum- toxinA, although this does not imply that OnabotulinumtoxinA is more effective than AbobotulinumtoxinA.

Many studies with botulinum toxin detrusor injection use different outcome measures for results and are variable in reporting the presence of residual urine and the need for intermittent catheterization, but 6-75% of cases may develop a high post void residual urine [469,471,473,476]. A retrospective study looking at risk factors for adverse events in a series of 217 patients treated with OnabotulinuntoxinA showed an overall 63.3% success, with male gender, base line PVR ≥100 ml and dosage >100U as predictors of urinary retention or difficulty voiding. Besides being an alternative for treatment of refractory DO, currently available data do not support superiority of any specific treatment plan, and therapy options should be tailored to the specific patient and physician preference [515]. Higher doses such as 200 units in IDO resulted in incomplete emptying, necessitating intermittent catheterization in 6 out of 16 patients (37.5%) in one study [476]. Sahai suggests a careful follow up of the patients after the injections, starting IC in symptomatic patients if post void residual urine is more than 100-150 ml [516].

Many reports do not separate genders and mix neurogenic and idiopathic etiologies. A large number of publications are reviews of the literature [517-535]. There is a randomized double blind OnabotulinumtoxinA placebo controlled trial showing favourable difference against saline injections for frequency and incontinence, but not for urgency [476]. Quality of life analysis showed improvement even with the occurrence of 38% of urinary retention [536]. In a dose-finding randomized double blind placebo controlled study with a total of 313 IDO patients of both sexes, all OnabotulinumtoxinA dosages (50-300U) were better than placebo, but the 100 and 150 U dosages were best in regard to the balance between efficacy and side effects [537,538]. In women, a placebo controlled randomized study with 200U of OnabotulinumtoxinA for IDO showed a 60% clinical response but was terminated early due to 43% of patients having increased PVR [539].

Conclusions

Efficacy of botulinum toxin A for IDO: **level 1 of evidence, Grade of recommendation A** (for OnabotulinuntoximA). Fewer studies for AbobotulinuntoximA and the lack of studies for other A toxins do not allow similar recommendation.

Dosage of botulinum toxin A for IDO: between 100 and 150 U (for OnabotulinuntoximA). No studies for other types. **Level 1 of evidence; Grade of recommendation A.**

Location of injection: the majority of studies use 20 or 30 injections, and spare the trigone (**Table 13**). Alternative sites such as submucosal or including the trigone, have **levels 2 and 3 of evidence. Grade of recommendation C.**

Predictability of complications: Risk factors for retention or difficulty voiding are: male gender, baseline PVR≥100ml and a dosage >100U. **Level 3 of evidence; Grade of recommendation C** (for OnabotulinuntoximA – for other types, no conclusion possible).

The committee cautions that although the efficacy and safety of botulinum toxin A for IDO is being established there are still concerns regarding the data. Its use in men is not as widely reported as its use in woman; the issue of voiding difficulty and the need for intermittent catheterization has not been addressed in men. There are no long-term or cost effectiveness studies compared to alternatives. Furthermore the recommendations cannot be extended to other toxins due to lack of studies.

b) Electrical stimulation and neuromodulation

Electrical stimulation of the genital area was first used to control incontinence due to DO of different etiologies on an empirical basis [540]. Later, it was suggested that sphincteric contraction induced by electrical stimulation can promote an inhibitory effect on detrusor activity, thus suppressing DO [541]. Many studies of external electrical stimulation for bladder inhibition of idiopathic urgency incontinence have been published, mainly in female patients [542-549]. The results vary from 45% to 85% success, with a mean of 38%, and 26% improved. Electrodes implanted in the pelvic floor, have not yielded good results [547].

Sacral neuromodulation has been reported as alternative therapy for urgency incontinence, urinary retention, chronic pelvic pain, and for simultaneous urinary and fecal incontinence [550]. Good results have also been published in treating neurogenic bladder dysfunction [551,552]. The working mechanism of neuromodulation in the treatment of lower tract dysfunction is still unknown [553,554]. A suggested mechanism is somatic afferent inhibition of sensory processing in the spinal cord [555,556], therefore it may be a centrally acting treatment modality that is different from botulinum toxin, which is an end-organ therapy that specifically targets the bladder [557].

Long-term results suggest a sustained effect on restoring voiding in appropriately selected cases, but a revision rate of 42% at 5-year follow up remains a problem [558]. The 14-year revision rate from a single center was 39%, which decreased after the introduction of new materials [559]. On-demand use, as suggested by Oerlemans et al. [560] may improve this revision rate by prolonging battery life. Its use in refractory idiopathic urgency incontinence has been limited to relatively few patients, mostly women. Bosch and Groen [561] presented results of chronic implantation in 15 women and 3 men, with

an average age of 46 years. Significant improvements in voiding frequency, average voided volume, number of incontinence episodes and number of pads used were found, with no deterioration in response to stimulation with time. However, with subsequent experience in 14 men only 2 patients had a partial response and the rest ultimately failed [562]. Shaker and Hassouna [563] implanted 18 patients with refractory urinary urgency incontinence, but only 2 were in men. Groen, Bosch and van Mastrigt reviewed 33 implanted women and found no effect on urethral resistance and bladder contraction strength, thought to be due to the depressant effect of sacral (S3) nerve neuromodulation on detrusor overactivity [564]. Groenendijk et al in a retrospective study for the Sacral Nerve Stimulation Study Group, reported urodynamic aspects of 111 patients implanted, but only 8 men were included [565]. They found a better result on urgency incontinence in patients without DO. The difference was not significant. This tendency was also found by South et al. in 67 women implanted [566]. Clinical or urodynamic values to predict the outcome of sacral nerve stimulation has been difficult do define. Evaluation of 19 women suggested that urethral overactivity seemed to be a good parameter to predict a favourable outcome [567].

Some studies do not specify the etiology of the DO and neurogenic and non-neurogenic causes are grouped together [563]. Some reports focus on technical or specific aspects of the procedure and the same patients may be included in different publications [565,568-570]. Implantation in children may be feasible in selected cases [571,572] and poorer results are expected in older women [102]. The outcome in older men is unknown since there are no reports.

Table 14 [478,558,573-582] shows recent studies.

Some reports are literature reviews [554,583-585] or detail technical modifications [586,587]. There is one systematic review on efficacy and safety of sacral neuromodulation for urgency incontinence, but 13 of the articles analyzed are abstracts and it is also difficult to ascertain whether the same patients are included in different publications [588].

There are some publications with level [1573,574 or 2562,576,577] evidence and with a grade of recommendation of B. However, due to relatively few men in the clinical trials, and poor results in one of the prospective trials, its general applicability to men with urgency incontinence may be limited. The scenario remains unchanged after about 26,000 patients implanted [589]. In a recent review, Apostolidis [590] concluded that further research is needed to improve patient selection, identify prognostic fac-

Table 14. Neuromodulation for treatment of refractory urgency incontinence due to detrusor overactivity (males and females)

Authors	N	Success (dry)	Improved	Control group	Study and comments
Schmidt et al. [573]	34	47%	29%	42	prospective randomized
Weil et al. [574]	21	56%	19%	23	prospective randomized
Bosch et al. [575]	34 (females) 6 (males)	38%16%	21%16%		prospective longitudinal
Siegel et al. [576]	41	46%	19%		prospective cohort
van Kerrebroeck et al. [558]	105 at 5-years (gender not specified)		58% for UI 40% for Frequency		5 –year follow up (non randomized)
Grunewald et al. [577]	18	39%	33%		prospective
Aboseif et al. [578]	43 (5 males)	77%			not clear about etiology
Hedlund et al. [579]	13	61,5%			2 men included, both dry
Roupret et al. [580]	6 (all female)	17%	67%		
Kessler et al. [478]	71 with urgency incontinence (total of 91)		70%		average follow up 2 years Gender not specifically discriminated (about 13% of all are males)
Groen et al. [581]	60 women	15%	62%		Longitudinal study 5-year follow up
Chartier-Kastler et al. [582]	1170 OAB (85% females)		85%		Multicenter prospective observational

tors, clarify the mechanism of action, and reduce complications and revision rates.

Level of evidence 3. Grade of recommendation C.

c) Surgical treatment by detrusor myectomy and augmentation

Previously used treatments of surgical bladder denervation, open bladder transection, cystolysis, endoscopic phenol injections, hydrostatic bladder distention did not yield good results.

Bladder autoaugmentation or detrusor myectomy has been reported as an alternative to augmentation in neurogenic and non-neurogenic dysfunction. **Table 15** [591-593] shows results of this treatment in patients with non-neurogenic detrusor overactivity. There are few long term results available [593]. The use of silastic intravesical balloon as a scaffold after myectomy seems to improve results in neurogenic patients but was not tested in IDO [594]. Additional and longer-term experience is still required to properly assess this procedure. **(Level of evidence 3; grade of recommendation C-D)**

Enterocystoplasty results are detailed in **table 16** [592,595-601], which includes both male and female patients. Some publications are not clear about the type of surgery specifically done in IDO and about the gender. Good results vary from 58% to 88%, with an average of 77%. Approximately 10 to 75% of patients require intermittent catheterization for bladder emptying. Ileum was the most frequently used bowel segment followed by sigmoid colon, although no scientific reason for the use of any particular segment was given. The surgery, as reported in other sections, has a significant complication rate and should be considered carefully when applying it to these patients. **(Level of evidence 3; grade of recommendation C)**

2. REDUCED BLADDER CAPACITY

Fibrosis of the wall produces a low-volume low-compliant bladder, leading to diminished functional capacity. Symptoms of frequency and nocturia occur as a result of progressive decrease in bladder volume, but urinary incontinence may also be the consequence of a very small capacity, especially if accompanied by urethral weakness. The diagnosis can be suggested by the micturition chart, and confirmed by urodynamics. The causes can be congenital or acquired. Acquired causes include multiple surgeries, inflammatory processes (chronic cystitis, interstitial cystitis, tuberculosis, schistosomiasis, and chemical cystitis) or following radiation.

Table 15. Detrusor myectomy for treatment of refractory urgency incontinence due to detrusor overactivity (both sexes)

Author	Idiopathic detrsor overactivity	Good results
Swami et al. 591 *	17	12
Kumar et al 593 **	24	19
Leng et al. 592	8	7
TOTAL	49	38 (77.6%)

***short term followup**
****longer term follow-up of the same series, 45% required IC**

Table 16 - Enterocystoplasty for treatment of refractory urgency incontinence due to detrusor overactivity (males and females)

Authors	Detrusor overactivity	Good or moderate result	Bowel segment
Hasan et al. [595]	35	19	46 ileum 2 colon
McInerney et al. [596]	50	44	
Bramble [786]	15	13	13 colon 2 ileum
Sethia et al.[598]	11	9	ileum
Mundy and Stephenson [599]	40	30	ileum
Leng et al. [592]	2	2	
Edlund et al. [600]	25	19	
Blaivas et al.[627]	9	9	Ileocaecal segment and ileum
Total	**187**	**145 (78%)**	

Bilharzial contracted bladder is a problem that is primarily limited to endemic areas in Africa and the Middle East. Schistosoma haematobium migrates to the veins of the vesical and pelvic plexuses, where the female begins to lay eggs, promoting a initial inflammatory response. As a result, granulomatous lesions form in the lamina propria. Mucosal reactions vary from hyperplasia to polypoid cystitis. A contracted bladder occurs in 2% of cases [602]. Bladder augmentation seems to offer reasonable results in these cases.

Similarly, small fibrotic bladders due to other etiologies can be treated successfully with enterocystoplasty. The results of this surgery are presented in **Table 17** [603-631]. The results are similar in all etiologies except for radiation. The poorer results after radiation may be due to other tissue damage in the surgical area. New conformal techniques for radiotherapy may improve results in the future, so that the need for augmentation cystoplasty decreases.

Almost all of these studies do not distinguish bowel segments or separate males from females in reporting results. Therefore, it is not possible to correlate any particular aspect with the chance of success or failure. However, overall the results seem reasonably good with the exception of patients who have undergone radiation. **(Level of evidence 3; Grade of recommendation C)**

X. URETHROCUTANEOUS AND RECTOURETHRAL FISTULAE

Urethrocutaneous or rectourethral fistula may have congenital, inflammatory, neoplastic or traumatic origins. It is important to recognize the varying etiologies because each type may require a different surgical strategy. All reports except one are retrospective case series. The report by Shakespeare et al. [632] is from a prospectively collected data base of patients treated with radiotherapy for prostate cancer. **(Level of evidence 3; grade of recommendation C).**

1. URETHROCUTANEOUS FISTULA (UCF)

a) Acquired UCF

Hidden foreign bodies have been described as a rare cause of both strangulation of the glans penis and urethrocutaneous fistula. Tash and Eid [633] presented the case of a 30-year-old man who developed a urethrocutaneous fistula and penile shaft necrosis after a condom broke during intercourse. Neither the patient nor several physicians could identify the retained ring of condom, which had been buried under newly epithelialized skin. He underwent removal of the foreign body under general anaesthesia, followed 5 months later by a formal urethrocutaneous fistula repair.

Urethroperineal fistula, as a complication of open perineal prostate cryosurgery, occurs as an immediate perioperative complication in 10.7% [634]. Thomas et al. [635] retrospectively evaluated 250 patients after radical perineal prostatectomy and revealed only 1 (0.4%) urethroperineal fistula. Fahal et al. [636] published an unusual complication of mycetoma. The patient had an infection with Actinomadura madurae that involved abdominal wall, perineum and urethra. This resulted in urinary extravasation with a urethrocutaneous fistula.

b) Management of UCF

The diagnosis of UCF is made by physical examination, retrograde urethrography (**Figure 3**), urethroscopy, fistulography, urethral ultrasound or color Doppler imaging. Urethral sonography provides additional information about any involvement of the surrounding tissue, location of vessels and associated abnormalities such as a periurethral abscess [637].

Treatment of UCF usually requires urethroplasty techniques with modifications involving fistula excision and multiple layer closure [638]. **(Level of evidence 3; Grade of recommendation C)**

2. RECTOURETHRAL FISTULAS (RUF)

Culp and Calhoon described five basic groups of RUF according to the etiology [639]: congenital, iatrogenic, traumatic, neoplastic, and inflammatory.

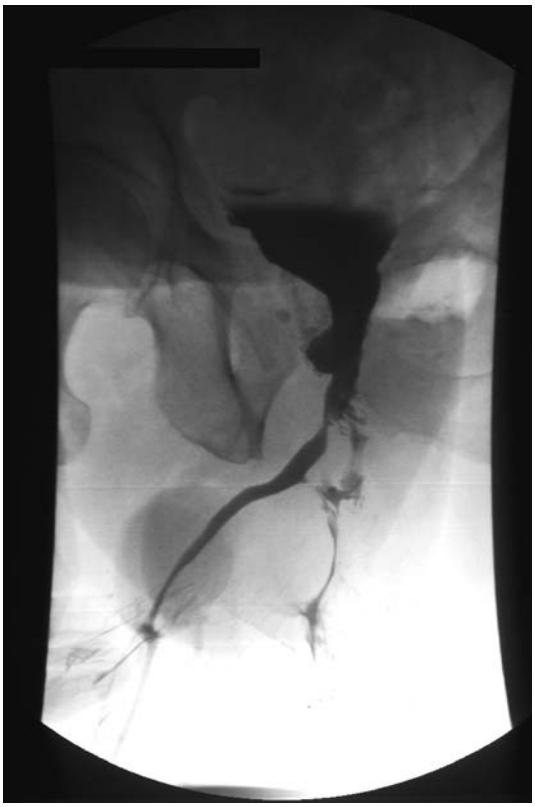


Figure 3. Voiding cystourethrogram after incision of the paraurethral abscess

Table 17. Enterocystoplasty results for reduced bladder capacity

Authors	Bilharziasis cystitis		Tuberculous cystitis		Radiation cystitis		Unknown cause	
	Total	Success	Total	Success	Total	Success	Total	Success
Smith et al.[603]	-	-	7	4	9	3	12	7
Kerr et al. [604]	-	-	12	12	-	-	-	-
Zinman and Libertino [605]	-	-	2	2	1	?	1	1
Dounis et al. [606]	-	-	31	27	-	-	1	1
Lunghi et al. [607]	-	-	15	15	4	4	3	3
Shawket and Muhsen [608]	8	8	-	-	-	-	-	-
Whitmore and Gittes [609]	-	-	7	7	-	-	2	1
Chan et al. [610]	-	-	-	-	-	-	10	9
Shirley et al. [611]	-	-	10	10	4	2	-	-
Goodwin et al. [612]	-	-	3	2	-	-	3	3
Winter and Goodwin [613]	-	-	1	1	3	1	-	-
Fall and Nilsson [614]	-	-	1	1	-	-	1	1
Goldwasser and Webster[615]	-	-	-	-	-	-	7	7
Weinberg et al. [616]	-	-	2	2	1	1	1	1
Novak [617]	-	-	11	11	-	-	-	-
Sayegh and Dimmette [618]	2	0	-	-	-	-	-	-
Beduk et al. [619]	-	-	-	-	-	-	1	1
Kuo [620]	-	-	-	-	1	1	-	-
Kawamura et al. [621]	-	-	-	-	-	-	1	1
Hradec [622]	-	-	-	-	27	23	-	-
El Otmany et al. [624]	-	-	1	1	-	-	-	-
Yamada et al. [625]	-	-	1	1	-	-	-	-
Miyano et al. [626]	-	-	-	-	-	-	1	1
Blaivas et al. [627]	-	-	-	-	3	2	3	3
de Figueiredo et al. [628]	-	-	25	20	-	-	-	-
Yashi et al. [629]	-	-	-	-	1	1	-	-
Lima et al. [630]	-	-	7	7	-	-	-	-
Singh et al. [631]	-	-	28	28	-	-	-	-
TOTAL	10	8 (80%)	164	151 (92%)	54	39 (72%)	48	40 (85%)

a) Congenital RUF

Endo et al. [640] described the results of the Japanese Study Group of Anorectal Anomalies (JSGA) to determine the relative incidence of specific types of these anomalies in Japan. They included discussion of RUF regarding the relationship between the fistula levels and the blind end of the rectum, low type deformity, rare types, and associated anomalies. A total of 1,992 patients (1,183 boys and 809 girls) registered from 1976 to 1995 were analysed according to the pathogenesis of anorectal malformation in the field of molecular genetics. They reported that more than 20% of RUF should be categorized as intermediate or low deformity from the position of the rectal pouch. A significant preponderance of Down´s syndrome in the deformities without fistulae suggests that investigation of associated anomalies and congenital diseases may provide further insights.

The purpose of Rintala's study was to compare the long-term outcome of sacroperineal-sacroabdominoperineal pull-through (SP-SAP) to that of posterior sagittal anorectoplasty (PSARP). In boys with high anorectal anomalies, PSARP was superior to SP-SAP pullthrough in terms of long-term bowel function and faecal continence [641].

b) Acquired RUF

Acquired RUF may occur after pelvic trauma, surgery of the prostate or rectum, pelvic cancer, radiation (either external beam or brachytherapy),

cryosurgery, prostatic hyperthermia, prostatic high intensity focussed ultrasound (HIFU), inflammatory bowel disease affecting rectum, or rarely prostatic inflammation.

Benchekroun and co-workers [642] report a series of 11 RUF observed over a 25-year period. The etiologies were surgical trauma (5 cases), fracture of the pelvis (2 cases), inflammatory lesions (3 cases), and one fistula was congenital. Colostomy was performed in 2 patients, surgical closure of the fistula was performed in 7 patients: abdominoperineal (3 cases), perineal (2 cases), transperitoneal (1 case) or by transanosphincteric incision (1 case).

In 1972 Smith and Veenema [643] reported their 20-year experience with 160 patients undergoing radical retropubic prostatectomy (RRP) with an incidence of 15 rectal injuries. Only 4 fistulas developed in this group.

Roberts et al. [644] published a series of 11,452 men who underwent open (RRP) or laparoscopic (LRP) radical prostatectomy. Rectal injury occurred in 18 men -12 in the RRP group (0.12%) and 6 in the LRP group (0.47%). When recognized intraoperatively and primarily repaired, rectourethral fistula was prevented in 87.5% of men. Primary repair performed with vascularized tissue interposition prevented rectourethral fistula development. In men with unrecognized rectal injury, the rectourethral fistula tended to persist and eventually required delayed surgical repair. Thomas et al. [645] reported that rectourethral fistulas developed in 13 of 2,447 patients (0.53%) after RP. In 7 of 13 patients (54%) a rectal lesion was primarily closed at radical prostatectomy. With conservative management in 3 patients, all 3 healed spontaneously. None of these patients had fecaluria. Three of the 9 patients 3 (33%) experienced spontaneous fistula closure after temporary colostomy and transurethral catheterization. In this group 6 patients (67%) required additional surgical fistula closure, which was successful in all. Surgical fistula closure (1) without colostomy in presence of fecaluria failed.

The most common single cause of RUF in the series of 23 male patients published by Tiptaft et al. [646] was a fracture of the pelvis and iatrogenic causes (two cases after transurethral prostatic surgery, two cases after open prostatectomy, and three cases after urethral instrumentation. Noldus et al. [647] reported 23 (3.9%) rectal injuries during 589 RRP and cystoprostatectomy procedures. Eastham and Scardino [648] summarized the incidence of rectal injury during RRP in 3834 patients with an average of 0.7% (range 0.2-2.9%). The incidence of RUF, as an immediate perioperative complication of open perineal prostate surgery, is 1.4 %.

Nyam et al. [649] reviewed records of all patients who were diagnosed with RUF between January 1981 and December 1995 and 16 males were identified. All patients were interviewed by telephone for follow-up. The mean age was 68 years and the mean follow-up was 80 months. Adenocarcinoma of the prostate in 15 patients and recurrent transitional cell carcinoma of the bladder in one patient were the underlying malignant diseases. Nine patients had had a RRP with 2 fistulas after radiation, 2 after brachytherapy, and 3 after a combination of radiation and brachytherapy. One patient formed a fistula after cystectomy and dilation of a stricture. This heterogenous group of patients received multiple therapies including initial colostomy (7 patients), transanal repair (2 patients), parasacral repair (2 patients), transperineal repair (2 patients), coloanal anastomosis (3 patients), and muscle transposition (3 patients). Four of the patients required a permanent stoma.

Badalament et al. [650] managed one patient (0.4%) with a urethrorectal fistula after cryoablation therapy for prostate cancer. Zippe [651] reviewed preliminary results of prostate cryosurgery and reported a 2 to 5% incidence of RUF. Porter 634 found a 2.5% rate of RUF in 210 patients after TRUS-guided prostate cryosurgery and no urethroperineal fistulae. Ismail et al. [652] reported the experience of using salvage targeted cryoablation of the prostate (TCAP) in 100 patients for the recurrence after radiotherapy. The mean follow-up was 33.5 months and RUF occurred in 1%.

Montorsi et al. [653] reported a RUF after transrectal prostatic hyperthermia (43 degree C) in patients with advanced prostatic cancer after multiple treatment sessions. The fistula was cured after a urethral catheter was left in place for one month.

Kleinberg et al. [654] summarized results of 31 patients with stage T1 or T2 prostatic carcinoma following CT guided transperineal I_{125} implants and reported that only one patient developed a prostatorectal fistula that was managed with an ileal conduit.

Fengler and Abcarian [655] published their experience of eight patients with RUF in the course of treatment of prostate cancer (3 fistulae after radiation therapy alone, 3 after prostatectomy and 2 after both surgery and radiation therapy). Larson et al. [656] evaluated 5719 patients after radiation for prostate cancer. Ten had documented RUF. Lane et al. [657] treated 21 men with RUF following primary external beam radiotherapy and one after adjuvant external beam radiation therapy for prostate cancer. Time from the last radiation treatment to fistula presentation was 6 months to 20 years. Four patients underwent proctectomy with permanent fecal and urinary diversion. Successful fistula closure was achieved in the 9 patients who underwent urethral reconstruction. Chrouser et al. [658] identified a total of 51 patients with a history of external beam radiation for prostate cancer that subsequently had

a urinary fistula. Of 20 patients meeting inclusion criteria, 30% received external beam RT alone, 30% received brachytherapy and 40% had received combined external beam RT/brachytherapy. Most fistulas (80%) were from the rectum to the urinary tract with an average diameter of 3.2 cm. Of patients with rectal fistulas 81% had a history of rectal stricture, urethral stricture, rectal biopsy, rectal argon beam therapy or transurethral prostate resection after radiation. All patients with rectourethral fistulas who achieved symptomatic resolution required urinary and fecal diversion.

Shakespeare et al. [632] reviewed the potential factors in fistula development and identified three cases (0.2%) of RUF among 1455 patients treated with prostate brachytherapy (BT), occurring at 19-27 months following BT. All these patients had BT monotherapy and had been investigated with endoscopy and low rectal biopsy. They concluded that gastrointestinal specialists should not perform biopsy of the anterior rectum in patients who have had BT unless there is a very high clinical suspicion of malignancy. Marguet et al. [659] described 6 cases of RUF in patients treated with brachytherapy plus external beam radiotherapy for localized prostate cancer and subsequent rectal biopsies or rectal surgery. Four patients underwent hyperbaric oxygen therapy, which failed. Three patients underwent fecal diversion with gracilis interposition flaps, and two underwent pelvic exenteration. They also concluded that biopsy of rectal ulcers in the clinical setting of combined radiotherapy should not be performed.

Chang et al. [660] published a case of prostatic malakoplakia masquerading as a rectal tumor due to formation of a fistulous tract to the rectal muscular layers. Cools et al. [661] reported a very uncommon type of fistula between the large bowel and the prostatic urethra due to Crohn's disease. Felipetto et al. [662] described a prostatocutaneous fistula as a complication of pseudomonas prostatitis.

Transrectal high-intensity focused ultrasound (HIFU) destroys prostate cells by coagulative necrosis of the tissue. Recent reports of efficacy also include morbidity. Rebillard et al. [372] reported RUF in 0-3% in a review involving 37 articles/abstracts.

Buckley et al. [663] concluded that there has been a major shift in the cause of RUF from primarily surgical to approximately 50% resulting from radiation/ablation therapy. Surgically induced RUFs typically are small, located in bladder neck/trigonal region and can be closed primarily. Radiation/ablation induced fistula are large (>2 cm), involve the prostatic urethra and are fibrotic often requiring a combination of onlay grafting and interposition muscle flap for closure. The anterior, perineal sphincter-sparing approach may be the optimal approach for closure of most RUF (simple or complex). Lacarriere et al. [664] noted that the use of radiotherapy had a major impact on its prognosis. The flap, which seemed to have the best results, was the gracilis muscle flap.

c) Diagnosis of RUF

RUF may be strongly suspected from the patient's history (fecaluria, abnormal urethral discharge, pneumaturia, leakage of urine from the rectum during micturition). Rectal examination, proctoscopy, careful urethroscopy, intraurethral injection of methylene blue dye, radiopaque contrast agent placed into the bladder and then voided usually appears in the rectum on X-ray, are the most important diagnostic steps [637,665] (**Figure 4**).

d) Therapy of RUF

Small fistulae may resolve spontaneously with urinary and/or fecal diversion. Therefore, an initial trial of conservative therapy is reasonable. Selected patients with chronic fistulas who are poor surgical candidates may also be managed conservatively with antibiotics, pads and symptomatic care. Timing of repair is often individualized, mainly according to the etiology, delay in diagnosis, size of fistula, whether it is the first or subsequent repairs, and the general condition of patient.

Diversion of urine (suprapubic cystostomy) is generally recommended as well as correction of any urethral stricture distal to the fistula. Fecal diversion, with colostomy is used by some as a mandatory part of double diversion or selectively by others [645]. Gibbons 666 stressed the need for a diverting colostomy for 3-4 months.

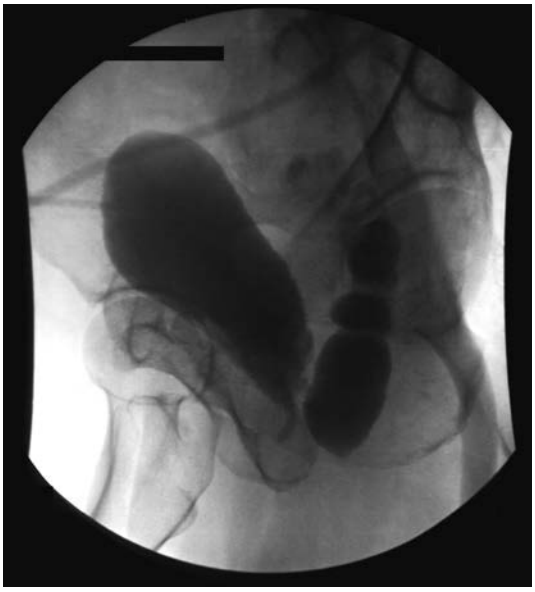


Figure 4. Cystogram demonstrates a rectourethral fistula that occurred after a laparoscopic radical prostatectomy

However, as surgeons obtained more experience, bowel preparations became standardized, and effective antibiotics were developed, and the enthusiasm for colostomy diminished. Currently, colostomy is recommended in circumstances where antibiotics alone cannot control the inflammation and infection associated with the fistula or when the fistula involves radiated tissue. Low residue diet is also useful for healing. Suitable drainage (perineal and urethral splinting) is stressed.

e) Surgical Approaches

Surgical management for rectourinary fistulas remains a reconstructive challenge. Two-layer closure of the urethra and rectum with suture lines at right angles and with interposition of soft tissue (eg. omentum [667], gracilis muscle [668], or scrotal flap [669]) has been described. Surgical approaches include transabdominal, transvesical, or direct exposure of the RUF.

There are only a few guidelines to direct the surgeon to the most successful and least morbid technique. Rivera et al. [670] staged RUF as: stage I, low (less than 4 cm from anal verge and nonirradiated); stage II, high (more than 4 cm from anal verge and nonirradiated); stage III, small (less than 2 cm irradiated fistula); stage IV, large (more than 2 cm irradiated fistula); and stage V, large (ischial decubitus fistula). Diverting colostomy was performed for stages III to V 6 weeks before definitive therapy. Some of the patients in addition to the RUF will also have urethral strictures that have to managed. Reconstruction of both aspects to restore functional anatomy is possible with complex reconstructions. [671]

The surgical approaches including the numbers of reported patients are listed in **Table 18** [639, 642, 643, 646, 647, 655, 665, 669, 672 - 688]

1. Perineal Approach

In 1926, Young [672] dissected the rectum away from sphincters, divided the fistula, closed the urethra, and mobilized the rectum further cephalad in such a fashion as to pull the affected rectum caudally out of the anus where it was then transected and discarded, suturing the proximal rectum to the anal skin. Subsequently Lewis, in 1947 [673], described suturing the levator muscle fibers together in the anterior midline when possible.

Goodwin et al. [674] reported a series of 22 RUF approached perineally. They extensively mobilized the rectum posteriorly and the bladder anteriorly through wide perineal exposure allowing interposition of the levator ani muscles between the urinary tract and rectum. Singh et al. [689] described the management of a delayed post-traumatic RUF repaired via transperineal access without rectal or sphincteric transgression. An example of a preoperative and postoperative urethrogram is in **Figure 5**. Pratap et al. [690] described a simultaneous perineal and abdominal approach in a series of 8 patients with traumatic perineal injuries who had both complex urethral disruptions and RUF.

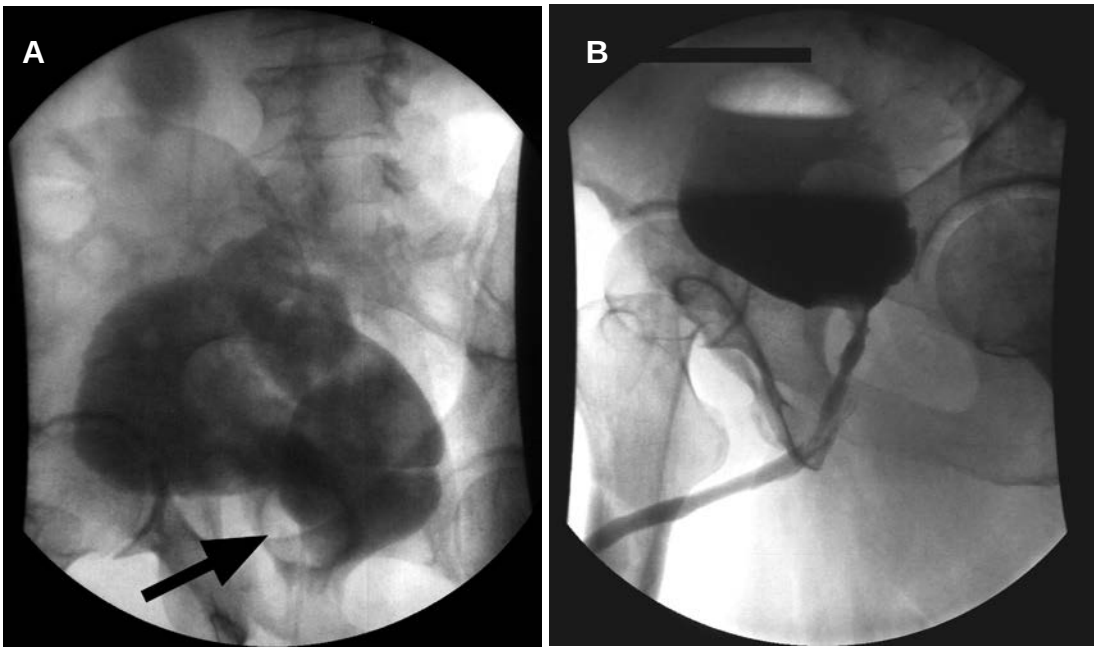


Figure 5A. Cystogram demonstrates RUF caused by a TURP. Negative shadow from Foley catheter is seen in the bladder.
Figure 5B. Retrograde urethrogram after transperineal closure of RUF

Table 18. Surgical approaches to rectourethral fistulas

APPROACH	AUTHOR, YEAR	No. PTS
PERINEAL	Young, 1926 [672] Lewis, 1947 [673] Goodwin, 1958 [674] Culp and Calhoon, 1964 [639] Smith and Veenema,1972 [643] Youssef,1999 [675]*(perineal dartos flap)* Benchekroun,1999 [642] Ng, 2004 [676]*(buccal graft)* Pratap, 2006 [690] Samplaski 2011 [691]	11 13 22 20 4 12 11 27 8 13
POSTERIOR - SAGITTAL	Kilpatrick and Thompson, 1962 [677]	6
POSTERIOR – TRANSSPHINCTERIC	Stephenson,1996 [678] Kilpatrick and Mason, 1969 [679] Culp, 1964 Fengler,1997 [655] Fournier, 1996 [680] Bukowski,1995 [681] Dal Moro, 2006 [693] Erickson, 2006 [694] Lorente, 2011[695] Pera, 2008 [696]	15 7 20 8 1 7 7 1 10 5
TRANSANAL	Vose,1949 [682] Parks and Motson, 1983 [683] Tiptaft,1983 [646] Noldus,1997 [647] Culkin, 2003 [684]	4 1 3 5 5
COMBINED*(posterior transsphincteric anterior rectal wall advancement*)	Al-Ali,1997 [665]	16
ANTERIOR TRANSANORECTAL	Geceleter,1973 [685] Venable,1989 [669] Zinman, 2003 [686]	19 1 22
ENDOSCOPIC	Wilbert, 1996 [687] Bardari, 2001[688] Pigalarga, 2011[701]	2 1 1

Samplaski et al. [691] reported transperineal repair with gracilis muscle interposition in 13 patients with complex RUFs of varying etiologies. One patient developed recurrence. They demonstrated low morbidity, high success rates, and reasonable bowel and bladder function postoperatively.

2. Posterior Sagittal Approach

Kraske in 1885 [692] described a posterior midline incision extending to the left paramedian aspect of the coccyx and sacrum that involved partial removal of the sacrum in addition to coccygectomy. His method did not involve division of the sphincters, but rather sweeping the rectum laterally to ultimately facilitate resection and reanastomosis of a tumour-bearing rectal segment, thereby preserving fecal continence. In 1962, Kilpatrick and Thompson [677] used this approach when the rectum was completely mobilized circumferentially proximal and distal to the fistula. The RUF was then divided, sparing as much as possible on the urethral aspect. The rectal part of the fistula was excised and closed in two layers, and the urethra was repaired and stented with a catheter.

3. Posterior (Parasacrococcygeal) Transsphincteric Approach

In 1969 Kilpatrick and Mason [679] updated this method and advocated a more radical method of dividing the rectal sphincters to give direct access to the RUF. The procedure (the York-Mason approach) is simpler than some complicated trans-

abdominal or transperineal approaches to RUF. It is still used because it allows direct visualization of the fistula via parasacrococcygeal (transsphincteric) incision especially to fistulae in the mid to lower rectum [655]. After the skin incision the mucocutaneous junction is marked with sutures and the internal sphincter is exposed. Division of the sphincter mechanism and posterior rectal wall allows exposure of the fistula. Each sphincter muscle is tagged with color-coded sutures. The next step of this procedure is the incision around fistula, followed by excision of the fistulous tract exposing the catheter in the prostatic urethra. The undermining of rectal wall allows sufficient mobilization. After closure of the prostatic urethra it is recommended that the full-thickness rectal wall flaps are close in a "vest over pants" technique (**Figure 6**). It is important to make sure that the suture lines do not overlie each other. The procedure is completed by suture of the rectal wall and approximation of the sphincter muscles (**Figure 7**). Fengler and Abcarian [655] reported healing of RUF in all of 8 patients with the York-Mason approach. Bukowski et al. [681] managed 7 acquired recurrent RUF (3 after prostatectomy, 3 after trauma and 1 after perineal abscess) using York-Mason technique and a similar experience was described by Fournier et al. [680] in the management of a case of the urethro-prostato-rectal fistula after a gunshot wound.

Stephenson and Middleton [678] modified the York-Mason repair and reported their experience with posterior sagittal, transanal, transrectal repair of RUF in 15 patients. The transsphincteric, transanal surgical approach provides many advantages, including easy access and identification of the fistula tract, good surgical exposure, adequate resection back to well vascularized tissue, and access to several vascularized flaps for interposition between the repaired urinary and gastrointestinal tracts.

Culkin [684] reported preliminary experience with the transsphincteric, transanal surgical approach to correct acquired urethrorectal fistula in five men. Mean patient age was 56.6 years (range 37 to 72). The etiology was surgical (radical prostatectomy) in 3 cases, traumatic in 1 and idiopathic in 1.The time from the diagnosis of urethrorectal fistula to surgery was 4 weeks to 4 years. Five men underwent excision and closure of a urethrorectal fistula with diverting colostomy. In 4 men (80%) urinary continence subsequently returned with adequate sphincter tone, while in 1 (20%) with perineal trauma and active proctitis the fistula recurred 6 weeks after surgery.

Dal Moro et al. [693] reviewed a 15-year experience using the York-Mason posterior sagittal transrectal approach to iatrogenic RUF in 7 patients. In one patient with Crohn's disease the fistula recurred 11 years after the first surgery. The colostomy remained in place only in one patient with Crohn's disease and in another with ulcerative rectocolitis.

Erickson et al. [694] reported a novel surgical technique used to repair a rectourethral fistula associated with two short-segment urethral strictures located in the anterior and posterior segments of the urethra in a patient with prior unsuccessful repairs. The anterior urethral stricture was reconstructed with a ventral onlay of buccal mucosa in the ex-

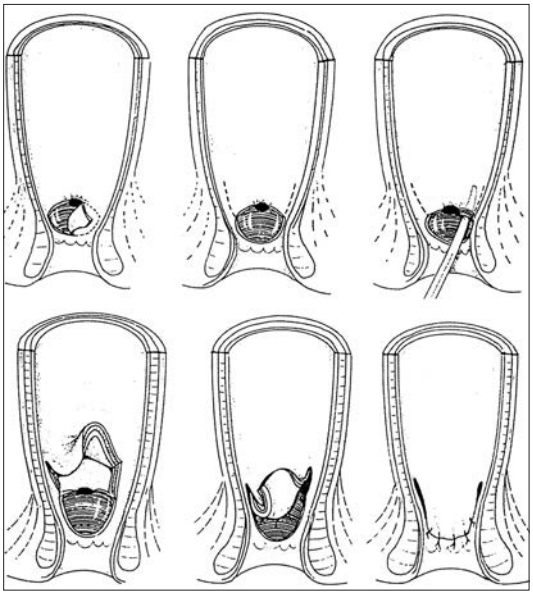


Figure 6. Rectourethral fistula repair. Full thickness rectal wall is mobilized to close in a "vest over pants" technique to close the fistula.

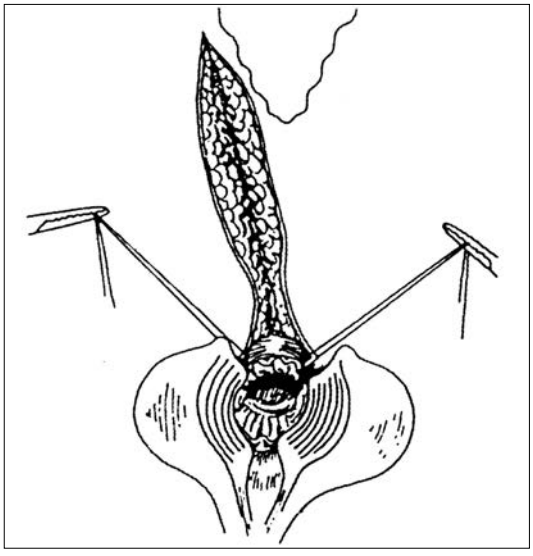


Figure 7. York-Mason approach to a rectourethral fistula via a parasacrococcygeal (transsphincteric) incision. Sutures are used to mark the sphincters. The speculum has been placed at the bottom of the incision and the anterior rectal wall is visible.

aggerated lithotomy position. In a modified prone position, the rectourethral fistula was repaired using the transrectal transsphincteric (York-Mason) technique and the posterior urethral stricture with a radial forearm fasciocutaneous free flap which was anastomosed to the inferior gluteal artery and vein. The coexistence of a rectourethral fistula and distal urethral stricture requires simultaneous repair, because the urethral pressure from the distal obstruction may compromise fistula closure.

Lorente et al. [695] reported early successful closure in 10 patients with the posterior transsphincteric York-Mason technique, with good recovery of urinary and fecal continence. Pera et al. [696] reported on 5 patients successfully treated after RP with the York Mason technique. They reported minor morbidity and no impairment of continence.

4. Transanal Approach

Parks and Motson [683] popularized the addition of a full thickness local flap of anterior rectal wall as an adjunct to fistula repair through the intact anal canal **(Figures 8** [697] and **9**). They modified the transanal technique by denuding the rectal mu-

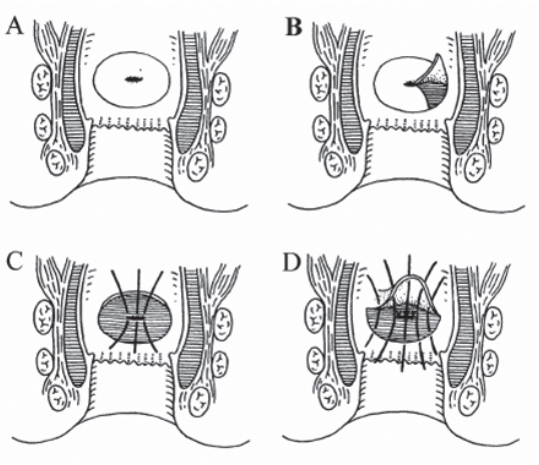


Figure 8. Transanal repair of rectourethral fistula.
A. Elliptical incision of the rectal mucosa around the fistula.
B. Denudation of the rectal mucosa.
C. Fistula closed with absorbable suture.
D. Rectal mucosal flap sutured with absorbable suture.

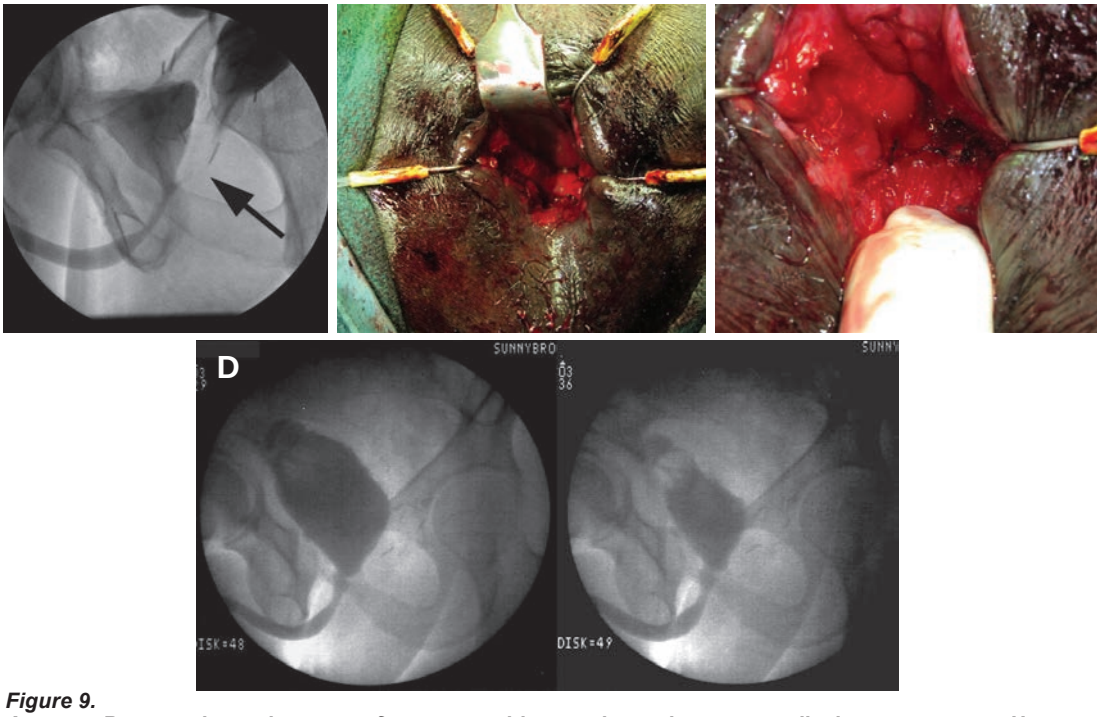


Figure 9.
A. Retrograde urethrogram of a 55 year-old man who underwent a radical prostatectomy. He complained of fecaluria and urine per rectum. This shows urethral contrast in the rectum through a rectourethral fistula (Black arrow).
B. Intraoperative photograph of transanal rectourethral fistula repair. The anus is held open by the ring retractor to permit direct access to the fistula.
C. Intraoperative view of the rectal mucosal sutures in the rectourethral fistula repair.
D. Retrograde urethrogram 3 months after transanal rectourethral fistula repair. There is no contrast entering the rectum from the urethra. The patient's suprapubic tube was removed and his colostomy was reversed.

cosa lateral and distal to the fistula, and mobilized the rectal wall away from Denonvilliers´ fascia proximal to the fistula for four centimeters. Tiptaft et al. [646] also used a special anal retractor for this surgery.

With the Latzko procedure the RUF is closed in three layers with absorbable suture. A transurethral catheter is placed for 3 weeks. Noldus et al. [647] reported 23 patients (3.9%) with rectal injury during 589 RP and cystoprostatectomies. Of these 23 patients, 12 developed a RUF. Seven fistulas closed spontaneously with prolonged catheter drainage. The remaining 5 fistulas were all successfully closed with the transanal Latzko procedure.

Al-Ali et al. [665] treated 30 men with RUF caused by war wounds. He used the method of posterior transsphincteric anterior rectal wall advancement as the treatment of choice. Double diversion (end sigmoid colostomy and suprapubic cystostomy) for one month was performed in all patients. Double diversion alone resulted in 'spontaneous' RUF healing in 47% of patients but 53% required reconstruction. Early repair was recommended for large fibrous fistulas. Undiversion was done after two months when the urethra and anorectal canals were normal.

5. Anterior Transphincteric, Transanal Surgical Approach (Astra)

In 1973 Gecelter [685] performed a midline perineal incision to gain access to the urinary tract after placing the patient in exaggerated lithotomy position. The anal sphincter was incised anteriorly, tag sutures carefully placed, and the rectal incision was carried to the fistulous tract, which was excised and repaired in multiple layers with transposition of tissue as available. Castillo et al. [698] reviewed their first 110 consecutive laparoscopic extraperitoneal radical prostatectomies and reported 3 RUF. Only one was cured with conservative management. The other 2 patients were repaired by anterior transphincteric, transanal surgical approach (ASTRA).

6. Endoscopic Approach

Wilbert et al. [687] reported two patients with RUF who were repaired endoscopically transanally. The patients were positioned prone and the rectoscope mounted to the operating table was inserted into the rectum .The fistula was visualized and the opening excised to the level of the perirectal tissues with cautery. The rectal wall was mobilized full thickness with scissors and closed primarily in two layers with a microscope. The patient was then placed in lithotomy position and the urethral side of the fistula was coagulated and injected with fibrin.

Bardari et al. [688] used cyanoacrilic biological glue to close one prostato-perineal fistula complicating an abdominoperineal resection of rectum and one persistent neobladder-ileal fistula. The biologic sealant was administrated endoscopically through an open-end 6F ureteral catheter. Quinlan et al. [699] presented the case of an iatrogenic fistula in a 71-year-old man treated by a transanal endoscopic microsurgical (TEM) approach, without recourse to a stoma. Bochove-Overgaauw et al. [700] reported successful repair of 1 of 2 RUF with transanal endoscopic microsurgery (TEM): the RUF occurred after laparoscopic radical prostatectomy. Pigalarga et al. [701] described a case of successful repair of iatrogenic RUF through a multidisciplinary approach consisting of cystoscopy, urethral stent placement, colonoscopy, and transanal endoscopic microsurgery assisted rectal advancement flap.

7. Other Modifications

Youssef et al. [675] successfully treated 12 male patients who presented with RUF from 1990 to 1997 using the perineal subcutaneous dartos flap procedure. The RUF resulted from crush pelvic injury in 6 cases, gunshot wounds in 2, and post prostatectomy in 4. The fistula was associated with a urethral stricture in 4 cases. A perineal approach was used and combined with a transsymphyseal approach in the 4 patients with posterior urethral stricture. They interposed a subcutaneous dartos flap as a tissue flap between the repaired rectum and urethra. No leakage or perineal collection developed and there was no fistula recurrence. Follow-up ranged from 9 to 42 months. This technique of a perineal subcutaneous dartos flap may fulfill the principles for successful repair of RUF. Varma et al. [702] also concluded that dartos muscle interposition is a straightforward technique that can result in successful fistula repair. but should not be used in immune-compromised patients or after radiation therapy.

Felipetto et al. [662] used human fibrin sealant (Tissucol) to close a prostato-cutaneous fistula (as a complication of pseudomonas prostatitis). Venkatesh and Ramanujam [703] prospectively studied the efficacy of autologous fibrin glue for closure of recurrent anorectal fistulas. Overall success rate was 60% however patients with acquired immunodeficiency syndrome who had fistulas associated with the urinary tract failed to respond. Verriello et al. [704] used fibrin sealant (Quixil) to inject it into the fistula tract and a rectal mucosal flap was used to close the internal opening. The fistula healed in few weeks, and the patient remained symptom free after 1 year of follow-up.

Chirica et al. [705] reported their experience with coloanal sleeve anastomosis (Soave procedure) as a salvage procedure for complex

rectourinary fistulas after radical prostatectomy or following anterior resection for rectal cancer after radiochemotherapy. All eight patients had a temporary ileostomy, which was successfully reversed in 7. Lesser et al. [706] reported a case of radiation and salvage cryoablation induced RUF after treatment of prostate cancer which was successfully repaired with a combined endorectal advancement flap with an Alloderm graft.

f) Summary

A review of recent literature shows an increasing number of papers describing treatment. All available studies are retrospective cases and case series (level 3 evidence). There are many causes of these fistulas described in the literature but there is a lack of valid epidemiologic data about the incidence of UCF and RUF. The diagnostic algorithm has not changed in many years.

The aim of the surgical approach is the closure of all types of fistulas. While spontaneous closure and success with a one-stage procedure has been reported, most cases to date involve 3 stages (double diversion, closure technique, and undiversion). An endoscopic approach using biological sealants is promising. Only a few urologists and general surgeons have gained wide experience in the management of UCF or RUF, and the management of these difficult conditions should remain in the hands of experts working in tertiary referral centres. No single procedure has yet proved to be best or universally applicable. Conservative treatment is generally ineffective in the management of large RUF. Surgical intervention offers symptomatic relief and improved quality of life in most patients.

All reports are still only retrospective case series **(Level of evidence 3; grade of recommendation C).**

XI. THE ARTIFICIAL URINARY SPHINCTER (AUS)

Different devices designed to control urinary incontinence in the male began to appear in the middle of the 18th century [707]. The gold standard today is the artificial urinary sphincter (AUS) designed by F.B. Scott, W.E. Bradley, and G.W. Timm in 1973 [708]. The original model underwent a number of modifications, but the basic principle remained the same. It consists of a fluid filled hydraulic system with a cuff around the urethra, a pressure regulating balloon and an activating device, the pump, placed in the scrotum.

1. AVAILABILITY AND COST

The use of the AUS has increased dramatically since its introduction in 1975 when 90 AUS devices were implanted until 2008 when 4818 procedures were done, with 61% implanted for PPI. [709, 710] In 2005, just over 10% of US urologists perform AUS surgery with the vast majority (92%) performing 5 or fewer surgeries a year and there were only 8 surgeons who implanted 21 or more AUS devices per year. [710]

The results of an e-mail survey among urologists and gynecologists were previously published in the 3rd ICI, whereby members of the International Continence Society were asked if the AUS was available in their country; and if so, what was the price of the device (in US dollars). About 10% of the members responded by email from 31 countries. The high price in some countries at the time (Georgia, Hong-Kong, Romania and Saudi Arabia) precluded its use. Very few gynecologists implant the AUS, probably since the majority of patients receiving the device are male.

2. INDICATIONS

The indication for AUS placement is for the treatment of SUI that is persistently bothersome despite 6-12 months of active conservative management. As the most common cause of SUI in men is iatrogenic injury during prostate cancer surgery, it follows that the most common indication for AUS is post-prostatectomy incontinence (PPI). The use of the AUS for the treatment of PPI varies regionally. For example, within the United States, state-by-state use of the AUS ranges from 1% to 10% of all RRP patients, with an average of 6% of RRP patients ultimately undergoing AUS implantation.[711]

Previous radiotherapy to the pelvis is not a contraindication for AUS placement in males,712 as the ultimate outcome seems to be similar in men whether or not they have received radiation therapy [713], although a higher incidence of urethral atrophy, erosion and infection requiring surgical revision has been reported in irradiated patients compared to those not irradiated (41% vs 11%). Despite this observation, long term continence and patient satisfaction appear not to be adversely affected in the irradiated male patient [713].

The compressive effect of the AUS is temporarily relieved when the patient squeezes the scrotal pump, transferring fluid from the urethral cuff to the pressure-regulating balloon. Subsequently, the bladder can then empty either by bladder contraction and/or by abdominal straining. Accordingly, patients voiding with the Valsalva maneuver because of an underactive or neurologically acontractile bladder, do not seem to be at an increased risk of complications [714]. It should also be noted that patients with previous anti-incontinence procedures show a significantly higher explantation rate [715].

Clinical experience suggests that enterocystoplasty or gastrocystoplasty can be done simultaneously

with the implantation of the AUS [716,717]. However, AUS placement at the time of cystoplasty is associated with earlier infections, especially during the first 3 years post-operatively [718]. In the long-term (> 3 years) the infection rate is the same whether the AUS is implanted after or at the time of cystoplasty. AUS can also be successfully implanted in patients after bladder substitution [387], and in those with locally recurrent prostate cancer with a relatively good prognosis [719], or those with severe post-radical prostatectomy anastomotic stricture in whom a stent has been placed previously [398].

Finally, advanced age is not a contraindication to AUS placement. A retrospective analysis by O'Connor and colleagues of a cohort of men over age 75, revealed excellent success rates, with 21 of 29 men (72%) achieving successful continence. Revision rate was 14% at an average of 5 years follow-up, with 14% requiring explantation, and 21% requiring device deactivation due to deterioration in overall health precluding proper use of the AUS at an average of 47 months after placement [720].

3. SURGICAL TECHNIQUES

The original technique of implantation is illustrated in **Figure 10**. The cuff of the sphincter is placed around the bulbar urethra via a midline perineal incision, while the pressure regulating balloon and the scrotal pump are inserted via a separate inguinal incision. The inguinal incision is carried through the fascia, above the level of the ligament and an area in the prevesical space is bluntly cleared. The pressure-regulating balloon is placed there and filled with 23 cc of saline or contrast after which the fascia is closed. A tunnel is made under Scarpas fascia into the scrotum deep to the dartos fascia where a pocket for the pump is developed. The cuff tubing is transferred from the perineum to the inguinal incision after which the excess tubing is cut off and the appropriate connections are made with the quick connect system.

Another surgical approach has been described using a single, upper transverse scrotal incision which allows the placement of all 3 components of the system, the cuff, the pump in a scrotal pouch, and the reservoir behind the fascia transversalis [304]. Alternatively, the pressure-regulating balloon may be placed through a separate inguinal incision, with the cuff and control pump placed via a single trans-scrotal incision, with the connections among scrotal pump, balloon reservoir, and urethral cuff tubing made in the usual inguinal incision. While the trans-scrotal approach potentially minimizes the invasiveness of the AUS surgery, by limiting the surgical approach to a single incision [304], a few reports have revealed that surgical success might be diminished compared with perineal cuff placement and abdominal balloon reservoir placement [721,722]. A multicenter retrospective study by Henry et al of 158 patients operated on at 4 centers noted that in patients treated with a perineal versus trans-scrotal AUS the perineal group had a completely dry rate of 44%, versus 28% in the scrotal group ($p<0.03$) and had much higher rates of "social continence" as well. Thus the perineal approach for initial artificial urinary sphincter implantation appears to control male stress incontinence better than the trans-scrotal approach.

The trans-scrotal approach appears particularly useful for simultaneous placement of an AUS and inflatable penile prosthesis through a single incision, with Kendirci and colleagues [723] reporting a urethral erosion rate of 9%, an overall revision rate of 14%, and a social continence rate of 100% in 22 patients at 17 months average follow-up. Sellers, et al. [724] recommend the simultaneous surgery for cost-efficacy. They demonstrated a $7,000 cost savings when both devices were implanted simultaneously through a scrotal approach, compared to staged implantation with 2 separate surgeries.

Recent experience with the relatively new 3.5 cm cuff has demonstrated significant efficacy with no increase in complications during 14 months of study at one site [725]. The 3.5 cm cuff has become the predominant size used for primary and revision surgery at that center.

4. COMPLICATIONS

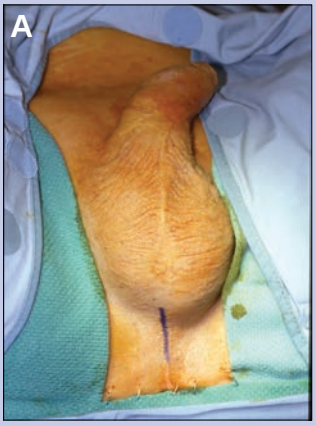
Complications following implantation of the AUS can be divided into the categories of incontinence, erosion and/or infection, and unusual complications. While the number of AUS procedures performed varies geographically throughout the world. Certain "centers of excellence" perform substantially more procedures than do community hospitals [711]. However, the total number of procedures done in a given center does not seem to be a determining risk factor for complications. Comparable erosion/infection rates have been reported from centers with fewer than 50 or more than 100 cases [282]. This suggests that erosion and infection may be more closely related to the physiologic state of the patient rather than the experience of the surgical team, provided standard precautions are strictly applied. Nevertheless, as experience with the AUS has grown the overall revision rate has reportedly decreased [710].

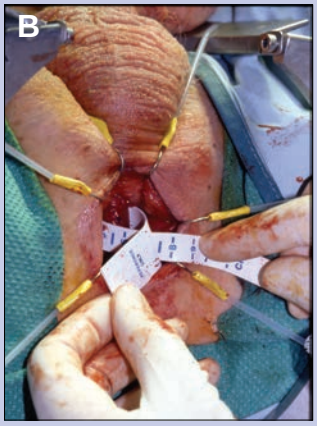
a) Incontinence

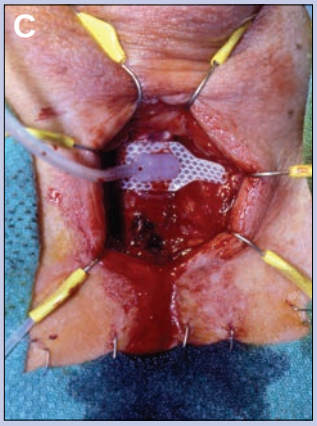
Incontinence following implantation of an AUS can result from (1) alteration in bladder function, (2) atrophy of the urethra, or (3) mechanical failure of the device. These causes may co-exist.

1. Alteration in bladder function

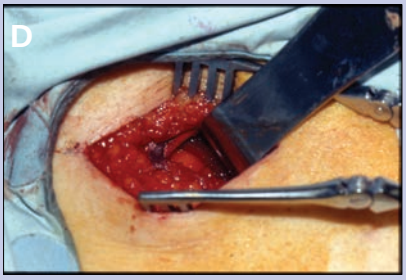
Lai and Boone noted that based on postoperative patient symptoms and the need for anticholinergic medication up to 23% of men undergoing AUS for PPI can develop denovo OAB [268]. UDS were not repeated postoperatively to define the bladder changes associated with this.



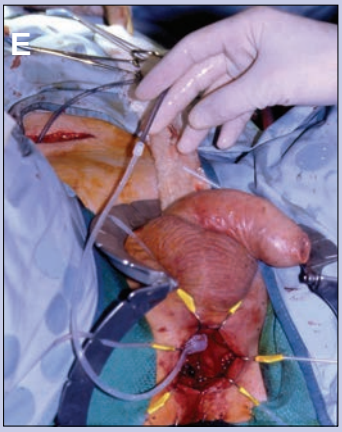


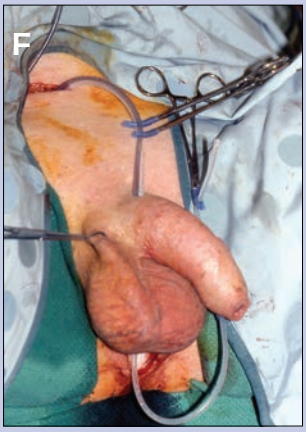


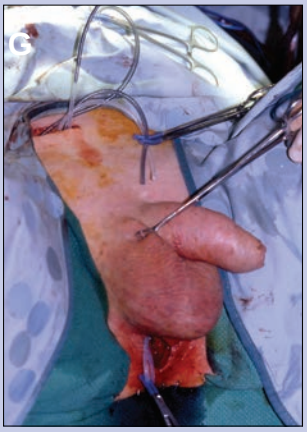
A. With the patient in lithotomy position, a perineal incision is made behind the scrotum to expose the bulbar urethra.
B. The urethra is mobilized circumferentially within the bulbospongiosus muscle and the measuring tape is used to obtain the cuff size.
C. The belt-like cuff is positioned around the urethra.

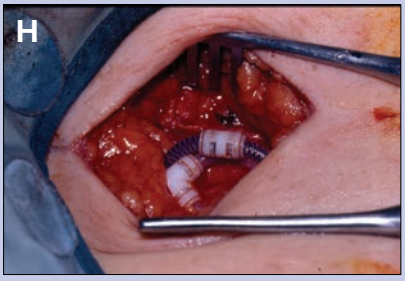


D. A right lower quadrant (RLQ) abdominal incision is made and the extraperitoneal space is entered lateral to the rectus muscle for insertion of the reservoir.









H. Connectors are placed to join the tubes from the cuff and reservoir to the corresponding tubes from the pump in the RLQ incision.

Figure 10. Artificial Sphincter Technique

Alteration in bladder function has been reported principally in patients with neurogenic bladder dysfunction, especially in children [726-731]. These changes include de novo involuntary detrusor contractions, decrease in bladder compliance, and the development of a high-pressure system, causing incontinence, hydronephrosis and ultimately renal failure. Modifications in detrusor behavior (including its consequences on the upper urinary tract) occur in up to 57% of such cases [726-737]. It should be pointed out, however, that there has never been a published report of hydronephrosis following implantation of an AUS for incontinence after prostatectomy [738]. While the ideal candidates for sphincter implantation are those with an incompetent urethral sphincter, and a low pressure, relaxed, and compliant bladder [735], data described earlier demonstrated that even those with "unfavourable" urodynamic factors may have a good outcome after AUS placement [58].

2. Atrophy of the urethra

Urethral atrophy may occur at the cuff site secondary to long-term mechanical compression of the periurethral and urethral tissues. However, some authors do not mention it as a possible cause of AUS failure [336,738,739]. About 4 months following implantation, cuff efficiency diminishes, presumably because pressure atrophy occurs in every patient to some extent 740. The incidence of urethral atrophy leading to revision varies from 3% to 9.3% [253,259,262,423,736,741-743]. Atrophy can be lessened with nocturnal deactivation of the cuff [744].

b) Mechanical failure

The causes include perforation: of one of the components with loss of fluid from the system, air bubbles or organic debris within the system causing inadequate function of the pump, disconnection of one of the tubes, or kinking of a tube. Introduction of "kink-free" tubing has virtually eliminated this last complication. The incidence of these complications varies widely and ranges from 0% [741] to 52.5% [269] with the longest follow-up. In this latter study, the cuff seemed to be the most vulnerable part of the system (22 cuff failures in 18 patients, most of them occurring during the first 2 to 3 years following implantation), followed by pump failure (6 times in 4 patients). Blockage is an exceptional event, occurring only once in 61 patients followed from 10 to 15 years [269]. In a publication from Baylor [262], chronicling a 13-year experience with the AUS, mechanical failure occurred at an average of 68.1 months postoperatively. An unusual mechanical complication has been reported. The locking tab became displaced distally into the cycling portion of the cuff preventing the fluid from flowing into the cuff surrounding the urethra.[745]

c) Erosion and/or infection

Erosion and infection are two major complications that almost invariably necessitate removal of the prosthesis. Their incidence may be reported separately, or more commonly together as a single complication. The incidence of these complications varies from 0% to 24.6% [253,336,423,729,735,736,741-743,746,747]. Most recent large series report an incidence of infection and erosion generally less than 8% [56,261,262,274,738,739,748,749]. As would be expected, the highest incidence has been reported with the longest follow-up (10-15 years) [253]. Lai and colleagues [262] from Baylor reported that erosion occurred at an average of 19.8 months postoperatively rather than in the peri-operative period. Previous surgery [750] at the site of cuff placement increases the risk of erosion. This, however, may be decreased by delayed cuff activation [751]. A recent study by Lai et al. [752] noted that patients undergoing a "secondary" implant (after a prior explant for erosion or infection) had a four-fold higher erosion rate compared to "virgin" cases. Some authors, however, did not find an increased incidence of complications when a new cuff was implanted at the site where several months before, a cuff has been removed for infection or erosion [753]. Other risk factors include urethral catheterization and urethral endoscopic manipulations with an activated sphincter in place [754]. This point is important and it is crucial that patients with an AUS understand that if they are to have a catheter placed they should ask their physician to have a urologist deactivate the AUS first.

A likely etiology of early erosion is intra-operative laceration of the urethra when dissecting it from the corpora cavernosa, where a difficult anatomical plane exists. Intraoperative recognition of urethral injury can be facilitated by retrograde perfusion sphincterometry using a flexible cystoscope35. While recognition of a urethral injury may alert the surgeon to the necessary termination of the procedure, urethral erosion may still occur without a known urethral laceration [755].

As mentioned above, while the majority of authors consider previous radiotherapy a risk factor for increased infection and erosion, it is not a contraindication to implantation of an AUS in the male patient with PPI [252,254,276,332,713,739,756]. Overall patient satisfaction is similar in those who have been irradiated, compared to those who have not been [252,263,713]. Furthermore, the degree of satisfaction does not diminish with an increased number of surgical revisions [267,757].

d) Rare complications

Several unusual and rare complications have been reported in the literature, such as the intravesical migration of the reservoir with secondary stone formation in the bladder [758], or a giant urethral diverticulum at the site of a previously removed cuff because of erosion and urinary extravasation [759].

5. DURABILITY OF AUS COMPONENTS

When defining durability of one of the components or the AUS as a whole, one should distinguish

between explantation of the device due to device malfunction (e.g. leak in one of the components) or complications caused by an otherwise properly functioning sphincter unit (e.g. cuff erosion, infection at the site of implantation, etc.). This distinction is rarely made in the literature. Durability of a device is defined as time elapsed during which no mechanical problem alters the normal function of the device. This should exclude the second group from further analysis.

There are very few references in the literature pertaining to the length of time a device functioned normally before its removal due to mechanical failure. In a multicenter trial, for neurogenic bladders, conducted in France [736], the authors mention that the "mean operational life" of the sphincter was 56 months (range 3-118 months). Haab et al [259] analyzed 68 patients and noted that the mechanical failure rate dropped from 44.4% to 12.4% since modifications were made to the device, mainly the cuff component. Survival time of these components was not provided. Similar conclusions can be drawn from a series from the Mayo Clinic [265] where the modification of the cuff design (narrower back) resulted in a substantial drop of the reoperation rate at 5 years. In the "narrow back" group 17% (31/184) required reoperation. In that cohort, non-mechanical failure decreased from 17% to 9% and mechanical failure decreased from 21% to 8% following introduction of the narrow back cuff [265]. Mean time to reoperation was 26.2 months (mean 2-68 months). Using Kaplan-Meier statistical analysis for this group of patients, the overall 5-year expected product survival was 75%. In Lai's report regarding Baylor's 13-year experience with the AUS, only 6% of devices failed mechanically, at an average of 68.1 months, with 75% of patients requiring no revisions at 5 years [262]. In a review, Venn et al. [336] analysed the outcome of 100 patients in whom an artificial urinary sphincter was implanted for more than 10 years. Thirty-six percent of them still had the original sphincter and were continent at a median follow-up of 11 years. The bulbar cuff, as compared to the bladder neck cuff provided a slightly better continence rate at 10 years, 92% and 84%, respectively. The lowest erosion rate occurred with the bulbar cuff. Device survival rate at 10 years was 66% in this series.

In a series of 30 boys with spina bifida Spiess et al. [760] found that the mean lifetime of all AUS was 4.7 years, with no statistically significant difference in sphincter survival of those inserted at the bladder neck or the bulbous urethra (4.6 and 4.9 years, respectively). A sharp drop was observed at 100 months with only 8.3% of the original sphincters still functioning beyond this point. In a series of 35 adolescents with neurogenic voiding dysfunction implanted with a bladder neck cuff over an 11-year period, with an average follow-up of 5.5 years, Lopez Pereira and colleagues [761] reported a 20% mechanical failure rate, with an additional 8.6% erosion rate. Adverse bladder storage changes developed in 31.8% of patients, who thereby required augmentation cystoplasty. However, continence was achieved in 91.4% of individuals.

In other series, the global long-term (2 to 7.7 years) revision rate, for any of the above mentioned reasons varies between 16% and 50% [261,262,266,267,424,757,761-763]. In Webster's report [757] of 554 implantations over a 10 year period, (i.e. performed since the 1987 device modification), he noted a mechanical failure rate of only 31/554 (5.5%). Non-mechanical failure was 88/554 (15.9%), with 63/554 (11.3%) due to urethral atrophy and 21/554 (3.8%) due to cuff erosion. Of the total cohort, 21.4% required at least one revision surgery, while 78.6% did not. Of those 119 patients who required reoperation, 76.5% required no further treatment (similar to the non-reoperation rate of the initial cohort), while 23.5% required re-operation for either mechanical or non-mechanical failure. Five-year durability of the AUS following primary or secondary implantation was comparable, with 80% for the initial placement, and 88% following revision surgery. Similarly, continence status was comparable, with 90% of primary and 82% of revision patients achieving 0-1 pad per day urinary control. Patients with neurological deficits seem to have a higher risk of non-mechanical failure and the overall continence rate may be lower compared to non-neurologic patients [32].

6. DIAGNOSTIC PROCEDURES RELATED TO ARTIFICIAL SPHINCTER FAILURE

The diagnostic evaluation of urinary incontinence after the placement of the AUS is critical for the management of these patients and represents a challenging problem for the urologist. Several diagnostic and management algorithms have been proposed, some relatively simple, others more complex [32, 33, 276, 282, 737, 764-766]. **Figure 11** shows an algorithm to investigate and treat the male patient with a previously functioning AUS who becomes incontinent.

Physical examination should exclude infection at the site of the cuff or the scrotal/labial pump. Difficulty compressing the pump suggests tube kinking, fluid loss or an obstructed system. Loss of fluid from the system may be suggested by the inability of the pump to appropriately refill after just one or two pumps.

Plain X-rays of the abdomen or pelvis may show fluid loss, if the system is filled with radioopaque solution [767, 768] (**Figure 1**). Alternatively, sonography of the pressure-regulating balloon may show volume loss. One should obtain a baseline plain film after the primary implantation when the reservoir is filled with contrast for subsequent comparison as radio-

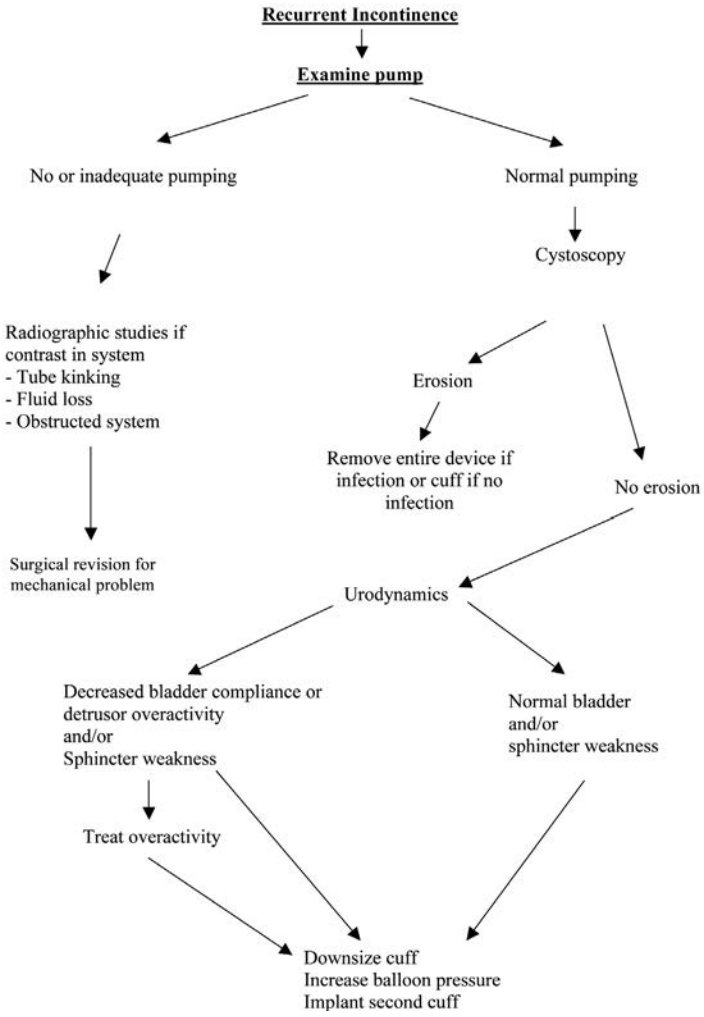


Figure 11. Algorithm for managing incontinence after AUS placement.

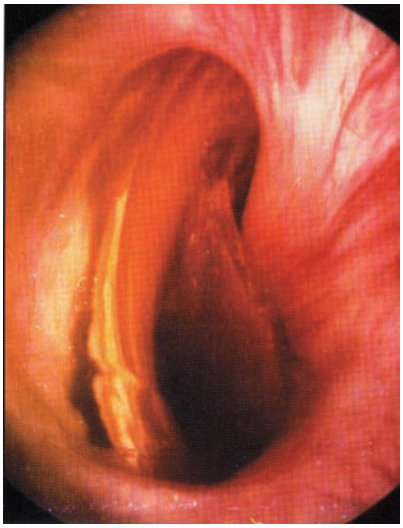


Figure 12. Endoscopic view of AUS cuff erosion into the bulbar urethra. The patient had undergone radiation after radical prostatectomy.

graphic imaging of the balloon does not detect changes until at least 50% of its volume has been lost [15]. Cystometrogram or complete urodynamic study will demonstrate changes in bladder behavior following insertion of the AUS as described above. Cystourethrography could eventually demonstrate a urethral diverticulum at the site of previous cuff erosion (**Figure 2**). Endoscopy will disclose any urethral erosion by the cuff (**Figure 12**).

Retrograde perfusion sphincterometry has been reported to diagnose the loss of compressive pressure in the urethral cuff [32]. It is done by infusing fluid from the meatus in a retrograde fashion. If the AUS cuff is functional and the urethral is intact there should be no flow when the pressure equals the AUS balloon pressure. This technique can also be used intraoperatively to detect urethral perforation or to adjust the pressure in the cuff [35]. This seems to be more useful than urethral pressure profile (UPP) [733].

Intraoperative electrical testing, using an ohmmeter [747,765] has been described to determine the site of fluid leakage from the system. This test can be helpful to avoid the need to change the whole system, and allow replacement of the leaking part only.

7. TREATMENT OF COMPLICATIONS

As outlined above, complications directly related to the presence of an artificial sphincter can be divided into categories: de novo OAB (which is typically treated as OAB), urethral atrophy, and/or mechanical failure, and infection/erosion. The treatment of these complications deserves comment, as no detailed reference can be found in the literature dealing exclusively with the treatment of these complications.

a) Atrophy of the urethra

Several therapeutic options exist to increase cuff pressure around the atrophied urethral wall: changing the balloon reservoir for one generating a higher pressure, downsizing the cuff diameter [15, 254, 769], or increasing the amount of fluid in the system. The most common approach is downsizing of the cuff. Another approach consists of placing the cuff inside the corporal tunica albuginea on the dorsal aspect of the urethra (transcorporal). This allows a safer mobilization of the urethra and adds some supplementary bulk of tissue to the circumference of the urethra, possibly decreasing the risk of erosion [272]. It should be mentioned, however, that there is a risk of reduced erectile function with this technique. The vast majority of such patients, however, already suffer from erectile dysfunction secondary to the prostate cancer surgery.

The implantation of a double-cuff AMS 800 had a recent period of increased popularity, as a primary procedure in the totally or severely incontinent patient [273,770], or as a salvage procedure, by adding a second cuff, following a failed previous single cuff [270,271,770]. Dimarco's group [271] and others showed excellent results with the addition of a second urethral cuff, placed 1.5–2.0 cm distal to the primary cuff. Alternatively, a circumurethral wrap of an organic bulking agent can be fitted, with subsequent placement of the AUS cuff over the biologic external urethral bulking agent [771]. Early reports of primary double cuff placement did not demonstrate any significant increase in morbidity with the double-cuff as compared with the single cuff system [273], and patient satisfaction also seemed to be higher [274] at an average of 21-41 months follow-up. However, O'Connor et al. [275] recently described their experience with 28 men who underwent double cuff placement and in contrast to an earlier report of theirs found that with longer follow-up there was no difference in continence between those men and 28 who underwent single cuff placement. In addition those who had the double cuff placement had a higher rate of additional surgery due to complications.

b) Mechanical failure

As with any device, mechanical failure can be expected with the AMS 800 AUS. The treatment involves surgical replacement of the failed component and reconnecting the system.

c) Infection

With overt infection the accepted treatment option is removal of the entire device and appropriate antibiotics. A second system can be subsequently implanted with equally good results [751]. It has been demonstrated, however, that immediate reimplantation of a new AUS after the removal of an infected, but not eroded, prosthesis can be a valid option with an overall success rate of 87% [772]. In 2007, AMS introduced the InhibiZone-coated artificial urinary sphincter (rifampin and minocycline hydrochloride coating) [773].

d) Erosion

In cases of urethral cuff erosion, the "offending" cuff must be removed. No clear guidelines exist whether removal of the whole system is superior to removal of the cuff alone but it must be assessed for infection and if present the whole device should be removed. When in doubt remove the entire system. Reservoir erosion into the bladder has been described following the removal of an eroded cuff [758]. Furthermore, it is not known whether it is nec-

essary to allow the urethra to heal over a catheter versus surgical repair. Most though would leave a catheter to allow for spontaneous healing and wait at least 4-6 months before placing another cuff. When a new cuff is placed it should be positioned away from the erosion site. In case of the erosion of one of the cuffs of a double system removal of the eroded cuff can successfully convert a double-cuff system into a single cuff system [774]. It is logical that intra-operative urethral injury may precipitate cuff erosion if unrecognized.

8. CONSENSUS PROTOCOL FOR FOLLOW-UP OF PATIENTS WITH AUS

As complications continue to be seen for years after implantation [775], it is helpful to have a structured follow-up plan. However, no standardized recommendations are available in the literature.

The consensus upon which the members of this subcommittee agreed and which is based on expert opinion are as follows:

1. Perioperative antibiotics are required. Gram-negative enteric bacteria and Staphylococcus epidermidis are the most frequently encountered microorganisms in infected prostheses [754].

2. Hospital stay should be kept to a minimum.

3. Urethral catheters, if inserted, should be withdrawn within 24-48 hours of surgery and the preoperative continence management continued.

4. The sphincter device should not be activated immediately postoperatively. In the initial period scrotal edema and pain prevent patients from manipulating the pump adequately. When this subsides after 6 to 8 weeks the device can be activated. Earlier activation may also be acceptable. Irradiated patients may benefit from a longer initial period of deactivation, up to 12 weeks [254]. Nocturnal deactivation should be considered in high-risk patients [253].

5. Patients are reviewed at 3 months after activation to ensure the device is working adequately, and to assess the continence status.

6. Long-term follow-up is different in the neurogenic and non-neurogenic patient. With time, alteration in bladder function may jeopardize renal function in the neurogenic patients. Periodic ultrasound evaluation of the upper urinary tract and monitoring of renal function is essential. If changes occur, urodynamic studies should be done to rule out detrusor overactivity. In non-neurogenic patients, periodic ultrasound may not be necessary.

7. When changes in the continence status occur diagnostic procedures depicted in **Figure 11** should be considered.

(Level of evidence 3; Grade of recommendation B-C)

XII. SUMMARY AND RECOMMENDATIONS

1. EVALUATION OF MALE INCONTINENT PATIENTS

Prior to surgery a basic patient evaluation should consist of history and physical examination, urinalysis and postvoid residual urine (**Level of evidence 1-2: grade of recommendation A**).

- A voiding diary is helpful to assess functional capacity and total urine output (**Level of evidence 1-2: grade of recommendation B**).
- Pad tests may be useful in certain circumstances (**Level of evidence 1-2: grade of recommendation B**).
- Blood testing (BUN, creatinine, glucose) is recommended if compromised renal function is suspected or if polyuria or poor urinary concentrating ability (in the absence of diuretics) is documented.
- Additional testing with cystoscopy and appropriate imaging of the urinary tract may be helpful in guiding therapy **(Level of evidence 2-3: grade of recommendation B).**
- The committee felt that multichannel urodynamics may be useful prior to invasive treatment for incontinence. **(Level of evidence 3: grade of recommendation C)**

2. INCONTINENCE POST-PROSTATECTOMY FOR BPO AND POST-RADICAL PROSTATECTOMY FOR PROSTATE CANCER

After a period of conservative management, which may also be from 6 to 12 months **(Level of evidence 3-4; grade of recommendation C):**

- The artificial sphincter is the preferred treatment for properly selected men who have stress incontinence after radical prostatectomy with the longest record of safety and efficacy. The AUS has been reported extensively for men with moderate to severe incontinence. **(Level of evidence 2-3; grade of recommendation B)**
- Male slings are an alternative approach with intermediate data supporting their safety and efficacy in men with more moderate degrees of PPI. Long-term data are beginning to accumulate. However,

the literature contains results on many different kinds of slings. **(Level of evidence 3; grade of recommendation C)**

- Injectable agents are an inferior option. **(Level of evidence 3-4; grade of recommendation C)**
- Adjustable balloons have also been reported. **(Level of evidence 3; grade of recommendation D (no recommendation possible))**

3. INCONTINENCE FOLLOWING OTHER TREATMENTS FOR PROSTATE CANCER

- The artificial sphincter is most widely used but ra§diation may be a risk factor for an increase in complications. **(Level of evidence 3; grade of recommendation B)**
- Slings have variable results after radiation. **(Level of evidence 3; grade of recommendation C)**
- Injectable agents **(Level of evidence 3-4; grade of recommendation C)**
- Adjustable balloons have not been successful in this setting. **(Level of evidence 3; grade of recommendation D (not recommended))**

4. INCONTINENCE FOLLOWING PELVIC TRAUMA (Level of evidence 3; grade of recommendation C)

- The artificial sphincter is most widely reported.
- Lower urinary tract reconstruction has also been reported on a limited basis.

5. INCONTINENCE IN ADULT EPISPADIAS-EXSTROPHY COMPLEX (level of evidence 3; grade of recommendation C)

- Patients should be treated in centres of excellence.
- A patient-directed approach should be taken.
- The choices include further bladder neck reconstructive surgery, bladder neck closure, bladder reconstruction or diversion with bowel.
- The data are insufficient for a specific recommendation.
- Transition is important between the pediatric and adult urologist.
- Life-long follow-up is mandatory in terms of continence, voiding efficiency, upper tract status and other urological complications

6. REFRACTORY URGENCY INCONTINENCE AND DETRUSOR OVERACTIVITY

- Botulinum toxin-A bladder injection is a minimally invasive treatment with efficacy **(Level of evidence 1-2; grade of recommendation B).**
- Neuromodulation is a treatment option with success reported in a limited number of male patients. **(Level of evidence 3; grade of recommendation C)**
- Detrusor myectomy has also been reported to be successful in a small number of male patients. **(Level of evidence 3; grade of recommendation C)**
- Augmentation cystoplasty is potentially successful in controlling symptoms but may be associated with unacceptable side effects**. (Level of evidence 3; grade of recommendation C)**
- Urinary diversion is a final option. **(Level of evidence 3; grade of recommendation C)**

7. REDUCED CAPACITY BLADDER

- Augmentation cystoplasty has been successful in most etiologies. **(Level of evidence 3; grade of recommendation C)**

8. URETHROCUTANEOUS FISTULA AND RECTOURETHRAL FISTULA (Level of evidence 3; grade of recommendation C)

- Etiologic factors causing acquired urethrocutaneous fistulae are demonstrated by clinical, endoscopic and imaging studies.
- Similar diagnostic maneuvers are applied to rectourethral fistulae.
- Surgical reconstruction is applied as required.
- In those that do not close with or without temporary urinary and fecal diversion, surgical reconstruction may be carried out.
- Most repairs are now carried out after prior fecal diversion.
- Various techniques are available for closure and can be done in collaboration with colorectal surgeons.

9. MANAGEMENT OF AUS COMPLICATIONS (Level of evidence 3; grade of recommendation C)

- Incontinence may result from alteration in bladder function, urethral atrophy, or mechanical malfunction.
- Infection and/or erosion of components demand surgical removal of all or part of the prosthesis.
- A treatment algorithm is presented to aid in management and in follow-up of patients.

10. NEW TECHNOLOGIES (Level of evidence C; grade of recommendation D)

- Tissue engineering has not been widely reported in males apart from isolated reports of preliminary studies. [776, 777]
- A new one-piece adjustable artificial sphincter has been reported with social continence (0-1 pads/day) in 28/36 men at 6 months after device activation. [778] The removal rate was 11% for erosion/infection.

FUTURE RESEARCH DIRECTIONS

- New technologies, bulking agents, sling materials, prosthetic devices should continue to be evaluated
- Accuracy in reporting of early research results is mandatory
- Mechanisms of post-prostatectomy incontinence and device effects need further research

CLINICAL TRIAL RECOMMENDATIONS

- Randomized trials (AUS and slings)
- Standardized workup and outcome measures including QoL
- Evaluation of the role of urodynamics in the workup
- Complete reporting of complications and outcomes especially those of slings
- Standardised definitions of cure/improved/unchanged/worse
- Reporting of procedures to salvage failures
- Long-term results (>2 years)
- Standardized reporting of durability

REFERENCES

1. Srivastava A, Grover S, Sooriakumaran P, Joneja J, Tewari AK. Robotic-assisted laparoscopic prostatectomy: a critical analysis of its impact on urinary continence. Curr Opin Urol 2011;21:185-94.
2. Nam RK, Herschorn S, Loblaw DA, et al. Population based study of long-term rates of surgery for urinary incontinence after radical prostatectomy for prostate cancer. J Urol 2012;188:502-6.
3. Kumar A, Litt ER, Ballert KN, Nitti VW. Artificial urinary sphincter versus male sling for post-prostatectomy incontinence--what do patients choose? J Urol 2009;181:1231-5.
4. Herschorn S, Thuroff J, Bruschini H, et al. Surgical Treatment of Urinary Incontinence in Men. In: Abrams P, Cardozo L, Khoury AE, Wein A, eds. Incontinence: Third International Consultation. Paris: Health Publications Ltd.; 2005:1241-96.
5. Herschorn S, Bruschini H, Comiter CV, Grise P, Hanus T, Kirschner-Hermanns R. Surgery for urinary incontinence in men. In: Abrams P, Cardozo L, Khoury AE, Wein A, eds. Incontinence: 4th International Concultation. Paris: Health Publications Ltd.; 2009:1121-90.
6. Blaivas JG, Zayed AA, Labib KB. The bulbocavernosus reflex in urology: a prospective study of 299 patients. J Urol 1981;126:197-9.
7. Griffiths DJ, McCracken PN, Harrison GM, Gormley EA. Relationship of fluid intake to voluntary micturition and urinary incontinence in geriatric patients. Neurourol Urodyn 1993;12:1-7.
8. Wyman JF, Choi SC, Harkins SW, Wilson MS, Fantl JA. The urinary diary in evaluation of incontinent women: a test-retest analysis. Obstet Gynecol 1988;71:812-7.
9. Schick E, Jolivet-Tremblay M, Dupont C, Bertrand PE, Tessier J. Frequency-volume chart: the minimum number of days required to obtain reliable results. Neurourol Urodyn 2003;22:92-6.
10. Mouritsen L, Berild G, Hertz J. Comparison of different methods for quantification of urinary leakage in incontinent women. Neurourol Urodyn 1989;8:579-87.
11. Starer P, Libow LS. The measurement of residual urine in the evaluation of incontinent nursing home residents. Arch Gerontol Geriatr 1988;7:75-81.
12. Diokno AC, Brown MB, Brock BM, Herzog AR, Normolle DP. Clinical and cystometric characteristics of continent and incontinent noninstitutionalized elderly. J Urol 1988;140:567-71.
13. Fantl JA, Newman D, Colling J, al. e. Urinary incontinence in adults: acute and chronic management. Clinical Practice Guideline, No 2,. Rockport,MD: U.S. Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research; 1996 March, 1996. Report No.: AHCPR Publication No 96-0682.
14. Foote J, Yun S, Leach GE. Postprostatectomy incontinence. Pathophysiology, evaluation, and management. Urol Clin North Am 1991;18:229-41.
15. Petrou SP, Williams HJ, Young PR. Radiographic imaging of the artificial urinary sphincter pressure regulating balloon. J Urol 2001;165:1773-5.
16. Leach GE, Yip CM. Urologic and urodynamic evaluation of the elderly population. Clin Geriatr Med 1986;2:731-55.
17. Goode PS, Locher JL, Bryant RL, Roth DL, Burgio KL. Measurement of postvoid residual urine with portable transabdominal bladder ultrasound scanner and urethral catheterization. Int Urogynecol J Pelvic Floor Dysfunct 2000;11:296-300.

18. Richter S, Hag'ag R, Shalev M, Nissenkorn I. [Measuring residual urine by portable ultrasound scanner]. Harefuah 1999;137:93-5, 176, 5.

19. Strasser H, Frauscher F, Helweg G, Colleselli K, Reissigl A, Bartsch G. Transurethral ultrasound: evaluation of anatomy and function of the rhabdosphincter of the male urethra. J Urol 1998;159:100-4; discussion 4-5.

20. McGuire EJ, Fitzpatrick CC, Wan J, et al. Clinical assessment of urethral sphincter function. J Urol 1993;150:1452-4.

21. Schick E. Objective assessment of resistance of female urethra to stress. A scale to establish degree of urethral incompetence. Urology 1985;26:518-26.

22. Smith AL, Ferlise VJ, Wein AJ, Ramchandani P, Rovner ES. Effect of A 7-F transurethral catheter on abdominal leak point pressure measurement in men with post-prostatectomy incontinence. Urology 2011;77:1188-93.

23. Bump RC, Elser DM, Theofrastous JP, McClish DK. Valsalva leak point pressures in women with genuine stress incontinence: reproducibility, effect of catheter caliber, and correlations with other measures of urethral resistance. Continence Program for Women Research Group. Am J Obstet Gynecol 1995;173:551-7.

24. Decter RM, Harpster L. Pitfalls in determination of leak point pressure. J Urol 1992;148:588-91.

25. Flood HD, Alevizatos C, Liu JL. Sex differences in the determination of abdominal leak point pressure in patients with intrinsic sphincter deficiency. J Urol 1996;156:1737-40.

26. Faerber GJ, Vashi AR. Variations in Valsalva leak point pressure with increasing vesical volume. J Urol 1998;159:1909-11.

27. Haab F, Dmochowski R, Zimmern P, Leach GE. [The variability of the leakage pressure threshold due to exertion "the Valsalva Leak Point Pressure" as a function of the filling volume of the bladder]. Prog Urol 1997;7:422-5.

28. Theofrastous JP, Cundiff GW, Harris RL, Bump RC. The effect of vesical volume on Valsalva leak-point pressures in women with genuine stress urinary incontinence. Obstet Gynecol 1996;87:711-4.

29. Petrou SP, Kollmorgen TA. Valsalva leak point pressure and bladder volume. Neurourol Urodyn 1998;17:3-7.

30. Swift SE, Utrie JW. The need for standardization of the valsalva leak-point pressure. Int Urogynecol J Pelvic Floor Dysfunct 1996;7:227-30.

31. McCormack M, Pike J, Kiruluta G. Leak point of incontinence: a measure of the interaction between outlet resistance and bladder capacity. J Urol 1993;150:162-4.

32. Leach GE. Incontinence after artificial urinary sphincter placement: the role of perfusion sphincterometry. J Urol 1987;138:529-32.

33. Wang Y, Hadley HR. Management of persistent or recurrent urinary incontinence after placement of artificial urinary sphincter. J Urol 1991;146:1005-6.

34. Comiter CV, Sullivan MP, Yalla SV. Retrograde leak point pressure for evaluating postradical prostatectomy incontinence. Urology 1997;49:231-6.

35. Choe JM, Battino BS, Bell TE. Retrograde perfusion sphincterometry with a flexible cystoscope: method of troubleshooting the AMS 800. Urology 2000;56:317-9.

36. Comiter CV, Nitti V, Elliot C, Rhee E. A new quadratic sling for male stress incontinence: retrograde leak point pressure as a measure of urethral resistance. J Urol 2012;187:563-8.

37. Horstmann M, Fischer I, Vollmer C, et al. Pre- and postoperative urodynamic findings in patients after a bulbourethral composite suspension with intraoperative urodynamically controlled sling tension adjustment for postprostatectomy incontinence. Urology 2012;79:702-7.

38. Beck R, Fowler C. Clinical neurophysiology in the investigation of genitourinary tract dysfunction. In: Rushton DN, ed. Handbook of Neurourology. New York: Marcel Dekker; 1994:151-80.

39. Brown MC, Sutherst JR, Murray A, Richmond DH. Potential use of ultrasound in place of X-ray fluoroscopy in urodynamics. Br J Urol 1985;57:88-90.

40. Bidair M, Tiechman JM, Brodak PP, Juma S. Transrectal ultrasound urodynamics. Urology 1993;42:640-4; discussion 4-5.

41. Manieri C, Carter SS, Romano G, Trucchi A, Valenti M, Tubaro A. The diagnosis of bladder outlet obstruction in men by ultrasound measurement of bladder wall thickness. J Urol 1998;159:761-5.

42. Blatt AH, Titus J, Chan L. Ultrasound measurement of bladder wall thickness in the assessment of voiding dysfunction. J Urol 2008;179:2275-8; discussion 8-9.

43. Ozawa H, Chancellor MB, Ding YY, Nasu Y, Yokoyama T, Kumon H. Noninvasive urodynamic evaluation of bladder outlet obstruction using Doppler ultrasonography. Urology 2000;56:408-12.

44. Abrams P. Detrusor instability and bladder outlet obstruction. Neurourol Urodyn 1985;4:317-28.

45. Dikranian AH, Chang JH, Rhee EY, Aboseif SR. The male perineal sling: comparison of sling materials. J Urol 2004;172:608-10.

46. Fischer MC, Huckabay C, Nitti VW. The male perineal sling: assessment and prediction of outcome. J Urol 2007;177:1414-8.

47. Migliari R, Pistolesi D, Leone P, Viola D, Trovarelli S. Male bulbourethral sling after radical prostatectomy: intermediate outcomes at 2 to 4-year followup. J Urol 2006;176:2114-8; discussion 8.

48. Hubner WA, Schlarp OM. Adjustable continence therapy (ProACT): evolution of the surgical technique and comparison of the original 50 patients with the most recent 50 patients at a single centre. Eur Urol 2007;52:680-6.

49. Rehder P, Gozzi C. Transobturator sling suspension for male urinary incontinence including post-radical prostatectomy. Eur Urol 2007;52:860-6.

50. Fassi-Fehri H, Badet L, Cherass A, et al. Efficacy of the InVance male sling in men with stress urinary incontinence. Eur Urol 2007;51:498-503.

51. Lebret T, Cour F, Benchetrit J, et al. Treatment of postu prostatectomy stress urinary incontinence using a minimally invasive adjustable continence balloon device, ProACT: results of a preliminary, multicenter, pilot study. Urology 2008;71:256-60.

52. Imamoglu MA, Tuygun C, Bakirtas H, Yigitbasi O, Kiper A. The comparison of artificial urinary sphincter implantation and endourethral macroplastique injection for the treatment of postprostatectomy incontinence. Eur Urol 2005;47:209-13.

53. John H. Bulbourethral composite suspension:: a new operative technique for post-prostatectomy incontinence. J Urol 2004;171:1866-70; discussion 9-70.

54. Schaal CH, Costa RP, Sala FC, Vanni AP, Cortez JP. Longitudinal urethral sling with prepubic and retropubic fixation for male urinary incontinence. Int Braz J Urol 2004;30:307-11; discussion 12.

55. Thiel DD, Young PR, Broderick GA, et al. Do clinical or urodynamic parameters predict artificial urinary sphincter outcome in post-radical prostatectomy incontinence? Urology 2007;69:315-9.

56. Trigo Rocha F, Gomes CM, Mitre AI, Arap S, Srougi M. A prospective study evaluating the efficacy of the artificial sphincter AMS 800 for the treatment of postradical

prostatectomy urinary incontinence and the correlation between preoperative urodynamic and surgical outcomes. Urology 2008;71:85-9.

57. Ballert KN, Nitti VW. Association between detrusor overactivity and postoperative outcomes in patients undergoing male bone anchored perineal sling. J Urol 2010;183:641-5.

58. Lai HH, Hsu EI, Boone TB. Urodynamic testing in evaluation of postradical prostatectomy incontinence before artificial urinary sphincter implantation. Urology 2009;73:1264-9.

59. Hu JC, Elkin EP, Pasta DJ, et al. Predicting quality of life after radical prostatectomy: results from CaPSURE. J Urol 2004;171:703-7; discussion 7-8.

60. Rodriguez E, Jr., Skarecky DW, Ahlering TE. Post-robotic prostatectomy urinary continence: characterization of perfect continence versus occasional dribbling in pad-free men. Urology 2006;67:785-8.

61. Krupski TL, Saigal CS, Litwin MS. Variation in continence and potency by definition. J Urol 2003;170:1291-4.

62. Olsson LE, Salomon L, Nadu A, et al. Prospective patient-reported continence after laparoscopic radical prostatectomy. Urology 2001;58:570-2.

63. Du Moulin MF, Hamers JP, Ambergen AW, Janssen MA, Halfens RJ. Prevalence of urinary incontinence among community-dwelling adults receiving home care. Research in nursing & health 2008;31:604-12.

64. Coyne KS, Zhou Z, Thompson C, Versi E. The impact on health-related quality of life of stress, urge and mixed urinary incontinence. BJU Int 2003;92:731-5.

65. Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. Annals of internal medicine 2008;148:435-48.

66. Johansson E, Steineck G, Holmberg L, et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. The lancet oncology 2011;12:891-9.

67. Wallerstedt A, Carlsson S, Nilsson AE, et al. Pad use and patient reported bother from urinary leakage after radical prostatectomy. J Urol 2012;187:196-200.

68. Litwin MS, Pasta DJ, Yu J, Stoddard ML, Flanders SC. Urinary function and bother after radical prostatectomy or radiation for prostate cancer: a longitudinal, multivariate quality of life analysis from the Cancer of the Prostate Strategic Urologic Research Endeavor. J Urol 2000;164:1973-7.

69. Liss MA, Osann K, Canvasser N, et al. Continence definition after radical prostatectomy using urinary quality of life: evaluation of patient reported validated questionnaires. J Urol 2010;183:1464-8.

70. Penson DF, McLerran D, Feng Z, et al. 5-year urinary and sexual outcomes after radical prostatectomy: results from the prostate cancer outcomes study. J Urol 2005;173:1701-5.

71. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002;346:1138-44.

72. Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002;347:790-6.

73. Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. Jama 2000;283:354-60.

74. Kielb S, Dunn RL, Rashid MG, et al. Assessment of early continence recovery after radical prostatectomy: patient reported symptoms and impairment. J Urol 2001;166:958-61.

75. Sebesta M, Cespedes RD, Luhman E, Optenberg S, Thompson IM. Questionnaire-based outcomes of urinary incontinence and satisfaction rates after radical prostatectomy in a national study population. Urology 2002;60:1055-8.

76. Lepor H, Kaci L. The impact of open radical retropubic prostatectomy on continence and lower urinary tract symptoms: a prospective assessment using validated self-administered outcome instruments. J Urol 2004;171:1216-9.

77. Madalinska JB, Essink-Bot ML, de Koning HJ, Kirkels WJ, van der Maas PJ, Schroder FH. Health-related quality-of-life effects of radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed localized prostate cancer. J Clin Oncol 2001;19:1619-28.

78. Deliveliotis C, Protogerou V, Alargof E, Varkarakis J. Radical prostatectomy: bladder neck preservation and puboprostatic ligament sparing--effects on continence and positive margins. Urology 2002;60:855-8.

79. Harris MJ. Radical perineal prostatectomy: cost efficient, outcome effective, minimally invasive prostate cancer management. Eur Urol 2003;44:303-8; discussion 8.

80. Maffezzini M, Seveso M, Taverna G, Giusti G, Benetti A, Graziotti P. Evaluation of complications and results in a contemporary series of 300 consecutive radical retropubic prostatectomies with the anatomic approach at a single institution. Urology 2003;61:982-6.

81. Hofmann T, Gaensheimer S, Buchner A, Rohloff R, Schilling A. An unrandomized prospective comparison of urinary continence, bowel symptoms and the need for further procedures in patients with and with no adjuvant radiation after radical prostatectomy. BJU Int 2003;92:360-4.

82. Ruiz-Deya G, Davis R, Srivastav SK, A MW, Thomas R. Outpatient radical prostatectomy: impact of standard perineal approach on patient outcome. J Urol 2001;166:581-6.

83. Augustin H, Pummer K, Daghofer F, Habermann H, Primus G, Hubmer G. Patient self-reporting questionnaire on urological morbidity and bother after radical retropubic prostatectomy. Eur Urol 2002;42:112-17.

84. Rassweiler J, Seemann O, Schulze M, Teber D, Hatzinger M, Frede T. Laparoscopic versus open radical prostatectomy: a comparative study at a single institution. J Urol 2003;169:1689-93.

85. Jacobsen NE, Moore KN, Estey E, Voaklander D. Open versus laparoscopic radical prostatectomy: a prospective comparison of postoperative urinary incontinence rates. J Urol 2007;177:615-9.

86. Anastasiadis AG, Salomon L, Katz R, Hoznek A, Chopin D, Abbou CC. Radical retropubic versus laparoscopic prostatectomy: a prospective comparison of functional outcome. Urology 2003;62:292-7.

87. Sacco E, Prayer-Galetti T, Pinto F, et al. Urinary incontinence after radical prostatectomy: incidence by definition, risk factors and temporal trend in a large series with a long-term follow-up. BJU Int 2006;97:1234-41.

88. Krambeck AE, DiMarco DS, Rangel LJ, et al. Radical prostatectomy for prostatic adenocarcinoma: a matched comparison of open retropubic and robot-assisted techniques. BJU Int 2009;103:448-53.

89. Rocco B, Matei DV, Melegari S, et al. Robotic vs open prostatectomy in a laparoscopically naive centre: a matched-pair analysis. BJU Int 2009;104:991-5.

90. Boris RS, Kaul SA, Sarle RC, Stricker HJ. Radical prostatectomy: a single surgeon comparison of retropubic, perineal, and robotic approaches. The Canadian journal of urology 2007;14:3566-70.

91. Di Pierro GB, Baumeister P, Stucki P, Beatrice J, Danuser H, Mattei A. A prospective trial comparing

consecutive series of open retropubic and robot-assisted laparoscopic radical prostatectomy in a centre with a limited caseload. Eur Urol 2011;59:1-6.

92. Reynolds WS, Shikanov SA, Katz MH, Zagaja GP, Shalhav AL, Zorn KC. Analysis of continence rates following robot-assisted radical prostatectomy: strict leak-free and pad-free continence. Urology 2010;75:431-6.
93. Choi JM, Nelson CJ, Stasi J, Mulhall JP. Orgasm associated incontinence (climacturia) following radical pelvic surgery: rates of occurrence and predictors. J Urol 2007;177:2223-6.
94. Patel VR, Coelho RF, Palmer KJ, Rocco B. Periurethral suspension stitch during robot-assisted laparoscopic radical prostatectomy: description of the technique and continence outcomes. Eur Urol 2009;56:472-8.
95. Noguchi M, Kakuma T, Suekane S, Nakashima O, Mohamed ER, Matsuoka K. A randomized clinical trial of suspension technique for improving early recovery of urinary continence after radical retropubic prostatectomy. BJU Int 2008;102:958-63.
96. Moore KN, Truong V, Estey E, Voaklander DC. Urinary incontinence after radical prostatectomy: can men at risk be identified preoperatively? J Wound Ostomy Continence Nurs 2007;34:270-9; quiz 80-1.
97. Wei JT, Dunn RL, Marcovich R, Montie JE, Sanda MG. Prospective assessment of patient reported urinary continence after radical prostatectomy. J Urol 2000;164:744-8.
98. Majoros A, Bach D, Keszthelyi A, Hamvas A, Romics I. Urinary incontinence and voiding dysfunction after radical retropubic prostatectomy (prospective urodynamic study). Neurourol Urodyn 2006;25:2-7.
99. Khan Z, Mieza M, Starer P, Singh VK. Post-prostatectomy incontinence. A urodynamic and fluoroscopic point of view. Urology 1991;38:483-8.
100. Horie S, Tobisu KI, Fujimoto H, Doi N, Kakizoe T. Urinary incontinence after non-nerve-sparing radical prostatectomy with neoadjuvant androgen deprivation. Urology 1999;53:561-7.
101. Catalona WJ, Carvalhal GF, Mager DE, Smith DS. Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies. J Urol 1999;162:433-8.
102. Eastham JA, Kattan MW, Rogers E, et al. Risk factors for urinary incontinence after radical prostatectomy. J Urol 1996;156:1707-13.
103. Zincke H, Oesterling JE, Blute ML, Bergstralh EJ, Myers RP, Barrett DM. Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. J Urol 1994;152:1850-7.
104. Leandri P, Rossignol G, Gautier JR, Ramon J. Radical retropubic prostatectomy: morbidity and quality of life. Experience with 620 consecutive cases. J Urol 1992;147:883-7.
105. Novara G, Ficarra V, D'Elia C, et al. Evaluating urinary continence and preoperative predictors of urinary continence after robot assisted laparoscopic radical prostatectomy. J Urol 2010;184:1028-33.
106. Yang BS, Ye DW, Peng JY, et al. [Analysis of risk factors for urinary continence after radical prostatectomy]. Zhonghua yi xue za zhi 2011;91:2239-42.
107. Steiner MS, Morton RA, Walsh PC. Impact of anatomical radical prostatectomy on urinary continence. J Urol 1991;145:512-4; discussion 4-5.
108. Young MD, Weizer AZ, Silverstein AD, et al. Urinary continence and quality of life in the first year after radical perineal prostatectomy. J Urol 2003;170:2374-8.
109. Lepor H, Kaci L, Xue X. Continence following radical retropubic prostatectomy using self-reporting instruments. J Urol 2004;171:1212-5.
110. Mohamad BA, Marszalek M, Brossner C, et al. Radical prostatectomy in Austria: a nationwide analysis of 16,524 cases. Eur Urol 2007;51:684-8; discussion 9.
111. Rogers CG, Su LM, Link RE, Sullivan W, Wagner A, Pavlovich CP. Age stratified functional outcomes after laparoscopic radical prostatectomy. J Urol 2006;176:2448-52.
112. Nilsson AE, Schumacher MC, Johansson E, et al. Age at surgery, educational level and long-term urinary incontinence after radical prostatectomy. BJU Int 2011;108:1572-7.
113. van Roermund JG, van Basten JP, Kiemeney LA, Karthaus HF, Witjes JA. Impact of obesity on surgical outcomes following open radical prostatectomy. Urol Int 2009;82:256-61.
114. Wolin KY, Luly J, Sutcliffe S, Andriole GL, Kibel AS. Risk of urinary incontinence following prostatectomy: the role of physical activity and obesity. J Urol 2010;183:629-33.
115. Jonler M, Madsen FA, Rhodes PR, Sall M, Messing EM, Bruskewitz RC. A prospective study of quantification of urinary incontinence and quality of life in patients undergoing radical retropubic prostatectomy. Urology 1996;48:433-40.
116. Lowe BA. Comparison of bladder neck preservation to bladder neck resection in maintaining postprostatectomy urinary continence. Urology 1996;48:889-93.
117. Pierorazio PM, Spencer BA, McCann TR, McKiernan JM, Benson MC. Preoperative risk stratification predicts likelihood of concurrent PSA-free survival, continence, and potency (the trifecta analysis) after radical retropubic prostatectomy. Urology 2007;70:717-22.
118. Loeb S, Smith ND, Roehl KA, Catalona WJ. Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer. Urology 2007;69:1170-5.
119. Gacci M, Carini M, Simonato A, et al. Factors predicting continence recovery 1 month after radical prostatectomy: results of a multicenter survey. Int J Urol 2011;18:700-8.
120. Poon M, Ruckle H, Bamshad BR, Tsai C, Webster R, Lui P. Radical retropubic prostatectomy: bladder neck preservation versus reconstruction. J Urol 2000;163:194-8.
121. Srougi M, Nesrallah LJ, Kauffmann JR, Nesrallah A, Leite KR. Urinary continence and pathological outcome after bladder neck preservation during radical retropubic prostatectomy: a randomized prospective trial. J Urol 2001;165:815-8.
122. Pick DL, Osann K, Skarecky D, Narula N, Finley DS, Ahlering TE. The impact of cavernosal nerve preservation on continence after robotic radical prostatectomy. BJU Int 2011;108:1492-6.
123. Nandipati KC, Raina R, Agarwal A, Zippe CD. Nerve-sparing surgery significantly affects long-term continence after radical prostatectomy. Urology 2007;70:1127-30.
124. Burkhard FC, Kessler TM, Fleischmann A, Thalmann GN, Schumacher M, Studer UE. Nerve sparing open radical retropubic prostatectomy--does it have an impact on urinary continence? J Urol 2006;176:189-95.
125. Wille S, Heidenreich A, Hofmann R, Engelmann U. Preoperative erectile function is one predictor for post prostatectomy incontinence. Neurourol Urodyn 2007;26:140-3; discussion 4.
126. Thorsteinsdottir T, Stranne J, Carlsson S, et al. LAPPRO: a prospective multicentre comparative study of robot-assisted laparoscopic and retropubic radical prostatectomy for prostate cancer. Scand J Urol Nephrol 2011;45:102-12.
127. Ficarra V, Novara G, Fracalanza S, et al. A prospective, non-randomized trial comparing robot-assisted

laparoscopic and retropubic radical prostatectomy in one European institution. BJU Int 2009;104:534-9.

128. Salomon L, Sebe P, De La Taille A, et al. Open versus laparoscopic radical prostatectomy: Part II. BJU Int 2004;94:244-50.

129. Gray M, Petroni GR, Theodorescu D. Urinary function after radical prostatectomy: a comparison of the retropubic and perineal approaches. Urology 1999;53:881-90; discussion 90-1.

130. Weldon VE, Tavel FR, Neuwirth H. Continence, potency and morbidity after radical perineal prostatectomy. J Urol 1997;158:1470-5.

131. Hollenbeck BK, Lipp ER, Hayward RA, Montie JE, Schottenfeld D, Wei JT. Concurrent assessment of obstructive/irritative urinary symptoms and incontinence after radical prostatectomy. Urology 2002;59:389-93.

132. Groutz A, Blaivas JG, Chaikin DC, Weiss JP, Verhaaren M. The pathophysiology of post-radical prostatectomy incontinence: a clinical and video urodynamic study. J Urol 2000;163:1767-70.

133. Ficazzola MA, Nitti VW. The etiology of post-radical prostatectomy incontinence and correlation of symptoms with urodynamic findings. J Urol 1998;160:1317-20.

134. Bruschini H, Simonetti R, Antunes AA, Srougi M. Urinary incontinence following surgery for BPH: the role of aging on the incidence of bladder dysfunction. International braz j urol : official journal of the Brazilian Society of Urology 2011;37:380-6; discussion 7.

135. Porena M, Mearini E, Mearini L, Vianello A, Giannantoni A. Voiding dysfunction after radical retropubic prostatectomy: more than external urethral sphincter deficiency. Eur Urol 2007;52:38-45.

136. Giannantoni A, Mearini E, Di Stasi SM, et al. Assessment of bladder and urethral sphincter function before and after radical retropubic prostatectomy. J Urol 2004;171:1563-6.

137. Giannantoni A, Mearini E, Zucchi A, et al. Bladder and urethral sphincter function after radical retropubic prostatectomy: a prospective long-term study. Eur Urol 2008;54:657-64.

138. Coakley FV, Eberhardt S, Kattan MW, Wei DC, Scardino PT, Hricak H. Urinary continence after radical retropubic prostatectomy: relationship with membranous urethral length on preoperative endorectal magnetic resonance imaging. J Urol 2002;168:1032-5.

139. Van Kampen M, De Weerdt W, Van Poppel H, et al. Prediction of urinary continence following radical prostatectomy. Urol Int 1998;60:80-4.

140. Hammerer P, Huland H. Urodynamic evaluation of changes in urinary control after radical retropubic prostatectomy. J Urol 1997;157:233-6.

141. Hakimi AA, Faleck DM, Agalliu I, Rozenblit AM, Chernyak V, Ghavamian R. Preoperative and intraoperative measurements of urethral length as predictors of continence after robot-assisted radical prostatectomy. J Endourol 2011;25:1025-30.

142. Pfister C, Cappele O, Dunet F, Bugel H, Grise P. Assessment of the intrinsic urethral sphincter component function in postprostatectomy urinary incontinence. Neurourol Urodyn 2002;21:194-7.

143. Bader P, Hugonnet CL, Burkhard FC, Studer UE. Inefficient urethral milking secondary to urethral dysfunction as an additional risk factor for incontinence after radical prostatectomy. J Urol 2001;166:2247-52.

144. John H, Sullivan MP, Bangerter U, Hauri D, Yalla SV. Effect of radical prostatectomy on sensory threshold and pressure transmission. J Urol 2000;163:1761-6.

145. Comiter CV, Sullivan MP, Yalla SV. Correlation among maximal urethral closure pressure, retrograde leak point pressure, and abdominal leak point pressure in men with postprostatectomy stress incontinence. Urology 2003;62:75-8.

146. Van Kampen M, De Weerdt W, Van Poppel H, De Ridder D, Feys H, Baert L. Effect of pelvic-floor reeducation on duration and degree of incontinence after radical prostatectomy: a randomised controlled trial. Lancet 2000;355:98-102.

147. Parekh AR, Feng MI, Kirages D, Bremner H, Kaswick J, Aboseif S. The role of pelvic floor exercises on postprostatectomy incontinence. J Urol 2003;170:130-3.

148. Franke JJ, Gilbert WB, Grier J, Koch MO, Shyr Y, Smith JA, Jr. Early post-prostatectomy pelvic floor biofeedback. J Urol 2000;163:191-3.

149. Wille S, Sobottka A, Heidenreich A, Hofmann R. Pelvic floor exercises, electrical stimulation and biofeedback after radical prostatectomy: results of a prospective randomized trial. J Urol 2003;170:490-3.

150. Ribeiro LH, Prota C, Gomes CM, et al. Long-term effect of early postoperative pelvic floor biofeedback on continence in men undergoing radical prostatectomy: a prospective, randomized, controlled trial. J Urol 2010;184:1034-9.

151. Moore KN, Griffiths D, Hughton A. Urinary incontinence after radical prostatectomy: a randomized controlled trial comparing pelvic muscle exercises with or without electrical stimulation. BJU Int 1999;83:57-65.

152. Burgio KL, Stutzman RE, Engel BT. Behavioral training for post-prostatectomy urinary incontinence. J Urol 1989;141:303-6.

153. Meaglia JP, Joseph AC, Chang M, Schmidt JD. Postprostatectomy urinary incontinence: response to behavioral training. J Urol 1990;144:674-6.

154. Hunter KF, Moore KN, Cody DJ, Glazener CM. Conservative management for postprostatectomy urinary incontinence. Cochrane Database Syst Rev 2004:CD001843.

155. Glazener C, Boachie C, Buckley B, et al. Urinary incontinence in men after formal one-to-one pelvic-floor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. Lancet 2011;378:328-37.

156. Collado Serra A, Rubio-Briones J, Puyol Payas M, Iborra Juan I, Ramon-Borja JC, Solsona Narbon E. Postprostatectomy established stress urinary incontinence treated with duloxetine. Urology 2011;78:261-6.

157. McGuire EJ, Appell RA. Transurethral collagen injection for urinary incontinence. Urology 1994;43:413-5.

158. Aboseif SR, O'Connell HE, Usui A, McGuire EJ. Collagen injection for intrinsic sphincteric deficiency in men. J Urol 1996;155:10-3.

159. Cummings JM, Boullier JA, Parra RO. Transurethral collagen injections in the therapy of postradical prostatectomy stress incontinence. J Urol 1996;155:1011-3.

160. Sanchez-Ortiz RF, Broderick GA, Chaikin DC, et al. Collagen injection therapy for post-radical retropubic prostatectomy incontinence: role of Valsalva leak point pressure. J Urol 1997;158:2132-6.

161. Smith DN, Appell RA, Rackley RR, Winters JC. Collagen injection therapy for post-prostatectomy incontinence. J Urol 1998;160:364-7.

162. Klutke JJ, Subir C, Andriole G, Klutke CG. Long-term results after antegrade collagen injection for stress urinary incontinence following radical retropubic prostatectomy. Urology 1999;53:974-7.

163. Tiguert R, Gheiler EL, Gudziak MR. Collagen injection in the management of post-radical prostatectomy intrinsic sphincteric deficiency. Neurourol Urodyn 1999;18:653-8.

164. Cespedes RD, Leng WW, McGuire EJ. Collagen injec-

tion therapy for postprostatectomy incontinence. Urology 1999;54:597-602.

165. Gomes CM, Broderick GA, Sanchez-Ortiz RF, Preate D, Jr., Rovner ES, Wein AJ. Artificial urinary sphincter for post-prostatectomy incontinence: impact of prior collagen injection on cost and clinical outcome. J Urol 2000;163:87-90.

166. Comiter CV. The male sling for stress urinary incontinence: a prospective study. J Urol 2002;167:597-601.

167. Onur R, Singla A. Comparison of bone-anchored male sling and collagen implant for the treatment of male incontinence. Int J Urol 2006;13:1207-11.

168. Bugel H, Pfister C, Sibert L, Cappele O, Khalaf A, Grise P. [Intraurethral Macroplastic injections in the treatment of urinary incontinence after prostatic surgery]. Prog Urol 1999;9:1068-76.

169. Kylmala T, Tainio H, Raitanen M, Tammela TL. Treatment of postoperative male urinary incontinence using transurethral macroplastique injections. J Endourol 2003;17:113-5.

170. Lightner DJ, Fox J, Klingele C. Cystoscopic injections of dextranomer hyaluronic acid into proximal urethra for urethral incompetence: efficacy and adverse outcomes. Urology 2010;75:1310-4.

171. Hurtado EA, McCrery RJ, Appell RA. Complications of ethylene vinyl alcohol copolymer as an intraurethral bulking agent in men with stress urinary incontinence. Urology 2008;71:662-5.

172. Secin FP, Martinez-Salamanca JI, Eilber KS. [Limited efficacy of permanent injectable agents in the treatment of stress urinary incontinence after radical prostatectomy]. Arch Esp Urol 2005;58:431-6.

173. Mitterberger M, Marksteiner R, Margreiter E, et al. Myoblast and fibroblast therapy for post-prostatectomy urinary incontinence: 1-year followup of 63 patients. J Urol 2008;179:226-31.

174. Strasser H, Marksteiner R, Margreiter E, et al. Transurethral ultrasonography-guided injection of adult autologous stem cells versus transurethral endoscopic injection of collagen in treatment of urinary incontinence. World J Urol 2007;25:385-92.

175. Kleinert S, Horton R. Retraction—autologous myoblasts and fibroblasts for treatment of stress urinary incontinence: a randomised controlled trial. Lancet 2008;372:789-90.

176. Strasser H, Marksteiner R, Margreiter E, et al. Autologous myoblasts and fibroblasts versus collagen for treatment of stress urinary incontinence in women: a randomised controlled trial. Lancet 2007;369:2179-86.

177. Nikolavsky D, Chancellor MB. Stem cell therapy for stress urinary incontinence. Neurourol Urodyn 2010;29 Suppl 1:S36-41.

178. Kaufman JJ. A new operation for male incontinence. Surg Gynecol Obstet 1970;131:295-9.

179. Kaufman JJ. Treatment of post-prostatectomy urinary incontinence using a silicone gel prosthesis. Br J Urol 1973;45:646-53.

180. Kaufman JJ. Surgical treatment of post-prostatectomy incontinence: use of the penile crura to compress the bulbous urethra. J Urol 1972;107:293-7.

181. Gudziak MR, McGuire EJ, Gormley EA. Urodynamic assessment of urethral sphincter function in post-prostatectomy incontinence. J Urol 1996;156:1131-4; discussion 4-5.

182. Kielb SJ, Clemens JQ. Comprehensive urodynamics evaluation of 146 men with incontinence after radical prostatectomy. Urology 2005;66:392-6.

183. Klingler HC, Marberger M. Incontinence after radical prostatectomy: surgical treatment options. Curr Opin Urol 2006;16:60-4.

184. Schaeffer AJ, Clemens JQ, Ferrari M, Stamey TA. The male bulbourethral sling procedure for post-radical prostatectomy incontinence. J Urol 1998;159:1510-5.

185. Clemens JQ, Bushman W, Schaeffer AJ. Questionnaire based results of the bulbourethral sling procedure. J Urol 1999;162:1972-6.

186. Clemens JQ, Bushman W, Schaeffer AJ. Urodynamic analysis of the bulbourethral sling procedure. J Urol 1999;162:1977-81; discussion 81-2.

187. Stern JA, Clemens JQ, Tiplitsky SI, Matschke HM, Jain PM, Schaeffer AJ. Long-term results of the bulbourethral sling procedure. J Urol 2005;173:1654-6.

188. Migliari R, Pistolesi D, De Angelis M. Polypropilene sling of the bulbar urethra for post-radical prostatectomy incontinence. Eur Urol 2003;43:152-7.

189. Xu YM, Zhang XR, Sa YL, Chen R, Fei XF. Bulbourethral composite suspension for treatment of male-acquired urinary incontinence. Eur Urol 2007;51:1709-14; discussion 15-6.

190. Madjar S, Jacoby K, Giberti C, et al. Bone anchored sling for the treatment of post-prostatectomy incontinence. J Urol 2001;165:72-6.

191. Comiter CV. The male perineal sling: intermediate-term results. Neurourol Urodyn 2005;24:648-53.

192. Ullrich NF, Comiter CV. The male sling for stress urinary incontinence: urodynamic and subjective assessment. J Urol 2004;172:204-6.

193. Onur R, Rajpurkar A, Singla A. New perineal bone-anchored male sling: lessons learned. Urology 2004;64:58-61.

194. Rajpurkar AD, Onur R, Singla A. Patient satisfaction and clinical efficacy of the new perineal bone-anchored male sling. Eur Urol 2005;47:237-42; discussion 42.

195. Giberti C, Gallo F, Schenone M, Cortese P. The bone-anchor sub-urethral sling for the treatment of iatrogenic male incontinence: subjective and objective assessment after 41 months of mean follow-up. World J Urol 2008;26:173-8.

196. Carmel M, Hage B, Hanna S, Schmutz G, Tu le M. Long-term efficacy of the bone-anchored male sling for moderate and severe stress urinary incontinence. BJU Int 2010;106:1012-6.

197. Palma PC, Dambros M, Thiel M, et al. Readjustable transobturator sling: a novel sling procedure for male urinary incontinence. Urol Int 2004;73:354-6.

198. Comiter CV, Rhee EY. The 'ventral urethral elevation plus' sling: a novel approach to treating stress urinary incontinence in men. BJU Int 2008;101:187-91.

199. Rapp DE, Reynolds WS, Lucioni A, Bales GT. Surgical technique using AdVance sling placement in the treatment of post-prostatectomy urinary incontinence. Int Braz J Urol 2007;33:231-5; discussion 6-7.

200. Cornu JN, Sebe P, Ciofu C, Peyrat L, Cussenot O, Haab F. Mid-term evaluation of the transobturator male sling for post-prostatectomy incontinence: focus on prognostic factors. BJU Int 2011;108:236-40.

201. Rehder P, Mitterberger MJ, Pichler R, Kerschbaumer A, Glodny B. The 1 year outcome of the transobturator retroluminal repositioning sling in the treatment of male stress urinary incontinence. BJU Int 2010;106:1668-72.

202. Bauer RM, Soljanik I, Fullhase C, et al. Mid-term results for the retroluminar transobturator sling suspension for stress urinary incontinence after prostatectomy. BJU Int 2011;108:94-8.

203. Gill BC, Swartz MA, Klein JB, et al. Patient perceived effectiveness of a new male sling as treatment for post-prostatectomy incontinence. J Urol 2010;183:247-52.

204. Cornel EB, Elzevier HW, Putter H. Can advance tran-

sobturator sling suspension cure male urinary postoperative stress incontinence? J Urol 2010;183:1459-63.

205. Grise P, Vautherin R, Njinou-Ngninkeu B, Bochereau G, Lienhart J, Saussine C. I-STOP TOMS transobturator male sling, a minimally invasive treatment for post-prostatectomy incontinence: continence improvement and tolerability. Urology 2012;79:458-63.

206. de Leval J, Waltregny D. The inside-out trans-obturator sling: a novel surgical technique for the treatment of male urinary incontinence. Eur Urol 2008;54:1051-65.

207. Leruth J, Waltregny D, de Leval J. The inside-out transobturator male sling for the surgical treatment of stress urinary incontinence after radical prostatectomy: midterm results of a single-center prospective study. Eur Urol 2012;61:608-15.

208. Soljanik I, Becker AJ, Stief CG, Gozzi C, Bauer RM. Repeat retrourethral transobturator sling in the management of recurrent postprostatectomy stress urinary incontinence after failed first male sling. Eur Urol 2010;58:767-72.

209. Moreno Sierra J, Victor Romano S, Galante Romo I, Barrera Ortega J, Salinas Casado J, Silmi Moyano A. [New male sling «Argus» for the treatment of stress urinary incontinence]. Arch Esp Urol 2006;59:607-13.

210. Sousa-Escandon A, Rodriguez Gomez JI, Uribarri Gonzalez C, Marques-Queimadelos A. Externally readjustable sling for treatment of male stress urinary incontinence: points of technique and preliminary results. J Endourol 2004;18:113-8.

211. Romano SV, Metrebian SE, Vaz F, et al. An adjusta able male sling for treating urinary incontinence after prostatectomy: a phase III multicentre trial. BJU Int 2006;97:533-9.

212. Romano SV, Metrebian SE, Vaz F, et al. [Long-term results of a phase III multicentre trial of the adjustable male sling for treating urinary incontinence after prostatectomy: minimum 3 years]. Actas Urol Esp 2009;33:309-14.

213. Hubner WA, Gallistl H, Rutkowski M, Huber ER. Adjustable bulbourethral male sling: experience after 101 cases of moderate-to-severe male stress urinary incontinence. BJU Int 2010.

214. Bochove-Overgaauw DM, Schrier BP. An adjustable sling for the treatment of all degrees of male stress urinary incontinence: retrospective evaluation of efficacy and complications after a minimal followup of 14 months. J Urol 2011;185:1363-8.

215. Dalpiaz O, Knopf HJ, Orth S, Griese K, Aboulsorour S, Truss M. Mid-term complications after placement of the male adjustable suburethral sling: a single center experience. J Urol 2011;186:604-9.

216. Tuygun C, Imamoglu A, Gucuk A, Goktug G, Demirel F. Comparison of outcomes for adjustable bulbourethral male sling and artificial urinary sphincter after previous artificial urinary sphincter erosion. Urology 2009;73:1363-7.

217. Navalon Verdejo P, Pallas Costa Y, Ordono Dominguez F, et al. Our experience in the treatment of male stress urinary incontinence with the male Remeex system. Arch Esp Urol 2010;63:432-9.

218. Jimenez Parra JD, Cebrian Lostal JL, Hualde Alfaro A, et al. [REMEEX(R) system for the treatment of male urinary stress incontinence: our experience]. Actas Urol Esp 2010;34:802-5.

219. Thuroff JW, Hohenfellner M, Schultz-Lampel D. Die Harninkontinenz des Mannes. Faszienzügelplastik zur Therapie der Streßinkontinenz. Akt Urol 1992;23:149.

220. Cespedes RD, Jacoby K. Male slings for postprostatectomy incontinence. Tech Urol 2001;7:176-83.

221. Castle EP, Andrews PE, Itano N, Novicki DE, Swanson SK, Ferrigni RG. The male sling for post-prostatectomy incontinence: mean followup of 18 months. J Urol 2005;173:1657-60.

222. Gallagher BL, Dwyer NT, Gaynor-Krupnick DM, Latini JM, Kreder KJ. Objective and quality-of-life outcomes with bone-anchored male bulbourethral sling. Urology 2007;69:1090-4.

223. Guimaraes M, Oliveira R, Pinto R, et al. Intermediate-term results, up to 4 years, of a bone-anchored male perineal sling for treating male stress urinary incontinence after prostate surgery. BJU Int 2009;103:500-4.

224. Athanasopoulos A, Konstantinopoulos A, McGuire E. Efficacy of the InVance male sling in treating stress urinary incontinence: a three-year experience from a single centre. Urol Int 2010;85:436-42.

225. Mahdy A, Elmissiry M, Ghoniem G. Recurrent stress urinary incontinence after dislodged screws in patient with bone-anchored suburethral sling. Urology 2008;72:1185 e11-3.

226. Bauer RM, Mayer ME, May F, et al. Complications of the AdVance transobturator male sling in the treatment of male stress urinary incontinence. Urology 2010;75:1494-8.

227. Harris SE, Guralnick ML, O'Connor RC. Urethral erosion of transobturator male sling. Urology 2009;73:443 e19-20.

228. Rehder P. Re: Can advance transobturator sling suspension cure male urinary postoperative stress incontinence?: E. B. Cornel, H. W. Elzevier and H. Putter J Urol 2010; 183: 1459-1463. J Urol 2010;184:1575-6; author reply 6-7.

229. Sousa-Escandon A, Cabrera J, Mantovani F, et al. Adjustable suburethral sling (male remeex system) in the treatment of male stress urinary incontinence: a multicentric European study. Eur Urol 2007;52:1473-9.

230. Comiter CV. Surgery Insight: surgical management of postprostatectomy incontinence--the artificial urinary sphincter and male sling. Nat Clin Pract Urol 2007;4:615-24.

231. Comiter CV. Male incontinence surgery in the 21st century: past, present, and future. Curr Opin Urol 2010;20:302-8.

232. Han JS, Brucker BM, Demirtas A, Fong E, Nitti VW. Treatment of post-prostatectomy incontinence with male slings in patients with impaired detrusor contractility on urodynamics and/or who perform Valsalva voiding. J Urol 2011;186:1370-5.

233. Berger AP, Strasak A, Seitz C, Rein P, Hobisch A. Single institution experience with the transobturator sling suspension system AdVance(R) in the treatment of male urinary incontinence: mid-term results. International braz j urol : official journal of the Brazilian Society of Urology 2011;37:488-94.

234. Bauer RM, Mayer ME, Gratzke C, et al. Prospective evaluation of the functional sling suspension for male postprostatectomy stress urinary incontinence: results after 1 year. Eur Urol 2009;56:928-33.

235. Gozzi C, Becker AJ, Bauer R, Bastian PJ. Early results of transobturator sling suspension for male urinary incontinence following radical prostatectomy. Eur Urol 2008;54:960-1.

236. Bauer RM, Soljanik I, Fullhase C, et al. Results of the AdVance transobturator male sling after radical prostatectomy and adjuvant radiotherapy. Urology 2011;77:474-9.

237. Giberti C, Gallo F, Schenone M, Cortese P, Ninotta G. The bone anchor suburethral synthetic sling for iatrogenic male incontinence: critical evaluation at a mean 3-year followup. J Urol 2009;181:2204-8.

238. Guidelines on Urinary Incontinence. European Association of Urology, 2012. (Accessed at http://www.uroweb.org/gls/pdf/18_Urinary_Incontinence_LR_Algorithms adjusted 20 July 2012.pdf.)

239. The management of lower urinary tract symptoms in men. National Clinical Guidelines Centre at the Royal College of Physicians, 2010. (Accessed June 20, 2012, at http://www.nice.org.uk/nicemedia/live/12984/48554/48554.pdf.)

240. Hubner W. Adjustable Continence Therapy (ACT) for male post prostatectomy stress incontinence. In: Brazilian Congress of Urology; 2000; Rio de Janeiro, Brazil; 2000.

241. Gregori A, Simonato A, Lissiani A, Scieri F, Rossi R, Gaboardi F. Transrectal ultrasound guided implantation of the ProACT adjustable continence therapy system in patients with post-radical prostatectomy stress urinary incontinence: a pilot study. J Urol 2006;176:2109-13; discussion 13.

242. Hubner WA, Schlarp OM. Treatment of incontinence after prostatectomy using a new minimally invasive device: adjustable continence therapy. BJU Int 2005;96:587-94.

243. Trigo-Rocha F, Gomes CM, Pompeo AC, Lucon AM, Arap S. Prospective study evaluating efficacy and safety of Adjustable Continence Therapy (ProACT) for post radical prostatectomy urinary incontinence. Urology 2006;67:965-9.

244. Cansino Alcaide JR, Alvarez Maestro M, Martin Hernandez M, et al. [Paraurethral ballon implantation in the treatment of male urinary incontinence. La Paz University Hospital experience]. Arch Esp Urol 2007;60:647-55.

245. Kocjancic E, Crivellaro S, Ranzoni S, Bonvini D, Gontero P, Frea B. Adjustable Continence Therapy for the treatment of male stress urinary incontinence: a single-centre study. Scand J Urol Nephrol 2007;41:324-8.

246. Gregori A, Romano AL, Scieri F, et al. Transrectal ultrasound-guided implantation of Adjustable Continence Therapy (ProACT): surgical technique and clinical results after a mean follow-up of 2 years. Eur Urol 2010;57:430-6.

247. Roupret M, Misrai V, Gosseine PN, Bart S, Cour F, Chartier-Kastler E. Management of stress urinary incontinence following prostate surgery with minimally invasive adjustable continence balloon implants: functional results from a single center prospective study. J Urol 2011;186:198-203.

248. Crivellaro S, Singla A, Aggarwal N, Frea B, Kocjancic E. Adjustable continence therapy (ProACT) and bone anchored male sling: Comparison of two new treatments of post prostatectomy incontinence. Int J Urol 2008;15:910-4.

249. Leach GE, Trockman B, Wong A, Hamilton J, Haab F, Zimmern PE. Post-prostatectomy incontinence: urodynamic findings and treatment outcomes. J Urol 1996;155:1256-9.

250. Davidson PJ, van den Ouden D, Schroeder FH. Radical prostatectomy: prospective assessment of mortality and morbidity. Eur Urol 1996;29:168-73.

251. Perez LM, Webster GD. Successful outcome of artificial urinary sphincters in men with post-prostatectomy urinary incontinence despite adverse implantation features. J Urol 1992;148:1166-70.

252. Gomha MA, Boone TB. Artificial urinary sphincter for post-prostatectomy incontinence in men who had prior radiotherapy: a risk and outcome analysis. J Urol 2002;167:591-6.

253. Montague DK. The artificial urinary sphincter (AS 800): experience in 166 consecutive patients. J Urol 1992;147:380-2.

254. Martins FE, Boyd SD. Artificial urinary sphincter in patients following major pelvic surgery and/or radiotherapy: are they less favorable candidates? J Urol 1995;153:1188-93.

255. Fleshner N, Herschorn S. The artificial urinary sphincter for post-radical prostatectomy incontinence: impact on urinary symptoms and quality of life. J Urol 1996;155:1260-4.

256. Mottet N, Boyer C, Chartier-Kastler E, Ben Naoum K, Richard F, Costa P. Artificial urinary sphincter AMS 800 for urinary incontinence after radical prostatectomy: the French experience. Urol Int 1998;60 Suppl 2:25-9; discussion 35.

257. Madjar S, Gousse AE, Lambert MM, Fishman IJ. Artificial urinary sphincter implantation for radical prostatectomy urinary incontinence: which factors influence patient satisfaction? BJU Int 2000;86 (suppl. 3):121.

258. Klijn AJ, Hop WC, Mickisch G, Schroder FH, Bosch JL. The artificial urinary sphincter in men incontinent after radical prostatectomy: 5 year actuarial adequate function rates. Br J Urol 1998;82:530-3.

259. Haab F, Trockman BA, Zimmern PE, Leach GE. Quality of life and continence assessment of the artificial urinary sphincter in men with minimum 3.5 years of followup. J Urol 1997;158:435-9.

260. Goldwasser B, Furlow WL, Barrett DM. The model AS 800 artificial urinary sphincter: Mayo Clinic experience. J Urol 1987;137:668-71.

261. Kim SP, Sarmast Z, Daignault S, Faerber GJ, McGuire EJ, Latini JM. Long-term durability and functional outcomes among patients with artificial urinary sphincters: a 10-year retrospective review from the University of Michigan. J Urol 2008;179:1912-6.

262. Lai HH, Hsu EI, Teh BS, Butler EB, Boone TB. 13 years of experience with artificial urinary sphincter implantation at Baylor College of Medicine. J Urol 2007;177:1021-5.

263. Litwiller SE, Kim KB, Fone PD, White RW, Stone AR. Post-prostatectomy incontinence and the artificial urinary sphincter: a long-term study of patient satisfaction and criteria for success. J Urol 1996;156:1975-80.

264. Kuznetsov DD, Kim HL, Patel RV, Steinberg GD, Bales GT. Comparison of artificial urinary sphincter and collagen for the treatment of postprostatectomy incontinence. Urology 2000;56:600-3.

265. Elliott DS, Barrett DM. Mayo Clinic long-term analysis of the functional durability of the AMS 800 artificial urinary sphincter: a review of 323 cases. J Urol 1998;159:1206-8.

266. Clemens JQ, Schuster TG, Konnak JW, McGuire EJ, Faerber GJ. Revision rate after artificial urinary sphincter implantation for incontinence after radical prostatectomy: actuarial analysis. J Urol 2001;166:1372-5.

267. Gousse AE, Madjar S, Lambert MM, Fishman IJ. Artificial urinary sphincter for post-radical prostatectomy urinary incontinence: long-term subjective results. J Urol 2001;166:1755-8.

268. Lai HH, Boone TB. Implantation of artificial urinary sphincter in patients with post-prostatectomy incontinence, and preoperative overactive bladder and mixed symptoms. J Urol 2011;185:2254-9.

269. Fulford SC, Sutton C, Bales G, Hickling M, Stephenson TP. The fate of the 'modern' artificial urinary sphincter with a follow-up of more than 10 years. Br J Urol 1997;79:713-6.

270. Brito CG, Mulcahy JJ, Mitchell ME, Adams MC. Use of a double cuff AMS800 urinary sphincter for severe stress incontinence. J Urol 1993;149:283-5.

271. DiMarco DS, Elliott DS. Tandem cuff artificial urinary sphincter as a salvage procedure following failed primary sphincter placement for the treatment of post-prostatectomy incontinence. J Urol 2003;170:1252-4.

272. Guralnick ML, Miller E, Toh KL, Webster GD. Transcorporal artificial urinary sphincter cuff placement in cases requiring revision for erosion and urethral atrophy. J Urol 2002;167:2075-8; discussion 9.

273. Kowalczyk JJ, Spicer DL, Mulcahy JJ. Erosion rate

of the double cuff AMS800 artificial urinary sphincter: long-term followup. J Urol 1996;156:1300-1.

274. O'Connor RC, Gerber GS, Avila D, Chen AA, Bales GT. Comparison of outcomes after single or DOUBLE-CUFF artificial urinary sphincter insertion. Urology 2003;62:723-6.

275. O'Connor RC, Lyon MB, Guralnick ML, Bales GT. Long-term follow-up of single versus double cuff artificial urinary sphincter insertion for the treatment of severe postprostatectomy stress urinary incontinence. Urology 2008;71:90-3.

276. Manunta A, Guille F, Patard JJ, Lobel B. Artificial sphincter insertion after radiotherapy: is it worthwhile? BJU Int 2000;85:490-2.

277. Galli S, Simonato A, Bozzola A, et al. Oncologic outcome and continence recovery after laparoscopic radical prostatectomy: 3 years' follow-up in a «second generation center». Eur Urol 2006;49:859-65.

278. Colombo R, Naspro R, Salonia A, et al. Radical prosɵ tatectomy after previous prostate surgery: clinical and functional outcomes. J Urol 2006;176:2459-63; discussion 63.

279. Schneider T, Sperling H, Rossi R, Schmidt S, Rubben H. Do early injections of bulking agents following radical prostatectomy improve early continence? World J Urol 2005;23:338-42.

280. Jones JS, Vasavada SP, Abdelmalak JB, et al. Sling may hasten return of continence after radical prostatectomy. Urology 2005;65:1163-7.

281. McConnell JD, Barry MJ, Bruskewitz RC, et al. Benign prostatic hyperplasia: diagnosis and treatment. Clinical practice guidelines, No. 8. Rockville, MD: Agency for Health Care Policy and Research, Public health service, US department of Health and Human Services; 1994. Report No.: AHPCR Publication No.94-0582.

282. Herschorn S, Boccon-Gibod L, Bosch JL, et al. Surgical treatment of urinary incontinence in men. In: Abrams P, Khoury S, Wein A, eds. First International Consultation on Urinary Incontinence. Plymouth, U.K.: Health Publications Ltd.; 1999:691-729.

283. Herschorn S, Bosch JL, Bruschini H, Hanus T, Low A, Schick E. Surgical treatment of urinary incontinence in men. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. Second International Consultation on Incontinence. Plymouth, U.K.: Health Publications Ltd.; 2002:785-821.

284. Wendt-Nordahl G, Bucher B, Hacker A, Knoll T, Alken P, Michel MS. Improvement in mortality and morbidity in transurethral resection of the prostate over 17 years in a single center. J Endourol 2007;21:1081-7.

285. Guideline on the Management of Benign Prostatic Hyerplasia (BPH). American Urological Association, 2003. (Accessed at http://www.auanet.org/guidelines/bph.cfm.)

286. Wasson JH, Reda DJ, Bruskewitz RC, Elinson J, Keller AM, Henderson WG. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. N Engl J Med 1995;332:75-9.

287. Kaplan SA, Te AE. Transurethral electrovaporization of the prostate: a novel method for treating men with benign prostatic hyperplasia. Urology 1995;45:566-72.

288. Orandi A. Transurethral incision of prostate (TUIP): 646 cases in 15 years--a chronological appraisal. Br J Urol 1985;57:703-7.

289. Saporta L, Aridogan IA, Erlich N, Yachia D. Objective and subjective comparison of transurethral resection, transurethral incision and balloon dilatation of the prostate. A prospective study. Eur Urol 1996;29:439-45.

290. Sparwasser C, Riehmann M, Knes J, Madsen PO. [Long-term results of transurethral prostate incision (TUIP) and transurethral prostate resection (TURP). A prospective randomized study]. Urologe A 1995;34:153-7.

291. Results of the Treatment Outcomes Analyses. American Urological Association Educationand Research Inc., 2003. (Accessed October 10, 2010, at http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines/archived-guidelines/chapt_3_appendix.pdf.)

292. Results of the Treatment Outcome Analyses. American Urological Association Educationand Research Inc., 2010. (Accessed September 1, 2012, at http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines/main-reports/bph-management/chap_3_ResultsTreatmentOutcomesAnalyses.pdf.)

293. Gilling PJ, Mackey M, Cresswell M, Kennett K, Kabalin JN, Fraundorfer MR. Holmium laser versus transurethral resection of the prostate: a randomized prospective trial with 1-year followup. J Urol 1999;162:1640-4.

294. Das A, Kennett K, Fraundorfer M, Gilling P. Holmium laser resection of the prostate (HoLRP): 2-year follow-up data. Tech Urol 2001;7:252-5.

295. Tan A, Liao C, Mo Z, Cao Y. Meta-analysis of holmium laser enucleation versus transurethral resection of the prostate for symptomatic prostatic obstruction. Br J Surg 2007;94:1201-8.

296. Gupta N, Sivaramakrishna, Kumar R, Dogra PN, Seth A. Comparison of standard transurethral resection, transurethral vapour resection and holmium laser enucleation of the prostate for managing benign prostatic hyperplasia of >40 g. BJU Int 2006;97:85-9.

297. Kuntz RM, Ahyai S, Lehrich K, Fayad A. Transurethral holmium laser enucleation of the prostate versus transurethral electrocautery resection of the prostate: a randomized prospective trial in 200 patients. J Urol 2004;172:1012-6.

298. Montorsi F, Naspro R, Salonia A, et al. Holmium laser enucleation versus transurethral resection of the prostate: results from a 2-center, prospective, randomized trial in patients with obstructive benign prostatic hyperplasia. J Urol 2004;172:1926-9.

299. Tan AH, Gilling PJ, Kennett KM, Frampton C, Westenberg AM, Fraundorfer MR. A randomized trial comparing holmium laser enucleation of the prostate with transurethral resection of the prostate for the treatment of bladder outlet obstruction secondary to benign prostatic hyperplasia in large glands (40 to 200 grams). J Urol 2003;170:1270-4.

300. Vavassori I, Valenti S, Naspro R, et al. Three-year outcome following holmium laser enucleation of the prostate combined with mechanical morcellation in 330 consecutive patients. Eur Urol 2008;53:599-604.

301. Geavlete B, Georgescu D, Multescu R, Stanescu F, Jecu M, Geavlete P. Bipolar plasma vaporization vs monopolar and bipolar TURP-A prospective, randomized, long-term comparison. Urology 2011;78:930-5.

302. Tasci AI, Ilbey YO, Luleci H, et al. 120-W GreenLight laser photoselective vaporization of prostate for benign prostatic hyperplasia: midterm outcomes. Urology 2011;78:134-40.

303. Scott FB. The artificial urinary sphincter: experience in adults. Urol Clin North Am 1989;16:105.

304. Wilson SK, Delk JR, 2nd, Henry GD, Siegel AL. New surgical technique for sphincter urinary control system using upper transverse scrotal incision. J Urol 2003;169:261-4.

305. Faerber GJ, Richardson TD. Long-term results of transurethral collagen injection in men with intrinsic sphincter deficiency. J Endourol 1997;11:273-7.

306. Westney OL, Bevan-Thomas R, Palmer JL, Cespedes RD, McGuire EJ. Transurethral collagen injections for male intrinsic sphincter deficiency: the University of Texas-Houston experience. J Urol 2005;174:994-7.

307. Frangenheim P. Zur operativen Behandlung der Inkontinenz der männlichen Harnröhre. Verh Dtsch Ges Chir 1914;43:149.

308. Godbole P, Mackinnon AE. Expanded PTFE bladder neck slings for incontinence in children: the long-term outcome. BJU Int 2004;93:139-41.

309. Ullrich NF, Comiter CV. The male sling for stress urinary incontinence: 24-month followup with questionnaire based assessment. J Urol 2004;172:207-9.

310. Lawton CA, Won M, Pilepich MV, et al. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. Int J Radiat Oncol Biol Phys 1991;21:935-9.

311. Perez CA, Lee HK, Georgiou A, Lockett MA. Technical factors affecting morbidity in definitive irradiation for localized carcinoma of the prostate. Int J Radiat Oncol Biol Phys 1994;28:811-9.

312. Shipley WU, Zietman AL, Hanks GE, et al. Treatment related sequelae following external beam radiation for prostate cancer: a review with an update in patients with stages T1 and T2 tumor. J Urol 1994;152:1799-805.

313. Weil MD, Crawford ED, Cornish P, et al. Minimal toxicity with 3-FAT radiotherapy of prostate cancer. Semin Urol Oncol 2000;18:127-32.

314. Hanlon AL, Watkins Bruner D, Peter R, Hanks GE. Quality of life study in prostate cancer patients treated with three-dimensional conformal radiation therapy: comparing late bowel and bladder quality of life symptoms to that of the normal population. Int J Radiat Oncol Biol Phys 2001;49:51-9.

315. Sandhu AS, Zelefsky MJ, Lee HJ, Lombardi D, Fuks Z, Leibel SA. Long-term urinary toxicity after 3-dimensional conformal radiotherapy for prostate cancer in patients with prior history of transurethral resection. Int J Radiat Oncol Biol Phys 2000;48:643-7.

316. Scalliet PG, Remouchamps V, Curran D, et al. Retrospective analysis of results of p(65)+Be neutron therapy for treatment of prostate adenocarcinoma at the cyclotron of Louvain-la-Leuve. Part II: Side effects and their influence on quality of life measured with QLQ-C30 of EORTC. Int J Radiat Oncol Biol Phys 2004;58:1549-61.

317. Fransson P, Bergstrom P, Lofroth PO, Widmark A. Prospective evaluation of urinary and intestinal side effects after BeamCath stereotactic dose-escalated radiotherapy of prostate cancer. Radiother Oncol 2002;63:239-48.

318. Ponholzer A, Brossner C, Struhal G, Marszalek M, Madersbacher S. Lower urinary tract symptoms, urinary incontinence, sexual function and quality of life after radical prostatectomy and external beam radiation therapy: real life experience in Austria. World J Urol 2006;24:325-30.

319. Miller DC, Sanda MG, Dunn RL, et al. Long-term outcomes among localized prostate cancer survivors: health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy. J Clin Oncol 2005;23:2772-80.

320. Budaus L, Bolla M, Bossi A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. Eur Urol 2012;61:112-27.

321. Jonler M, Ritter MA, Brinkmann R, Messing EM, Rhodes PR, Bruskewitz RC. Sequelae of definitive radiation therapy for prostate cancer localized to the pelvis. Urology 1994;44:876-82.

322. Green N, Treible D, Wallack H. Prostate cancer: postirradiation incontinence. J Urol 1990;144:307-9.

323. Lee WR, Schultheiss TE, Hanlon AL, Hanks GE. Urinary incontinence following external-beam radiotherapy for clinically localized prostate cancer. Urology 1996;48:95-9.

324. Petrovich Z, Lieskovsky G, Langholz B, et al. Comparison of outcomes of radical prostatectomy with and without adjuvant pelvic irradiation in patients with pathologic stage C (T3N0) adenocarcinoma of the prostate. Am J Clin Oncol 1999;22:323-31.

325. Petrovich Z, Lieskovsky G, Langholz B, Jozsef G, Streeter OE, Jr., Skinner DG. Postoperative radiotherapy in 423 patients with pT3N0 prostate cancer. Int J Radiat Oncol Biol Phys 2002;53:600-9.

326. Fontaine E, Ben Mouelli S, Thomas L, Otmezguine Y, Beurton D. Urinary continence after salvage radiation therapy following radical prostatectomy, assessed by a self-administered questionnaire: a prospective study. BJU Int 2004;94:521-3.

327. Petroski RA, Warlick WB, Herring J, et al. External beam radiation therapy after radical prostatectomy: efficacy and impact on urinary continence. Prostate Cancer Prostatic Dis 2004;7:170-7.

328. Ornstein DK, Oh J, Herschman JD, Andriole GL. Evaluation and management of the man who has failed primary curative therapy for prostate cancer. Urol Clin North Am 1998;25:591-601.

329. Rogers E, Ohori M, Kassabian VS, Wheeler TM, Scardino PT. Salvage radical prostatectomy: outcome measured by serum prostate specific antigen levels. J Urol 1995;153:104-10.

330. Nguyen PL, D'Amico AV, Lee AK, Suh WW. Patient selection, cancer control, and complications after salvage local therapy for postradiation prostate-specific antigen failure: a systematic review of the literature. Cancer 2007;110:1417-28.

331. Cozzarini C, Fiorino C, Da Pozzo LF, et al. Clinical factors predicting late severe urinary toxicity after postoperative radiotherapy for prostate carcinoma: a single-institute analysis of 742 patients. Int J Radiat Oncol Biol Phys 2012;82:191-9.

332. Wang Y, Hadley HR. Experiences with the artificial urinary sphincter in the irradiated patient. J Urol 1992;147:612-3.

333. Gundian JC, Barrett DM, Parulkar BG. Mayo Clinic experience with the AS800 artificial urinary sphincter for urinary incontinence after transurethral resection of prostate or open prostatectomy. Urology 1993;41:318-21.

334. Raj GV, Peterson AC, Webster GD. Outcomes following erosions of the artificial urinary sphincter. J Urol 2006;175:2186-90; discussion 90.

335. Wang R, McGuire EJ, He C, Faerber GJ, Latini JM. Long-term outcomes after primary failures of artificial urinary sphincter implantation. Urology 2012;79:922-8.

336. Venn SN, Greenwell TJ, Mundy AR. The long-term outcome of artificial urinary sphincters. J Urol 2000;164:702-6; discussion 6-7.

337. Bevan-Thomas R, Wesley OL, Cespedes RD, al. e. Long-term follow-up of periurethral collagen injections for male intrinsic deficiency. J Urol 1999;161:257 (Abstr.).

338. Griebling TL, Kreder KJ, Jr., Williams RD. Transurethral collagen injection for treatment of postprostatectomy urinary incontinence in men. Urology 1997;49:907-12.

339. Elsergany R, Ghoniem GM. Collagen injection for intrinsic sphincteric deficiency in men: a reasonable option in selected patients. J Urol 1998;159:1504-6.

340. Martins FE, Bennett CJ, Dunn M, Filho D, Keller T, Lieskovsky G. Adverse prognostic features of collagen injection therapy for urinary incontinence following radical retropubic prostatectomy. J Urol 1997;158:1745-9.

341. Beyer C, Priestly JB. Biochemical disease-free survival following 1-125 prostate implantation. Int J Radiat Oncol Biol Phys 1995;32:254 (abstr.).

342. Blasko JC, Ragde H, Grimm PD. Transperineal ultrasound-guided implantation of the prostate: morbidity and complications. Scand J Urol Nephrol Suppl 1991;137:113-8.

343. Stock RG, Stone NN, Dewyngaert JK. PSA findings and biopsy results following interactive ultrasound guided transperineal brachtherapy for early stage prostate cancer. In: Proceedings of the American Radium Society 78th Annual Meeting; 1995; Paris, France; 1995. p. 58.

344. Wallner K, Roy J, Zelefsky M, Fuks Z, Harrison L. Fluoroscopic visualization of the prostatic urethra to guide transperineal prostate implantation. Int J Radiat Oncol Biol Phys 1994;29:863-7.

345. Kaye KW, Olson DJ, Payne JT. Detailed preliminary analysis of 125iodine implantation for localized prostate cancer using percutaneous approach. J Urol 1995;153:1020-5.

346. Blasko JC, Ragde H, Luse RW, Sylvester JE, Cavanagh W, Grimm PD. Should brachytherapy be considered a therapeutic option in localized prostate cancer? Urol Clin North Am 1996;23:633-50.

347. Hu K, Wallner K. Urinary incontinence in patients who have a TURP/TUIP following prostate brachytherapy. Int J Radiat Oncol Biol Phys 1998;40:783-6.

348. Benoit RM, Naslund MJ, Cohen JK. Complications after prostate brachytherapy in the Medicare population. Urology 2000;55:91-6.

349. Merrick GS, Butler WM, Lief JH, Dorsey AT. Temporal resolution of urinary morbidity following prostate brachytherapy. Int J Radiat Oncol Biol Phys 2000;47:121-8.

350. Crook J, Lukka H, Klotz L, Bestic N, Johnston M. Systematic overview of the evidence for brachytherapy in clinically localized prostate cancer. Cmaj 2001;164:975-81.

351. Talcott JA, Clark JA, Stark PC, Mitchell SP. Long-term treatment related complications of brachytherapy for early prostate cancer: a survey of patients previously treated. J Urol 2001;166:494-9.

352. Bottomley D, Ash D, Al-Qaisieh B, et al. Side effects of permanent I125 prostate seed implants in 667 patients treated in Leeds. Radiother Oncol 2007;82:46-9.

353. Barkati M, Williams SG, Foroudi F, et al. High-dose-rate brachytherapy as a monotherapy for favorable-risk prostate cancer: a Phase II trial. Int J Radiat Oncol Biol Phys 2012;82:1889-96.

354. Petit JH, Gluck C, Kiger WS, 3rd, et al. Androgen deprivation-mediated cytoreduction before interstitial brachytherapy for prostate cancer does not abrogate the elevated risk of urinary morbidity associated with larger initial prostate volume. Brachytherapy 2007;6:267-71.

355. Grills IS, Martinez AA, Hollander M, et al. High dose rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. J Urol 2004;171:1098-104.

356. Shinohara K, Connolly JA, Presti JC, Jr., Carroll PR. Cryosurgical treatment of localized prostate cancer (stages T1 to T4): preliminary results. J Urol 1996;156:115-20; discussion 20-1.

357. Bahn DK, Lee F, Solomon MH, Gontina H, Klionsky DL, Lee FT, Jr. Prostate cancer: US-guided percutaneous cryoablation. Work in progress. Radiology 1995;194:551-6.

358. Cox RL, Crawford ED. Complications of cryosurgical ablation of the prostate to treat localized adenocarcinoma of the prostate. Urology 1995;45:932-5.

359. Wieder J, Schmidt JD, Casola G, vanSonnenberg E, Stainken BF, Parsons CL. Transrectal ultrasound-guided transperineal cryoablation in the treatment of prostate carcinoma: preliminary results. J Urol 1995;154:435-41.

360. Cohen JK, Miller RJ, Rooker GM, Shuman BA. Cryosurgical ablation of the prostate: two-year prostate-specific antigen and biopsy results. Urology 1996;47:395-401.

361. Coogan CL, McKiel CF. Percutaneous cryoablation of the prostate: preliminary results after 95 procedures. J Urol 1995;154:1813-7.

362. Sosa ER, Martin T, Lynn K. Cryosurgical treatment of prostate cancer: a multicenter review of compilations. J Urol 1996;155:361 (Abstr.).

363. Long JP, Fallick ML, LaRock DR, Rand W. Preliminary outcomes following cryosurgical ablation of the prostate in patients with clinically localized prostate carcinoma. J Urol 1998;159:477-84.

364. Pisters LL, von Eschenbach AC, Scott SM, et al. The efficacy and complications of salvage cryotherapy of the prostate. J Urol 1997;157:921-5.

365. Derakhshani P, Neubauer S, Braun M, Zumbe J, Heidenreich A, Engelmann U. Cryoablation of localized prostate cancer. Experience in 48 cases, PSA and biopsy results. Eur Urol 1998;34:181-7.

366. Long JP, Bahn D, Lee F, Shinohara K, Chinn DO, Macaluso JN, Jr. Five-year retrospective, multi-institutional pooled analysis of cancer-related outcomes after cryosurgical ablation of the prostate. Urology 2001;57:518-23.

367. de la Taille A, Hayek O, Benson MC, et al. Salvage cryotherapy for recurrent prostate cancer after radiation therapy: the Columbia experience. Urology 2000;55:79-84.

368. Robinson JW, Donnelly BJ, Coupland K, et al. Quality of life 2 years after salvage cryosurgery for the treatment of local recurrence of prostate cancer after radiotherapy. Urologic oncology 2006;24:472-86.

369. Dhar N, Ward JF, Cher ML, Jones JS. Primary full-gland prostate cryoablation in older men (> age of 75 years): results from 860 patients tracked with the COLD Registry. BJU Int 2011;108:508-12.

370. Izawa JI, Ajam K, McGuire E, et al. Major surgery to manage definitively severe complications of salvage cryotherapy for prostate cancer. J Urol 2000;164:1978-81.

371. Chapelon JY, Margonari J, Vernier F, Gorry F, Ecochard R, Gelet A. In vivo effects of high-intensity ultrasound on prostatic adenocarcinoma Dunning R3327. Cancer research 1992;52:6353-7.

372. Rebillard X, Soulie M, Chartier-Kastler E, et al. High-intensity focused ultrasound in prostate cancer; a systematic literature review of the French Association of Urology. BJU Int 2008;101:1205-13.

373. Cordeiro ER, Cathelineau X, Thuroff S, Marberger M, Crouzet S, de la Rosette JJ. High-intensity focused ultrasound (HIFU) for definitive treatment of prostate cancer. BJU Int 2012.

374. Alcini E, Racioppi M, D'Addessi A, Menchinelli P, Grassetti F, Alcini A. Bladder replacement by detubularized ileal loop: 10 years of experience using a personal technique. Br J Urol 1996;77:688-93.

375. Cancrini A, De Carli P, Pompeo V, et al. Lower urinary tract reconstruction following cystectomy: experience and results in 96 patients using the orthotopic ileal bladder substitution of Studer et al. Eur Urol 1996;29:204-9.

376. Elmajian DA, Stein JP, Skinner DG. Orthotopic urinary diversion: the Kock ileal neobladder. World J Urol 1996;14:40-6.

377. Studer UE, Danuser H, Hochreiter W, Springer JP, Turner WH, Zingg EJ. Summary of 10 years' experience with an ileal low-pressure bladder substitute com-

bined with an afferent tubular isoperistaltic segment. World J Urol 1996;14:29-39.

378. Benson MC, Seaman EK, Olsson CA. The ileal ureter neobladder is associated with a high success and a low complication rate. J Urol 1996;155:1585-8.

379. Abol-Enein H, Ghoneim MA. Further clinical experience with the ileal W-neobladder and a serous-lined extramural tunnel for orthotopic substitution. Br J Urol 1995;76:558-64.

380. Rogers E, Scardino PT. A simple ileal substitute bladder after radical cystectomy: experience with a modification of the Studer pouch. J Urol 1995;153:1432-8.

381. Hautmann RE, Miller K, Steiner U, Wenderoth U. The ileal neobladder: 6 years of experience with more than 200 patients. J Urol 1993;150:40-5.

382. Hautmann RE, de Petriconi R, Gottfried HW, Kleinschmidt K, Mattes R, Paiss T. The ileal neobladder: complications and functional results in 363 patients after 11 years of followup. J Urol 1999;161:422-7; discussion 7-8.

383. Steven K, Poulsen AL. The orthotopic Kock ileal neobladder: functional results, urodynamic features, complications and survival in 166 men. J Urol 2000;164:288-95.

384. Abol-Enein H, Ghoneim MA. Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: experience with 450 patients. J Urol 2001;165:1427-32.

385. Carrion R, Arap S, Corcione G, et al. A multi-institutional study of orthotopic neobladders: functional results in men and women. BJU Int 2004;93:803-6.

386. Nieuwenhuijzen JA, de Vries RR, Bex A, et al. Urinary diversions after cystectomy: the association of clinical factors, complications and functional results of four different diversions. Eur Urol 2008;53:834-42; discussion 42-4.

387. O'Connor RC, Kuznetsov DD, Patel RV, Galocy RM, Steinberg GD, Bales GT. Artificial urinary sphincter placement in men after cystectomy with orthotopic ileal neobladder: continence, complications, and quality of life. Urology 2002;59:542-5.

388. Simma-Chiang V, Ginsberg DA, Teruya KK, Boyd SD. Outcomes of artificial urinary sphincter placement in men after radical cystectomy and orthotopic urinary diversions for the treatment of stress urinary incontinence: the University of Southern California experience. Urology 2012;79:1397-401.

389. Cerqueira M, Xambre L, Silva V, et al. [Bulbourethral sling. The experience of our service]. Actas Urol Esp 2005;29:401-7.

390. Tchetgen MB, Sanda MG, Montie JE, Faerber GJ, English S. Collagen injection for the treatment of incontinence after cystectomy and orthotopic neobladder reconstruction in women. J Urol 2001;163:212 (Abstr.).

391. Herschorn S, Thijssen A, Radomski SB. The value of immediate or early catheterization of the traumatized posterior urethra. J Urol 1992;148:1428-31.

392. Kotkin L, Koch MO. Impotence and incontinence after immediate realignment of posterior urethral trauma: result of injury or management? J Urol 1996;155:1600-3.

393. Raj GV, Peterson AC, Toh KL, Webster GD. Outcomes following revisions and secondary implantation of the artificial urinary sphincter. J Urol 2005;173:1242-5.

394. Mundy AR, Andrich DE. Pelvic fracture-related injuries of the bladder neck and prostate: their nature, cause and management. BJU Int 2010;105:1302-8.

395. Iselin CE, Webster GD. The significance of the open bladder neck associated with pelvic fracture urethral distraction defects. J Urol 1999;162:347-51.

396. Jayanthi VR, Churchill BM, McLorie GA, Khoury AE. Concomitant bladder neck closure and Mitrofanoff diversion for the management of intractable urinary incontinence. J Urol 1995;154:886-8.

397. Meulen T, Zambon JV, Janknegt RA. Treatment of anastomotic strictures and urinary incontinence after radical prostatectomy with urolume wallstent and AMS 800 artificial sphincter. J Endourol 1999;13:517-20.

398. Elliott DS, Boone TB. Combined stent and artificial urinary sphincter for management of severe recurrent bladder neck contracture and stress incontinence after prostatectomy: a long-term evaluation. J Urol 2001;165:413-5.

399. Simonato A, Gregori A, Lissiani A, Carmignani G. Two-stage transperineal management of posterior urethral strictures or bladder neck contractures associated with urinary incontinence after prostate surgery and endoscopic treatment failures. Eur Urol 2007;52:1499-504.

400. Shapiro E, Jeffs RD, Gearhart JP, Lepor H. Muscarinic cholinergic receptors in bladder exstrophy: insights into surgical management. J Urol 1985;134:308-10.

401. Rosch W, Christl A, Strauss B, Schrott KM, Neuhuber WL. Comparison of preoperative innervation pattern and postreconstructive urodynamics in the exstrophy-epispadias complex. Urol Int 1997;59:6-15.

402. Hipp J, Andersson KE, Kwon TG, Kwak EK, Yoo J, Atala A. Microarray analysis of exstrophic human bladder smooth muscle. BJU Int 2008;101:100-5.

403. Mathews R, Wills M, Perlman E, Gearhart JP. Neural innervation of the newborn exstrophic bladder: an immunohistochemical study. J Urol 1999;162:506-8.

404. Poli-Merol ML, Watson JA, Gearhart JP. New basic science concepts in the treatment of classic bladder exstrophy. Urology 2002;60:749-55.

405. Stec AA, Pannu HK, Tadros YE, Sponseller PD, Fishman EK, Gearhart JP. Pelvic floor anatomy in classic bladder exstrophy using 3-dimensional computerized tomography: initial insights. J Urol 2001;166:1444-9.

406. Gearhart JP, Yang A, Leonard MP, Jeffs RD, Zerhouni EA. Prostate size and configuration in adults with bladder exstrophy. J Urol 1993;149:308-10.

407. Borer JG, Gargollo PC, Kinnamon DD, et al. Bladder growth and development after complete primary repair of bladder exstrophy in the newborn with comparison to staged approach. J Urol 2005;174:1553-7; discussion 7-8.

408. Trendelenburg F. XIII. The Treatment of Ectopia Vesicae. Ann Surg 1906;44:281-9.

409. Toguri AG, Churchill BM, Schillinger JF, Jeffs RD. Continence in cases of bladder exstrophy. J Urol 1978;119:538-40.

410. Grady RW, Mitchell ME. Complete primary repair of exstrophy. J Urol 1999;162:1415-20.

411. Gargollo P, Hendren WH, Diamond DA, et al. Bladder neck reconstruction is often necessary after complete primary repair of exstrophy. J Urol 2011;185:2563-71.

412. Jarzebowski AC, McMullin ND, Grover SR, Southwell BR, Hutson JM. The Kelly technique of bladder exstrophy repair: continence, cosmesis and pelvic organ prolapse outcomes. J Urol 2009;182:1802-6.

413. Capolicchio G, McLorie GA, Farhat W, Merguerian PA, Bagli DJ, Khoury AE. A population based analysis of continence outcomes and bladder exstrophy. J Urol 2001;165:2418-21.

414. Woodhouse CR, Redgrave NG. Late failure of the reconstructed exstrophy bladder. Br J Urol 1996;77:590-2.

415. Yerkes EB, Adams MC, Rink RC, Pope JI, Brock JW, 3rd. How well do patients with exstrophy actually void? J Urol 2000;164:1044-7.

416. Wilson CJ, Pistrang N, Woodhouse CR, Christie D. The psychosocial impact of bladder exstrophy in ado-

lescence. The Journal of adolescent health : official publication of the Society for Adolescent Medicine 2007;41:504-8.

417. Dave S, Grover VP, Agarwala S, Mitra DK, Bhatnagar V. Cystometric evaluation of reconstructed classical bladder exstrophy. BJU Int 2001;88:403-8.

418. Hollowell JG, Hill PD, Duffy PG, Ransley PG. Bladder function and dysfunction in exstrophy and epispadias. Lancet 1991;338:926-8.

419. Dave S, Grover VP, Agarwala S, Mitra DK, Bhatnagar V. The role of imipramine therapy in bladder exstrophy after bladder neck reconstruction. BJU Int 2002;89:557-60; discussion 60-1.

420. Burki T, Hamid R, Ransley PG, Mushtaq I, Duffy PG. Injectable polydimethylsiloxane for treating incontinence in children with the exstrophy-epispadias complex: long-term results. BJU Int 2006;98:849-53.

421. Burki T, Hamid R, Duffy P, Ransley P, Wilcox D, Mushtaq I. Long-term followup of patients after redo bladder neck reconstruction for bladder exstrophy complex. J Urol 2006;176:1138-41; discussion 41-2.

422. Gearhart JP, Canning DA, Jeffs RD. Failed bladder neck reconstruction: options for management. J Urol 1991;146:1082-4.

423. Fishman IJ, Shabsigh R, Scott FB. Experience with the artificial urinary sphincter model AS800 in 148 patients. J Urol 1989;141:307-10.

424. Ruiz E, Puigdevall J, Moldes J, et al. 14 years of experience with the artificial urinary sphincter in children and adolescents without spina bifida. J Urol 2006;176:1821-5.

425. Herndon CD, Rink RC, Shaw MB, et al. The Indiana experience with artificial urinary sphincters in children and young adults. J Urol 2003;169:650-4; discussion 4.

426. Hohenfellner R, Stein R. Primary urinary diversion in patients with bladder exstrophy. Urology 1996;48:828-30.

427. Mayo CH, Hendricks WA. Exstrophy of the bladder. Surgery, Gynecology, and Obstretrics 1926;43:129.

428. Fisch M, Wammack R, Muller SC, Hohenfellner R. The Mainz pouch II (sigma rectum pouch). J Urol 1993;149:258-63.

429. Gobet R, Weber D, Horst M, Yamamoto S, Fischer J. Long-term followup (37 to 69 years) in patients with bladder exstrophy treated with ureterosigmoidostomy: psychosocial and psychosexual outcomes. J Urol 2009;182:1819-23.

430. Alemu MH. Mainz II pouch: continent urinary diversion, for bladder extrophy epispadia complex and irreparable VVF: a 5 year comprehensive retrospective analysis. Ethiopian medical journal 2010;48:57-62.

431. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;59:666-89.

432. Surer I, Ferrer FA, Baker LA, Gearhart JP. Continent urinary diversion and the exstrophy-epispadias complex. J Urol 2003;169:1102-5.

433. Fontaine E, Leaver R, Woodhouse C. The effect of intestinal urinary reservoirs on renal function: a 10-year follow-up. BJU Int 2000;86:195-8.

434. Smeulders N, Woodhouse CR. Neoplasia in adult exstrophy patients. BJU Int 2001;87:623-8.

435. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167-78.

436. Ahlberg J, Edlund C, Wikkelso C, Rosengren L, Fall M. Neurological signs are common in patients with urodynamically verified «idiopathic» bladder overactivity. Neurourol Urodyn 2002;21:65-70.

437. Turner-Warwick R. Observations upon techniques for reconstruction of the urethral meatus, the hypospadiac glans deformity and the penile urethra. Urol Clin North Am 1979;6:643-55.

438. Abrams P. Bladder instability: concept, clinical associations and treatment. Scand J Urol Nephrol Suppl 1984;87:7-12.

439. Malone-Lee JG. New data on urodynamics in the symptomatic elderly. Neurourol Urodyn 1990;9:409.

440. Takahashi S, Kitamura T. Overactive bladder: magnetic versus electrical stimulation. Curr Opin Obstet Gynecol 2003;15:429-33.

441. Quek P. A critical review on magnetic stimulation: what is its role in the management of pelvic floor disorders? Curr Opin Urol 2005;15:231-5.

442. Bradshaw HD, Barker AT, Radley SC, Chapple CR. The acute effect of magnetic stimulation of the pelvic floor on involuntary detrusor activity during natural filling and overactive bladder symptoms. BJU Int 2003;91:810-3.

443. Almeida FG, Bruschini H, Srougi M. Urodynamic and clinical evaluation of 91 female patients with urinary incontinence treated with perineal magnetic stimulation: 1-year followup. J Urol 2004;171:1571-4; discussion 4-5.

444. Gilling PJ, Wilson LC, Westenberg AM, et al. A double-blind randomized controlled trial of electromagnetic stimulation of the pelvic floor vs sham therapy in the treatment of women with stress urinary incontinence. BJU Int 2009;103:1386-90.

445. Chai TC, Gray ML, Steers WD. The incidence of a positive ice water test in bladder outlet obstructed patients: evidence for bladder neural plasticity. J Urol 1998;160:34-8.

446. Cruz F, Guimaraes M, Silva C, Rio ME, Coimbra A, Reis M. Desensitization of bladder sensory fibers by intravesical capsaicin has long lasting clinical and urodynamic effects in patients with hyperactive or hypersensitive bladder dysfunction. J Urol 1997;157:585-9.

447. Kuo HC. Effectiveness of intravesical resiniferatoxin for anticholinergic treatment refractory detrusor overactivity due to nonspinal cord lesions. J Urol 2003;170:835-9.

448. Palma PCR, Thiel M, Riccetto CLZ, Dambros M, Miyaoka R, Rodriguez Netto Jr N. Resiniferatoxin for detrusor instability refractory to anticholinergics. Int Brazilian J Urol 2004;30:53-8.

449. Rios M, Mattos J, D., Panhoca R, al. e. Intravesical resiniferatoxin for the treatment of idiopathic detrusor overactivity in women: a randomized double-blind placebo controlled study. Neurourol Urodyn 2004;23:Abstr.

450. Silva C, Ribeiro MJ, Cruz F. The effect of intravesical resiniferatoxin in patients with idiopathic detrusor instability suggests that involuntary detrusor contractions are triggered by C-fiber input. J Urol 2002;168:575-9.

451. Kuo HC. Multiple intravesical instillation of low-dose resiniferatoxin is effective in the treatment of detrusor overactivity refractory to anticholinergics. BJU Int 2005;95:1023-7.

452. Kuo HC, Liu HT, Yang WC. Therapeutic effect of multiple resiniferatoxin intravesical instillations in patients with refractory detrusor overactivity: a randomized, double-blind, placebo controlled study. J Urol 2006;176:641-5.

453. Rios LA, Panhoca R, Mattos D, Jr., Srugi M, Bruschini H. Intravesical resiniferatoxin for the treatment of women with idiopathic detrusor overactivity and urgency incontinence: A single dose, 4 weeks, double-blind,

randomized, placebo controlled trial. Neurourol Urodyn 2007;26:773-8.

454. Cruz F, Dinis P. Resiniferatoxin and botulinum toxin type A for treatment of lower urinary tract symptoms. Neurourol Urodyn 2007;26:920-7.

455. Yokoyama T, Nozaki K, Fujita O, Nose H, Inoue M, Kumon H. Role of C afferent fibers and monitoring of intravesical resiniferatoxin therapy for patients with idiopathic detrusor overactivity. J Urol 2004;172:596-600.

456. Fowler CJ. Bladder afferents and their role in the overactive bladder. Urology 2002;59:37-42.

457. Liu HT, Kuo HC. Increased expression of transient receptor potential vanilloid subfamily 1 in the bladder predicts the response to intravesical instillations of resiniferatoxin in patients with refractory idiopathic detrusor overactivity. BJU Int 2007;100:1086-90.

458. Silva C, Silva J, Castro H, et al. Bladder sensory desensitization decreases urinary urgency. BMC urology 2007;7:9.

459. Apostolidis A, Gonzales GE, Fowler CJ. Effect of intravesical Resiniferatoxin (RTX) on lower urinary tract symptoms, urodynamic parameters, and quality of life of patients with urodynamic increased bladder sensation. Eur Urol 2006;50:1299-305.

460. Saitoh C, Chancellor MB, de Groat WC, Yoshimura N. Effects of intravesical instillation of resiniferatoxin on bladder function and nociceptive behavior in freely moving, conscious rats. J Urol 2008;179:359-64.

461. Cruz CD, Charrua A, Vieira E, Valente J, Avelino A, Cruz F. Intrathecal delivery of resiniferatoxin (RTX) reduces detrusor overactivity and spinal expression of TRPV1 in spinal cord injured animals. Exp Neurol 2008;214:301-8.

462. Harper M, Popat RB, Dasgupta R, Fowler CJ, Dasgupta P. A minimally invasive technique for outpatient local anaesthetic administration of intradetrusor botulinum toxin in intractable detrusor overactivity. BJU Int 2003;92:325-6.

463. Loch A, Loch T, Osterhage J, al. e. Botulinum-A toxin detrusor injection in the treatment of non-neurogenic and neurologic cases of urge incontinence. Eur Urol Suppl 2003;2:172.

464. Radziszewski P, Borkowski A. Botulinum toxin type A intravesical injections for intractable bladder overactivity. Eur Urol Suppl 2002;1:174.

465. Rapp DE, Lucioni A, Katz EE, O'Connor RC, Gerber GS, Bales GT. Use of botulinum-A toxin for the treatment of refractory overactive bladder symptoms: an initial experience. Urology 2004;63:1071-5.

466. Kuo HC. Urodynamic evidence of effectiveness of botulinum A toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents. Urology 2004;63:868-72.

467. Chancellor MB, O'Leary M, Erickson J, al. e. Successful use of bladder botulinum toxin injection to treat refractory overactive bladder. J Urol 2003;169 (suppl.):351 (Abstr. DP50).

468. Jeffery S, Fynes M, Lee F, Wang K, Williams L, Morley R. Efficacy and complications of intradetrusor injection with botulinum toxin A in patients with refractory idiopathic detrusor overactivity. BJU Int 2007;100:1302-6.

469. Kuschel S, Werner M, Schmid DM, Faust E, Schuessler B. Botulinum toxin-A for idiopathic overactivity of the vesical detrusor: a 2-year follow-up. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:905-9.

470. Schmid DM, Sauermann P, Werner M, et al. Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. J Urol 2006;176:177-85.

471. Lee JC, Yokoyama T, Hwang HJ, et al. Clinical application of Clostridium botulinum type A neurotoxin purified by a simple procedure for patients with urinary incontinence caused by refractory destrusor overactivity. FEMS Immunol Med Microbiol 2007;51:201-11.

472. Popat R, Apostolidis A, Kalsi V, Gonzales G, Fowler CJ, Dasgupta P. A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. J Urol 2005;174:984-9.

473. Rajkumar GN, Small DR, Mustafa AW, Conn G. A prospective study to evaluate the safety, tolerability, efficacy and durability of response of intravesical injection of botulinum toxin type A into detrusor muscle in patients with refractory idiopathic detrusor overactivity. BJU Int 2005;96:848-52.

474. Kuo HC. Comparison of effectiveness of detrusor, suburothelial and bladder base injections of botulinum toxin a for idiopathic detrusor overactivity. J Urol 2007;178:1359-63.

475. Ghalayini IF, Al-Ghazo MA. Intradetrusor injection of botulinum-A toxin in patients with idiopathic and neurogenic detrusor overactivity: urodynamic outcome and patient satisfaction. Neurourol Urodyn 2007;26:531-6.

476. Sahai A, Khan MS, Dasgupta P. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial. J Urol 2007;177:2231-6.

477. Rackley R, Abdelmalak J. Urologic applications of botulinum toxin therapy for voiding dysfunction. Curr Urol Rep 2004;5:381-8.

478. Kessler TM, Danuser H, Schumacher M, Studer UE, Burkhard FC. Botulinum A toxin injections into the detrusor: an effective treatment in idiopathic and neurogenic detrusor overactivity? Neurourol Urodyn 2005;24:231-6.

479. Apostolidis A, Popat R, Yiangou Y, et al. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol 2005;174:977-82; discussion 82-3.

480. Wyndaele JJ, Van Dromme SA. Muscular weakness as side effect of botulinum toxin injection for neurogenic detrusor overactivity. Spinal Cord 2002;40:599-600.

481. Sinha D, Karri K, Arunkalaivanan AS. Applications of Botulinum toxin in urogynaecology. Eur J Obstet Gynecol Reprod Biol 2007;133:4-11.

482. De Laet K, Wyndaele JJ. Adverse events after botulinum A toxin injection for neurogenic voiding disorders. Spinal Cord 2005;43:397-9.

483. Pistolesi D, Selli C, Rossi B, Stampacchia G. Botulinum toxin type B for type A resistant bladder spasticity. J Urol 2004;171:802-3.

484. Reitz A, Schurch B. Botulinum toxin type B injection for management of type A resistant neurogenic detrusor overactivity. J Urol 2004;171:804; discussion -5.

485. Herschorn S, Gajewski J, Ethans K, et al. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: a randomized, double-blind trial. J Urol 2011;185:2229-35.

486. Information for Healthcare Professionals: OnabotulinumtoxinA (marketed as Botox/Botox Cosmetic), AbobotulinumtoxinA (marketed as Dysport) and RimabotulinumtoxinB (marketed as Myobloc). 2011. (Accessed July 20, 2012, at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174949.htm.)

487. Denys P, Even-Schneider A, Thiry Escudie I, Ben Smail D, Ayoub N, Chartier-Kastler E. [Efficacy of botulinum toxin A for the treatment of detrusor hyperreflexia]. Ann Readapt Med Phys 2003;46:326-8.

488. Schulte-Baukloh H, Michael T, Sturzebecher B, Knispel HH. Botulinum-a toxin detrusor injection as a novel approach in the treatment of bladder spasticity in children with neurogenic bladder. Eur Urol 2003;44:139-43.

489. Riccabona M, Koen M, Schindler M, et al. Botulinum-A toxin injection into the detrusor: a safe alternative in the treatment of children with myelomeningocele with detrusor hyperreflexia. J Urol 2004;171:845-8; discussion 8.

490. Giannantoni A, Di Stasi SM, Stephen RL, Bini V, Costantini E, Porena M. Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study. J Urol 2004;172:240-3.

491. Schurch B, Corcos J. Botulinum toxin injections for paediatric incontinence. Curr Opin Urol 2005;15:264-7.

492. DasGupta R, Murphy FL. Botulinum toxin in paediatric urology: a systematic literature review. Pediatric surgery international 2009;25:19-23.

493. Kalsi V, Apostolidis A, Popat R, Gonzales G, Fowler CJ, Dasgupta P. Quality of life changes in patients with neurogenic versus idiopathic detrusor overactivity after intradetrusor injections of botulinum neurotoxin type A and correlations with lower urinary tract symptoms and urodynamic changes. Eur Urol 2006;49:528-35.

494. Game X, Khan S, Panicker JN, et al. Comparison of the impact on health-related quality of life of repeated detrusor injections of botulinum toxin in patients with idiopathic or neurogenic detrusor overactivity. BJU Int 2011;107:1786-92.

495. Khan S, Kessler TM, Apostolidis A, et al. What a patient with refractory idiopathic detrusor overactivity should know about botulinum neurotoxin type a injection. J Urol 2009;181:1773-8.

496. Kalsi V, Popat RB, Apostolidis A, et al. Cost-consequence analysis evaluating the use of botulinum neurotoxin-A in patients with detrusor overactivity based on clinical outcomes observed at a single UK centre. Eur Urol 2006;49:519-27.

497. Biers SM, Venn SN, Greenwell TJ. The past, present and future of augmentation cystoplasty. BJU Int 2012;109:1280-93.

498. Leong RK, de Wachter SG, Joore MA, van Kerrebroeck PE. Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder. BJU Int 2011;108:558-64.

499. Siddiqui NY, Amundsen CL, Visco AG, Myers ER, Wu JM. Cost-effectiveness of sacral neuromodulation versus intravesical botulinum A toxin for treatment of refractory urge incontinence. J Urol 2009;182:2799-804.

500. Watanabe JH, Campbell JD, Ravelo A, Chancellor MB, Kowalski J, Sullivan SD. Cost analysis of interventions for antimuscarinic refractory patients with overactive bladder. Urology 2010;76:835-40.

501. Hirst GR, Watkins AJ, Guerrero K, et al. Botulinum toxin B is not an effective treatment of refractory overactive bladder. Urology 2007;69:69-73.

502. Karsenty G, Elzayat E, Delapparent T, St-Denis B, Lemieux MC, Corcos J. Botulinum toxin type a injections into the trigone to treat idiopathic overactive bladder do not induce vesicoureteral reflux. J Urol 2007;177:1011-4.

503. Kuo HC. Bladder base/trigone injection is safe and as effective as bladder body injection of onabotulinumtoxinA for idiopathic detrusor overactivity refractory to antimuscarinics. Neurourol Urodyn 2011;30:1242-8.

504. Manecksha RP, Cullen IM, Ahmad S, et al. Prospective randomised controlled trial comparing trigone-sparing versus trigone-including intradetrusor injection of abobotulinumtoxinA for refractory idiopathic detrusor overactivity. Eur Urol 2012;61:928-35.

505. Onyeka BA, Shetty A, Ilangovan K, Saxena A. Submucosal injections of botulinum toxin A in women with refractory idiopathic detrusor overactivity. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2010;110:68-9.

506. Petrou SP, Parker AS, Crook JE, Rogers A, Metz-Kudashick D, Thiel DD. Botulinum a toxin/dimethyl sulfoxide bladder instillations for women with refractory idiopathic detrusor overactivity: a phase 1/2 study. Mayo Clin Proc 2009;84:702-6.

507. Smith CP, Radziszewski P, Borkowski A, Somogyi GT, Boone TB, Chancellor MB. Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. Urology 2004;64:871-5; discussion 5.

508. Apostolidis A, Dasgupta P, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. Eur Urol 2006;49:644-50.

509. Kuo HC. Reduction of urgency severity is associated with long-term therapeutic effect after intravesical onabotulinumtoxin A injection for idiopathic detrusor overactivity. Neurourol Urodyn 2011;30:1497-502.

510. Sahai A, Dowson C, Khan MS, Dasgupta P. Re: Efficacy and complications of intradetrusor injection with botulinum toxin A in patients with refractory idiopathic detrusor overactivity. BJU Int 2008;101:515-6; author reply 6-7.

511. Wohlfarth K, Schwandt I, Wegner F, et al. Biological activity of two botulinum toxin type A complexes (Dysport and Botox) in volunteers: a double-blind, randomized, dose-ranging study. Journal of neurology 2008;255:1932-9.

512. Gomes CM, Castro Filho JE, Rejowski RF, et al. Experience with different botulinum toxins for the treatment of refractory neurogenic detrusor overactivity. International braz j urol : official journal of the Brazilian Society of Urology 2010;36:66-74.

513. Alloussi SH, Lang C, Eichel R, et al. Videourodynamic changes of botulinum toxin A in patients with neurogenic bladder dysfunction (NBD) and idiopathic detrusor overactivity (IDO) refractory to drug treatment. World J Urol 2012;30:367-73.

514. Mangera A, Andersson KE, Apostolidis A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). Eur Urol 2011;60:784-95.

515. Smaldone MC, Chancellor MB. Neuromodulation versus neurotoxin for the treatment of refractory detrusor overactivity: for neurotoxin. Nat Clin Pract Urol 2008;5:120-1.

516. Sahai A. A prospective study to evaluate the safety, tolerability, efficacy and durability of response of intravesical injection of botulinum toxin type A into detrusor muscle in patients with refractory idiopathic detrusor overactivity. BJU Int 2006;97:413.

517. Nitti VW. Botulinum toxin for the treatment of idiopathic and neurogenic overactive bladder: state of the art. Rev Urol 2006;8:198-208.

518. Patel AK, Patterson JM, Chapple CR. The emerging role of intravesical botulinum toxin therapy in idiopathic detrusor overactivity. Int J Clin Pract Suppl 2006:27-32.

519. Casanova N, McGuire E, Fenner DE. Botulinum toxin: a potential alternative to current treatment of neurogenic and idiopathic urinary incontinence due to detrusor overactivity. Int J Gynaecol Obstet 2006;95:305-11.

520. Patel AK, Patterson JM, Chapple CR. Botulinum toxin injections for neurogenic and idiopathic detrusor overactivity: A critical analysis of results. Eur Urol 2006;50:684-709; discussion -10.

521. Patterson JM, Chapple CR. Botulinum toxin in urinary incontinence. Curr Opin Urol 2006;16:255-60.

522. Dmochowski R, Sand PK. Botulinum toxin A in the overactive bladder: current status and future directions. BJU Int 2007;99:247-62.

523. Apostolidis A, Fowler CJ. The use of botulinum neurotoxin type A (BoNTA) in urology. J Neural Transm 2008;115:593-605.

524. Ho MH, Lin LL, Haessler AL, Bhatia NN. Intravesical injection of botulinum toxin for the treatment of overactive bladder. Curr Opin Obstet Gynecol 2005;17:512-8.

525. Kim DK, Thomas CA, Smith C, Chancellor MB. The case for bladder botulinum toxin application. Urol Clin North Am 2006;33:503-10, ix.

526. MacDonald R, Fink HA, Huckabay C, Monga M, Wilt TJ. Botulinum toxin for treatment of urinary incontinence due to detrusor overactivity: a systematic review of effectiveness and adverse effects. Spinal Cord 2007;45:535-41.

527. Smith CP, Somogyi GT, Chancellor MB, Appell RA. A case for botulinum toxin-A in idiopathic bladder overactivity. Curr Urol Rep 2004;5:432-6.

528. Gomez CS, Kanagarajah P, Gousse A. The use of botulinum toxin a in idiopathic overactive bladder syndrome. Curr Urol Rep 2010;11:353-9.

529. Mangera A, Chapple CR. Use of botulinum toxin in the treatment of lower urinary tract disorders. Current status. Arch Esp Urol 2010;63:829-41.

530. Amend B, Castro-Diaz D, Chartier-Kastler E, et al. [Second-line therapy of idiopathic detrusor overactivity. Sacral neuromodulation and botulinum toxin A]. Urologe A 2010;49:245-52.

531. Chancellor MB. Ten years single surgeon experience with botulinum toxin in the urinary tract; clinical observations and research discovery. Int Urol Nephrol 2010;42:383-91.

532. da Silva CM, Cruz F. Has botulinum toxin therapy come of age: what do we know, what do we need to know, and should we use it? Curr Opin Urol 2009;19:347-52.

533. Shaban AM, Drake MJ. Botulinum toxin treatment for overactive bladder: risk of urinary retention. Curr Urol Rep 2008;9:445-51.

534. Apostolidis A, Dasgupta P, Denys P, et al. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus report. Eur Urol 2009;55:100-19.

535. Schmid DM, Roy S, Sulser T, Scheiner D. Prospects and limitations of treatment with botulinum neurotoxin type A for patients with refractory idiopathic detrusor overactivity. BJU Int 2008;102 Suppl 1:7-10.

536. Sahai A, Dowson C, Khan MS, Dasgupta P. Improvement in quality of life after botulinum toxin-A injections for idiopathic detrusor overactivity: results from a randomized double-blind placebo-controlled trial. BJU Int 2009;103:1509-15.

537. Rovner E, Kennelly M, Schulte-Baukloh H, Zhou J, Haag-Molkenteller C, Dasgupta P. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. Neurourol Urodyn 2011;30:556-62.

538. Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol 2010;184:2416-22.

539. Brubaker L, Richter HE, Visco A, et al. Refractory idiopathic urge urinary incontinence and botulinum A injection. J Urol 2008;180:217-22.

540. Godec C, Cass AS, Ayala GF. Electrical stimulation for incontinence. Technique, selection, and results. Urology 1976;7:388-97.

541. Tanagho E. Concepts of neuromodulation. Neurourol Urodyn 1993;12:487-8.

542. Trsinar B, Kraij B. Maximal electrical stimulation in children with unstable bladder and nocturnal enuresis and/or daytime incontinence: a controlled study. Neurourol Urodyn 1996;15:133-42.

543. Primus G, Kramer G. Maximal external electrical stimulation for treatment of neurogenic or non-neurogenic urgency and/or urge incontinence. Neurourol Urodyn 1996;15:187-94.

544. Fall M. Does electrostimulation cure urinary incontinence? J Urol 1984;131:664-7.

545. McGuire EJ, Zhang SC, Horwinski ER, Lytton B. Treatment of motor and sensory detrusor instability by electrical stimulation. J Urol 1983;129:78-9.

546. Siegel SW, Richardson DA, Miller KL, et al. Pelvic floor electrical stimulation for the treatment of urge and mixed urinary incontinence in women. Urology 1997;50:934-40.

547. Merrill DC. The treatment of detrusor incontinence by electrical stimulation. J Urol 1979;122:515-7.

548. Nakamura M, Sakurai T, Tsujimoto Y, Tada Y. Bladder inhibition by electrical stimulation of the perianal skin. Urol Int 1986;41:62-3.

549. Nakamura M, Sakurai T, Sugao H, Sonoda T. Maximum electrical stimulation for urge incontinence. Urol Int 1987;42:285-7.

550. Caremel R, Damon H, Ruffion A, et al. Can sacral neuromodulation improve minor incontinence symptoms in doubly incontinent patients successfully treated for major incontinence symptoms? Urology 2012;79:80-5.

551. Dijkema HE, Weil EH, Mijs PT, Janknegt RA. Neuromodulation of sacral nerves for incontinence and voiding dysfunctions. Clinical results and complications. Eur Urol 1993;24:72-6.

552. Schmidt RA. Treatment of unstable bladder. Urology 1991;37:28-32.

553. van der Pal F, Heesakkers JP, Bemelmans BL. Current opinion on the working mechanisms of neuromodulation in the treatment of lower urinary tract dysfunction. Curr Opin Urol 2006;16:261-7.

554. Daneshgari F, Moy ML. Current indications for neuromodulation. Urol Clin North Am 2005;32:37-40, vi.

555. Leng WW, Chancellor MB. How sacral nerve stimulation neuromodulation works. Urol Clin North Am 2005;32:11-8.

556. Keppene V, Mozer P, Chartier-Kastler E, Ruffion A. [Neuromodulation in the management of neurogenic lower urinary tract dysfunction]. Prog Urol 2007;17:609-15.

557. Nakib N, Siegel S. Neuromodulation versus neurotoxin for the treatment of refractory detrusor overactivity: for neuromodulation. Nat Clin Pract Urol 2008;5:118-9.

558. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol 2007;178:2029-34.

559. Al-zahrani AA, Elzayat EA, Gajewski JB. Long-term outcome and surgical interventions after sacral neuromodulation implant for lower urinary tract symptoms: 14-year experience at 1 center. J Urol 2011;185:981-6.

560. Oerlemans DJ, van Voskuilen AC, Marcelissen T, Weil EH, de Bie RA, Van Kerrebroeck PE. Is on-demand sacral neuromodulation in patients with OAB syndrome a feasible therapy regime? Neurourol Urodyn 2011;30:1493-6.

561. Bosch JL, Groen J. Sacral (S3) segmental nerve stimulation as a treatment for urge incontinence in patients with detrusor instability: results of chronic electrical stimulation using an implantable neural prosthesis. J Urol 1995;154:504-7.

562. Bosch JL, Groen J. Disappointing results of neuromodulation in men with urge incontinence due to detrusor instability. Neurourol Urodyn 1997;16:347-9.

563. Shaker HS, Hassouna M. Sacral nerve root neuromodulation: an effective treatment for refractory urge incontinence. J Urol 1998;159:1516-9.

564. Groen J, Ruud Bosch JL, van Mastrigt R. Sacral neuromodulation in women with idiopathic detrusor overactivity incontinence: decreased overactivity but unchanged bladder contraction strength and urethral resistance during voiding. J Urol 2006;175:1005-9; discussion 9.

565. Groenendijk PM, Lycklama a Nyeholt AA, Heesakkers JP, et al. Urodynamic evaluation of sacral neuromodulation for urge urinary incontinence. BJU Int 2008;101:325-9.

566. South MM, Romero AA, Jamison MG, Webster GD, Amundsen CL. Detrusor overactivity does not predict outcome of sacral neuromodulation test stimulation. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:1395-8.

567. Groenendijk PM, Heesakkers JP, Lycklama ANAA. Urethral instability and sacral nerve stimulation-a better parameter to predict efficacy? J Urol 2007;178:568-72; discussion 72.

568. Hassouna MM, Siegel SW, Nyeholt AA, et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety. J Urol 2000;163:1849-54.

569. Edlund C, Hellstrom M, Peeker R, Fall M. First Scandinavian experience of electrical sacral nerve stimulation in the treatment of the overactive bladder. Scand J Urol Nephrol 2000;34:366-76.

570. Herbison GP, Arnold EP. Sacral neuromodulation with implanted devices for urinary storage and voiding dysfunction in adults. Cochrane Database Syst Rev 2009:CD004202.

571. Humphreys MR, Vandersteen DR, Slezak JM, et al. Preliminary results of sacral neuromodulation in 23 children. J Urol 2006;176:2227-31.

572. McAchran SE, Daneshgari F. Sacral neuromodulation in the older woman. Clin Obstet Gynecol 2007;50:735-44.

573. Schmidt RA, Jonas U, Oleson KA, et al. Sacral nerve stimulation for treatment of refractory urinary urge incontinence. Sacral Nerve Stimulation Study Group. J Urol 1999;162:352-7.

574. Weil EH, Ruiz-Cerda JL, Eerdmans PH, Janknegt RA, Bemelmans BL, van Kerrebroeck PE. Sacral root neuromodulation in the treatment of refractory urinary urge incontinence: a prospective randomized clinical trial. Eur Urol 2000;37:161-71.

575. Bosch JL, Groen J. Sacral nerve neuromodulation in the treatment of patients with refractory motor urge incontinence: long-term results of a prospective longitudinal study. J Urol 2000;163:1219-22.

576. Siegel SW, Catanzaro F, Dijkema HE, et al. Long-term results of a multicenter study on sacral nerve stimulation for treatment of urinary urge incontinence, urgency-frequency, and retention. Urology 2000;56:87-91.

577. Grunewald V, Hofner K, Thon WF, Kuczyk MA, Jonas U. Sacral electrical neuromodulation as an alternative treatment option for lower urinary tract dysfunction. Restor Neurol Neurosci 1999;14:189-93.

578. Aboseif S, Tamaddon K, Chalfin S, Freedman S, Kaptein J. Sacral neuromodulation as an effective treatment for refractory pelvic floor dysfunction. Urology 2002;60:52-6.

579. Hedlund H, Schultz A, Talseth T, Tonseth K, van der Hagen A. Sacral neuromodulation in Norway: clinical experience of the first three years. Scand J Urol Nephrol Suppl 2002:87-95.

580. Roupret M, Chartier-Kastler E, Almeras C, Ayoub N, Haertig A, Richard F. Sacral neuromodulation for refractory detrusor overactivity in women with an artificial urinary sphincter. J Urol 2004;172:236-9.

581. Groen J, Blok BF, Bosch JL. Sacral neuromodulation as treatment for refractory idiopathic urge urinary incontinence: 5-year results of a longitudinal study in 60 women. J Urol 2011;186:954-9.

582. Chartier-Kastler E, Ballanger P, Belas M, et al. [Sacral neuromodulation with InterStim system: Results from the French national register]. Prog Urol 2011;21:209-17.

583. Abrams P, Blaivas JG, Fowler CJ, et al. The role of neuromodulation in the management of urinary urge incontinence. BJU Int 2003;91:355-9.

584. Hussain Z, Harrison SC. Neuromodulation for lower urinary tract dysfunction--an update. ScientificWorldJournal 2007;7:1036-45.

585. Oerlemans DJ, van Kerrebroeck PE. Sacral nerve stimulation for neuromodulation of the lower urinary tract. Neurourol Urodyn 2008;27:28-33.

586. Diokno AC, Leu PB, Konstandt DB. A simplified method of implanting a neuromodulator device. J Urol 2003;169:1466-9.

587. Spinelli M, Malaguti S, Giardiello G, Lazzeri M, Tarantola J, Van Den Hombergh U. A new minimally invasive procedure for pudendal nerve stimulation to treat neurogenic bladder: description of the method and preliminary data. Neurourol Urodyn 2005;24:305-9.

588. Brazzelli M, Murray A, Fraser C. Efficacy and safety of sacral nerve stimulation for urinary urge incontinence: a systematic review. J Urol 2006;175:835-41.

589. Van Kerrebroeck PE, Marcelissen TA. Sacral neuromodulation for lower urinary tract dysfunction. World J Urol 2012;30:445-50.

590. Apostolidis A. Neuromodulation for intractable OAB. Neurourol Urodyn 2011;30:766-70.

591. Swami KS, Feneley RC, Hammonds JC, Abrams P. Detrusor myectomy for detrusor overactivity: a minimum 1-year follow-up. Br J Urol 1998;81:68-72.

592. Leng WW, Blalock HJ, Fredriksson WH, English SF, McGuire EJ. Enterocystoplasty or detrusor myectomy? Comparison of indications and outcomes for bladder augmentation. J Urol 1999;161:758-63.

593. Kumar SP, Abrams PH. Detrusor myectomy: long-term results with a minimum follow-up of 2 years. BJU Int 2005;96:341-4.

594. Rocha FT, Bruschini H, Figueiredo JA, et al. Use of an inflatable silicone balloon improves the success rate of bladder autoaugmentation at long-term followup. J Urol 2011;185:2576-81.

595. Hasan ST, Marshall C, Robson WA, Neal DE. Clinical outcome and quality of life following enterocystoplasty for idiopathic detrusor instability and neurogenic bladder dysfunction. Br J Urol 1995;76:551-7.

596. McInerney PD, DeSouza N, Thomas PJ, Mundy AR. The role of urodynamic studies in the evaluation of patients with augmentation cystoplasties. Br J Urol 1995;76:475-8.

597. Bramble F. The clam cystoplasty. [Review] [21 refs]. British Journal of Urology 1990;66:337-41.

598. Sethia KK, Webb RJ, Neal DE. Urodynamic study of ileocystoplasty in the treatment of idiopathic detrusor instability. Br J Urol 1991;67:286-90.

599. Mundy AR, Stephenson TP. «Clam» ileocystoplasty for the treatment of refractory urge incontinence. Br J Urol 1985;57:641-6.

600. Edlund C, Peeker R, Fall M. Clam ileocystoplasty: successful treatment of severe bladder overactivity. Scand J Urol Nephrol 2001;35:190-5.

601. Blaivas JG, Weiss J, Desai P, Flisser AJ, Stember D, Stahl P. Long-term followup of augmentation enterocystoplasty and continent diversion in patients with benign disease. J Urol 2005;173:1631-4.

602. Shokeir AA, Ibrahim AM, Hamid MY, Shalaby MA, Hussein HE, Badr M. Urinary bilharziasis in upper Egypt. I. A clinicopathological study. East Afr Med J 1972;49:298-311.

603. Smith RB, van Cangh P, Skinner DG, Kaufman JJ, Goodwin WE. Augmentation enterocystoplasty: a critical review. J Urol 1977;118:35-9.

604. Kerr WK, Gale GL, Peterson KS. Reconstructive surgery for genitourinary tuberculosis. J Urol 1969;101:254-66.

605. Zinman L, Libertino JA. Technique of augmentation cecocystoplasty. Surg Clin North Am 1980;60:703-10.

606. Dounis A, Abel BJ, Gow JG. Cecocystoplasty for bladder augmentation. J Urol 1980;123:164-7.

607. Lunghi F, Nicita G, Selli C, Rizzo M. Clinical aspects of augmentation enterocystoplasties. Eur Urol 1984;10:159-63.

608. Shawket TN, Muhsen J. Treatment of bilharzial-contracted bladder by ileocystoplasty or colocystoplasty. J Urol 1967;97:285-7.

609. Whitmore WF, 3rd, Gittes RF. Reconstruction of the urinary tract by cecal and ileocecal cystoplasty: review of a 15-year experience. J Urol 1983;129:494-8.

610. Chan SL, Ankenman GJ, Wright JE, McLoughlin MG. Cecocystoplasty in the surgical management of the small contracted bladder. J Urol 1980;124:338-40.

611. Shirley SW, Mirelman S. Experiences with colocystoplasties, cecocystoplasties and ileocystoplasties in urologic surgery: 40 patients. J Urol 1978;120:165-8.

612. Goodwin WE, Turner RD, Winter CC. Results of ileocystoplasty. J Urol 1958;80:461-6.

613. Winter CC, Goodwin WE. Results sigmoidocystoplasty. J Urol 1958;80:467-72.

614. Fall M, Nilsson S. Volume augmentation cystoplasty and persistent urgency. Scand J Urol Nephrol 1982;16:125-8.

615. Goldwasser B, Webster GD. Augmentation and substitution enterocystoplasty. J Urol 1986;135:215-24.

616. Weinberg AC, Boyd SD, Lieskovsky G, Ahlering TE, Skinner DG. The hemi-Kock augmentation ileocystoplasty: a low pressure anti-refluxing system. J Urol 1988;140:1380-4.

617. Novak R. [Surgical treatment of contracted tuberculous bladder]. Plucne Bolesti Tuberk 1969;21:109-14.

618. Sayegh ES, Dimmette RM. The fibrotic contracted urinary bladder associated with schistosomiasis and chronic ulceration: a clinicopathological study including treatment. J Urol 1956;75:671-9.

619. Beduk Y, Anafarta K, Baltaci S, Adsan O, Iskit N. Urinary tract reconstruction in a patient with urethral stricture, contracted bladder and erectile impotence. Int Urol Nephrol 1994;26:173-8.

620. Kuo HC. Clinical outcome and quality of life after enterocystoplasty for contracted bladders. Urol Int 1997;58:160-5.

621. Kawamura S, Kumasaka K, Noro K, Aoki H, Kubo T, Abe T. [A case of replacement ileocystoplasty for contracted bladder]. Hinyokika Kiyo 1991;37:1049-52.

622. Hradec EA. Bladder substitution: indications and results in 114 operations. J Urol 1965;94:406-17.

623. Lima SV, Araujo LA, Montoro M, Maciel A, Vilar FO. The use of demucosalized bowel to augment small contracted bladders. Br J Urol 1998;82:436-9.

624. el Otmany A, Hamada H, al Bouzidi A, et al. [Squamous cell carcinoma in an augmentation of the ilial bladder for tuberculosis]. Prog Urol 1999;9:534-6.

625. Yamada Y, Takenaka A, Gotoh K, Yamanaka N. Augmentation ileocystoplasty and ileal ureter replacement for distal ureteral cancer in a patient with a contracted bladder. Int J Urol 1999;6:475-8.

626. Miyano G, Yamataka A, Okada Y, et al. Sigmoidocolocystoplasty for augmentation of iatrogenic small capacity bladder caused by direct injury to the bladder during inguinal hernia repair: long-term follow-up. Pediatric surgery international 2004;20:61-4.

627. Blaivas JG, Weiss JP, Desai P, Flisser AJ, Stember DS, Stahl PJ. Long-term followup of augmentation enterocystoplasty and continent diversion in patients with benign disease. J Urol 2005;173:1631-4.

628. de Figueiredo AA, Lucon AM, Srougi M. Bladder augmentation for the treatment of chronic tuberculous cystitis. Clinical and urodynamic evaluation of 25 patients after long term follow-up. Neurourol Urodyn 2006;25:433-40.

629. Yashi M, Muraishi O, Kobayashi Y, Tokue A. Gastrocystoplasty in a woman with radiation-induced ureteral obstruction and low-compliance bladder. Urol Int 1998;61:55-7.

630. Lima SV, Araujo LA, Vilar Fde O, Lima RS, Lima RF. Nonsecretory intestinocystoplasty: a 15-year prospective study of 183 patients. J Urol 2008;179:1113-6; discussion 6-7.

631. Singh V, Sinha RJ, Sankhwar SN, Sinha SM. Reconstructive surgery for tuberculous contracted bladder: experience of a center in northern India. Int Urol Nephrol 2011;43:423-30.

632. Shakespeare D, Mitchell DM, Carey BM, et al. Rectourethral fistula following brachytherapy for localized prostate cancer. Colorectal Dis 2007;9:328-31.

633. Tash JA, Eid JF. Urethrocutaneous fistula due to a retained ring of condom. Urology 2000;56:508.

634. Porter AT, Littrup P, Grignon D, al. e. Radiotherapy and Cryotherapy for Prostate Cancer. In: Walsh PC, Retik AB, Vaughan Jr ED, Wein AJ, eds. Campbell's Urology. 7th ed. Philadelphia: W.B. Saunders Co.; 1998:2605-6.

635. Thomas R, Davis R, Ahuja S. Toward out-patient radical prostatectomy: a cost effective cost management of patients with localized prostate cancer. BJU Int 1997;80:261.

636. Fahal AH, Sharfi AR, Sheik HE, el Hassan AM, Mahgoub ES. Internal fistula formation: an unusual complication of mycetoma. Trans R Soc Trop Med Hyg 1996;90:550-2.

637. Chiou RK, Anderson JC, Tran T, Patterson RH, Wobig R, Taylor RJ. Evaluation of urethral strictures and associated abnormalities using high-resolution and color Doppler ultrasound. Urology 1996;47:102-7.

638. Blandy JP, Singh M. Fistulae involving the adult male urethra. Br J Urol 1972;44:632-43.

639. Culp OS, Calhoon HW. A Variety of Rectourethral Fistulas: Experiences with 20 Cases. J Urol 1964;91:560-71.

640. Endo M, Hayashi A, Ishihara M, et al. Analysis of 1,992 patients with anorectal malformations over the past two decades in Japan. Steering Committee of Japanese Study Group of Anorectal Anomalies. J Pediatr Surg 1999;34:435-41.

641. Rintala RJ, Lindahl HG. Posterior sagittal anorectoplasty is superior to sacroperineal-sacroabdominoperineal pull-through: a long-term follow-up study in boys with high anorectal anomalies. J Pediatr Surg 1999;34:334-7.

642. Benchekroun A, Lachkar A, Soumana A, et al. [Urethrorectal fistula. Report of 11 cases]. Ann Urol (Paris) 1999;33:93-6.

643. Smith AM, Veenema RJ. Management of rectal injury and rectourethral fistulas following radical retropubic prostatectomy. J Urol 1972;108:778-9.

644. Roberts WB, Tseng K, Walsh PC, Han M. Critical appraisal of management of rectal injury during radical prostatectomy. Urology 2010;76:1088-91.

645. Thomas C, Jones J, Jager W, Hampel C, Thuroff JW, Gillitzer R. Incidence, clinical symptoms and management of rectourethral fistulas after radical prostatectomy. J Urol 2010;183:608-12.

646. Tiptaft RC, Motson RW, Costello AJ, Paris AM, Blandy JP. Fistulae involving rectum and urethra: the place of Parks's operations. Br J Urol 1983;55:711-5.

647. Noldus J, Graefen M, Huland H. An old technique for a new approach for repair of rectourinary fistulas. J Urol 1997;157 (Suppl.):1547.

648. Eastham JA, Scardino PT. Radical prostatectomy. In: Walsh PC, Retik AB, Vaughan Jr ED, Wein AJ, eds. Campbell's Urology. 7th ed. Philadelphia: W.B. Saunders Co.; 1997:2547-64.

649. Nyam DC, Pemberton JH. Management of iatrogenic rectourethral fistula. Dis Colon Rectum 1999;42:994-7; discussion 7-9.

650. Badalament RA, Bahn DK, Kim H, Kumar A, Bahn JM, Lee F. Patient-reported complications after cryoablation therapy for prostate cancer. Urology 1999;54:295-300.

651. Zippe CD. Cryosurgery of the prostate: techniques and pitfalls. Urol Clin North Am 1996;23:147-63.

652. Ismail M, Ahmed S, Kastner C, Davies J. Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. BJU Int 2007;100:760-4.

653. Montorsi F, Guazzoni G, Bergamaschi F, al. e. Transrectal prostatic hyperthermia and advanced prostatic cancer: Clinical results of one year follow up. Acta Urol Ital 1992;6 (Suppl. ^6):471-4.

654. Kleinberg L, Wallner K, Roy J, et al. Treatment-related symptoms during the first year following transperineal 125I prostate implantation. Int J Radiat Oncol Biol Phys 1994;28:985-90.

655. Fengler SA, Abcarian H. The York Mason approach to repair of iatrogenic rectourinary fistulae. Am J Surg 1997;173:213-7.

656. Larson DW, Chrouser K, Young-Fadok T, Nelson H. Rectal complications after modern radiation for prostate cancer: a colorectal surgical challenge. J Gasc trointest Surg 2005;9:461-6.

657. Lane BR, Stein DE, Remzi FH, Strong SA, Fazio VW, Angermeier KW. Management of radiotherapy induced rectourethral fistula. J Urol 2006;175:1382-7; discussion 7-8.

658. Chrouser KL, Leibovich BC, Sweat SD, et al. Urinary fistulas following external radiation or permanent brachytherapy for the treatment of prostate cancer. J Urol 2005;173:1953-7.

659. Marguet C, Raj GV, Brashears JH, et al. Rectourethral fistula after combination radiotherapy for prostate cancer. Urology 2007;69:898-901.

660. Chang KM, Lee RC, Chiu AW, Wang JH, Chiang H. Malakoplakia of the prostate forming a fistulous tract to rectum: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 1996;58:439-43.

661. Cools P, Vanderputte S, Van der Stighelen Y, Colemont L, Denis B. Rectourethral fistula due to Crohn's disease. Acta Urol Belg 1996;64:47-8.

662. Felipetto R, Vigano L, Cecchi M, Florentini L, Minervini R. Use of fibrin sealant in the treatment of prostatic cutaneous fistula in a case of Pseudomonas prostatitis. Int Urol Nephrol 1995;27:563-5.

663. Buckley JC. Complications after radical prostatectomy: anastomotic stricture and rectourethral fistula. Curr Opin Urol 2011;21:461-4.

664. Lacarriere E, Suaud L, Caremel R, Rouache L, Tuech JJ, Pfister C. [Rectourethral fistulae: diagnosis and management. Review of the literature]. Prog Urol 2011;21:585-94.

665. al-Ali M, Kashmoula D, Saoud IJ. Experience with 30 posttraumatic rectourethral fistulas: presentation of posterior transsphincteric anterior rectal wall advancement. J Urol 1997;158:421-4.

666. Gibbons RP. Radical perineal prostatectomy. In: Walsh PC, Retik AB, Vaughan Jr ED, Wein AJ, eds. Campbell's Urology. 7th ed. Philadelphia: W.B. Saunders Co.; 1997:2589-603.

667. Turner-Warwick R. The use of the omental pedicle graft in urinary tract reconstruction. J Urol 1976;116:341-7.

668. Ryan JA, Jr., Beebe HG, Gibbons RP. Gracilis muscle flap for closure of rectourethral fistula. J Urol 1979;122:124-5.

669. Venable DD. Modification of the anterior perineal transanorectal approach for complicated prostatic urethrorectal fistula repair. J Urol 1989;142:381-4.

670. Rivera R, Barboglio PG, Hellinger M, Gousse AE. Staging rectourinary fistulas to guide surgical treatment. J Urol 2007;177:586-8.

671. Elliott SP, McAninch JW, Chi T, Doyle SM, Master VA. Management of severe urethral complications of prostate cancer therapy. J Urol 2006;176:2508-13.

672. Young HH. Repair of rectourethral fistula. In: Young HH, Davis DM, eds. Young's Practice of Urology. Philadelphia: W.B. Saunders Co.; 1926:582.

673. Lewis LG. Repair of rectourethral fistulas. J Urol 1947;57:1173-81.

674. Goodwin WE, Turner RD, Winter CC. Rectourinary fistula: principles of management and a technique of surgical closure. J Urol 1958;80:246-54.

675. Youssef AH, Fath-Alla M, El-Kassaby AW. Perineal subcutaneous dartos pedicled flap as a new technique for repairing urethrorectal fistula. J Urol 1999;161:1498-500.

676. Ng L, Sorcini A, Mourtzinos A, al. e. Management of the complex rectourinary fistula with buccal mucosal patch graft and muscle flap support. J Urol 2004;17 Suppl. 4:62.

677. Kilpatrick FR, Thompson HR. Post-operative rectoprostatic fistula and closure by Kraske's approach. Br J Urol 1962;34:470-4.

678. Stephenson RA, Middleton RG. Repair of rectourinary fistulas using a posterior sagittal transanal transrectal (modified York-Mason) approach: an update. J Urol 1996;155:1989-91.

679. Kilpatrick FR, Mason AY. Post-operative recto-prostatic fistula. Br J Urol 1969;41:649-54.

680. Fournier R, Traxer O, Lande P, Tuech JJ, Vergos M. [Posterior trans-anal-sphincter approach in the management of urethro-prostate-rectal fistula]. J Urol (Paris) 1996;102:75-8.

681. Bukowski TP, Chakrabarty A, Powell IJ, Frontera R, Perlmutter AD, Montie JE. Acquired rectourethral fistula: methods of repair. J Urol 1995;153:730-3.

682. Vose SN. A technique for repair of recto-urethral fistula. J Urol 1949;61:790-4.

683. Parks AG, Motson RW. Peranal repair of rectoprostatic fistula. Br J Surg 1983;70:725-6.

684. Culkin DJ, Ramsey CE. Urethrorectal fistula: transanal, transsphincteric approach with locally based pedicle interposition flaps. J Urol 2003;169:2181-3.

685. Gecelter L. Transanorectal approach to the posterior urethra and bladder neck. J Urol 1973;109:1011-6.

686. Zinman L. The challenge of the complex rectourethral fistula: algorithm of management. AUA News 2003:47-8.

687. Wilbert DM, Buess G, Bichler KH. Combined endoscopic closure of rectourethral fistula. J Urol 1996;155:256-8.

688. Bardari F, D'Urso L, Muto G. Conservative treatment of iatrogenic urinary fistulas: the value of cyanoacrylic glue. Urology 2001;58:1046-8.

689. Singh I, Mittal G, Kumar P, Gangas R. Delayed posttraumatic prostatic-urethrorectal fistula: transperineal rectal sparing repair - point of technique. Int J Urol 2006;13:92-4.

690. Pratap A, Agrawal CS, Pandit RK, Sapkota G, Anchal N. Factors contributing to a successful outcome of combined abdominal transpubic perineal urethroplasty for complex posterior urethral disruptions. J Urol 2006;176:2514-7; discussion 7.

691. Samplaski MK, Wood HM, Lane BR, Remzi FH, Lucas A, Angermeier KW. Functional and quality-of-life outcomes in patients undergoing transperineal repair with gracilis muscle interposition for complex rectourethral fistula. Urology 2011;77:736-41.

692. Kraske P. Zur Extirpation hochsitzender Mastdarmkrebse. Verh Dtsch Ges Chir 1885;14:464-74.

693. Dal Moro F, Mancini M, Pinto F, Zanovello N, Bassi PF, Pagano F. Successful repair of iatrogenic rectourinary fistulas using the posterior sagittal transrectal approach (York-Mason): 15-year experience. World journal of surgery 2006;30:107-13.

694. Erickson BA, Dumanian GA, Sisco M, Jang TL, Halverson AL, Gonzalez CM. Rectourethral fistula associated with two short segment urethral strictures in the anterior and posterior urethra: single-stage reconstruction using buccal mucosa and a radial forearm fasciocutaneous free flap. Urology 2006;67:195-8.

695. Lorente JA, Bielsa O, Rijo E, Frances A, Pera M, Arango O. Experience in the treatment of rectourethral fistulae after radical prostatectomy. Arch Esp Urol 2011;64:517-23.

696. Pera M, Alonso S, Pares D, et al. [Treatment of a rectourethral fistula after radical prostatectomy by York Mason posterior trans-sphincter exposure]. Cirugia espanola 2008;84:323-7.

697. Hata F, Yasoshima T, Kitagawa S, et al. Transanal repair of rectourethral fistula after a radical retropubic prostatectomy: report of a case. Surg Today 2002;32:170-3.

698. Castillo OA, Bodden E, Vitagliano G. Management of rectal injury during laparoscopic radical prostatectomy. Int Braz J Urol 2006;32:428-33.

699. Quinlan M, Cahill R, Keane F, Grainger R, Butler M. Transanal endoscopic microsurgical repair of iatrogenic recto-urethral fistula. Surgeon 2005;3:416-7.

700. Bochove-Overgaauw DM, Beerlage HP, Bosscha K, Gelderman WA. Transanal endoscopic microsurgery for correction of rectourethral fistulae. J Endourol 2006;20:1087-90.

701. Pigalarga R, Patel NM, Rezac C. Transanal endoscopic microsurgery-assisted rectal advancement flap is a viable option for iatrogenic rectourethral fistula repair: a case report. Techniques in coloproctology 2011;15:209-11.

702. Varma MG, Wang JY, Garcia-Aguilar J, Shelton AA, McAninch JW, Goldberg SM. Dartos muscle interposition flap for the treatment of rectourethral fistulas. Dis Colon Rectum 2007;50:1849-55.

703. Venkatesh KS, Ramanujam P. Fibrin glue application in the treatment of recurrent anorectal fistulas. Dis Colon Rectum 1999;42:1136-9.

704. Verriello V, Altomare M, Masiello G, Curatolo C, Balacco G, Altomare DF. Treatment of post-prostatectomy rectourethral fistula with fibrin sealant (Quixil) injection: a novel application. Techniques in coloproctology 2010;14:341-3.

705. Chirica M, Parc Y, Tiret E, Dehni N, McNamara D, Parc R. Coloanal sleeve anastomosis (Soave procedure): the ultimate treatment option for complex rectourinary fistulas. Dis Colon Rectum 2006;49:1379-83.

706. Lesser T, Aboseif S, Abbas MA. Combined endorectal advancement flap with Alloderm graft repair of radiation and cryoablation-induced rectourethral fistula. The American surgeon 2008;74:341-5.

707. Madjar S, Raz S, Gousse AE. Fixed and dynamic urethral compression for the treatment of post-prostatectomy urinary incontinence: is history repeating itself? J Urol 2001;166:411-5.

708. Scott FB, Bradley WE, Timm GW. Treatment of urinary incontinence by implantable prosthetic sphincter. Urology 1973;1:252-9.

709. Matsushita K, Chughtai BI, Maschino AC, Lee RK, Sandhu JS. International variation in artificial urinary sphincter use. Urology 2012;80:667-72.

710. Lee R, Te AE, Kaplan SA, Sandhu JS. Temporal trends in adoption of and indications for the artificial urinary sphincter. J Urol 2009;181:2622-7.

711. Reynolds WS, Patel R, Msezane L, Lucioni A, Rapp DE, Bales GT. Current use of artificial urinary sphincters in the United States. J Urol 2007;178:578-83.

712. Montague DK, Angermeier KW, Paolone DR. Long-term continence and patient satisfaction after artificial sphincter implantation for urinary incontinence after prostatectomy. J Urol 2001;166:547-9.

713. Walsh IK, Williams SG, Mahendra V, Nambirajan T, Stone AR. Artificial urinary sphincter implantation in the irradiated patient: safety, efficacy and satisfaction. BJU Int 2002;89:364-8.

714. Gomha MA, Boone TB. Voiding patterns in patients with post-prostatectomy incontinence: urodynamic and demographic analysis. J Urol 2003;169:1766-9.

715. ter Meulen PH, Zambon V, Kessels AG, van Kerrebroeck PE. Quality of life, functional outcome and durability of the AMS 800 artificial urinary sphincter in patients with intrinsic sphincter deficiency. Urol Int 2003;71:55-60.

716. Gonzalez R, Nguyen DH, Koleilat N, Sidi AA. Compatibility of enterocystoplasty and the artificial urinary sphincter. J Urol 1989;142:502-4; discussion 20-1.

717. Abdel-Azim MS, Abdel-Hakim AM. Gastrocystoplasty in patients with an areflexic low compliant bladder. Eur Urol 2003;44:260-5.

718. Catto JW, Natarajan V, Tophill PR. Simultaneous augmentation cystoplasty is associated with earlier rather than increased artificial urinary sphincter infection. J Urol 2005;173:1237-41.

719. Grein U, Meyer WW. Local recurrent cancer after radical prostatectomy and incontinence. Is the artificial urinary sphincter a useful therapeutic option? Urol Int 2001;66:9-12.

720. O'Connor RC, Nanigian DK, Patel BN, Guralnick ML, Ellision LM, Stone AR. Artificial urinary sphincter placement in elderly men. Urology 2007;69:126-8.

721. Stone AR, Nguyen M, Tse V. Letter, re: New surgical technique for sphincterurinary control system using upper transverse scrotal incision. J Urol 2003;170:550-1.

722. Henry GD, Graham SM, Cleves MA, Simmons CJ, Flynn B. Perineal approach for artificial urinary sphincter implantation appears to control male stress incontinence better than the transscrotal approach. J Urol 2008;179:1475-9; discussion 9.

723. Kendirci M, Gupta S, Shaw K, et al. Synchronous prosthetic implantation through a transscrotal incision: an outcome analysis. J Urol 2006;175:2218-22.

724. Sellers CL, Morey AF, Jones LA. Cost and time benefits of dual implantation of inflatable penile and artificial urinary sphincter prosthetics by single incision. Urology 2005;65:852-3.

725. Hudak SJ, Morey AF. Impact of 3.5 cm artificial urinary sphincter cuff on primary and revision surgery for male stress urinary incontinence. J Urol 2011;186:1962-6.

726. Murray KH, Nurse DE, Mundy AR. Detrusor behaviour following implantation of the Brantley Scott artificial urinary sphincter for neuropathic incontinence. Br J Urol 1988;61:122-8.

727. Light JK, Pietro T. Alteration in detrusor behavior and the effect on renal function following insertion of the artificial urinary sphincter. J Urol 1986;136:632-5.

728. Bauer SB, Reda EF, Colodny AH, Retik AB. Detrusor instability: a delayed complication in association with the artificial sphincter. J Urol 1986;135:1212-5.

729. Roth DR, Vyas PR, Kroovand RL, Perlmutter AD. Urinary tract deterioration associated with the artificial urinary sphincter. J Urol 1986;135:528-30.

730. Bitsch M, Nerstrom H, Nordling J, Hald T. Upper urinary tract deterioration after implantation of artificial urinary sphincter. Scand J Urol Nephrol 1990;24:31-4.

731. Churchill BM, Gilmour RF, Khoury AE, McLorie GA. Biological response of bladders rendered continent by insertion of artificial sphincter. J Urol 1987;138:1116-9.

732. Scott FB, Fishman IJ, Shabsigh R. The impact of the artificial urinary sphincter in the neurogenic bladder on the upper urinary tracts. J Urol 1986;136:636-42.

733. Warwick DJ, Abrams P. The perineal artificial sphincter for acquired incontinence--a cut and dried solution? Br J Urol 1990;66:495-9.

734. O'Flynn KJ, Thomas DG. Artificial urinary sphincter insertion in congenital neuropathic bladder. Br J Urol 1991;67:155-7.

735. Aprikian A, Berardinucci G, Pike J, Kiruluta G. Experience with the AS-800 artificial urinary sphincter in myelodysplastic children. Can J Surg 1992;35:396-400.

736. Simeoni J, Guys JM, Mollard P, et al. Artificial urinary sphincter implantation for neurogenic bladder: a multi-institutional study in 107 children. Br J Urol 1996;78:287-93.

737. Ghoniem GM, Lapeyrolerie J, Sood OP, Thomas R. Tulane experience with management of urinary incontinence after placement of an artificial urinary sphincter. World J Urol 1994;12:333-6.

738. Montague DK, Angermeier KW. Postprostatectomy urinary incontinence: the case for artificial urinary sphincter implantation. Urology 2000;55:2-4.

739. Petrou SP, Elliott DS, Barrett DM. Artificial urethral sphincter for incontinence. Urology 2000;56:353-9.

740. Bosch JL. The contemporary role of the artificial urinary sphincter. Curr Opin Urol 2000;10:219-23.

741. Light JK, Reynolds JC. Impact of the new cuff design on reliability of the AS800 artificial urinary sphincter. J Urol 1992;147:609-11.

742. Leibovich BC, Barrett DM. Use of the artificial urinary sphincter in men and women. World J Urol 1997;15:316-9.

743. Marks JL, Light JK. Management of urinary incontinence after prostatectomy with the artificial urinary sphincter. J Urol 1989;142:302-4.

744. Elliott DS, Barrett DM, Gohma M, Boone TB. Does nocturnal deactivation of the artificial urinary sphincter lessen the risk of urethral atrophy? Urology 2001;57:1051-4.

745. Smith DN, Fralick R, Appell RA. Incontinence after placement of a sphincter. Urology 1997;50:974.

746. Nurse DE, Mundy AR. One hundred artificial sphincters. Br J Urol 1988;61:318-25.

747. Webster GD, Sihelnik SA. Troubleshooting the malfunctioning Scott artificial urinary sphincter. J Urol 1984;131:269-72.

748. Flynn B, Webster GD. New advances in the treatment of post-prostatectomy incontinence. Grand Rounds in Urology 2003;3:9-15.

749. Hussain M, Greenwell TJ, Venn SN, Mundy AR. The current role of the artificial urinary sphincter for the treatment of urinary incontinence. J Urol 2005;174:418-24.

750. Decter RM, Roth DR, Fishman IJ, Shabsigh R, Scott FB, Gonzales ET, Jr. Use of the AS800 device in exstrophy and epispadias. J Urol 1988;140:1202-3.

751. Motley RC, Barrett DM. Artificial urinary sphincter cuff erosion. Experience with reimplantation in 38 patients. Urology 1990;35:215-8.

752. Lai HH, Boone TB. Complex artificial urinary sphincter revision and reimplantation cases--how do they fare compared to virgin cases? J Urol 2012;187:951-5.

753. Frank I, Elliott DS, Barrett DM. Success of de novo reimplantation of the artificial genitourinary sphincter. J Urol 2000;163:1702-3.

754. Martins FE, Boyd SD. Post-operative risk factors associated with artificial urinary sphincter infection-erosion. Br J Urol 1995;75:354-8.

755. Petrou SP, Thiel DD, Elliot DS, Broderick GA, Wehle MJ, Young PR. Does indigo carmine prevent early artificial urinary sphincter cuff erosion? Can J Urol 2006;13:3195-8.

756. Lai HH, Smith CP, Teh BS, Butler EB, Boone TB. Pelvic radiotherapy does not increase the complication rates of artificial urinary sphincter implantation. Int J Radiat Oncol Biol Phys 2003;57:S273.

757. Webster GD, Sherman ND. Management of male incontinence following artificial urinary sphincter failure. Curr Opin Urol 2005;15:386-90.

758. Bartoletti R, Gacci M, Travaglini F, Sarti E, Selli C. Intravesical migration of AMS 800 artificial urinary sphincter and stone formation in a patient who underwent radical prostatectomy. Urol Int 2000;64:167-8.

759. Laungani RG, Angermeier KW, Montague DK. Giant urethral diverticulum in an adult male: a complication of the artificial urinary sphincter. J Urol 2003;170:1307-8.

760. Spiess PE, Capolicchio JP, Kiruluta G, Salle JP, Berardinucci G, Corcos J. Is an artificial sphincter the best choice for incontinent boys with Spina Bifida? Review of our long term experience with the AS-800 artificial sphincter. The Canadian journal of urology 2002;9:1486-91.

761. Lopez Pereira P, Somoza Ariba I, Martinez Urrutia MJ, Lobato Romero R, Jaureguizar Monroe E. Artificial urinary sphincter: 11-year experience in adolescents with congenital neuropathic bladder. Eur Urol 2006;50:1096-101; discussion 101.

762. Dalkin BL, Wessells H, Cui H. A national survey of urinary and health related quality of life outcomes in men with an artificial urinary sphincter for post-radical prostatectomy incontinence. J Urol 2003;169:237-9.

763. Patki P, Hamid R, Shah PJ, Craggs M. Long-term efficacy of AMS 800 artificial urinary sphincter in male patients with urodynamic stress incontinence due to spinal cord lesion. Spinal Cord 2006;44:297-300.

764. Herschorn S, Boccon-Gibod L, Bosch JL, al. e. Surgical treatment of urinary incontinence in men. In: Abrams P, Khoury S, Wein A, eds. First International Consultation on Urinary Incontinence. Plymouth, UK: Health Publication Ltd; 1999:691-729.

765. Kreder KJ, Webster GD. Evaluation and management of incontinence after implantation of the artificial urinary sphincter. Urol Clin North Am 1991;18:375-81.

766. Wahl GR. Urinary incontinence after radical prostatectomy. Semin Urol Oncol 2000;18:66-70.

767. Taylor GA, Lebowitz RL. Artificial urinary sphincters in children: radiographic evaluation. Radiology 1985;155:91-7.

768. Lorentzen T, Dorph S, Hald T. Artificial urinary sphincters. Radiographic evaluation. Acta Radiol 1987;28:63-6.

769. Barrett DM, Licht MR. Implantation of the artificial genitourinary sphincter in men and women. In: Walsh PC, Retik AB, Vaughan Jr ED, Wein AJ, eds. Campbell's Urology. 7th ed. Philadelphia: W.B. Saunders Co.; 1998:1121-34.

770. Kabalin JN. Addition of a second urethral cuff to enhance performance of the artificial urinary sphincter. J Urol 1996;156:1302-4.

771. Rahman NU, Minor TX, Deng D, Lue TF. Combined external urethral bulking and artificial urinary sphincter for urethral atrophy and stress urinary incontinence. BJU Int 2005;95:824-6.

772. Bryan DE, Mulcahy JJ, Simmons GR. Salvage procedure for infected noneroded artificial urinary sphincters. J Urol 2002;168:2464-6.

773. Magera JS, Jr., Elliott DS. Tandem transcorporal artificial urinary sphincter cuff salvage technique: surgical description and results. J Urol 2007;177:1015-9; discussion 9-20.

774. Bell BB, Mulcahy JJ. Management of cuff erosion of the double cuff artificial urinary sphincter. J Urol 2000;163:85-6.

775. Hajivassiliou CA. A review of the complications and results of implantation of the AMS artificial urinary sphincter. Eur Urol 1999;35:36-44.

776. Yamamoto T, Gotoh M, Hattori R, et al. Periurethral injection of autologous adipose-derived stem cells for the treatment of stress urinary incontinence in patients undergoing radical prostatectomy: report of two initial cases. Int J Urol 2010;17:75-82.

777. Sumino Y, Hirata Y, Hanada M, Akita Y, Sato F, Mimata H. Long-term cryopreservation of pyramidalis muscle specimens as a source of striated muscle stem cells for treatment of post-prostatectomy stress urinary incontinence. Prostate 2011.

778. Staerman F, C GL, Leon P, Leclerc Y. ZSI 375 artificial urinary sphincter for male urinary incontinence: a preliminary study. BJU Int 2012.

779. Claudon P, Spie R, Bats M, Saint F, Petit J. [Male stress urinary incontinence: medium-term results of treatment by sub-urethral bone anchored sling InVance]. Prog Urol 2011;21:625-30.

780. Purves JT, Gearhart JP. The Bladder Exstrophy-Epispadias-Cloacal Exstrophy Complex. In: Gearhart JP, Rink RC, Mouriquand PE, eds. Pediatric Urology. 2nd ed. Philadelphia, PA: Saunders; 2009:386-415.

781. Mitchell ME. Bladder exstrophy repair: complete primary repair of exstrophy. Urology 2005;65:5-8.

782. Werner M, Schmid DM, Schussler B. Efficacy of botulinum-A toxin in the treatment of detrusor overactivity incontinence: a prospective nonrandomized study. Am J Obstet Gynecol 2005;192:1735-40.

783. Mohanty NK, Nayak RL, Alam M, Arora RP. Role of botulinum toxin-A in management of refractory idiopathic detrusor overactive bladder: Single center experience. Indian journal of urology : IJU : journal of the Urological Society of India 2008;24:182-5.

784. Flynn MK, Amundsen CL, Perevich M, Liu F, Webster GD. Outcome of a randomized, double-blind, placebo controlled trial of botulinum A toxin for refractory overactive bladder. J Urol 2009;181:2608-15.

785. Lie KY, Wong MY, Ng LG. Botulinum toxin a for idiopathic detrusor overactivity. Annals of the Academy of Medicine, Singapore 2010;39:714-5.

786. Bramble FJ. The treatment of adult enuresis and urge incontinence by enterocystoplasty. Br J Urol 1982;54:693-6.

Committee 14

Surgery for Urinary Incontinence in Women

Chair

Roger Dmochowski (U.S.)

Members

Stavros Athanasiou (Greece)

Fiona Reid (U.K.)

Steven Kraus (U.S.)

Victor Nitti (U.S.)

Alex Gomelsky (U.S.)

Dudley Robinson(U.K.)

A.R.B. Smith (U.K.)

CONTENTS

A. Introduction

I. SURGERY FOR STRESS INCONTINENCE (INCLUDING COMPLICATIONS)

1. URETHRAL BULKING AGENTS
2. RETROPUBIC MID-URETHRAL SLINGS (MUS)
3. TRANSOBTURATOR MID-URETHRAL SLINGS
4. SINGLE INCISION MINI SLINGS (SIS)
5. TRADITIONAL SLING PROCEDURES
6. LAPAROSCOPIC COLPOSUSPENSION (TABLE 5)

II. STRESS INCONTINENCE AND PELVIC ORGAN PROLAPSE

1. OVERT SUI WITH POP
2. OCCULT SUI WITH POP
3. NO OVERT OR OCCULT SUI AND POP
4. UUI AND POP
5. CONCLUSIONS

III. NEUROMODULATION

1. SACRAL NEUROMODULATION
2. PERCUTANEOUS TIBIAL NERVE STIMULATION (PTNS)

IV. ENTEROCYSTOPLASTY

V. AUTO AUGMENTATION

VI. URETHRAL DIVERTICULUM

1. PREOPERATIVE STAGING
2. TREATMENT
3. RECOMMENDATIONS

VII. ARTIFICIAL URINARY SPHINCTER IN WOMEN

VIII. CONFOUNDING VARIABLES

1. INTRODUCTION
2. AGE
3. RACE
4. OBESITY
5. PSYCHIATRIC ILLNESS
6. ACTIVITY
7. PREVIOUS CONTINENCE SURGERY
8. CONCOMITANT HYSTERECTOMY
9. SEVERITY AND DURATION OF SYMPTOMS
10. DETRUSOR OVERACTIVITY AND STRESS INCONTINENCE
11. URETHRAL OCCLUSIVE FORCES
12. SURGEON'S EXPERIENCE
13. ADJUVANT OESTROGEN THERAPY

IX. CLINICAL TRIAL OUTCOMES USED IN STRESS URINARY INCONTINENCE RESEARCH

REFERENCES

Surgery for Urinary Incontinence in Women

Roger Dmochowski

Stavros Athanasiou, Fiona Reid, Steven Kraus, Victor Nitti, Alex Gomelsky, Dudley Robinson, A.R.B. Smith

A. Introduction

This chapter is intended to present a further assessment of surgical interventions for urinary incontinence in women. The intent of this chapter is to build upon data that were previously collated for the ICUD Report of 2009. This chapter updates the current status of surgical interventions for stress urinary incontinence and includes additional data that have been forthcoming regarding new interventions (such as transobturator tapes and single incision slings).

The further enhancement on sections related to clinical research and specific outcomes reporting on clinical trial design has been updated with experience from recently reported multi-institutional trials which assess surgical interventions for incontinence.

SEARCH STRATEGY

Material collected for this chapter was based on electronic searches of Medline, EMBASE, Cinhai, Cochrane Database of Systematic Reviews and the NICE website (www.nice.org.uk). Review papers were separately searched for additional references not identified by initial database search. Individual papers where then selected from April, 2008 to present in European, UK and North American journals of Urology, Gynecology, and Urogynaecology. Additionally, conference preceedings from 2008 were also reviewed inclusive of ICS, IUGA, AUA, AUGS. Hence, some more recent abstracts are included in the following reviews based upon time to press and non-identification of associated publications with those abstracts. Approximately 454 articles were identified for inclusion in addition to the original 762 which were included in the 2009 chapter. Search terms included; Urinary incontinence: stress, mixed, urge. Surgical procedures; minimally invasive, urogenital, gynaecologic, urologic, urinary tract, urethra, vagina, bladder, ligaments; colposuspension, vesicosuspension, urethrosuspension; vesicourethral or urethrovesical; colpourethrosuspension; colpofixation; Burch; Marshalls, Marchetti, Krantz; paravaginal, pubococcygeal, obturator; bladder, neck needle; ligament fixation; colporraphy; anterior or vagina; Surgical mesh; sling, bladder, surgical or synthetic, or biological or autologous; tape; urethra, suburethra, midurethra, transurethra, pubovesical; retropubic, suprapubic; pubovaginal, implant: Bologna, Ingelman, Sundberg; Prostheses: injections; bulking agents, Contigen; collagen; Macroplastique, silicones; microparticulate; hyaluronic acid; carbon particles; polytetrafluoroethylene; biocompatible materials; urinary sphincter, artificial.

Since the last review more high quality evidence is available based upon randomised controlled trials at multi-institutional programs. Level I, Level II and Level III evidence are included in the current publication. Additionally, systematic reviews where appropriate have also been included to update those referenced in the 2009 chapter. Additionally, national and international guidelines such as the National Institute for Health and Clinical Excellence (NICE) in the UK were also included where appropriate for complete summation of current status of interventions for stress urinary incontinence in women. It is to be noted that transobturator tape data are now of sufficient maturity to be included at length in addition to other midurethral data, both regarding standard retropubic as well as single incision approaches.

I. SURGERY FOR STRESS INCONTINENCE (INCLUDING COMPLICATIONS)

1. URETHRAL BULKING AGENTS

Since the last International Consultation, bovine collagen (Contigen®) has become obsolete due to manufacturing cessation. Currently available agents include; calcium hydroxyl apatite (Coaptite®), carbon coated Zirconium (Durasphere®), polydimethylsiloxane elastomer (Macroplastique®) and polyacrylamide hydrogel (Bulkamid®) . Additionally limited data has been published regarding non-animal stabilized hyaluronic acid/dextranomer NASHA-dx (Zuidex®). Recent experience has also been reported with adult stem cells for the indication of stress urinary incontinence.

Urethral bulking agents may be injected either transurethrally or periurethrally in a retrograde manner, using either ultrasonographic, direct cystoscopic or implacer-guided device implantation. Device implantation optimally occurs in the proximal urethra, either single or multiple injections with strategic planning for reinjection at some point after initial injection. Clinical trials have defined specific injection schedules (usually three injections) as part of trial therapeutic algorithms. Optimal injection technique has yet to be standardized, although it does appear that urethral mucosa visualization at procedure completion is not predictive of final outcome. Prior systematic reviews have formed the basis of NICE guidance [National Collaborative Center for Women's and Children's Health, 2006, National institute for Health and Clinical Excellence, 2006b]. Methodologic problems with most non-regulatory trials limit the ability to generalize the results of those trials to clinical experience.

Ghoniem, *et al* [2009][1] reported a randomized controlled trial of polydimethylsiloxane elastomer versus Contigen in 247 women. Repeat injection was allowed at three months after initial delivery for persistent incontinence. Efficacy was determined at one year post last injection using Stamey Grade scoring, pad weight change and quality of life assessment. 122 patients received polydimethylsiloxane elastomer. Additionally, 125 patients received Contigen. At one year post treatment, 61.5% of patients who received polydimethylsiloxane elastomer had improved by one Stamey Grade as compared to 48% of controls. The cure rate at one year was 36.9% of the Macroplastique group and 24.8% in the Contigen group, which was statistically significant. Pad weight changes (one hour pad weight) were 25.4 mL from baseline in the polydimethylsiloxane elastomer group and 28 mL in the Contigen group. Both groups had improvement in quality of life assessments (28.7% and 26.4% respectively).

Ghoniem, *et al* recently reviewed clinical outcomes associated with the use of polydimethylsiloxane elastomer as a bulking agent for stress incontinence. They identified a total of 958 patients in 23 cohorts in their review. Overall, short term (defined as less than six months) improvement rates were 75% with 64% improvement rates long-term (greater than 18 months). Cure rates were 43% at less than six months and 36% at greater than 18 months using a variety of definitions including pad weight, number of pads used and subjective reporting. The authors noted that as re-injection rates increased, there was improvement in long-term stress incontinence outcomes. Safety events associated with injection included retention, irritative voiding symptoms, dysuria, and urinary tract infection. [Ghoniem, 2012] [2]

The same study population was assessed at 24 months from last injection in subsequent publication. At that time, 67 patients in the polydimethylsiloxane elastomer arm were available for follow-up of whom 45 or 67% were continent. Of those patients who were dry at 12 months [38], 33 remained cured at 12 months. Additionally, 12 of 29 patients improved at 12 months, progressed to urinary continence at 24 months. Global quality of life scores and subscales all were statistically improved from baseline. Pad weight changes decreased from 24 grams at baseline to 4 grams at 12 and 24 months. There was no long-term complication noted in this population. [Ghoniem, 2010].[3]

Polyacrylamide hydrogel has also been reported as a potential agent for bulking. Lose, et al [2010],[4] reported on the use of polyacrylamide hydrogel in 135 women with urinary incontinence (either stress or mixed) who were followed-up for 12 months after injection. Of that group, 47 (35%) required repeat injection. At one year, overall subjective response rate was 66%. Incontinence episodes per 24 hours decreased from baseline of 3 to 0.7 at one year. Additionally, overall urine leakage by pad gram weight decreased from 29 grams at baseline to 4 grams at end of trial. Overall ICIQ demonstrated improvement in quality of life. The most frequent adverse event in this trial was urinary tract infection (10 patients).

Toozs-Hobson, et al, [2011][5] reported a two year follow-up of polyacrylamide hydrogel in 135 women. At twenty four months, 64% of patients remained responders (as compared to 67% at twelve months). Responder was defined as subjective improvement. Overall decreases in urinary incontinence episodes and volume of urine incontinence (pad weight) were stable as compared to twelve months evaluation, as were other objective outcomes and quality of life data.

Gopinath [2011][6] reported a periurethral abscess associated with the use of this agent which required surgical drainage.

Non-animal stabilized hyaluronic acid/dextranomer has been compared to bovine collagen by Lightner, et al [2009].[7] This trial utilized an implacing device for non-animal stabilized hyaluronic acid/dextranomer injection. Bovine collagen was delivered endoscopically under direct vision. This trial failed to demonstrate equivalence of non-animal stabilized hyaluronic acid/dextranomer to direct vision injected bovine collagen in all primary and secondary outcome variables. 84% of women who were injected with bovine collagen experienced a 50% reduction in urinary incontinence in provocative testing versus 65% in the non-animal stabilized hyaluronic acid/dextranomer group. Of note, non-animal stabilized hyaluronic acid/dextranomer was associated with injection site sterile abscesses in 8.4% of patients, injection site mass in 4.4% of patients and pseudo cyst formation in 2.2% of patients. Irritative voiding

symptoms and injection site pain were more common with non-animal stabilized hyaluronic acid/dextranomer than with bovine collagen.

Lightner, et al [2010][8] reported a single institutional review of 56 patients who underwent implantation with non-animal stabilized hyaluronic acid/ dextranomer. This trial included 35 women and 6 men. Of the women, 4 developed pseudo abscess formation requiring multiple operative interventions also associated with a high rate of failure amongst all women with ISD.

Mohr, et al [2012][9] reported a large series of 514 women treated with bulking therapy with either collagen, hyaluronic acid, ethylene vinyl alcohol (no longer marketed,) or polyacrylamide hydrogel. Outcomes were reported using standardized pad tests, visual analogue score for severity of incontinence and Kings Health Questionnaire. 61 patients in the entire study were lost to follow-up. Overall pad testing was negative in 73.2% of women after bulking therapy with statistical improvement in both pad weight and visual analogue score changes for each of the agents used at one year post implantation. Re-injection was permitted six weeks after initial injection in this study.

The role of bulking agents as salvage therapy for women who undergone prior mid-urethral sling procedures and were no satisfied with postoperative results was assessed by Lee, et al [2009].[10] The authors reported 23 women who had undergone mid-urethral slings who then received therapy with polydimethylsiloxane elastomer or carbon coated zirconium beads. They noted a cure rate of 34.8% at a median follow-up of ten months and improvement in secondary outcomes. Overall, 92% of patients reported benefit from therapy and the authors reported no complications.

Isolated reports of bladder masses or urethral outlet obstruction continue to emerge in the literature. Crites, et al [2010][11] reported a single case of bladder mass post bovine collagen injection which required transurethral resection for improvement of symptoms. Kumar, et al [2011][12] reported a pseudo-diverticulum of the urethra due to an encysted collagen implant.

Recently an update to the Cochrane Analysis of Urethral injection therapy has been published [Kirchin, 2012]. [13] This analysis identified 14 further trials for non-injectable agents. The Cochrane Analysis concluded there was no difference in manner of delivery (peri- versus trans-urethral injection) method, although there was a trend towards higher early complications with peri-urethral injection. Additionally, weak evidence supports mid-urethral injection resulting in improved patient satisfaction compared to bladder neck injection. The Cochrane analysis also concluded that all bulking agents appeared to provide similar overall improvements as compared to bovine collagen. Non-animal stabilized hyaluronic acid/ dextranomer appeared to be associated with higher rates of injection site complications (16% with non-animal stabilized hyaluronic acid/ dextranomer as compared to none with bovine collagen). In the few trials that have compared injection therapy with surgical management, better overall objective cure was obtained in surgical as compared to the injection groups.

The overall conclusion of the Cochrane analysis was that the evidence base remained insufficient to guide practice, specifically regarding optimal choice regarding bulking device, mechanism delivery, or identification of the optimal patient for bulking.

Research in autologous stem cell based urethral bulking continues. To date, no large scale randomized trials have been published, although, abstracts have been presented at various meetings. Durability and length of follow-up will be critical to assess the contribution of this possible bulking option. [Du,2012][14]

Recommendation

Bulking agents provide an option in the management of women with stress incontinence. Optimization of results is dependent upon repeat injections to achieve and sustain efficacy. Additionally, efficacy with at least some bulking agents appears to diminish with time and may be inferior to surgical interventions. Overall complication rates associated with bulking agents appear to be relatively low (Grade B). Continued development of new materials for injection should be under strict regulatory guidance and evaluation using RCT design construct and long-term follow-up (at least 12 months after last injection) (**Grade D**) (**Evidence level II/III**).

2. RETROPUBIC MID-URETHRAL SLINGS (MUS)

The tension-free vaginal tape (TVT) procedure for treatment of female stress urinary incontinence was first introduced by Ulmsten et al. in 1996. [15] The development of the TVT operation was an attempt to support the middle portion of the urethra, instead of restoring anatomy and correcting urethral hypermobility at the bladder neck. The idea of supporting the “mid-urethra” has been derived from the results of several research projects conducted during the last thirty years. The work of Zaccharin in 1968 and DeLancey in 1994 had already shown that the pubourethral ligaments inserted at the mid-urethra and that the urogenital diaphragm also was closer to the middle portion of the urethra than the bladder neck. [16, 17] In 1978, Owman et al. found that the most densely innervated portion of the urethra was the middle part and Huisman in 1983 showed in histological studies that the mid-urethra had the most abundant vascularisation. [18] Additionally, Westby et al. in 1982 showed in radiographic studies how the urine stream was interrupted at the mid-urethra

on holding in continent women and Asmussen et al. in 1983 showed that the maximal urethral closure pressure was situated at the midurethra.[19, 20] It quickly became apparent that focusing on the mid-urethra might bring improvement in the performance of incontinence surgery.

Prospective observational cohort studies revealed that placing a macroporous, monofilament polypropylene tape at the mid urethra resulted in cure rates between 80-90 % in primary cases of SUI [Ulmsten et al., 1996; Ulmsten et al., 1998; Nilsson, 1998; Ulmsten et al., 1999; Nilsson et al., 2001], [15, 21-24] in recurrent cases [Rezapour and Ulmsten, 2001; Kuuva and Nilsson, 2003],[25, 26] in mixed incontinence cases [Rezapour and Ulmsten, 2001], [25] and in an unselected group of women including primary, recurrent and mixed incontinence as well as women with intrinsic sphincter deficiency [Nilsson and Kuuva, 2001]. [24] Since those initial reports of success, several groups have reported long-term outcomes exceeding 5 years [Ankardal et al., 2006; Doo et al., 2006; Deffieux et al., 2007; Chene et al., 2007; Song et al., 2009] and 10 years after the TVT procedure [Nilsson et al., 2008; Olsson et al., 2010][27] [28] A variety of follow-up regimens and definitions of success reveal that the effects of the TVT on resolution of SUI are durable over the long-term.

Since the last ICI review was conducted, the literature regarding the TVT and other retropubic MUS procedures has expanded at an almost exponential pace. As an example, only 12 RCTs comparing MUS to other procedures were available for review and most of these were small (<50 patients in each arm) and underpowered. The number of RCTs and large cohort studies available today significantly exceeds the previous review, and, unless otherwise mentioned, only fully-published studies have been included herein.

a) Retropubic MUS vs. no treatment (*table 1*)

A multicentre, prospective RCT performed by Campeau et al. enrolled 69 elderly who initially consented to be randomised to either undergo immediate TVT surgery or to wait for 6 months before submitting to the same surgery (control group). [29] The main outcomes measured at every visit (pre-randomisation, 8-12 weeks and 6 months) consisted of the Incontinence-Quality of Life (I-QOL) Questionnaire, the Patient Satisfaction Questionnaire and the Urinary Problems Self-assessment Questionnaire. The analysis included 31 patients in the immediate surgery group and 27 subjects in the control group. Perioperative complications in the immediate surgery group were bladder perforation (22.6%), urinary retention (12.9%), urinary tract infection (3.2%) and *de novo* urgency (3.2%). At 6 months, the mean scores on each questionnaire were significantly in favour of the TVT group. [EL=1/2]

b) Retropubic MUS vs. open colposuspension (*table 1*)

Since the ICI-4 review, only 3 additional studies have published comparing TVT and open colposuspension [McCracken et al., 2007; Tellez Martinez-Fornes et al., 2009; Wu et al., 2010]. [30-32] In a nonrandomised trial with significant failed-to-complete-follow-up, McCracken et al. found no difference in subjective success rates via questionnaire between colposuspension and TVT at 5 to 10 years. [30] In an RCT randomising 49 women to TVT or colposuspension, Tellez Martinez-Fornes found no significant difference in subjective success rates (cured/improved) between the 2 procedures at follow-up periods of 6, 12, and 36 months. [31] In a retrospective, nonrandomised trial comparing 105 women who underwent TVT with 81 women who underwent MMK, the authors found that while the short-term success rate of the MMK was 89%, the rate fell to 68.2% at 5 years and 32% at 10 years. [32] In comparison, the short-term success rate of the TVT was statistically similar to the MMK (90%) but decreased only to 84.3% at 5 years. Women who underwent TVT also experienced shorter operative time, less blood loss, and shorter hospital stay. [EL=3/4]

Four of the studies from ICI-4 comparing TVT with open colposuspension used objective outcome measures for defining cure: 1 hour pad test [Ward et al., 2002; Liapis et al., 2002; Wang et al., 2003; Ward et al., 2004; Ward et al., 2008], [33-37]cystometry [Ward et al., 2002], [33] and a cough-stress test [Ward et al., 2002; Ward et al., 2004; Bai et al., 2005].[33, 36, 38] One study only used subjective outcome measures [El-Barky et al., 2005]. [39] None of these studies found any statistical differences in objective cure rates between the two operations. The cure rate ranged between 63 and 87 % in the TVT groups and between 51% and 90 % in the open colposuspension groups. The time period of follow-up was between 3 and 24 months in all five trials except the 5-year extension of the U.K. & Ireland TVT Trial Group [Ward et al., 2008]. [37] These 5-year outcome data are hampered by a significant lost to follow-up rate (58% in the TVT group and 67 % in the colposuspension group). The criteria of subjective cure were for the most part poorly defined and validated QOL questionnaires were only used in the 2002 study.[33] There was no difference in subjective cure between the TVT and the colposuspension groups. [EL=1/2]

As in the study by Tellez Martinez-Fornes, operative time, hospital stay and time for resuming normal activity was significantly shorter in the TVT groups [Ward et al., 2002; Liapis et al., 2002; El Barky et al., 2005].[33, 34, 39] Ward et al. [2002] found that the percentage of intraoperative bladder perforations was significantly greater in the TVT group (9%) than in the colposuspension group (3%), while El Barky et al.

Table 1: Studies comparing retropubic midurethral slings with other interventions

Author	RPMUS	Comparator	No. Patients	F/U	Power calculation	# Lost to F/U	% Cure	Significance	LE	Notes
RP MUS vs. No treatment										
Campeau, 2007* [29]	TVT	-	31/27	6m	Yes	0/20	N/A	0.0001	1	Favors TVT
RP MUS vs. Open Colposuspension (OC)										
Ward, 2002*† [[33]	TVT	OC	175/169	6m	Yes	N/A	66/57 (o)	No	1	
Ward, 2004*^† [36]				24m		19/26	63/51 (o)	No	1	
Ward, 2008*^† [37]				60m		103/120	81/90 (o) 91/90 (s)	No	1/2	>50% lost to F/U
Liapis, 2002*^† [34]	TVT	OC	36/35	24m	No	N/A	84/86 (o)	No	2	
Wang, 2003*† [35]	TVT	OC	49/49	22m	No	N/A	82/76 (o) 92/93 (s)	No	2	
Bai, 2005*^† [38]	TVT	OC	31/33	12m	No	0/0	87/87.4 (s)	No	2	
El-Barky, 2005*^† [39]	TVT	OC	25/25	3-6m	No	0/0	72/72 (s)	No	2	
McCracken, 2007 [30]	TVT	OC	40/45	1.5-3m	No	8/14	88.5/92 (s)	No	3/4	
				60-120m		17/22	77/70 (s)			
Tellez Martinez-Fornes, 2009 [31]	TVT	OC	24/25	6m	No	3/1	76.2/87.5 (s)	No	2	Success=cure + improved
				12m		1/1	78.3/87.5 (s)			
				36m		3/2	77.3/91.3 (s)			
Wu, 2010 [32]	TVT	OC	105/81	12m	No	0/0	90/89.5 (o)	-	3	No statistical comparison performed
				60m			84.3/68.2 (o)			
				120m			-/32 (o)			
RP MUS vs. Laparoscopic Colposuspension (LC)										
Persson, 2002*^† [43]	TVT	LC	28/32	12m	Yes	2/2	89/87 (o) 57/52 (s)	No	1	
Ustun, 2003*^† [166]	TVT	LC	23/23	3m	No	0/0	82.6/82.6 (o) 82.6/82.6 (s)	No	2	
Paraiso, 2004*^† [41]	TVT	LC	36/36	12m	Yes	8/6	97/81 (o)	0.056	1	Trends to TVT
Jelovsek, 2008^ [46]				12-88m (Median 65m)		74% had F/U 48-96m	52/42 (s)	No	2	Cure=no reported incontinence
Valpas, 2004*^† [47]	TVT	LC	70/51	12m	Yes	6/4	85.7/56.9 (o) 82/58 (s)	0.001	1	Favors TVT
Foote, 2006*† [44]	SPARC	LC	49/48	27m	Yes	10/10	77.4/81.4 (s)	No	2	

Table 1: Studies comparing retropubic midurethral slings with other interventions (continued)

Author	RPMUS	Comparator	No. Patients	F/U	Power calculation	# Lost to F/U	% Cure	Significance	LE	Notes
Tong, 2008 [45]	TVT	LC	67/30	9m (Mean)	No	0/0	95.5/86.5 (s)	No	3	
RP MUS vs. RP MUS										
Rechberger, 2003* [57]	TVT	IVS	50/50	4-18m	No	0/0	88/80 (s+o)	No	2	
Dietz, 2004 [56]	TVT	SPARC	69/37	1-18m	No	0/0	94.2/78.4 (o)	0.019	3	Favors TVT
Andonian, 2005* [50]	TVT	SPARC	43/41	12m	Yes	0/0	95/83 (o) IIQ (s)	No	1	
Lim, 2005* [58]	TVT	IVS/SPARC	65/65/65	1.5-3m	No	4/5/4	87.9/81.5/72.4 (o) 78.5/67.7/64.6 (o; ITT)	No	1/2	
Tseng, 2005* [52]	TVT	SPARC	31/31	24-30m (Median 25m)	Yes	0/0	87.1/80.7 (o)	No	2	0% vs. 12.9% bladder puncture (p=0.112)
Gandhi, 2006 [55]	TVT	SPARC	73/49	>1.5m (Median ~4m)	No	0/0	86/60 (s) 95/70 (o)	0.001	3	Favors TVT; short F/U
Kim, 2006 [54]	TVT	SPARC	62/62	12m	No	20/14	91.7/100 (o)	No	2/3	Satisfaction rate similar
Lord, 2006* [51]	TVT	SPARC	147/154	1.5m	Yes	0/0	97.3/97.4 (o) 87.1/76.5 (s)	No 0.03	1	Short F/U Favors TVT
Meschia, 2006* [59]	TVT	IVS	95/95	24m	Yes	3/8	85/72 (o) 87/78 (s)	No	1	
Yoon, 2007 [65]	TVT	IRIS	32/34	12m 36m	No	0/0	96.9/88.2 (s+o) 90.6/85.3 (s+o)	No	2/3	
Agarwala, 2008 [64]	TVT	Lynx	48/48	-	No	0/0	94/92 (s) 96/94 (o)	No	2	Consecutively assigned to sling
Paick, 2008 [53]	TVT	SPARC	72/22	6m	No	0/0	95.8/90 (s+o; SUI) 81.9/86.4 (s+o; MUI)	No	3/4	
Prien-Larsen, [60]	TVT	IVS	103/213	3m 12m 60m	No		98/86 (o) 82/79 (s) 95/86 (o) 79/81 (s) 94/80 (o) 74/71 (s)	<0.03 (o) No (s)	3	Objective cure favors TVT; 0% vs. 11.8% vaginal extrusion

**: Included in ICI-4*
^: Included in Systematic Review (Novara, 2010)
†: Included in Cochrane Review (Ogah, 2011)

Key: RP MUS=retropubic midurethral sling; F/U=follow-up (months); LE=level of evidence; TVT=tension-free vaginal tape; o=objective; s=subjective; N/A=not available; OC=open colposuspension; LC=laparoscopic colposuspension; ITT=intention to treat

reported no perforations in the colposuspension group and two in the TVT group ($p< 0.05$). [33, 37] Wound infections were more common in the colposuspension group ($p<0.05$). Significantly more patients experienced delayed voiding in the colposuspension group in the Ward et al. [2002] study and in the 2 years follow-up report of the same study there were significantly more patients in the colposuspension group needing intermittent self catheterisation ($p<0.0045$) and surgery for pelvic organ prolapse ($p<0.0042$). [33, 36] [EL=1/2]

The Cochrane review comparing the outcomes of minimally-invasive suburethral sling operations with open colposuspension included 9 trials, and included 5 of the trials mentioned above [Ward et al., 2002; Liapis et al., 2002; Wang et al., 2003; Bai et al., 2005; El Barky et al., 2005].[40] The remainder of the studies were either in abstract form or provided a comparison between transobturator MUS and colposuspension. A total of 729 women studied within the first 12 months after surgery showed subjective cure rates of 79% with MUS and 82% after open colposuspension. This difference was not statistically significant (RR 096, 95% CI 0.90 to 1.03). In 2 trials [including Ward et al., 2004] follow-up at 2 years also failed to show a statistically significant difference (RR 1.11, 95% CI 0.91 to 1.34). In the 3 trials evaluating objective cure rates [including Liapis et al., 2002, and Wang et al., 2003], there was no significant difference at 12 months (RR 1.04, 95% CI 0.94 to 1.14), after 2 years (RR 1.01, 95% CI 0.92 to 1.11) and after 5 years (RR 0.90, 95% CI 0.77 to 1.04). [EL=1/2]

A limitation to the conclusions that can be drawn from the aforementioned study results is the fact that most of the trials include fewer than 50 patients in each arm and lacked any mention of power calculations. The trials by Ward et al. enrolled a greater number of patients and included power calculations, but did not reach the required number of patients. [33, 36, 37]

*c) Retropubic MUS vs. laparoscopic colposuspension (***table 1***)*

Four of the 12 RCTs in ICI-4 comparing retropubic MUS with traditional incontinence procedures compare TVT with laparoscopic colposuspension [Persson et al., 2000; Ustun et al., 2003; Paraiso et al., 2004; Valpas et al., 2004]. [41] [40] [39] [38] [37] [36] [35] [34] [33] [32] [31] [30] [29] [28] [27] [26] [42, 43] Two additional trials have been published since that review [Foote et al., 2006; Tong et al., 2008] as well as an update of the Paraiso et al. study [Jelovsek et al., 2008]. [44-46] The Cochrane review included 5 fully-published manuscripts [Persson et al., 2000; Ustun et al., 2003; Paraiso et al., 2004; Valpas et al., 2004; Foote et al., 2006] along with 2 abstracts. [40]

In the studies comparing TVT or Supra Pubic Arc Sling (SPARC; a monofilament polypropylene MUS placed through a top-down approach) with laparoscopic colposuspension objective cure was assessed by a pad test in 2 of the 6 studies [Persson et al., 2000; Valpas et al., 2004], [43, 47] and by a cough-stress test in 3 of the studies [Ustun et al., 2003; Paraiso et al., 2004; Valpas et al., 2004]. [41, 42, 47] The criteria for cure or improvement were unclear in the study by Foote et al. [44]. The trial by Valpas et al. with the greatest number of patients enrolled showed a significantly higher objective and subjective cure rate in the TVT group than in the laparoscopic colposuspension group ($p<0.0001$), [47] while the other studies showed similar cure rates for both procedures ranging between 72.9% and 96.8% in the TVT groups and between 58.8% and 87% in the laparoscopic colposuspension groups. It was thought that the Valpas et al. trial may have shown a significant difference in outcomes in favour of TVT due to a difference in laparoscopic technique (using mesh rather than sutures to perform colposuspension). [40] In their trial, Paraiso et al. performed postoperative multichannel urodynamic studies in 32 laparoscopic Burch colposuspension and 31 TVT patients showed a higher rate of urodynamic stress incontinence at 1 year in the laparoscopic Burch colposuspension group, 18.8% versus 3.2% ($p=0.056$).[41] There was a significant improvement in the number of incontinent episodes per week and in UDI and IIQ scores in both groups at 1 and 2 years after surgery ($p<0.001$). However, postoperative subjective symptoms of incontinence (stress, urge, and any urinary incontinence) were reported significantly more often in the laparoscopic Burch colposuspension group than in the TVT group ($p<0.04$ for each category). At long-term follow-up of the previous study, Jelovsek et al. confirmed that the TVT has similar efficacy to the laparoscopic Burch for the treatment of SUI. [100] While not always bothersome, the authors cited a substantial number of women in either group who had some degree of incontinence 4 to 8 years after surgery. Although laparoscopically-performed colposuspension is regarded as a less-invasive operation than the open colposuspension the MUS procedures had significantly shorter operating time, hospital stay, and time for resuming normal activity than the laparoscopic colposuspension. [40] [EL=2]

As with the studies comparing open colposuspension with MUS, the conclusions of studies comparing MUS with laparoscopic colposuspension may be limited due to underpowering. Dean et al. performed a systematic review of laparoscopic colposuspension (n=264) and TVT (n=290) which included 7 trials. [101] There was no statistically significant difference in the reported subjective cure rate between laparoscopic colposuspension and TVT within 18 months (RR 1.12, 95% CI 0.98 to 1.29). However, within the same time period, the overall objective cure rate was statistically significantly higher for TVT (RR 1.16, 95% CI 1.07 to 1.25). There were no significant differences be-

tween the two procedures with regards to perioperative complications, *de novo* detrusor overactivity, voiding dysfunction, procedural costs and QoL scores. The authors confirmed that the TVT procedure was quicker to perform and was associated with a shorter hospital stay. [EL=1/2]

A systematic review by Novara et al. evaluated open and laparoscopic colposuspensions together with retropubic MUS. [48] Women receiving MUS had significantly higher overall (OR 0.61; 95% CI 0.46 to 0.82, p=0.00009) and objective (OR 0.38; 95% CI 0.25 to 0.57, p<0.0001) cure rates than those receiving colposuspension. A clinical and economic subanalysis of the Valpas et al. study suggested that over a follow-up period of 1 year the TVT is more cost-effective than laparoscopic mesh colposuspension as a primary treatment for female SUI. [103] [49][EL=1/2]

d) Retropubic MUS vs. traditional sling

This comparison will be addressed in the section on traditional pubovaginal slings.

e) Retropubic MUS vs. retropubic MUS (*table1*)

The favorable results obtained with the TVT operation have resulted in several modifications of the procedure and the use of different tape materials. These retropubic modifications have been poorly clinically evaluated and only 6 randomised studies comparing these with the TVT have been published. The meta-analysis by Novara et al. did not evaluate the comparison between different types of retropubic MUS procedures. [48] In ICI-4, 3 RCTs compare the TVT with the SPARC [Andonian et al., 2005; Tseng et al., 2005; Lord et al., 2006]. [50-52] The study by Lord et al. included 147 TVT and 154 SPARC cases and showed no statistical difference in estimated blood loss of >100 mL (TVT, 21.8% vs. SPARC, 18.2%), *de novo* urgency (TVT, 40.5% vs. SPARC, 42.4%), objective cure (TVT, 97.3% vs. SPARC, 97.4%) or vaginal mesh extrusion (TVT, 4.8% vs. SPARC, 10.5%). [51] Acute urinary retention (TVT, 0% vs. SPARC 6.5%; OR ∞, 95% CI 2.2-∞; p=0.002) and subjective cure (TVT 87.1% vs. SPARC 76.5%; OR 2.07, 95% CI 1.13-3.81; p=0.03) were statistically significantly different. Tseng et al. reported a 12.9 % of bladder perforation in the SPARC group with none in the TVT group. [52] While the difference did not reach statistical significance in this small study (31 patients in each group), the authors felt it to be clinically significant. [EL=1/2]

Four additional non-randomised studies compared TVT with SPARC [Dietz et al., 2004; Gandhi et al., 2006; Kim et al., 2006; Paick et al., 2008].[53-56] In the Dietz et al. study, there were no significant differences for subjective cure/improvement, patient satisfaction, or symptoms of incontinence. [56] The cough-stress test was positive in 8 of 37 women who underwent SPARC compared to 4 of 69 TVT patients (p=0.019). The TVT had a more negative effect (p=0.001) on postoperative voiding. In the Gandhi et al. study, 107 of 122 women returned for objective postoperative evaluation after surgery. [55] The TVT procedure was associated with higher subjective (86% vs. 60%, p=0.001) and objective (95% vs. 70%, p<0.001) SUI cure rates, while there was no difference between the TVT and SPARC groups in the resolution of subjective and objective UUI. Kim et al. found no difference in objective cure rates at 1 year of follow-up and complication rates were similarly low. [54] Paick et al. found no significant difference in cure of SUI or cure of all incontinence between TVT and SPARC at 6 months. [53] [EL=3/4]

In ICI-4, 3 RCTs compared TVT with the intravaginal slingplasty (IVS) procedure, which utilises a multifilament, miniporous polypropylene tape material [Rechberger et al., 2003; Lim et al., 2005; Meschia et al., 2006]. [57-59] Only the study by Lim et al. was included in the Cochrane analysis. [40] In the study by Meschia et al. that included 95 patients in each group, the objective cure rate was 85% for the TVT and 72% for the IVS and the subjective cure rate was 87% and 78%, respectively, with no difference between groups. [58] There was a 9% vaginal extrusion rate during the 2 years of follow-up in the IVS group, and 0% extrusion in the TVT group. Rechberger et al. found no significant difference in cure rates between the groups at a mean of 13 months of follow-up.[57] Lim et al. compared TVT with both IVS and SPARC, with 65 patients in each group. [58] The subjective cure rates between 6 and 12 weeks of follow-up were 87.9% in the TVT group, 81.5% in the IVS group and 72.4% in the SPARC group, the differences not being significant. Interestingly, the authors found a significantly greater rate of tape extrusion in the SPARC group compared to both TVT and IVS (p<0.04). An additional retrospective study found a significant difference in favour of TVT in objective SUI cure rate at 3, 12, and 60 months compared with IVS, while the subjective cure rates did not differ significantly at any of those time intervals (Prien-Larsen & Hemmingsen, 2009]. [60] Vaginal extrusions were found in 11.8% of the women in the IVS group compared with 0% in the TVT group. [EL=1/2]

Most concerning is the report by Balakrishnan et al. in which they followed the subgroup of IVS patients of the Lim et al. study for up to 30 months and found that 13% had sling extrusions requiring sling removal. [61] Additionally, of the 29 patients (47%) of the initial IVS group who were seen 12 to 34 months post-operatively, 24% experienced sling erosion with sinus formation requiring sling removal. Further infectious complications, like retropubic abscess and pyogenic granuloma associated with

vaginal extrusion, indicate that the IVS may behave clinically like microporous synthetic materials rather than other polypropylene slings.[62, 63] [EL=3/4]

Two additional studies compared TVT against other retropubic midurethral MUS procedures. Agarwala found no difference in subjective (94% vs. 92%) and objective (96% vs. 94%) cure rates in 96 women consecutively assigned to TVT or to Lynx mid-urethral sling (Boston Scientific; monofilament polypropylene), respectively. [64] Yoon et al. compared TVT to the IRIS (innovative replacement of incontinence surgery) with a follow-up of 3 years. [65] The instrument of the IRIS system is comprised of a nondisposable metal handle to which two metal needles can be attached. The needles have an outer diameter of 5-6 mm and the non-absorbable polypropylene tape, which is 11 mm wide and 450 mm long with a plastic sheath cover, is fixed to the needles. The tape of the IRIS system is polypropylene monofilament mesh (Trelex; Meadox Medicals, Oakland, NJ/Boston Scientific, NJ, U.S.A.), and the diameter of the pore size is greater than 75 µm such as the tape of TVT. Success rate encompassing both objective and subjective criteria were not statistically different between the 2 procedures at 12 and 36 months. Likewise, the incidence of perioperative complications and postoperative voiding dysfunction was not statistically different. [EL=3]

The Cochrane review encompassing 4 aforementioned RCTs [Andonian et al., 2005; Lim et al., 2005; Tseng et al., 2005; Lord et al., 2006] and an abstract, found that, in 492 women studied within the first 12 months after surgery, women were significantly more often subjectively dry with the TVT than SPARC (85% vs. 77%; RR 1.10, 95% CI 1.01 to 1.20). [40] In a total of 636 participants, women were statistically significantly more likely to be objectively cured with the TVT than SPARC or IVS (92% vs. 87%; RR 1.06, 95% CI 1.01 to 1.11). There were significantly fewer women experiencing bladder punctures during trocar passage after TVT compared with SPARC (4.7% vs. 8.5%; RR 0.55, 95% CI 0.31 to 0.98), as well as fewer vaginal extrusions (RR 0.27, 95% CI 0.08 to 0.95). No statistically significant difference was seen in overall perioperative complications, but the confidence interval was wide (RR 0.98, 95% CI 0.53 to 1.84). There were no statistically significant differences between the 2 groups with respect to postoperative *de novo* urgency symptoms and UUI, as well as urodynamic detrusor overactivity. Finally, there were no statistical differences in QoL indices between the 2 procedure groups. [EL=1/2]

The Cochrane review also evaluated 3 of the aforementioned RCTs [Rechberger et al., 2003; Lim et al., 2005; Meschia et al., 2006] that compared TVT to IVS.[40] At 12 months, the higher subjective cure rates seen with TVT did not reach statistical significance (83% vs. 77%; RR 1.08, 95% CI 0.98 to 1.19). Objective cure for the TVT was significantly higher than for the IVS (83% vs. 72%; RR 1.15, 95% CI 1.02 to 1.30). There were few perioperative complications and the combined results from 2 small trials did not show a statistically significant difference (RR 1.16, 95% CI 0.36 to 3.69). However, the confidence intervals were wide. There were no statistically significant differences in the rates of *de novo* urgency symptoms and UUI, detrusor overactivity, and postoperative voiding dysfunction. [EL=1/2]

***f) Retropubic MUS vs. transobturator mus* (table 2)**

A unique complication of the retropubic MUS procedures has been inadvertent puncture of retropubic and, on occasion, intra-abdominal viscera or neurovascular structures. The most common organ punctured is the bladder and the rates of puncture have varied between 0.8% and 21 % in different reports [Wang et al., 2004; Andonian et al., 2005]. [50, 66] Two systematic registries on the rates of complications associated with the TVT operation have been published, one from Finland including the first 1455 operations performed nation-wide and one from Austria including 2795 operations [Kuuva and Nilsson, 2002; Tamussino et al., 2001]. [26, 67] The rates of bladder perforation were 3.8% and 2.7%, respectively. In an effort to minimise the incidence and morbidity of bladder injuries, Delorme in 2001 introduced a modified tape procedure in which the tape was brought to support the mid-urethra from inside the thighs through the obturator foramina on both sides.[68] De Leval further modified the outside-in transobturator tape procedure (TOT) procedure to be an inside-out procedure, now called the tension-free vaginal tape-obturator (TVT-O). [69]

The comparison between the retropubic and transobturator MUS procedure has become the most-documented topic in sling surgery over the last 5 years. ICI-4 reported on a total of 9 RCTs comparing RP with TO midurethral slings. TVT was compared with the inside-out TVT-O in 6 randomized trials [Liapis et al., 2006; Laurikainen et al., 2007; Meschia et al., 2007; Zullo et al., 2007; Araco et al., 2008; Rinne et al., 2008], [70-75] and with the outside-in TOT in 2 trials [Andonian et al., 2007; Porena et al., 2007]. [76, 77] Wang et al. compared the TOT with SPARC and found no difference in cure rate or rates of complications between the group of 31 TOT patients and 29 SPARC patients.[78]

The studies evaluated in ICI-4 were quite heterogeneous. Five of the studies comparing TVT with TVT-O included power calculations either for detection of differences in cure rates and complication rates [Meschia et al., 2006; Laurikainen et al., 2007; Rinne et al., 2008], [70, 71, 75] or only for detection of differences in complications [73]. The study by Liapis et al. reported no power calculations. [70] No differences in the overall objective or subjective cure rates were seen between the TVT and the TVT-O procedures

Table 2: Studies comparing retropubic midurethral slings with transobturator midurethral slings

Author	RP MUS	Comparator	No. Patients	F/U	Power calculation	# Lost to F/U	% Cure	Significance	LE	Notes
RP MUS vs. TO MUS										
Ansquer, 2004 [100]	TVT	TOT?	25/24	1m	No	0/0	80/83 (s)	No	3/4	
Mellier, 2004 [101]	TVT	Monarc	90/85	6w	No	0/0	91/95 (s)	No	3	
Enzelsberger, 2005^† [80]	TVT	TOT	52/53	12m	No	0/0	86/84 (o)	No	1/2	
Kim, 2005^† [81]	Sparc	Monarc	22/21	6m	No	0/0	81.8/80.9 (s+o)	No	2	
Wang A, 2006*^† [78]	Sparc	Monarc	31/31	6-14m (Median 9m)	Yes	2/0	Significant improvement in pad weight for both	No	2	Cure rate never mentioned
Liapis, 2006*^† [79]	TVT	TVT-O	46/43	12m	No	0/0	89/90 (o) 73.9/76.7 (s)	No	1/2	
Morey, 2006 [102]	TVT, Sparc	Monarc, ObTape	350/154	6m	No	0/0	85.6/89.4 (o)	No	3	
Andonian, 2007^† [76]	TVT	TOT	80/78	12m	Yes	0/0	86/83 (o)	No	1	
Darai, 2007†[82]	I-Stop	I-Stop	42/46	3m 6-12m	Yes	0/0	90.5/89.1 (s+o) 88.5/86.5 (s+o)	No	2	
Falkert, 2007 [103]	TVT	TOT	56/49	12m	No	0/0	90/96 (o)	No	3	
Laurikainen, 2007*^ [70]Rinne, 2008*^† [[75]Palva, 2010 [91]	TVT	TVT-O	136/131	2m 12m 36m	Yes	0/0 2/0 5/5	98.5/95.4 (o) 95.5/93.1 (o) 90/93 (s) 94.6/89.5 (o)	No	1	ITT analysis not significantly different
Lee, 2007† [83]	TVT	TVT-O	60/60	12m	No	0/0	86.8/86.8 (s+o)	No	2	Quasi-RCT (alternation)
Meschia, 2007*^† [71]	TVT	TVT-O	114/117	6m (Median)	Yes	6/7	92/89 (o) 92/87 (s)	No	1	
Neuman, 2007 [104]	TVT	TVT-O	75/75	6m	No	0/0	97.3/98.7 (s)	No	3	
Paick, 2007 [105]	TVT	TOT	252/212	6m	Yes	0/0	92.1/84.9 (s+o)	0.015	2	Favors TVT
Porena, 2007*^† [77]	TVT	ObTape	73/75	12m	Yes	3/0	71.4/77.3 (o)	No	1	
Sola, 2007 [106]	TVT	TVT-O	76/98	3m	No	0/0	96/100 (s)	No	3	~80% each group additional surgery
Zhu, 2007^† [84]	TVT	TVT-O	28/27	22m	No	0/0	92.6/92.9 (s)	No	2	All had concomitant prolapse surgery
Zullo, 2007*^† [73]	TVT	TVT-O	35/37	12m	Yes	0/0	91/89 (o)	No	1/2	

Table 2: Studies comparing retropubic midurethral slings with transobturator midurethral slings (continued)

Author	RP MUS	Comparator	No. Patients	F/U	Power calculation	# Lost to F/U	% Cure	Significance	LE	Notes
Araco, 2008*^† [74]	TVT	TVT-O	120/120	12m	Yes	12/20	100/66 (o) (severe SUI) 100/100 (o) (mild SUI)	0.001 No	1	Favors TVT for severe SUI
Barber, 2008^† [97]	TVT	Monarc	88/82	12m	Yes	2/6	58.8/62.3 (s)	0.006	1	Monarc not inferior to TVT
Barry, 2008^† [86]	TVT	Monarc	107/80	3m	Yes	25/22	86.6/72.4 (s) 79.3/84.5 (o)	No	1/2	Short F/U
Charalambous, 2008 [107]	TVT	TVT-O	265/50	12m	No	0/0	87/94 (not stated)	No	3	
Jeon, 2008 [108]	TVT	Iris	61/60	3m 6m 12m	No	0/0	96.7/95 (s+o) 90.2/91.7 (s+o) 88.5/88.3 (s+o)	No	3	
Long, 2008 [109]	TVT	TVT-O	53/29	36m/14m	No	0/0	92.5/79.3 (s) 94.3/86.2 (o)	No	3/4	
Paick, 2008[53]	TVT	TOT	72/50	6m	No	0/0	95.8/94 (SUI) 81.9/82 (all incontinence)	No	3/4	
Paick, 2008 [53]	Sparc	TOT	22/50	6m	No	0/0	90/94 (SUI) 86.4/82 (all incontinence)	No	3/4	
Schierlitz, 2008^† [87]	TVT	Monarc	82/82	6m	Yes	15/11	79/55 (o)	0.004	1	Favors TVT; all women w/ISD
Wang W, 2008 [110]	TVT	TVT-O	35/34	14.5m (Mean)	No	0/0	88.6/85.3 (s)	No	2	
Aniuliene, 2009^ [93]	TVT	TVT-O	114/150	12m	No	0/0	94.6/94.6 (s)	No	2	Vague criteria for “effectiveness”
Gungorduk, 2009 [111]	TVT	Safyre-t	180/120	12m 48m	No	0/0 -	93.9/82.5 (s+o) 78.3/52.5 (s+o)	0.0002 0.0001	3	Favors TVT
Houwert, 2009 [112]	TVT	TVT-O Monarc	214/173	12m	Yes	0/0	82/75 (s)	No	2/3	
Hsiao, 2009 [167]	TVT	Monarc	61/60	12m	No	0/0	82/78.3 (s+o)	No	3	
Karateke, 2009^ [94]	TVT	TVT-O	81/83	12-16m	Yes	2/1	88.9/86.7 (s+o)	No	1	
Rapp, 2009 [113]	Sparc	Monarc	107/43	12m	No	10/4	29/41 (s; dry) 76/77 (s; success)	No	3	
Rechberger, 2009^ [88](Rechberger, 2007† abstract only)	IVS-02	IVS-04	269/268	18m	Yes	68/71	75.1/74.1 (s)	No	1	
Reich, 2009 [114]	TVT	TVT-O	120/120	3m	No	0/0	85/77 (s+o)	No	2/3	
Ross, 2009^ [168]	TVT	Obtryx	105/94	12m	Yes	18/10	77/81 (o)	No	1	TOT palpable in 80% (vs. 27% TVT group)

Table 2: Studies comparing retropubic midurethral slings with transobturator midurethral slings (continued)

Author	RP MUS	Comparator	No. Patients	F/U	Power calculation	# Lost to F/U	% Cure	Significance	LE	Notes
Wang W, 2009^ [95] Wang W, 2011 [96]	TVT	TVT-O	160/155	6m 12m 24m 36m	No	6/9 45/37 82/68 125/125	93.5/91.1 (o) 89.6/89.8 (o) 87.2/86.2 (o) 82.9/83.3 (o)	No	1/2	
Castillo-Pino, 2010 [115]	TVT	Safyre-t	55/49	12m 24m	No	0/0	74.5/77.6 (o) 81.8/83.7 (s+o)	No	3	
Deffieux, 2010; [89](Deffieux, 2007^† abstract only)[169]	TVT	TVT-O	75/74	6m 12m 24m	Yes	3/3 6/5 8/9	88/91 (s+o) 89/88 (s+o) 83/83 (s+o)	No	1	
Duckett, 2010 [116]	TVT	TOT	34/34	6w/6m/ 12m	No	0/0	100/70.6 (no repeat surgery)	Yes	3	All had DO; OR 10.1, 95% CI 2.6 to 38.2 for TOT to have additional surgery
George, 2010 [117]	TVT	Uretex-TO	76/73	24m	No	0/0	97.3/94.5 (s+o)	No	3	
Krofta, 2010^ [92]	TVT	TVT-O	141/147	12m	No	0/0	90.1/88.4 (o) 84.7/80.9 (s)	No	1	
Richter, 2010 [170]	TVT	TVT-O Monarc	298/299	12m	Yes	17/15	80.8/77.7 (o) 62.2/55.8 (s)	No	1	Per protocol analysis
Tanuri, 2010 [118]	Safyre-rp	Safyre-t	10/20	12m	No	1/1	88.8/84.2 (o) 88.8/85 (s)	No	2	
Wang F, 2010^ [99]	TVT	TOT	70/70	12m	No	0/0	90/91.4 (s) 92.8/91.4 (o)	No	1/2	
Teo, 2011 [90] (Teo, 2007^† abstract only)	TVT	TVT-O	66/61	6m 12m	Yes	7/8 25/32	78/83 (o) 81.4/77.4 (s) 80.5/86.2 (o) 85.4/89.7 (s)	No	1	ITT analysis NS at both F/U intervals; trial stopped early (leg pain w/TVT-O)

**: Included in ICI-4*
^: Included in Systematic Review (Novara, 2010)
†: Included in Cochrane Review (Ogah, 2011)

Key: RP=retropubic; MUS=midurethral sling; F/U=follow-up; LE=level of evidence; TVT=tension-free vaginal tape; TOT=transobturator tape; m=months; s=subjective; o=objective; TVT-O=tension-free vaginal tape obturator; ITT=intention to treat; RCT=randomized controlled trial; SUI=stress urinary incontinence; ISD=intrinsic sphincter deficiency; IVS=intravaginal slingplasty; DO=detrusor overactivity; OR=odds ratio; CI=confidence interval; NS=not significant.

during follow-up periods of 6 to 12 months. The only statistically significant difference in objective cure rate was seen in the Araco et al. report where stratification between mild and severe stress incontinence had been made.[74] They found a significantly higher cure rate in the TVT patients with severe SUI than in the TVT-O patients with the same condition: 100% versus 66 % cure respectively (p<0.001). [EL=1/2]

The trials presented contradictory results concerning postoperative complications. The reports by Meschia et al. [71] and Laurikainen et al., [70] including 3-4 times more patients than the reports by Zullo et al. [73] and Liapis et al. [79] show either no differences in the overall number of complications or a significantly higher rate of overall complications in the TVT-O group (Laurikainen et al.). It is not clear from the Zullo et al. study, which showed a higher complication rate for the TVT, how the overall complication rate was calculated. The two trials comparing TVT with TOT [Andonian et al., 2007; Porena et al., 2007] found no difference in cure rates between the procedures. [76, 77] There were no differences in complication rates between the procedures in the Porena et al. study, while Andonian et al. reported significantly greater rates of complications in the TOT than in the TVT group. [EL=1/2]

As an example of the continued and exponentially-increasing interest in these procedures, the Cochrane systematic review evaluated 16 fully-published RCTs and 7 additional meeting abstracts. [40] The published studies included the following: Enzelsberger et al., 2005; Kim et al., 2005; Wang A et al., 2006; Liapis et al., 2006; Andonian et al., 2007; Darai et al., 2007; Lee et al., 2007; Meschia et al., 2007; Porena et al., 2007; Zhu et al., 2007; Zullo et al., 2007; Araco et al., 2008; Barber et al., 2008; Barry et al, 2008; Rinne et al., 2008; Schierlitz et al., 2008. [71, 73-87]. Three of the abstracts included in the Cochrane review have since been published as full manuscripts [Rechberger et al., 2009; Deffieux et al., 2010; Teo et al., 2011],[88-90] while the population in the study by Rinne et al. has recently been updated with long-term outcomes. [91]

The Cochrane review reported subjective cure within 12 months in 10 trials with a total of 1281 participants. [43] Assessment of cure was self-reported by participants and by responses to symptom based questionnaires. The combined results from the 10 trials showed no statistically significant difference in the subjective cure rates between the RP and TO routes (RR 1.00, 95% CI 0.96 to 1.05). Subjective cure rate in each group was approximately 83%. In this instance, the confidence interval is narrow and may not include a clinically significant difference. The confidence interval is compatible with the cure rate for the transobturator route being 6% better, or being 3% better for the retropubic route. [EL=1/2]

Objective cure was assessed by 17 studies with 2434 participants using a variety of measures such as urodynamic assessment, negative cough-stress test, 1-hour pad test of ≤ 2 g, 1-hour pad test of ≤ 1 g, and 24-hour pad test of ≤ 5 g. [40] The cure rate using the obturator route was significantly lower at 84% versus 88% for the retropubic route (RR 0.96, 95% CI 0.93 to 0.99). However, the confidence interval was narrow and the difference between the groups (4%) may not represent a clinically significant difference in the short term. There was no significant difference in women whose improvement and cure rates were demonstrated objectively (RR 0.96, 95% CI 0.91 to 1.02). [EL=1/2]

In 14 trials, there were no statistically significant differences in the rates of tape erosions (RR 1.58, 95% CI 0.83 to 3.00) or, in 5 trials, the need for repeat incontinence surgery (RR 1.52, 95% CI 0.90 to 2.59). [40] However, once again, the confidence intervals in both cases could include a clinically significant difference favouring the RP approach. There was significantly higher occurrence of groin pain (12%) in women with a TO approach compared with suprapubic pain in women with a retropubic sling (1.7%, RR 6, 95% CI 3 to 11). There was no statistically significant difference between the groups in terms of detrusor overactivity (RR 1.22, 95% CI 0.56 to 2.63) in 3 trials, or *de novo* urgency and urgency incontinence (7% with the TO route versus 6% via the RP route (RR 1.08, 95% CI 0.75 to 1.56) in 14 trials, but the confidence intervals were wide because these were relatively rare events and clinically significant differences could not be ruled out. However, postoperative voiding dysfunction occurred significantly less frequently in the TO route group (4% versus 7%, RR 0.63, 95% CI 0.44 to 0.89). [EL=1/2]

The systematic review by Novara et al. included 13 RCTs that compared classic TVT with inside-out TOT: TVT-O in 10 studies [71-75, 84, 89, 90, 92-96] and a less invasive free tape in a single study [Naumann et al., 2006 (abstract only)].[48] Nine studies compared TVT to outside-in TOT: ObTape in 3 studies, [76, 77, 80] Monarc in 4 studies, [86, 87, 97], Freeman et al., 2008 (abstract only)] Iris-TOT in a single study, [Kim et al., 2004 (abstract only)] and Obtryx in a single study. [98] The implanted devices were not specified in a single study.[99] A single trial compared TVT to both TVT-O and Monarc, [Scheiner et al., 2009 (abstract only)] a single trial compared retropubic IVS to outside-in IVS, [142], and 2 trials compared SPARC sling to Monarc.[78, 81]

Overall (OR: 1.02; 95% CI OR: 0.78 to 1.33; p = 0.90), and subjective (OR: 0.97; 95% CI OR: 0.75 to 1.24; p = 0.80) continence rates were overlapping in the two procedures. [48] Among the studies providing subjective outcomes using validated questionnaires, postoperative UDI-6 (WMD: 0.07; 95% CI: -0.39 to 0.53; p = 0.76) and IIQ-7 (WMD: 0.01; 95% CI: -0.22 to 0.24; p = 0.95) scores were

similar. Notably, retropubic MUS were followed by significantly higher objective continence rates (OR: 0.80; 95% CI OR: 0.65 to 0.99; p = 0.04). Moreover, a statistically significant difference in favour of TVT was shown when comparing objective continence rates between TVT and inside-out TOT (OR: 0.71; 95% CI OR: 0.52 to 0.96; p = 0.03), whereas no difference was found comparing TVT to outside-in TOT (OR: 0.90; 95% CI OR: 0.66to 1.22; p = 0.51). Sensitivity analyses limited to studies of higher methodological quality showed only a nonstatistically significant trend in favour of TVT with regard to objective cure rate (OR: 0.74; 95% CI OR: 0.54 to 1.01; p = 0.05). No differences in subjective and overall continence rates were found in the other sensitivity analyses. [EL=1/2]

With regard to complications, bladder or vaginal perforations (OR: 2.5; 95% CI OR: 1.75 to 3.57; p < 0.0001) were significantly more common following retropubic MUS, without any significant difference between inside-out and outside-in TOT.[48] Again, as expected, the prevalence of postoperative haematoma was significantly more common following placement of retropubic MUS (OR: 2.62; 95% CI OR: 1.35to 5.08; p = 0.005). In fact, the rates of vaginal extrusion were slightly higher following TOT (OR: 0.64; 95% CI OR: 0.41to 0.97; p = 0.04), due to the studies using ObTape, a device removed from the market due to a high risk of erosion and extrusion. Finally, the risk of urinary tract infections (OR: 0.95; 95% CI OR: 0.69 to 1.31; p = 0.74), the need for clean intermittent catheterisation or re-catheterization (OR: 1.16; 95% CI OR: 0.84 to 1.59; p = 0.37), and the reoperation rate (OR: 1.1; 95% CI OR: 0.75 to 1.59; p = 0.62) were not significantly different between retropubic and transobturator MUS. Interestingly, the prevalence of storage LUTS was significantly higher in those patients randomised to RT (OR: 1.35; 95% CI OR: 1.05to 1.72; p = 0.02), without any significant difference between inside-out and outside-in TOT. A nonstatistically significant difference in favour of TOT was found for voiding LUTS (OR: 1.56; 95% CI OR: 0.97 to 2.5; p = 0.07). In sensitivity analyses limited to studies of higher methodological quality, only a nonstatistically significant trend in favour of TOT was found for storage LUTS (OR: 1.44; 95% CI OR: 0.99 to 2.09; p = 0.06) and voiding LUTS (OR: 1.59; 95% CI OR: 0.85 to 2.97; p = 0.15). Similarly, with regard to the risk of all the other complications and reoperation, no differences were identified in the other sensitivity analyses. [EL=1/2]

The largest RCT to date comparing retropubic and transobturator MUS was recently published by Richter et al.[37] This was a multicentre, randomised equivalence trial with the primary outcome being objective (a negative stress test, a negative pad test, and no retreatment) and subjective (self-reported absence of symptoms, no leakage episodes recorded, and no retreatment) success at 12 months. The predetermined equivalence margin was ±12% points. A total of 597 women were randomly assigned to a study group and 565 (94.6%) completed the 12-month assessment. The rates of objectively assessed treatment success were 80.8% in the RP group and 77.7% in the TO group (3.0%-point difference; 95% CI: −3.6 to 9.6). The rates of subjectively assessed success were 62.2% and 55.8%, respectively (6.4%-point difference; 95% CI, −1.6 to 14.3). The rates of voiding dysfunction requiring surgery were 2.7% in the RP group and 0% in the TO group (P = 0.004), and the respective rates of neurological symptoms were 4.0% and 9.4% (P = 0.01). There were no significant differences between groups in postoperative urgency incontinence, satisfaction with the results of the procedure, or quality of life. Thus, the success rates met the predetermined criteria for equivalence of the 2 procedures. [EL=1]

There have been numerous additional, non-randomised trials published in peer-reviewed literature. [100-118] The majority of these concluded that there is no statistically significant difference in subjective or objective outcome measures between retropubic and transobturator MUS procedures. As concluded in the RCTs, postoperative complications are more common in the retropubic MUS group. [EL=3/4]

g) Other studies

Two additional topics deserve mention. Pelvic floor muscle training (PFMT) with or without biofeedback is a recognised and effective treatment for various pelvic floor conditions, including SUI, UUI, and pelvic pain. While a trial comparing MUS procedures and PFMT has not been published, there is a design for a prospective RCT in place to address this question [Labrie et al., 2009]. [58] This multi-centre RCT will be include women between 35 - 80 years old with moderate to severe, predominantly SUI, who have not received specialised PFMT or previous anti-incontinence surgery. Women will be assigned to either PFMT for a standard of 9-18 sessions in a 6-month period or TVT-O surgery. The main endpoint of the study is the subjective improvement of urinary incontinence. Objective cure, a secondary outcome, will be assessed from history and clinical parameters. Subjective improvement in QoL will be measured by generic (EQ-5D) and disease-specific (UDI & IIQ) QoL instruments. The economical endpoint is short term (1 year) incremental cost-effectiveness in terms of costs per additional year free of urinary incontinence and costs per Quality Adjusted Life Years gained. Finally, treatment strategy and patient characteristics will be combined in a prediction model, to allow for individual treatment decisions in future patients. Four hundred female patients will be recruited from over 30 hospitals in the Netherlands.

Finally, single-incision mini-slings (SIMS) have emerged as an additional option for the woman

with SUI. These procedures theoretically require minimal anesthesia and may be performed entirely under local anesthestic. While most outcomes and comparisons between SIMS and traditional MUS procedures have not yet reached medium-term follow-up, a recent abstract at the 2011 International Continence Society Annual Meeting presented a systematic review and meta-analysis of SIMS and MUS procedures [Abdel-Fattah et al., 2011].[59] Nine studies were included, comparing TVT-Secur (6 studies; n=548), Mini-arc (2 studies; n=160) and Ophira (one study; n=50) to traditional MUS. A total of 758 women were included and 60 women were lost to follow-up (MUS n=23, vs. SIMS n=37). The meta-analyses showed a significantly lower patient-reported cure rate with SIMS when compared to MUS, specifically TVT-O (RR 0.84, 95% CI 0.71 to 0.99), however a non-significant difference in favour of TVT was seen (RR 0.79, 95% CI 0.37 to 1.67). These results were supported on sensitivity analysis when studies of unclear quality were excluded. SIMS were associated with significantly lower objective cure rates when compared to MUS, specifically TVT-O (RR 0.88, 95% CI 0.77 to 0.99). In addition there was a significant difference in favour of TVT when compared to SIMS. This was also confirmed on sensitivity analysis when studies of unclear quality were excluded. A shorter operation time was associated with SIMS (WMD -8.67 minutes, 95% CI -17.32 to -0.02), and this was due to the significant difference in operation time in the single TVT comparison. There were significantly lower day-one pain scores in the SIMS group (WMD -1.74, 95% CI -2.58 to -0.09). Repeat continence surgery was significantly higher in the SIMS group (RR 6.72, 95% CI 2.39 to 18.89). Tape erosion and de-novo urgency incontinence were significantly higher in the SIMS group (RR 3.86, 95% CI 1.45 to 10.28 and RR 2.08, 95% CI 1.01 to 4.28, respectively). There were non-significant differences between both groups in respect to post-operative voiding difficulties (RR 1.47, 95% CI 0.78 to 2.74) and other minor (postoperative wound infection, haematoma, UTI, and haematuria) post-operative complications (RR 1.59, 95% CI 0.74 to 3.45). There was no significant difference in the QoL scores between the groups (WMD -33.46, 95% CI -87.55 to 20.62). Statistical heterogeneity was found throughout the analysis and was highest in patient reported cure rate, QoL scores, and operative time. [EL=1/2]

h) CONCLUSIONS / RECOMMENDATIONS

There is evidence that the retropubic TVT is more effective than colposuspension and is equally effective as traditional autologous fascial sling operations. **[EL=1/2]** Operation time, hospital stay, and time to resume normal daily activity is shorter with the TVT than with colposuspension. Post-operative voiding problems and need for urogenital prolapse surgery are more commonly associated with colposuspension, while bladder perforation is more commonly associated with TVT. **[EL=1/2]** TVT is more effective than the IVS and the SPARC procedure; however, the studies are heterogeneous. Inadvertent bladder puncture during SPARC (top-down) placement is more common than bladder puncture during TVT (bottom-up). **[EL=1/2]** Overall, retropubic and transobturator MUS procedures perform equally at a short term follow-up of 6 to 12 months. (Level 1/2) The rate of complications, including bladder puncture, vaginal extrusion, and hematoma formation are higher for the retropubic MUS. **[EL=1/2]**

Retropubic MUS is recommended as an effective treatment for stress urinary incontinence, which has longevity. **[Grade A]** Outcomes using subjective and objective criteria indicate that the retropubic MUS is at least equivalent, and usually superior, to other anti-incontinence procedures. **[Grade B]**

3. TRANSOBTURATOR MID-URETHRAL SLINGS

a) Evolution of the TOT including proposed advantages

The introduction of the tension-free vaginal tape (TVT) in 1995 [171] as well as the[172] development of other retropubic mid urethral slings, changed the way stress urinary incontinence (SUI) is treated. These procedures, although effective, were not without complications. Beyond voiding phase dysfunction, complications including bladder perforation, bowel perforation and vascular injury were described. [26, 173, 174] [175]The majority of serious complications reported from these procedures were thought to be related to penetration of the retropubic space. [176]

In 2001, Delorme first described placement of a synthetic sling avoiding the retropubic space by placing the sling through the obturator foramina.[68] Thus the first alternative to the retropubic tapes, the transobturator tape (TOT) was born. By avoiding the retropubic space, the major complications associated with retropubic passage of trocars were theoretically avoided. Another potential advantage of the transobturator method was the potential elimination of intraoperative cystoscopy. This point is still debated today.[177] Delorme's original description of the TOT required passage of the trocar from "outside-in". In 2003, de Leval aimed to further reduce the chance of bladder and urethral injury and described placing the trocar of the vaginal tape from "inside-out".[69] These two methods remain the major division of transobturator slings and are both still widely used today.

Further efforts have been recently made to modify the inside-out method. In an attempt to minimise post-surgical leg pain, the length of mesh used has been shortened and surgeons have tried to minimise the number of punctures to the obturator membrane [172, 178] Initial results have shown improvement in leg pain in the immediate post-operative

period, without sacrificing efficacy (at 1 year). Further confirmatory studies are needed to strengthen these findings.

b) Initial prospective cohort trials

The original TOT procedure was performed in 40 women, 16 of whom had isolated SUI. The authors reported 15/16 were "totally continent" and the remaining patients improved with short term follow up (3-12 months). [68]There were no intraoperative complications. Post-operatively, the only complication was 1 episode of sepsis. Following this study, Delorme et al. published a series of 32 patients treated with the transobturator tape with at least one year follow-up (UraTape® Mentor-Porge`s, a non-woven, non-knitted thermally-bonded polypropylene) [179, 180] With a mean follow-up of 17 months, and a rigorous definition of cure (defined by patients reporting no protection and no SUI, along with a negative cough test with a full bladder) 22/29 patients (90.6%) were cured and 3/32 (9.4%) were improved. Preoperatively, 43.7% (14 patients) had pure SUI, and 56.3% (18 patients) had mixed incontinence. Of note, 4 patients had prior anti-incontinence procedures (3 TVT, 1 Burch and 1 with multiple procedures) and 5/32 had preoperative urethral closure pressures of <20cm H20. Again, no intraoperative complications were recorded. There was one patient who required self-catheterisation but retention resolved in this patient by 4 weeks. There were 5 patients with voiding disorders suggestive of bladder outflow obstruction. Two patients developed de novo urgency incontinence and one had worsening of her preoperative urgency.

Short term safety and efficacy data are also available from a prospective multicentre cohort study. [176] In this study, 183 women received the UraTape (outside-in TOT) and follow up data were obtained at a mean of 7 months (1-21 months). All women had SUI associated with hypermobility, 26 had mixed incontinence and 26 had concomitant (POP) surgery performed at the time of their TOT. Intraoperatively, there was a complication rate of 2.2% including 1 bladder perforation, 2 urethral perforations and 1 lateral vaginal sulcus perforation. Seventeen patients were not cured of stress incontinence including 5 patients that had the sling removed for vaginal extrusion (3) and urethral erosion (2). 4 patients reported post-operative de novo urgency, 2 of which also complained of urinary leakage. At 6 months 83% (of 130 patients) were cured and 5.4% were improved.

Based on data from the prospective series from Costa et al. and other case reports, extrusions and infections were linked to the silicon part of the UraTape and the tape was modified to the Obtape®. [176, 181, 182] This modification was introduced in 2003. This newer tape was made of monofilament strands of nonwoven polypropylene fibre with interlacing monofilaments forming pores of 50 mcg (smaller than the 75 mcg needed to allow for the migration of macrophages and leukocytes). The materials used for transobturator slings have continued to be modified to decrease risk of erosion, extrusion and infection. Today, all commercially available synthetic transobturator slings (as well as retropubic slings) are made of Amid type I polypropylene mesh and have an extrusion and erosion rate well below 5%. This is much lower when compared to the transobturator Obtape® with vaginal erosion rates as high as 13%.[183] [184]

The first description of the "inside-out" modification by de Leval also included feasibility/safety data from 107 patients.[69] Of these, 74 suffered from isolated SUI, and the remaining 33 women had POP, 15 had associated SUI, and the remaining 18 had prophylactic slings for occult SUI. There were no intraoperative complications or perioperative complications reported. At one month, one patient had a minor vaginal erosion and 2.8% of patients had urinary retention (2 of the 3 had concomitant prolapse surgery). 15.9% of patients complained that they had moderate pain or discomfort in the thigh fold. All pain had resolved by one month.

After the original inside-out cohort was described, patients from the same institution were then offered participation in a prospective observational study (TVT-obturator or TVT-O, Ethicon, Sommerville NJ, USA). [185]102 patients out of 253 consecutive patients fulfilled the inclusion criteria and agreed to participate in the trial. 4.9% (5/102) of this group did not complain of SUI but had occult SUI. There were no urethral or bladder perforations and one patient had a vaginal sulcus laceration noted intra-operatively. No patients presented with vaginal or urethral erosion at follow-up. After catheter removal, 2 patients had an "important PVR" of >400ml. This voiding dysfunction resolved (after CIC in one and SPT What's SPT in the other) by the last reported follow-up. There were 99 women with least 12 month follow-up (mean follow-up of 14.9 months) and the complete cure rate was 91% while SUI symptoms improved in 5% of patients. Worsening or de novo urgency symptoms or urgency urinary incontinence (UUI) were reported by less than 10% of the patients. Approximately 75% of those with preoperative urgency and/or UUI experienced disappearance or improvement of these symptoms postoperatively. Voiding difficulties developed in 7% of the patients.

This same group of 102 women, who underwent a transobturator inside-out sling, were followed for a minimum of 3 years (median 40 months) and complete data were available for 91 (89.2%). [185] Issues of erosion or persistent pain were not found with this medium term follow-up. Four patients required tape release or tape incision, all within the first year. Disappearance and im-

provement of SUI were observed in 88.4% and 9.3% of the patients respectively. These cure rates were similar to those obtained 1 year after the operation. [185] Cure of SUI was defined as the disappearance of subjective SUI, as assessed by a SUI symptom scale score equal to zero. One patient developed a vesicovaginal fistula 2 years after sling placement. The authors did not believe that this was secondary to the TVT-obturator, but rather was due to a prior history of pelvic radiation. An additional 2 patients developed symptomatic POP between the first and second year and each went on to have an uncomplicated laparoscopic repair.

There are several large, multicentre European studies that examined the safety of the original TVT. [67, 186, 187] Similarly, a study was performed to address the safety of the inside-out transobturator approach. [188] This study compiled a registry of 984 women from 86 centers in France. There was an overall perioperative complication rate of 2.2%, with vaginal wall perforation (1.3%) and hematoma (0.7%) being the most common. The post-operative complication rate was 5.2%, with residual leg pain being the most common complication (2.7%). Reintervention, urinary retention, vaginal erosion, and paravesicle hematoma were all reported with percentages of less than 1 (0.9%, 0.8%, 0.6% and 0.1% respectively). Although the design of this study was aimed at safety, the paper does report efficacy at 4-12 weeks. Surgeons assessed 90% of patients as completely cured and 8.7% as improved, with only 1.2% of patients being similar to their preoperative status. Of those 303 patients with preoperative overactive bladder (OAB), cure was reported in 54.5%, improvement in 40.25%, and 5.3% noting no change. Other large single institution studies have also looked at safety of the inside-out transobturator sling. [189]

c) Transobturator Outside-in versus Inside-out

It was suggested by Delorme et al. that there is a greater risk of nerve injury (dorsal nerve of the clitoris) with the inside-out passage of the trocar. [180] A cadaveric study suggested that the inside-out technique required the trocar to pass closer to the obturator canal and was more likely to injure the obturator nerve (or vessels) that travel in this space. [190]

The association between inside-out obturator slings and an increased risk of complications compared to outside-in obturator slings has not been supported in clinical studies. Latthe et al. used a meta-analysis with direct and indirect comparisons of randomised trials to assess the effectiveness and complications for the inside-out (TVT-O) and outside-in (TOT) transobturator slings.[191] The conclusion was that there was equivalent short-term effectiveness between the two methods. By indirect comparison, fewer bladder injuries and voiding difficulties were seen in the inside-out tapes.

In 2009, a Cochrane Review of minimally invasive synthetic sub-urethral sling operations for SUI contained an analysis of the inside-out outside-in approaches (comparison #5) and concluded that there were no statistically significant differences in any of the outcomes measured.[40] However, the review acknowledged that the four trials randomised trials that this conclusion was based on were all small in size. [192-195]

Houwert et al. presented medium term follow up from their prospective comparative randomised trial.[196] They did not find any statistical significant difference, but it is not clear that the study was powered appropriately to show a difference. Abdel-fattah et al. published a study that was powered to show a 10% difference in success rates between the two methods of obturator sling placements. [197] They enrolled 107 inside-out and 171 outside-in patients. This prospective single blinded study did not show any differences in objective cure rates (87.6% inside-out vs. 83.2% outside-in, $p = 0.2$) or patient reported success rates as reported by Patient Global Impression of Improvement (83% inside-out vs. 77% outside-in, respectively, $p = 0.138$) at 6 months follow-up.[197] There were statistically more vaginal angle perforations with the outside-in approach compared the inside-out method (17 vs. 3, respectively, $p=0.001$). Women in the inside-out group more commonly reported severe post-operative thigh pain, but this was not statistically significant (6.7% vs. 3.5%, $p=0.19$).

d) Comparator Trials: Transobturator versus Retropubic MUS in the Index Patient

Once cohort studies had confirmed the feasibility of transobturator mid-urethral slings, a number of small RCTs and quasi-RCTs were performed comparing transobturator to the then gold standard, retropubic mid-urethral sling. A Cochrane review [40] and two recently updated meta-analyses [48, 191] use the pooled data of these RCTs to compare the outcomes of retropubic and transobturator MUSS.

In a Cochrane Review, Ogah et al. found 24 trials comparing outcomes between retropubic and transobturator MUSS.[40] Subjective cure or improvement rates were reported in 10 of these trials and meta-analysis revealed no statistically significant difference between approaches (83% subjective cure in each group, RR 1.00, 95% CI: 0.96-1.05). Objective cure was measured by urodynamic evaluation, cough-stress test, one hour pad test of ≤ 2 g, one hour pad test of ≤ 1 g, or 24 hour pad test of ≤ 5 g various means in 17 studies. The transobturator route was found to have a significantly lower cure rate than the retropubic route (84% vs. 88%, RR 0.96, 95% CI 0.93-0.99). The clinical significance of this 4% difference in objective cure versus no difference in subjective cure has been questioned.

In a recent systematic review and meta-analysis, Latthe et al. found 12 RCTs that compared TOT with TVT, and 15 that compared TVT-O with TVT.[191] When compared at 1–44 months, the subjective (OR 1.16; 95% CI 0.83–1.6) and objective (OR 0.94; 95% CI 0.66–1.32) cure of TOT was similar to TVT. For TVT-O, the subjective (OR 1.06, 95% CI 0.85–1.33) and objective cure (OR 1.03, 95% 0.77–1.39) was also similar to TVT.

Novara et al examined 11 RCTs comparing TVT with inside-out TOT and 9 RCTs comparing TVT with outside-in TOT.[48] Meta analysis revealed that continence rate according to any definition of cure (OR: 1.02; 95% CI: 0.78–1.33; p = 0.90), and subjective continence rates (OR: 0.97; 95% CI: 0.75–1.24; p = 0.80) were similar between the two procedures. Overall, retropubic tapes had significantly higher objective continence rates when compared to the transobturator tape group (OR: 0.80; 95% CI: 0.65–0.99; p = 0.04). Interesting, a statistically significant difference in favour of TVT was shown when comparing objective continence rates between TVT and inside-out TOT (OR: 0.71; 95% CI: 0.52–0.96; p = 0.03) but no difference was found comparing TVT to outside-in TOT (OR: 0.90; 95% CI: 0.66–1.22; p = 0.51). However, when studies of lower methodological quality were excluded only a non-statistically significant trend in favour of TVT was found. (OR: 0.74; 95% CI: 0.54– 1.01; p = 0.05).

The majority of RCTs used in the aforementioned Cochrane review and meta-analyses were small, had short- to medium term follow-up and were designed only to detect superiority. This has precluded robust conclusions regarding long-term success and equivalence efficacy with this data.

Angioli et al. provide long-term data regarding the success rates of TVT and TVT-O in a multicentre RCT. [198] At 5 years follow-up, objective cure, defined as a negative cough stress test, was similar between TVT and TVT-O (71.4% vs. 72.9%; p=1). After 5 years, patients in this trial were asked to describe their overall satisfaction. 60% and 62% of women reported that they were satisfied or very satisfied with the results of their TVT and TVT-O respectively (p=1).

TOMUS (Trial of Mid-Urethral Slings) is a large multicentre, equivalence RCT designed to compare the efficacy and safety of retropubic and transobturator mid-urethral slings. [170] The 12-month outcomes of 565 women were recently reported. The criteria required for objective treatment success were a negative provocative stress test, a negative 24-hour pad test, and no retreatment (behavioural, pharmacological, or surgical) for SUI. The unadjusted rates of objective treatment success met the predefined criteria for equivalence, less than a 12 percentage-point difference. (80.8% in the retropubic sling group and 77.7% in the transobturator sling group; 3.0 percentage-point difference; 95% CI: 3.5to 9.6). The subjective treatment success criteria were the absence of self-reported SUI symptoms as assessed with the use of the Medical, Epidemiological and Social Aspects of Aging questionnaire, no leakage recorded in a 3-day voiding diary, and no retreatment for SUI. The unadjusted rates of subjective treatment success did not significantly differ between groups but the predetermined criteria for equivalence was not met (62.2% in the retropubic sling group and 55.8% in the transobturator group, 6.4 percentage point difference; 95% CI, −1.6 to 14.3).

e) Comparator Trials: Transobturator versus Retropubic MUS in patients with Intrinsic Sphincter Deficiency (ISD)

The diagnosis of ISD in the literature has traditionally been based on the urodynamic finding of a Valsalva leak-point pressure (VLPP) < 60 cmH20 or a mean urethral closure pressure (MUCP) < 20 cm H20. A retrospective study of 300 women with SUI and ISD found an overall cure rate for TVT to be significantly higher than TOT (78.3% vs. 52.5%; p<0.0001). [111] Jeon et al. retrospectively compared 253 patients with ISD and found that after 2 years cure rates were 86.94% and 34.89% for TVT and TOT respectfully (p<0.0001). [156] Schielitz et al. [87] randomised 184 women with urodynamic evidence of SUI and ISD to receive TVT or TOT. At 6 months, urodynamic SUI was present in 21% in the TVT group compared to 45% in the TOT group. [87] Similarly, in a large RCT, a VLPP < 60 cmH20 was a predictor of poor outcome in the transobturator sling group but not in the retropubic sling group.[88] In these studies ISD was defined by a low VLPP or MUCP, but there is no mention of urethral mobility. Contradictory to these findings, Rapp et al. retrospectively reviewed their results and found no significant differences in continence rates across different preoperative VLPPs. [113] In a large observational study, women with SUI were stratified according to preoperative MUCP and VLPP and followed for 5 years after TOT. The objective overall cure rates were similar across all strata indicating that MUCP and VLPP may not be predictive of outcome in TOT. [199] In the TOMUS trial, there was no material change in the rates of treatment success according to objective or subjective criteria when the analyses were adjusted for VLPP and MUCP. [170]

The data comparing retropubic and transobturator MUSS outcomes in patients with ISD appears equivocal. Recent studies suggest that evaluation of urethral mobility in ISD patients can be more informative. A cohort of 107 women with SUI had their urethral mobility measured prior TOT and at 10 months subjective cure was assessed. Women with preoperative urethral mobility < 45 degrees were at least 4 times more likely to report postoperative incontinence compared to women with preoperative urethral mobility > or = 45 degrees (29.4% vs 6.9%, RR 4.29, 95% CI 1.59-11.60, p=0.005).[200] Haliloglu et al. divided 65 women with SUI into three groups prior to receiving TOT: I) patients with ISD with a VLPP < or = 60 cm

H2O and a Q-tip test > 30 degrees (ISD and hypermobile urethra), II) patients with ISD who have VLPP < or = 60 cm H2O and Q-tip test < or = 30 degrees (ISD without hypermobile urethra), and III) patients without ISD who had VLPP > 60 cm H2O and Q-tip test > 30 degrees (hypermobile urethra without ISD). [201] All cure and improvement rates were statistically lower in group II at 6, 12, and 24 months leading authors to conclude that lack of urethral hypermobility may be an important risk factor for TOT failure in patients with ISD.

f) Complications of Obturator Slings

Complications of MUS are categorised as intraoperative complications (bladder, urethral, visceral and vessel injury), immediate postoperative complications (voiding dysfunction, groin pain, infection) and chronic problems (de novo urgency, sling erosion/extrusion). Placement through the obturator foramen avoids the space of Retzius, decreasing more serious intraoperative trocar complications. In 2008 Novara et al. conducted a systematic review and meta-analysis of complication rates in mid-urethral slings. [202] When comparing retropubic vs. transobturator approach, bladder perforations (OR 2.33; 95% CI: 1.26–4.32; p = 0.007), pelvic hematoma (OR 4.83; 95% CI: 1.22–19.15; p = 0.03) and storage lower urinary tract symptoms (OR 1.81; 95% CI: 1.13–2.91; p = 0.01) were less frequent in women who had undergone a transobturator sling. Rates of vaginal erosions, urinary tract infections and reoperation rates were similar amongst groups. The 2009 Cochrane review by Ogah et al. on mid-urethral slings found that the transobturator approach was associated with a shorter operating time, less blood loss, less postoperative voiding dysfunction, and fewer bladder perforations, but more groin pain (12% vs. 1.7%, RR 6, 95% CI: 3–11) than the retropubic route.[40] In 2010 Latthe et al. updated their systematic review which assessed the effectiveness and complications of transobturator slings.[191] Adverse events such as bladder injuries (TOT, OR 0.11, 95% CI 0.05–0.25; TVTO, OR 0.15, 95% CI 0.06–0.35) and hematomas (OR 0.06, 95% CI 0.01–0.30) were less in the TOT than TVT. Voiding difficulties (TOT, OR 0.61, 95% CI 0.35–1.07); TVTO, OR 0.81, 95% CI 0.48–1.31) were slightly lower in TOT but this was not statistically significant. Groin/thigh pain (TVT-O, OR 8.05, 95% CI 3.78–17.16) and vaginal injuries (TOT, OR 5.82, 95% CI 1.85–18.3; TVTO, OR 1.69, 95% CI 0.73–3.91) were more common in the transobturator tapes. Mesh erosion in TVT-O (OR 0.77, 95% CI 0.22–2.72) and TOT (OR 1.11, 95% CI 0.54–2.28) was similar to TVT.

A recent publication by Brubaker et al. reported on 2 year adverse events in patients enrolled in the TOMUS trial who were undergoing retropubic or transobturator midurethral slings. [203] UTIs were the most common adverse events in both groups with a higher incidence in the retropubic group (16.7% vs. 9.1%, p =.02). Patients in the retropubic group had higher rates of bladder perforation (5% vs. 0%, p <.0001), voiding dysfunction requiring surgery or catheter use (3% vs. 0%, p =.002) and postoperative bleeding (2% vs. 0%, p =.02). Neurological symptoms, defined as new paresthesias or alterations in motor function in the first 6 weeks after surgery, were more frequent in the transobturator group than in the retropubic group (9.7% vs. 5.4%, p =.04). Mesh complications were reported in 3-5 % of women and these rates were similar in both groups.

But and Fagenelj randomised 120 patients to Monarc (inside-out transobturator sling) or to TVT-O (outside-in). [193] There was a higher incidence of vaginal wall perforations and lacerations in the Monarc (0% vs. 15%), and the TVT-O was more painful than the Monarc (p =.00015). Liapis et al. evaluated 114 patients randomised to TVT-O and Monarc, finding no statistically significant differences between the two procedures. [195] In patients that have undergone the Obtape, there have been reports of higher rates of vaginal erosion, ischiorectal abscesses, adductor myositis with symptoms of leg pain, difficulty ambulating and cellulitis. The newer polypropylene slings have been associated with a lower incidence of complications. However, the true incidence of major complications is probably limited by the heterogeneity of the outcome measures and the short-term follow-up of most of the studies. Future studies with validated outcomes and long-term follow-up are needed.

g) Transobturator Slings in Special Populations

1. Mixed Urinary Incontinence

Mixed urinary incontinence (MUI) is defined as the complaint of involuntary leakage from the urethra, associated with urgency, and also with exertion, effort, sneezing or coughing. How mid-urethral slings affect patients with MUI is less apparent. Many studies have demonstrated an improvement or cure in OAB symptoms and UUI in those patients undergoing sling procedures for the stress component of MUI with cure rates ranging from 50-74%. [204] Other studies have reported a decrease in subjective and objective cure rates but still quality of life improvement after treatment in women with MUI [53, 205]. Two studies by Paick et al reported on patients with MUI.[53, 205] The first, which reported on 73/274 with MUI who underwent TVT with more than six months follow-up, showed that the mixed UI group had the same cure rate for stress urinary incontinence (SUI) as the SUI-only group. They also found that 16.4% of the mixed UI group had persistent UUI, so that the overall UI cure rate was lower for the mixed UI than the SUI group, but still quite favourable (78.1% vs. 95.5%). In their second study, they evaluated 144 women with mixed UI who had undergone TVT, Sparc or TOT slings. There were no significant differences in the three groups in terms of the cure rate for SUI (SUI; TVT, 95.8%; SPARC, 90.0%; TOT, 94.0%; p = 0.625) and for total cure (TVT, 81.9%; SPARC, 86.4%; TOT, 82.0%; p = 0.965). There were no risk factors for cure of SUI, except detru-

sor overactivity (DO) on urodynamic studies. There was one difference between groups preoperatively; the TOT patients had less severe UUI than those patients who underwent the SPARC or TVT.

In 2008 Gamble et al. evaluated 305 women with MUI and found 31.5% of women had postoperative resolution of detrusor overactivity (DO). [204] Sling type was strongly related to persistence of DO with a 53% persistence of DO in the transobturator tape group, followed by retropubic (64% after TVT, 66% after SPARC), and 86% after bladder neck slings ($p < .001$). Botros et al. evaluated 276 patients with MUI who underwent retropubic slings (TVT, N = 99; SPARC, N = 52) or transobturator slings (Monarc, N = 125).[206] Patients who underwent transobturator sling placement (8%) had significantly less de novo subjective UUI compared to the patients who had TVT (33%) and SPARC (17%) ($p = 0.04$). In patients with preoperative UUI, 14-16% who underwent TVT or SPARC had worsening of their UUI symptoms while only 6% of the transobturator sling group did ($p = 0.02$). There was no difference in rates of resolution of DO or de novo DO among the three groups. Ballert et al. evaluated 83 women who underwent TVT [203] and TOT-O ? TVT-O? [87]using pre- and post-operative AUASI (American Urologic Association Symptom Index) scores to evaluate lower urinary tract symptoms.[207] Patients with SUI had lower postoperative AUASI scores than patients with MUI. There were no differences between patients who underwent TVT or TVT-O in any category. In 2011 Lee et al. performed an observational cohort study evaluating risk factors for persistence of urgency or UUI after midurethral slings. [208] Out of 1112 women who completed the questionnaire, 754 patients had preoperative urgency or urgency urinary incontinence. 955 patients underwent retropubic slings and 270 patients underwent transobturator slings. The overall subjective rate for persistent urgency and UUI was 40.3% and 32.3% respectively. Age (OR 1.03, 95% CI: 1.02-1.04), baseline symptoms severity (OR 1.41, 95% CI: 1.10-1.78) and coexistent DO (OR 2.04, 95% CI: 1.39-3.01), were risk factors for persistent urgency while concomitant prolapse surgery (OR 0.54, 95% CI: 0.38-0.75) and transobturator sling surgery (OR 0.61, 95% CI: 0.39-0.94) decreased the risk. There was no difference in type of sling surgery and persistence of UUI. These studies are consistent with results published by Novara et al. who performed a meta- analysis of randomised controlled trials comparing transobturator vs. retropubic MUSS.(33) Results showed a higher prevalence of storage lower urinary tract symptoms in patients randomized to retropubic slings than in patients randomized to transobturator slings (OR 1.35; 95% CI OR: 1.05–1.72; $p = 0.02$).

In conclusion, women with mixed urinary incontinence benefit from sling surgery. It appears that placement of a transobturator sling provides the greatest improvement in OAB and UUI symptoms and seems to have the lowest rates of de novo urgency and UUI; it also appears to have the greatest resolution of DO. However, women with mixed urinary incontinence should be carefully counseled preoperatively as persistence or worsening of symptoms may have a negative impact on quality of life and may lead to poor overall satisfaction after surgery.

2. Recurrent Sui

There have been multiple studies reporting on outcomes after repeat anti-incontinence surgery, however the appropriate choice of a secondary continence procedure for women with recurrent SUI is poorly studied and the available studies are limited by their small numbers. Two studies of repeated mid-urethral slings report cure rates of 74–76% at 18 months, which is lower than cure rates for primary surgery.[209, 210] Lee et al. performed a retrospective study on repeat midurethral slings.[209] 13 patients underwent retropubic and 16 patients underwent transobturator slings. Overall cure was 75.9% and overall improvement was 6.9%. Cure rates were 92.3% for the retropubic approach and 62.5% for the transobturator approach, however this was not statistically significant ($p = 0.089$). Stav et al. evaluated 1,225 women with SUI, among these 77 patients had repeat mid-urethral slings.[211] The subjective stress incontinence rate was 62% in the repeat group compared to 86% in the primary group ($p <0.001$). A repeat retropubic approach was significantly more successful than a repeat transobturator approach (71% vs. 48%, $p= 0.04$). These results could be due to a higher incidence of intrinsic sphincter deficiency or lack of urethral mobility in patients undergoing a repeat mid-urethral sling (31% vs. 13%, $p <0.001$). A recently published study by Abdel-Fattah et al. reported on outcomes on a total of 46 women with recurrent SUI after previous failed continence surgery.[212] 18 patients underwent “outside-in” and 28 underwent “inside-out” procedure. Overall subjective and objective success rates in this group were 70% and 77% but it should be noted that these numbers included 10 women with failed colposuspension. Higher success rates were seen in women who underwent the inside-out TVT-O compared to the ‘outside-in’ TOT but this study was not adequately powered to make this comparison. Biggs et al. evaluated 27 patients who underwent TVT-O after a previous anti-incontinence procedure.[213] There was an 80% success rate assessed by PGI-I (“very much better” or “much better) at a mean follow-up of 25.7 months.

A repeat synthetic mid-urethral sling procedure has significantly lower cure rates than a primary sling procedure. Although the data are limited, it seems that in patients who failed a primary anti-incontinence surgery, a repeat retropubic approach has a higher success rate than the repeat transobturator approach especially in cases with intrinsic sphincter deficiency.

3. Elderly

Thirty-seven million people are aged > 65 years (12% of the total US population) and 5.3 million of these are aged > 85 years. With the national life span

increasing, it is estimated that by 2030, 1 in 5 people in the United States will be aged > 65 years, and 1 in 4 elderly individuals will be aged > 85 years. Advanced age is related to increased prevalence of urinary incontinence and there is evidence of a higher rate of DO and ISD in the elderly population. Surgical intervention is considered the most efficient and durable approach to treat SUI and mid urethral slings have become the treatment of choice in the majority of patients. The effect of age on outcomes of mid urethral slings is still scarce and the definition of elderly varies across studies. There are some studies that evaluate the efficacy of retropubic slings in the older population but there are limited data assessing safety and efficacy of the transobturator slings in elderly vs. younger patients. Sevestre et al. analysed a series of 76 patients with a mean age of 76 years who underwent TVT.[214] There were no major postoperative complications, however, 13.7% of the patients had postoperative persistent SUI and 18.4% had urgency incontinence. De novo urgency without incontinence was detected in 21% of the patients. In another study, pre- and postoperative quality of life parameters were compared in a small series of 21 elderly and 46 younger stress-incontinent patients that underwent TVTs.[215] At postoperative follow-up of 3-24 months, SUI was improved in 91% of the younger and 80% of the elderly patients and all quality of life parameters were significantly improved in all age groups. Perioperative morbidity and complications are also a consideration in older patients. In the study of Gordon et al. the incidence of early postoperative morbidity was similar in both age groups who underwent TVTs. [216] However, several cases of significant age-related morbidity were noted among elderly patients: two cases of pulmonary embolism, two cases of cardiac arrhythmia, one case of severe pneumonia, and one case of deep vein thrombosis. All major complications occurred in elderly patients who were undergoing concomitant prolapse surgery. The risk of de novo urgency was 18% at one year in older vs. 4% in the younger patients. Barber et al. identified predictors of recurrent urinary incontinence one year after treatment with retropubic and transobturator slings. [85] They found that increasing age was the only identified variable that was independently associated with recurrent SUI (adjusted OR 1.7; 95% CI: 1.1-2.6 per decade). Chen et al. found that surgical failure after inside-out transobturator sling was significantly greater in women aged 60 years old or older, compared with those younger than 60 years (adjusted OR 11.7, 95% CI: 1.8-76) in a small series of 54 women. [217] Groutz et al. evaluated patients aged 70 or older (n=97) and compared them to patients younger than 70 (n=256) who underwent TVT-O.[218] The mean follow up was 30 months ± 17 months. The incidence of persistent, urodynamically confirmed, SUI was similar in both age groups (5%). However, asymptomatic urodynamic SUI was significantly more common among elderly patients (19% vs. 3.7%, p <0.05). The incidence of persistent OAB was similar in elderly and younger patients (68% and 62%, respectively), while de novo OAB was significantly more common in elderly patients (11.9% vs. 4.7%, p <0.05). Postoperative morbidity was similar in both groups except the elderly group had a higher incidence of recurrent UTI's (13.7% vs. 6.2). Even though there are limited data and further studies are needed, it appears that transobturator slings are both safe and efficient in elderly patients and women should not be excluded from mid-urethral slings based on their age.

4. Concomitant Prolapse Surgery

Approximately 40% of women with pelvic organ prolapse (POP) also report SUI.[219] Asymptomatic women who undergo prolapse surgery have a 11-20% risk of developing de novo stress incontinence. [220] Patients who leak during preoperative testing after reduction of their prolapse have a risk of up to 80% of developing de novo SUI.[221] The role of concomitant slings in patients undergoing POP repair has been debated, with some studies showing differences in cure rates or complications and others finding no differences. In a prospective observational study, Liang et al. evaluated 49 patients with stage 3 or 4 prolapse and occult stress incontinence.[222] In 32 (65.3%) patients a concomitant TVT procedure was performed and the remaining 17 (34.7%) patients had a prolapse repair only. The rate of postoperative SUI was significantly lower in those who had a TVT placed (9% vs. 65%) and the rate of detrusor overactivity was lower in patients who had prolapse repair alone after surgery (6% vs. 16%). Casiano et al. compared outcomes after retropubic mid-urethral slings with and without concomitant prolapse repair. [223] After 2.7 years survival free of "any" incontinence (Incontinence Severity Index score, >0) was similar in both groups (adjusted hazard ratio, 1.07; p=0.77). Women with concomitant repair for advanced prolapse tended to be more bothered by frequent urination (adjusted OR 1.78; p=0.08) and more likely to require urethrolysis (OR 6.11; p=0.04) than those without prolapse repair. There is only one study that reports on transobturator slings and prolapse surgery. Wang et al evaluated 140 women who underwent TVT (n = 70) and TOT (n = 70) with SUI with or without POP.[224] In the TVT group 30 patients and in the TOT group 22 patients had concomitant prolapse surgery. Surgical results were similar in both groups and concomitant pelvic reconstructive procedures had no effect on surgical results. At 1-year follow-up, the objective cure rates for patients with isolated SUI were 95% in the TVT group and 93.75% in the TOT group. For patients with concomitant POP, the cure rates were 90% in the TVT group and 86.36% in the TOT group. There are no randomised trials in patients undergoing pelvic organ prolapse surgery and obturator slings but with the currently available literature, it would appear that it is beneficial to treat concomitant SUI and prolapse. There are no current studies on the role of transobturator slings in occult SUI.

5. Obesity

Obesity is gradually increasing worldwide and epidemiological studies have found a link between obesity and urinary incontinence with odds ratio for the presence of urinary incontinence as high as 1.6 to 5 with each unit increase in body mass index (BMI). [225, 226]The role of mid-urethral slings in obese women has been debated due to concerns for higher failures and a potential increase in intraoperative and postoperative complications. Numerous studies have been carried out evaluating obesity as an independent predictor in patients that have undergone TVTs. [227, 228] [229] [230] [231-234]

Hellberg et al. reported a decrease in cure of 52.1% in patients with a BMI higher than 35 compared to 81.2% in those with a BMI less than 25. Six other studies have shown overall cure rates that approach 90% with no difference in the obese vs. the non obese patient.[231] However Greer et al. in their meta-analysis included these seven studies and did find a significant difference in cure rates between the two groups with cure rates being 81% and 85%, respectively (p= 0.001; OR 0.576, 95% CI: 0.426–0.779).[227] There are very limited data evaluating outcomes for transobturator slings in obese women. Liu et al did a retrospective review evaluating the TVT-O procedure in overweight and obese and women. [235]They retrospectively evaluated 129 patients who had undergone TVT-O and they were stratified according to their BMI, normal weight (n=29), overweight (n = 58), and obese (n = 32) groups. The median follow up was 24 months and there were no statistically significant differences in between groups comparing objective or subjective surgical outcomes, in the incidence of de novo DO, in quality of life scores or postoperative complications. Another study undertaken by Rechberger et al. found no significant association between BMI and surgical outcome at 18 months of follow-up among normal weight (n = 43), overweight (n = 81), and obese (n = 73) women who underwent transobturator slings.[88] However, they did notice a trend towards worse outcomes in overweight patients. Haverkorn et al. conducted a retrospective study evaluating patients that had undergone a transobturator sling (Monarc) in women with a BMI higher than 30 (n = 117) and BMI less than 30 (n = 161) with a minimum follow up of 12 months. [236] The percentage of women achieving global cure and SUI cure was significantly higher in non-obese women (83.9% and 91.9%) than in obese women (70.9% and 81.2%) (p < 0.001). Obese women achieved improvement in quality of life similar to those of non-obese women. Although the results from these studies are conflicting, it seems that regardless of BMI, transobturator slings may be an acceptable method of treatment for SUI in obese patients. Follow up in these studies is limited and larger studies are needed to confirm these findings and to evaluate the long terms effects of the procedure.

h) Conclusion and recommendation

Sufficient **Level I /II** evidence exists which evaluate mid-urethral tapes (retropubic). Current series include retrospective cohort studies and high level RCTs . There is a need for further prospective randomised assessment of this intervention – especially from the durability standpoint. **Quality of evidence is A / B**.

4. SINGLE INCISION MINI SLINGS (SIS) (TABLE 3)

The single incision mini slings have been developed in an attempt to further reduce the morbidity associated with continence surgery and to provide an outpatient or office procedure to treat stress urinary incontinence. The blind passage of needles, during TVT and TOT procedures, through the retropubic space or the obturator foramen respectively is associated with a small risk of vascular , nerve or visceral injury [202]. The shorter SIMS will theoretically minimise this risk.

The concept of the single incision sling is not novel. Smith presented a small series of SIMS in 1987[237], however this was a porcine dermis sling which in vivo probably degrades and hence long term cure rates were poor.

The first commercially available mid-urethral single incision sling , TVT-Secur (Gynaecare), was launched in 2006 with no published human trial data. The last 6 years have seen a increase in the number of commercially available single incision slings. There are currently 9 different products available. All are made of type I polypropylene mesh however the length & anchoring mechanisms are variable. (**Figure 1**)

The method of insertion is either U shaped, inserted in the same manner as the TVT or the H “hammock” insertion of the TOT. There is currently very little good quality RCT data to support the use of these slings.

Ten trials have been published including 1072 women. 6 of the RCTs published compared TVT- Secur to MUS, 2 compared MiniArc to MUS, 1 compared TVT-Secur to MiniArc and to MUS, and one compared Contasure to TVT-O. The numbers in each trial are relatively small (60- 194).

Five of the seven trials of TVT-secur found it to be inferior to TVT or TVT-O. Several different outcome measures were report in these 7 trials , making it difficult to compare the trials directly. Two of these trials were stopped prematurely following an interim analysis which demonstrated TVT-secur results to be significantly less effective than the comparator MUS. Hamer et al [245] also reported concerns about the morbidity associated with TVT-secur. They reported three significant complications in 67 cases, one hemorrhage 1000ml, one urethral perforation and one perforation of the bladder.

Three trials compared MiniArc to MUS , two found no significant difference between MiniArc and obturator tapes however the third trial by Basu et al[240] reported a considerably worse outcome for MiniArc compared to TVT, 9 out of the 37 patients who underwent the MiniArc subsequently had a TVT. **Table 3** summarises the data currently available.

Figure 1. Variation in anchorage of SIS

Table 3 Summarises the data on SIS currently available.

Author	Year	Comparison	Patients	FU (m)	power calculation	% lost FU	Primary outcome	objective cure	subjective cure	EL	Note
Tardiu [238]	2011	Contasure v TVT-O	158	12	yes	16.4	CST	87.5 v 90.0%	75.4 v 87.3%	2	Quasi Randomised Non-inferiority design
Enzelsberger [239]	2010	MiniArc v TOT (Monarc)	90	24	no	0	Subjective UI	NR	82 v 85% *	2	Quasi Randomised
Basu [240]	2010	MiniArc v TVT	71	6	yes	0	SUI (KHQ)	USI OR 7.58 (CI 2.7–24.7)	OR 8.14(2.7–24.7)	2	
Oliveira [241]	2011	MiniArc v TVT-S v TVT-O	90	12	yes	0	CST+ no pad+ no leak	87 v 67 v 83%		2	
Tommaselli	2010	TVT -S v TVT-O	84	12	no	10.7	USI	83.8 v 81.6% *	ICI-Q SF*	2	
Hinoul [242]	2011	TVT -S v TVT-O	194	12	yes	17.5	CST	84 v 98% p <0.05	76 < 92 % p< 0.05	1	
Hota[243]	2011	TVT -S v TVT-O	142 (86)	3	yes	NR	CST	52.8 v97.4%	PFIQ PFID *	2	Stopped at 86
Abdelwahab [244]	2010	TVT-S v TVT	60	9	no	0	NR	NR	93 V 90% *	2	
Hamer[245]	2011	TVT-S v TVT	308(133)	2	yes	1.6	Subjective UI	NR	72 v 92% p=0.01	2	Stopped at 133
Wang [246]	2011	TVT-S v TVT-O v TVT	106	12	yes	3.7	CST + Subjective UI	67.6 v 91.7 v 93.8%		2	

In 2011 Abdel-Fattah et al[247] published a meta-analysis of RCT comparing SIMS to standard MUS, the review included both full text publications and conference abstracts. A total of 758 women in nine RCTs with a mean follow-up of 9.5 months were included. SIMS were associated with significantly lower patient-reported and objective cure rates compared with MUS (risk ratio [RR]: 0.83; 95% confidence interval [CI], 0.70–0.99, and RR: 0.85; 95% CI, 0.74–0.97, respectively).

One of the reasons for the development of SIMS is to reduce the morbidity of continence surgery. Hence trial design should include an assessment of morbidity, including perforation, hemorrhage, chronic pain and voiding difficulty. The meta-analysis demonstrated that there was no significant difference in the perforation rate between SIMS and MUS, the confidence intervals (CI) for these parameters were however extremely wide. There was also a trend toward more voiding difficulties following SIS but again the CI were very wide.

Proponents of SIMS have speculated that the initial poor results reflect an incorrect insertion technique used in early trials. SIMS were initially inserted in the tension free manner by which TVT are inserted, however SIMS insertion has evolved and the current insertion technique is in closer proximity to the urethra and with greater tension than TVT.

Jeffery et al[248] have published the protocol Cochrane review of SIMS which will enable ongoing assessment of data.

Due to the considerable variation in the anchoring mechanism of each type of SIMS, data from one device cannot be extrapolated to another. There is a need for further RCT. Currently the recommendation is that SIMS should only be performed in the context of research.

All reports are Level I - III in terms of evidence and there continues to be a lack of durable outcomes reporting for this technique. Current series suggest that some efficacy may be inherent to these interventions, however, comparable efficacy to either retropubic or mid-urethral tapes has yet to be proven. Grade of recommendation is –B/ C.

5. TRADITIONAL SLING PROCEDURES

As in the previous ICI4 review, the term ‘traditional’ sling procedure is used here, in line with the terminology used in the latest Cochrane review. [249] This is done mainly to distinguish open sling procedures typically placed at the region of the bladder neck from the newer, minimally-invasive mid-urethral sling (MUS) procedures.

Sling procedures came into prominence in the beginning of the twentieth century. In 1907, Giordano transplanted gracilis muscle and wrapped it around the urethra. [250] Soon thereafter, other autologous tissues were transplanted under the urethra to provide additional support: pyramidalis [251], levator ani [252], rectus fascia [253], gracili [254], and bulbocavernosus muscle and fat [255]. While it was

hypothesised that the transplanted muscle would retain its contractility and act as a neo-sphincter to prevent SUI, these procedures compressed the urethra and created a partial obstruction. Complications such as recurrent cystitis, urethral sloughing, and fistula formation were common.

The modern autologous bladder neck sling exists mainly due to the work of Aldridge in the 1940's and McGuire and Blaivas in the latter part of the twentieth century. [256-258] The majority of sling procedures have involved a combined abdominovaginal approach, although procedures performed entirely through an abdominal approach have been described. Suspended, or 'sling on a string,' methods have been developed in order to reduce the invasiveness of the procedure and to shorten the length of sling material. These shorter slings can also vary in length, from a "mid-length" sling (7-10 cm) to a "patch" sling (2-4 cm). As with needle suspension procedures, bone anchoring has been used as an alternative form of sling suspension, although the benefit of this additional step has not been adequately studied.

Sling materials may vary widely and individual materials may have only a modest effect on initial sling efficacy. However, these materials may considerably affect the long-term outcomes of sling procedures and the associated morbidity. Materials may be synthetic or biological. The latter include autografts (rectus fascia, fascia lata, round ligament, dermis, vaginal skin, and gracilis, levator, and rectus muscles), cadaveric allografts (fascia, dermis, and dura mater) and xenografts (porcine dermis and small intestinal submucosa, bovine dermis and pericardium). Case series of autologous rectus fascial (ARF) sling were reviewed within the systematic review underlying the NICE guidance on urinary incontinence. [259] Ten series including a total of 1280 women were considered. Studies had a mean or median duration of follow-up between 2 and 6 years, while in three studies, maximum follow-up of 15–18 years was reported. Subjective cure rates ranged from 26% to 97% (median 81%); and cure rates that included subjective and objective elements ranged from 73% to 95%. Satisfaction rates of 86% and 92% were reported in two studies.

Synthetic sling materials have included nylon, polyethylene, polytetrafluoroethylene (PTFE), and polypropylene. On occasion, these polymers have been 'enhanced' with synthetic or biologic coatings in an attempt to improve their biocompatibility profiles. Many additional variations in the technique have been described, although it is unclear which of these materially influence the outcome. Several case series have published outcomes for polyethylene and PTFE slings with short-term cure rates typically in the 80-90% range, depending on the definition [EL=3]. Vaginal extrusion, erosion, and sinus formation have been common with these materials. Since the last ICI review, there have been no additional studies published and the number of these procedures performed appears to have waned significantly in favour of polypropylene midurethral slings.

Both biological and synthetic sling materials are analysed together in the Cochrane review [Rehman et al., 2011], although these were considered separately in the systematic review underlying the NICE guidance on urinary incontinence. [249, 259] NICE has also published a non-systematic review of biological sling procedures under its Interventional Procedures Programme. [260]The most recent Cochrane review included 26 RCTs (or quasi-randomised trials) describing a total of 2284 women of whom 1287 were treated with suburethral traditional slings. Sample sizes ranged from 20 to 655 participants. Several of these trials are available only in abstract form and remain unpublished as full peer-reviewed papers. Owing to the significant number of recent meeting abstracts about surgical procedures for SUI, only full publications have been included in this section. Additional studies have been included, but the majority of these are case-control studies and have a relatively low level of evidence.

There have been no trials identified that compared traditional suburethral sling operation vs. no treatment, sham operation, conservative management (e.g. pelvic floor muscle training, electrical stimulation, cones, biofeedback), anterior repair, laparoscopic retropubic suspension, or artificial urinary sphincter [Rehman et al., 2011]. [249] One trial studied patients with MUI treated with oxybutynin or surgery [Osman, 2003]. [261] The type of surgery was selected according to Valsalva leak point pressure (VLPP): those women with VLPP ?> 90 cm H2O underwent an ARF sling and those with VLPP ?> 90cm H2O underwent Burch colposuspension. The results for the total surgically managed group were similar to those for the subgroup having slings. The study suggested that slings are significantly better for treating MUI than oxybutynin. Results were analysed in terms of patient reported incontinence within one year (RR 0.18; 95% CI 0.08 to 0.43). Fewer women had persistent UUI after the sling surgery (RR 0.29; 95% CI 0.09 to 0.94).

a) Traditional sling vs. bulking agent (*table 4E*)

One RCT compared ARF sling with periurethral silicone injection in women with SUI secondary to ISD in whom conservative treatment had failed [Maher et al., 2005]. [165] At 6 months, no significant differences were seen between groups in subjective cure (1-hour pad test) or satisfaction, QOL (UDI-6, IIQ). Significantly more women undergoing sling surgery were objectively cured on the basis of urodynamic assessment (81% vs. 9%; p=0.0001), but duration

Table 4: Published evidence relating to traditional sling procedures for the treatment of SUI.

Author	RCT	Sling	Comparator	N/N (n1/n2)	F/U	Cure; effect size	EL	Comments
Table 4A: Traditional Sling vs. Colposuspension								
Henriksson, 1978*^ [119]	Quasi	Zoedler, Vaginal	MMK	30/30 (15:15)	3m	100% vs. 100% (o)	2	Quasi-RCT: by alternation; No ss calculation; analysis not clear if ITT
Hilton, 1989*^† [120]	Yes	Porcine Dermis	Stamey	20/20 (10/10)	3m	90% vs. 80% (o)	2	Included only SUI w/vaginal narrowing unsuitable for colposuspension
					24m	90% vs. 70% (s)		
Enzelsberger, 1996*^† [121]	Yes	Dura Mater	Colpo	72/72 (36:36)	32-48m	92% vs. 86% (s)	2	All patients had recurrent SUI after failed incontinence surgery; no ss calculation; analysis not clear if ITT
Sand, 2000*^† [122]	Yes	Gore-Tex	Colpo	36/37 (17:19)	3m	100% vs. 90% (o); p=ns	2	
Culligan, 2003*† [123]				28 (13:15)	33-116m (Mean 72.6m)	100% vs. 85% (o); p=ns 84% vs. 93% (s); p=ns		
Demirci, 2001*^ [124]	Quasi	ARF	Colpo	34/46 (17:17)	12m	94% vs. 88% (o); RR 2.0; 95% CI 0.20, 20.04	2	Quasi RCT by alternation; no ss calculation; analysis not clear if ITT
Bai, 2005*^† [38]	Yes	ARF	Burch	61/61 (28:33)	6m	92.8% vs. 90.9% (s+o); p=ns	2	No ss calculation; minimal details about randomization; some disparities between text and tables
					12m	92.8% vs. 87.8% (s+o); p=sig		
Albo, 2007;* ^ [125] Chai, 2009 [126]	Yes	ARF	Colpo	520/655 (326:329)	24m	SUI cure: 47% vs. 38% (s+o); p=sig Overall cure: 66% vs. 49% (s+o); p=sig	1	50% concomitant surgery for POP; 79% outcome assessment at 24m (265:255); postoperative UTIs, voiding and storage symptoms higher in ARF group
Table 4B: Traditional Sling vs. Traditional Sling								
Kaplan, 1996† [127]	No	ARF	Vaginal Wall	79 (43:39)	6-51m (Mean 21.4m)	84% vs. 89% (s+o)	3	89% vs. 94% satisfied or very satisfied
Barbalias, 1997*^† [128]	Yes	ARF	Gore-Tex	48/48 (32:16)	6m & 30m	81% vs. 88% (s-6m) 65% vs. 88% (s-12m)	2	No baseline data reported per treatment group, no analysis of results
Wright, 1998† [129]	No	AFL	CFL	92 (33:59)	1-28m (Mean 11.5m)	SEAPI improvement; p=ns	3/4	
Brown, 2000† [130] O'Reilly, 2002† [131]	No	AFL	CFL	167 (46:121)	44m:12m (Mean)	90% vs. 85% (s)	3	High satisfaction rates in both groups; an additional 8 women experienced failure at 4-13m F/U
Choe, 2000*† [132]	Quasi	PTFE MycroMesh	Vaginal Wall	40/40 (20:20)	12-27m	95% vs. 75% (s+o; mean 22m)	2	
Lucas, 2000*^† [133] Guerrero, 2007*^† [134]	Yes	ARF (20cm)	ARF (8-10cm)	165/168 (81:84)	12m 25-60m (Mean 42m) 61-89m (Mean 74m)	68-84% vs. 70-80% on sensitivity analysis (s); p=ns 47-60% vs. 49-64% (s); p=ns 29-62% vs. 44-57% (s); p=sig on ITT analysis only	1	ss calculated; cure ranges reflect ITT, per protocol, and best possible % cure
Kuo, 2001† [135]	Quasi	ARF	Prolene	50 (24:26)	Median 23-24m	91.6% vs. 92.3 (s); p=ns	2	ss not calculated
Maher, 2001† [136]	No	ARF	ARF & Vicryl Mesh	51 (24:27)	Mean 8m:5m	58% vs. 85% (s); p=sig 50% vs. 52% (o); p=ns	3	
Soergel, 2001† [137]	No	ARF	CFL	45:50 (33:12)	3-6m	69.7% vs. 16.7% (o); p=sig	3/4	
Flynn, 2002† [138]	No	ARF/AFL	CFL	134/140 (71/63)	24m	77% vs. 71% (o-pad test); p=ns	3	
Viseshsindh, 2003*^† [139]	Yes	ARF	Vaginal Wall	26/26 (15:11)	3-12m	93% vs. 100%; p=ns	2	Lack of details regarding randomization, analysis of results
Almeida, 2004† [140]	No	AFL	CFL	60 (30:30)	22-44m (Mean 33-36m)	40% vs. 70%; p=sig	3/4	
Rodrigues, 2004† [141]	No	ARF	Vaginal Wall	232 (128:104)	Mean 70.3m: 44.9m	93.7% vs. 79.8% (s; SUI cure rate) 73.4% vs. 61.5% (s; no SUI + no storage/ voiding dysfunction)	3	No statistical comparison between cures
McBride, 2005† [142]	No	AFL	CFL	47/71 (39:32)	24m	100% vs. 58.3% (o-CST); p=sig	3/4	Subjective indices criteria similar
Simsiman, 2005† [143]	No	ARF	Porcine Dermis	241 (78:83:80)	12m	87% vs. 54% vs. 64% (o); p=sig for ARF	3	
			CFL					
Giri, 2006 [144]	No	ARF	Porcine Dermis	94/101 (46/48)	36m	80.4% vs. 54% (s; cure + improved); p=sig	3	
Morgan, 2007 [145]	No	ARF	Porcine Dermis	111 (81:30)	Mean 24m:25m	Symptom severity higher for Porcine Dermis; p=sig	3	
Onur, 2008 [146]	No	ARF	Cadaver Dermis	49 (25:24)	Mean 18m:13m	84% vs. 79% (s; cure+ improved); p=ns	3/4	
Wilson, 2008 [147]	No	ARF	Bovine Dermis	85 (48:37)	12m	81.3% vs. 83.8% (s+o; SUI cure); p=ns 60.4% vs. 54.1% (s; global cure); p=ns	3/4	
Winckler, 2010 [148]	No	ARF	Marlex	474 (158:316)	12m; Mean (44m:43m)	81% vs. 88.9% (s); p=ns	3	

Table 4: Published evidence relating to traditional sling procedures for the treatment of SUI.(continued)

Author	RCT	Sling	Comparator	N/N (n1/n2)	F/U	Cure; effect size	EL	Comments
Table 4C: Traditional Sling vs. Retropubic Midurethral Sling								
Arunkalaivanan, 2003*^† [149]	Yes	Porcine Dermis	TVT	128/142 (74:68)	Median 12m	89% vs. 85% (s); p=ns	2	No ss calculation
Abdel-Fattah, 2004*† [150]				(68:60)	Median 36m	82.4% vs. 88.3% (s); p=ns		90.1% response rate to questionnaire at 36m
Hung, 2004 [[151]	No	Prolene	TVT	80 (57:23)	Mean 20m:23m	93% vs. 91.3% (o); p=ns 68.8% vs. 77.4% (s); p=ns	3	TVT better than prolene at BMI<27.3 kg/m^2
Bai, 2005*^† [38]	Yes	ARF	TVT	59/59 (28:31)	6m	92.8% vs. 90.3% (s+o); p=ns	2	No ss calculation; minimal details about randomization; some disparities between text and tables
					12m	92.8% vs. 87.0% (s+o); p=sig		
Wadie, 2005*^† [152]	Yes	ARF	TVT	53/53 (25:28)	6m	92% vs. 92.9% (o-1 week); p=ns	2	No ss calculation; may be underpowered; cure determined at first F/U visit because of results of interim analysis; UDI-6, IIQ-7 significantly decreased at 24m
Wadie, 2010 [153]				63/75 (39:24)	24m (median 54m)	93.7% vs. 95.2% (s+o); p=ns		
Kondo, 2006^ [154]	Yes	ARF	TVT	60/63 (29:31)	24m	66.7% vs. 82.6% (s); p=ns 47.6% vs. 69.6% (o); p=ns	2	Subjects for analysis reduced to 21 in ARF group & 23 in TVT group
Morgan, 2007 [145]	No	ARF	TVT	143 (81:62)	Mean 24m: 18m	Similar symptom severity; p=ns	3	
Basok, 2008^ [155]	Yes	CFL	IVS	139 (67:72)	12m	79% vs. 70.8% (o); p=ns 82% vs. 87.5% (s); p=ns	2	Method of randomization not stated; 67% had MUI; significantly higher persistent UUI and de novo DO for CFL
Jeon, 2008 [156]	No	PVS	TVT	181 (87:94)	24m	87.3% vs. 86.9% (s+o); p=ns	3	Retrospective; complication rates similar at 24m
					84m	59.1% vs. 55.1% (s+o); p=ns		
Sharifiaghdas, 2008^ [157]	Yes	ARF	TVT	61/100 (36:25)	12m (mean 39m)	75% vs. 76% (o-pad weight); p=ns	2	No ss calculation; 39% dropped out by 12m; no details about randomization; subjective cure (IIQ) similar
Amaro, 2009^ [158]	Yes	ARF	TVT	41/41 (21/20)	12m	57% vs. 65% (s); p=ns	2	No statistical difference in satisfaction, KHQ domains, de novo urgency; op time shorter for TVT
					36m	55% vs. 63% (s); p=ns		
Trabuco, 2009 [159]	No	ARF	Uretex	242/290 (79:163)	36m	Survival rate free of SUI: 73.8% vs. 87.9% (s); p=ns	2	RR for SUI after ARF=1.8x higher that Uretex at 36m; satisfaction lower in ARF group, voiding dysfunction higher
Guerrero, 2010^ [160] (Lucas, 2004*^ in abstract form) [[161]	Yes	ARF Porcine Dermis	TVT	189/201 (73/45/71)	6m	95% vs. 73% vs. 92% (s; improved); p=sig, PD vs. others	2	ss performed, but porcine dermis arm suspended following interim analysis at 12m
				182 (67/46/69)	12m	48% vs. 22% vs. 55% (s; dry); p=sig, PD vs. others		
Table 4D: Traditional Sling vs. Transobturator Midurethral Sing								
Silva-Filho, 2006^ [162]	Yes	ARF	Safyre-t	20 (10:10)	6m	39g vs. 8.4g (o; pad weight); p=sig	2	Mean operating time & hospital stay significantly shorter in Safyre group
Jeon, 2008 [156]	No	PVS	TOT	159 (87:72)	24m	87.3% vs. 34.9% (s+o); p=sig	3	Retrospective; complication rates similar at 24m; RR treatment failure of TOT=4.6x higher than ARF
Tcherniakovsky, 2009^ [163]	Yes	ARF	Safyre-t	41/41 (20:21)	12m	95% vs. 90.5% (s+o); p=ns	2	Randomization technique not stated; no ss calculation
Table 4E: Traditional Sling vs. Bulking Agent								
Corcos, 2005† [164]	Yes	ARF/Colpo	Bovine Collagen	133 (67:66)	12m	55% vs. 52% ; p=ns	2	ITT analysis
						72% vs. 53% ; p=sig		
Maher, 2005*^† [165]	Yes	ARF	Macro-plastique	45/45 (22:23)	6m	81% vs. 9%; p=sig	2	Silicone injected transurethrally

**: Included in ICI-4*
^: Included in Systematic Review (Novara, 2010)
†: Included in Cochrane Review (Ogah, 2011)

Key: RP MUS=retropubic midurethral sling; F/U=follow-up (months); LE=level of evidence; TVT=tension-free vaginal tape; o=objective; s=subjective; N/A=not available; OC=open colposuspension; LC=laparoscopic colposuspension; ITT=intention to treat

of the procedure, catheterisation, inpatient stay, and time to return to normal activities were significantly longer in the sling group. A survey of two-thirds of the women at 5 years found no statistically significant differences between groups in urinary symptoms or in satisfaction with surgery, although fewer women in the silicone bulking group were satisfied (29% vs. 69%) (n=45). [EL=2] .

Open continence surgery (a suspension procedure in 46% and ARF sling in 54%) was compared with periurethral collagen in women with SUI or MUI in an additional RCT [Corcos et al., 2005]. [164] As in the previous study, there were no significant differences in patient satisfaction or QOL (SF-36, IIQ) between groups at 1 year. Using ITT analysis, there was no significant difference in continence rates at 1 year (52% collagen, 55% surgery). If only the 89% of women who underwent the randomised intervention were considered, the continence rate with surgery was significantly higher (72% vs. 53%; *p*=0.01). The incidence of adverse effects was significantly higher in the surgery group: urinary retention 13% vs. 2%, transient voiding difficulty 36% vs. 17%, UTI 6% vs. 0% (n = 133). [EL=2]

b) Traditional sling vs. colposuspension (*Table 4A*)

Nine randomised or quasi-randomised trials were identified from the literature. Six of the trials compared suburethral slings with open abdominal retropubic suspension [Henriksson & Ulmsten, 1978, Enzelsberger et al., 1996, Sand et al., 2000, Demirci & Yucel, 2001, Bai et al., 2005, Albo et al., 2007] while one trial reported the long-term outcomes [Culligan et al., 2003] and another reported the complications [Chai et al., 2009] of aforementioned trials. [38, 119, 121-126] One additional trial compared sub urethral slings with the Stamey transvaginal needle suspension [Hilton, 1989]. [120] The Cochrane review systematically evaluated the six trials comparing suburethral slings with open retropubic suspension and an additional trial that was only published in abstract form [Rehman et al., 2011]. [249]

One RCT compared dura mater sling with open colposuspension in 72 women with recurrent SUI after hysterectomy [Enzelsberger et al., 1996]. [121] At a minimum follow-up of 32 months, the combined objective and subjective cure rates were 92% after dura mater sling compared with 86% after colposuspension. While both were common, significantly more women in the sling group developed postoperative voiding difficulty or urinary retention. More women in the colposuspension group developed a postoperative rectocele. Bladder perforation and de novo urgency were common in both groups. The time to spontaneous voiding was significantly longer in the sling group (n = 72). [EL=1/2].

Three trials compared ARF sling with open colposuspension. In a small trial alternating ?17 women each to ARF and colposuspension, ARF was superior to colposuspension at 12 months follow up by objective measures (94% vs. 88%) [Demirci & Yucel, 2001]. [124] In a second trial randomising women to ARF, colposuspension, and TVT, ARF was significantly superior to colposuspension at 12 months (92.8% vs. 87.8%) using a subjective and objective definition of cure [Bai et al., 2005]. [38] The significant difference in the two procedures was not evident at 6 months follow-up (92.8% vs. 90.9%). Finally, a large RCT performed by the Urinary Incontinence Treatment Network revealed that ARF was significantly superior to colposuspension both in its cure of SUI (47% vs. 38%) and overall incontinence cure (66% vs. 49%) at 24 months [Albo et al., 2007]. [125] Fifty percent of the women underwent concomitant surgery for pelvic organ prolapse (POP) and 79% (265:255) were available for the 24-month outcome assessment. Women undergoing ARF sling had a higher percentage of postoperative UTIs within the first six weeks of follow-up, voiding and storage urinary symptoms [Chai et al., 2009]. [126][EL=1]

Two small RCTs evaluated an expanded polytetrafluoroethylene patch sling (PTFE; Gore-Tex®) and open colposuspension, with the second trial providing long-term subjective and objective outcomes [Sand et al., 2000; Culligan et al., 2003]. [122] [123] Although the groups were different at baseline in terms of the proportion with detrusor overactivity (DO) (95% colposuspension vs. 41% sling), cure rates with PTFE were not significantly different from open colposuspension at 3 months (objective 100% vs. 90%) and 2.5 years (objective 100% vs. 85%; subjective 84% vs. 93%) (n = 36). No significant differences were found between groups in hospital stay or time to catheter removal. [EL=2]

In the Cochrane review, trials comparing rectus fascia with other materials heavily weighted the comparison of different types of sling [Rehman et al., 2011]. [249] Furthermore, the results of the most recent, and by far the largest and most rigorous RCT of colposuspension and ARF sling heavily weighted the results of the analysis [Albo et al., 2007]. [125]This trial randomised 655 women of whom 520 were assessed at 24 months, while the next largest trial randomised 72 women [Enzelsberger et al., 1996]. [121] The summary statistic, combining urodynamic and symptom only diagnosis, showed a lower incontinence rate with sling procedures (RR 0.75; 95% CI 0.62 to 0.90). The data from the trials where women all had urodynamic SUI showed no significant difference in urinary incontinence after one year (RR 0.72, 95% CI 0.31 to 1.67). Data beyond five years were provided by only one trial [Sand et al., 2000], and there was no statistically significant difference between the groups, but with very wide confidence intervals (RR 2.31; 95% CI 0.24 to 22.62). [122] Adverse events in general (47% vs.63% (*p*<0.001)

and voiding difficulty in particular (14% vs. 2%, $p<0.001$) were more common in sling group [Chai et al., 2009]. [126][EL=1].

Only one small trial is available to allow comparison between sling (porcine dermis) and needle suspension (Stamey) in a group of women unsuitable for abdominal colposuspension because of vaginal narrowing secondary to either previous interventions or atrophic change [Hilton, 1989]. [120]. Although there were no differences in objective cure rates at 3 or 24 months, perioperative complications (RR 4.50; 95% CI 1.28 to 15.81) and length of hospital stay (RR 13.00; 95% CI 5.00 to 21.00) favored the needle suspension procedure (n=20). [EL=2]

c) Traditional sling vs. traditional sling (*Table 4B*)

Our review identified 3 RCTs and 2 quasi-RCT comparing one type of traditional sling with another [Barbalias et al., 1997; Lucas et al, 2000; Viseshsindh et al., 2003; Choe et al., 2000; Kuo, 2001], with an additional RCT providing long-term outcomes of one of the aforementioned studies [Guerrero et al., 2007]. [128, 132-135, 139] The remainder were cohort and case control studies.

ARF and vaginal wall slings were compared in one RCT and two non-randomised retrospective studies [Viseshsindh et al., 2003; Kaplan et al., 1996; Rodrigues et al., 2004]. [127, 139, 141]All of these trials were considered to be of poor quality. The RCT reported high subjective cure, and satisfaction rates (80–100%) for both procedures, with median follow-up of 7 months and minimum follow-up of only 3 months (n = 26) [Viseshsindh et al., 2003] [139][EL=2]. The non-randomised studies reported similar 'success' rates with both interventions, ranging from 80% to 97%, with follow-up of 21 months, and 70 months versus 45 months (n = 232, n = 79) [Kaplan et al., 1996; Rodrigues et al., 2004]. [EL=2/3]. Other than the proportions of patients requiring intermittent catheterisation after surgery (2% in the ARF group and 0% in the vaginal wall group), no additional differences were noted in rates of other postoperative complications (e.g. voiding and storage dysfunction, wound infection and seroma formation, and bladder or urethral injury).

One RCT compared two techniques of fascial sling in 168 women with urodynamic SUI 89% of whom had had prior continence surgery [Lucas et al., 2000]. [133] Women underwent a standard fascial sling procedure or a 'sling on a string' (a shorter sling mounted on each end with a nylon thread). At 1 year, subjective cure rates were 84% using both techniques. Satisfaction and changes in IIQ scores were also similar in both groups, whereas improvements in UDI scores were greater with the standard approach (adjusted for differences in baseline UDI data). A further evaluation of women in this study was reported at 5 to 7 years of follow-up [Guerrero et al., 2007]. [134] There were no significant differences in symptoms of SUI or UUI between groups, with 40%-53% vs. 36%-51% reporting SUI in sensitivity analysis. [EL=1]

Eight non-randomised studies compared the outcomes of autologous and allograft slings in a total of 859 women with SUI [Wright et al., 1998, Brown & Govier, 2000, Soergel et al., 2001, Flynn & Yap, 2002, O'Reilly & Govier, 2002, Almeida et al., 2004, McBride et al., 2005, Onur et al., 2008], while one additional study also compared both interventions with a xenograft material (porcine dermis) [Simsiman et al., 2005]. [129-131, 137, 138, 140, 142, 143, 146]All were retrospective reviews, each with differences in duration of follow-up for the interventions evaluated (between 1 month and 3 years), with dropout rates of 4% to 34%. Additionally, between 16% and 82% in different studies underwent other concomitant surgeries, and all of these studies were considered to be of poor quality. [EL=3]

Four of these studies compared autologous with allograft (cadaveric) fascia lata. Three reported similar results for all outcomes (subjective cure, satisfaction, and UDI-6, IIQ-7 and SEAPI scores) [Wright et al., 1998, Brown & Govier, 2000, McBride et al., 2005], while the fourth study reported significantly higher cure rates in the autologous group [Almeida et al., 2004]. [129, 130, 140, 142] [EL=3] In three studies that compared autologous rectus fascia or fascia lata with allograft fascia lata, two found a significantly higher cure rate in the autologous group [Soergel et al., 2001, Simsiman et al., 2005]; [137, 143]the other found no significant differences in cure rate, although satisfaction rates were higher in the autologous group after 2 years follow-up [Flynn & Yap, 2002]. [36] In the study with a xenograft arm, cure rates were significantly higher with autograft material [Simsiman et al., 2005]. [143]The study comparing ARF to cadaveric dermis found no significant difference in subjective cure rates at a mean follow-up of 18 months and 13 months, respectively [Onur et al., 2008]. [146] [EL=3].

One RCT compared the porcine dermis sling vs. ARF and tension-free vaginal tape (TVT), a retropubic MUS [Guerrero et al., 2010]. [160]It should be noted that the ARF and porcine dermis slings were placed at the midurethra rather than the bladder neck, but suspended above the rectus fascia like traditional slings. The primary outcome was patient-reported improvement rates at 6 months and 1 year. At 6 months, the porcine dermis arm had significantly poorer improvement rates (73%) than TVT (92%) and ARF (95%), and, at 1 year, only 61% of the porcine dermis slings remained as improved, vs. 93% and 90% of the TVT and ARF arms, respectively. At 1 year, women undergoing porcine dermis slings had significantly lower dry rates (22%) as compared to TVT (55%) and ARF

slings (48%), respectively. Subsequently, the porcine dermis arm was suspended following interim analysis. There was no difference in success rates between the TVT and ARF arms. [EL=1/2].

One non-randomised trial compared porcine dermis sling vs. ARF [Giri et al., 2006], a second compared porcine dermis sling vs. both ARF and TVT [Morgan et al., 2007], and a third trial mentioned earlier compared porcine dermis vs. both ARF and allograft slings [Simsiman et al., 2005]. [143-145] At a follow-up of 36 months, the subjective success rate (cure and improved) after ARF sling was significantly higher than porcine dermis sling (80.4% vs. 54%) [Giri et al., 2006]. [144] Women undergoing porcine dermis slings were found to have significantly higher postoperative symptom severity than women undergoing either ARF sling or TVT [Morgan et al., 2007]. [145]Objective cure rates after ARF were significantly higher (87%) than either porcine dermis sling (54%) or cadavercis fascia lata (64%) [Simsiman et al., 2005]. [143][EL=2/3]

A quasi-RCT compared an ARF sling with a self-fashioned polypropylene mesh sling placed at the bladder neck [Kuo, 2001]. [135, 148] At a median follow-up of approximately 24 months, cure and satisfaction rates were similar but operating time and hospital stay were significantly shorter in the prolene sling group. Delayed voiding occurred in more women in the ARF sling group. No other significant differences were seen between groups in complications (e.g. haematoma, dysuria, de novo urgency or UUI) (n=50). [EL=2] A second, retrospective, non-randomised trial found no significant difference in subjective cure rate (81% vs. 88.9%) in women undergoing ARF and polypropylene mesh (Marlex) slings [Winckler et al., 2010]. [45] It should be noted that both slings in this study were placed at the midurethral but tied without tension above the rectus fascia as in the traditional bladder neck sling. Interestingly, vaginal extrusion rates and rates of surgical intervention for extrusion were not significantly different between ARF and Marlex slings. [EL=3]

One RCT compared ARF and PTFE slings in women with SUI, 92% of whom had had previous continence surgery [Barbalias et al., 1997]. [128] Combined objective and subjective cure rates at 6 months follow-up were 81% and 88%, respectively. No complications were reported in the ARF sling group; however, urethral erosion, recurrent UTI and *de novo* DO were very common with PTFE (n = 48). [EL = 1] A quasi-randomised comparison of MycroMesh patch sling (PTFE mesh impregnated with silver diacetate and chlorhexidine) with vaginal wall sling gave no statistical analysis, but found combined subjective and objective cure in 95% vs. 75% at mean follow-up of 22 months [Choe et al., 2000]. [132][EL=2] Again, the need for sling removal was common, reported in up to 31% (median 8%) in a review of case series within the systematic review underlying the NICE guidance on UI [National Collaborating Centre for Women's & Children's Health, 2006, National Institute for Health & Clinical Excellence]. [259][EL=3].

A retrospective cohort study compared an ARF sling with one reinforced with polyglactin mesh in women with urodynamic SUI, one-third of whom also had UUI (n=51) [Maher et al., 2001]. [136]Follow-up differed between groups and, overall, no clear difference was seen between groups in success rates. As with most studies, results depended on the definition of success used. No significant differences were noted between groups in terms of complications (e.g. wound infection, incisional hernia, voiding dysfunction, and de novo DO). [EL=3]

A small, non-randomised trial compared ARF to bovine dermis sling (n=85) [Wilson et al., 2008]. [147] Patients were allocated to material by institution and all had ISD, advanced age, and/or recurrent SUI after previous anti-incontinence surgery. At 12 months follow-up, the SUI-specific cure rates (consisting of subjective stress SEAPI domain and negative cough stress test) and global cure rates (consisting of SEAPI composite score and visual analog score) were not significantly different between the two slings. QOL indices (UDI-6, IIQ-7) were significantly improved in both groups. There were significant differences in several preoperative demographic variables between the groups.

The Cochrane review included 4 published trials in their statistical comparison [Barbalias et al., 1997; Lucas et al., 2000; Viseshsindh et al., 2003; Guerrero et al., 2008], as well as 2 trials in abstract form [Rehman et al., 2011]. [249]A total of 379 women studied after 12 months showed no statistically significant difference in incontinence rates (RR 0.89; 95% CI 0.72 to 1.10). However, results reported improvement after one year in favour of the traditional ARF sling (RR 0.33; 95% CI 0.17 to 0.64). The incontinence rate after five years was reported in only one trial [Lucas et al., 2000] and showed no statistically significant difference between different lengths of the autologous material used (RR 1.17; 95% CI 0.86 to 1.59). There was significant heterogeneity in the incidence of perioperative complications between groups in two trials, which was attributed more to complications with the use of Gore-Tex in one trial (RR 0.05; 95% CI 0.00 to 0.80, Barbalias et al., 1997). In the other trial, there was no statistically significant difference between two biological slings (RR1.14, 95% CI 0.78 to 1.66, Lucas et al., 2000). No statistically significant difference was found in assessment of the following adverse events, reported in only one trial [Lucas et al., 2000]: bladder perforation (RR 0.69; 95% CI 0.12 to 4.03), UTI (RR 1.73; 95% CI 0.66 to 4.54), de novo DO or urge symptoms (RR 3.11; 95% CI 0.65 to 14.97), and voiding dysfunction (RR 1.16; 95% CI 0.65 to 2.07).

d) Traditional sling vs. midurethral sling (Table 4C and D)

Our review identified 17 trials that addressed the comparison between traditional sling operations and MUS operations. Eight RCTs compared traditional slings placed at the bladder neck with the retropubic MUS [Arunkalaivanan & Barrington, 2003; Lucas et al., 2004; Bai et al., 2005; Wadie et al., 2005; Kondo el al., 2006; Basok et al., 2008; Sharifiaghdas & Mortazavi, 2008; Amaro et al., 2009;] and 3 additional RCTs provided long-term outcomes of aforementioned studies [Abdel-Fattah et al., 2004; Guerrero et al., 2010; Wadie et al., 2010]. [38, 149, 150, 152, 154, 155, 158, 160, 161, 262] One of the trials [Lucas et al., 2004] was only available as an abstract and 3 studies were non-randomised case control or cohort studies (Hung et al., 2004; Morgan et al., 2007; Trabuco et al., 2009). [145, 151, 153] [159] Two RCTs compared a traditional ARF sling to a transobturator (TO) MUS (Safyre-t) (Silva-Filho et al., 2006; Tcherniakovsky et al., 2009). [162, 163] Finally, a non-randomised trial compared pubovaginal slings (material not stated) with TVT and TOT (Jeon et al., 2008). [156]

Five RCTs compared ARF sling with TVT and reported on a total of 403 patients (Lucas et al., 2004, Bai et al., 2005, Wadie et al., 2005; Sharifiaghdas & Mortazavi, 2008; Amaro et al., 2009). [38, 152, 158, 161, 262]Two of the studies were recently updated at a longer-term follow-up (Guerrero et al., 2010; Wadie et al., 2010). [153, 160]Cure rates at 12-36 months (subjective +/- objective) varied widely depending on definition and were 55%-95% for both ARF and TVT. Although a statistical difference was not observed at 6 months, one trial (Bai et al., 2005) showed a significant difference in subjective + objective cure rate at 12 months favoring TVT (92.8% vs. 87%).[38] This trial also had a colposuspension arm, which had a 12 month cure rate of 88%. Another trial had a porcine dermis sling arm with a cure rate of only 53% (Lucas et al., 2004; Guerrero et al., 2010). [160, 161] The remainder of the RCTs did not reveal a statistical difference in cure rates between ARF and TVT. [EL=1/2]. One RCT found no statistical difference in objective and subjective cure rates at 12 months after cadaveric fascia lata slings and the intravaginal slingplasty (IVS), a multifilament, polypropylene MUS (Basok et al., 2008). [155]

One non-randomized trial that also included a porcine dermis arm found no statistical difference between ARF slings and TVT (Morgan et al., 2007). [145] Symptom severity, as assessed by validated questionnaire, was not significantly different between the ARF sling and TVT groups. As mentioned in the previous section, symptom severity was significantly higher in the porcine dermis group than in the other 2 groups. [EL=2/3] A second retrospective study compared traditional sling (material not stated), TVT, and the transobturator tape (TOT) (Jeon et al., 2008). [156]Overall complication rates were not significantly different between the sling groups. At 2 years postoperatively, the cumulative cure rates of the traditional sling, TVT, and TOT groups were significantly different (87.3% vs. 86.7% vs. 34.9%, respectively; $p<0.0001$). The risk of treatment failure in women who received TOT was 4.6 times higher than in women who underwent traditional sling. The 7-year cumulative cure rates of traditional sling and TVT groups were 59.1% and 55.1%, respectively. [EL=2/3] One trial each found no statistical difference in outcomes between traditional polypropylene sling and TVT (Hung et al., 2004) and ARF sling and Uretex, a monofilament polypropylene sling (Trabuco et al., 2009). [151, 159][EL=2/3]

One RCT comparing porcine dermis sling with TVT found no significant differences operating time, hospital stay, complication rates, or subjective cure at 1 year (85% vs. 89%) (Arunkalaivanan & Barrington, 2003), nor in cure (88% vs. 82%) or satisfaction at 3 years, assessed by mailed questionnaire (77% vs. 80%) (Abdel-Fattah et al., 2004). [48, 55] [EL=1]. It is not clear why this study found comparable results between porcine dermis and TVT, whereas the 3-arm trial cited above found such significantly poorer results after porcine dermis to require the premature curtailment of recruitment (Lucas et al., 2004; Guerrero et al., 2010). [160, 161]

Two small RCTs compared ARF sling to Safyre-t transobturator MUS (Silva-Filho et al., 2006; Tcherniakovsky et al., 2009). [59, 60] At a follow-up of 12 months, subjective + objective cure rates were not statistically different (95% vs. 90.5%) in one trial (Tcherniakovsky et al., 2009), while higher pad weight at 6 months was observed for the ARF group in another trial (39g vs. 8.4g) (Silva-Filho et al., 2006). [162, 163] [EL=2]

The Cochrane database identified 12 trials that addressed the comparison between traditional sling procedures and minimally invasive, MUS operations. [249]Ten of these studies have been summarised in our assessment and 2 studies were only in abstract form. [38, 149, 152, 154-156, 158, 160, 163, 262]Data on incontinence after the first year were available from four RCTs (Arunkalaivanan & Barrington, 2003; Bai et al., 2005; Kondo et al., 2006; Guerrero et al., 2010). [38, 149, 154, 160]Incontinence was reported by 31.6% of those women in the traditional sling and 25.3% of those in the MUS groups. This was not statistically significant (RR 1.23; 95% CI 0.91 to 1.66). This translates to 311 per 1000 women being incontinent after a traditional sling compared with 253 per 1000 after a MUS. Improvement after a year was addressed by two trials (Arunkalaivanan & Barrington, 2003; Guerrero et al., 2010) and there was no statistically significant difference between the two types of sling (RR 1.30; 95% CI 0.57 to 2.94). [149, 160]

Pooled data from 3 trials (Arunkalaivanan & Barrington, 2003; Kondo et al., 2006; Tcherniakovsky et al, 2009) showed a statistically significant higher risk of perioperative complications after traditional sling operations (RR 1.59; 95% CI 1.03 to 2.44). [149, 154, 163]Seven RCTs (Arunkalaivanan & Barrington, 2003; Bai et al., 2005; Kondo et al., 2006; Sharifiaghdas & Mortazavi, 2008; Song et al., 2004 (abstract only); Tcherniakovsky et al., 2009; Wadie et al., 2005) reported bladder perforation. [38, 149, 152, 154, 163, 262]There were more perforations after MUS procedures, but this did not reach statistical significance (RR 0.62; 95% CI 0.34 to 1.11) and the confidence interval was wide. The combined results from 3 trials showed less *de novo* urgency symptoms after MUS (RR 3.13; 95% CI 0.96 to 10.24) but this did not reach statistical significance and the confidence interval was wide. However, 3 trials showed that development of *de novo* DO was significantly less after MUS operations (RR 3.21; 95% CI 1.29 to 8.03). This was principally due to the higher weighting given to the largest trial (Basok et al., 2008). [155] The combined results from 5 trials showed that more women had postoperative voiding dysfunction after traditional slings than after MUS (RR 1.60; 95% CI 0.94 to 2.71) but this did not quite reach statistical significance and the confidence interval was wide. More women in the traditional sling group required release of sling (9% versus 2%), reported in two trials (RR 3.67; 95% CI 0.95 to 14.22) but again this was not statistically significant. There was no statistically significant difference in urinary retention up to 6 weeks (RR 5.51; 95% CI 0.68 to 44.63) from one trial and vaginal erosion (RR 0.35; 95% CI 0.02 to 8.10) based on one trial.

e) CONCLUSIONS / RECOMMENDATIONS

The conclusion of the Cochrane review was that data on traditional sling operations remain too few to adequately address the effects of this type of surgical treatment. They highlight the fact that many studies fail to address appropriate outcome measures to address the broader effects of the surgery, such as general health status and health economics. They also emphasise that reliable evidence on which to judge whether or not traditional slings are better or worse than other surgical or conservative management is currently not available.

From the available evidence, ARF sling is the most widely evaluated biological sling and is an effective and durable treatment for SUI. **[EL=1]** Limited data suggest that pubovaginal sling using porcine dermis is also effective, **[EL=1]** although data relating to other biological slings are few, and generally of poor quality. The inclusion of the large trial on traditional slings (Albo et al., 2007) strengthened the trend towards a better performance of the traditional slings in terms of patient reported incontinence rates, but higher early post-operative voiding dysfunction rates compared to open colposuspension. **[EL=1]** The limited data available suggest that the overall rates of late surgical complications are similar after sling and colposuspension; however, the pattern of complications may vary.

Meta-analysis showed a significantly greater patient-reported improvement of symptoms, using autologous materials, both within and after 1 year. There is no high level evidence of a difference in efficacy between biological and synthetic sling materials, although adverse events may be more common following the use of synthetic materials for 'traditional' sling procedures **[EL=3]**. Some synthetic slings, such as Gore-Tex, may have a higher incidence of erosion, infections and urgency symptoms. There is no high level evidence of a difference in efficacy between different biological sling materials, although those studies that find a difference all favour autologous materials **[EL=2]** However trials were few in number, with short follow-up and small populations. More evidence is needed to compare slings made of autologous materials with synthetic or exogenous biological materials.

Minimally invasive MUS operations appeared to be as effective as traditional suburethral slings in the short term (RR 0.97; 95% CI 0.78 to 1.20), although the confidence interval was compatible with minimally invasive slings being 20% better or 12% worse. **[EL=1]** The operating time and length of stay were also significantly shorter with minimally invasive synthetic MUS operations, and women had less perioperative complications and DO. The main perioperative complication of minimally invasive sling procedures is bladder puncture, although this does not appear to have longer term implications.

Autologous fascial sling is recommended as an effective treatment for stress urinary incontinence, which has longevity. **[Grade A]** Further high quality research is required to clarify the place of 'traditional' sling procedures in relation to other procedures, and to establish the optimum sling materials. **[Grade D]**

6. LAPAROSCOPIC COLPOSUSPENSION (TABLE 5)

a) Laparoscopic versus open colposuspension

The Cochrane review of laparoscopic colposuspension includes details of 22 RCTs that include laparoscopic colposuspension [263], 14 more than their initial review [264]. Of these 22 trials, ten compared laparoscopic colposuspension with open colposuspension [265-274].

Eight of the ten studies comparing laparoscopic colposuspension with open colposuspension were included along with eight retrospective cohort studies in a recently published meta-analysis [275].

We identified two further RCTs on laparoscopic colposuspension [276, 277]; in addition one study

Table 5. Published level 1 & 2 evidence relating to laparoscopic colposuspension for the treatment of stress urinary incontinence

	Study references	Type	Comparator	N/N (n1:n2)	FU	Cure (obj or subj)/ effect size	EL	Comments
1	[288]	RCT	Transperitoneal vs. extraperitoneal	22 (?:?)	1-12m	92% (s+o)	2	Mixture of suturing/stapling techniques; outcomes not separately evaluable.
2	[286]	RCT	Sutures vs. mesh/staples	69/69 (35:34)	1y	91% vs. 94%; RR 0.97; 95% CI 0.85, 1.11	2	
3	[271]	RCT	Open colpo	92/92 (46:46)	6m	80% vs. 96%; p=0.044 (o)	2	Part preference, part randomised; sample size calculation req'd 152.
4	[285]	RCT	2 single bite vs. 1 double bite sutures	161/? (83:78)	1y	83% vs. 58%; p<0.001	2	Enrolment curtailed early after interim analysis
5	[276] [287] [300] [301]	RCT	Sutures vs. mesh/staples	53/60 (27:26)	1 & 3y	89% vs. 75% (o - at 1y) 70% vs. 42%(o - at 2y) 58% vs. 38% (o – at 3y); p<0.05	2	Only completers analysed in 2001 paper; ITT used in 3 year follow-up.
6	[269]	RCT	Open colpo	74/74 (34:40)	18m	88% vs. 85%; p=ns (o+s)	2	No ss calculation.
7	[282]	RCT	TVT	68/79 (31:37)	1y	87% vs. 89% RR 0.98; 95% CI 0.82, 1.16	2	270 approached; 79 randomised. Study designed to examine costs.
8	[268]	RCT	Open colpo	90/90 (47:43)	1y	85% vs. 86%; p=ns (o)	2	15% vs. 37% underwent concomitant hysterectomy
9	[166]	RCT	TVT	46/46 (23:23)	3-24m	83% vs. 83%; RR1.00; 95% CI 0.77, 1.30 (s+o)	2	No information on randomisation; no allowance for variation in FU
10	[302] [283] [279]	RCT	TVT	121/128 (51:70)	1y	57% vs. 86% (95% CI for diff. 12.7, 43.9); p=0.000 (o)	2	Lap. colpo with mesh. SS calculation required 176.
11	[281] [46]	RCT	TVT	71/72 (35:36)	12-43m 12-88m	97% vs 81% (o – at median 18m) 43% vs. 52% (s – at median 65m)	2	SS 130; recruitment stopped early because of slow recruitment. 63 (88%) FU at 1y; 33 (46%) at 2y
12	[266]	RCT	Open colpo Lap colpo (mesh)	184/211 (49:63:72)	1y	90% vs. 92% vs. 63% (o) p<0.05 open vs. mesh	2	Unclear randomisation; all pts randomised to Burch or lap colpo (mesh) also included in separate multicentre study [265]. Only completers analysed.
13	[277]	RCT	Open colpo	52/52 (26:26)	3-24m	81% vs. 81%; p=ns	2	Many concurrent procedures - varied between groups
14	[270] [289]	RCT	Open colpo	242/291 (144:147)	2y	80% vs. 70% (o)	1	5 had no op., & 12 changed op. after randomis'n. Objective data on 83%.
15	[267]	RCT	Open colpo	164/200 (76:88)	3-5y	72% vs. 78%; p=0.22 (o at 6m) 69% vs. 80%; p=0.38 (s at 2y)	2	Telephone interview at 3-5y; results 'similar' to 24m

Notes: patient numbers are given as – total no. followed up or analysed /total no. recruited (no. in index group: no. in comparator group)
SS = sample size; ITT = intention to treat

previously only in abstract form has recently been published [267], and two have further publications with longer-term follow-up [278] or cost-effectiveness data [279].

Studies included in the Cochrane review had different lengths of follow-up, although eight studies had follow-up in the region 6 to 18 months. In comparison with open colposuspension they found subjective cure rates to range from 58% to 96% in the open and 62% to 100% in the laparoscopic group within the 18 months follow up, with a non-significant 5% lower relative subjective cure rate for laparoscopic colposuspension (RR 0.95, 95% CI 0.90 to 1.00) [263] [EL=1]. The two studies with follow-up at five years or beyond unfortunately remain unpublished and available in abstract form only. Both these studies were relatively small, and their results are inconsistent, one finding better subjective outcome from the laparoscopic procedure [273], and one favouring the open procedure [272]; the methodology of this latter study in particular has been questioned [EL=2].

Overall, the objective cure rate as judged by cough stress testing or pad test within 18 months was statistically significantly lower following laparoscopic colposuspension (RR 0.91, 95%CI 0.86 to 0.96) [EL=1]. Between 18 months and five years there was no significant difference (RR 1.01, 95% CI 0.88 to 1.16); again however, there was heterogeneity with one small trial greatly favouring open procedure [272] and the other favouring laparoscopic [273] [EL=2]. When objective cure was judged by urodynamic investigations there was a significantly higher success rate following open colposuspension (RR 0.91, 95%CI 0.85 to 0.99).

b) Laparoscopic colposuspension versus other techniques

Eight trials have compared laparoscopic colposuspension with minimally invasive mid-urethral slings [166, 280-284].

In comparison with minimally invasive mid-urethral slings there was no statistically significant difference in subjective cure rates within 18 months (RR 0.91, 95% CI 0.80 to 1.02) [EL=1]. The definition of objective cure varied widely between studies, although overall the objective cure rate was higher for minimally invasive mid-urethral slings than laparoscopic colposuspension (RR 0.92, 95% CI 0.85 to 0.99) [EL=1].

Although laparoscopic colposuspension is regarded as a less invasive operation than the open colposuspension the mid-urethra tape procedures had significantly shorter operating time (<0.001), hospital stay (<0.001) and time for resuming normal activity (<0.01 -0.001) than the laparoscopic colposuspension.

c) Different techniques of laparoscopic colposuspension

Different aspects of the laparoscopic technique (one vs. two sutures [285], sutures vs. Mesh [266, 286, 287] and transperitoneal vs. extraperitoneal approach to laparoscopy [288].

Two sutures either side of the bladder neck resulted in higher subjective (RR 1.37, 95% CI 1.14 to 1.64) and objective (RR 1.42, 95% CI 1.14 to 1.77) cure rate than one [285] [EL=2].

When comparing sutures and mesh to secure paraurethral support, sutures resulted in higher subjective (RR 1.28, 95% CI 1.11 to 1.47) and objective (RR 1.20, 95%CI 1.07 to 1.35) cure rate than mesh [266, 276, 286, 287] [EL=1].

The transperitoneal versus extraperitoneal study reported above employed different techniques (sutures vs mesh) and therefore gives little insight into the value of either approach given the superior results obtained with sutures.

The use of glue or fibrin sealants has not been reported outside small case series.

d) Cost effectiveness of laparoscopic colposuspension

Cost effectiveness was assessed in only one trial [270, 289]. This study showed that whilst laparoscopic surgery produced greater quality adjusted life years (QALYs), there was an additional cost when compared to open surgery. The differential mean cost was GB £372 (95% credibility interval [CrI]: 274–471), and at 6 months QALYs were slightly higher in the laparoscopic arm relative to the open arm (0.005; 95% CrI: –0.012 to 0.023). The cost of each additional QALY in the laparoscopic group or incremental cost-effectiveness ratio (ICER) was £74,400 at 6 months, but reduced to £9,300 by 24 months, in view of a further increase in QALYs, but no additional costs (assumed) [289] [EL=1].

Earlier studies have shown TVT™ to be dominant in cost effectiveness terms over both open [290] and laparoscopic colposuspension (albeit using a mesh technique) [279] [EL=1].

e) Complications of laparoscopic colposuspension

Bladder, ureteric and vascular injuries are recognised complications of colposuspension. The Cochrane review reported 21 bladder injuries among 521 laparoscopic procedures (compared with 10 among 507 open procedures) and two studies reported obturator vein lacerations. However, when compared with the traditional open colposuspension, the laparoscopic group was found to have significantly fewer postoperative complications (RR 0.74, 95% CI 0.58–0.96) with lower estimated blood losses and shorter duration of catheterisation.

Longer operating times are a significant disadvantage of the laparoscopic approach; however, women have reported significantly less pain, (Carey et al 2000, Burton 1999)[272, 291] shorter hospital admissions, faster recoveries and quicker return to normal activities. (Cheon et al 2003, Fatthy et al 2001, Kitchener et al 2006 and Su et al 1997)[292-295].

f) Longevity of laparoscopic colposuspension

A long-term review of women who had undergone laparoscopic colposuspension more than 10 years previously (Barr et al 2009)[296] compared the results with a group of women who had open colposuspension. Subjective cure rates deteriorated over time from 71% and 67% at 6 months to 52% and 36% at 10 years for the laparoscopic and open procedures, respectively.

The conclusion from the Cochrane review was that the available evidence suggests that laparoscopic colposuspension may be as effective as open colposuspension two years postoperatively [263]. The systematic review specific to laparoscopic colposuspension and TVT™ concluded that the evidence so far appears to favour the latter as the minimal-access technique of choice for USI [297]. In both cases however the authors indicated that the place of laparoscopic colposuspension in clinical practice could not be clearly defined without further long-term results.

It should also be noted that much of the published research in this area is from individuals with enthusiasm and skill in laparoscopic surgery; their results should not necessarily be seen as being generalisable to the urogynecological/urological community at large. The NICE guidance includes amongst its recommendations that laparoscopic colposuspension is not recommended as a routine procedure for the treatment of SUI in women, but that the procedure should be performed only by an experienced laparoscopic surgeon working in a multidisciplinary team with expertise in the assessment and treatment of UI [298, 299]; this same point is emphasised in the meta-analysis from Tan and colleagues [275] [EL=4].

g) Summary:

Laparoscopic colposuspension shows comparable subjective and objective outcome to open colposuspension in the short to medium term; longer term outcomes are unknown **[EL=2]**.

Limited evidence suggests that whilst the subjective outcome from laparoscopic colposuspension is similar to the TVT™ the objective outcome is poorer. **(EL=2)**

Laparoscopic colposuspension may not be good value for money when compared with open colposuspension in the short term (i.e. first 6 months following surgery), but it could be a cost-effective alternative over 24 months **[EL=1]**; other comparisons however suggest that minimally invasive mid-urethral tape procedures may be dominant in health economic terms.

h) Recommendations:

Laparoscopic colposuspension can only be recommended for the surgical treatment of SUI in women by surgeons with appropriate training and expertise. **(Grade D)**

Women should be advised about the limited evidence available about the longevity of laparoscopic colposuspension. **(Grade D)**

Laparoscopic colposuspension might be considered for the treatment of SUI in women who also require concurrent laparoscopic surgery for other reasons. **[Grade D]**

II. STRESS INCONTINENCE AND PELVIC ORGAN PROLAPSE

Women who present with urinary incontinence as their primary symptom may often have symptomatic or asymptomatic pelvic organ prolapse (POP). In a patient with POP, SUI may be evident and overt or POP may be protective of, or mask, obvious urinary incontinence via urethral kinking. This is termed “occult” SUI and is elicited only during maneuvers to reduce the POP. SUI and POP are intimately related. Coexistent symptoms of SUI may be present in over 60% of women with POP, [38] and occult SUI may occur in up to 80% of clinically continent women with severe POP. [303-306] Postmenopausal women may have up to twice the risk of developing occult SUI. Furthermore, women with both SUI and POP have more lower urinary tract symptoms and more functional impairment than women with POP only. [307]

There is some evidence from Medicare claims data that addressing POP at the time of SUI surgery may avoid an early repeat operation for either POP or SUI; however, the rates of postoperative outlet obstruction are higher. [308] As such, the decision to treat POP surgically at the same operation as the SUI should be determined by the symptoms and bother the POP produces to the patient and the influence that the POP surgery may have on the outcome of the surgery for SUI. In instances where the prolapse is symptomatic, it will be a matter of subjective opinion whether the incontinence or the prolapse is more significant and bothersome (rather than a pathological diagnosis). If the treatment selection is based on subjective assessment, it follows that the outcome from treatment must also be based on subjective rather than objective measures. As with most issues in pelvic floor reconstruction, the decision to perform an anti-incontinence procedure

and the choice of the procedure itself is a source of great debate. The literature evaluating the following clinical scenarios will be evaluated: (a) overt SUI with POP; (b) occult SUI with POP reduction; (c) high grade POP in the absence of occult or overt SUI; and, (d) the status of preoperative urgency urinary incontinence (UUI) and overactive bladder symptoms (OAB) after POP repair.

1. OVERT SUI WITH POP

Women who present with SUI commonly have deficient support of the anterior vaginal wall. Significant POP is generally defined anatomically as the presenting part of the prolapse reaching to within a centimetre of the hymenal remnant. The presence of preoperative POP may have an impact on the efficacy of anti-incontinence surgery, and the outcomes of any surgery to correct SUI should be evaluated along with the incidence of *de novo* or worsened postoperative obstructive and storage urinary symptoms.

Milani et al noted that the presence of preoperative POP led to a lower cure rate of SUI after either the Burch colposuspension or the MMK procedure, with greater degrees of POP associated with lower SUI cure rates. [309] (Level 3) Additionally, Colombo et al performed a RCT to compare Burch colposuspension with anterior colporrhaphy in women with SUI and Grade 2-3 anterior vaginal wall prolapse. [310] Level 1/2) The authors found that the Burch colposuspension was better in controlling SUI but that cystocele recurred in 34% of patients. The cure rate for cystocele with anterior colporrhaphy was high (97%) but cure rate of SUI was very low. The authors concluded that neither operation was recommended for combined SUI and advanced cystocele.

In a recent RCT, Costantini *et al* revealed that Burch colposuspension does not provide a significant cure of SUI in incontinent women undergoing sacrocolpopexy. [10] (Level 1/2) Out of 47 women with POP and SUI, 24 underwent sacrocolpopexy and Burch and 23 underwent sacrocolpopexy alone. The primary outcome measures were anatomical outcome and changes in incontinence status as indicated by a bladder diary, daily pad use, and CST, while secondary end points were changes in subjective symptoms and quality of life as measured by the UDI and IIQ. In the Burch group, 13 of 24 patients (54.2%) were still incontinent after surgery compared with 9 of 23 (39.1%) in the non-Burch group. Two women in the Burch group (8.3%) and one in the non-Burch group (4.3%) complained of *de novo* urinary storage symptoms. There was no significant intergroup difference (p=0.459). No significant intergroup difference emerged in anatomical outcome and UDI and IIQ scores improved in both groups (p = 0.0001) and the intergroup difference was not significant in either questionnaire (p = 0.769 and p = 0.327, respectively).

Moon *et al* compared the Burch colposuspension (n=49) and TOT (n=60) in consecutive women undergoing sacrocolpopexy for POP ≥ Grade III and SUI. [311] (Level 2) Mean hospital stay was longer in the Burch group (11.3 days vs. 7.8 days, p<0.001), as were the rates of postoperative urinary retention (53.1% vs. 11.7%, p<0.001), *de novo* urgency (18.4% vs. 3.3%, p=0.01), and recurrent SUI (18.4% vs. 1.7%, p=0.003). The SUI cure rate was significantly higher in the TOT group than in the Burch group (98.3% vs. 69.7%, p <0.001).

Gordon *et al* prospectively followed 30 patients short-term who underwent TVT at the same time as surgery for severe POP. [312] (Level III) No patients had postoperative symptoms of SUI despite three patients (10%) having positive postoperative stress tests. *De novo* detrusor overactivity occurred in 13% of subjects. Yip and Pang recruited 302 patients, 250 (82.8%) of when completed 1-year follow-up. [313] (Level II/III) There were 157 (62.8%) patients who had a TVT alone, and 93 (37.2%) had TVT and concomitant POP surgery. All patients had urodynamic studies before and one year following surgery. The objective cure rate for SUI was 87.3% for patients with TVT alone and 80.6% for TVT with concomitant procedures (p>0.05). The subjective SUI cure rates for TVT alone and TVT plus concomitant procedures were 89.2% and 86.0% at 4 months, and 93.0% and 94.6% at 1 year, respectively (p>0.05). The most common complications were postoperative urinary retention (15.2%), *de novo* detrusor overactivity at one year (10%), and intraoperative bladder puncture (8%). In an additional prospective cohort study and a case series, the TVT combined with vaginal reconstruction resulted in 85% to 95% cure rates for urodynamic SUI. [314, 315] (Level III) The rates of postoperative urinary urgency and voiding dysfunction were 10% and 11%, respectively. Voiding difficulties and post void residuals of > 100 mL were treated with urethral dilatation and the authors did not report any cases of long-term urinary retention.

Transobturator midurethral slings may also be effective in the setting of overt SUI and POP. The addition of TVT-O to anterior colporrhaphy in 50 women with SUI and high grade anterior POP resulted in 1-year objective cure rates for SUI and POP of 92% and 91%, respectively. [316] (Level 3) Overall early postoperative complication rate was 16%, although all were minor. At 12-month follow-up, tape extrusion requiring surgical removal developed in only one patient. The ICIQ-UI SF questionnaire scores were 13.4 +/- 6.8 and 3.5 +/- 3.2 (p <0.01) between preoperative and 12-month follow-up, respectively.

In data from the National Hospital Discharge Survey, the addition of an anti-incontinence procedure did not significantly increase the immediate morbidity in women who underwent POP surgery. [317] Of the 1931 women who underwent POP procedures, concomitant anti-incontinence procedures

were performed in 26.6% and complications were reported in 14.9%. Complications were associated with medical comorbidity (OR 11.2) and concomitant hysterectomy (OR 1.5), while concomitant procedure for SUI was not.

2. OCCULT SUI WITH POP

Overall, the level of evidence supporting a specific anti-incontinence procedure in women with POP and occult SUI is low. Chaikin *et al* discovered occult SUI after reduction of prolapse with a pessary in 14 of 24 women (58%). [304] (Level III) Ten women with no urodynamic evidence of sphincteric incontinence underwent anterior colporrhaphy and no additional anti-incontinence procedure was performed. Mean follow-up was 44 months (range 12 to 96). None had postoperative SUI but one (10%) had a recurrent grade 2 cystocele. The 14 remaining women with urodynamic stress incontinence after POP reduction underwent anterior colporrhaphy with a bladder neck pubovaginal sling procedure. Mean follow-up in these cases was 47 months (range 12 to 108). In two patients (14%) SUI developed postoperatively and one (7%) had a recurrent grade 3 cystocele. The incidence of UUI did not appear to be significantly influenced by either surgical intervention. Overall 12 patients had preoperative UUI, of whom 9 (75%) had persistent UUI postoperatively. *De novo* UUI developed in another woman. The authors' findings suggest that patients without occult SUI may be effectively treated with POP repair alone, while women with occult SUI on urodynamics should be offered anti-incontinence surgery.

Barnes *et al* reported on 34 women with grade 3-4 POP and occult SUI who underwent a bladder neck pubovaginal sling as the anti-incontinence procedure. [318] (Level III) Sling materials included autologous rectus fascia, cadaveric fascia lata, or a free vaginal wall graft. Mean follow-up was 15 months (range 6 to 39). The mean time required before spontaneous voiding resumed without the need for catheterisation was 11.8 days (range 2 to 46) and no patient developed permanent urinary retention. Two (9.5%) of 21 women without preoperative UUI developed *de novo* UUI; however, preexisting UUI resolved in 45%. SUI occurred in two women (7%) at four and 19 months postoperatively, while clinically significant uterine prolapse developed in one woman two years after surgery.

Groutz *et al* reported on 100 women with occult SUI undergoing concomitant transvaginal POP surgery and TVT.[319] (Level 3) The mean follow-up period was 27 months (range: 12-52 months). Two patients had postoperative urinary retention necessitating catheterisation for more than seven days, but neither required any surgical intervention. Vaginal extrusion was diagnosed in three patients, all of whom were successfully treated by partial TVT excision. Two (2%) patients developed urodynamically-confirmed SUI within one year postoperatively; however, postoperative urodynamics revealed asymptomatic urodynamic stress incontinence in 15% of other patients. Thirteen (72%) of 18 patients with preoperative UUI had postoperative persistent UUI, while *de novo* UUI developed postoperatively in 8 (8%) of patients.

A RCT compared concomitant endopelvic fascia plication at the urethrovesical junction vs. TVT in 50 women with severe POP and occult SUI. [320] (Level 1/2). The addition of a TVT resulted in a higher 2-year objective continence rate than endopelvic fascia plication (92% vs. 56%, respectively; $p<0.01$). The subjective cure rates were 96% for TVT compared to 64% for plication ($p=0.01$). Time for resumption of spontaneous voiding, rates of urinary retention, *de novo* UUI, and perioperative complications did not differ between the groups. Despite negative cystometrograms, *de novo* UUI symptoms were reported in 12% of the TVT group compared to 4% of the suburethral plication group ($p=0.66$).

Karateke *et al* reported on the outcomes of TOT in the treatment of women with occult SUI and POP. [321] (Level 3) Urodynamic evaluation revealed occult SUI in 25 of 79 patients with POP. Post-operative OAB, SUI, and MUI were found in three (12%), two (8%), and one (4%) patients in the occult SUI group, respectively. The corresponding numbers were six (11%), five (9%), and three (6%) in the preoperatively continent group. No significant difference was found between the groups in terms of post-operative OAB symptoms, SUI, and MUI. Groutz *et al* also reported on the outcomes of TVT-O in the management of occult SUI in women with significant POP. [322] (Level 3) Of the 117 patients, 6 (5.1%) had immediate postoperative voiding difficulties necessitating catheterisation for more than two days. Late postoperative morbidity was assessed in 110 patients with ≥3 months of follow-up (mean 27.2 ± 17.7). Of these 110 patients, 7 (6.4%) had protracted postoperative thigh pain with spontaneous resolution within 1-3 months and 7 (6.4%) had developed recurrent UTIs. There were no cases of vaginal extrusion. The functional outcome analysis was restricted to 92 patients with ≥12 months follow-up. Of these, 13 (14%) were found to have urodynamic stress incontinence; however, only two patients (2.2%) were symptomatic, amounting to a subjective and objective cure rate of 97.8% and 86%, respectively. Of the 34 patients who had had urinary storage symptoms preoperatively, 22 (64.7%) had persistent symptoms postoperatively. An additional four patients (6.9%) had developed *de novo* urinary storage symptoms, and one patient developed bladder outlet obstruction.

3. NO OVERT OR OCCULT SUI AND POP

There has been a tremendous amount of debate on how to treat women with significant POP who have no complaints of SUI and occult SUI cannot be demonstrated on either cough-stress test or urodynamic evaluation after prolapse reduction. The case for a concomitant anti-incontinence procedure is to

potentially prevent a second surgical intervention in a cohort at high risk for developing SUI. The case against performing anti-incontinence surgery in the same time hinges on the potential for developing *de novo* or worsened urinary storage and voiding symptoms in a population with minimal to no preoperative symptoms. The literature appears divided on the topic. As mentioned previously, Chaikin *et al* found that the majority of women with significant POP who do not have overt or occult SUI will not develop overt SUI after transvaginal POP repair alone. [304] (Level III)

The decision to perform a concomitant colposuspension at the time of sacrocolpopexy has been passionately debated. In a well-publicised study by Brubaker *et al* as part of the Colpopexy and Urinary Reduction Efforts (CARE) trial, stress-continent women undergoing sacrocolpopexy were randomised to receive or not to receive a concomitant Burch colposuspension. [323] (Level I) At two years, 302 of 322 randomised participants were available for analysis. Two years after surgery, 32.0% and 45.2% of women in the Burch and control groups, respectively, met the SUI endpoint (presence of SUI symptoms, positive CST, or interval treatment for SUI, p=0.026). The apex was well supported in 95% of women, and this was not affected by concomitant Burch. There was a trend toward fewer urgency symptoms in the Burch group (32.0% vs. 44.5% no Burch, p=0.085). In a subanalysis of the CARE trial, Visco *et al* confirmed that women who demonstrated preoperative occult SUI were more likely to report postoperative SUI, regardless of concomitant Burch colposuspension (controls 58% vs. 38%, p=0.04; Burch 32% vs. 21%, p=0.19). [324] The authors also concluded that occult SUI detection rates varied widely based on the method of prolapse reduction. Interestingly enough, while only 23% of the 1134 members of the American Urogynecological Society (AUGS) responded to a survey about their practice patterns regarding high-grade POP, 57% of the respondents stated that they would not perform a prophylactic Burch colposuspension at the time of sacrocolpopexy in a woman without symptoms of SUI. [325]

Conversely, Costantini *et al* found that the Burch procedure did not confer a significant benefit in terms of SUI cure to women undergoing surgical prolapse repair.[326] (Level I/II) A total of 66 continent women with POP were randomly assigned to abdominal sacrocolpopexy and concomitant Burch in 34 (group 1) or sacrocolpopexy alone in 32 (group 2). Median follow-up was 97 months (range 72 to 134). Nine of 31 group 1 patients (29%) were incontinent compared with 5 of 31 (16%) in group 2 (p=0.553). In group 1, all except one patient were successfully treated for voiding dysfunction. Storage symptoms had disappeared in one patient and *de novo* storage symptoms had developed in two since the previous follow-up. *De novo* incontinence developed in two group 2 patients after midterm outcomes were reported. Median UDI-6 and IIQ-7 scores were improved in all groups at last follow-up (p<0.0001).

Ballert *et al* suggested a protocol to determine if MUS should be placed at the time of transvaginal POP repair. [327] (Level 3) A total of 50 women reported clinical (symptomatic) SUI preoperatively, while 55 did not. Regardless of clinical presentation, patients with urodynamic or occult SUI underwent simultaneous MUS, while those without urodynamic or occult SUI did not. The risk of intervention due to obstruction after receiving MUS was 8.5%, while the risk of intervention for *de novo* SUI in patients with no clinical, urodynamic, or occult SUI who did not undergo MUS was 8.3%. The risk of intervention for SUI in patients with clinical SUI but no urodynamic or occult SUI and no MUI was 30%. These data suggest that a prophylactic sling in women without clinical, urodynamic, or occult SUI may be as likely to cause postoperative urinary retention requiring reoperation as it is to prevent postoperative de novo SUI requiring surgery. The evidence also suggests that MUS should be considered for women with clinical SUI (regardless of the presence or absence of urodynamic or occult SUI), as there is a much higher possibility for further intervention for SUI in this population. While this report lacks a control group, the findings of this study underscore the importance of a detailed informed consent discussion between the patient and surgeon.

A study by Liang *et al* further supported the suggestion that urodynamic evidence be used to guide possible treatment of SUI during POP surgery. [222] (Level III) Among the 79 patients evaluated for severe POP without symptoms of SUI, 32 patients had a positive pessary test and underwent vaginal hysterectomy, anterior and posterior colporrhaphy, and TVT (Group 1). In group 2, 47 patients (17 of whom had positive pessary tests and 30 of whom had negative pessary tests) underwent vaginal hysterectomy and anterior and posterior colporrhaphy alone. Eleven (64.7%) of 17 patients with positive pessary tests who did not undergo TVT had urine leakage after their hysterectomies. Conversely, none of the 30 patients who had negative pessary tests developed symptomatic SUI after vaginal hysterectomy. Among the 32 patients with positive pessary tests who had TVT with their hysterectomies, three developed urine leakage later for a cure rate of 90.6%. Had all patients with high-grade POP undergone TVT, 35% would have undergone an unnecessary anti-incontinence procedure. This study supports the notion that women without symptoms of overt or occult SUI are not likely to leak after undergoing POP surgery alone. Additionally, the Cochrane database recently evaluated the value of anti-incontinence surgery at the time of prolapse repair in continent women and concluded that this practice did not reduce the rate of postoperative SUI (RR 1.39, 95% CI 0.53 to 3.70). [328]

Thus, the value of adding an anti-incontinence procedure to a POP repair in women who are dry before operation remains to be adequately assessed; however, available evidence suggests that the majority of women without occult or overt SUI may remain continent after POP repair alone. While the addition of a Burch colposuspension to a sacrocolpopexy may not add a significant amount of additional morbidity, it may not confer a benefit in terms of preventing the development of overt SUI. Furthermore, the potential benefit of Burch colposuspension cannot necessarily be extrapolated to other prophylactic anti-incontinence procedures. An urodynamic approach to decision making appears to be a prudent one. Adequately powered RCTs are urgently needed to answer these questions and high level evidence may be on the horizon. The details of multicentre, prospective RCTs comparing POP and anti-incontinence surgery in women with overt SUI and those with occult SUI (CUPIDO) have recently been described and recruitment is under way. [329] A second, multicentre RCT is in preparation to determine whether the prevalence of postoperative urinary incontinence differs between stress continent women receiving vaginal prolapse repair with concomitant TVT and those with only sham incisions at 3 months after surgery. [330] A second objective of the OPUS trial is to determine whether it is more cost-effective to place a TVT prophylactically than to treat the SUI symptoms postoperatively as they occur over a 12-month period after the index surgery.

4. UUI AND POP

Symptoms of OAB such as urinary urgency, frequency, and UUI are often seen in women with POP and community-based, hospital-based, and cross-sectional studies have shown that the prevalence of OAB is higher in women with POP vs. those without POP. [331, 332] The prevalence of any OAB symptom approached 50% and increases with advancing age. [332]Symptoms of POP may be an independent risk factor for symptomatic OAB.[332] As such, the impact of POP repair on OAB symptoms and UUI is of great value in preoperative counseling of women with high-grade POP.

The impact of anterior vaginal wall prolapse repair on bladder function has been much debated. Digesu *et al* reported on a 12-month prospective cohort study of 93 women who had a standard anterior colporrhaphy for cystocele. [333] (Level 3) Post-operatively, urinary frequency resolved in 60%, urgency resolved in 70%, and UUI resolved in 82%, illustrating that anterior repair may lead to resolution of the majority of OAB symptoms. Similar findings were reported in a prospective cohort study of prolapse repair in elderly women by Foster et al. [334] (Level 3) The authors also noted that vaginal reconstructive or obliterative surgery produced a similar improvement in urinary symptoms at 12 months after surgery. Nguyen and Bhatia noted that UUI resolved in 24 of 38 women (63%) and persisted in 14 (37%) after surgical repair of uterine and/or vaginal vault POP. [335] (Level 3) The authors included both transvaginal and transabdominal POP repairs in their analysis. Uninhibited bladder contractions < 25 cm H2O during cystometry (p=0.01) and bladder trabeculation (p=0.03) were each an independent predictor of UUI resolution after POP repair. In a review of MEDLINE and Embase literature, de Boer et al found no evidence for a distinct relationship between the compartment or stage of the POP and the presence of OAB symptoms. [331] The authors also concluded that all treatments for POP, including surgery and pessary management, resulted in an improvement of OAB symptoms. There is no consensus regarding the predictors for OAB symptom resolution and individual OAB symptoms had different predictors. [331] When there is concomitant DO and POP, DO resolves in a proportion of the patients and bladder outlet obstruction appears to be the primary mechanism by which POP induces OAB symptoms and urodyanmics DO.

5. CONCLUSIONS

There is **Level II/III** evidence to support a concomitant anti-incontinence procedure at the same time as repair of POP in a woman with overt SUI. There is **Level II/III** evidence supporting pubovaginal sling, retropubic MUS, and transobturator MUS as effective anti-incontinence options in a woman with overt SUI and POP. Anterior colporrhaphy alone and pubocervical fascia plication are not effective options for overt SUI in women undergoing POP repair. **(Level I/II)** Burch colposuspension may not be more effective than no additional surgery in curing overt SUI in women undergoing sacrocolpopexy. **(Level I/II)** There is Level III evidence that bladder neck pubovaginal sling, retropubic MUS, and transobturator MUS are effective in resolving occult SUI during POP repair. There is controversy whether prophylactic Burch colposuspension is effective in improving the chances of developing overt SUI after sacrocolpopexy. **(Level I)** There is Level 3 evidence to support not performing a concomitant anti-incontinence procedure in a continent woman at time of POP repair. There is **Level III** evidence that treatment of prolapse by reconstructive or obliterative surgery improves overactive bladder symptoms.

III. NEUROMODULATION

1. SACRAL NEUROMODULATION

a) Recent Cochrane review

A recent Cochrane review [336] examined, systematically the evidence of the effects of implantable stimulation devices in the treatment of urgency urinary incontinence, urgency or frequency, and urinary retention.

Eight RCTs were considered eligible and were included in the analysis.

At 6 months follow up SNM was found to be superior to no treatment for all indications as there were highly significant changes in all the outcomes measured (leakage episodes, number of voids, rating of urgency, having no leakages, reduction in number of voids, pad usage, volume at first contraction, and bladder capacity). Both the SF-36 mental and physical scales favoured the immediate implant group but the results were not statistically significantly different between the treatment and no treatment groups

The quality of the studies included was rated poor. There were no studies comparing SNM with other treatment methods.

The review concluded that SNM can be of benefit in selected patients with overactive bladder symptoms, retention without organic obstruction, and in those for whom other methods of treatment have failed.

b) Long term results

1. Refractory Uui

The long term results of SNM have been addressed by several case studies. There are 4 studies reporting median or mean follow up of >5 years. Two of the studies are presented in the last ICI report and these are the largest ones. Most of the long-term studies do not report the complete continence rates.

2. Long Term Results – Efficacy Over Time

De Groen et al [337] evaluated the long-term results of neuromodulation in 60 patients with refractory idiopathic urgency urinary incontinence. All subjects recruited from a single institution and were assessed prospectively at regular intervals for at least 5 years after implantation. The success rate gradually decreased from 52 patients (87%) at 1 month to 37 (62%) at 5 years. Complete continence persisted in 15% of patients. The analysis was extended to the 41 patients who passed the 10-year follow-up. At least 25 of these women (61%) were still on active SNS. The 10-year success rates did not appear to be different from the 5-year results suggesting that a deterioration of the results is observed during the first 5 years which stabilised thereafter. A total of 57 adverse events occurred in 32 (53%) patients the majority of those being related to hardware failure and pain or discomfort at various sites. Pain was managed conservatively. A total of 23 reoperations, including the 2 explantations, were done in 15 patients (25%). **(Level 3 evidence)**

3. Urgency And Frequency

There are no new studies examining the long term results of SNM in patients with urgency frequency. The largest study so far (van Kerrebroeck) has been presented in the last ICI report.

A more recent small case series [338]examined the long term efficacy of sacral neuromodulation in patients with IC/PBS not responding to medical treatment. Overall 22 patients had a permanent generator implantation. Success with the device was defined as greater than 50% improvement in the chief complaint of urinary pain, urgency and frequency or urgency incontinence. For an average follow up of 59.9 months 17 of 22 patients (77%) reported long-term cure or more than 50% improvement in those symptoms. However 50% of patients underwent explantation due to technical reasons, infection, battery depletion, or pain at the implantation site **(Level 3 evidence).**

Zabihi et al [339]evaluated the efficacy of bilateral caudal epidural sacral neuromodulation for the treatment of refractory chronic pelvic pain (CPP), painful bladder syndrome, and interstitial cystitis (IC). Thirty consecutive patients (21 female, 9 male) with severe refractory symptoms underwent bilateral S2–S4 sacral neuromodulation for CPP/IC. Patients were evaluated with the O'Leary IC symptom and problem index (ICSI, ICPI), the short form of the Urogenital Distress Inventory (UDI-6), and the RAND 36-item health survey (SF-36) preoperatively and 6 months postoperatively. The mean and minimum follow-up were 15 and 6 months, respectively. Of the 30 patients, 23 (77%) had a successful trial stimulation and were permanently implanted. Among these patients, the ICSI and ICPI scores improved by 35 (p = 0.005) and 38% (p = 0.007), respectively. The pain score improved by 40% (p = 0.04) and the UDI-6 score by 26% (p = 0.05). On average, patients reported a 42% improvement in their symptoms. SF-36 scores did not improve significantly. **(Level 3 evidence)**

4. Non Obstructive Urinary Retention (Table 6)

The effectiveness of SNM in women with urinary retention has been confirmed by previous RCT (Jonas 2001) and hs been presented in the last ICI report.

The long term efficacy of SNM for women with urinary retention particularly those with urethral hyperactivity (Fowler's syndrome) has been presented by Datta et al [340].

Thirty (50%) had a one stage and the rest a two stage procedure. Overall, 43 of 60 (72%) women were voiding spontaneously, with a mean postvoid residual volume of 100 mL; 30 (50%) no longer needed to use CISC. The efficacy of the 2 stage compared to the one stage procedure was similar (73% vs 70%). Women with a normal urethral sphincter electromyogram had worse outcomes than women with an abnormal test (43% vs 76%). There were 99 adverse events (AEs) and 63 surgical revisions for the women during a total of 2878

months of SNS experience. In all, 73% of the women had an AE during their treatment with SNS **(Level 3 evidence).**

A recent retrospective single centre study [341] examined the long-term efficacy and durability of sacral nerve stimulation (SNS) for the treatment of refractory, non-obstructive urinary retention. Forty patients were included (29 with complete retention requiring CISC) and 11 with incomplete retention (high post -micturition residuals). Of the 40 patients 28 (70%) responded successfully to the test stimulation and underwent a placement of an IPG. At a mean follow-up of 40.03 +/- 19.61 months, 24 (85.7%) of 28 patients demonstrated sustained improvement of greater than 50% with significantly reduced number and volumes of catheterisations/day and improvement of post-micturition residuals. The Interstim device was removed in 4 patients (14.3%) and required revision in further 6 (21.4%) **(Level 3 evidence).**

5. Effect Of SNM On Sexual Function

The effect of SNM on the female sexual function was investigated by a small pilot prospective single centre study[342]. Overall 36 women with severe frequency, urgency, retention, and chronic pelvic pain refractory to medical and other treatments were enrolled and were assessed by the Female Sexual Function Index (FSFI) questionnaire preoperatively and 6 months postoperatively. Twenty-one patients had some form of pelvic pain component to their symptoms, and 15 had voiding dysfunction without pain. The overall score on the FSFI improved by 52% (p = 0.05). Results were better in patients who underwent the treatment for voiding dysfunction (n = 15) compared to those who had pain as their primary complaint. In this group, the overall score improved by 157% (p = 0.004). Those who underwent the procedure for the indication of IC/CPP (n = 21) did not show a statistically significant change in their scores.

Another small study [342] showed that in sexually active women who had a permanent sacral neuromodulator implanted there was no difference in the sexual function before and 6 months after implantation as assessed by the FSFI.

6. Patient Satisfaction

Long-term clinical efficacy of SNM has been assessed and confirmed by many studies. However it is quite unclear how this can be translated to patient satisfaction and improvement of quality of life bearing in mind that there are technical problems and adverse effects needing constant medical attention in a significant proportion of these patients.

The long term QOL data were assessed in 2 previous reports. [343] [344]

Leong et al [345] examined the longterm satisfaction of patients with an implanted SNM for various medical indications such as overactive bladder syndrome, non-obstructive urinary retention, combined overactive bladder and retention, and pelvic pain. Overall 275 patients received a postal questionnaire regarding satisfaction and experiences with the system, such as side effects, complications, burden, impact on sexuality and defecation changes. The response rate was 75% (207 patients) with a median post-implantation period 77 months (range 12 to 214). The patient satisfaction rate was high at 90% and significantly related to the perceived clinical effect and 85% if all explanted cases (13 patients) were considered as failures. Satisfaction had no direct relationship with patient age, gender, duration of therapy or type of complaint for which SNM was offered, but was significantly lower in patients with more than 1 pelvic floor comorbidity. The patient's attitude towards

Table 6 : Summarises the follow-up data for patients with non obstructive urinary retention who were treated with SNM (from 1. Bosch JL. An update on sacral neuromodulation: Where do we stand with this in the management of lower urinary tract dysfunction in 2010? BJU Int 2010, Nov;106(10):1432-42.)

Reference	Patients, *n*	Follow-up duration, months	% with >50% decrease no. of CISC/day	% without need for CISC
Jonas *et al.* [70]	24	At 18	NR	58
Aboseif *et al.* [71]	20	Mean 24	NR	90
van Kerrebroeck *et al.* [56]	31	At 60	58	NR
De Ridder *et al.* [75]	62	Mean 43	NR	55
Kessler *et al.* [40]	13	Median 12	69 (9/13 not failed)	NR
Datta *et al.* [72]	60	Mean 48	72 (voiding spontaneously)	50
White *et al.* [73]	20 (no. on CISC)	Mean 41	86	55

NR, not reported.

yearly follow-up and the ability to use the patients programmer was positively related to the degree of satisfaction. Overall 40% reported having some limitations or concerns with SNM such as exclusion from MRI and passing through metal detectors after an INS was implanted, possible changes in future reimbursement. Most patients perceived regular pain (56%) and discomfort (40%) at the INS site. **(Level 3 evidence)**

7. Neurogenic Lower Urinary Tract Dysfunction (LUTD)

The efficacy and safety of the use of SNM for the treatment of neurogenic lower urinary tract dysfunction was examined in a recent meta-analysis [346]. This included overall 357 patients from 26 independent studies (prospective and retrospective cohort studies and case reports) with level of evidence ranging from 2b to 4. There was no RCT available for analysis. The pooled success rate was 68% and 92% for the testing and the permanent phase of SNM respectively for a mean follow up of 26 months. With regards to adverse events the pooled rate was 0% during the first stage to 24% for the chronic phase of the treatment. The most frequent adverse events were lead migration and pain at the site of permanent neuromodulator further surgery was performed in 45 of 224 patients. The available evidence from this meta-analysis suggest that SNM may be effective and safe for the treatment of patients with neurogenic LUTD (level of evidence 2) but further well designed adequately powered studies are needed before SNM is routinely recommended for the treatment of neurogenic LUTD.

The use of SNM in patients with neurogenic LUTD is limited by the fact that quite often they need to be investigated by magnetic resonance imaging studies.

The progressive nature of the neurologic disease in some patients could be a limiting factor in the effectiveness of the SNM.

8. Selection Of Patients

• Testing procedure

The application of the two-stage procedure using the permanent tined lead appears to be superior to the percutaneous PNE technique

A study by Bannowsky et al.[347], in a retrospective case control study examined urodynamic and clinical outcomes of the two different testing techniques and found that permanent quadripolar electrodes led to significant differences in the overall response rate (81.8% versus 47.6%) and urodynamic parameters (max detrusor pressure, bladder capacity) compared to the PNE.

This has to be balanced against the cost implications: the permanent electrodes are several times the cost of the cheaper PNE wires.

In a recent study [348] 41 of 76 (54%) who failed to respond to PNE were subsequently tested with tined lead procedure permanent stimulators. Of those 18(44%) were implanted with a neurostimulator after a successful response suggesting that the tined lead procedure is more sensitive screening tool. At 53-month follow-up 12 of these patients (67%) had a successful outcome, which was not statistically different from the success rate in patients with a positive response to an initial PNE or TLP test.

The response rate to PNE as compared to the 1st stage tined-lead placement test ((FSTLP) were directly compared in a prospective single centre study[349].

One hundred patients with refractory idiopathic overactive bladder syndrome (OAB) or non-obstructive urinary retention, screened with both PNE and FSTLP. The positive response rate on PNE was 47%. FSTLP showed a 69% positive response rate, which was negatively related to age. The 22% gain in positive response was statistically significant ($p < 0.001$) and positively associated with female gender and younger age. This study also suggests that the FSTLP may be a more sensitive screening method than PNE. (Level of evidence 2)

• Unilateral versus Bilateral lead placement at screening phase

A retrospective study by Pham et al. [350] compared the success of the bilateral to unilateral neuromodulator lead placement in 124 patients undergoing screening for permanent placement of sacral neuromodulation. Fifty-five (44%) patients underwent unilateral stage I lead placement and 69 (56%) received bilateral S3 leads. Successful stage I trials were reported in 32/55 (58%) and 53/69 (76%) of unilateral and bilateral cohorts, respectively (P = 0.03). There was no difference in wound infection or other complications. **(Level of evidence 3)**

• Pre-treatment psychological problems

Psychiatric comorbidity has previously been proposed as a negative predictor by some authors.

In a recent single centre prospective study the relationship between psychiatric history and the outcome of chronic SNM treatment was assessed. Fifty four patients with symptoms of OAB or chronic non-obstructive problems completed the Amsterdam Biographic Questionnaire (ABQ), which measures the personality traits of the patient, and the Symptom Check-List-90-Revised (SCL-90-R), which is a screening instrument for

neuroticism, and for current level of complaints. Of those 15(28%) reported a history of psychiatric disorder in their medical history. The authors found that a history of psychiatric disease was not related to the outcome of test stimulation, but was shown to be a positive predictor for the occurrence of AEs with permanent SNM treatment.**(Level of evidence 4)**

• Urodynamics

A recent study [351] examined urodynamic diagnosis as a predictor of outcome. 111 patients undergoing permanent SNM after a successful PNE test were divided into those with DO (67) on urodynamics and those without DO (44). Both groups showed a statistically significant improvement in bladder volumes at first sensation of filling (FSF) and at maximum fill volume (MFV) before voiding for both UI subgroups, compared with baseline. Resolution of DO post treatment occurred in 51% of patients, however the success in those patients was not significantly different from those with persistent DO. Interestingly patients with UI and no DO had a higher rate of clinical success (73%) than those with UI and DO (61%) although this did not reach to statistical significance. (Level of evidence 3)

• Comparison to the botulinum toxin-A (BTX-A)

The efficacy rates reported for both SNM and BTX-A in patients with refractory OAB appear to be similar.

The use of BTX-A has recently been approved by the FDA for use in patients with OAB due to neurological conditions such as spinal cord injury and multiple sclerosis. SNM is more invasive but offers long term efficacy whereas treatment with BTX-A injections is less invasive but needs to be repeated on a less-than a year basis in order to provide sustained efficacy. In addition it has been reported that 20% of patients treated with BTX-A injections need to enhance treatment efficacy with anticholinergics and a small proportion report reversible voiding difficulties and need to self catheterisation.

At present there is no RCT published to compare the efficacy and safety of the two methods.

However there are published studies examining the cost-effectiveness of these 2 methods.

Siddiqui et al [352] suggested that BTX-A would be a cost-effective therapeutic option for refractory urgency incontinence in the first 2 years of therapy. Costs were analysed from the societal perspective and in relation to effectiveness. All direct costs related to the treatment modalities as well as the costs of incontinence were calculated but not the indirect costs (lost productivity secondary to incontinence) due to the limited data available. Two years is a short duration for a chronic condition. The prolonged effect of SNS and the cost and time needed for repeat BTX-A injections might change significantly the comparison of cost effectiveness for a longer duration of treatment.

In another study Leong et al [353] by comparing the costs and effects value of the two methods in patients with refractory OAB concluded that starting with SNM, treatment is cost-effective after 5 years compared to BTX. However, when different scenarios were examined, such as the use of local anaesthesia for BTX treatment and SNM peripheral nerve evaluation or bilateral test, SNM was not cost-effective.

It is also acknowledged that the costs for surgery and for the devices may vary significantly between countries and even between hospitals within one country.

c) Conclusion and Recommendations

Sufficient **Level II /III** evidence exists evaluating implantable neuromodulation. Current series include retrospective cohort studies and no high level RCTs. There is a need for further prospective randomised assessment of this intervention – especially from the durability standpoint. **Grade of recommendation is A / B**

2. PERCUTANEOUS TIBIAL NERVE STIMULATION (PTNS)

a) Efficacy

Several case series have shown a reduction of frequency, urgency, urgency urinary incontinence in 60-80% of patients with no serious adverse events. Recent research provides level I evidence that PTNS is efficacious in the treatment of refractory OAB.

b) PTNS vs Placebo (sham device)

A multicentre, double-blind, RCT (SUmiT) [354] compared the efficacy of PTNS to sham through 12 weeks of therapy. A total of 220 adults with overactive bladder symptoms were randomised 1:1 to 12 weeks of treatment with weekly percutaneous tibial nerve stimulation or sham therapy. In the sham group a Streitberger placebo needle was used to simulate the location and sensation of PTNS needle electrode insertion without actually puncturing the skin. In addition two active TENS surface electrodes were placed, one under the little toe and one on the top of the foot. Sham stimulation parameters were determined based on subject first sensory level of localised stimulation through a TENS unit.

Patients were evaluated by overactive bladder and quality of life questionnaires as well as 3-day voiding diaries before treatment and at week 13.

At 13 weeks follow-up there was moderate or marked improvement in overall bladder symptoms in 54.5%(60/110) and 20.9% (23/110) of subjects respectively (p<0.001). All individual symptoms such as frequency, nighttime voids, voids with moderate to severe urgency and uregency urinary incontinence episodes demonstrated statistically significant improvement from baseline to 13 weeks for the PTNS group compared to the sham group (**Table 7**). This was also confirmed on voiding diaries.

There were no serious adverse effects with 4% (5/110) reporting bleeding and discomfort at the needle site and one case of ankle bruising and a further one with leg tingling.

In a further RCT[355], 35 patients not responding to anticholinergics were randomised to PTNS or control group. The control group (17 patients) received an original placebo treatment using a 34 gauge needle placed in the medial part of the gastrocnemius muscle. Patients were considered to be responders if they had a reduction in urgency incontinence episodes greater than 50%. After 12 weeks of weekly treatments 71% (12/17) in the PTNS group and 0% (0/12) in the placebo group were considered responders (p < 0.001). **(Level of evidence I - II)** ?

All reports are Level III in terms of evidence and there continues to be a lack of comparative reports assessing different techniques. All current series are retrospective in nature and there is a need for prospective randomised assessment of management of these patients. Functional assessment across all domains of pelvic floor activity (pain, continence, urinary storage, and sexual function) are critical to the complete assessment of response to this intervention

c) PTNS vs tolterodine ER

Another multicentre RCT showed comparable efficacy of PTNS to medical treatment (OrBIT trial)[356].

A total of 100 adults with urinary frequency (> 8 times/day) were randomised 1:1 to 12 weeks of treatment with weekly PTNS or to 4 mg daily extended-release tolterodine. Voiding diaries and an overactive bladder questionnaire were completed at baseline and at the end of therapy. Global response assessments were completed by subjects and investigators after 12 weeks of therapy. The two groups were comparable for baseline characteristics and OAB symptoms.

At 12 weeks 79.5%(35/44) of the PTNS and 54.8% (23/42) of the tolterodine patients considered themselves to be cured or improved (p = 0.01).

Urinary frequency, urgency urinary incontinence episodes, urgency severity and nighttime voids, voided volume and QoL improved significantly in both groups but there was no difference between the PTNS and the tolterodine patients. **(Level of evidence I)**

d) Long term data

A long-term follow-up of the OrBIT Trial evaluated the durability of PTNS benefits[357].

Patients who were randomised to weekly PTNS in the OrBIT trial were offered an additional 9 months of treatment with assessments at 6 and 12 months from baseline. Outcome measures included voiding diary data, overactive bladder questionnaires, global response assessments and safety assessments. A total of 33 percutaneous tibial nerve stimulation responders continued therapy with 32 and 25 subjects completing 6 and 12 months of therapy, respectively. Subjects received a mean of 12.1 treatments at various intervals during an average of 263 days, with a mean of 21 days (median 17) between treatments.

Sustained improvement was shown with 94% (30/32) of patients continuing periodic treatment considering themselves to be cured or improved at 6 months and 96% (24/25) at 12 months follow-up. Overactive bladder questionnaire symptom severity was significantly improved from 12 weeks to 12 months (p <0.01) as well as from 6 to 12 months (p <0.01). No serious adverse events were reported.

Table 7: PTNS: Improvement of global response assessment at 13 weeks compared to baseline (Level of evidence I)

Overall bladder symptoms (intent to treat)	60/110 (54.5)	23/110 (20.9)	<0.001
Overall bladder symptoms	60/103 (58.3)	23/105 (21.9)	<0.001
Urinary urgency	44/103 (42.7)	24/105 (22.9)	0.003
Urinary frequency	49/103 (47.6)	23/105 (21.9)	<0.001
Urinary urge incontinence	39/103 (37.9)	23/104 (22.1)	0.02

e) Mode of action

The exact mechanism of PTNS on bladder function is unclear but it is thought that this is mediated through the retrograde stimulation of the sacral nerve plexus. The posterior tibial nerve is a peripheral nerve with mixed sensory and motor fibres. It originates from spinal roots L4 through S3, which also contribute directly to sensory and motor control of the urinary bladder and pelvic floor. A recent study suggests that a plastic reorganisation of cortical network triggered by peripheral neuromodulation could be a mechanism of action of PTNS[358].

f) Neurogenic DO

The efficacy and safety of PTNS was evaluated by a prospective multicentre study in 16 women with MS and LUTS unresponsive to anticholinergics.[359] Patients were offered 12 sessions of PTNS. Assessment of LUTS was by validated, self-administered chart and questionnaires, testing the subjective and objective relevance of LUTS for patients and their impact on QoL before and after treatment. There was a significant reduction in daytime frequency, nocturia and the mean post-micturition residual and there was an increase of the mean voided volume. Eighty-nine percent of patients reported treatment satisfaction of 70%. Significant improvement in QoL was seen in most domains of the King's Health Questionnaire. No adverse events were reported. **(Level of evidence III)**

Kabay et al.[360] suggested that PTNS can be acutely effective to suppress detrusor overactivity in patients with neurogenic detrusor overactivity due to Multiple Sclerosis. The researchers performed urodynamics before and during PTNS treatment and found that there was a significant improvement of mean volume of first involuntary detrusor contraction from 145.2 ml, to 244.7 ml and of the maximum cystometric capacity from 204.8 ml, to 301.2 ml during the stimulation period. The results have been criticised as the PTNS was applied after a 2nd filling of the bladder and this repeat cystometry during the stimulation could have affected the urodynamic parameters. **(Level of evidence III)**

In a further study [361] the same group of researcher found similar results of an acute effect of PTNS on detrusor contraction in patients with neurogenic DO due to Parkinson's Disease. **(Level of evidence III)**

g) CONCLUSION AND RECOMMENDATIONS

Reports are **Level I - III** in terms of evidence and there are few comparative reports assessing different techniques. Most current series are retrospective in nature however recent prospective randomised (against sham) assessment of management of these patients has improved the overall quality of reporting. **Current recommendations range from A – C.**

IV. ENTEROCYSTOPLASTY

Vesical enlargement, or augmentation cystoplasty (AC), has been used for many years with varying degrees of success for refractory detrusor overactivity (DO) and related incontinence. Other than idiopathic detrusor overactivity (IDO), indications for enterocystoplasty include small capacity bladders due to fibrosis, tuberculosis, radiation, or chronic infection, neurogenic detrusor overactivity (NDO), poor bladder compliance, as well as others [362-365] AC typically involves a segment of the bowel that is removed from continuity with the fecal stream, detubularised, and patched into the bisected bladder. This method increases bladder capacity and decreases bladder pressure caused by uninhibited detrusor contractions. Additionally, incorporation of bowel into the bladder results in decreased bladder contractility and an increased interval in the volume to first involuntary bladder contraction during cystometric evaluation.

Virtually any portion of the GI tract can be utilised for enterocystoplasty, and each segment has its own unique favourable properties as well as inherent complications [365, 366] There is no ideal segment for all cases. Technically, the surgeon must be aware that the selected bowel segment should contain a suitable length of mesentery to reach into the deep pelvis for a tension free anastomosis between bowel and bladder. There has been no general agreement on whether it is more favourable to bivalve the bladder sagittally or transversely during enterocystoplasty; however, it is considered ideal to create the broadest possible opening in the bladder and thereby create the widest possible anastomosis between bladder and bowel resulting in the most spherical configuration possible. The bowel is divided and detubularised on its antimesenteric side prior to anastomosis to maximally reduce peristaltic contractions. Again, the goal of enterocystoplasty is to create a high capacity, low-pressure reservoir during the filling/storage phase of the micturition cycle. When successful, and properly combined with other concomitant reconstructive procedures (i.e. ureteroneocystostomy, slings, artificial urinary sphincters, continent catheterisable channels, etc.), enterocystoplasty can protect the upper urinary tract from pressure-related injury, infection, and vesicoureteric reflux while ideally providing complete urinary continence.

Apart from the inherent risks of open abdominal surgery associated with bowel and bladder anastomoses, AC carries several distinct long-term risks. The risks of this surgery include kidney or bladder infections, new-onset recurrent UTIs, metabolic derangements, mucus production, and,

in rare cases, bladder tumours. As a segment of bowel is used for AC, the available absorptive surface area of the bowel is reduced, and the incorporation of bowel segments into the urinary tract may have metabolic consequences [367]. Hyperchloraemic metabolic acidosis can occur if ileal and/or colon segments are used, as well as malabsorption of vitamin B12 and bile acid after the use of ileal segments. Blackburn et al demonstrated a reduction in serum B12 level with time following ileocystoplasty in 44% of their patients at 7-year follow-up and recommended that these patients should have their B12 levels measured in the long term [368].

There has been concern about the incidence of secondary malignancies that may develop as a long-term consequence of bladder augmentation. Using colonic segments, tumours are most likely to occur at the ureteral implantation site. To prevent metabolic complications, careful patient selection and meticulous and lifelong follow up, as well as prophylactic treatment, are mandatory. Endoscopy for early detection has been recommended, starting 10 years postoperatively for patients who underwent surgery for a benign condition. Of interest, Higuchi et al retrospectively review their registry of 153 patients with an ileal/colonic AC and a matched control population and found that AC does not appear to increase the risk of bladder malignancy over the inherent cancer risk associated with the patient's underlying congenital abnormality [369]. Immunosuppression irrespective of bladder treatment was an independent risk factor for malignancy in their patient population.

Conclusion and Recommendtions

Level I Evidence:

There have been no randomised controlled trials, double blind or sham-controlled trials or cohort studies which have examined the effects of enterocystoplasty for the treatment of NDO or directly compared it to another therapy for the same indication, **(Recommendation grade C)**. Also the role of enterocystoplasty is not defined in subjects with idiopathic detrusor overactivity. **(Recommendation grade D)**

Other Evidence:

The conclusions of several recent reviews on the role of AC indicate that the overwhelming predominance of literature is dedicated to AC in patients with a neurogenic bladder [370, 371]. By some estimates, approximately 10% of reports in the literature have examined the results of AC in adults with IDO. These include only case series **(LOE=4)**. Since the publication of the 4th International Consultation on Incontinence, there have been few additions to the AC literature for IDO (See Table). The studies differ in several ways. Most include both males and females, and some include a varying number of patients with NDO. Additionally, length of follow-up differs widely and the criteria for success may be considerably different and inconsistently reported [372]. Outcome measures have included mostly non-validated questionnaires and subjective patient assessments. Furthermore, continence rates must also be considered with caution, as many AC procedures are combined with bladder outlet procedures [364]. Overall, there does not appear to be a consensus whether patients with IDO or NDO achieve better outcomes [364, 373, 374] The reasons for the inconsistencies in patient satisfaction in neuropathic patients and non-neuropathic patients remain unclear.

Several variations on the standard AC have been recently described. Novel bowel options include urothelium lined seromuscular colocystoplasty and an appendicular-based caecal flap [375-377]. The recent incorporation of robotic-assisted laparoscopic surgery (RALS) and laparoendoscopic single site (LESS) procedures has further added to the surgical options for AC [34-40]. While the initial results are encouraging, long-term outcomes are uniformly absent. Overall, due to its invasive nature and potential for long-term adverse effects, AC is considered to be one of the last choices of treatment in refractory IDO cases [378].

V. AUTO AUGMENTATION

Initially described by Cartwright and Snow, auto augmentation of the bladder was described as an alternative option to AC, especially in children with neuropathic bladder [379, 380]. Auto augmentation may be performed by incision (detrusor myotomy) or excision (detrusor myectomy) of a portion of the detrusor muscle. Either technique aims to create an iatrogenic bladder mucosal "bulge" or pseudodiverticulum and an increase in the storage capacity of the bladder with a concomitant decrease in storage pressures. The reported advantages of detrusor auto augmentation over enterocystoplasty is the avoidance of complications related to the use of bowel in the urinary tract including malignancy, mucous formation, stones, surgical morbidity related to opening and reanastomosis of the GI tract, and metabolic acidosis [364, 381, 382].

Level I Evidence:

There have been no randomised controlled trials, double blind trials or cohort studies which have examined the effects of auto-augmentation as a treatment for non-neurogenic detrusor overactivity incontinence. **(Recommendation grade D)**

Other evidence:

There are few studies on auto-augmentation in the adult non-neurogenic population and there

have been no additions to the literature since the publication of the 4th International Consultation on Incontinence (See **Table 8**). One small study of 5 patients with urgency incontinence showed promising results in all patients at the initial postoperative visit, but clinical deterioration and failure occurred in 4 of the 5 patients at three months follow-up [383]. **(LOE=4)** Mean bladder capacity increased but mean volume to first involuntary bladder contraction decreased. Four of the 5 patients continued to have involuntary bladder contractions on cystometry. One additional retrospective study including 61 patients with NDO and IDO compared detrusor myectomy to AC [384]. Comparable clinical success was reported for the two procedures; however, there was a 22% incidence of serious complications in the 27 patients undergoing AC, compared to only 3% of the 33 patients undergoing detrusor myectomy.

Long term follow-up of auto augmentation i**n children** with neurogenic bladder have for the most part demonstrated disappointing results, which have been attributed to eventual fibrosis of the pseudodiverticulum [382, 385, 386]. Recently, Chrzan et al reported promising results on 49 detrusorectomies performed for neuropathic bladder at a mean follow-up approaching 10 years [387]. Bladder behaviour was assessed as good, fair or poor depending on the volume and intravesical pressure. In 24 patients, good bladder compliance and capacity were seen before detrusorectomy. Good and fair outcomes were observed in 35 (71%) patients at 1 year and in 39 (79%) patients 6 years after detrusorectomy. In 30 (60%) patients, there was hardly any difference between the first and second follow-up. In 9 (18%) patients, formal AC was necessary. Seven patients improved during follow-up, 5 of them after resuming oxybutynin. In 11 patients, oxybutynin could be stopped, and in 2 the dosage could be reduced to once daily.

In an attempt to improve long-term outcomes with this procedure and create a biological "backing" and blood supply for the pseudodiverticulum, a number of variations of this procedure have been described. These variations have included the use of demucosalised bowel segments, stomach, peritoneum and rectus abdominis muscle [382, 388-392]. Additionally, the use of an inflatable balloon placed in the bladder for 2 weeks after auto-augmentation improved long-term capacity and compliance [393]. Long-term follow-up demonstrating favourable clinical results with these variations is lacking. This technique is no longer considered as an option for surgical management of detrusor overactiivty. **(Recommendation grade F).**

VI. URETHRAL DIVERTICULUM

1. PREOPERATIVE STAGING

Since the last consultation, relatively insignificant data have emerged on the treatment and surgical management urethral diverticula. No new data have been published regarding classification systems and many are now characterised on the basis of MRI, presentation and size. A variety of imaging techniques need to be investigated for urethral diverticula. The MRI is widely used for evaluation. Dwarkasing, et al., in 2011 [408] reported a study of 60 women undergoing evaluation of urethral diverticula. They emphasized the importance of T2-weighted sequences and the use of endoluminal coil placement in the vagina to produce best overall results. Using a combination of techniques, they had 100% sensitivity and specificity for diagnostic tests. Some groups, however, have found MRI to be nonconsistent with findings at surgery. Chung, et al., [409] [2010] assessed a case series of 76 women who underwent diverticulectomy (41 actually ? had pre-operative MRI scanning. In ten of those patients the discrepancy between MRI imaging and surgical findings was noted. MRI mis-diagnosed one diverticulum as a Bartholin's cyst. In another case a sterile abscess was diagnosed as urethral diverticulum. In two cases MRI was not sensitive enough to determine a malignancy within the diverticulum. Porten et al., [2011] [410] assessed MRI evaluation and other imaging modalities including VCUG and CT scan. MRI was felt by these authors to be a useful adjunct for determining the extent of surgical dissection and any other complicating factors related to the diverticulum size or presentation. Han, et al., [411] [2007] analysed 30 women undergoing diverticulectomy with pre-operative MRI. They found the MRI useful for surgical planning especially in cases of large, complicated or circumferential diverticula.

Foster et al., [412] [2007]) also identified the utility of MRI imaging in diagnosis and surgical planning in women. In a study of 27 women, 15% of the patients had altered surgical management based upon preoperative staging with MRI scanning.

Additional staging studies continue to be utilised including VCUG. Double blend retrograde urethrography is not considered of historic interest only. Recent data regarding transvaginal ultrasonographic evaluation also demonstrated the utility of this technqiue Wu,et al., [413] (2009) reported the utility of transvaginal ultrasound for determination of size, content and location of the diverticulum and had good correlation with operative findings.

2. TREATMENT

Since the last report, various management options have been reported. Ljungqvist, et al., [414]

Table 8: Outcomes of AC for non-neurogenic detrusor overactivity

Author	Yr	Dx	No. Pts	Pop	Mean F/U (m)	Type of Augment	% Complete Continence	>50% Continence	% Subjective Success	
Bramble [394]	'82	I		15	Adult	30	Ileum Sigmoid	-	-	87 (C+I)
Mundy [395]	'85	I N		32 8	Adult	12	Ileum	-	-	90
Kockelbergh [396]	'91	I N		42 3	Adult	20	Ileum (40) Colon (5)	-	-	71 (C+I)
George [397]	'91	I		31	Adult	48	Ileum	-	-	74
Kennelly [398]	'94	I N		2 3	Adult	9	Detrusor Myectomy	-	100 (C+I)	-
Hasan [373]	'95	I N		35 13	Adult	38	Ileum (46) Colon (2)	-	-	58 (C+I)
Kelly [399]	'97	I N		19 8	Adult	18	Ileum	-	-	72 (C+I)
ter Meulen [383]	'97	I N		1 4	Adult	3	Detrusor Myotomy	20	-	-
Awad [400]	'98	I		51	Adult	75	Ileum	-	-	78 (C+I) 53 (happy)
Venn[401]	'98	I N		(267)	Adult	36 min	Ileum	93 (for IDO)	-	-
Swami [402]	'98	I N		17 10	Adult	27	Detrusor Myectomy	-	-	63 (C+I)
Leng [384]	'99	I N		37	Adult	N/A	Detrusor Myectomy	-	73 (C+I)	-
Edlund [403]	'01	I N		25 5	Adult	60	Ileum	-	-	78-90
Ivil [404]	'02	I N		17 1	Adult	11	Ileum (17) Sigmoid (1)	83	-	-
Kumar [405]	'05	I N		24 6	Ped+ Adult	79 med	Detrusor Myectomy	-	70 (C+I)	-
Blaivas [406]	'05	I N		9 41	Adult	107	Ileum (65) [11 supravesical diversion]	-	100 (IDO only)	-
		O		26						
Barrington [407]	'06	I		12	Adult	12	Porcine Dermis	-	-	83 (improved)

Key: Dx: diagnosis; N: neurogenic; I: idiopathic; O: other; C+I: cured and improved.

(2007) reported a long follow-up series of 68 women who underwent standard urethral diverticulectomy. They noticed over a 26 year follow-up, that 11 of the 68 women experienced diverticula recurrence and urinary incontinence of varying degrees. Dyspareunia was also noted in these patients with recurrence. Despite this, 92% of the patients would recommend surgery, in their study. One small fistula was also identified over long-term follow-up in their patients. Recent analysis of surgical procedures performed in the United States of America over a twenty year period, (Burrows, et al, 2005) [415] assessed frequency of interventions for diverticulectomy in the United States at 6.7 per 1 million women per year. Rates of intervention were three-fold higher for African American as opposed to Caucasian women. Overall frequency of surgical intervention for diverticula has decreased over time.

Several authors have described standard resection techniques and these appear to be the most commonly and now currently reported (open diverticulectomy, transvaginal resection with periurethral dissection and layered closure being the most common technique). This technique now is the most commonly performed, (Rovner, et al, 2007) [416]. Lee et al (2009) [417] reported the use of SIS graft and noted good response in a single patient where this was utilized. Additionally, bovine pericardium has also been used for this purpose (Tolosa Eizaguirre, et al, 2012) [418]. Native tissue appears to be best for this purpose. Additionally, pericardium has recently been described as another type of interpositional graft with good results in a single case study (Gunasekaran et al, 2011) [419] Recent urologic guidelines, Dmochowski et al., [420] stressed the importance of not placing synthetic materials over a fresh urethrotomy at the time of diverticular repair due to concerns regarding erosion.

Recently, increased reports of diverticula formation related to midurethral tape formation have been identified. The first report in the English literature occurred in 2007 (Hammad) [421], since then Mahdy, et al, 2008, [422] and Athanasopoulos, 2008 [423] have both described diverticula occurring after implantation of transvaginal tape presumably due to excess tension placed on the midurethral tape.

The importance of differential diagnosis continues to be critical as women with chronic pelvic pain are sometimes found to have a urethral diverticulum (Fletcher, et al 2009) [424]. Foley et al,2011,[425] identified the importance of critical evaluation in differential diagnosis and accurate assessment of these individuals. Another important aspect in consideration of surgical management of urethral diverticula is potential risk of malignant chane within these. Thomas et al. 2008 [426], Ninety women going through diverticulectomy at a single institution. Neoplastic changes were identified in five patients of whom all were glandular carcinomas. The potential for metaplasia occurring in these lesions is needs to be stressed. Reoperation for diverticulum has recently been assessed. (Ockrim, et al 2009)[427] evaluated a group of women who had undergone previous intervention for diverticulum requiring repeat resection. The resection was secondary either to incomplete resection and/or recurrence of the diverticulum. The authors found that a standard approach utilising a sling or Martius fat pad labial graft interposition provided the best results in their complicated series.

3. RECOMMENDATIONS

All reports are Level III in terms of evidence and there continues to be a lack of comparative reports assessing different techniques. All current series are retrospective in nature there is a need for prospective randomised assessment of management of these patients. Functional assessment across all domains of pelvic floor activity (pain, continence, urinary storage, and sexual function) are critical to the complete assessment of urethral diverticulae. **(Grade of recommendation B/C)**

VII. ARTIFICIAL URINARY SPHINCTER IN WOMEN

The artificial urinary sphincter continues to be used as a surgical option for sphincter dysfunction in women solely a salvage procedure (after multiple failed previous procedures or special circumstances). There is limited but now some long term experience with the sphincter as a primary intervention.

Since the last publication, there have been several longer term follow-up studieswhich will be referenced below. The device may be placed either transvaginally, trans-abdominally or recently described as being placed laparoscopically. Success (cure or improvement of stress incontinence) rates overall range between 76 and 89 per cent.

More recent results have been reported in small groups (Hoda,et al) [428] reported experience with two women who underwent open implantation of a sphincter(endoscopic extraperitoneal approach, laparoscopic) . The overall operating time for these cases was 120 minutes. Both women were reported as being continent after the device implantation A slightly larger experience with laparoscopic insertion of artificial urinary sphincter reported has been reported by Roupret et al [429] . Twelve women underwent laparoscopic insertion of a sphincter over a two year period, eleven of whom had undergone previous procedures. After a variable period of activation ranging from four to fourteen weeks, with a mean follow-up of 12.1 month (range 5.2 to 27) incontinence was cured in 88% of the women. Com-

plications included the need for open conversion in two patients, two bladder injuries, two vaginal injuries with an overall complication rate of 25%.

Mandron, et al, [430] contemporaneously reported their experience with 25 patients undergoing laparoscopic AUS implantation over a four year timeframe. No cases required open conversion and the authors reported only an intraoperative complication, Of vaginal perforation. Five of the patients developed urinary retention which required re-catheterisation for a short period (no longer than four weeks). At a mean follow-up of 26.1 months, two patients failed due to vaginal erosion and required removal of the AUS, however, 23 patients reported continence, either total [19] or social (minimal pad use) [4].

Longer term follow-up has been reported by several groups recently. Chung et al [431] reported twenty-five year a single institution experience with sphincter implantation in 47 consecutive women, of whom 35 had failed previous anti-incontinence surgery. Two wound infections were identified after insertion. Of the 47 patients 83% still retained a functional sphincter at follow-up. Eight (17%) required removal due to erosion or infection. Additionally 20 revisions were required; the majority due to mechanical complications. Kaplan–Meier analysis revealed slightly over 80% of devices still working after 100 months. Continence rate (no pad use) at the time of follow-up was 59%.

Vayleux, et al., [432] reported an analysis of 215 women undergoing sphincter implantation over a 22 year period. 88% of women had undergone previous treatment for incontinence. 73.5% of the patients were considered continent (0 to 1 pad use) at follow-up. 170 (or 79%) were satisfied. The revision rate in this group was 15.3% after a mean interval of 8.47 years. 15 explantations (7% of total) were performed. The major risk factor for intraoperative complications was a history of smoking (10.7%). Multivariate analysis revealed age to be the major risk factor for failure (odds ratio 2.46), which occurred in 23.7% of the subjects. In addition, pelvic radiotherapy was also associated with failure (4.37 odds ratio). The largest long term analysis was recently published by Costa, et al., [433] . Over a 20 year period, 376 devices were implanted in 344 women. At mean follow-up of 9.6 years, 85.6% of patients were fully continent (no incontinence), 8.8 were socially incontinent (occasional incontinence epsiode) and 5.6% were incontinent (defined as one pad or more incontinence). Three, five and ten year device survival rates by Kaplan-Meier analysis were 92%, 88.6% and 69.2%. Mean mechanical survival time was 176 months (14.7 years). The authors identified three factors for AUS survival including number of previous incontinent procedures, presence of associated neurogenic disease, and simultaneous augmentation procedure. Recent Cochrane Database Review (Lipp,et al), [434] failed to identify any subsequent new data regarding the experience of artificial urinary sphincters.

Two trials have also assessed role of the sphincter in women as a salvage procedure. Chung et al., [435] reviewed 29 patients in whom AUS was implanted after failed anti-incontinence procedures. 5 (17%) of those patients required explantation of the device either due to erosion or infection. In addition, 13 revisions were performed with device malfunction accounting for 95% of those cases. Overall survival analysis revealed 90% malfunction of the device at less than 100 months from the time of implant. There was a significant decrease in pad use noted in the trials and overall continence rates (no pad use) were 70% in this study.

Other additional device modifications have included the use of a larger implanted cuff (greater than 8cm). Revaux, et al., [436] reported 50 women who underwent implantation with a large cuff device over a 23 year period, of whom 86% had undergone previous incontinence procedures.

At a mean follow-up of eight years, 34 women had complete resolution of their incontinence (68%). Factors that were associated with device survivability included less than two pregnancies, urethral closure pressure higher than 19cm of H2O and a cuff size equivalent to 8 cm.

Several consensus statements regarding use of the artificial urinary sphincter have recently been published. Chartier-Kastler, et al., [437] noted a higher risk of erosion and revision rates in women after multiple previous procedures. The authors concluded that the theAUS should be implanted at high volume specialist centres with appropriate knowledge and experience in the management of complex cases of incontinence.

Richard, et al., [438] reported the recommendations of the committee in Women's Urology and pelviperineology of the French Association of Urology. This guideline recommended avoidance of patients who had not had multiple prior procedures and where a well standardised technique performed by surgeons with regular experience and sufficiently long deactivation after implantation, long term monitoring as key aspects for device success.

Lovatsis et al., [439] summarised the guidelines for the evaluation of treatment of urinary incontinence for the Society of Obstetricians and Gynaecologists of Canada. The authors concluded that the AUS was an option in patients with significantly decreased dexterity and mobility (recommendation of III-C).

Modifications of the sphincter have been reported and evolution of the device types continues.

Garcia-Montes, et al., [440] reported a new type of sphincter known as the FlowSecure device. Feasibility of implantation was assessed and noted to be reasonable. The authors concluded that further research and development of the device should continue.

Conclusion and Recommendations

All reports are **Level III/IV** in terms of evidence and there continues to be a lack of comparative reports assessing different techniques. All current series are retrospective in nature and there is a need for prospective randomised assessment of management of these patients. **(Evidence Level III/IV).** Evidence is available to support the use of the artificial sphincter for the indications of recurrent and primary incontinence **(Grade of recommendation is B/C)**.

VIII. CONFOUNDING VARIABLES

1. INTRODUCTION

Surgery remains the main stay in the management of women with stress urinary incontinence and there are many different operations and procedures reported. Success rates are often found to vary significantly; this may be due to many confounding factors some of which may be modifiable and some which are not.

The purpose of this review is to update the previous report on confounding variables published in the 4th consensus with the more recently reported evidence. A Medline search was performed from 2008 onwards and, for convenience; the confounding variables are subdivided as in the previous report. For the purposes of this update only new studies will be included.

2. AGE

There have been several recent papers investigating the effect of age on continence surgery since the last report and a large Australian epidemiological study has demonstrated that the number of procedures, particularly in the elderly is increasing. [441] Data from Medicare Australia from 1994 -2009 were analysed and showed that there was almost a doubling of procedures for stress urinary incontinence over a three year period following the introduction of mid-urethral tapes. Over the 15 year period there was an 87% increase in women over 55 years old as compared to a 1% increase in younger women. Mid urethral slings were the most commonly performed procedure and accounted for 85.5% of all operations for stress urinary incontinence performed in 2009 (14 mid urethral slings for every one colposuspension).

Although now less commonly performed both colposuspension and pubovaginal sling remain efficacious procedures for stress urinary incontinence. The Stress Incontinence Surgical Treatment Efficacy Trial investigated the effect of age on both perioperative and postoperative outcome with both procedures in 659 women. [442] The older group (mean age 69.7 years) were compared with a younger group (mean age 49.4 years). Overall older women had slightly longer return to normal activities (50 days vs 42 days; p=0.05) although there were no differences in the return to normal voiding (14 days vs 11 days; p=0.42). In addition older women were more likely to have a positive stress test at follow up (OR 3.7; 95%CI: 1.70-7.97; p=0.001), less subjective improvement in both stress and urgency symptoms and were also more likely to require redo surgery (OR 3.9; 95%CI: 1.30-11.48).

The safety and efficacy of mid urethral sling surgery has been investigated in a large Australian series of 1225 women (955 retropubic and 270 transobturator) which compared outcomes in the elderly (96 women ≥ 80 years) to those in younger women (1016 women < 80 years). [443] Overall there was no significant difference in subjective cure between the two groups (elderly 81% vs younger 85%; p=0.32). Whilst there were no differences in bladder perforation rates the hospital stay was longer in the elderly group (1.6 ± 1.7 days vs 0.7 ± 1.1 days; p<0.001). In addition there was a higher incidence of short term voiding difficulties in the elderly with 37% failing their initial trial of void as compared to 9% in the younger group (p<0.001). However there were no differences in long term voiding problems (elderly 8% vs younger 6%; p=0.21) and de novo urge symptoms occurred in 7% of both groups.

These findings are supported by a further study investigating the safety and efficacy of TVTO in a consecutive series of 97 older women aged over 70 years (mean 75 years) and 256 younger women (mean 55 years). [218] Mean follow up was 30 ±17 months and post operative morbidity was similar in both groups although there were significantly more recurrent urinary tract infections in the elderly (13.7% vs 6.2%). Post operative asymptomatic urodynamic stress incontinence (USI) was found more commonly in the elderly group (19% vs 3.7%; p<0.05) although the rate of overt USI was 5% in both. Whilst the incidence of persistent overactive bladder (OAB) was similar in both elderly and younger women (68% and 62% respectively) de novo OAB was higher in the elderly group (11.9% vs 4.7%; p<0.05).

A smaller prospective questionnaire survey of 100 women undergoing tension Free Vaginal Tape (TVT) has also investigated the effect of age on outcome of surgery. Those women with more severe symptoms preoperatively were found to have a greater improvement in the symptom of stress incontinence and Quality of Life (QoL) and age did not appear to have an effect on outcome [444] although these findings are contradicted by a larger study of 537 women undergoing a retropubic or transobturator mid urethral

sling which found a significant detrimental effect of age and menopausal status.[445]

Patient reported outcomes have become increasingly important in the evaluation of women following surgery and a small retrospective cohort study has been reported in 122 younger women (<65 years) and 70 older women (≥ 65 years) who had combined surgery for SUI and urogenital prolapse. [446] At mean follow up of 10 ± 1.2 months both groups reported significant subjective improvement in symptoms and QoL although the older group had an increased risk of SUI treatment failure (OR 1.10; 95% CI: 1.05-2.5) but not prolapse treatment failure (OR 0.90; 95%CI: 0.29-2.8). A further study investigated preoperative and postoperative factors which correlated with surgical satisfaction in 371 women following fascial or mid urethral sling surgery. [447] Overall increasing age (OR 0.8; p=0.002), body mass index (BMI) (OR 0.8; p=0.003) and autologous fascial sling (OR 0.5; p=0.003) were associated with decreased odds of satisfaction.

3. RACE

There have been four papers evaluating the effect of race on the outcome of continence surgery since the last report. A large epidemiological study examining 129 778 women who underwent continence surgery in the United States in 2003 found the overall rate of 12 surgical procedures per 10 000 women. This figure was 10 per 10 000 (95% CI: 7-12) in white women and dropped to 3 per 10 000 (95% CI: 0-9) and 6 per 10 000 (95% CI: 0-13) in women of other ethnicity. [448] This is further supported by Medicare data from the United States which showed higher operation rates for SUI in white and Hispanic women when compared to black or Asian women (p<0.01). [449]

A further analysis of the Stress Incontinence Surgical Treatment Efficacy Trial examined the effect of racial group in 654 women (11% Hispanic, 73% non – Hispanic white, 6.7% non- Hispanic black and 8.9% were of other ethnicity) following colposuspension or pubovaginal sling. Overall there were no differences seen between groups in any of the urinary incontinence measures investigated. [450]

The function of the continence mechanism has also been compared in a cross sectional population based study of 335 black and white women aged 35-64 years classified as continent (n=137), stress incontinent (n=102) and urge incontinent (n=96). [451] When comparing black women to white women the maximum urethral closure pressure (MUCP) was 22% higher (68.0 vs 55.8 cmH20; p<0.0001). In addition white and black women complaining of stress incontinence were found to have an MUCP 19% and 23% respectively lower than controls. The MUCP in white women with urgency incontinence was as low as those white women with stress incontinence although black women with urgency incontinence had normal urethral function.

4. OBESITY

Whilst there are now considerable data linking severity of incontinence with obesity the evidence regarding the effect on continence surgery is less robust. Evidence from a large series of mid urethral tape procedures has shown no effect of BMI in terms of outcome. [445] This is supported by a further study of 195 women who were followed up for one year following TVT which showed no difference in outcome in different BMI cohorts. [452] The risk of perioperative morbidity however is higher with an increased risk of pain following transobturator sling placement (OR 2.51; 95% CI: 1.01-6.22) and of hip and thigh pain (OR 1.99; 95%: 0.79-4.99) in obese women. [453] This however is contradicted by a retrospective review of 129 women with BMI < 30 kg/m2 and 69 with BMI ≥ 30 kg/m2. Overall the bladder injury rate was significantly higher in those patients with lower BMI (14.0% vs 4.3%; p=0.04). After controlling for confounding factors BMI < 30 kg/m2 remained a risk factor for bladder injury (OR 4.63; 95% CI: 1.20 -17.86) as did previous continence surgery (OR 3.55; 95% CI: 1.01-12.50). [454]

5. PSYCHIATRIC ILLNESS

There have been no new relevant publications since the last report.

6. ACTIVITY

There have been no new relevant publications since the last report.

7. PREVIOUS CONTINENCE SURGERY

Surgical success rates often tend to be lower in those women having redo continence surgery and there have been several studies examining this since the last consensus statement. The efficacy of redo colposuspension has been reported in a case series of 52 women from one centre with an objective cure rate of 78% and a subjective cure rate of 80%. [455] The role of redo laparoscopic colposuspension following a failed mid urethral tape has also been assessed in a smaller retrospective case series of 16 women. At a median follow up of 24.5 months objective and subjective cure rates were 54.5% and 92.9% respectively. [456]

There is now also a considerable amount of data examining the efficacy of mid-urethral tape procedures following failed previous surgery. The efficacy of TVT following failed previous continence surgery has been reported in a prospective follow up study of 130 women in Finland. Of these 60 women had recurrent and 70 primary incontinence. Overall there were no differences between the groups in terms of transient voiding difficulties and complications. At three year follow up satisfaction rates were 86% and 91% in the recurrent and primary groups respectively and the subjective cure rate was 93%

in both. At follow up 20% of those having recurrent surgery complained of de novo urge symptoms as compared to 5.7% in the primary group. [457] A small series of 24 women with recurrent urinary incontinence and intrinsic sphincter deficiency following Burch colposuspension has also reported an objective success rate of 70.8% following TVT. [458]

In addition to studies investigating the use of the retropubic approach there are also several studies investigating the efficacy of the transobturator approach in recurrent stress incontinence. A secondary analysis in a large Scottish study comparing inside-out TOT with outside-in TOT in 341 women assessed outcome in a subgroup of 46 women with recurrent incontinence at one year. [212] Overall the subjective and objective success rates were 69.9% and 76.5% respectively and there were no differences between the two routes. Once again in this study a low MUCP (<30 cmH2O) was the only independent risk factor for failure (OR: 4.52; 95%CI: 1.51-56.1; p=0.016). A smaller series of 29 women with recurrent stress incontinence following a previous colposuspension has also been reported in 29 women who had a TVT or TOT with cure rates of 62.1% after one previous procedure and 57.1% after two. [459]

There is now also increasing evidence to support the use of a redo mid-urethral sling in those women who have previously had a failed mid-urethral sling. In a large series of 1 225 women reported from Australia 1 112 were a primary procedure and 77 were secondary procedures. [460] All redo slings were placed without removal of the first. Those women having a redo procedure were more likely to have intrinsic sphincter deficiency (31% vs 13%; p<0.001) and cure rates were 86% and 62% in the primary and secondary procedures respectively. A repeat retropubic approach was significantly more successful that a repeat transobturator approach (71% vs 48%; p=0.04). Whilst complications were similar in both groups de novo urgency (30% vs 14%; p<0.001) and urgency incontinence (22% vs 5%; p<0.001) were more common with redo surgery. A further study has reported on 31 patients who had a TVT after a failed mid urethral tape with an 18 month follow up. Overall objective cure assessed using a pad test was 74% with a 6% improvement rate and 19.5% failure rate whilst objective cure assessed with urodynamics was 77.4%. The subjective cure rate was 71%. [210] (also, see section on mid-urethral slings).

8. CONCOMITANT HYSTERECTOMY

There have been no new relevant publications since the last report.

9. SEVERITY AND DURATION OF SYMPTOMS

There have been no new relevant publications since the last report.

10. DETRUSOR OVERACTIVITY AND STRESS INCONTINENCE

There have been four papers assessing the effect of detrusor overactivity as a confounding variable in stress incontinence surgery since the last report.

A large Australian cohort study has reported on 754 consecutive women with stress urinary incontinence and urgency (SUI) and 514 women with stress urinary incontinence and urgency urinary incontinence (UUI) who had a mid urethral sling and were followed up for a mean of 50 months. [208] Overall persistent urgency was commonly reported in both groups (SUI 40% and UUI 32%). In the SUI group coexistent detrusor overactivity (OR 2.04; 95%CI: 1.39-3.01), baseline symptom severity (OR 1.41; 95% CI: 1.10-1.78) and age (OR 1.03; 95%CI: 1.02-1.04) increased the risk of persistent urgency. Conversely transobturator sling (OR 0.61; 95%CI: 0.39-0.94) and concomitant prolapse surgery (OR 0.54; 95% CI: 0.38-0.75) decreased the risk. In the UUI group coexistent detrusor overactivity (OR 1.86; 95% CI: 1.18-2.93) baseline symptom severity (OR 1.88; 95% CI: 1.38-2.56), previous continence surgery (OR 2.18; 95% CI: 1.28-3.70) increased the risk of persistent urgency whilst apical prolapse surgery (OR 0.33; 95% CI: 0.15-0.70) decreased the risk.

A further study of 121 women has investigated the risk factors affecting outcome after TVT and TOT. Multivariate analysis revealed that preoperative detrusor overactivity was an independent risk factor affecting cure after TVT (OR 113.1; 95%CI: 1.84-6592.77; p=0.02) or TOT (OR 23.7; 95%CI: 1.63-344.53; p=0.02) and MUCP <40 cmH2O (OR 8.34; 95%CI: 1.52-45.65; p=0.01) was a risk factor in the TOT group. [167]

A case control study in 34 women with mixed incontinence matched for age and type of procedure has shown a significantly higher rate of failure in the TOT group (29.4%) compared to the TVT group (0%). In addition women were significantly more likely to require repeat surgery following TOT (OR 10.1: 95% CI: 2.6-38.2). [116]

11. URETHRAL OCCLUSIVE FORCES

Since the last report there have been several papers investigating the role of the urethra on outcome following continence surgery.

The role of urethral mobility and intrinsic deficiency on outcome following mid urethral tape has been assessed in two studies. The first of these investigated 134 women following transobturator tape insertion. Overall 86% reported subjective cure and 14% complained of persistent symptoms. Median preoperative urethral mobility was significantly lower amongst treatment failures compared to those women who were cured (40 (10-60) degrees vs 50 (10-90) degrees ; p=0.0049). In addition women with

preoperative mobility <45 degrees were at least four time more likely to report incontinence when compared to those with ≥45 degrees mobility (29.4% vs 6.9%; RR 4.29; 95% CI: 1.59-11.60; *p*=0.005). [200]

A prospective 2 year study of 65 women has also found that intrinsic sphincter deficiency with a fixed urethra is associated with a poorer objective outcome at 24 months following TOT when compared to intrinsic sphincter deficiency and urethral hypermobilty and hypermobility alone (66.7% vs 87.5% and 96.6% respectively). [201]

Two studies have also examined the role of urethral retro-resistance pressure (URP) and surgical outcome. The first of these reported on 100 women and found no relationship between URP and severity of incontinence assessed by a 24 hour pad test. In addition there was no correlation between URP and incontinence severity. Following mid urethral tape insertion the objective cure rate was 84.9% although there were no significant differences in pre and post operative URP values (62.7±19.4 cm H2O vs 61.2 ± 20.4 cm H2O; *p*=0.57). [461] A further study of 69 women has shown that URP is not predictive of outcome following TVT. [462]

12. SURGEON'S EXPERIENCE

All surgical procedures and surgeons are subjected to the effect of a 'learning curve' and this has recently been assessed in two studies evaluating the outcome of mid urethral tapes. The learning curves of TVT and TOT have been compared in a study of 83 women and overall found TVT procedures were longer (*p*=0.025) although the duration was reduced after the surgeon had performed 15 procedures. [463] The effect on outcome was not assessed.

The impact of surgical experience and the effect of the learning curve has also been investigated in the use of Single Incision Mini Slings (SIMS) in a prospective study of 131 patients who had TVT Secur. Overall the study clearly demonstrated improved surgical outcome in those patients who had their procedures performed by more experienced surgeons. In addition whilst surgical time and intraoperative complications were not associated with surgical experience, the length of postoperative catheter use and hospital stay decreased with increasing experience. [464]

13. ADJUVANT OESTROGEN THERAPY

The role of oestrogens and lower urinary tract dysfunction remains controversial although there is evidence to suggest that vaginal oestrogen therapy may be useful in women with symptoms suggestive of OAB Since the last report two studies have investigated the role of adjuvant oestrogen therapy in women having continence surgery.

The role of adjuvant vaginal oestrogen therapy has been assessed in a prospective study of 59 post-menopausal women having a TVT procedure. [465] Patients were randomised to surgery with and without vaginal oestrogen therapy and followed up over 6 months. Overall the incidence of OAB symptoms at baseline was 7% and this rose to 32% at 6 months. Urinary urgency was significantly higher in those women not receiving vaginal oestrogen therapy (28% vs 4%; *p*=0.01) although decreases in frequency and nocturia were not significantly different.

More recently the role of adjuvant vaginal oestradiol (Vagifem, Novo Nordisk) 25mcg has been assessed in a prospective randomised study of 190 postmenopausal women who had a TVTO procedure with 6 month follow-up. Overall there was no statistically significant difference between those women who received oestradiol and those who did not in terms of peri operative complications and hospital stay. However in the post-operative period those women treated with vaginal oestradiol showed a statistically significant decrease in the symptoms of urgency and frequency although not nocturia and urgency incontinence. Equally there were no difference in efficacy rates between the two groups. [466]

IX. CLINICAL TRIAL OUTCOMES USED IN STRESS URINARY INCONTINENCE RESEARCH

The last decade has seen a massive expansion in the field of stress urinary incontinence (SUI) research. While initially criticised for poor quality research, significant advances have been made especially in the area of clinical trials. Indeed, in the United States, the National Institute of Health has helped foster this improvement with development of clinical trials networks such as the UITN and the PFDN. In addition, we have seen a maturation in the field of SUI research including improvements in the quality of trials and the instruments utilised. Use of validated outcome measures and properly conducted prospective trials are now the standard with emphasis being placed on comparative efficacy trials.

The increase and improvements seen in SUI research has also brought to light the problems that investigators typically encounter when assessing SUI outcomes. Strohbehn reported "there are as many shades of dry as there are shades of gray" in his editorial response to the UITN's SISTER trial which reported a wide range between different SUI outcome measures [467]. In this prospective randomised clinical trial comparing the Fascial Sling and Burch procedures, success for overall incontinence was 47% vs 38%, respectively compared to SUI specific success which was 66% vs 49% respectively. [125] Indeed, it is difficult to think one can clearly report SUI surgery outcomes when investigators have trouble defining the population before treatment is initiated. Brubaker reported variations in the categorisation of a cohort of wom-

en enrolled in a clinical trial who were planning to undergo SUI surgery. While all women were reported to have pure or predominant SUI for study inclusion, the range of women with mixed incontinence was 8.3% to 93.3% depending on what definition was used. If such variations exist in the defining of subjects enrolled in SUI trials from the onset, it is natural to expect wide variations in how outcomes are reported post operatively. [468] Rapp reported such wide variations when looking at different definitions of success after SUI surgery. In the same cohort of women, successful outcomes ranged from 33% to 87% depending on the definition used for success. [469]

Outcome assessments can be broken down into objective and subjective measures. [470] Objective parameters typically include: physical exam, pad tests, voiding diaries, urodynamic studies. Subjective assessments typically include patient reported measures such as validated instruments that measure symptoms , patient bother, satisfaction and HRQOL. However, these outcome tools are usually limited to a specific area and improvement in one area may not mean improvement in other areas or could even be at the detriment of another area. In addition, the degree of improvement experienced by one patient might be considered a "success" in that patient however the same improvement may be perceived differently by another patient. Furthermore, outcome measures limited to specific domains may not take other symptomology into account. For example, resolution of SUI might be considered a success by itself however if it were to occur in conjunction with urinary retention or worsening irritative voiding symptoms and urgency incontinence, the patient might not agree. Indeed, the majority of SUI outcome assessments rarely take complications into account. It is clear that focusing on a single measure is often inadequate and necessitates the need for measuring multiple outcomes which imposes greater burden on patients. [471] (SUNG). Lastly, no single instrument is universally accepted by all investigators although significant headway has been seen in the adoption of instruments advocated by professional organisations such as the International Continence Society and the International Consultation on Incontinence.

In response to the shortcomings seen with traditional SUI research outcomes, investigators have increasingly relied on greater use of composite outcomes as well as patient reported outcomes that especially assess global response. The use of composite outcomes have increased especially with the advent of clinical trial networks. While providing more comprehensive assessments, composite outcome often create a stricter definition of success especially if all of the components of the composite must be satisfied. Many of the large scale trials often include multiple outcomes measures as primary or secondary outcomes which allows them to be more comprehensive. However, a vast number of outcome measures have been utilised in the field of SUI research. While more comprehensive listings of SUI clinical trials can be found in the respective sections of this chapter, examples of trials utilising different outcome parameters that have been published since the last ICI report are listed in the following tables. **Table 9** provides a sampling of composite outcomes used in SUI trials. **Table 10** provides a sampling of patient reported outcomes measures used in SUI trials.

Table 9: Examples of Composite Outcomes

Author	SUI Surgery	Composite Outcome	Results
Albo[125]	Facial Sling vs Burch 655 women 24 months	*Negative pad test and *Negative (no UI) on 3 day diary and *#Negative cough test and *#No Self reported SUI on MESA and *#No retreatment for SUI *Required for overall success # required for SUI specific success	Overall Success: Sling =47% vs. Burch= 38%, P = 0.01) SUI specific success: Sling=66% vs. Burch=49%, P<0.001).
Richter[170]	Retropubic vs transobuturator midurethral sling 597 women 12 months	Objective Negative stress test and Negative pad test and No SUI retreatment and Subjective No Self reported SUI symptoms and No leakage reported on 3 day diary and No report of SUI retreatment and	Objective success: retropubic =80.8% vs transobturator =77.7% (equivalent) Subjective Success: retropubic=62.2% vs transobturator=55.8% (equivalent)
Barber[97]	TVT vs TOT 170 women 12 months	Abnormal bladder function defined by composite presence of any of the following: incontinence symptoms of any type positive cough stress test retreatment for stress incontinence postoperative urinary retention	Abnormal bladder function was: TVT: 46.6% TOT: 42.7% Conclusion: TOT was not inferior based on noninferiority test

While many of the self-reported measures can be considered “patient reported”, the concept of true Patient Reported Outcomes (PRO) is one that is more complex and encompasses a more global assessment. The use of PRO’s has gained acceptance as noted by the fact that most research funding sponsors, industry and regulatory agencies now require inclusion of outcome measures that include the patient’s perspective. The NIH recently established the Patient Reported Outcomes Measurement Information System (PROMIS) for women with urinary incontinence [471] (Sung). True PRO’s measure patient impressions in a more global context by encompassing 4 domains: 1) Symptoms, 2) Functioning, 3) General Health Perception and 4) HRQOL. The International Consultation on Incontinence has adopted the use of PRO’s and established the ICI Modular Questionnaire (ICIQ) Project that includes the assessment of a wide spectrum of urinary, bowel and vaginal symptoms along with their impact on HRQOL (Coyne)[477].

Another outcome measure that has recently gained popularity is the patient global impression of severity (PGIS) and the patient global impression of improvement (PGII). Initially validated by Yalcin, use of such global assessment instruments provides a single response which is easier for the patient and clinican to understand [478] (Yalcin). Furthermore, the measurement is all encompassing since the subject takes success and complications into account when responding. Indeed, the UITN recently adopted the use of the PGIS and PGII for use as a major eligibility criterion and as the primary outcome in the VALUE trial which will look at the impact of urodynamic studies on SUI Surgery outcomes. [479]

Table 10: Example of Patient Reported Outcomes

Author	Study Details	Outcome Measure	Results
Freeman [472]	N=183 Monarc TVT=100 Gynecare TVT=93	ICI Modular Questionnaire-Female LUTS	TVT: 65.6% TOT: 63.4% Conclusion: TOT not inferior to TVT
Brubaker [473]	655 randomised to Burch or Sling 450 Sexually active	POP/Urinary Incontinence Sexual Questionnaire (PISQ)	PISQ improved after SUI surgery Fewer felt restriction of sexual activity due to fear of incontinence Successful SUI surgery associated with greater improvement in PISQ
Filocamo [474]	157 women who underwent Mid-urethral sling Included women who were not sexually active	Female Sexual Function Index (FSFI)	Female sexual function improved after MUS 40% of women previously not sexually active later became sexually active after MUS
Tennstedt [475]	655 Randomised to Burch or Sling	Incontinence Impact Questionnaire (QOL)	QOL improved (scores decreased) more in women with successful SUI surgery
Miles	N=329 randomised to TVT or TVT-O	UDI-6 IIQ-7 PISQ	Similar improvements in UDI-6, IIQ-7 and PSIQ between both procedures TVT-O appears as effective as TVT
Lier [476]	194 women randomised to TOT or TVT	Cost Utility Analysis 15D questionnaire Quality Adjusted Life-years (QALYS) Cost estimates	Statistically non-significant cost savings with TOT of $1133 per patient despite no difference in health outcome between TVT and TOT
Biggs [213]	TOT in 27 who failed previous SUI surgery	PGII	Success: 80%

REFERENCES

1. Ghoniem, G., et al., *Cross-linked polydimethylsiloxane injection for female stress urinary incontinence: results of a multicenter, randomized, controlled, single-blind study.* J Urol, 2009. **181**(1): p. 204-10.
2. Ghoniem, G.M. and C.J. Miller, *A systematic review and meta-analysis of Macroplastique for treating female stress urinary incontinence.* Int Urogynecol J, 2012.
3. Ghoniem, G., et al., *Durability of urethral bulking agent injection for female stress urinary incontinence: 2-year multicenter study results.* J Urol, 2010. **183**(4): p. 1444-9.
4. Lose, G., et al., *An open multicenter study of polyacrylamide hydrogel (Bulkamid(R)) for female stress and mixed urinary incontinence.* Int Urogynecol J, 2010. **21**(12): p. 1471-7.
5. Toozs-Hobson, P., et al., *Two-year follow-up of an open-label multicenter study of polyacrylamide hydrogel (Bulkamid(R)) for female stress and stress-predominant mixed incontinence.* Int Urogynecol J, 2012.
6. Gopinath, D., A.R. Smith, and F.M. Reid, *Periurethral abscess following polyacrylamide hydrogel (Bulkamid(R)) for stress urinary incontinence.* Int Urogynecol J, 2012.
7. Lightner, D., et al., *Randomized controlled multisite trial of injected bulking agents for women with intrinsic sphincter deficiency: mid-urethral injection of Zuidex via the Implacer versus proximal urethral injection of Contigen cystoscopically.* Urology, 2009. **74**(4): p. 771-5.
8. Lightner, D.J., J. Fox, and C. Klingele, *Cystoscopic injections of dextranomer hyaluronic acid into proximal urethra for urethral incompetence: efficacy and adverse outcomes.* Urology, 2010. **75**(6): p. 1310-4.
9. Mohr, S., et al., *Bulking agents: an analysis of 500 cases and review of the literature.* Int Urogynecol J, 2012.
10. Lee, H.N., et al., *Transurethral injection of bulking agent for treatment of failed mid-urethral sling procedures.* Int Urogynecol J, 2010. **21**(12): p. 1479-83.
11. Crites, M.A. and G.M. Ghoniem, *Bladder mass "collagenoma".* Int Urogynecol J, 2011. **22**(5): p. 621-3.
12. Kumar, D., M.R. Kaufman, and R.R. Dmochowski, *Case reports: periurethral bulking agents and presumed urethral diverticula.* Int Urogynecol J, 2011. **22**(8): p. 1039-43.
13. Kirchin, V., et al., *Urethral injection therapy for urinary incontinence in women.* Cochrane Database Syst Rev, 2012. **2**: p. CD003881.
14. Du, X.W., et al., *Experimental study of therapy of bone marrow mesenchymal stem cells or muscle-like cells/calcium alginate composite gel for the treatment of stress urinary incontinence.* Neurourol Urodyn, 2012.
15. Ulmsten, U., et al., *An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 1996. **7**(2): p. 81-5; discussion 85-6.
16. ZaccharinR., *The anatomic support of teh female urethra.* Obstetrics and Gynecology, 1968. **21**: p. 754-759.
17. DeLancey, J.O., *Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis.* Am J Obstet Gynecol, 1994. **170**(6): p. 1713-20; discussion 1720-3.
18. Huisman, A.B., *Aspects on the anatomy of the female urethra with special relation to urinary continence.* Contrib Gynecol Obstet, 1983. **10**: p. 1-31.
19. Westby, M., M. Asmussen, and U. Ulmsten, *Location of maximum intraurethral pressure related to urogenital diaphragm in the female subject as studied by simultaneous urethrocystometry and voiding urethrocystography.* Am J Obstet Gynecol, 1982. **144**(4): p. 408-12.
20. Asmussen, M. and U. Ulmsten, *On the physiology of continence and pathophysiology of stress incontinence in the female.* Contrib Gynecol Obstet, 1983. **10**: p. 32-50.
21. Ulmsten, U., et al., *A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 1998. **9**(4): p. 210-3.
22. Nilsson, C., *The tension-free vaginal tape procedure ITVT) for treatment of female urinary incontinence: a minimal invasive procedure. .* Acta Obstet Gynecol Scand, 1998. **168**: p. 34-37.
23. Ulmsten, U., P. Johnson, and M. Rezapour, *A three-year follow up of tension free vaginal tape for surgical treatment of female stress urinary incontinence.* Br J Obstet Gynaecol, 1999. **106**(4): p. 345-50.
24. Nilsson, C.G. and N. Kuuva, *The tension-free vaginal tape procedure is successful in the majority of women with indications for surgical treatment of urinary stress incontinence.* BJOG, 2001. **108**(4): p. 414-9.
25. Rezapour, M. and U. Ulmsten, *Tension-Free vaginal tape (TVT) in women with mixed urinary incontinence--a long-term follow-up.* Int Urogynecol J Pelvic Floor Dysfunct, 2001. **12 Suppl 2**: p. S15-18.
26. Kuuva, N. and C.G. Nilsson, *A nationwide analysis of complications associated with the tension-free vaginal tape (TVT) procedure.* Acta Obstet Gynecol Scand, 2002. **81**(1): p. 72-7.
27. Nilsson, C.G., et al., *Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(8): p. 1043-7.
28. Olsson, I., A.K. Abrahamsson, and U.B. Kroon, *Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence: a retrospective follow-up 11.5 years post-operatively.* Int Urogynecol J, 2010. **21**(6): p. 679-83.
29. Campeau, L., et al., *A multicenter, prospective, randomized clinical trial comparing tension-free vaginal tape surgery and no treatment for the management of stress urinary incontinence in elderly women.* Neurourol Urodyn, 2007. **26**(7): p. 990-4.
30. McCracken, G.R., N.A. Henderson, and R.G. Ashe, *Five year follow-up comparing tension-free vaginal tape and colposuspension.* Ulster Med J, 2007. **76**(3): p. 146-9.
31. TellezMartinez-FornesM, F., FouzLopez, C et al., *A three year follow-up of a prespective open randomised trial to compare tension-free vaginal tape with Burch colposuspension for treatment of female stress urinary incontinence.* Actas Urologicas Espanolas, 2009. **33**: p. 1088-1096.
32. Wu, J.Y., et al., *Surgical therapies of female stress urinary incontinence: experience in 228 cases.* Int Urogynecol J, 2010. **21**(6): p. 645-9.
33. WardKL, H., &on behalf of the UK and Ireland TVT Trial-Group., *Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence.* British Medical Journal, 2002. **325**: p. 67-70.
34. Liapis, A., P. Bakas, and G. Creatsas, *Burch colposuspension and tension-free vaginal tape in the management of stress urinary incontinence in women.* Eur Urol, 2002. **41**(4): p. 469-73.
35. Wang, A.C. and M.C. Chen, *Comparison of tension-free vaginal taping versus modified Burch colposuspension on urethral obstruction: a randomized controlled trial.* Neurourol Urodyn, 2003. **22**(3): p. 185-90.
36. WardKL, H., &on behalf of the UK and Ireland TVT Trial-Group., *A prospective multicenter randomized trial of tenson-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up.* Americna Journal of Obstetrics & Gynecology, 2004. **190**: p. 324-331.
37. WardKL, H., &on behalf of the UK and Ireland TVT Trial-Group., *Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up.* British Journal of Obstetrics and Gynecology, 2008. **115**: p. 226-233.
38. Bai, S.W., et al., *Comparison of the efficacy of Burch colposuspension, pubovaginal sling, and tension-free vaginal*

tape for stress urinary incontinence. Int J Gynaecol Obstet, 2005. **91**(3): p. 246-51.

39. El-Barky, E., et al., *Tension free vaginal tape versus Burch colposuspension for treatment of female stress urinary incontinence.* Int Urol Nephrol, 2005. **37**(2): p. 277-81.

40. Ogah, J., J.D. Cody, and L. Rogerson, *Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women.* Cochrane Database Syst Rev, 2009(4): p. CD006375.

41. Paraiso, M.F., et al., *Laparoscopic Burch colposuspension versus tension-free vaginal tape: a randomized trial.* Obstet Gynecol, 2004. **104**(6): p. 1249-58.

42. Ustun, Y., et al., *Tension-free vaginal tape compared with laparoscopic Burch urethropexy.* J Am Assoc Gynecol Laparosc, 2003. **10**(3): p. 386-9.

43. Persson, J., T. Bossmar, and P. Wolner-Hanssen, *Laparoscopic colposuspension: a short term urodynamic follow-up and a three-year questionnaire-study.* Acta Obstet Gynecol Scand, 2000. **79**(5): p. 414-20.

44. Foote, A.J., V. Maughan, and C. Carne, *Laparoscopic colposuspension versus vaginal suburethral slingplasty: a randomised prospective trial.* Aust N Z J Obstet Gynaecol, 2006. **46**(6): p. 517-20.

45. Tong, J.L., L. Zhu, and J.H. Lang, *[Effects of laparoscopic Burch colposuspension and tension-free vaginal tape in treatment of female stress urinary incontinence: a comparative study].* Zhonghua Yi Xue Za Zhi, 2008. **88**(45): p. 3192-4.

46. Jelovsek, J.E., et al., *Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow up.* BJOG: An International Journal of Obstetrics & Gynaecology, 2008. **115**(2): p. 219-225.

47. Valpas, A., et al., *Tension-free vaginal tape and laparoscopic mesh colposuspension for stress urinary incontinence.* Obstet Gynecol, 2004. **104**(1): p. 42-9.

48. Novara, G., et al., *Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence.* Eur Urol, 2010. **58**(2): p. 218-38.

49. Valpas, A., et al., *A cost-effectiveness analysis of tension-free vaginal tape versus laparoscopic mesh colposuspension for primary female stress incontinence.* Acta Obstet Gynecol Scand, 2006. **85**(12): p. 1485-90.

50. Andonian, S., et al., *Randomized clinical trial comparing suprapubic arch sling (SPARC) and tension-free vaginal tape (TVT): one-year results.* Eur Urol, 2005. **47**(4): p. 537-41.

51. Lord, H.E., et al., *A randomized controlled equivalence trial of short-term complications and efficacy of tension-free vaginal tape and suprapubic urethral support sling for treating stress incontinence.* BJU Int, 2006. **98**(2): p. 367-76.

52. Tseng, L.H., et al., *Randomized comparison of the suprapubic arc sling procedure vs tension-free vaginal taping for stress incontinent women.* Int Urogynecol J Pelvic Floor Dysfunct, 2005. **16**(3): p. 230-5.

53. Paick, J.S., et al., *Tension-free vaginal tape, suprapubic arc sling, and transobturator tape in the treatment of mixed urinary incontinence in women.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(1): p. 123-9.

54. KimWT, K., KimJW, et al., *Comparative study of the tension-free vaginal tape (TVT) and eh suprapubic arc sling (SPARC) procedure for treating female stress urinary incontinence:a 1-year follow-up.* Korean Journal of Urology, 2006. **47**: p. 397-401.

55. Gandhi, S., et al., *TVT versus SPARC: comparison of outcomes for two midurethral tape procedures.* Int Urogynecol J Pelvic Floor Dysfunct, 2006. **17**(2): p. 125-30.

56. Dietz, H.P., et al., *TVT and Sparc suburethral slings: a case-control series.* Int Urogynecol J Pelvic Floor Dysfunct, 2004. **15**(2): p. 129-31; discussion 131.

57. Rechberger, T., et al., *A randomized comparison between monofilament and multifilament tapes for stress incontinence surgery.* Int Urogynecol J Pelvic Floor Dysfunct, 2003. **14**(6): p. 432-6.

58. Lim, Y.N., et al., *Suburethral slingplasty evaluation study in North Queensland, Australia: the SUSPEND trial.* Aust N Z J Obstet Gynaecol, 2005. **45**(1): p. 52-9.

59. Meschia, M., et al., *Tension-free vaginal tape (TVT) and intravaginal slingplasty (IVS) for stress urinary incontinence: a multicenter randomized trial.* Am J Obstet Gynecol, 2006. **195**(5): p. 1338-42.

60. Prien-Larsen, J.C. and L. Hemmingsen, *Long-term outcomes of TVT and IVS operations for treatment of female stress urinary incontinence: monofilament vs. multifilament polypropylene tape.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(6): p. 703-9.

61. Balakrishnan, S., et al., *Sling distress: a subanalysis of the IVS tapes from the SUSPEND trial.* Aust N Z J Obstet Gynaecol, 2007. **47**(6): p. 496-8.

62. Lim, Y.N. and A. Rane, *Suburethral vaginal erosion and pyogenic granuloma formation: an unusual complication of intravaginal slingplasty (IVS).* Int Urogynecol J Pelvic Floor Dysfunct, 2004. **15**(1): p. 56-8.

63. Glavind, K. and P. Sander, *Erosion, defective healing and extrusion after tension-free urethropexy for the treatment of stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2004. **15**(3): p. 179-82.

64. Agarwala, N., *A randomized comparison of two synthetic mid-urethral tension-free slings.* UroToday International Journal, 2008. **1**(4): p. doi:10.3834/uij.1939-4810.2008.10.05.

65. Yoon, C.J. and H.C. Jung, *Three-year outcomes of the innovative replacement of incontinence surgery procedure for treatment of female stress urinary incontinence: comparison with tension-free vaginal tape procedure.* J Korean Med Sci, 2007. **22**(3): p. 497-501.

66. Wang, A.C., et al., *A histologic and immunohistochemical analysis of defective vaginal healing after continence taping procedures: a prospective case-controlled pilot study.* Am J Obstet Gynecol, 2004. **191**(6): p. 1868-74.

67. Tamussino, K.F., et al., *Tension-free vaginal tape operation: results of the Austrian registry.* Obstet Gynecol, 2001. **98**(5 Pt 1): p. 732-6.

68. Delorme, E., *[Transobturator urethral suspension: mini-invasive procedure in the treatment of stress urinary incontinence in women].* Prog Urol, 2001. **11**(6): p. 1306-13.

69. DeLevalJ., *Novel surgical technique for the treatment of female stress urinary incontinence: transobturator vaginal tape inside-out.* Eur Urol, 2003. **44**: p. 724-730.

70. Laurikainen, E., et al., *Retropubic compared with transobturator tape placement in treatment of urinary incontinence: a randomized controlled trial.* Obstet Gynecol, 2007. **109**(1): p. 4-11.

71. Meschia, M., et al., *Peri-operative morbidity and early results of a randomised trial comparing TVT and TVT-O.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(11): p. 1257-61.

72. Liapis, A., et al., *Tension-free vaginal tape for elderly women with stress urinary incontinence.* Int J Gynaecol Obstet, 2006. **92**(1): p. 48-51.

73. Zullo, M.A., et al., *One-year follow-up of tension-free vaginal tape (TVT) and trans-obturator suburethral tape from inside to outside (TVT-O) for surgical treatment of female stress urinary incontinence: a prospective randomised trial.* Eur Urol, 2007. **51**(5): p. 1376-82; discussion 1383-4.

74. Araco, F., et al., *TVT-O vs TVT: a randomized trial in patients with different degrees of urinary stress incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(7): p. 917-26.

75. Rinne, K., et al., *A randomized trial comparing TVT with TVT-O: 12-month results.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(8): p. 1049-54.

76. Andonian, S., et al., *Prospective clinical trial comparing Obtape and DUPS to TVT: one-year safety and efficacy results.* Eur Urol, 2007. **52**(1): p. 245-51.

77. Porena, M., et al., *Tension-free vaginal tape versus transobturator tape as surgery for stress urinary incontinence: results of a multicentre randomised trial.* Eur Urol, 2007. **52**(5): p. 1481-90.

78. Wang, A.C., et al., *Prospective randomized comparison of transobturator suburethral sling (Monarc) vs suprapubic arc (Sparc) sling procedures for female urodynamic stress incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2006. **17**(5): p. 439-43.

79. Liapis, A., et al., *Tension-free vaginal tape versus tension-free vaginal tape obturator in women with stress urinary incontinence.* Gynecol Obstet Invest, 2006. **62**(3): p. 160-4.

80. EnzelsbergerH, S., HeiderR , et al., *TVT versus TOT-A prospective randomized stdy for the treatment of female stress urinary incontinence at a followup of 1 year.* Geburtshilfe und Frauenheilkunde, 2005. **65**: p. 506-511.

81. KimYW, N., SulCK., *Randomized prospective study between pubovaginal sling using SPARC sling system and MONARC sling system for the treatment of female stress urinary incontinence: short term results.* Korean Journal of Urology, 2005. **46**: p. 1078-1082.

82. Darai, E., et al., *Functional results after the suburethral sling procedure for urinary stress incontinence: a prospective randomized multicentre study comparing the retropubic and transobturator routes.* Eur Urol, 2007. **51**(3): p. 795-801; discussion 801-2.

83. Lee, K.S., et al., *A prospective trial comparing tension-free vaginal tape and transobturator vaginal tape inside-out for the surgical treatment of female stress urinary incontinence: 1-year followup.* J Urol, 2007. **177**(1): p. 214-8.

84. Zhu, L., et al., *Comparing vaginal tape and transobturator tape for the treatment of mild and moderate stress incontinence.* Int J Gynaecol Obstet, 2007. **99**(1): p. 14-7.

85. Barber, M.D., et al., *Risk factors associated with failure 1 year after retropubic or transobturator midurethral slings.* Am J Obstet Gynecol, 2008. **199**(6): p. 666 e1-7.

86. Barry, C., et al., *A multi-centre, randomised clinical control trial comparing the retropubic (RP) approach versus the transobturator approach (TO) for tension-free, suburethral sling treatment of urodynamic stress incontinence: the TORP study.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(2): p. 171-8.

87. Schierlitz, L., et al., *Effectiveness of tension-free vaginal tape compared with transobturator tape in women with stress urinary incontinence and intrinsic sphincter deficiency: a randomized controlled trial.* Obstet Gynecol, 2008. **112**(6): p. 1253-61.

88. Rechberger, T., et al., *The clinical effectiveness of retropubic (IVS-02) and transobturator (IVS-04) midurethral slings: randomized trial.* Eur Urol, 2009. **56**(1): p. 24-30.

89. Deffieux, X., et al., *Transobturator TVT-O versus retropubic TVT: results of a multicenter randomized controlled trial at 24 months follow-up.* Int Urogynecol J, 2010. **21**(11): p. 1337-45.

90. Teo, R., et al., *Randomized trial of tension-free vaginal tape and tension-free vaginal tape-obturator for urodynamic stress incontinence in women.* J Urol, 2011. **185**(4): p. 1350-5.

91. Palva, K., et al., *A randomized trial comparing tension-free vaginal tape with tension-free vaginal tape-obturator: 36-month results.* Int Urogynecol J, 2010. **21**(9): p. 1049-55.

92. Krofta, L., et al., *TVT and TVT-O for surgical treatment of primary stress urinary incontinence: prospective randomized trial.* Int Urogynecol J, 2010. **21**(2): p. 141-8.

93. Aniuliene, R., *Tension-free vaginal tape versus tension-free vaginal tape obturator (inside-outside) in the surgical treatment of female stress urinary incontinence.* Medicina (Kaunas), 2009. **45**(8): p. 639-43.

94. Karateke, A., et al., *Comparison of TVT and TVT-O in patients with stress urinary incontinence: short-term cure rates and factors influencing the outcome. A prospective randomised study.* Aust N Z J Obstet Gynaecol, 2009. **49**(1): p. 99-105.

95. Wang, W., L. Zhu, and J. Lang, *Transobturator tape procedure versus tension-free vaginal tape for treatment of stress urinary incontinence.* Int J Gynaecol Obstet, 2009. **104**(2): p. 113-6.

96. Wang, W.Y., et al., *[A prospective randomized trial of comparing the clinical outcome of tension-free vaginal tape and transobturator tape for stress urinary incontinence].* Zhonghua Yi Xue Za Zhi, 2011. **91**(13): p. 898-901.

97. Barber, M.D., et al., *Transobturator tape compared with tension-free vaginal tape for the treatment of stress urinary incontinence: a randomized controlled trial.* Obstet Gynecol, 2008. **111**(3): p. 611-21.

98. Ross, J., *Two techniques of laparoscopic Burch repair for stress incontinence: a prospective, randomized study.* J Am Assoc Gynecol Laparosc, 1996. **3**(3): p. 351-7.

99. Wang, F., Y. Song, and H. Huang, *Prospective randomized trial of TVT and TOT as primary treatment for female stress urinary incontinence with or without pelvic organ prolapse in Southeast China.* Arch Gynecol Obstet, 2010. **281**(2): p. 279-86.

100. Ansquer, Y., et al., *The suburethral sling for female stress urinary incontinence: a retropubic or obturator approach?* J Am Assoc Gynecol Laparosc, 2004. **11**(3): p. 353-8.

101. Mellier, G., et al., *Suburethral tape via the obturator route: is the TOT a simplification of the TVT?* Int Urogynecol J Pelvic Floor Dysfunct, 2004. **15**(4): p. 227-32.

102. Morey, A.F., et al., *Transobturator versus transabdominal mid urethral slings: a multi-institutional comparison of obstructive voiding complications.* J Urol, 2006. **175**(3 Pt 1): p. 1014-7.

103. Falkert, A. and B. Seelbach-Gobel, *TVT versus TOT for surgical treatment of female stress urinary incontinence.* Int J Gynaecol Obstet, 2007. **96**(1): p. 40-1.

104. Neuman, M., *TVT and TVT-Obturator: comparison of two operative procedures.* Eur J Obstet Gynecol Reprod Biol, 2007. **131**(1): p. 89-92.

105. Paick, J.S., et al., *Factors influencing the outcome of mid urethral sling procedures for female urinary incontinence.* J Urol, 2007. **178**(3 Pt 1): p. 985-9; discussion 989.

106. Sola, V., et al., *TVT versus TVT-O for minimally invasive surgical correction of stress urinary incontinence.* Int Braz J Urol, 2007. **33**(2): p. 246-52; discussion 253.

107. Charalambous, S., et al., *Transvaginal vs transobturator approach for synthetic sling placement in patients with stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(3): p. 357-60.

108. Jeon, M.J., et al., *Surgical therapeutic index of tension-free vaginal tape and transobturator tape for stress urinary incontinence.* Gynecol Obstet Invest, 2008. **65**(1): p. 41-6.

109. Long, C.Y., et al., *Clinical and ultrasonographic comparison of tension-free vaginal tape and transobturator tape procedure for the treatment of stress urinary incontinence.* J Minim Invasive Gynecol, 2008. **15**(4): p. 425-30.

110. Wang, W.Y., et al., *[Clinical study on tension-free vaginal tape and tension-free vaginal tape obturator for surgical treatment of severe stress urinary incontinence].* Zhonghua Fu Chan Ke Za Zhi, 2008. **43**(3): p. 180-4.

111. Gungorduk, K., et al., *Which type of mid-urethral sling procedure should be chosen for treatment of stress urinary incontinance with intrinsic sphincter deficiency? Tension-free vaginal tape or transobturator tape.* Acta Obstet Gynecol Scand, 2009. **88**(8): p. 920-6.

112. Houwert, R.M., et al., *Risk factors for failure of retropubic and transobturator midurethral slings.* Am J Obstet Gynecol, 2009. **201**(2): p. 202 e1-8.

113. Rapp, D.E., F.E. Govier, and K.C. Kobashi, *Outcomes following mid-urethral sling placement in patients with intrinsic sphincteric deficiency: comparison of Sparc and Monarc slings.* Int Braz J Urol, 2009. **35**(1): p. 68-75; discussion 75.

114. Reich, A., et al., *Comparison of transobturator vaginal tape and retropubic tension-free vaginal tape: clinical outcome and sonographic results of a case-control study.* Gynecol Obstet Invest, 2009. **68**(2): p. 137-44.

115. Castillo-Pino, E., A. Sasson, and J.E. Pons, *Comparison of retropubic and transobturator tension-free vaginal implants for the treatment of stress urinary incontinence.* Int J Gynaecol Obstet, 2010. **110**(1): p. 23-6.

116. Duckett, J.R. and M. Basu, *TVT vs TOT: a case controlled study in patients with mixed urodynamic stress incontinence and detrusor overactivity.* Int Urogynecol J, 2010. **21**(7): p. 763-6.

117. George, S., et al., *Two-year comparison of tension-free vaginal tape and transobturator tape for female urinary stress incontinence.* J Obstet Gynaecol, 2010. **30**(3): p. 281-4.

118. Tanuri, A.L., et al., *[Retropubic and transobturator sling in treatment of stress urinary incontinence].* Rev Assoc Med Bras, 2010. **56**(3): p. 348-54.

119. Henriksson, L. and U. Ulmsten, *A urodynamic evaluation of the effects of abdominal urethrocystopexy and vaginal sling urethroplasty in women with stress incontinence.* Am J Obstet Gynecol, 1978. **131**(1): p. 77-82.

120. Hilton, P., *A clinical and urodynamic study comparing the Stamey bladder neck suspension and suburethral sling procedures in the treatment of genuine stress incontinence.* Br J Obstet Gynaecol, 1989. **96**(2): p. 213-20.

121. Enzelsberger, H., H. Helmer, and C. Schatten, *Comparison of Burch and lyodura sling procedures for repair of unsuccessful incontinence surgery.* Obstet Gynecol, 1996. **88**(2): p. 251-6.

122. Sand, P.K., et al., *A prospective randomized study comparing modified Burch retropubic urethropexy and suburethral sling for treatment of genuine stress incontinence with low-pressure urethra.* Am J Obstet Gynecol, 2000. **182**(1 Pt 1): p. 30-4.

123. Culligan, P.J., R.P. Goldberg, and P.K. Sand, *A randomized controlled trial comparing a modified Burch procedure and a suburethral sling: long-term follow-up.* Int Urogynecol J Pelvic Floor Dysfunct, 2003. **14**(4): p. 229-33; discussion 233.

124. Demirci, F. and O. Yucel, *Comparison of pubovaginal sling and burch colposuspension procedures in type I/II genuine stress incontinence.* Arch Gynecol Obstet, 2001. **265**(4): p. 190-4.

125. Albo, M.E., et al., *Burch colposuspension versus fascial sling to reduce urinary stress incontinence.* N Engl J Med, 2007. **356**(21): p. 2143-55.

126. Chai, T.C., et al., *Complications in women undergoing Burch colposuspension versus autologous rectus fascial sling for stress urinary incontinence.* J Urol, 2009. **181**(5): p. 2192-7.

127. Kaplan, S.A., R.P. Santarosa, and A.E. Te, *Comparison of fascial and vaginal wall slings in the management of intrinsic sphincter deficiency.* Urology, 1996. **47**(6): p. 885-9.

128. Barbalias, G., E. Liatsikos, and D. Barbalias, *Use of slings made of indigenous and allogenic material (Goretex) in type III urinary incontinence and comparison between them.* Eur Urol, 1997. **31**(4): p. 394-400.

129. Wright, E.J., et al., *Pubovaginal sling using cadaveric allograft fascia for the treatment of intrinsic sphincter deficiency.* J Urol, 1998. **160**(3 Pt 1): p. 759-62.

130. Brown, S.L. and F.E. Govier, *Cadaveric versus autologous fascia lata for the pubovaginal sling: surgical outcome and patient satisfaction.* J Urol, 2000. **164**(5): p. 1633-7.

131. O'Reilly, K.J. and F.E. Govier, *Intermediate term failure of pubovaginal slings using cadaveric fascia lata: a case series.* J Urol, 2002. **167**(3): p. 1356-8.

132. Choe, J.M., K. Ogan, and B.S. Battino, *Antimicrobial mesh versus vaginal wall sling: a comparative outcomes analysis.* J Urol, 2000. **163**(6): p. 1829-34.

133. LucasM, E., StephensonT., *A randomised study to assess and compare the clinical effectiveness of two surgial techniques for the treatment of stress urinary incontinence in women.* Cardiff, The Wales Office of Research and Development for Health and Social Care., 2000.

134. Guerrero, K., et al., *A randomised controlled trial comparing two autologous fascial sling techniques for the treatment of stress urinary incontinence in women: short, medium and long-term follow-up.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(11): p. 1263-70.

135. Kuo, H.C., *Comparison of video urodynamic results after the pubovaginal sling procedure using rectus fascia and polypropylene mesh for stress urinary incontinence.* J Urol, 2001. **165**(1): p. 163-8.

136. Maher, C., et al., *Pubovaginal or vicryl mesh rectus fascia sling in intrinsic sphincter deficiency.* Int Urogynecol J Pelvic Floor Dysfunct, 2001. **12**(2): p. 111-6.

137. Soergel, T.M., S. Shott, and M. Heit, *Poor surgical outcomes after fascia lata allograft slings.* Int Urogynecol J Pelvic Floor Dysfunct, 2001. **12**(4): p. 247-53.

138. Flynn, B.J. and W.T. Yap, *Pubovaginal sling using allograft fascia lata versus autograft fascia for all types of stress urinary incontinence: 2-year minimum followup.* J Urol, 2002. **167**(2 Pt 1): p. 608-12.

139. Viseshsindh, W., et al., *A randomized controlled trial of pubovaginal sling versus vaginal wall sling for stress urinary incontinence.* J Med Assoc Thai, 2003. **86**(4): p. 308-15.

140. Almeida, S.H., et al., *Pubovaginal sling using cadaveric allograft fascia for the treatment of female urinary incontinence.* Transplant Proc, 2004. **36**(4): p. 995-6.

141. Rodrigues, P., et al., *Pubo-fascial versus vaginal sling operation for the treatment of stress urinary incontinence: a prospective study.* Neurourol Urodyn, 2004. **23**(7): p. 627-31.

142. McBride, A.W., et al., *Comparison of long-term outcomes of autologous fascia lata slings with Suspend Tutoplast fascia lata allograft slings for stress incontinence.* Am J Obstet Gynecol, 2005. **192**(5): p. 1677-81.

143. Simsiman, A.J., et al., *Suburethral sling materials: best outcome with autologous tissue.* Am J Obstet Gynecol, 2005. **193**(6): p. 2112-6.

144. Giri, S.K., et al., *The long-term results of pubovaginal sling surgery using acellular cross-linked porcine dermis in the treatment of urodynamic stress incontinence.* J Urol, 2006. **175**(5): p. 1788-92; discussion 1793.

145. Morgan, D.M., et al., *Comparative analysis of urinary incontinence severity after autologous fascia pubovaginal sling, pubovaginal sling and tension-free vaginal tape.* J Urol, 2007. **177**(2): p. 604-8; discussion 608-9.

146. Onur, R., A. Singla, and K.C. Kobashi, *Comparison of solvent-dehydrated allograft dermis and autograft rectus fascia for pubovaginal sling: questionnaire-based analysis.* Int Urol Nephrol, 2008. **40**(1): p. 45-9.

147. Wilson, C.M., et al., *Bovine dermis: a novel biologic substitute for autologous tissue in sling surgery.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(12): p. 1671-6.

148. Winckler, J.A., et al., *Comparative study of polypropylene and aponeurotic slings in the treatment of female urinary incontinence.* Int Braz J Urol, 2010. **36**(3): p. 339-47.

149. Arunkalaivanan, A.S. and J.W. Barrington, *Randomized trial of porcine dermal sling (Pelvicol implant) vs. tension-free vaginal tape (TVT) in the surgical treatment of stress incontinence: a questionnaire-based study.* Int Urogynecol J Pelvic Floor Dysfunct, 2003. **14**(1): p. 17-23; discussion 21-2.

150. Abdel-Fattah, M., J.W. Barrington, and A.S. Arunkalaivanan, *Pelvicol pubovaginal sling versus tension-free vaginal tape for treatment of urodynamic stress incontinence: a prospective randomized three-year follow-up study.* Eur Urol, 2004. **46**(5): p. 629-35.

151. HungMJ LiuFS, S., et al., *Analysis of two sling procedures using polypropylene mesh for treatment of stress urinary incontinence.* International Journal of Gynecology& Obstretrics, 2004. **84**: p. 133-141.

152. Wadie, B.S., A. Edwan, and A.M. Nabeeh, *Autologous fascial sling vs polypropylene tape at short-term followup: a prospective randomized study.* J Urol, 2005. **174**(3): p. 990-3.

153. Wadie, B.S., et al., *Minimum 2-year follow-up of mid-urethral slings, effect on quality of life, incontinence impact and sexual function.* Int Urogynecol J, 2010. **21**(12): p. 1485-90.

154. Kondo, A., et al., *Efficacy, safety and hospital costs of tension-free vaginal tape and pubovaginal sling in the surgical treatment of stress incontinence.* J Obstet Gynaecol Res, 2006. **32**(6): p. 539-44.

155. Basok, E.K., et al., *Cadaveric fascia lata versus intravaginal slingplasty for the pubovaginal sling: surgical outcome, overall success and patient satisfaction rates.* Urol Int, 2008. **80**(1): p. 46-51.

156. Jeon, M.J., et al., *Comparison of the treatment outcome of pubovaginal sling, tension-free vaginal tape, and transobturator tape for stress urinary incontinence with intrinsic sphincter deficiency.* Am J Obstet Gynecol, 2008. **199**(1): p. 76 e1-4.

157. Sharifiaghdas, F. and N. Mortazavi, *Tension-free vaginal tape and autologous rectus fascia pubovaginal sling for the treatment of urinary stress incontinence: a medium-term follow-up.* Med Princ Pract, 2008. **17**(3): p. 209-14.

158. Amaro, J.L., et al., *Clinical and quality-of-life outcomes after autologous fascial sling and tension-free vaginal tape: a prospective randomized trial.* Int Braz J Urol, 2009. **35**(1): p. 60-6; discussion 66-7.

159. Trabuco, E.C., et al., *Medium-term comparison of continence rates after rectus fascia or midurethral sling placement.* Am J Obstet Gynecol, 2009. **200**(3): p. 300 e1-6.

160. Guerrero, K.L., et al., *A randomised controlled trial comparing TVT, Pelvicol and autologous fascial slings for the treatment of stress urinary incontinence in women.* BJOG, 2010. **117**(12): p. 1493-502.

161. LucasM, E., AlanW & KathyW., *filure of procine xenograft sling in a randomised controlled trial of three sling materials in surgery for stress incontience.* , in *International Continence Society & International Urogynecological Association.*2004: Paris, France.

162. Silva-Filho, A.L., et al., *Comparative study of autologous pubovaginal sling and synthetic transobturator (TOT) SAFYRE sling in the treatment of stress urinary incontinence.* Arch Gynecol Obstet, 2006. **273**(5): p. 288-92.

163. Tcherniakovsky, M., et al., *Comparative results of two techniques to treat stress urinary incontinence: synthetic transobturator and aponeurotic slings.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(8): p. 961-6.

164. Corcos, J., et al., *Multicenter randomized clinical trial comparing surgery and collagen injections for treatment of female stress urinary incontinence.* Urology, 2005. **65**(5): p. 898-904.

165. Maher, C.F., et al., *Pubovaginal sling versus transurethral Macroplastique for stress urinary incontinence and intrinsic sphincter deficiency: a prospective randomised controlled trial.* BJOG, 2005. **112**(6): p. 797-801.

166. Ustun, Y., et al., *Tension-free vaginal tape compared with laparoscopic Burch urethropexy.* Journal of the American Association of Gynecologic Laparoscopists, 2003. **10**(3): p. 386-389 [erratum appears in J Am Assoc Gynecol Laparosc. 2003 Nov;10(4):581].

167. Hsiao, S.M., T.C. Chang, and H.H. Lin, *Risk factors affecting cure after mid-urethral tape procedure for female urodynamic stress incontinence: comparison of retropubic and transobturator routes.* Urology, 2009. **73**(5): p. 981-6.

168. Ross, S., et al., *Transobturator tape compared with tension-free vaginal tape for stress incontinence: a randomized controlled trial.* Obstet Gynecol, 2009. **114**(6): p. 1287-94.

169. Deffieux, X., et al., *Long-term results of tension-free vaginal tape for female urinary incontinence: follow up over 6 years.* Int J Urol, 2007. **14**(6): p. 521-6.

170. Richter, H.E., et al., *Retropubic versus transobturator midurethral slings for stress incontinence.* N Engl J Med, 2010. **362**(22): p. 2066-76.

171. Ulmsten, U. and P. Petros, *Intravaginal slingplasty (IVS): an ambulatory surgical procedure for treatment of female urinary incontinence.* Scand J Urol Nephrol, 1995. **29**(1): p. 75-82.

172. Hinoul, P., et al., *Anatomical variability in the trajectory of the inside-out transobturator vaginal tape technique (TVT-O).* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(10): p. 1201-6.

173. Brink, D.M., *Bowel injury following insertion of tension-free vaginal tape.* S Afr Med J, 2000. **90**(5): p. 450, 452.

174. Kobashi, K.C. and F.E. Govier, *Perioperative complications: the first 140 polypropylene pubovaginal slings.* J Urol, 2003. **170**(5): p. 1918-21.

175. Meschia, M., et al., *Bowel perforation during insertion of tension-free vaginal tape (TVT).* Int Urogynecol J Pelvic Floor Dysfunct, 2002. **13**(4): p. 263-5; discussion 265.

176. Costa, P., et al., *Surgical treatment of female stress urinary incontinence with a trans-obturator-tape (T.O.T.) Uratape: short term results of a prospective multicentric study.* Eur Urol, 2004. **46**(1): p. 102-6; discussion 106-7.

177. Foley, C., P. Patki, and G. Boustead, *Unrecognized bladder perforation with mid-urethral slings.* BJU Int, 2010. **106**(10): p. 1514-8.

178. de Leval, J., A. Thomas, and D. Waltregny, *The original versus a modified inside-out transobturator procedure: 1-year results of a prospective randomized trial.* Int Urogynecol J, 2011. **22**(2): p. 145-56.

179. Delorme, E., et al., *[Transobturator tape (Uratape). A new minimally invasive method in the treatment of urinary incontinence in women].* Prog Urol, 2003. **13**(4): p. 656-9.

180. Delorme, E., et al., *Transobturator tape (Uratape): a new minimally-invasive procedure to treat female urinary incontinence.* Eur Urol, 2004. **45**(2): p. 203-7.

181. Caquant, F., et al., *Perineal cellulitis following trans-obturator sub-urethral tape Uratape.* Eur Urol, 2005. **47**(1): p. 108-10.

182. Al Nakib, M., et al., *[Management of serious infectious complications of transobturator suburethral tape: report of 2 cases].* Prog Urol, 2005. **15**(4): p. 707-9.

183. Lowery, W.J., Y. Dooley, and E. Kost, *Small-pore polypropylene slings: still out there.* Int Urogynecol J, 2010. **21**(1): p. 125-7.

184. Mendonca, T.M., D. Martinho, and J.P. Dos Reis, *Late urethral erosion of transobturator suburethral mesh (Obtape): a minimally invasive management under local anaesthesia.* Int Urogynecol J, 2011. **22**(1): p. 37-9.

185. Waltregny, D., et al., *Inside out transobturator vaginal tape for the treatment of female stress urinary incontinence: interim results of a prospective study after a 1-year minimum followup.* J Urol, 2006. **175**(6): p. 2191-5.

186. HinoulP, B., DeRooverC, et al., *An anatomic comparison of the traditional TVT-O versus a modified TVT-O porecdure* . Gynecol Obstet Invest, 2010.

187. SchraffordtKoppsSE, B.H., et al., *Prospective analysis of complicaitons of tension-free vaginal tape from The Netherlands Tension-free Vaginal Tape study.* Am. J. Obstet. Gynecol., 2005. **193**(1): p. 45-52.

188. Collinet, P., et al., *The safety of the inside-out transobturator approach for transvaginal tape (TVT-O) treatment in stress urinary incontinence: French registry data on 984 women.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(5): p. 711-5.

189. Poza, J.L., et al., *Trans-obturator suburethral tape for female stress incontinence: a cohort of 254 women with 1-year to 2-year follow-up.* Acta Obstet Gynecol Scand, 2008. **87**(2): p. 232-9.

190. Achtari, C., et al., *Anatomical study of the obturator foramen and dorsal nerve of the clitoris and their relationship to minimally invasive slings.* Int Urogynecol J Pelvic Floor Dysfunct, 2006. **17**(4): p. 330-4.

191. Latthe, P.M., et al., *Two routes of transobturator tape procedures in stress urinary incontinence: a meta-analysis with direct and indirect comparison of randomized trials.* BJU Int, 2010. **106**(1): p. 68-76.

192. HouwertM, V., *Transobturator tape (TOT), inside-out versus outside-in approaches: outcome after 1 year (Abstract no. 056).* Int Urogynecol J, 2007.

193. But, I. and M. Faganelj, *Complications and short-term results of two different transobturator techniques for surgical treatment of women with urinary incontinence: a randomized study.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(6): p. 857-61.

194. Lee, K.S., et al., *Prospective comparison of the 'inside-out' and 'outside-in' transobturator-tape procedures for the treatment of female stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(4): p. 577-82.

195. Liapis, A., P. Bakas, and G. Creatsas, *Monarc vs TVT-O for the treatment of primary stress incontinence: a randomized study.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(2): p. 185-90.

196. Houwert, R.M., et al., *TVT-O versus Monarc after a 2-4-year follow-up: a prospective comparative study.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(11): p. 1327-33.

197. Abdel-Fattah, M., et al., *Randomised prospective single-blinded study comparing 'inside-out' versus 'outside-in' transobturator tapes in the management of urodynamic stress incontinence: 1-year outcomes from the E-TOT study.* BJOG, 2010. **117**(7): p. 870-8.

198. Angioli, R., et al., *Tension-free vaginal tape versus transobturator suburethral tape: five-year follow-up results of a prospective, randomised trial.* Eur Urol, 2010. **58**(5): p. 671-7.

199. Costantini, E., et al., *Preoperative MUCP and VLPP did not predict long-term (4-year) outcome after transobturator mid-urethral sling.* Urol Int, 2009. **83**(4): p. 392-8.

200. Minaglia, S., et al., *Effectiveness of transobturator tape in women with decreased urethral mobility.* J reprod med, 2009. **54**(1): p. 15-9.

201. Haliloglu, B., et al., *The role of urethral hypermobility and intrinsic sphincteric deficiency on the outcome of transobturator tape procedure: a prospective study with 2-year follow-up.* Int Urogynecol J, 2010. **21**(2): p. 173-8.

202. Novara, G., et al., *Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices.* Eur Urol, 2008. **53**(2): p. 288-308.

203. Brubaker, L., et al., *Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the Trial of Midurethral Slings (TOMUS) study.* Am J Obstet Gynecol, 2011. **205**(5): p. 498 e1-6.

204. Gamble, T.L., et al., *Predictors of persistent detrusor overactivity after transvaginal sling procedures.* Am J Obstet Gynecol, 2008. **199**(6): p. 696 e1-7.

205. Paick, J.S., et al., *Tension-free vaginal tape procedure for the treatment of mixed urinary incontinence: significance of maximal urethral closure pressure.* J Urol, 2004. **172**(3): p. 1001-5.

206. Botros, S.M., et al., *Detrusor overactivity and urge urinary incontinence following trans obturator versus midurethral slings.* Neurourol Urodyn, 2007. **26**(1): p. 42-5.

207. Ballert, K.N., J.A. Kanofsky, and V.W. Nitti, *Effect of tension-free vaginal tape and TVT-obturator on lower urinary tract symptoms other than stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(3): p. 335-40.

208. Lee, J.K., et al., *Persistence of urgency and urge urinary incontinence in women with mixed urinary symptoms after midurethral slings: a multivariate analysis.* BJOG, 2011. **118**(7): p. 798-805.

209. Lee, K.S., et al., *Outcomes following repeat mid urethral synthetic sling after failure of the initial sling procedure: re-discovery of the tension-free vaginal tape procedure.* J Urol, 2007. **178**(4 Pt 1): p. 1370-4; discussion 1374.

210. Liapis, A., P. Bakas, and G. Creatsas, *Tension-free vaginal tape in the management of recurrent urodynamic stress incontinence after previous failed midurethral tape.* Eur Urol, 2009. **55**(6): p. 1450-5.

211. Stav, K., et al., *Long-term outcomes of patients who failed to attend following midurethral sling surgery--a comparative study and analysis of risk factors for non-attendance.* Aust N Z J Obstet Gynaecol, 2010. **50**(2): p. 173-8.

212. Abdel-Fattah, M., et al., *Evaluation of transobturator tension-free vaginal tapes in management of women with recurrent stress urinary incontinence.* Urology, 2011. **77**(5): p. 1070-5.

213. Biggs, G.Y., et al., *Patient-reported outcomes for tension-free vaginal tape-obturator in women treated with a previous anti-incontinence procedure.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(3): p. 331-5.

214. Sevestre, S., et al., *Results of the tension-free vaginal tape technique in the elderly.* Eur Urol, 2003. **44**(1): p. 128-31.

215. Walsh, K., et al., *The influence of age on quality of life outcome in women following a tension-free vaginal tape procedure.* J Urol, 2004. **171**(3): p. 1185-8.

216. Gordon, D., et al., *Tension-free vaginal tape in the elderly: is it a safe procedure?* Urology, 2005. **65**(3): p. 479-82.

217. Chen, H.Y., et al., *Analysis of risk factors associated with surgical failure of inside-out transobturator vaginal tape for treating urodynamic stress incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(4): p. 443-7.

218. Groutz, A., et al., *The safety and efficacy of the "inside-out" trans-obturator TVT in elderly versus younger stress-incontinent women: a prospective study of 353 consecutive patients.* Neurourol Urodyn, 2011. **30**(3): p. 380-3.

219. Long, C.Y., et al., *Urodynamic comparison of continent and incontinent women with severe uterovaginal prolapse.* J reprod med, 2004. **49**(1): p. 33-7.

220. Roovers, J.P. and M. Oelke, *Clinical relevance of urodynamic investigation tests prior to surgical correction of genital prolapse: a literature review.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(4): p. 455-60.

221. Kleeman, S., et al., *The ability of history and a negative cough stress test to detect occult stress incontinence in patients undergoing surgical repair of advanced pelvic organ prolapse.* Int Urogynecol J Pelvic Floor Dysfunct, 2006. **17**(1): p. 27-9.

222. Liang, C.C., et al., *Pessary test to predict postoperative urinary incontinence in women undergoing hysterectomy for prolapse.* Obstet Gynecol, 2004. **104**(4): p. 795-800.

223. Casiano, E.R., et al., *Does concomitant prolapse repair at the time of midurethral sling affect recurrent rates of incontinence?* Int Urogynecol J, 2011. **22**(7): p. 819-25.

224. Wang, S.S., et al., *Evidence-based urology in practice: when to believe a subgroup analysis?* BJU Int, 2010. **105**(2): p. 162-4.

225. Hunskaar, S., *A systematic review of overweight and obesity as risk factors and targets for clinical intervention for urinary incontinence in women.* Neurourol Urodyn, 2008. **27**(8): p. 749-57.

226. Brown, J.S., et al., *Urinary incontinence in older women: who is at risk? Study of Osteoporotic Fractures Research Group.* Obstet Gynecol, 1996. **87**(5 Pt 1): p. 715-21.

227. Greer, W.J., et al., *Obesity and pelvic floor disorders: a systematic review.* Obstet Gynecol, 2008. **112**(2 Pt 1): p. 341-9.

228. Mukherjee, K. and G. Constantine, *Urinary stress incontinence in obese women: tension-free vaginal tape is the answer.* BJU Int, 2001. **88**(9): p. 881-3.

229. Skriapas, K., et al., *Tension-free vaginal tape (TVT) in morbidly obese patients with severe urodynamic stress incontinence as last option treatment.* Eur Urol, 2006. **49**(3): p. 544-50.

230. Lovatsis, D., et al., *Tension-free vaginal tape procedure is an ideal treatment for obese patients.* Am J Obstet Gynecol, 2003. **189**(6): p. 1601-4; discussion 1604-5.

231. Hellberg, D., et al., *The very obese woman and the very old woman: tension-free vaginal tape for the treatment of stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(4): p. 423-9.

232. Rafii, A., et al., *Body mass index and outcome of tension-free vaginal tape.* Eur Urol, 2003. **43**(3): p. 288-92.

233. Chung, M.K. and R.P. Chung, *Comparison of laparoscopic Burch and tension-free vaginal tape in treating stress urinary incontinence in obese patients.* JSLS, 2002. **6**(1): p. 17-21.

234. Ku, J.H., et al., *Outcome of mid-urethral sling procedures in Korean women with stress urinary incontinence according to body mass index.* Int J Urol, 2006. **13**(4): p. 379-84.

235. Liu, P.E., et al., *Outcome of tension-free obturator tape procedures in obese and overweight women.* Int Urogynecol J, 2011. **22**(3): p. 259-63.

236. Haverkorn, R.M., et al., *Is obesity a risk factor for failure and complications after surgery for incontinence and prolapse in women?* J Urol, 2011. **185**(3): p. 987-92.

237. Smith, A.R.B., *The vaginal urethral sling- a new operation for the treatment of stress incontinence of urine.* , in *17th annual meeting International continence society.*1987: Bristol.

238. Tardiu, A.M.F., E; Vicens, JML., *Contasure-Needleless® compared with transobturator-TVT® for the treatment of stress urinary incontinence.* Int Urogynecol J 2011. **22**: p. 827-833.

239. Enzelsberger H, C.I., Enzelsberger S, Schalupny J., *Mini-Arc versus Monarc: A propsective randomised study of the treatment of female sress urinary incontinence with follow up of 2 years.* Geburtsh Frauenheilk 2010. **70**: p. 499-502.

240. Basu, M.D., J., *A randomised trial of a retropubic tension-free vaginal tape versus a mini-sling for stress incontinence.* BJOG, 2010. **117**: p. 730-735.

241. Oliveira, R.B., F; Silva, P; Resende, A; Silva, C; Dinis, P; Cruz, F., *Exploratory study assessing efficacy and complications of TVT-O, TVT-Secur, and Mini-Arc: results at 12-month follow-up.* European Urology, 2011. **59**(6): p. 940-4.

242. Hinoul, P.V., HA. den Boon, J. Venema, PL. Lakeman, MM. Milani, AL. Roovers, JP., *A randomized, controlled trial comparing an innovative single incision sling with an established transobturator sling to treat female stress urinary incontinence.* J Urol. , 2011. **185**(4): p. 1356-62.

243. Hota, L.H., K; Hacker, M; Disciullo, A; Elkadry, E; Dramitinos, P; Shapiro, A; Ferzandi, T; Rosenblatt, P, *TVT-Secur versus TVT-Obturator: A randomized trial of suburethral sling operative procedures* Female Pelvic Medicine & Reconstructive Surgery. , 2012. **18**(1): p. 39-43.

244. Abdelwahab O, S.I., Al-Adl AM. , *Tension-free vaginal tape versus secure tension-free vaginal tape in treatment of female stress urinary incontinence.* Curr Urol, 2010. **4**: p. 93–8.

245. Hamer, M.L., PG .Teleman, P. Etén-Bergqvist, C. Persson, J., *Short-term results of a prospective randomized evaluator blinded multicenter study comparing TVT and TVT-Secur.* Int Urogynecol J 2011. **22**: p. 781-787.

246. Wang, Y.L., FP; Wang, Q;Yang, S; Cai, XG; Chen ,YH., *Comparison of three mid-urethral tension-free tapes (TVT, TVT-O, and TVT-Secur) in the treatment of female stress urinary incontinence: 1-year follow-up.* International Urogynecology Journal, 2011. **22**(11): p. 1369-74.

247. Abdel-Fattah, M.F., J; Lim,CP; Madhuvrata, P, *Single-Incision Mini-Slings Versus Standard Midurethral Slings in Surgical Management of Female Stress Urinary Incontinence: A Meta-Analysis of Effectiveness and Complications.* European Urology, 2011. **60**: p. 468-480.

248. Jeffery, S.D.J., P. Abdool, Z. Van Wijk, F. Lucente, V. Murphy,M. , *Single-incision sling operations for urinary incontinence in women (Protocol).* Cochrane Database of Systematic Reviews, 2010. **6**(Cochrane Incontinence Group Cochrane Database of Systematic Reviews. 6).

249. Rehman, H., et al., *Traditional suburethral sling operations for urinary incontinence in women.* Cochrane Database Syst Rev, 2011(1): p. CD001754.

250. HohenfelnerR&PetrieE, *Sling procedure in surgery*, in *Surger of Female Incontinence*, S.L.S.a.E. Tanagho, Editor. 1986, Spring-Verlag: Berlin. p. 105-113.

251. GoebelR, *Zur operativen Beseitigung der Angelborenen incontinenz vesicae.* Zeitschrift fur gynakologisch Urologie, 1910. **2**: p. 187-190.

252. SquireJB, *Post-operatiave urinary incontinence: urethroplastic operation.* Medical Recored, 1911. **79**: p. 868.

253. FrangenheimP, *Zur operativen Behandlung der Inkontinenz der mannlichen Harnrohre. Verhandlunge [der] Tagung.* Deutsche Gesellschaft fur Chirurgie, 1914. **43**: p. 149-158.

254. DemingCL, *Transplantation of fascia for relief of urinary stress incontinence.* J Am Medical Association, 1926. **86**: p. 822-825.

255. MartiusH, *Sphincter-und Harnrohrnplastik aus dem Musculus Bulbocavernosus. Der Chirurg.* Zeitschrift fur alle Gebeite der operative Medizen, 1929. **1**: p. 769-773.

256. AldridgeA, *Transplantation of fascia for relief of urinary stress incontinence. .* Amer J of Obstretrics and GYN, 1942. **44**: p. 398-411.

257. McGuire, E.J. and B. Lytton, *Pubovaginal sling procedure for stress incontinence.* J Urol, 1978. **119**(1): p. 82-4.

258. Blaivas, J.G. and B.Z. Jacobs, *Pubovaginal fascial sling for the treatment of complicated stress urinary incontinence.* J Urol, 1991. **145**(6): p. 1214-8.

259. NationalCollaboratingCentreforWomen's&Children'sHealth (a). 2006, National Institute for Health & Clinical Excellence.

260. NationalCollaboratingCentreforWomen's&Children'sHealth (b). 2006, National Institute for Health & Clinical Excellence.

261. Osman, T., *Stress incontinence surgery for patients presenting with mixed incontinence and a normal cystometrogram.* BJU Int, 2003. **92**(9): p. 964-8.

262. N, S.F.M., *Tension-free vaginal tape and autologous rectus fascia pubovaginal sling for the treatment of urinary stress incontinence: a medium-term follow-up.* Med Princ Pract., 2008. **17**(3): p. 209-214.

263. Dean, N.M., et al., *Laparoscopic colposuspension for urinary incontinence in women.* Cochrane Database of Systematic Reviews, 2006: p. Issue 3. Art. No.: CD002239. DOI: 10.1002/14651858.CD002239.pub2.

264. Moehrer, B., et al., *Laparoscopic colposuspension for urinary incontinence in women.* Cochrane Database of Systematic Reviews, 2000: p. Issue 3. Art. No.: CD002239. DOI: 10.1002/14651858.CD002239. .

265. Ankardal, M., et al., *A randomised trial comparing open Burch colposuspension using sutures with laparoscopic colposuspension using mesh and staples in women with stress urinary incontinence.* BJOG: An International Journal of Obstetrics & Gynaecology, 2004. **111**(9): p. 974-981.

266. Ankardal, M., et al., *A three-armed randomized trial comparing open Burch colposuspension using sutures with laparoscopic colposuspension using sutures and laparoscopic colposuspension using mesh and staples in women with stress urinary incontinence.* Acta Obstetricia et Gynecologica Scandinavica, 2005. **84**(8): p. 773-779.

267. Carey, M.P., et al., *Laparoscopic versus open Burch colposuspension: a randomised controlled trial.* BJOG: An International Journal of Obstetrics & Gynaecology, 2006. **113**(9): p. 999-1006.

268. Cheon, W.C., et al., *Prospective randomised controlled trial comparing laparoscopic and open colposuspension.* Hong Kong Medical Journal, 2003. **9**(1): p. 10-14.

269. Fatthy, H., et al., *Modified Burch colposuspension: laparoscopy versus laparotomy.* Journal of the American Association of Gynecologic Laparoscopists, 2001. **8**(1): p. 99-106.

270. Kitchener, H.C., et al., *Laparoscopic versus open colposuspension--results of a prospective randomised controlled trial.* BJOG: An International Journal of Obstetrics & Gynaecology, 2006. **113**(9): p. 1007-1013.

271. Su, T.H., et al., *Prospective comparison of laparoscopic and traditional colposuspensions in the treatment of genuine stress incontinence.* Acta Obstetricia et Gynecologica Scandinavica, 1997. **76**(6): p. 576-582.

272. Burton, G., *A five year prospective randomised urodynamic study comparing open and laparoscopic colposuspension.* Neurourology & Urodynamics, 1999. **18**(4): p. 295-296 (abstract).

273. Morris, A., et al., *5-7 year follow-up of a randomised trial comparing laparoscopic colposuspension (LC) and open colposuspension (OC) in the treatment of genuine stress incontinence.* International Urogynecology Journal & Pelvic Floor Dysfunction, 2001. **12**(suppl 3): p. s6 (abstract).

274. Summitt, R., et al., *Randomised comparison of laparoscopic and transabdominal Burch urethropexy for the treatment*

of genuine stress incontinence. Obstetrics & Gynecology, 2000. **94**(4, suppl 1): p. 2 (abstract).

275. Tan, E., et al., *Laparoscopic versus open colposuspension for urodynamic stress incontinence.* Neurourology & Urodynamics, 2007. **26**(2): p. 158-169.

276. Piccione, F., et al., *Different techniques of laparoscopic Burch colposuspension.* Italian Journal of Gynaecology & Obstetrics, 2001. **13**(1): p. 10-13.

277. Ustun, Y., et al., *Randomized comparison of Burch urethropexy procedures concomitant with gynecologic operations.* Gynecologic & Obstetric Investigation, 2005. **59**(1): p. 19-23.

278. Jelovsek, J.E., M.D. Walters, and M.D. Barber, *Psychosocial impact of chronic vulvovagina conditions.* J reprod med, 2008. **53**(2): p. 75-82.

279. Valpas, A., et al., *A cost-effectiveness analysis of tension-free vaginal tape versus laparoscopic mesh colposuspension for primary female stress incontinence.* Acta Obstetricia et Gynecologica Scandinavica, 2006. **85**(12): p. 1485-1490.

280. Maher, C., et al., *Laparoscopic colposuspension or tension-free vaginal tape for recurrent stress urinary incontinence and/or urethral sphincter deficiency - a randomised controlled trial.* Neurourology & Urodynamics, 2004. **23**: p. 433-434 (abstract).

281. Paraiso, M.F., et al., *Laparoscopic Burch colposuspension versus tension-free vaginal tape: a randomized trial.* Obstetrics & Gynecology, 2004. **104**(6): p. 1249-1258.

282. Persson, J., et al., *Cost-analyzes based on a prospective, randomized study comparing laparoscopic colposuspension with a tension-free vaginal tape procedure.* Acta Obstetricia et Gynecologica Scandinavica, 2002. **81**(11): p. 1066-73.

283. Valpas, A., et al., *Tension-free vaginal tape and laparoscopic mesh colposuspension for stress urinary incontinence.* Obstetrics & Gynecology, 2004. **104**(1): p. 42-49.

284. Mirosh, M. and A. Epp, *TVT vs laparoscopic Burch colposuspension for the treatment of stress urinary incontinence*, in *International Continence Society, 35th annual meeting*2005: Montreal, Canada. p. 640 (abstract).

285. Persson, J. and P. Wolner-Hanssen, *Laparoscopic Burch colposuspension for stress urinary incontinence: a randomized comparison of one or two sutures on each side of the urethra.* Obstetrics & Gynecology, 2000. **95**(1): p. 151-155.

286. Ross, J., *Two techniques of laparoscopic Burch repair for stress incontinence: a prospective, randomized study.* Journal of the American Association of Gynecologic Laparoscopists, 1996. **3**(3): p. 351-357.

287. Zullo, F., et al., *Laparoscopic Burch colposuspension: a randomized controlled trial comparing two transperitoneal surgical techniques.* Obstetrics & Gynecology, 2001. **98**(5, part 1): p. 783-788.

288. Wallwiener, D., et al., *Endoscopic retropubic colposuspension: "Retziusscopy" versus laparoscopy - a reasonable enlargement of the operative spectrum in the management of recurrent stress incontinence?* Endoscopic Surgery & Allied Technologies, 1995. **3**(2-3): p. 115-118.

289. Dumville, J.C., et al., *Cost-effectiveness analysis of open colposuspension versus laparoscopic colposuspension in the treatment of urodynamic stress incontinence.* BJOG: An International Journal of Obstetrics & Gynaecology, 2006. **113**(9): p. 1014-1022.

290. Manca, A., et al., *A cost-utility analysis of tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence.* BJOG: An International Journal of Obstetrics & Gynaecology, 2003. **110**(3): p. 255-62.

291. Carey, M., et al., *Laparoscopic versus open colposuspension: a prospective multi-centre randomised single-blinded comparison.* Neurology and Urodynamics, 2000. **19**(4): p. 389-91.

292. Cheon, W.C., J.H. Mak, and J.Y. Liu, *Prospective randomised controlled trial comparing laparoscopic and open colposuspension.* Hong Kong Med J, 2003. **9**(1): p. 10-4.

293. Fatthy, H., et al., *Modified Burch colposuspension: laparoscopy versus laparotomy.* J Am Assoc Gynecol Laparosc, 2001. **8**(1): p. 99-106.

294. Kitchener, H.C., et al., *Laparoscopic versus open colposuspension--results of a prospective randomised controlled trial.* BJOG, 2006. **113**(9): p. 1007-13.

295. Su, T.H., et al., *Prospective comparison of laparoscopic and traditional colposuspensions in the treatment of genuine stress incontinence.* Acta Obstet Gynecol Scand, 1997. **76**(6): p. 576-82.

296. Barr, S., et al., *The long-term outcome of laparoscopic colposuspension: a 10-year cohort study.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(4): p. 443-5.

297. Dean, N.M., et al., *Laparoscopic colposuspension and tension-free vaginal tape: a systematic review.* BJOG: An International Journal of Obstetrics & Gynaecology, 2006. **113**(12): p. 1345-1353.

298. National Collaborating Centre for Women's & Children's Health, *Urinary incontinence: the management of urinary incontinence in women*, in *Clinical Guideline*2006, RCOG Press: London. p. i-221.

299. National Institute for Health & Clinical Excellence, *Urinary incontinence: the management of urinary incontinence in women*, in *Clinical guideline CG40*2006, National Institute for Health and Clinical Excellence: London.

300. Zullo, F., et al., *Two techniques of laparoscopic retropubic urethropexy.* Journal of the American Association of Gynecologic Laparoscopists, 2002. **9**(2): p. 178-181.

301. Zullo, F., et al., *Laparoscopic colposuspension using sutures or prolene meshes: a 3-year follow-up.* European Journal of Obstetrics, Gynecology, & Reproductive Biology, 2004. **117**(2): p. 201-203.

302. Valpas, A., et al., *Tension-free vaginal tape and laparoscopic mesh colposuspension in the treatment of stress urinary incontinence: immediate outcome and complications--a randomized clinical trial.* Acta Obstetricia et Gynecologica Scandinavica, 2003. **82**(7): p. 665-71.

303. BergmanA, K., BallardCA., *Predicting post-operative urinary incontinence development in women undergoing operation for genitourinary prolapse. .* American Journal of Obstetrics & Gynecology., 19988. **158**: p. 1171-1175.

304. Chaikin, D.C., A. Groutz, and J.G. Blaivas, *Predicting the need for anti-incontinence surgery in continent women undergoing repair of severe urogenital prolapse.* J Urol, 2000. **163**(2): p. 531-4.

305. Richardson, D.A., A.E. Bent, and D.R. Ostergard, *The effect of uterovaginal prolapse on urethrovesical pressure dynamics.* Am J Obstet Gynecol, 1983. **146**(8): p. 901-5.

306. Reena, C., A.N. Kekre, and N. Kekre, *Occult stress incontinence in women with pelvic organ prolapse.* Int J Gynaecol Obstet, 2007. **97**(1): p. 31-4.

307. Richter, H.E., et al., *Lower urinary tract symptoms, quality of life and pelvic organ prolapse: irritative bladder and obstructive voiding symptoms in women planning to undergo abdominal sacrocolpopexy for advanced pelvic organ prolapse.* J Urol, 2007. **178**(3 Pt 1): p. 965-9; discussion 969.

308. Anger, J.T., et al., *The effect of concomitant prolapse repair on sling outcomes.* J Urol, 2008. **180**(3): p. 1003-6.

309. Milani, R., et al., *Marshall-Marchetti-Krantz procedure and Burch colposuspension in the surgical treatment of female urinary incontinence.* Br J Obstet Gynaecol, 1985. **92**(10): p. 1050-3.

310. Colombo, M., et al., *Randomised comparison of Burch colposuspension versus anterior colporrhaphy in women with stress urinary incontinence and anterior vaginal wall prolapse.* BJOG, 2000. **107**(4): p. 544-51.

311. Moon, Y.J., et al., *Comparison of Burch colposuspension and transobturator tape when combined with abdominal sacrocolpopexy.* Int J Gynaecol Obstet, 2011. **112**(2): p. 122-5.

312. Gordon, D., et al., *Combined genitourinary prolapse repair and prophylactic tension-free vaginal tape in women with severe prolapse and occult stress urinary incontinence: preliminary results.* Urology, 2001. **58**(4): p. 547-50.

313. Yip, S.K. and M.W. Pang, *Tension-free vaginal tape sling procedure for the treatment of stress urinary incontinence in Hong Kong women with and without pelvic organ prolapse: 1-year outcome study.* Hong Kong Med J, 2006. **12**(1): p. 15-20.

314. Huang, K.H., et al., *Concomitant surgery with tension-free vaginal tape.* Acta Obstet Gynecol Scand, 2003. **82**(10): p. 948-53.

315. Partoll, L.M., *Efficacy of tension-free vaginal tape with other pelvic reconstructive surgery.* Am J Obstet Gynecol, 2002. **186**(6): p. 1292-5; discussion 1295-8.

316. Zullo, M.A., et al., *Anterior colporrhaphy plus inside-out tension-free vaginal tape for associated stress urinary incontinence and cystocele.* J Minim Invasive Gynecol, 2008. **15**(4): p. 446-51.

317. Handa, V.L., et al., *Perioperative complications of surgery for genital prolapse: does concomitant anti-incontinence surgery increase complications?* Urology, 2005. **65**(3): p. 483-7.

318. Barnes, N.M., et al., *Pubovaginal sling and pelvic prolapse repair in women with occult stress urinary incontinence: effect on postoperative emptying and voiding symptoms.* Urology, 2002. **59**(6): p. 856-60.

319. Groutz, A., et al., *Tension-free vaginal tape (TVT) for the treatment of occult stress urinary incontinence in women undergoing prolapse repair: a prospective study of 100 consecutive cases.* Neurourol Urodyn, 2004. **23**(7): p. 632-5.

320. Meschia, M., et al., *A randomized comparison of tension-free vaginal tape and endopelvic fascia plication in women with genital prolapse and occult stress urinary incontinence.* Am J Obstet Gynecol, 2004. **190**(3): p. 609-13.

321. Karateke, A., et al., *Concomitant surgical correction of occult stress urinary incontinence by TOT in patients with pelvic organ prolapse.* Eur J Obstet Gynecol Reprod Biol, 2011. **154**(1): p. 105-7.

322. Groutz, A., et al., *"Inside-out" transobturator tension-free vaginal tape for management of occult stress urinary incontinence in women undergoing pelvic organ prolapse repair.* Urology, 2010. **76**(6): p. 1358-61.

323. Brubaker, L., et al., *Two-year outcomes after sacrocolpopexy with and without burch to prevent stress urinary incontinence.* Obstet Gynecol, 2008. **112**(1): p. 49-55.

324. Visco, A.G., et al., *The role of preoperative urodynamic testing in stress-continent women undergoing sacrocolpopexy: the Colpopexy and Urinary Reduction Efforts (CARE) randomized surgical trial.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(5): p. 607-14.

325. Aungst, M.J., et al., *Prophylactic Burch colposuspension at the time of abdominal sacrocolpopexy: a survey of current practice patterns.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(8): p. 897-904.

326. Costantini, E., et al., *Pelvic organ prolapse repair with and without prophylactic concomitant Burch colposuspension in continent women: a randomized, controlled trial with 8-year followup.* J Urol, 2011. **185**(6): p. 2236-40.

327. BallertKN, B., IsenalumhejrA, et al., *Managing the urethra at transvaginal pelvic organ prolapse repair: a urodynamic approach.* j Urol, 2009. **181**: p. 679-800.

328. Maher, C., et al., *Surgical management of pelvic organ prolapse in women.* Cochrane Database Syst Rev, 2010(4): p. CD004014.

329. VanDerSteenA, V., DijkgraafMG, et al., *Protocol for the CUPIDO trials: multicenter randomized controlled trials to assess the value of combining prolapse surgery and incontinence surgery in patients with genital prolapse and evident stress incontinence (CUPIDO I) and in patieints with genital prolapse and occult stress incontinence (CUPIDO II).* BMC Womens Health, 2010. **10**(16).

330. Wei, J., et al., *Outcomes following vaginal prolapse repair and mid urethral sling (OPUS) trial--design and methods.* Clin Trials, 2009. **6**(2): p. 162-71.

331. DeBoerTA, S., CardozoL, et al., *Pelvic organ prolapse and overactive bladder* Neurourology & Urodynamics, 2010. **29**: p. 30-39.

332. de Boer, T.A., et al., *The prevalence and risk factors of overactive bladder symptoms and its relation to pelvic organ prolapse symptoms in a general female population.* Int Urogynecol J, 2011. **22**(5): p. 569-75.

333. DigesuGA, S., ChalihaC, et al., *To overactive bladder symptoms improve after repair of anterior vaginal wall prolapse? .* In Urogynecology Journal, 2007. **18**: p. 1439-1443.

334. Foster, R.T., Sr., et al., *A prospective assessment of overactive bladder symptoms in a cohort of elderly women who underwent transvaginal surgery for advanced pelvic organ prolapse.* Am J Obstet Gynecol, 2007. **197**(1): p. 82 e1-4.

335. Nguyen, J.K. and N.N. Bhatia, *Resolution of motor urge incontinence after surgical repair of pelvic organ prolapse.* J Urol, 2001. **166**(6): p. 2263-6.

336. Herbison, G.P. and E.P. Arnold, *Sacral neuromodulation with implanted devices for urinary storage and voiding dysfunction in adults.* Cochrane Database Syst Rev, 2009(2): p. CD004202.

337. Groen, J., B.F. Blok, and J.L. Bosch, *Sacral neuromodulation as treatment for refractory idiopathic urge urinary incontinence: 5-year results of a longitudinal study in 60 women.* J Urol, 2011. **186**(3): p. 954-9.

338. Powell, C.R. and K.J. Kreder, *Long-term outcomes of urgency-frequency syndrome due to painful bladder syndrome treated with sacral neuromodulation and analysis of failures.* J Urol, 2010. **183**(1): p. 173-6.

339. Zabihi, N., et al., *Short-term results of bilateral S2-S4 sacral neuromodulation for the treatment of refractory interstitial cystitis, painful bladder syndrome, and chronic pelvic pain.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(4): p. 553-7.

340. Datta, S.N., et al., *Sacral neurostimulation for urinary retention: 10-year experience from one UK centre.* BJU Int, 2008. **101**(2): p. 192-6.

341. White, W.M., et al., *Sacral nerve stimulation for treatment of refractory urinary retention: long-term efficacy and durability.* Urology, 2008. **71**(1): p. 71-4.

342. Ingber, M.S., et al., *Neuromodulation and female sexual function: does treatment for refractory voiding symptoms have an added benefit?* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(9): p. 1055-9.

343. Cappellano, F., et al., *Quality of life assessment in patients who undergo sacral neuromodulation implantation for urge incontinence: an additional tool for evaluating outcome.* J Urol, 2001. **166**(6): p. 2277-80.

344. Foster, R.T., Sr., et al., *In patients undergoing neuromodulation for intractable urge incontinence a reduction in 24-hr pad weight after the initial test stimulation best predicts long-term patient satisfaction.* Neurourol Urodyn, 2007. **26**(2): p. 213-7.

345. Leong, R.K., et al., *Satisfaction and patient experience with sacral neuromodulation: results of a single center sample survey.* J Urol, 2011. **185**(2): p. 588-92.

346. Kessler, T.M., et al., *Sacral neuromodulation for neurogenic lower urinary tract dysfunction: systematic review and meta-analysis.* Eur Urol, 2010. **58**(6): p. 865-74.

347. Bannowsky, A., et al., *Urodynamic changes and response rates in patients treated with permanent electrodes compared to conventional wire electrodes in the peripheral nerve evaluation test.* World J Urol, 2008. **26**(6): p. 623-6.

348. Marcelissen, T., et al., *Is the screening method of sacral neuromodulation a prognostic factor for long-term success?* J Urol, 2011. **185**(2): p. 583-7.

349. Leong, R.K., et al., *PNE versus 1st stage tined lead procedure: a direct comparison to select the most sensitive test method to identify patients suitable for sacral neuromodulation therapy.* Neurourol Urodyn, 2011. **30**(7): p. 1249-52.

350. Pham, K., M.L. Guralnick, and R.C. O'Connor, *Unilateral versus bilateral stage I neuromodulator lead placement for the treatment of refractory voiding dysfunction.* Neurourol Urodyn, 2008. **27**(8): p. 779-81.

351. Groenendijk, P.M., et al., *Urodynamic evaluation of sacral*

neuromodulation for urge urinary incontinence. BJU Int, 2008. **101**(3): p. 325-9.

352. Siddiqui, N.Y., et al., *Cost-effectiveness of sacral neuromodulation versus intravesical botulinum A toxin for treatment of refractory urge incontinence.* J Urol, 2009. **182**(6): p. 2799-804.

353. Leong, R.K., et al., *Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder.* BJU Int, 2011. **108**(4): p. 558-64.

354. Peters, K.M., et al., *Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial.* J Urol, 2010. **183**(4): p. 1438-43.

355. Finazzi-Agro, E., et al., *Percutaneous tibial nerve stimulation effects on detrusor overactivity incontinence are not due to a placebo effect: a randomized, double-blind, placebo controlled trial.* J Urol, 2010. **184**(5): p. 2001-6.

356. Peters, K.M., et al., *Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy trial.* J Urol, 2009. **182**(3): p. 1055-61.

357. MacDiarmid, S.A., et al., *Long-term durability of percutaneous tibial nerve stimulation for the treatment of overactive bladder.* J Urol, 2010. **183**(1): p. 234-40.

358. Finazzi-Agro, E., et al., *Percutaneous tibial nerve stimulation produces effects on brain activity: study on the modifications of the long latency somatosensory evoked potentials.* Neurourol Urodyn, 2009. **28**(4): p. 320-4.

359. Gobbi, C., et al., *Percutaneous posterior tibial nerve stimulation as an effective treatment of refractory lower urinary tract symptoms in patients with multiple sclerosis: preliminary data from a multicentre, prospective, open label trial.* Mult Scler, 2011. **17**(12): p. 1514-9.

360. Kabay, S.C., M. Yucel, and S. Kabay, *Acute effect of posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with multiple sclerosis: urodynamic study.* Urology, 2008. **71**(4): p. 641-5.

361. Kabay, S.C., et al., *Acute urodynamic effects of percutaneous posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with Parkinson's disease.* Neurourol Urodyn, 2009. **28**(1): p. 62-7.

362. Goldwasser, B. and G.D. Webster, *Augmentation and substitution enterocystoplasty.* J Urol, 1986. **135**(2): p. 215-24.

363. Gough, D.C., *Enterocystoplasty.* BJU Int, 2001. **88**(7): p. 739-43.

364. Greenwell, T.J., S.N. Venn, and A.R. Mundy, *Augmentation cystoplasty.* BJU Int, 2001. **88**(6): p. 511-25.

365. Niknejad, K.G. and A. Atala, *Bladder augmentation techniques in women.* Int Urogynecol J Pelvic Floor Dysfunct, 2000. **11**(3): p. 156-69.

366. Duel, B.P., R. Gonzalez, and J.S. Barthold, *Alternative techniques for augmentation cystoplasty.* J Urol, 1998. **159**(3): p. 998-1005.

367. Stein, R., A. Schroder, and J.W. Thuroff, *Bladder augmentation and urinary diversion in patients with neurogenic bladder: non-surgical considerations.* J Pediatr Urol, 2012. **8**(2): p. 145-52.

368. Blackburn, S.C., et al., *Ileal bladder augmentation and vitamin B12: levels decrease with time after surgery.* J Pediatr Urol, 2012. **8**(1): p. 47-50.

369. Higuchi, T.T., et al., *Augmentation cystoplasty and risk of neoplasia: fact, fiction and controversy.* J Urol, 2010. **184**(6): p. 2492-6.

370. Reyblat, P. and D.A. Ginsberg, *Augmentation enterocystoplasty in overactive bladder: is there still a role?* Curr Urol Rep, 2010. **11**(6): p. 432-9.

371. Biers, S.M., S.N. Venn, and T.J. Greenwell, *The past, present and future of augmentation cystoplasty.* BJU Int, 2012. **109**(9): p. 1280-93.

372. Campbell, J.D., et al., *Treatment success for overactive bladder with urinary urge incontinence refractory to oral antimuscarinics: a review of published evidence.* BMC Urol, 2009. **9**: p. 18.

373. Hasan, S.T., et al., *Clinical outcome and quality of life following enterocystoplasty for idiopathic detrusor instability and neurogenic bladder dysfunction.* Br J Urol, 1995. **76**(5): p. 551-7.

374. Herschorn, S. and R.J. Hewitt, *Patient perspective of long-term outcome of augmentation cystoplasty for neurogenic bladder.* Urology, 1998. **52**(4): p. 672-8.

375. Gonzalez, R., B. Ludwikowski, and M. Horst, *Determinants of success and failure of seromuscular colocystoplasty lined with urothelium.* J Urol, 2009. **182**(4 Suppl): p. 1781-4.

376. Jung, H.J., et al., *Prerequisite for successful surgical outcome in urothelium lined seromuscular colocystoplasty.* J Urol, 2012. **187**(4): p. 1416-21.

377. Shakeri, S., A. Aminsharifi, and Z. Jahanabadi, *Application of appendicular-based cecal flap for less invasive augmentation cystoplasty: a novel technique.* Urol Int, 2009. **83**(3): p. 271-6.

378. Knupfer, S., et al., *[Therapy-refractory overactive bladder: alternative treatment approaches].* Urologe A, 2011. **50**(7): p. 806-9.

379. Cartwright, P.C. and B.W. Snow, *Bladder autoaugmentation: partial detrusor excision to augment the bladder without use of bowel.* J Urol, 1989. **142**(4): p. 1050-3.

380. Cartwright, P.C. and B.W. Snow, *Bladder autoaugmentation: early clinical experience.* J Urol, 1989. **142**(2 Pt 2): p. 505-8; discussion 520-1.

381. Appell, R.A., *Surgery for the treatment of overactive bladder.* Urology, 1998. **51**(2A Suppl): p. 27-9.

382. Dewan, P.A., *Autoaugmentation demucosalized enterocystoplasty.* World J Urol, 1998. **16**(4): p. 255-61.

383. ter Meulen, P.H., J.P. Heesakkers, and R.A. Janknegt, *A study on the feasibility of vesicomyotomy in patients with motor urge incontinence.* Eur Urol, 1997. **32**(2): p. 166-9.

384. Leng, W.W., et al., *Enterocystoplasty or detrusor myectomy? Comparison of indications and outcomes for bladder augmentation.* J Urol, 1999. **161**(3): p. 758-63.

385. MacNeily, A.E., et al., *Autoaugmentation by detrusor myotomy: its lack of effectiveness in the management of congenital neuropathic bladder.* J Urol, 2003. **170**(4 Pt 2): p. 1643-6; discussion 1646.

386. Marte, A., et al., *A long-term follow-up of autoaugmentation in myelodysplastic children.* BJU Int, 2002. **89**(9): p. 928-31.

387. Chrzan, R., et al., *Detrusorectomy reduces the need for augmentation and use of antimuscarinics in children with neuropathic bladders.* J Pediatr Urol, 2012.

388. Close, C.E., *Autoaugmentation gastrocystoplasty.* BJU Int, 2001. **88**(7): p. 757-61.

389. Dewan, P.A. and W. Stefanek, *Autoaugmentation gastrocystoplasty: early clinical results.* Br J Urol, 1994. **74**(4): p. 460-4.

390. Oge, O., et al., *Urothelium-preserving augmentation cystoplasty covered with a peritoneal flap.* BJU Int, 2000. **85**(7): p. 802-5.

391. Perovic, S.V., et al., *Bladder autoaugmentation with rectus muscle backing.* J Urol, 2002. **168**(4 Pt 2): p. 1877-80.

392. Shekarriz, B., et al., *Surgical complications of bladder augmentation: comparison between various enterocystoplasties in 133 patients.* Urology, 2000. **55**(1): p. 123-8.

393. Rocha, F.T., et al., *Use of an inflatable silicone balloon improves the success rate of bladder autoaugmentation at long-term followup.* J Urol, 2011. **185**(6 Suppl): p. 2576-81.

394. Bramble, F.J., *The treatment of adult enuresis and urge incontinence by enterocystoplasty.* Br J Urol, 1982. **54**(6): p. 693-6.

395. Mundy, A.R. and T.P. Stephenson, *"Clam" ileocystoplasty for the treatment of refractory urge incontinence.* Br J Urol, 1985. **57**(6): p. 641-6.

396. Kockelbergh, R.C., et al., *Clam enterocystoplasty in general urological practice.* Br J Urol, 1991. **68**(1): p. 38-41.

397. George, V.K., et al., *Clam ileocystoplasty.* Br J Urol, 1991. **68**(5): p. 487-9.

398. Kennelly, M.J., E.A. Gormley, and E.J. McGuire, *Early clinical experience with adult bladder auto-augmentation.* J Urol, 1994. **152**(2 Pt 1): p. 303-6.

399. Kelly, J.D., R.M. Kernohan, and P.F. Keane, *Symptomatic outcome following clam ileocystoplasty.* Eur Urol, 1997. **32**(1): p. 30-3.

400. Awad, S.A., et al., *Long-term results and complications of augmentation ileocystoplasty for idiopathic urge incontinence in women.* Br J Urol, 1998. **81**(4): p. 569-73.

401. Venn, S.N. and A.R. Mundy, *Long-term results of augmentation cystoplasty.* Eur Urol, 1998. **34 Suppl 1**: p. 40-2.

402. Swami, K.S., et al., *Detrusor myectomy for detrusor overactivity: a minimum 1-year follow-up.* Br J Urol, 1998. **81**(1): p. 68-72.

403. Edlund, C., R. Peeker, and M. Fall, *Clam ileocystoplasty: successful treatment of severe bladder overactivity.* Scand J Urol Nephrol, 2001. **35**(3): p. 190-5.

404. Ivil, K.D. and G. Suresh, *Review of augmentation 'clam' cystoplasy in a district general hospital setting.* Int Urol Nephrol, 2002. **34**(1): p. 129-32.

405. Kumar, S.P. and P.H. Abrams, *Detrusor myectomy: long-term results with a minimum follow-up of 2 years.* BJU Int, 2005. **96**(3): p. 341-4.

406. Blaivas, J.G., et al., *Long-term followup of augmentation enterocystoplasty and continent diversion in patients with benign disease.* J Urol, 2005. **173**(5): p. 1631-4.

407. Barrington, J.W., R. Dyer, and F. Bano, *Bladder augmentation using Pelvicol implant for intractable overactive bladder syndrome.* Int Urogynecol J Pelvic Floor Dysfunct, 2006. **17**(1): p. 50-3.

408. Dwarkasing, R.S., et al., *MRI evaluation of urethral diverticula and differential diagnosis in symptomatic women.* AJR Am J Roentgenol, 2011. **197**(3): p. 676-82.

409. Chung, D.E., et al., *Urethral diverticula in women: discrepancies between magnetic resonance imaging and surgical findings.* J Urol, 2010. **183**(6): p. 2265-9.

410. Porten, S. and S. Kielb, *Diagnosis of female diverticula using magnetic resonance imaging.* Adv Urol, 2008: p. 213516.

411. Han, D.H., et al., *Outcomes of surgery of female urethral diverticula classified using magnetic resonance imaging.* Eur Urol, 2007. **51**(6): p. 1664-70.

412. Foster, R.T., C.L. Amundsen, and G.D. Webster, *The utility of magnetic resonance imaging for diagnosis and surgical planning before transvaginal periurethral diverticulectomy in women.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(3): p. 315-9.

413. Wu, Y.Y., et al., *Transvaginal sonographic diagnosis of female urethral diverticula.* J Clin Ultrasound, 2009. **37**(1): p. 40-2.

414. Ljungqvist, L., R. Peeker, and M. Fall, *Female urethral diverticulum: 26-year followup of a large series.* J Urol, 2007. **177**(1): p. 219-24; discussion 224

415. Burrows, L.J., et al., *Surgical procedures for urethral diverticula in women in the United States, 1979-1997.* Int Urogynecol J Pelvic Floor Dysfunct, 2005. **16**(2): p. 158-61.

416. Rovner, E.S., *Urethral diverticula: a review and an update.* Neurourol Urodyn, 2007. **26**(7): p. 972-7.

417. Lee, J.W., S.K. Doumouchtsis, and M.M. Fynes, *A modified technique for the surgical correction of urethral diverticula using a porcine xenograft.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(1): p. 117-20.

418. Tolosa Eizaguirre, E., et al., *Xenograft iterposition in female urethral diverticulum surgery.* Arch Esp Urol, 2012. **65**(2): p. 255-8.

419. Gunasekaran, K., G.W. Davila, and G.M. Ghoniem, *Giant urethral diverticulum -- repair augmented with bovine pericardium collagen matrix graft and tension-free vaginal tape.* J Indian Med Assoc, 2011. **109**(7): p. 513, 515.

420. Dmochowski, R.R., et al., *Update of AUA guideline on the surgical management of female stress urinary incontinence.* J Urol, 2010. **183**(5): p. 1906-14.

421. Hammad, F.T., *TVT can also cause urethral diverticulum.* Int Urogynecol J Pelvic Floor Dysfunct, 2007. **18**(4): p. 467-9.

422. Mahdy, A., M. Elmissiry, and G.M. Ghoniem, *Urethral diverticulum after tension-free vaginal tape procedure: case report.* Urology, 2008. **72**(2): p. 461 e5-6.

423. Athanasopoulos, A. and E.J. McGuire, *Urethral diverticulum: a new complication associated with tension-free vaginal tape.* Urol Int, 2008. **81**(4): p. 480-2.

424. Fletcher, S.G. and P.E. Zimmern, *Differential diagnosis of chronic pelvic pain in women: the urologist's approach.* Nat Rev Urol, 2009. **6**(10): p. 557-62.

425. Foley, C.L., T.J. Greenwell, and R.A. Gardiner, *Urethral diverticula in females.* BJU Int, 2011. **108 Suppl 2**: p. 20-3.

426. Thomas, A.A., et al., *Urethral diverticula in 90 female patients: a study with emphasis on neoplastic alterations.* J Urol, 2008. **180**(6): p. 2463-7.

427. Ockrim, J.L., et al., *A tertiary experience of urethral diverticulectomy: diagnosis, imaging and surgical outcomes.* BJU Int, 2009. **103**(11): p. 1550-4.

428. Hoda, M.R., et al., *[Management of female stress urinary incontinence. Endoscopic extraperitoneal artificial urinary sphincter--early experience].* Urologe A, 2008. **47**(8): p. 1004-8.

429. Roupret, M., et al., *Laparoscopic approach for artificial urinary sphincter implantation in women with intrinsic sphincter deficiency incontinence: a single-centre preliminary experience.* Eur Urol, 2010. **57**(3): p. 499-504.

430. Mandron, E., P.E. Bryckaert, and A.G. Papatsoris, *Laparoscopic artificial urinary sphincter implantation for female genuine stress urinary incontinence: technique and 4-year experience in 25 patients.* BJU Int, 2010. **106**(8): p. 1194-8; discussion 1198.

431. Chung, E. and R.A. Cartmill, *25-year experience in the outcome of artificial urinary sphincter in the treatment of female urinary incontinence.* BJU Int, 2010. **106**(11): p. 1664-7.

432. Vayleux, B., et al., *Female urinary incontinence and artificial urinary sphincter: study of efficacy and risk factors for failure and complications.* Eur Urol, 2011. **59**(6): p. 1048-53.

433. Costa, P., et al., *Long-Term Results of Artificial Urinary Sphincter for Women with Type III Stress Urinary Incontinence.* Eur Urol, 2012.

434. Lipp, A., C. Shaw, and K. Glavind, *Mechanical devices for urinary incontinence in women.* Cochrane Database Syst Rev, 2011(7): p. CD001756.

435. Chung, E., A. Navaratnam, and R.A. Cartmill, *Can artificial urinary sphincter be an effective salvage option in women following failed anti-incontinence surgery?* Int Urogynecol J, 2011. **22**(3): p. 363-6.

436. Revaux, A., et al., *Is the implantation of an artificial urinary sphincter with a large cuff in women with severe urinary incontinence associated with worse perioperative complications and functional outcomes than usual?* Int Urogynecol J, 2011. **22**(10): p. 1319-24.

437. Chartier-Kastler, E., et al., *Artificial urinary sphincter (AMS 800) implantation for women with intrinsic sphincter deficiency: a technique for insiders?* BJU Int, 2011. **107**(10): p. 1618-26.

438. Richard, F., U. Committee on Women's, and F.A.o.U. peliperineology, *[Guidelines for the treatment of non-neurological urinary incontinence in women using the artificial urinary sphincter].* Prog Urol, 2010. **20 Suppl 2**: p. S155-60.

439. Lovatsis, D., et al., *Guidelines for the evaluation and treatment of recurrent urinary incontinence following pelvic floor surgery.* J Obstet Gynaecol Can, 2010. **32**(9): p. 893-904.

440. Garcia-Montes, F., et al., *Surgical implantation of the new FlowSecure artificial urinary sphincter in the female bladder neck.* Urol Int, 2007. **79**(2): p. 105-10.

441. Lee, J. and P.L. Dwyer, *Age-related trends in female stress urinary incontinence surgery in Australia - Medicare data for 1994-2009.* Aust N Z J Obstet Gynaecol, 2010. **50**(6): p. 543-9.

442. Richter, H.E., et al., *Two-year outcomes after surgery for stress urinary incontinence in older compared with younger women.* Obstet Gynecol, 2008. **112**(3): p. 621-9.

443. Stav, K., et al., *Midurethral sling procedures for stress urinary incontinence in women over 80 years.* Neurourol Urodyn, 2010. **29**(7): p. 1262-6.

444. Jha, S., et al., *Factors influencing outcome following the tension-free vaginal tape (TVT).* Eur J Obstet Gynecol Reprod Biol, 2009. **144**(1): p. 85-7.

445. Rechberger, T., et al., *Body mass index does not influence the outcome of anti-incontinence surgery among women whereas menopausal status and ageing do: a randomised trial.* Int Urogynecol J, 2010. **21**(7): p. 801-6.

446. Sung, V.W., et al., *Patient-reported outcomes after combined surgery for pelvic floor disorders in older compared to younger women.* Am J Obstet Gynecol, 2009. **201**(5): p. 534 e1-5.

447. TrabucoEC, K., WeaverAL, et al., *Preoperative and post operative predictors of satisfaction after surgical treatment of stress urinary incontinence.* Am J Obstet Gynecol, 2011. **204(5)**(444): p. 1-6.

448. Shah, A.D., et al., *Surgery for stress urinary incontinence in the United States: does race play a role?* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(8): p. 1085-92.

449. Anger, J.T., et al., *Racial disparities in the surgical management of stress incontinence among female Medicare beneficiaries.* J Urol, 2007. **177**(5): p. 1846-50.

450. KrausSR, M., ChaiTC, et al., *Urinary Incontinence Treatment network.* Am J Obstet Gynecol, 2007. **197(1)**(92): p. e1-6.

451. DeLanceyJO, F., GuireK, et al., *Differences in continence system between community dwelling black and white women witih and without urinary incontinence.* Am J Obstet Gynecol, 2010. **202(6)**(584): p. e 1-584. e 12.

452. Killingsworth, L.B., et al., *One-year outcomes of tension-free vaginal tape (TVT) mid-urethral slings in overweight and obese women.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(9): p. 1103-8.

453. Cadish, L.A., et al., *Association of body mass index with hip and thigh pain following transobturator midurethral sling placement.* Am J Obstet Gynecol, 2010. **203**(5): p. 508 e1-5.

454. Dunivan, G.C., et al., *Body mass index as a risk factor for cystotomy during suprapubic placement of mid-urethral slings.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(9): p. 1127-31.

455. Cardozo, L., et al., *Colposuspension after previous failed incontinence surgery: a prospective observational study.* Br J Obstet Gynaecol, 1999. **106**(4): p. 340-4.

456. DeCuyperEM, I., MaherCF., *Laparoscopic Burch colposuspension after failed suburethral tape procedures: a retrospective audit.* In Urogynecology Journal, 2008. **19(5)**: p. 681-685.

457. Ala-Nissila, S., M. Haarala, and J. Makinen, *Tension-free vaginal tape - a suitable procedure for patients with recurrent stress urinary incontinence.* Acta Obstet Gynecol Scand, 2010. **89**(2): p. 210-6.

458. Shao, Y., et al., *Tension-free vaginal tape retropubic sling for recurrent stress urinary incontinence after Burch colposuspension failure.* Int J Urol, 2011. **18**(6): p. 452-7.

459. Sivaslioglu, A.A., et al., *The management of recurrent cases after the Burch colposuspension: 7 years experience.* Arch Gynecol Obstet, 2011. **283**(4): p. 787-90.

460. Stav, K., et al., *Repeat synthetic mid urethral sling procedure for women with recurrent stress urinary incontinence.* J Urol, 2010. **183**(1): p. 241-6.

461. Roderick, T., et al., *Urethral retro-resistance pressure: association with established measures of incontinence severity and change after midurethral tape insertion.* Neurourol Urodyn, 2009. **28**(1): p. 86-9.

462. Culligan, P.J., et al., *Can urethral retroresistance pressures predict midurethral sling outcomes?* J reprod med, 2010. **55**(3-4): p. 103-7.

463. Ito, H., et al., *Efficacy of tension-free vaginal tape compared with transobturator tape in the treatment of stress urinary incontinence in women: analysis of learning curve, perioperative changes of voiding function.* BMC Urol, 2011. **11**: p. 13.

464. VervestH, v., LammerinkE, et al., *TVT Secur: The Learning Curve.* Int Urogynecol J, 2008. **19**: p. S3-4.

465. Zullo, M.A., et al., *Vaginal estrogen therapy and overactive bladder symptoms in postmenopausal patients after a tension-free vaginal tape procedure: a randomized clinical trial.* Menopause, 2005. **12**(4): p. 421-7.

466. Liapis, A., et al., *The use of oestradiol therapy in postmenopausal women after TVT-O anti-incontinence surgery.* Maturitas, 2010. **66**(1): p. 101-6.

467. Strohbehn, K., *Shades of dry--curing urinary stress incontinence.* N Engl J Med, 2007. **356**(21): p. 2198-200.

468. Brubaker, L., et al., *Mixed incontinence: comparing definitions in women having stress incontinence surgery.* Neurourol Urodyn, 2009. **28**(4): p. 268-73.

469. Rapp, D.E. and K.C. Kobashi, *Outcomes following sling surgery: importance of definition of success.* J Urol, 2008. **180**(3): p. 998-1002.

470. Kaufman Mr, S.H., Dmochowski RR, *Assessing Outcomes of Stress Urinary Incontinence Surgery in Women.* AUA Update Series, 2009. **28**(7): p. 57-64.

471. Sung, V.W., et al., *Content validation of the patient-reported outcomes measurement information system (PROMIS) framework in women with urinary incontinence.* Neurourol Urodyn, 2011. **30**(4): p. 503-9.

472. Freeman, R., et al., *What patients think: patient-reported outcomes of retropubic versus trans-obturator mid-urethral slings for urodynamic stress incontinence--a multi-centre randomised controlled trial.* Int Urogynecol J, 2011. **22**(3): p. 279-86.

473. Brubaker, L., et al., *The impact of stress incontinence surgery on female sexual function.* Am J Obstet Gynecol, 2009. **200**(5): p. 562 e1-7.

474. Filocamo, M.T., et al., *The impact of mid-urethral slings for the treatment of urodynamic stress incontinence on female sexual function: a multicenter prospective study.* J Sex Med, 2011. **8**(7): p. 2002-8.

475. Tennstedt, S.L., et al., *Quality of life after surgery for stress incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(12): p. 1631-8.

476. Lier, D., et al., *Trans-obturator tape compared with tension-free vaginal tape in the surgical treatment of stress urinary incontinence: a cost utility analysis.* BJOG, 2011. **118**(5): p. 550-6.

477. Coyne, K. and C. Kelleher, *Patient reported outcomes: the ICIQ and the state of the art.* Neurourol Urodyn, 2010. **29**(4): p. 645-51.

478. Yalcin, I. and R.C. Bump, *Validation of two global impression questionnaires for incontinence.* Am J Obstet Gynecol, 2003. **189**(1): p. 98-101.

479. Nager, C.W., et al., *Design of the Value of Urodynamic Evaluation (ValUE) trial: A non-inferiority randomized trial of preoperative urodynamic investigations.* Contemp Clin Trials, 2009. **30**(6): p. 531-9.

Committee 15

Pelvic Organ Prolapse Surgery

Chair

Christopher Maher

Members

Kaven Baessler (Germany),

Matthew Barber (USA),

Cecilia Cheon (Hong Kong),

Vivianne Deitz (Netherlands),

Renaud DeTayrac (France)

Robert Gutman (USA),

Loic Sentilhes (France)

Mickey Karram (USA)

Acknowledgements: We would like to acknowledge the efforts of the prior ICI consultations led by Linda Brubaker(Brubaker 2009) and the work on mesh complication co-authored by Loic Sentilhes ((Deffieux 2011)

CONTENTS

I. INTRODUCTION

II. PREVALENCE AND INCIDENCE OF POP

III. OUTCOME ASSESSMENT

1. OUTCOME ASSESSMENT: ANATOMY
2. OUTCOME ASSESSMENT: SYMPTOMS
3. OUTCOME EVALUATION: QUALITY OF LIFE
4. OUTCOME ASSESSMENT: REOPERATION

IV. ANTERIOR COMPARTMENT SURGERY

1. NATIVE TISSUE REPAIRS
2. SYNTHETIC GRAFTS IN ANTERIOR COMPARTMENT SURGERY
3. BIOLOGIC GRAFTS ANTERIOR COMPARTMENT SURGERY

V. UTERINE PRESERVATION DURING POP SURGERY

1. PATIENT SELECTION
2. VAGINAL HYSTEROPEXY
3. ABDOMINAL HYSTEROPEXY
4. PREGNANCY AND HYSTEROPEXY

VI. APICAL SUPPORT PROCEDURES

1. SACROSPINOUS LIGAMENT SUSPENSION (SSLS)
2. UTEROSACRAL LIGAMENT SUSPENSION (USLS)
3. MAYO/MCCALL'S CULDOPLASTY
4. LEVATOR MYORRHAPHY
5. ILIOCOCCYGEUS FASCIA FIXATION
6. TRANSVAGINAL MESH APICAL PROLAPSE
7. SACRAL COLPOPEXY
8. OBLITERATIVE PROCEDURES: LEFORT COLPOCLEISIS, TOTAL COLPOCLEISIS

VII. SURGERY FOR POSTERIOR VAGINAL WALL PROLAPSE

1. ANATOMY OF THE POSTERIOR VAGINAL WALL
2. ANATOMIC DEFECTS THAT MAY CONTRIBUTE TO PROLAPSE OF THE POSTERIOR VAGINAL WALL
3. MIDLINE PLICATION OR TRADITIONAL POSTERIOR COLPORRAPHY
4. SITE SPECIFIC DEFECT REPAIR
5. TRANSANAL REPAIR OF RECTOCELE
6. GRAFT AUGMENTED RECTOCELE
7. MODIFIED SACROCOLPOPEXY

VIII. PELVIC ORGAN PROLAPSE SURGERY AND BLADDER FUNCTION

1. CONTINENT WOMEN UNDERGOING POP SURGERY. WHAT IS THE RISK OF DE NOVO SUI AND IS CONTINENCE SURGERY REQUIRED?
2. POP SURGERY AND STRESS URINARY INCONTINENT WOMEN
3. SHOULD WOMEN UNDERGOING POP SURGERY WITH OCCULT SUI IDENTIFIED PRE-OPERATIVELY UNDERGO CONTINENCE SURGERY AT TIME OF POP SURGERY?
4. OVERACTIVE BLADDER (OAB) SYMPTOMS
5. VOIDING PROBLEMS

IX. COMPLICATIONS AND METHODS OF PREVENTION

1. CLASSIFICATION OF COMPLICATIONS
2. REOPERATION AFTER VAGINAL MESH SURGERY
3. REOPERATION AFTER ABDOMINAL SURGERY
4. VAGINAL MESH EXPOSURE
5. VISCERAL (BLADDER, RECTUM) MESH EXPOSURE
6. INFECTION, ABSCESS, CELLULITIS, SPONDYLODISCITIS
7. PAINFUL MESH CONTRACTION
8. OTHER COMPLICATIONS
9. METHODS OF PREVENTION
10. VAGINAL MESH SURGERY
11. ABDOMINAL SACROCOLPOPEXY
12. PERITONEAL CLOSURE
13. TREATMENT OF VAGINAL MESH EXPOSURE

X. PELVIC ORGAN PROLAPSE AND SEXUAL FUNCTION

1. SEXUAL FUNCTION AFTER PROLAPSE SURGERY WITHOUT MESH
2. SEXUAL FUNCTION AFTER PROLAPSE SURGERY WITH MESH

XI. ECONOMIC EVALUATION

REFERENCES

LIST OF ABBREVIATIONS

Pelvic Organ Prolapse	POP	Deep Venous Thrombosis	DVT
Pelvic Organ Prolapse Qunatification	POPQ	Tissue Fixation System	TFS
Health-related quality of life	HRQOL	Intravaginal Slingplasty	IVS
Pelvic Organ Prolapse/Incontinence Sexual Questionnaire	PISQ	Abdominal Sacral Colpopexy	ASC
Female Sexual Function Index	FSFI	Laparoscopic Sacral Colpopexy	LSC
Urinary Distress Inventory	UDI	Uterosacral ligament suspension	USLS
Anterior Colporrhaphy	AC	Sacrospinous ligament suspension	SSLS
Incontinence Impact Questionnaire	IIQ	Total Vaginal mesh	TVM
Small Intestine Submucosa	SIS	Stress Urinary Incontinence	SUI
Patients global Impression of Improvement	PGII	Overactive Bladder	OAB
Sacrospinous Hysteropexy	SSPH	Food and Drug Administration	FDA
Total Vaginal Hysterectomy	TVH	Vaginal Reconstructive Surgery	VRS

Pelvic Organ Prolapse Surgery

Christopher Maher,

Kaven Baessler, Matthew Barber, Cecilia Cheon, Vivianne Deitz, Renaud DeTayrac, Robert Gutman, Loic Sentilhes, Mickey Karram

I. INTRODUCTION

Pelvic organ prolapse (POP) is a common problem affecting up to 50% of parous women and 6.3% of women will have undergone a surgical correction for pelvic organ prolapse by the age of 80. Prolapse surgery is an increasingly important aspect of gynaecological practice due to our ageing population, the decreasing rate of hysterectomy due to alternative treatments of menorrhagia and finally decreasing rates of cervical interventions for cervical dysplasia following introduction of vaccinations for Human Papilloma Virus. Already prolapse surgery is performed at least as frequently as continence surgery and, the operating and admission times are at least three times greater than for continence surgery. Given the increasing time and resources that will be required for POP surgery in the future it is paramount that we perform effective, durable, cost effective interventions with minimal morbidity. This chapter serves to outline and summarise the information relating to POP surgery reported in the English-language scientific literature after searching PubMed, Medline, Cochrane library and Cochrane database of systematic reviews, published up to January 2012, with Level 1 evidence. Level 2 or 3 evidence have been included if Level 1 data were lacking.

II. PREVALENCE AND INCIDENCE OF POP

There is a lack of epidemiological studies of the natural history, incidence and prevalence of POP.

It is widely accepted that 50 percent of women will develop prolapse but only 10 to 20 percent of those seek evaluation for their condition [Phillips 2006]. In the current literature, the overall prevalence of POP varies significantly depending upon the definition utilised, ranging from 3-50 percent (**Table 1**). Where POP is defined and graded on symptoms the prevalence is 3-6 percent as compared to 41-50 percent when based on examination, because mild prolapse on examination is common and frequently asymptomatic (Phillips 2006, Samuellson 1999, Nygaard 2004, Swift 2003). On examination anterior compartment prolapse is the most frequently reported site of prolapse and is detected twice as often as posterior compartment defects and three times more commonly than apical prolapse [Hendrix 2002, Handa 2004]. Following hysterectomy 6 to 12 percent of women will develop vaginal vault prolapse [Marchionni 1999, Aigmueller 2009] and in two-thirds of these cases multi-compartment prolapse is present [Morley 1988].

There is little knowledge about the natural history of POP. The reported incidence for cystocele is around 9 per 100 women-years, 6 per 100 women-years for rectocele and 1.5 per 100 women-years for uterine prolapse [Handa 2004]. Some data show that there is a 1-year incidence of POP of 26 percent and a 3-years incidence of 40 percent with regression rates of 21 percent and 19 percent, respectively. In general, older parous women are more likely to develop new or progressive POP than to show regression. Over a three year period 11 per cent of the women aged over 65 had prolapse progression of more than 2 cm whilst only 2.7 percent had a regression by the same amount [Bradley 2007].

Luber has shown in a large demographic study that the peak incidence of symptoms attributed to prolapse is between ages of 70 to79 whilst POP symptoms are still relatively common in women of younger age (**Figure 1**) [Luber 2001].

Demographic changes including an ageing population have significant implications for the future planning of women's health services. Wu et al [Wu 2009] have predicted that by 2050 the number of women suffering from symptomatic POP in the United States will increase at minimum by 46 percent (from 3.3 up to 4.9 million women and in a "worst-case scenario" up to 200 percent or 9.2 million women with POP. These figures were based upon population growth statistics in the United States however models that evaluate the impact of decreasing parity and increasing elective caesarean section rates are required to more accurately predict future rates of POP.

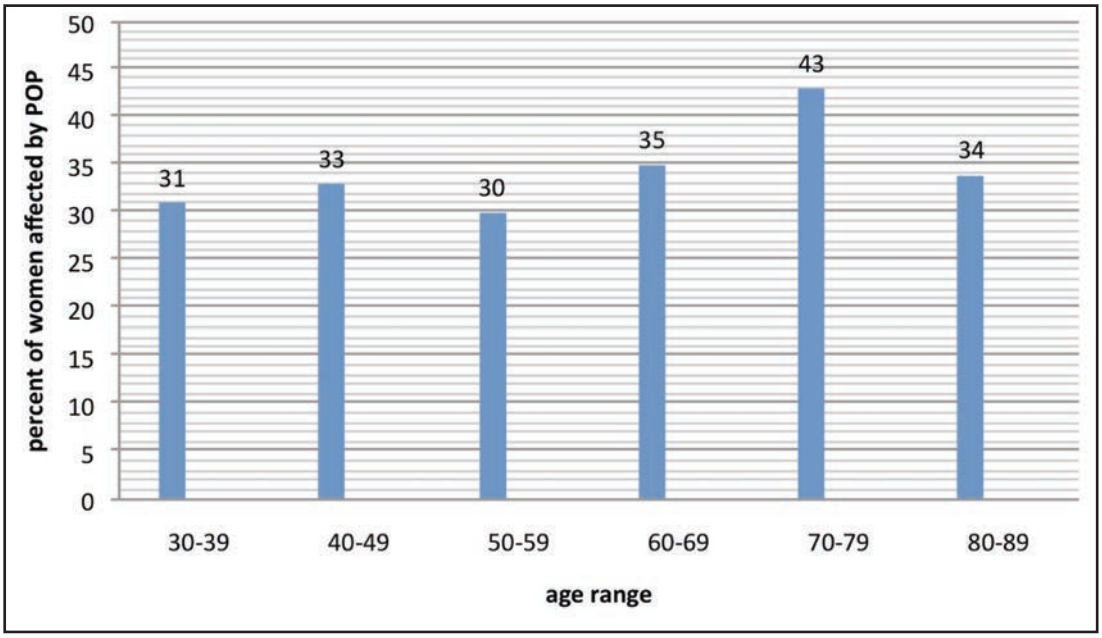


Figure 1. Shows the distribution of POP among women seeking care, US 2000 (Modified Luber 2001)

Table 1. Prevalence and Incidence POP

Study	Definition	Prevalence	Incidence	Country
Rorveit 2007	Symptom-based	5.7%		US
Nygaard 2008	Symptom-based	2.9%		US
Hendrix 2002	WHI-Study, Examination	Any prolapse: 41.1% Cystocele: 34.3% Rectocele: 18.6% Uterine: 14.2%		US
Swift 2003	Examination	6.4% stage 0 43.3% stage 1 47.7% stage 2 2.6% stage 3		US
Handa 2004	WHI-Study, Examination	Cystocele: 24.6% Rectocele: 12.9% Uterine: 3.8%	Cystocele: 9.3/100 Rectocele: 5.7/100 Uterine: 1.5/100	US
Nygaard 2004	Examination	2.3% stage 0 33% stage 1 63% stage 2 1.9% stage 3		US
Bradley 2007	Examination	23.5 - 49.9%	26%/1 year 40%/3 year	US
Maccharoni 1999	Examination	Vault-prolapse: 12%		Italy
Aigmueller 2009	Examination	Vault-prolapse: 6-8%		Austria

Incidence and Prevalence of Prolapse Surgery

Both incidence and prevalence for prolapse surgery increase with age. Women older than 80 years are currently the fastest growing segment of the population. The estimated lifetime risk of an American woman undergoing at least one surgical intervention by the age of 80 is 6.3 percent with 30% requiring subsequent surgery [Olsen 1997]. However, a more recent, prospective study showed a significantly lower reoperation rate of only 13 percent which may be explained by improved surgical procedures [Clark 2003]. The longevity and durability of POP surgery are important variables for planning and require ongoing evaluation .

The annual incidence for POP surgery is stated to be between 1.5 [Boyles 2003]and 1.8 [Shah 2007]cases per 1000 women-years with the incidence peaking in women between 60-69 years. Shah et al also demonstrated a peak incidence in 70 year old women however surprisingly high numbers of younger women were also undergoing surgical treatments reflecting a similarity in the prolapse symptoms reported in younger women by Luber 2001 (**Figure 2**) [Shah 2007]. In a more recent study Smith et al [Smith et al 2010] reported a lifetime risk of undergoing prolapse surgery as high as 19% in Western Australia. This figure is three times higher than the 6.3% lifetime risk for POP surgery reported by Olsen and requires further evaluation of local factors and definitions that may have contributed.

In the US, POP is thought to be the leading cause for more than 300.000 surgical procedures per year [22.7 per 10.000 women] with 25% undergoing reoperations at a total annual cost of more than 1 billion dollars [Brown 2002, Boyles 2003,Silva 2006, Shah 2007]. Also of note during a nine year period [1996 – 2005] the ambulatory costs related to pelvic floor disorder increased by 40% and if these figures are extrapolated to POP surgery the total annual cost would be over 1.4 billion dollars.

The incidence of prolapse which required surgical correction following a hysterectomy is 3.6 per 1000 women-years according to Mant et al from his large cohort study in the UK. The cumulative risk rises to 5 percent 15 years after hysterectomy [Mant 1997].

Further more detailed modelling of factors that will impact on future rates of POP in the community are required so that services can be provided to match the future demands of POP surgical interventions.

III. OUTCOME ASSESSMENT

Pelvic organ prolapse, like all pelvic floor disorders, is a multidimensional phenomenon and “success” of treatment is often difficult to define. Historically, most studies evaluating the treatment of pelvic organ prolapse have focused exclusively on anatomic success without considering other important areas such as symptoms, vaginal compliance, quality of life, or socioeconomic outcomes. For an individual patient, the most important outcome of a surgical procedure is the relief of her symptoms and improvement in her quality of life [Barber 2009], yet until recently these areas have largely been ignored. Fortunately, over the last 15 years, measures to evaluate POP have

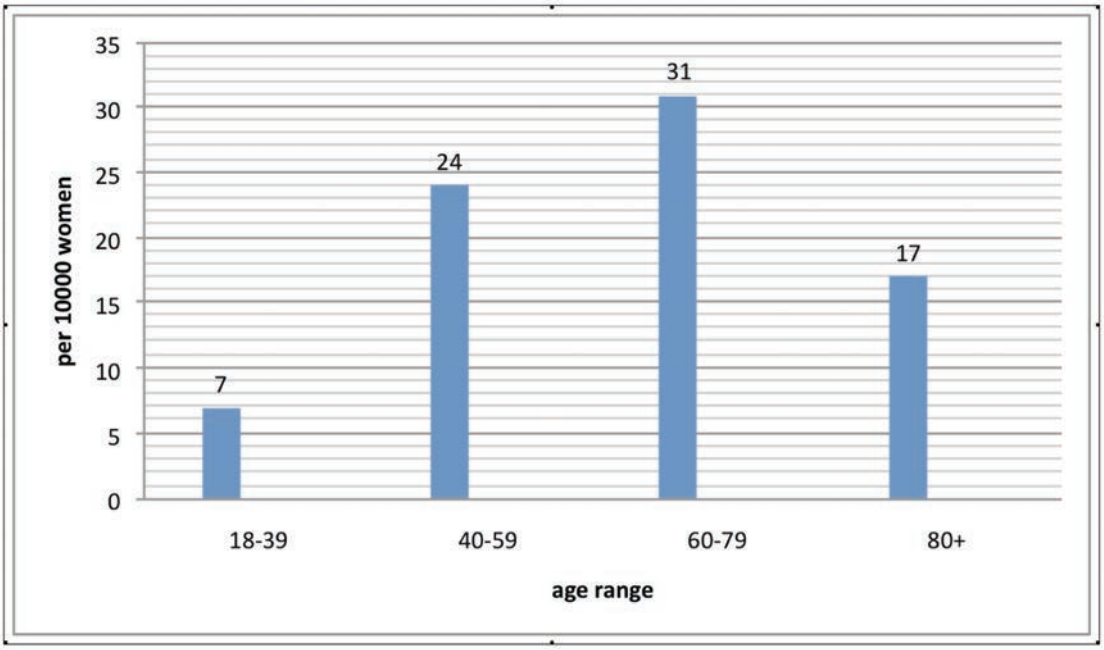


Figure 2. Shows the surgical treatment for POP/ rate per 10000 women (2003)

improved; there is now an internationally-accepted and reliable assessment of the anatomic support of the uterus and vagina [POPQ] and a number of valid, reliable and responsive symptom questionnaires and condition-specific HRQOL instruments.[Bump 1996; Barber 2001; Barber 2005; Digesu 2005; Price 2006; Baessler 2010]. A recent joint report from the International Continence Society [ICS] and International Urogynecological Association [IUGA] recommended that the following outcomes be reported in studies of POP surgery: Objective (e.g. POPQ), Patient reported outcomes (particularly the presence or absence of vaginal bulge symptoms), Satisfaction, Quality of Life, and Perioperative data (e.g. operative time, hospital stay, etc) (Toozs-Hobson, 2012). A careful report of short- and long-term complications are also essential to properly weigh the risk-benefit ratio of each procedure.

1. OUTCOME ASSESSMENT: ANATOMY

The Pelvic Organ Prolapse Quantification system (POPQ), introduced in 1996, is the international standard for describing female pelvic organ support. [Bump 1996] The POPQ allows a reproducible and reliable description of the support of the anterior, posterior and apical vaginal segments using precise measurements to a fixed reference point, the hymen, and established criteria for “staging” the various levels of pelvic organ support from good support [POPQ stage 0 or I] to almost complete lack of support [POPQ stage IV].[Bump, 1996] The POPQ system has proved a valuable measurement tool that over the last 15 years has improved our understanding of POP and allowed a reliable assessment of the anatomical success of POP surgeries. However, there remain several critical challenges in the anatomical assessment of POP surgery.

First, it is difficult to establish dichotomous anatomical outcome criteria for success and failure, especially in the absence of symptoms. Traditionally researchers have defined surgical success using the NIH satisfactory anatomic outcome [POPQ stage 0 -1] and defined surgical failure as POPQ stage 2 or greater. More recently it is suggested that these anatomic definitions are too strict as over 75% of women presenting for annual gynaecological examinations without symptoms of pelvic organ prolapse would not meet the definition of “optimal anatomic outcome” and almost 40% would not meet the definition of “satisfactory anatomic outcome.”[Samuelsson 1999; Swift 2005] Thus, a substantial number of women considered “surgical failures” by these definitions would be within the normal distribution of vaginal support for parous women. The hymen maybe a more clinically relevant anatomic threshold for surgical success and some researchers have begun defining anatomic failure after surgery as POP that extends beyond the hymen.[Culligan 2005; Barber 2009; Zyczynski 2010; Chmielewski 2011; Sayer 2011].

Second, the five-level staging system of the current POP-Q (Stages 0-IV) may be insufficient to discriminate among clinically important groups of women with POP, placing virtually all such women into Stage II or III. While the staging may facilitate comparisons, it may not describe sufficient detail as the individual POP-Q measurements provide. A third area of uncertainty is whether or not apical prolapse should be considered by the same anatomic standards as prolapse of the anterior or posterior vaginal wall.

Controversy also surrounds the impact that the observer recording the anatomical outcomes has upon reported success rates. Traditionally in the retrospective assessment of anterior compartment trials the reported success rates ranged from 80-100%[Macer 1978; Stanton 1982; Walter 1982; Porges RF 1994]. However, prospective assessment of similar surgical interventions utilising similar definitions of success under the auspices of randomised controlled trials report significantly lower success rate ranging from 37-64%[Sand 2001; Weber 2001]. Further variation is also reported in prospective evaluations of prolapse staging depending upon whether the assessor is blinded to the surgical intervention. Antosh et al[Antosh 2011] demonstrated that the recurrence rate in a RCT comparing native tissue and transvaginal mesh repairs was significantly higher when performed by a blinded versus unblinded assessor at the 3 months (68 versus 53%) and at 1 year (57 versus 43%). Finally, there is an increasingly common trend for authors with financial conflict of interest related to the commercial products being evaluated reporting the outcomes of surgical interventions, which further increases the risk of reporting bias.

2. OUTCOME ASSESSMENT: SYMPTOMS

Women seeking care for POP often have concurrent pelvic symptoms. Ellkermann et al found that in 237 women evaluated for POP 73% reported urinary incontinence, 86% reported urinary urgency and/or frequency, 34-62% reported voiding dysfunction and 31% complained of faecal incontinence.[Ellerkmann 2001] The evaluation of a patient with vaginal prolapse requires a comprehensive review of the full spectrum of pelvic floor symptoms and an assessment of how these symptoms affect their quality of life. The most valid way of measuring the presence, severity, and impact of pelvic floor symptoms on a patient’s activities and well-being is through the use of psychometrically robust self-administered questionnaires [Bump 1996; Barber 2001; Barber 2005; Digesu 2005; Price 2006; Baessler 2010]

We have gained an improved understanding of the relationship between pelvic organ support and the development of symptoms. Most symptoms often attributed to POP have at best weak to moderate correlations with worsening pelvic organ support, however, the one symptom that is almost consis-

tently acknowledged by patients with advanced POP is the presence of a vaginal bulge that can be seen or felt.[Ellerkmann 2001; Swift 2003; Barber 2005; Bradley 2005; Tan 2005] The absence of vaginal bulge symptoms postoperatively has a significant relationship with a patient's assessment of overall improvement and improvement in quality of life after surgery, while anatomic success alone does not.[Barber 2009] The hymen seems to be an important "cut off point" for symptom development. Women with prolapse beyond the hymen have more pelvic floor symptoms and are more likely to report a vaginal bulge than women with prolapse at or above the hymen.[Ellerkmann 2001; Swift 2003; Barber 2005; Bradley 2005; Swift 2005; Tan 2005]

3. OUTCOME EVALUATION: QUALITY OF LIFE

Health-related quality of life [HRQOL] refers to a person's total sense of well-being and considers multiple dimensions including (but not limited to) their social, physical, and emotional health. Measures of HRQOL can be classified into two types: generic and condition-specific. Generic HQOL instruments are used to assess quality of life in a broad range of illness or populations while condition-specific measures are designed to measure the impact of a specific disease on HRQOL. Women with advanced POP (stage 3-4) have decreased generic and condition-specific HRQOL compared to women with normal vaginal support.[Jelovsek 2006] It is recommended that investigators describe the impact of POP surgical treatment on HRQOL. Most studies that have assessed condition-specific HRQOL after POP surgery have demonstrated a significant improvement postoperatively. Improvements in generic HRQOL after POP surgery have been seen in some studies but not others. Maher et al reported significant improvements in condition-specific and generic QOL after SSLF, similar to that after abdominal sacrocolpopexy.[Maher 2004] The CARE trial reported significant improvements in condition-specific quality of life following sacrocolpopexy at three months and two years. [Brubaker 2006; Brubaker 2008] Barber et al demonstrated significant improvements in generic and condition-specific HRQOL in a prospective cohort of elderly women receiving vaginal surgery for POP and demonstrated similar improvements in women undergoing reconstructive surgery and those receiving colpocleisis.[Barber 2007] While some of these condition specific HRQOL incorporate assessment of sexual function [Baessler 2010] specific validated questionnaires on sexual function are available and provide a discreet and reproducible method for evaluating sexual health. The Pelvic Organ Prolapse/Incontinence Sexual Questionnaire [PISQ][Rogers 2001] and the Female Sexual Function Index[FSFI][Rosen 2000] are two questionnaires frequently used. The joint ICS/IUGA paper on reporting outcomes after prolapse surgery has also recommended authors report the sexual function status of all individual participants pre and post intervention as seen in **Figure 3** (Toozs-Hobson, 2012).

4. OUTCOME ASSESSMENT: REOPERATION

Reoperation after POP surgery for recurrence is an important measure of procedure efficacy. It is important to realise that reoperation rates are likely to represent the "tip of the iceberg" in terms of unsuccessful surgical outcomes as many women with recurrence of symptomatic prolapse may not elect another operation, nonetheless the repeat surgery for recurrent POP is an undesirable outcome that should, in most cases, be considered a surgical failure. The rates of reoperation after POP surgery vary widely in the literature, in large part because of varying definitions and timeframes. Olsen et al using administrative data from a large U.S. healthcare system reported a lifetime reoperation rate of 29.2%.[Olsen 1997] Importantly, this study included both POP and stress incontinence surgery and did not distinguish between reoperation for incontinence or POP in their report. Moreover, the authors did not distinguish between reoperation for POP in the same compartments originally operated versus the development of new POP in a new segment of the vagina ["de novo POP"]. More recently several investigators have looked specifically at the issue of site-specific recurrence with re-operation rates ranging from 3.4%-9.7%.[Miedel 2008; Kapoor 2010] In a meta-analysis of 258 studies evaluating reoperation rates after apical prolapse repairs, Diwadkar et al, reported a reoperation rate of 3.9% [95%CI 3.5-4.4%] for traditional vaginal vault suspensions (sacrospinous ligament suspension and uterosacral vault suspensions) after a mean of 32 months, 2.3% (95% CI 1.9-2.7%) for sacrocolpopexy with a mean follow-up of 26 months and 1.3% (95% CI 1.0-1.7%) after transvaginal mesh procedures at a mean follow-up of 17 months.[Diwadkar 2009] Notably, the total reoperation rate if one includes reoperations for recurrent POP and for complications was highest in the transvaginal mesh group (8.5%). [Diwadkar 2009]

In order to provide some clarity for future studies reporting reoperation rates after POP surgery, the joint ICS/IUGA report on reporting outcomes after prolapse surgery has proposed the following standardised terminology for POP surgery studies[Toozs-Hobson 2012]:

Primary surgery for POP is the first procedure required for the treatment of POP in any compartment

Further surgery This gives a global figure for the number of subsequent procedures the patient undergoes directly or indirectly relating to the primary surgery. This is subdivided into:

a. Primary prolapse surgery/different site. A prolapse procedure in a new site/compartment following previous surgery in a different compartment (e.g. anterior repair following previous posterior repair).

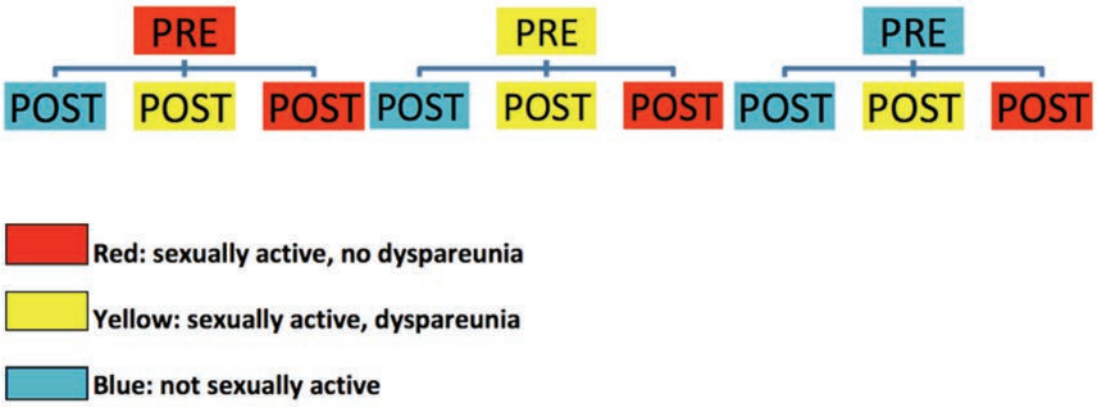


Figure 3. Describes color coordinated approach to systematically recording pre and post-intervention sexual function outcomes.

b. Repeat surgery: is a repeat operation for prolapse arising from the same site. Where combinations of procedures arise, e.g. new anterior repair plus further posterior repair these should be reported separately i.e. repeat posterior repair and primary anterior repair.

c. Surgery for Complications: e.g. mesh exposure or extrusion or pain or patient compromise e.g. haemorrhage (see complications section)

d. Surgery for non-prolapse related conditions: e.g. subsequent surgery for stress urinary incontinence or fecal incontinence.

5. DEFINING TREATMENT SUCCESS

The definition of success substantially affects treatment success rates following POP surgery.[Barber 2009] Since the publication of the NIH Workshop recommendations, considerable variability in defining treatment success still persists in studies evaluating surgery for prolapse. A number of trials define success as POPQ stage 0 or 1 consistent with the Workshop's "satisfactory anatomic outcome" definition with one reporting success rates as low as 30% using standard surgical techniques.[Weber 2001; Brubaker 2005] Some have used the Baden-Walker prolapse grading system rather than the POPQ system.[Maher 2004] Other studies have used a combination of anatomic criteria and the presence or absence of symptoms to define treatment success. [Paraiso 1996; Barber 2000; Brubaker 2005] Such variability makes it difficult to compare study results. Moreover, there are many unknowns, including clinical relevance of these definitions or how different outcome definitions might affect the comparison between treatment arms within a study.

A recent secondary analysis of the CARE trial described POP surgical success rates after sacrocolpopexy using 18 different definitions of treatment success with differing requirements for anatomic, symptomatic and/or retreatment outcomes.[Barber 2009] Treatment success varied widely depending upon definition used (19.2% to 97.2%). 71.4% considered their surgery "very successful" and 85.2% considered themselves "much better" than before surgery. Definitions of success requiring all anatomic support to be proximal to the hymen had the lowest treatment success (19.2% to 57.6%). 94.3% achieved surgical success when it was defined as the absence of prolapse beyond the hymen. Subjective cure (absence of bulge symptoms) occurred in 92.1% while absence of retreatment occurred in 97.2% of subjects. Subjective cure was associated with significant improvements in the patient's assessment of both treatment success and overall improvement, more so than any other definition considered [$p = .0002$ and $<.0001$ respectively]. Similarly, the greatest difference in symptom burden and HRQOL between treatment successes and failures was noted when success was defined as subjective cure (absence of vaginal bulge symptoms; $p<.0001$). These authors concluded that the absence of vaginal bulge symptoms postoperatively has a significant relationship with a patient's assessment of overall improvement, while anatomic success alone does not. Based on this analysis along with the currently available literature on the distribution of pelvic support loss in the general population and on data on the relationship between pelvic organ support loss and symptom development, authors from the NIH Pelvic Floor Disorders Network have recommended that: 1) any definition of success after POP surgery should include the absence of bulge symptoms in addition to anatomic criteria and the absence of re-treatment and 2) using the hymen as a threshold for anatomic success seems a reasonable and defensible approach.[Barber 2009].

Conclusion

The committee concludes that authors when reporting outcomes on the surgical management of prolapse should include a variety of standardised anatomical and functional outcomes. It is expected such measures will improve the reporting of surgical outcomes and aid in meaningful meta-analysis of pelvic organ prolapse outcome data in the future.

- Anatomical outcomes reported should include all POP-Q points and staging utilising traditional definition of success and also with the hymen as the threshold for success. Assessment should be prospective and assessors blinded as to the surgical intervention performed if possible and without any conflict of interest related to the assessment undertaken. (**Grade C**)
- Subjective success postoperatively should be defined as absence of vaginal bulge (**Grade C**).
- Functional outcomes are best reported using valid, reliable and responsive symptom questionnaires and condition-specific HRQOL instruments (**Grade C**).
- Sexual function is best reported utilising validated condition specific HRQOL that assess sexual function or validated sexual function questionnaires such as the Pelvic Organ Prolapse/Incontinence Sexual Questionnaire (PISQ) or the Female Sexual Function Index(FSFI). The sexual activity status of all study participants should be reported pre and post-operatively under the following categories: sexually active without pain, sexually active with pain or not sexually active (**Grade C**).
- Prolapse surgery should be defined as primary surgery, and repeat surgery sub- classified as primary surgery different site, repeat surgery, complications related to surgery and surgery for non-prolapse related conditions. (**Grade C**)

IV. ANTERIOR COMPARTMENT SURGERY

Ahlfelt stated in 1909 that the only remaining problem in plastic gynaecology was the permanent cure of cystocele and now more than a century later this problem persist[White GR 1909]. Following high reported objective failure rates and reoperation rates after native tissue repairs and the success of mesh tapes in continence surgery and mesh utilised abdominally at sacral colpopexy the last decade has seen an unprecedented introduction of biological and permanent meshes in the management of anterior compartment prolapse.

1. NATIVE TISSUE REPAIRS

Historically anterior colporrhaphy was the standard procedure in the management of anterior compartment prolapse with objective success rates ranging from 80-100% in retrospective series[Macer 1978; Stanton 1982; Walter 1982; Porges RF 1994]. White [White GR 1912] as early as 1912 demonstrated the importance of paravaginal defects in anterior compartment prolapse. Richardson [Richardson AC 1976] in 1976 described a series of defects in the pubocervical fascia explaining why no single repair should be applied indiscriminately to all with anterior compartment defects. He also advocated the abdominal paravaginal repair which has a 75-97% success rate for cystoceles reported in case series (**Table 2**) [Richardson AC 1976; Richardson 1981; Shull 1989; Scotti 1998; Bruce 1999]. The surgical technique of the laparoscopic paravaginal repair is well described however little information is available on the efficacy of this approach. Shull [Shull 1994] also reported on the safety and efficacy of the vaginal paravaginal repair in 1994. Although the success rates of the vaginal paravaginal repair for cystoceles in case series vary from 67 –100%[White GR 1912; Shull 1994; Grody. M 1995; Elkins. T 2000; Mallipeddi 2001; Young 2001] significant complications have been reported recently. Mallipeddi [Mallipeddi 2001] reported on complications in a series of 45 including: 1 bilateral ureteric obstruction, 1 retropubic hematoma requiring surgery, 2 vaginal abscesses; 2 transfusions. In a series of 100 women Young [Young 2001] reported a 21 major complications and a 16% transfusion rate.

No randomised control studies have evaluated the abdominal or vaginal paravaginal repair in isolation. Benson et al [Benson 1996] and Maher et al [Maher 2004] have reported RCT's on upper vaginal prolapse comparing abdominal sacral colpopexy and vaginal sacrospinous colpopexy. Abdominal paravaginal repair was performed in the abdominal group if required and an anterior colporrhaphy without or without vaginal paravaginal laterally. Both authors reported the abdominal group to have a statistically lower rate of postoperative anterior vaginal prolapse than the vaginal group.

Raz et al [Raz 1989] popularised the needle suspension type procedure for cystoceles and reported success rates in case series may vary from 90-98% [Gardy 1991; Raz 1991; Benizri 1996]. The addition of polyglactin mesh to the repair appears to have little impact on the success [Safir. M 1999] [160]. Dmochowski et al [Dmochowski 1997] reported a lower success rate using a stricter outcome definition of success.

Goldberg et al [Goldberg 2001] reported results from a case control study of women with cystocele and stress urinary incontinence. He suggested that the addition of the pubovaginal sling to the anterior colporrhaphy significantly reduced the recurrence rate of cystocele from 42% in the control group to 19% in the anterior colporrhaphy and sling group [P<0.05].

APR Abdominal paravaginal repair AC Anterior colporrhaphy Definition varies between authors

In line with our surgical colleagues there has been a move towards the use of prosthesis to augment native tissue repair in reconstructive Gynecology. This movement took much of its impetus from two early papers. Firstly, Olsen et al [Olsen 1997] reported a reoperation of 29% following prolapse and or continence surgery and Weber [Weber 2001] reported a 70% failure rate of native tissue anterior compartment repair. Recent re-evaluation of the Olsen's same demographic 10 years later revealed a significantly lower re-operation rate of 17% [Denman M 2008] and the reader should be cautious in making conclusions even from this data as the surgical interventions performed in 1995 are not representative of interventions performed today. More importantly, Weber et al [Weber 2001] and Sand et al [Sand 2001] in randomised control trials reported the anterior col-

Table 2. Anterior vaginal wall prolapse procedures

Author	Year	No.	Follow-up	Success Rate	
Anterior Colporrhaphy					
Stanton	1982	54	up to 2 yrs	85%	
Macer	1978	109	5-20yrs	80%	
Walter	1982	76	1.2yrs	100%	
Porges	1994	388	2.6yrs	97%	
Colombo	2000	33 AC 35 colposuspension	8-17yrs 8-17 yrs	97% 66%	
Sand	2001	70 AC 73 AC& vicryl mesh	1yr 1yr	57% 75% No mesh complications	
Weber	2001	57 AC 26 AC+ vicryl mesh	23month 23 month	37% 42% No mesh complications	
Vaginal Paravaginal Repair					
White	1912	19	up to 3 yrs	100%	
Shull	1994	62	.6 yrs		67%
Grody	1995	72	0.5-3yrs	99%	
Elkins	2000	25	0.5-3yrs	92%	
Mallipeddi	2001	45	.6yrs	97%	
Young	2001	100	11 months	78%	
Morse	2007	27 VPVR	13	54%	
		86 AC	24	45%	
Abdominal Paravaginal Repair					
Richardson	1976	60	1.7yrs	97%	
Richardson	1981	213	0.5-6yrs	95%	
Shull	1989	149	0.5-4yrs	95%	
Bruce	1999	27 APR& sling	17 months	93%	
		25 APR	17 months	76%	
Scotti	1998	40	39 months	97%	
Sling type support					
Raz	1989	107 AC & needle	2yrs	98%	
Raz	1991	50	2.8yrs	90%	
Gardy	1991	58 AC & needle	2yrs	95%	
Benirzi	1996	36 AC & vaginal wall sling	17months	95%	
Dmochowski	1997	47 Raz type	47months	43%	
Cross	1997	36 AC & sling	20months	92%	
Safir	1999	112 Raz + polyglactin mesh	21months	92%	
Goldberg	2001	53 AC& sling	1 yr	81%	
		90 AC	1yr	58%	

porrhaphy to be successful in the management of cystocele in only 30% and 57% respectively. Recent re-analysis of data from Weber's paper using the hymen as the threshold for objective success reported considerably better outcomes with only 10% of subjects developing anatomic recurrence beyond the hymen, 5% of subjects developing symptomatic recurrence and re-operations less than 1% at 23 months follow-up [Chmielewski 2011].

During the decade between these initial and subsequent publications surgeons have introduced a plethora of biological and mesh grafts to improve the outcomes of anterior compartment prolapse surger.

2. SYNTHETIC GRAFTS IN ANTERIOR COMPARTMENT SURGERY

As seen in **Table 3** as early as 1996 Julian et al [Julian 1996] demonstrated in a prospective case control study that in women who had undergone at least 2 previous vaginal repairs, the overlaying of a Marlex (Bard) mesh to the anterior colporrhaphy reduced the recurrence rate of cystocele from 33% to 0%. The Marlex mesh was associated with a mesh erosion rate of 25%. Flood et al [Flood 1998] in a retrospective review of 142 women with Marlex mesh augmentation of anterior colporrhaphy demonstrated a 100 % success rate for cystoceles at 3.2 years and a mesh erosion rate of only 2%.

Absorbable meshes are an attractive option as an augmenting material as they offered the increased strength during the early healing phase without the long-term complications of permanent mesh and have been evaluated in 2 randomised controlled trials. Weber et al [Weber 2001] in a randomized control trial compared the anterior colporrhaphy [33], ultrawide anterior colporrhaphy [24] or anterior colporrhaphy with absorbable polyglactin (Vicryl) 910 mesh [26] in the management of cystocele. The study size was too small to detect small differences in efficacy or adverse events. However, at a mean follow-up of nearly 2 years the groups had similar proportions of women experiencing satisfactory or optimal anatomic results, 30%, 46% and 42% respectively.

Sand et al [Sand 2001] in a larger RCT allocated cystoceles to anterior colporraphy alone [n=70] and to anterior colporraphy plus polyglactin mesh underlay [n=73]. At I year the success rate in the mesh group was 75% and significantly greater than the 57% success rate in the anterior repair group alone [P=0.02]. Concurrent paravaginal defect were present in 11 women and concomitant paravaginal repair was significantly associated with a lower recurrence of cystocele overall [P=0.02].

A variety of permanent polypropylene mesh overlays have been evaluated in case series for the management of anterior wall prolapse. The anatomical success rate varies from 76 to 100% [Cervigni ; Julian 1996; Salvatore S 2002; O'Reilly BA 2003]. Salvatore et al reported worrying functional outcomes after a prolene mesh overlay including a mesh erosion rate of 13%, overactive bladder increasing from 28 to 56% and dyspareunia increasing from 18 to 38% postoperatively [Salvatore S 2002]. More recently, three year follow-up after the polypropylene mesh

Table 3. Synthetic meshes utilised anterior compartment surgery

Author	Year	Type	No	Review Months	Success Rate (%)	Complication
Julian(Julian 1996)	1996	Marlex Control	12 12	24	100 66	25% mesh erosion, infection
Nicita(Nicita 1998)	1998	Prolene	44	14	100	3uterine prolapse
Flood (Flood 1998)	1998	Marlex	142	38	100	3mesh erosions
Migliari (Migliari 1999)	1999	Mixed fiber	15	23	93	
Migliari (Migliari 2000)	2000	Polypropylene	12	20	75	
Natale (Natale. F 2000)	2000	Polypropylene	138	19	97	13 mesh erosions,9 dyspareunia, 1 haematoma
Sand(Sand 2001)	2001	Polyglactin No mesh	73 70	12	75 57	no mesh complications
Weber(Weber 2001)	2001	Polyglactin No mesh	26 57	23 23	42 37	no mesh complications
Salvatore(Salvatore S 2002)	2002	Prolene	32	17	87	13% mesh erosions
O'Reilly (O'Reilly BA 2003)	2003	Polypropylene (Atrium)	81	28	88	no mesh erosions
Cervigini(Cervigni 2007)	2007	Polypropylene	218	38	76	12.3% erosions,7% Vaginal stenosis
Jo(Jo 2007)	2007	Polypropylene Gynemesh	38	18	94	0 erosions
Rodriguez (Rodriguez 2005)	2005	Polypropylene	98		85	0 erosions
Amrute(Amrute 2007)	2007	Polypropylene	76	30	95	3% erosions
de Tayrac (de Tayrac 2005)	2005	Polypropylene	84	24	92	8.3%
de Tayrac(de Tayrac 2006)	2006	Polypropylene	55	37	89	9.1% mesh erosion, 5.5% mesh shrinkage 16.7% dyspareunia
de Tayrac(de Tayrac 2006)	2006	Polypropylene	48	18	98	8.3% erosions
de Tayrac (de Tayrac 2006)	2007	low weight coated polypropylene	32	13	93	6.3% erosion,12.8% de novo dyspareunia
Nieminen (Nieminen 2010)	2010	RCT low weight self styled armed Polypropylene AC	104 97	36 36	87 59	19% erosions 24% reoperations 6 POP, 5tapes, 14 mesh exposure 19% reoperation 10 POP 9 tapes
Sivaslioglu(Sivaslioglu 2007)	2007	RCT:low weight, self styled Polypropylene Site specific vicryl AC 4	43 42	12 12	91 72	6.9% mesh erosions 4.6% de novo dyspareunia

Table 3. Augmenting Materials for Anterior Vaginal (continued)

Author	Year	Type	No	Review Months	Success Rate	Complications
Nguyen (Nguyen 2008)	2008	RCT Armed Polypropylene Perigee AC	38 38	12 12	89% 55%	5% Erosion 9% dyspareunia 16% dysparuenia 5% reoperations 1 tape , 1 POP
Altman (Altman 2007)	2007	Polypropylene Prolift	123	2	87%	1.5% mesh Erosions 3.2% organ perforation
Altman (Altman 2011)	2011	Multicentre RCT Polypropylene Prolift (Ethicon)armed	191 182	12	82% 47%	Subjective failure rate greater AC Operating time, blood loss, cystotomy ,mesh exposure, stress urinary incontinence and Denovo dyspareunia mesh groupi
Carey (Carey 2008)	2009	RCT repair with polypropylene gynemesh augmentation Ant &post colporrhaphy	69 70	12 12	81% 66%	6.5% mesh erosion O reoperation prolapse Denovo dyspareunia equal both groups
Vollebregt (Vollebregt 2011)	2011	RCT polypropylene Avulta Bard Vicryl AC	56 58	12	91% 41%	4% mesh exposure 0 reoperations POP Baseline dyspareunia resolved 20% Denovo dyspareunia 15% rectocele 10% Denovo dyspareunia 9% 5% reoperations POP, denovo rectocele 10% Baseline dyspareunia resolved 80%
Rane (Rane 2011)	2011	Retrospective review Perigee grade 3 cystocele	376	60	93%	11.1% mesh exposure 4% deteriorating sexual function

overlay in the anterior compartment has been reported. Cervigni reported on 218 women and found a 76% objective success rate at three years. Mesh erosions were identified in 12.3% and vaginal stenosis in 7.7% [Cervigni 2007]. De Tayrac reported on 55 women at 3-year review with a 89% success rate, 9.1% mesh erosions, 5.5% mesh shrinkage and 16.7% dyspareunia [de Tayrac 2006]. He concluded that lower weight and coated meshes were required to limit the rate of complications and duly reported on 132 women, 12 months following low weight coated polypropylene mesh with a 92% success rate [de Tayrac 2007]. Unfortunately local problems remained with mesh erosions in 6.3% and de novo dyspareunia in 12.8%. Rane et al provided a 5 year review of 376 consecutive women with grade 3 anterior compartment prolapse after Perigee (AMS) and reported a 94% success rate, 11.1% mesh extrusion rate and deteriorating sexual function in 4% [Rane 2011].

Carey et al [Carey 2009] performed an RCT comparing anterior and posterior fascial plication and repair with self styled anterior and posterior polypropylene Gynemesh (Ethicon) overlay and reported no significant advantage to adding a mesh overlay at one year. The morbidity in the mesh group was lower than that reported above with a mesh erosion rate of 6.5% and no difference in dyspareunia and denovo dyspareunia rates between the groups.

Five randomised control trials have been published comparing armed or trans-obturator polypropylene mesh and traditional anterior colporrhaphy (**Table 3**). Nieminen et al [Nieminen 2010] compared 104 women undergoing anterior compartment prolapse repair with self-styled 6x11cm low weight monofilament 4 armed polypropylene mesh (Parietene light, Sofradim Co, Trevoux, France) with 97 undergoing traditional anterior colporrhaphy. Concomitant hysterectomy and posterior compartment prolapse surgery was allowed. At 3 years the objective success (stage 0 or 1 Aa and Ba) rate was 87% in the mesh group and 59% in no mesh group [P<.001]. Awarness of bulge was seen in 18% in the repair group as compared to 10% [p=0.07] in the mesh group. The mesh exposure rate was 19% with 66% requiring surgical correction. The reoperation rate for prolapse was 10% in the native tissue group with all but one of the recurrences in anterior compartment. In the mesh group the prolapse reoperation was 6% with all six recurrences occurring in the posterior or apical compartments.

Sivaslioglu et al reported on 43 undergoing low weight self styled polypropylene mesh as compared to 42 undergoing site-specific vicryl repair and at 12 months found the objective success rate was significantly higher at 91% in the mesh group as compared to 72% in the non-mesh group[Sivaslioglu 2007]. The mesh erosion rate was 6.9% and de novo dyspareunia was reported in 4.6% in the mesh group. Quality of life assessment demonstrated no difference in outcomes between the groups and no patient in either group underwent further surgery for anterior compartment prolapse.

Nguyen compared anterior polypropylene [Perigee, AMS] mesh [n=37] with anterior colporrhaphy [38]. At 1 year the objective success rate was higher in the mesh group (89% vs. 55%). Functional outcomes including quality of life, sexual activity and dyspareunia were similar in both groups with a 5% mesh erosion and 2% unilateral leg pain that settled at 8 weeks following the mesh surgery.[Nguyen 2008].

Altman and colleagues reported on behalf of the Nordic transvaginal mesh group a multicentre study (funded by Karalinska Institute and Ethicon unrestricted grants) comparing anterior colporrhaphy [n=182] to anterior transvaginal trocar mesh kit

(Prolift)[n=186] in women with symptomatic stage II or greater cystocele [Altman 2011]. Although the need for concomitant prolapse and continence surgery were exclusions an undetermined number of women with posterior and apical compartment prolapse well beyond the introitus were included. Reviewers were unblinded, surgeons were reviewers and conflict of interest statements are not available for authors or members of Nordic transvaginal mesh group. At one year, the success rate [composite Point Ba <-1 and absence of vaginal bulging] was significantly greater after the mesh repair 61% as compared to colporrhaphy group 35%. The subjective success rate was also significantly greater after the mesh repair (75% versus 62% p=0.008) as compared to the native tissue repair while no difference was detected on validated pelvic floor questionnaires (Urinary Distress Inventory) between the groups. The Prolift mesh procedure was associated with greater morbidity with a longer operating time, greater blood loss, higher rate of intra-operative cystotomy (3.5 versus 0.5%) , post- operative denovo stress urinary incontinence [12.3 versus 6.0%], and combined reoperation rate for USI, prolapse and mesh exposure (6% versus 0.5%). Denovo dyspareunia was seen in 7.3% after the mesh surgery as compared to 2% after anterior colporrhaphy [p=0.07] however no difference was detected between the groups utilising the Pelvic organ Prolapse Urinary Incontinence questionnaire [PISQ-12]. The mesh exposure rate was 11.5% [21/183].

Lastly, Vollebregt and colleagues reported a multicentre randomised control trial from the Netherlands with blinded reviewers comparing anterior colporrhaphy [n=58] with polypropylene trans-obturator mesh kit Avaulta [n=56] [Bard] for stage 2 primary anterior compartment prolapse [Vollebregt 2011]. Concomitant hysteropexy and posterior compartment surgery was allowed with hysterectomies being excluded. At one year the objective success rate was significantly greater in the mesh group as compared to anterior colporrhaphy group (91% versus 41%). Reoperation for anterior compartment prolapse was performed in 5% after the native tissue repair and in no patients in the mesh group [p>0.05]. No difference in awareness of prolapse or outcomes using validated questionnaires (Urogenital Distress Inventory and Incontinence Impact Questionnaire) were identified between the groups. The authors attributed the low mesh exposure rate of 4% to not performing hysterectomy and or collagen coating on the polypropylene mesh. Resolution of preoperative dyspareunia occurred in 80% in the repair group as compared to 20% in the mesh group. Denovo dyspareunia was reported in 15% following mesh and 9% after native tissue repair and denovo rectocele in 23% versus 10% respectively. The authors concluded that despite the significantly improved anatomical outcome in the mesh arm when using a functional outcome as a definition of success that there was not enough evidence to support the trans-obturator mesh in primary anterior compartment prolapse surgery.

The 2012 Cochrane meta-analysis of these RCT found that transobturator meshes had a lower rate of recurrence on examination [59/424, 14%] as compared to anterior colporrhaphy alone [200/410, 49%] RR 3.50, 95% CI 2.71 to 4.52. This finding was consistent for both the self styled (Nieminen 2010; Sivaslioglu 2008] [RR 3.41, 95% CI 2.04 to 5.67] and commercial transobturator polypropylene mesh kits [Altman 2011; Nguyen 2008; Vollebregt 2011] [RR 3.53, 95% CI 2.62 to 4.74]. Three trials demonstrated that anterior colporrhaphy [94/333, 28%] also had a higher subjective failure rate than the anterior transvaginal mesh repair [60/344, 17%] [RR1.62, 95% CI 1.22, 2.14] [Altman 2011; Nieminen, Vollebregt 2008]. Further prolapse surgery was not significantly more common after anterior colporrhaphy 14/459 (3%) as compared to 6/470 (1.3%) after trans-obturator polypropylene mesh [RR 2.18 95% CI 0.93 to 5.10]. No difference was detected in individual studies in validated prolapse specific questions and meta-analysis was not possible due to variations in questionnaires utilised. The operating time and blood loss were significantly greater in the mesh group and there was a tendency towards lower cystotomy rate [0.4% versus 2.7%, RR.0.19 95%CI 0.03,1.07] Altman 2011;Nieminen 2010], denovo dyspareunia [4% versus 8%, RR 0.51 95% CI 0.21 to 1.23] and denovo stress urinary incontinence [7.3% versus 11.4% RR, 0.65 95% CI 0.4 to 1.07,] [Altman 2011, Sivaslioglu 2008; Nieminen 2010] after anterior colporrhaphy. Further continence surgery was performed in 15/368 women following anterior colporrhaphy and 12/380 after polypropylene mesh procedure [RR 1.29, 95% CI 0.63 to 2.63]. This data need to be interpreted with caution as variations in concomitant surgeries existed. Mesh erosions were reported in 10.4% [41/393] of women who had an anterior compartment polypropylene mesh and surgical intervention to correct mesh erosion occurred in 6.3% [34/540].

Withagen in an observational study of 150 women undergoing Polypropylene mesh kit (Prolift) found that after an isolated anterior polypropylene repair there was a 46% incidence of stage 2 prolapse in the untreated compartment [Withagen 2010]. Altman et al, performed no concomitant surgery in the study and no difference in posterior compartment prolapse was identified between the groups or post-operatively within the mesh group when evaluating median Point Bp. However, meta-analysis of those studies [Nieminen 2010; Vollebregt 2011] that reported denovo prolapse in the apical or posterior compartment following anterior compartment mesh repair found at a lower rate after the anterior colporrhaphy [14/147, 9.5%] as compared to trans-obturator mesh [26/148 17.7%] [RR 0.49 95% CI 0.24 to 0.97] Both study protocols allowed concomitant posterior compartment

prolapse surgery. Although the reoperation rates for prolapse was similar in Nieminen et al between the 2 groups all the reoperations in AC group were anterior compartment failures and all in trans-obturator mesh group were in the posterior or apical compartment [Nieminen 2010]. This outcome is not surprising as we have seen previously when the vaginal axis is significantly altered compensatory prolapse can develop in other compartments. Compensatory prolapse is described in the posterior compartment after colposuspension [Ward 2008] or in the anterior compartment after sacrospinous colpopexy [Paraiso 1996; Maher 2001].

In the 8 trials that evaluated 553 patients that underwent some form of transvaginal mesh in the management of anterior compartment prolapse no patient underwent surgical intervention for vaginal pain or dyspareunia. This is in contrast to the Food and Drug Administration (FDA) transvaginal mesh alert were vaginal pain and dyspareunia accounted for 39% of adverse events and was marginally more frequent than mesh erosions at 38% of adverse events reports. While mesh exposures and their management remain well described vaginal pain and dyspareunia associated with anterior transobturator polypropylene mesh remain poorly characterised and will be fully evaluated in the complications and sexual function section of this chapter.

Given the relatively robust anatomic outcomes associated with transobturator mesh many clinicians were surprised that many mesh kit manufactures recently elected to introduce trocarless mesh kits and the majority have little or no data supporting their claims of superiority. Most recently, Moore et al [Moore 2012] described single incision anterior elevate [American Medical Systems, Minnetonka, MN, USA] using a lightweight polypropylene graft (24g/m2) and reported 92% objective success rate at 13 months in 60 patients with anterior and or apical prolapse. No mesh exposures were reported and the authors who reviewed the patients reported a financial relationship with the company manufacturing the product being evaluated.

Another new system involves polypropylene mesh [Prosima, Ethicon] overlay with arms extending but not secured to deeper structures. Patients use a Vaginal Support Device that is removed in the outpatient setting 3-4 weeks postoperatively, to splint the mesh while it is being incorporated into the paravaginal tissues. On prospective evaluation performed by surgeons all of whom have declared financial agreements with the manufacturing company, they reported a 77% objective success rate [<stage 2 POP-Q] at 1 year [Zyczynski 2010] and 69% at 2 years [Sayer 2011] with a mesh exposure rate of 9% in women with Stage 2 anterior and/or posterior compartment prolapse. Significant further prospective comparative trials with blinded independent reviewers are required for all mesh kits.

3. BIOLOGIC GRAFTS ANTERIOR COMPARTMENT SURGERY

Alternatively to synthetic prosthetic grafts autologous material may have a lower risk of host rejection or infection. Cosson [Cosson 2001] described an autologous 6-8cm long and 4 cm wide vaginal patch suspended from the tendinous arches of the pelvic fascia and tucked under the anterior repair. The success rate [<grade 1 POP] was 93% at a mean follow-up of 16 months.

Allografts from post-mortem tissue banks have been used for many years in orthopaedic surgery and decrease the risk associated with harvesting autologous rectus sheath or fascia lata. Cadaveric fascia lata with or without pubovaginal sling has been utilised to correct anterior compartment prolapse with a success rate varying from 81-100% with acceptable complication rates[Groutz 2001; Kobashi 2002; Powell 2004; Frederick 2005]. Gandhi et al have reported preliminary results of a randomised control trial comparing anterior colporrhaphy alone and augmented with fascia lata graft for cystoceles [Gandhi 2005]. At 1 year they were not able to demonstrate that the addition of the fascial lata graft improved outcomes with the success rate after anterior colporrhaphy alone being 71% as compared to 82% in those augmented with the fascia lata graft [P=0.07]. No complications were reported. Cadaveric dermis has been employed as a graft material in the anterior compartment with success rates varying from 42-84% at 2 years [Chung 2002; Clemons 2003; Behnia-Willison 2007; Ward 2007]. Concerns regarding prion transmission causing infectious diseases [Simonds RJ 1992] or residual antigenicity [Hathaway 2002] that may cause host graft reactions have encouraged the use of porcine or bovine xenografts as detailed in **Table 4**.

Leboeuf et al retrospectively reviewed 24 women with native tissue four corner defect repair (FDR) and 19 FDR with porcine dermis [Leboeuf L 2004]. At 15 months the success rate was 100% in the FDR group and reduced to 84% if porcine dermis overlay was utilised. Wheeler et al reported on 36 women who all underwent high uterosacral vault suspension with anterior repair augmented with porcine dermis and at 17 months found a 50% recurrence rate [Wheeler 2006]. The authors highlighted that despite the high objective failure rate greater that 90% of the women were satisfied or somewhat satisfied with the repair and 83% would undergo the surgery again. Handel et al retrospectively compared anterior colporrhaphy [n=18], porcine dermis [n=56] and polypropelene graft [n=24] in those with cystocele [Handel 2007]. The success rate at 13 months was 94%, 64% and 96% respectively with a 21% rate of vaginal extrusion of the porcine dermis graft. Alternatively to these relatively disappointing

results, a number of groups have reported satisfactory objective results utilising porcine dermis. [Gomelsky 2004] [Simsiman 2006].

Meschia et al in a multicentre randomised clinical trial compared the anterior colporrhaphy [n=103] and anterior colporrhaphy-augmented with 4x7cm piece of porcine dermis [Meschia 2007]. The success rate at 1 year was 93% in the anterior colporrhaphy with porcine graft overlay group as compared to 81% in anterior colporrhaphy alone group [P<0.001] with a 1% rate of graft erosion.

Hviid et al reported a smaller randomised controlled trial comparing polyglactin plication anterior colporrhaphy and porcine dermis 4x7cm graft at one year [Hviid 2010]. The objective failure rate [defined as point Ba ≥-1] was 2/28 in the porcine dermis group as compared to 4/26 in the anterior colporrhaphy and was not significant. Guerette et al compared the anterior colporrhaphy group [n=17]and anterior colporrhaphy with bovine pericardium collagen [n=27] matrix graft reinforcement and reported no difference on objective examination with success rate of 63% after the AC and 77% in the bovine pericardium collagen repair at 2 years(Guerette 2009]. The reoperation rate for prolapse was 37% in AC group and 23% in the bovine pericardium group. Denovo dyspareunia occurred in 5% follow-

Table 4. Biological Grafts in anterior compartment prolapse

Author	Year	Graft	N	Months	Success rate	Complications
Cosson(Cosson 2001)	2001	Autologous Vaginal patch	47	16	93%	None
Groutz (Groutz 2001)	2001	cadaveric & pubovaginal sling	19	20	100%	None
Kobashi (Kobashi 2002)	2002	cadaveric fascia lata & sling	132	12	87%	1 osteitis pubis
Chung (Chung 2002)	2002	cadaveric dermis	19	24	84%	1 infection removal
Clemons (Clemons 2003)	2003	cadaveric dermis	33	18	59%	1 incision breakdown
Powell (Powell 2004)	2004	cadaveric fascia lata	58	24	81%	10% graft erosion 2 transfusions, 1 cystotomy 3 ureteral kinking
Frederick (Frederick 2005)	2005	cadaveric fascia lata & sling	251	6	93%	1 osteitis pubis
Gandhi (Gandhi 2005)	2005	RCT AC & fascia lata (Tutoplasta) AC no graft	76 78	13 13	82% 71%	no graft comlications
Ward (Ward 2007)	2007	cadaveric dermis	39	24	42%	1 de novo dyspareunia No graft erosions
Xenographs						
Lebouf (Leboeuf 2004)	2004	FDR & Pelvicol PDR	9 24	15 15	84% 100%	None None
Salomon (Salomon 2004)	2004	porcine dermis transobturator	27	14	81%	1 graft r/o vaginal pain
Gomelsky (Gomelsky 2004)	2004	porcine dermis	70	24	87%	None
Wheeler (Wheeler 2006))	2006	porcine dermis Uterosacral repair	28	18	50%	2% granulation tissue
Meschia (Meschia 2007)	2007	Porcine AC	98 103	12 12	93% 81%	1% vaginal extrusion
Handel (Handel 2007)	2007	Porcine dermis Polypropylene AC	56 25 18	13 13 13	64% 96% 94%	21% vaginal extrusions 4% mesh erosion
Simsiman(Simsiman	2006	Porcine graft	89	24	78%	17% erosions
Robles (Robles 2007)	2007	Porcine dermis Polypropylene arm	90	8	85%	no complications
Guerrette(Guerette 2009)	2009	AC Bovine pericardium collagen	27 17	24	63% 77%	Reoperation POP surg 37% 23%
Hviid (Hviid 2010)	2010	AC Porcine dermis graft	26 28	12	85% 93%	Recurrent POP Sur 8% 10%
Feldner(Feldner 2010)	2010	AC Porcine small intestine Submuosa	27 29	12	67% 86%	Dyspareunia 15% 25%
Natale (Natale 2009)	2009	porcine graft self-styled polypropylene mesh	94 96	24	58% 72%	Mesh erosion 0 6.3%
Menefee (Menefee 2011)	2011	AC Vag paravaginal porcine dermis Vag paravaginal polypropylene	19 23 25	24	55% 52% 86%	Mesh erosion 0 4% 14%

Variable definitions of success used.

ing AC only. There was no difference in quality of life outcomes between the groups utilizing Urinary Distress Inventory and Pelvic organ prolapse and Incontinence sexual questionnaire.

Feldner et al compared anterior colporrhaphy with 7x10cm small intestine submucosa (SIS) graft in a randomised control trial and demonstrated reduced operating time in AC group (30 min versus 46) as compared to SIS [p=0.02][Feldner 2010]. The objective failure rate of 33% [9/27] was significantly higher after the AC versus 14% [4/29] in the SIS group. The dyspareunia rate was similar in both groups [AC 4/27 versus 5/20 SIS] and no reoperations were reported. Prolapse quality of life assessment [P-QOL] improved postoperatively in both groups with no significant difference between the groups. In another RCT, Natale et al compared polypropylene mesh (Gynemesh) with porcine dermis (Pelvicol). At two years, significantly fewer women had anterior vaginal wall recurrence in the mesh group 28% [27/96] versus to 44% [41/94] of the porcine graft group [RR 0.64, 95% CI 0.43 to 0.96]. Mesh erosion was seen in 6.3% following mesh surgery. Although similar numbers of women reported dyspareunia [10 versus 12], the authors reported superior sexuality outcomes in the porcine graft group as compared to polypropylene mesh [p = 0.03][Natale 2009].

Finally, Menefee et al in a randomised control trial compared three operations, anterior colporrhaphy, vaginal paravaginal repair using porcine dermis graft and vaginal paravaginal with self-styled polypropylene mesh and also reported a higher objective success rate after the polypropylene mesh 86% [25/29] as compared to 52% [12/23] in the porcine dermis arm [Menefee 2011] and 53% [10/19] in the AC arm. The subjective failure rate was not significantly different and was 3.4%,12% and 13% respectively. The graft erosion rate was 1/23 [4.3%] in the porcine dermis group and 4/29 [13.8%] in the mesh group.

The 2012 Cochrane meta-analysis concluded that when anterior colporrhaphy was compared to any biological graft the objective failure rate in anterior compartment was significantly higher in the anterior colporrhaphy group 56/222 [25%] as compared to the biological graft group 31/218 [14%]. Results from 3 trials [Gandhi 2005; Meschia 2007,Guerette 2009] demonstrated no difference in prolapse symptoms when native tissue repair was compared to biological graft repair [RR 1.03 0.61 to 1.75]. Differences in the methodology and the nature of the different biological grafts utilised in five trials [Feldner 2010, Gandhi 2005, Guerette 2009, Hviid 2010, Meschia 2007, Menefee 2011] were considered to be too dissimilar to combine with any other results in a meta-analysis except to highlight that 2 RCT's [Feldner 2010, Menefee 2011] demonstrated superior objective outcomes following polypropylene mesh as compared to Porcine graft overlay.

While many clinicians believe the primary role of polypropylene mesh may be in complex or high risk prolapse such as recurrent prolapse there is little evidence to support these proposals. Fayyad et al prospectively evaluated 36 women with recurrent anterior compartment prolapse and reported an objective success rate (less than stage 2 anterior compartment prolapse) of 47% with a mesh exposure rate of 19%[Fayyad 2011].

In a prospective multicentre Dutch RCT trial women who had undergone prior prolapse surgery were randomised between native tissue repairs and tension free Vaginal polypropylene mesh [Withagen 2011]. Allocation concealment was not confirmed and neither patient, surgeon or assessor were blinded. Surgeons performed the reviews and all authors declared a financial relationship with the company manufacturing the commercial mesh product. Unfortunately preoperatively the two groups were significantly different pointing to a systematic failure in the randomization process which discredits the remaining findings of the manuscript.

The reported failure rate in the native tissue group using an unorthodox outcome definition (no prolapse in the treated compartment or reoperation) was 45% AC versus 9% mesh group at 1 year. Utilising the definition any grade 2 prolapse or subsequent prolapse surgery the failure rate was 66% in the conventional surgery group as compared to 49% [p=0.03] in the mesh group. The mesh exposure rate was 16.7% with 6% undergoing surgical intervention. Utilising Patients global Impression of Improvement [PGII] and Urogenital Distress Inventory both groups had similar outcomes.

Conclusion for anterior vaginal compartment repairs:

The following conclusion can be made regarding surgical interventions for anterior vaginal compartment repairs:

- absorbable mesh augmentation of native tissue repair improves the anatomical outcome as compared to native tissue repair alone with no increased complication rate in meta-analysis of 2 RCTS (**Grade B**)
- Biological grafts in meta-analysis have improved anatomical outcomes with no change in subjective outcomes as compared to native tissue repairs (**Grade B**). Conflicting level one evidence supports porcine dermis graft (Meschia, Hviid, Menefee) and single RCT supports small intestine submucosa as graft agent in anterior compartment prolapse surgery (Feldner) (**Grade B**) .
- Consistent level one data supports a superior anatomical outcome for Polypropylene mesh as compared to biological graft (Pelvicol) in the anterior compartment (Feldner, Menefee). Mesh exposure rate was significantly higher in the polypropylene mesh group. (**Grade A**)

- Consistent level 1 evidence demonstrates improved anatomical and subjective outcomes for polypropylene mesh as compared to anterior colporrhaphy (**Grade A**). These outcomes did not translate into improved functional outcomes using validated questionnaires or a lower reoperation rate for prolapse. The mesh group was also associated with longer operating time, greater blood loss and a non significant tendency towards higher cystotomy, denovo dyspareunia and denovo stress urinary incontinence rate as compared to AC. Apical or posterior compartment prolapse was significantly more common following polypropylene mesh and mesh extrusion rate was 10.4% with 6.3% undergoing surgical correction. (**Grade B**)
- single Level 3 evidence does not support use of polypropylene mesh for recurrent anterior vaginal wall prolapse (**Grade C**)

V. UTERINE PRESERVATION DURING POP SURGERY

Traditionally, surgical correction of uterovaginal prolapse includes a hysterectomy despite the fact that the uterus is believed to be a passive structure in the disease process. More recently, women have opted for uterine preservation for a variety of reasons including: desire to maintain future fertility, belief that the uterus affects sexual function or sense of identity, and concern about risks of hysterectomy. While the overall number of hysteropexy studies have increased, most are retrospective or lack a control group. Comparisons between the different hysteropexy procedures are challenging due to the limited numbers of prospective controlled trials measuring a variety of outcomes.

1. PATIENT SELECTION

Careful patient selection is critical prior to considering uterine preserving prolapse surgery. **Table 5** list contraindications to uterine preservation. Most studies exclude subjects with menstrual disorders and abnormal uterine or cervical pathology such as large fibroids, endometrial hyperplasia, and cervical dysplasia. A recent study by Frick illustrates the need for hysterectomy in woman with postmenopausal bleeding even with a negative workup because of the high risk [13%] of unanticipated endometrial cancer or hyperplasia [Frick 2010]. Postmenopausal women without bleeding and premenopausal women with regular menses without abnormal uterine bleeding and a negative workup are at low risk for unanticipated pathology.

2. VAGINAL HYSTEROPEXY

The vaginal route can be divided into repairs with and without mesh. The non-mesh repairs include Manchester repair and sacrospinous hysteropexy.

a) The Manchester procedure

The Manchester procedure is one of the oldest prolapse repairs that involves amputation of the cervix and reattachment to the cardinal ligaments. Modified Manchester procedures include plication of the uterosacral ligaments posteriorly and cardinal ligaments anteriorly for improved apical support. Nevertheless, this is primarily a procedure for cervical elongation in premenopausal women that wish to maintain fertility or older women with medical comorbidity. There are high rates of cervical stenosis and menstrual disorders [7-35%] associated with cervical amputation and the use of Sturmdorf sutures [Williams 1966; Tipton 1970; Thomas 1995; Ayhan 2006]. All studies using this technique are retrospective and show relatively good anatomic and symptomatic improvement. One retrospective cohort comparing modified Manchester to total vaginal hysterectomy and uterosacral ligament suspension showed 100% cure of the apical compartment but a 40% success rate based on overall stage in the Manchester group. [DeBoer 2009] Three other retrospective cohorts comparing Manchester to vaginal hysterectomy showed no difference in anatomic or symptomatic outcomes with decreased operating time and blood loss in the Manchester group [Thys ; Thomas 1995; Kalogirou 1996]. Despite good success rates, Kalogirou concluded, “that the Manchester procedure has a limited place in modern gynecology…” Better surgical options exist for pre-menopausal women that wish to preserve fertility including sacrospinous hysteropexy, laparoscopic uterosacral hysteropexy or laparoscopic sacral hysteropexy. For post-menopausal women with medical comorbidity that require a minimally invasive approach, sacrospinous hysteropexy or LeFort colpocleisis would be preferable depending on their desire to preserve vaginal function.

Table 5. Contraindications to uterine preserving surgery

Uterine abnormalities
Fibroids, adenomyosis, endometrial pathology sampling
History of current or recent cervical dysplasia
Abnormal menstrual bleeding
Post menopausal bleeding
Familial cancer BRAC1&2 ↑risk ovarian cancer and theoretical risk fallopian tube and serous endometrial cancer
Hereditary Non-Polyposis Colonic Cancer 40-50% lifetime risk endometrial cancer
Tamoxifen therapy
Unable to comply with routine gynecology surveillance

b) Sacrospinous Hysteropexy

At sacrospinous hysteropexy the cervix or uterosacral ligaments are transfixed to the sacrospinous ligament using permanent or delayed absorbable suture. In a recent RCT comparing sacrospinous hysteropexy [n=37] to vaginal hysterectomy with uterosacral ligament suspension [n=34], Dietz et al reported a higher rate of apical recurrences in the hysteropexy group 21% versus 3% hysterectomy group p=0.03].[Dietz 2010] Three women had stage 4 uterine prolapse preoperatively that underwent hysteropexy and all developed recurrent uterine prolapse within one year. Subjective outcomes improved for both groups. Hysteropexy was associated with shorter hospitalisation, quicker recovery with more rapid return to work and the total vaginal length was longer 8.8cm versus 7.3cm in hysterectomy group [p<0.01]. Both groups had high rates of postoperative anterior vaginal wall prolapse [51% vs. 64%]. Another RCT unfortunately failed to report objective or subjective outcomes and revealed no difference in sexual function between sacrospinous hysteropexy and vaginal hysterectomy [Jeng 2005]. Sexual function domains of the Female Sexual Function Index-7 remained relatively unchanged in the majority of subjects with low rates of dyspareunia [5%]. Transient buttock pain occurred in 15% of subjects, similar to sacrospinous ligament fixation. Among the other studies in our review, buttock pain was present in up to 18% of patients and was usually self-limited [Hefni 2003; Jeng 2005; Hefni 2006; Dietz 2007; Dietz 2008].

Three cohort studies comparing sacrospinous hysteropexy to vaginal hysterectomy with or without sacrospinous fixation showed no difference in anatomical or symptomatic improvement with the exception of a three-fold increase in overactive bladder and urge incontinence symptoms in the vaginal hysterectomy group [Maher 2001; Hefni 2003; van Brummen 2003]. The sacrospinous hysteropexy group had shorter operating time, less blood loss, faster recovery, and fewer complications with similar recurrence and reoperation rates.

Lin and colleagues performed an interesting and unique prospective two-part study [Lin 2005]. The first phase identified cervical elongation [relative risk 10.9] and severe prolapse as risk factors for recurrent prolapse after sacrospinous hysteropexy. Among the first 33 patients, cure of uterine prolapse was 93% for those without risk factors compared to 71% for those with at least one risk factor. Next, they excluded patients with severe prolapse and performed a partial trachelectomy for those with cervical elongation resulting in a 96-100% cure rate with no recurrences in the 7 women undergoing partial trachelectomy.

The majority of studies have revealed relatively high success rates for the apical compartment with low complication rates for sacrospinous hysteropexy. Evaluation of available data from **Table 6** re-

Table 6. Compares outcomes sacrospinous hysteropexy and vaginal hysterectomy.

Author	Study Type & Surgery	Review (months)	Success Rate SSHP	Success rate Vaginal hysterectomy	Complications
Dietz 2010	RCT	12	27/34 (79%)	30/31 (97%)	1 Ureteral obstruction TVH group
Jeng 2005	RCT	6	MD	MD	Buttock pain 12 (15%)
Hefni 2003	Prospective Cohort	33	57/61(94%)	46/48 (96%)	Buttock pain: 2(3%) vs 2(4%) All others in TVH/SSLF group Hematoma 3(6%) – 1 reoperation to drain ,Transfusion 2(4%)
Van Brummen 2003	Retrospective cohort	19	39/44 (89%)	28/30(93%)	Hemorrhage 1(2%) Nerve/organ injury 1(2%)
Maher 2001	Retrospective cohort	26 33	25/34(74%)	26/36 (72%)	Buttock pain 3(2 vs 1) Dyspareunia 7% vs 3%
Dietz 2008	Prospective	13	56/72 (78%)		Buttock pain 13(18%) Vaginal hematoma 2(3%) Vaginal adhesion 3(4%) Reoperation bleeding: 1
Lin 2005	Prospective	60-120	32/36 (89%)		Unknown
Dietz 2007	Retrospective	23	57/60(95%)		Buttock pain (15%) DVT 1 Reoperation: postop bleeding 1
Hefni 2006	Retrospective	57	60/65 (92%)	114/117 (97%)	Buttock pain 6.5%,Dyspareunia 2 Rectal injury 2,Transfusion 1 Vault hematomas (2%) Reoperation for bleeding 3
Kovac 1993	Retrospective	37.2	15/17(88%)		Rectal injury 1(5%)
Richardson 1989	Retrospective	6-24	5/5 (100%)		
Total			373/428 (87%) 95%CI 84-90%	244/262 (93%) 95%CI (90-96)	P=0.054

SSHP = sacrospinous hysteropexy; TVH = total vaginal hysterectomy; DVT = deep venous thrombosis
** variation in surgical techniques and definition success exist*

veals no difference in the mean objective success rate of 87% [373/428] sacrospinous hysteropexy versus 93% [244/262] in the hysterectomy group. While tha data on efficacy of sacrospinous hysteropexy are conflicting sacrospinous hysteropexy remains an alternative to vaginal hysterectomy in women who desire future fertility or uterine conservation. However, women with severe advanced prolapse desiring uterine conservation are at high risk of recurrence and should consider alternative approaches for hysteropexy [Lin 2005; Dietz 2010]. Those with cervical elongation should consider partial trachelectomy, which may affect future pregnancy outcomes.

c) Vaginal Mesh Hysteropexy

Several sacrospinous hysteropexy studies show high rates [11-51%] of recurrent anterior vaginal wall prolapse despite performance of a concomitant cystocele repair [Paraiso 1996; Maher 2001; Hefni 2003; Dietz 2007; Dietz 2008; Dietz 2010] and probably secondary to the posterior deflection of the vaginal axis with sacrospinous fixation. Level 1 evidence demonstrates improved anterior vaginal wall anatomical support with the addition of vaginally placed mesh. [Maher 2010] Intuitively, hysteropexy with anterior mesh placement seems ideal to improve anterior vaginal wall support and decrease recurrences in women desiring uterine conservation. Studies involving vaginal mesh repair with uterine conservation frequently include post-hysterectomy subjects and those undergoing concomitant hysterectomy making it difficult to identify outcomes specific to hysteropexy [Feiner 2010]. For the purposes of this section, we excluded anterior vaginal mesh repairs for uterovaginal prolapse that did not require an apical support procedure that would qualify as a hysteropexy.

Collinet et al reported 5-fold increased odds of mesh exposure with concomitant hysterectomy and 6-fold increased odds with an inverted T colpotomy incision [Collinet 2006]. Uterine preservation and minimising the size of the colpotomy were protective. These data support the role of hysteropexy for women with uterovaginal prolapse planning a vaginal mesh repair. However, there are no RCTs or prospective cohort studies comparing vaginal mesh hysteropexy to hysterectomy with prolapse repair. There are 3 retrospective cohort studies confirming the efficacy of vaginal mesh hysteropexy. McDermott et al reported similar high anatomic success, symptomatic improvement and perioperative outcomes with total Prolift hysteropexy and total Prolift colpopexy [McDermott 2011]. The mesh erosion rate was 13% in the hysteropexy group. Chu et al discovered excellent support and high satisfaction when hysteropexy and vaginal hysterectomy were performed in conjunction with Perigee and Apogee, apical arms placed through the sacrospinous ligaments (Chu). The hysteropexy group had shorter operating time, less blood loss, and lower rates of mesh erosions [4% vs. 13%, NS]. Neuman et al reported similar high success and satisfaction for posterior intravaginal slingplasty with hysteropexy and hysterectomy [Neuman 2007]. There was only 1 case of recurrent uterine prolapse despite the fact that cervical amputation was performed in 17% of hysteropexy subjects. Tape erosion rates were similar [11% vs. 14%, NS] and hospitalisation was shorter [1.5 vs. 4.2 days] in the hysteropexy group.

A prospective series of 100 anterior Prolift, sacrospinous hysteropexy and posterior colporrhaphy procedures revealed 75% objective success, 12% uterine recurrences and 11% mesh erosions [Feiner 2010]. Satisfaction was high [94%] because 84% had no prolapse symptoms and all recurrent uterine prolapse were mild, stage 2. Other retrospective and prospective hysteropexy series demonstrate higher cure rates with similar or lower mesh risk [Huang ; Nicita 2005; Inoue 2009]. Fatton et al demonstrated a high number of mesh related complications in a multicentre retrospective series of 110 Prolift procedures [Fatton 2007]. There was 1 bladder injury, 5 mesh exposures, 3 granulomas without mesh exposure, 18 cases of mesh shrinkage, and 1 vaginal synechia. Meta-analysis of the limited available data in **Table 7** demonstrates no difference in anatomic success rate of 86% [273/316] in the mesh hysteropexy versus 98% [81/83] in the mesh hysterectomy group [p=0.21]. Nor was there a significant reduction in the mesh exposure rate when mesh repairs were performed with hysteropexy 8.8% versus 13% with hysterectomy [p=0.22]. Newer trocarless kits using lower volume light weight mesh are being promoted for uterine conservation surgery without any supporting data in the peer reviewed literature to date.

3. ABDOMINAL HYSTEROPEXY

Abdominal hysteropexy has been performed for over a century. Early procedures transfixed the uterus to the anterior abdominal wall [Swain 1897; Giles 1930]. Other small series have successfully utilised ventral fixation to the pectineal ligaments with or without a graft [Nesbitt 1989; Joshi 1993]. However, abdominal sacral hysteropexy is generally the procedure of choice when performed through an open abdominal incision. Similar procedures can be performed laparoscopically or robotically including sacral hysteropexy and uterosacral ligament suspension. Other laparoscopic options have been described including round ligament suspension [O'Brien 1994] and anterior abdominal wall fixation [Chen 2010]. We present the data for the most common abdominal and laparoscopic techniques.

a) Abdominal Sacral Hysteropexy

Early studies performed in the 1950's either directly sutured the uterus to the anterior longitudinal ligament or used a thin strip of external abdominal oblique fascia tunneled retroperitoneally from the sacral promontory to the posterior cervix for support [Stoesser 1955; Arthure 1957]. More recently, a variety of grafts and techniques have been described. Frequently polypropylene mesh is secured posteriorly to the cervix/vagina or a second graft is passed through windows made in the broad ligament and secured to the anterior cervix/vagina. Addison and Van Lindert published a series of abdominal sacral colpopexy in 1993 containing subsets of women [11 total] undergoing successful abdominal sacral hysteropexy with synthetic mesh [Addison 1993; van Lindert 1993]. Over the past 15 years, there have been multiple small studies evaluating abdominal sacral hysteropexy [Costantini ; Banu 1997; Costantini 1998; Leron 2001; Roovers 2002; Barranger 2003; Roovers 2004; Bai 2005; Costantini 2005; Demirci 2006; Jeon 2008] as listed in **Table 8**.

Roovers and colleagues performed the only RCT comparing abdominal sacral hysteropexy [n=41] and Burch to vaginal hysterectomy, uterosacral ligament suspension, anterior and posterior colporrhaphy, and needle suspension [n=41] [Roovers 2004]. Anatomic outcomes were similar with high success rates for the apical [95%] and posterior [85-95%] compartments. Anterior recurrences occurred in 61 and 64% of women. Urogenital distress inventory scores improved for all domains with the greatest improvement in prolapse symptoms. There were more doctor visits and reoperations performed or planned in the abdominal hysteropexy group. No differences existed for operating time, blood loss, length of hospitalisation, and number of complications. Constantini et al reported results of a prospective cohort study comparing abdominal sacral hysteropexy to total abdominal hysterectomy and sacral colpopexy [Costantini 2005]. There were no differences in anatomic success [91% vs. 92%], symptomatic improvement or satisfaction. Three women required vaginal revision due to mesh erosions [8%] in the hysterectomy group. Hysteropexy was associated with shorter operating time, less blood loss, and shorter hospitalisation.

There are 2 retrospective cohort studies that each included 3 arms. Jeon et al compared abdominal sacral hysteropexy to abdominal hysterectomy with sacral colpopexy or uterosacral suspension [Jeon 2008]. There were no recurrences in the hysteropexy group. Recurrences were 6.2 times more likely to occur in the uterosacral suspension group compared to the sacral colpopexy group when hysterectomy was performed. Bai et al compared smaller numbers of abdominal sacral hysteropexy to sacral colpopexy with or without hysterectomy [Bai 2005; Jeon 2008]. Success rates were high for all groups [95-100%]. There were 3[16%] mesh erosions in the hysterectomy group that did not require reoperation and no erosions in the other groups. Hysteropexy had shorter operating time and length of hospitalisation. All of the prospective observational trials and retrospective series revealed satisfactory anatomic success [87-100%] and symptomatic improvement [92-100%] [Costantini ; Banu 1997; Costantini 1998; Leron 2001; Barranger 2003; Demirci 2006]. In 2 studies, cervical amputation was performed without subsequent problems for 7 women with cervical elongation.

b) Laparoscopic sacral hysteropexy

Laparoscopic sacral hysteropexy techniques are similar to those described with the abdominal sacral hysteropexy with an anatomic success rate

Table 7. Compares vaginal mesh hysteropexy and vaginal mesh hysterectomy outcomes.

Author	Study Type & Surgery	Review months	Success Rate Mesh hysteropexy	Success rate Mesh hysterectomy	Mesh exposure hysteropexy	Mesh exposure hysterectomy
McDermott 2011	Retrospective cohort Total Prolift Hysteropexy	11	20/24 (83%)		3/24	
Chu 2011	Retrospective cohort Perigee & Apogee SSHP vs. TVH	9.0	(50/52) 96%	39/39 (100%)	2/52	5/39
Neuman 2007	Retrospective cohort Posterior IVS Hysteropexy vs TVH	29	32/35(91%)	42/44 (95%)	4/35	6/44
Feiner 2010	Prospective Anterior Prolift, SSHP	12	69/92 (75%)		10/94	
Inoue 2009	Prospective observational TFS SSHP	MD	23/25 (92%)		1/25	
Huang 2011	Retrospective Polypropylene SSHP	20	60/67(90%)		8/67	
Nicita 2005	Retrospective	31	19/21(89%)		0/21	
Total			**273/316 (86%) 95% CI (82-90)**	**81/83 (98%) 95% CI (94-100)**	**28/318 (8.8%) 95% CI (5.7-11.9)**	**11/83 (13%) 95%CI 6-21**

**variety surgical techniques and definitions of success*

of 88-100% with equally high symptomatic improvement and satisfaction. Several of the studies include different combinations of patients including post hysterectomy prolapse undergoing laparoscopic sacral colpopexy, uterine prolapse undergoing both abdominal and vaginal hysterectomy or laparoscopic sacral hysteropexy making it difficult to determine specific results associated with laparoscopic sacral hysteropexy. **Table 8** describes the anatomic outcomes of sacral hysteropexy performed laparoscopically or open compared to hysterectomy and sacral colpopexy and demonstrates similar success rates in the two groups 91% [310/339] and 92% [84/91] respectively [p=.17]. The sacral hysteropexy was quicker to perform and also had a lower mesh exposure rate of 1.5% [5/339] versus 8.5% [11/129] versus sacral colpopexy with hysterectomy [p<0.05%].

c) Laparoscopic Uterosacral Hysteropexy

At surgery the plicated uterosacral ligaments are secured to the distal cervix or by plicating the ligaments in the midline with a McCall's technique. Some add a Moschcowitz culdoplasty at the time of uterosacral suspension. Rosen et al compared laparoscopic uterosacral hysteropexy to total laparoscopic hysterectomy with uterosacral suspension, both groups did reasonably well without noticeable differences in outcomes [Rosen 2008]. When laparoscopic uterosacral hysteropexy was compared to vaginal hysterectomy and colpopexy in 25 age matched pairs, anatomic and symptomatic improvement was slightly better for the laparoscopic group with less blood loss and shorter length of hospitalisation [Diwan 2006]. Other series show similar anatomic and symptomatic success [80-100%] with few complications in women undergoing laparoscopic uterosacral or McCall's hysteropexy. [Maher 2001; Krause 2006; Medina 2006]. Evaluation of available trials in **Table 9** demonstrates a mean objective success rate of 83% [148/176]after laparoscopic uterosacral hysteropexy as compared to 78% [21/27] after laparoscopic hysterectomy and 88% [22/25] after vaginal hysterectomy and uterosacral ligament suspension.

Laparoscopic round ligament suspension was not as successful with all women having a rapid re-

Table 8. Compares outcomes sacral hysteropexy (open or laparoscopic) and hysterectomy and sacral colpopexy outcomes.

Author	Study Type & Surgery	Follow-up months	ASHP Success rate	TAH SCP Success rate	ASHP Mesh Exposure	TAHSCP Mesh exposure	Complications
Roovers 2004	Multicenter RCT	12	26/41 (63%)		2/41		1Transfusion, 2 vault abscess &Infected implant
Constantini 2005	Prospective	51	31/34 (91%)	35/38(92%)	0/34	3/38	ASHP group 2Transfusion, 2Incisional hernia
Jeon 2008	Retrospective Cohort	36 (1-84)	35/35 (100%)	60/63 95%	0/35	5/63	TAH: 1 DVT, 3 SBO, 1 ureteric obstruction
Bai 2005	Retrospective cohort	12	10/10 (100%)	18/19 (95%)	0/10	3/19	Transfusion: 3 /5 Wound dehiscence secondary closure: 0/2 Ileus: 1 ASHP
Constantini 2011	Prospective observational ASHP (47) LSHP (8)	64(12-146)	45/52 (87%)		2/52		De novo constipation 5, Persistent sexual dysfunction 24%(4/17) Wound hernia 2 PE 1
Price 2010	Prospective LSHP	3-6	50/51(98%)		0/51		2 dyspareunia,
Demirci 2006	Prospective ASHP	25(3-60)	19/20 (95%)		0/20		Wound infection 2 Incisional hernia 1 Dyspareunia 3
Barranger 2003	Prospective ASHP	45 (2-156)	(28/30) (93%)		1/30		Hematoma 1, Presacral Hemorrhage 1 Wound infection 1, Incisional hernia 1, SBO 1, Sciatic pain 1, De novo dyspareunia 2
Constantini 1998	Retrospective ASHP	32 (12-68)	7/7 (100%	8/9 (89%)	0/7	0/9	DVT/PE 2 (10%) Femoral neuropathy 1(5%) Incisional hernia 2(10%)
Rosenblatt 2008	Retrospective LSHP	8	40/40 (100%)		0/40		1 rectal injury, umbilical hernia & transfusion
Banu 1997	Retrospective ASHP	36-60	19/19 (100%)		0/19		"no significant complications"
Total			**310/339 (91%)**	**121/129 (94%)**	**5/339 (1.5%)**	**11/129 (8.5%)**	

currence of prolapse [O'Brien 1994]. Laparoscopic attachment to the anterior wall with mesh was highly successful in a group of 28 women [Chen 2010]. This technique could potentially increase the risk of posterior compartment recurrences due to vaginal axis deflection anteriorly, similar to a retropubic urethropexy.

d) Hysterectomy at time of sacral colpopexy

The evidence supporting sacral colpopexy is largely based on post-hysterectomy vault prolapse and it is not clear from the literature whether the excellent outcomes reported in the post- hysterectomy group will be reproduced in the uterine prolapse group. When considering sacral colpopexy for women with uterovaginal prolapse, the literature is relatively sparse. The choice of hysterectomy includes supracervical, abdominal, laparoscopic assisted vaginal and vaginal. Additionally, the mesh can be attached vaginally or laparoscopically following a vaginal hysterectomy. Placement of synthetic mesh over a healing sutured incision plus exposure to vaginal microbes theoretically increases the risk of graft erosion when hysterectomy is performed at the time of sacral colpopexy. While the evidence in the literature is conflicting meta-analysis of all available comparative studies in **Table 10** demonstrate that the risk of mesh erosion is approximately 4 times greater if a hysterectomy is performed at the time of sacral colpopexy 8.6% [51/592] as compared to 2.2% [25/1125] without a hysterectomy and 1.7% [1/58] if subtotal hysterectomy is performed. Introducing synthetic mesh transvaginally or laparoscopically after vaginal hysterectomy or through a posterior vaginal excision appears to significantly increase the risk of mesh erosion after sacrocolpopexy[Visco 2001; Tan-Kim 2011].

Therefore, based on the current literature, hysterectomy at time of sacral colpopexy should be selected with caution and patients should be counseled regarding increased risk of mesh exposure. For this reason supracervical hysterectomy and sacral hysteropexy seem to be gaining in popularity however, there is a very significant paucity of data supporting this approach. Clinicians and the patients planning sacral hysteropexy and supracervical hysterectomy should also consider the significant surgical challenge of removing a retained cervix or uterus that is encompassed in mesh.

4. PREGNANCY AND HYSTEROPEXY

For women with uterovaginal prolapse who have not completed their family, conservative management with a pessary should be offered as a first line treatment before surgical hysteropexy. Most believe that definitive surgical management should be deferred until childbearing is completed due to the potential impact of future pregnancy and delivery on pelvic support and surgical repair. In situations where a pessary cannot be fitted properly or for younger patients that refuse conservative therapy for a prolonged period of time, hysteropexy is a reasonable option. There are no documented pregnancies after laparoscopic sacral hysteropexy or vaginal mesh hysteropexy. There were 12 pregnancies after a Manchester procedure with mostly full term vaginal deliveries and only 1 documented recurrence of prolapse. There were 17 pregnan-

Table 9. Compares laparoscopic uterosacral hysteropexy and hysterectomy outcomes.

Author	Methodology	Numbers	Follow-up months	LUSLHP	TLH+USCL	Vaginal hysterectomy	Complications
Rosen 2008	Prospective cohort	32	24	(22/28) 79%	21/27 (78%)		Dyspareunia 1 each group
Diwan 2005	Retrospective cohort	25 LUSLHP 25 TVH	7 12	25/25 100%		22/25 (88%)	De novo dyspareunia 2(8%)
Maher 2001	Prospective	43	12(6-32)	(34/43) 79%			Laparotomy Hemorrhage 2 Ureteral releasing incisions)
Medina 2006	Retrospective	23	16(6-40)	23/23 (100%)			Pneumonia 1
Krause 2006	Prospective	81 (5)	20 (7-31)	54/57 (95%)			DVT/PE: 1 2 Small bowel perforation

*LSHP = laparoscopic sacral hysteropexy; LUSLHP = laparoscopic uterosacral ligament hysteropexy; TLH = total laparoscopic hysterectomy; * significant variation in definition success and surgical technique*

Table 10. Describes rate of mesh exposures at sacral colpopexy with and without hysterectomy and with subtotal hysterectomy.

Author, Year	Design	Follow-up months	Surgery	Mesh	No hysterectomy	Concomitant total hysterectomy	Concomitant subtotal hysterectomy	*p*
Jeon, 2009	Retrospective comparative	36	Open	TEFLON MARLEX PP	2/35	5/63	MD	-
Cundiff 2008	Prospective comparison	24	Open	Mersilene PP GORETEX	8/239	12/83		
Wu, 2006	Retrospective comparative	15	Open	GORETEX MERSILENE PP	10/212	7/101	MD	-
Costantini, 2005	Prospective non randomised	50	Open	MARLEX	0/34	3/38	MD	-
Bensiger, 2005	Retrospective comparative	12	Open	PP	0/35	4/49	0/37	-
Brizzolara 2003	Retrospective Comparative	35	Open	80% PP 20% allografts	0/64	1/60		
Culligan 2002	Retrospective	24	Open	Synthetic mesh	3/234	3/11		
Total for open SC	-	-	-	-	23/853 (2.7%)	35/405 (8.6%)	0/37	0.001
Stepanian 2008	Retrospective	12	Lap	PP	2/272	3/130		
Tan Kim, 2011	Retrospective comparative	15	Lap	PP	MD	13/57*	1/21	-
Total	-	-	-	-	25/1125 (2.2%) 95% CI (1.4-3.1)	51/592 (8.6%) 95% CI (6.3-11%)	1/58	0.001

PP=polypropylene, Lap=Laparoscopic, MD=missing data

cies after sacrospinous hysteropexy with half vaginal and half cesarean deliveries at term followed by 2 recurrences. There were a few pregnancies after laparoscopic uterosacral hysteropexy that had mixed routes of delivery at term with 1 recurrence. Giles reported the majority of documented pregnancies that occurred after abdominal wall suture hysteropexy [Giles 1930]. There were 139 pregnancies and 110 full term deliveries that were mostly vaginal [75%] with only 1 recurrence. Ot, her abdominal hysteropexy studies revealed 9 pregnancies with mostly vaginal deliveries and no recurrences.[Stoesser 1955; Joshi 1993; Banu 1997; Barranger 2003]

Despite relatively good outcomes, limited information exists to aid in counseling patients that desire hysteropexy and plan to become pregnant in the future. Unfortunately, we do not know which type of hysteropexy is better for women that desire future pregnancy with respect to fertility, pregnancy and delivery, and postpartum support and durability? We also do not know the true impact of a future pregnancy on long-term success rates and whether a cesarean delivery prevents recurrent prolapse compared to vaginal delivery. Since relatively few women undergo hysteropexy and subsequent pregnancy, it would be difficult to design a feasible study to answer these questions

Summary

In summary a wide variety of surgical options remain for women presenting with uterine prolapse.

- Uterine preservation is a suitable option in women with uterine prolapse without contraindications to uterine preservation. However longterm data is limited and the need for subsequent hysterectomy unknown (**Grade C**).
- Sacrospinous hysteropexy is as effective as vaginal hysterectomy and repair in retrospective comparative studies and in a meta-analysis with reduced operating time, blood loss and recovery time. However in a single RCT there was a higher recurrence rate associated with sacrospinous hysteropexy as compared to vaginal hysterectomy (**Grade D**). Severe prolapse increases the risk of recurrent prolapse after sacrospinous hysteropexy.
- In consistent level 2 evidence sacrospinous hysteropexy with mesh augmentation of the anterior compartment was as effective as hysterectomy and mesh augmentation with no significant difference in the rate of mesh exposure between the groups. (**Grade B**)
- Level one evidence from a single RCT suggests vaginal hysterectomy and uterosacral suspension was superior to sacral hysteropexy based on reoperation rates despite similar anatomic and symptomatic improvement. (**Grade C**).

- Consistent level two and three evidence suggest sacral hysteropexy (open or laparoscopic) was as effective as sacral colpopexy and hysterectomy in anatomical outcomes however the sacral colpopexy and hysterectomy was associated with a five times higher rate of mesh exposure as compared to sacral hysteropexy (**Grade B**).
- At meta-analysis of hysterectomy at the time of sacral colpopexy as compared to sacral colpopexy without hysterectomy was associated with a four times higher risk of mesh exposure (**Grade B**).
- Abdominal sacral hysteropexy and hysterectomy with sacral colpopexy have better anatomic outcomes compared to abdominal hysterectomy with uterosacral suspension in a single retrospective comparison (**Grade C**).

VI. APICAL SUPPORT PROCEDURES

While anterior vaginal prolapse is most common, loss of apical support is usually present in women with prolapse that extends beyond the hymen [Swift 2000; Delancey 2002]. There is growing recognition that adequate support for the vaginal apex is an essential component of a durable surgical repair for women with advanced prolapse [Toozs-Hobson 1998; Shull 1999]. Because of the significant contribution of the apex to anterior vaginal support, the best surgical correction of the anterior and posterior walls may fail unless the apex is adequately supported [Rooney 2006; Hsu 2008]. While recognition of apical defects is one of the biggest challenges in the preoperative evaluation of pelvic support defects, surgical correction of the apex has several good options with relatively high success rates. Apical suspension procedures can broadly be separated into those performed transvaginally and those performed abdominally. Abdominal procedures can be performed via laparotomy or using conventional laparoscopic or robotically assisted-laparoscopic techniques. Although precise estimates are not available, most studies suggest that the vaginal approach is most common with 80-90% of procedures being performed through this route [Olsen 1997; Brown 2002; Boyles 2003; Brubaker 2005]. The individual woman's surgical history and goals, as well as her individual risks for surgical complications, prolapse recurrence and de novo symptoms affect surgical planning and choice of procedure for apical POP.

1. SACROSPINOUS LIGAMENT SUSPENSION (SSLS)

One of the most popular and widely reported transvaginal procedures for correcting apical prolapse is the SSLS. First described in 1958 [Sederl 1958], this procedure suspends the vaginal apex to the sacrospinous ligament either unilaterally or bilaterally, typically using an extraperitoneal approach. Observational series and clinical trials suggest that while apical recurrence after SSLS is uncommon [2.4% to 19%], recurrence of anterior vaginal prolapse is more problematic [6% to 28.5%] (**Table 11**). A meta-analysis by Morgan et al found an overall failure rate at any site of 28.8% [95% CI 18.4%-36.3%] with failure of the anterior segment seen in 21.3% [17-3-25.3%], apical segment of 7.2% [95% CI 4.0 – 10.4%] and posterior segment of 6.3% [95%CI 4.2-8.4%]. Whether the relatively high rate of anterior vaginal prolapse recurrence seen with SSLS is due to the posterior deflection of the vaginal axis, as many authors suggest,[Shull 1992; Benson 1996; Paraiso 1996; Colombo 1998] or simply represents a general predilection of anterior support to fail after pelvic reconstructive surgery remains unknown [Weber 2005]. Reoperation rates after SSLS range from 1.3% to 37%, with all but two series reporting rates less than 9% (**Table 11**).

Information on the functional or QOL outcomes of SSLS is limited. Maher et al demonstrated significant improvements in condition-specific and generic QOL after SSLS, similar to that after abdominal sacral colpopexy [Maher 2004]. A meta-analysis of randomised and observational studies found a pooled average for failure to provide relief of prolapse symptoms after SSLS of 10.3% [95% CI 4.4-16.2%] [Morgan 2007]. The pooled average for failure to provide patient satisfaction after SSLS in this analysis was 13% [95% CI 7.4%-18.6%] [Morgan 2007]. Although infrequent, serious complications associated with SSLS include buttock pain and sacral/ pudendal neurovascular injury. In a review of 22 studies that included 1229 SSLS procedures, 3 patients [0.2%] had life-threatening hemorrhage from sacral or pudendal vascular injury and the overall transfusion rate was 2% [Sze 1997]. Buttock pain occurred in 3% of subjects, the vast majority of which resolved by 6 weeks postoperatively [Sze 1997].

2. UTEROSACRAL LIGAMENT SUSPENSION (USLS)

The USLS was first described by Miller [Miller 1927] in 1927 and later popularised by Shull in the late 1990s. The USLS suspends the vaginal apex to the proximal remnants of the uterosacral ligaments using an intraperitoneal surgical approach. This procedure restores the vagina to its normal axis, avoiding the retroflexion associated with SSLS. The current evidence supporting the use of USLS is limited primarily to uncontrolled retrospective case-series and evaluation of these data confirm a mean objective success rate of 85% [range 48-96%] and mean reoperation rate for prolapse of 5.8% [range 0-12%] (**Table 12**). A meta-analysis performed by Margulies et al found

Table 11. Sacrospinous ligament suspension (SSLS) procedures.

First Author (year)	Study Design	N	Mean Follow-up Mo. (range)	Definition of anatomic success*	Anatomic success –all segments	Anatomic recurrence by segment	Reoperation for prolapse
Morley (1988) (Morley 1988)	retrospective	92	51.6 (1-132)	Not defined	90%	Apex 4% Anterior 6%	4 (5%)
Imparato (1992) (Imparato 1992) [53]	retrospective	155	Not stated	Not defined	90.3%	Not reported	None reported
Shull (1992) (Shull 1992)	retrospective	81	(24 – 60)	Grade 0-1	82%	Apex 4% Anterior 12% Posterior 1%	4 (5%)
Pasley (1995) (Pasley 1995)	retrospective	144	35 (6-83)	Asymptom-atic and above hymen	85.4%	Apex 5.6% Anterior 7.6% Posterior 1.4%	2 (1.3%)
Benson (1996)(Benson 1996)	RCT SSLS vs ASC	42	30 (12-66)	Vaginal walls above hymen or apical descent less than #	67%	Apex 12% Anterior 28.5% Posterior 2.3%	14 (37%)
Paraiso (1996) (Paraiso 1996)	retrospective	243	76. (1-190)	Grade 0 or asymptomatic grade 1	79.7% at 5 years	Apex 4.9% Anterior 15.9% Posterior 4.9%	11 (4.5%)
Penalver (1998) (Penalver 1998)	retrospective	160	40 (18-78)	'any symptomatic descent'	85%	Apex 6% Anterior 6% Posterior 2.5%	11 (6.8%)
Colombo (1998) (Colombo 1998)	retrospective	62	83 (48-108)	Grade 0-1	74%	Apex 8% Anterior 14% Posterior 3%	0 (0%)
Meschia (1999) (Meschia 1999)	retrospective	91	43 (12-86)	Grade 0-1	85%	Apex 4% Anterior 13% Posterior 9%	None reported
Sze (1997) (Sze 1999)	retrospective	75	24 (3-72)	above hymen	71%	Anterior 21% Other 8%	7 (12.9%)
Lantzsch (2001)(Lantzsch 2001)	retrospective	123	58 (6 – 108)	Not defined	87%	Apex 3.5% Anterior 8% Posterior 1.6%	2 (1.6%)
Lovatsis (2001) (Lovatsis 2002)	retrospective	293	(12-30)	At or beyond the introitus	97%	Apex 3% Anterior NR Posterior NR	3%
Cruikshank (2003) (Cruikshank 2003)	Prospective cohort	695	43 (6 – 60)	Reoperation for recurrence	89.4%	Apex – 5.1%	105 (15%)
Niemenen (2003)(Niemine n 2003)	Retrospective	138	24	POPQ Stage 2 or greater	78.7%	Apex 4.9% Anterior 11.5% Posterior NR	NR
Maher (2004) (Maher 2004)	RCT SSLS vs. ASC	48	22 (6-58)	Grade 0-1	69%	Apex 19% Anterior 14% Posterior 7%	3 (6.3%)
Hefni (2006) (Hefni 2006)	Prospective	305	57 (24-84)	Vaginal vault at least 6 cm distal to hymen	96%	Apex 4% Anterior 13% Posterior 0%	NR
Toglia (2008) (Toglia 2008)	Retrospective	64	26.5 (1-72)	Apex above introitus and no reoperation	78%	Apex 9% Anterior 17% Posterior 0%	2 (3%)
Aigmueller (2008)	Prospective	55	84 (24-180)	Above the hymen	64%	Apex 7% Anterior 29% Posterior 5%	5 (9%)
Chou (2010) (Chou 2010)	Retrospective	76	36 (12-60)	Grade 0	91%	Apex 5.3% Anterior 3.7% Posterior NR	4 (5.3%)

** Prospective and Retrospective cohorts with n >50 published since 1985 and SSLS arms of 3 RCTs comparing SSLS to Abdominal sacrocolpopexy (ASC) ;**POP staging systems, if used, are indicated as 'grade' for Baden-walker(Baden 1972) or 'stage' for POPQ(Bump 1996); # optimal and satisfactory outcomes combined*

pooled rates of anatomic success [POPQ Stage 0-1] of 81.2% [95%CI 67.5-94.5%] for the anterior segment, 98.3% [95% CI 95.7 -100%] for the apical segment and 87.4% (95% CI, 67.5%-94.5%) for the posterior segment [Margulies 2010]. Postoperative prolapse symptoms were reported in 5 of 11 studies in this review and were relieved in 82-100% of patients. These promising results are balanced by ureteral kinking/injury rate of 1%-11% with this procedure [Margulies 2010]. A review of 700 consecutive vaginal prolapse surgeries found intraoperative ureteral kinking/injury of 5.9% directly attributable to USLS. However, 87% were identified at cystoscopy before the completion of the index surgery and relieved by removing suspension sutures intraoperatively with no long-term consequence to the patient [Gustilo-Ashby 2006]. Only 3 of 355 ULS [0.9%] performed in this series required additional procedures to relieve or correct ureteral obstruction or injury. Margulies et al identified 10 studies including a total of 820 women that reported on perioperative complications of ULS [Margulies 2010]. The ureteral reimplantation rate in this series was only 0.6%. Blood transfusions were reported in 1.3%, cystotomy in 0.1%, and bowel injury in 0.2%. To date, no clinical trials comparing the ULS to sacrocolpopexy or to SSLS have been published. The Pelvic Floor Disorders Network has an ongoing RCT comparing USLS to SSLS that includes 440 subjects who will be followed for 2 years; results from this trial are expected in 2013. [Barber 2009]

While the USLS is traditionally performed using a intraperitoneal approach, Dwyer and Fatton have described an extraperitoneal variant of the USLS. [Dwyer 2008; Fatton 2009] In their series of 123 consecutive women undergoing an extraperitoneal ULS,

Table 12. Transvaginal uterosacral vault suspension procedures.

First Author	Year	No. of Pts.	Mean Follow-up Months (range)	Definition of anatomic	Anatomic success –all segments	Anatomic recurrence by segment	peration for prolapse
Jenkins(Jenkins 1997)	1997	50	(6-48)	Not defined	48/50 96%	Anterior 4%	MD
Comiter(Comiter 1999)	1999	100	17 (6.5-35)	Grade 0-1	96/100 96%	Apex 4%	4/100 (4%)
Barber(Barber 2000)	2000	46	15.5 (3.5-40)	Stage 0/1 or Stage 2 without symptoms	41/46 90%	Apex 5% Anterior 5% Posterior 5%	3/46 (6.5%)
Shull(Shull 2000)	2000	289	Not stated	Grade 0-1	275/289 95%	Apex 1% Anterior 3.5% Posterior 1.4%	MD
Karram(Karram 2001)	2001	168	21.6 (6 -36)	Grade 0-1	148/168 88%	Apex 1% Anterior or posterior 11%	11/168(5.5%)
Amundsen(Amundsen 2003)	2003	33	28 (6-43)	Stage 0 or 1	27/33 82%	Apex 6% Posterior 12%	MD
Silva(Silva 2006)	2006	72	61.2 (42-90)	Symptomatic Stage 2 or greater	61/72 85%	Apex 3% Anterior 7% Posterior 14%	2/72 (3%)
Antovska (Antovska 2006)	2006	32	25 (9-42)	Stage 0 or 1	MD	Apex 0% Anterior	MD
Wheeler(Wheeler 2006)	2007	35	24 (0-46)	Stage 0 apical prolapse	28/35 80%	Apex 20%	0/0 (0%)
De Boer(de Boer 2009)#	2009	48	12	Stage 0-1	23/48 48%	Apex 4.2% Anterior 47.9% Posterior 14.6%	MD
Doumaouchtsis(Doumouchtsis 2011)	2011	42	60	Grade 0 of vaginal vault	36/84 84.6%	Apex 15.4%	5/42 (11.9%)
Total					**783/925 85% 95%CI (83-87%)**		**25/428 (5.8%) 95%CI (3.6-7.0)**

*Includes retrospective and prospective cohorts of intraperitoneal transvaginal ULS. *POP staging systems, if used, are indicated as 'grade' for Baden-walker(Baden 1972) or 'stage' for POPQ. #Includes only subjects who underwent ULS;*

93 also received anterior and/or posterior synthetic mesh. The overall anatomic success (POPQ stage 0 – 1] at a mean follow-up of 2 years [range 6 mo – 5 years] was 85.5% with apical success of 95.4%. [Fatton 2009] The reoperation rate for recurrent prolapse was 7%. Ureteral injury occurred in only 1.7%, however the blood transfusion rate was 4.9% and the rate of mesh exposure was 19.3%.

Abdominal and laparoscopic USLS techniques have also been described. Lowenstein et al reported a retrospective review of 107 women who underwent prolapse surgery that included an abdominal USLS [Lowenstein 2009]. In the 75 patients who completed 1 year follow-up, 12% reported recurrent or persistent prolapse symptoms and 7% had an anatomic failure [POPQ Stage 2 or greater]. Complications were relatively few however erosion of the apical sutures [expanded PTFT, Gore-Tex] occurred in 9% at an average time of 56 months [range 3-75 mo] [Lowenstein 2009]. Rardin et al reported a retrospective comparison of 96 patients undergoing vaginal USLS to 22 undergoing a laparoscopic ULS procedure and found no significant differences perioperative morbidity or anatomic or subjective outcomes [Rardin 2009].

3. MAYO/MCCALL'S CULDOPLASTY

Like the USLS, the Mayo/McCall's culdoplasty uses the proximal uterosacral ligaments to suspend the vaginal apex. The major difference is that with the Mayo/McCall procedure the uterosacral ligaments are plicated in the mid-line to obliterate the posterior cul-de-sac. While commonly performed, data describing the outcomes for this procedure are limited. (**Table 13**) Colombo and Milani retrospectively compared the outcomes of a modified-McCall's culdoplasty to the SSLS [n = 62 in each group] [Colombo 1998]. Recurrence after the McCall's culdoplasty (Baden-Walker Grade >2] was 15% 4 to 9 years after surgery and not significantly different from the SSLS group. Recurrent anterior vaginal prolapse occurred less frequently in the McCall's group than the SSLS group (6% vs. 21%, p = .04; OR 4.1 [95% CI 1.3 to 14.2] [Colombo 1998]. A large retrospective series of 693 women from the Mayo clinic described an 82% satisfaction rate on subjective follow-up with few complications [Webb 1998]. The rate of subsequent prolapse repair in this population was 5.2%. A retrospective case series of 411 women undergoing Mayo culdoplasty found that a more dorsal "deep" placement of sutures through the uterosacral ligaments reduced the incidence of ureteral obstruction compared to other published series [Aronson 2005].

4. LEVATOR MYORRHAPHY

Francis and Jeffcoate described their retrospective series using levator myorrhaphy in which a wide midline plication of the levator ani muscles is performed to which the vaginal cuff is fixed in 1961.[Frances 1961] A large sponge pack in the rectum is used to avoid overplication and bowel dysfunction. Five of 35 women responding to the questionnaire had transient ureteral complications, one requiring re-operation. Seventeen women were quite satisfied, while six were dissatisfied. Natale et al compared the high levator myorrhaphy to the USLS in a randomised clinical trial of 229 women with Stage 2-4 prolapse. [Natale 2010] All women underwent a hysterectomy and all received placement of polypropylene mesh in the anterior vaginal segment. Anatomic success was not significantly different between groups. The mean total vaginal length was significantly shorter after levator myorrhaphy [7.9 cm vs. 8.9 cm, p = .04]. Urinary, bowel and sexual function did not differ between groups postoperatively. Intraoperative ureteral obstruction was less common in the levator myorrhaphy group [0% vs. 7.9%]; however all cases of ureteral obstruction in the ULS group were corrected intraoperatively with suture removal/replacement with no additional interventions required. [Natale 2010] Other complications including mesh erosion were similar between groups.

5. ILIOCOCCYGEUS FASCIA FIXATION

There are no randomised trials that support the use of this procedure. Several case series have provided

Table 13. Mayo/Mcall's culdoplasty

Author	Year	No. of Pts.	Mean Follow-up (range)	Postoperative ≥ grade/stage 2 –all segments	Postoperative ≥ grade/stage 2 by segment	Rerreopertion for prolapse
Webb(Webb 1998)	1998	693	(6 – 144)	NR	NR	5.2%
Colombo(Colombo 1998)*	1998	62	84 (48-108)	15%	Apex – 5% Anterior – 7% Posterior – 14%	0%
Montella(Montella 2005)	2005	51	12	NR	Apex – 3% Anterior – NR Posterior – 7%	7.8%
Koyama(Koyama 2005)**	2005	21	26	NR	Apex – 5% Anterior – 19% Posterior 5%	14%

** excludes SSLS group; ** excludes Inmon group*

some information. Shull reported that apical support was optimal in 39/42 [83%] of patients, but eight others had apical or other defects. [Shull 1993] Meeks and colleagues reported a 96% objective cure in 110 women followed up to 13 years.[Meeks 1994] In a retrospective case-control study, Maher and colleagues reported similar subjective [91% v 94%] and objective [53% vs. 67%] cure rates with iliococcygeus fixation [n=50] compared to sacrospinous fixation [n=78].[Maher 2001].

6. TRANSVAGINAL MESH APICAL PROLAPSE

Two randomised control trials are available that evaluated transvaginal polypropylene meshes in apical prolapse. Sokol et al reported a multicentre double blinded RCT comparing uterosacral colpopexy and native tissue repair [n=33] and monofilament polypropylene mesh kit [Prolift n=32] for stage 2 or greater uterovaginal prolapse or vaginal prolapse [Sokol 2011].

At one year the conventional surgery group had no subsequent surgical interventions as compared to 15.6% in the mesh group [p=0.017] including 3 for prolapse surgery (2x sacral colpopexy and 1 iliococcygeous fixation) and 2 interventions for mesh exposure. The objective failure rate (any stage 2 or greater prolapse) was 70% in the conventional surgery group versus 63% in the mesh group [P>0.05]. The subjective failure rate was also similar in both groups, 9.1% in native tissue repairs versus 3.8% in the mesh group. One patient was transfused and 2 inadvertent cystotomies occurred in the mesh group with no perioperative complications reported in the native tissue group. No differences were seen between the groups utilising a wide variety of validated outcome tools. Unfortunately, due to reaching an ethics committee imposed stopping criterion of 15.6% mesh exposure rate the study did not recruit the appropriate sample size and is underpowered to detect a significant difference between the groups if they exist.

Maher et al recently reported results from a randomised trial comparing LSC [n=53] to a total vaginal mesh kit [TVM] [Prolift, Ethicon Women's Health and Urology] [n=55] [Maher 2011]. LSC was associated with longer operating time (mean difference +52 min [95% CI 41.5-62.6], decreased hospital stay [mean difference -0.5 days [95% CI -.93 to -.10] and quicker return to normal activities (mean difference -5.3 days [95% CI -8.4 to -2.3]. Two years after surgery, objective success [Overall POPQ Stage 0 or 1] was seen in 77% of the LSC group compared with only 43% of the TVM group, p <.001] [Maher 2011]. Also, reoperations were significantly higher in the TVM group [22%] than in the group that received LSC [5%, p =.006].

As seen in **Table 14** the success rate of transvaginal meshes for apical prolapse in level 3 evidence

Table 14. Mesh Kits used for apical repairs

Author	Year	Type	No.	Follow up weeks	Success rate	Complications
Abdel Fattah	2008	Apogee AMS	38	12	95%(36/38)	Blood loss>400mls1, erosion 4,
						Dyspareunia 1, rectal injury 1
Gaurder-Burmester	2007	Apogee AMS	48	52	100%	
Moore	2012	Anterior Elevate AMS	60	57	92%	No extrusions
Fatton	2007	Prolift, Ethicon	88	25	93%	2 haematoma
Belot F	2005	Prolift Ethicon	277	Not stated	Not stated	Erosion 34/277
Abdel Fattah	2008	Prolift ethicon	143	12	94%	1rectal injury, bladder injury
		Johnson & Johnson,				16 vag ersion, 1 bladder
Van Raalte	2009	Prolift, total, anterior post	97	72	87%	No mesh extrusions 6 reoperations prolapse
Milani	2009	Total vaginal mesh Prolift	46	52	91% (41/45)	15% mesh exposure 2 blood loss>500mls
McDermott	2011	Total vaginal mesh Prolift hysteropexy 24 Colpopexy 65	89	26 - 52	96%	10% mesh exposure 5% complications
Maher (RCT)	2011	Total vaginal mesh Prolift Ethicon	55	104	43%	9% mesh exposure 22% total reoperation
Biertho	2007	PIVS tyco	34	12	91%	1erosion 1 hemorrhage
Foote	2007	PIVS tyco	52	20	83%	Erosion 11/52
Matox	2006	PIVS	21	7	37%	1 proctotomy 1 hemotoma
Vardy	2006	PIVS	98	3	99%	2 erosion
Neuman [194]	2007	PIVS	140	120	99%	12 erosions
de Tayrac[238]	2007	PIVS	21	42	95%	2 hemotoma
Lee	2010	PIVS	32	52	100%	1 transfusion
Amrute [261]	2007	Polypropelene H shaped	76	123	95%	2 erosion, 2 dyspareunia

is significantly higher and ranges from 87-100% for monofilament polypropylene meshes with mesh erosion rates varying from 0-15%.

7. SACRAL COLPOPEXY

Since its introduction by Lane in 1962 [Lane 1962], sacrocolpopexy has proven to be an effective and durable technique for correcting apical prolapse. In 2010, approximately 34,000 sacrocolpopexies were performed in the U.S. representing 11% of all prolapse surgeries performed during that time period. Traditionally, sacrocolpopexy has been performed via a laparotomy (i.e. abdominal sacral colpopexy) but the use of laparoscopic and robotic approaches is increasing.

a) Abdominal Sacral Colpopexy (ASC)

Observational studies and clinical trials suggest that ASC is a highly effective procedure for apical prolapse. The success rate of ASC, when defined as lack of apical prolapse, ranges from 78-100% (**Table 15**). When success is defined as no recurrent prolapse in any segment the published success rates are 56% - 100%. A systematic review of ASC performed by Nygaard et al reported a median reoperation rate for recurrent prolapse of 4.4% [range 0 -18.2%] and for postoperative stress incontinence of 4.9% [range 1.2% to 30.9%] [Nygaard 2004]. Clinical trials demonstrate significant improvements in prolapse symptoms, urinary function and quality of life after ASC [Maher 2004; Maher 2004; Brubaker 2008]. There is level 1 evidence that ASC has superior anatomic outcomes when compared to SSLS but this is balanced by longer operating time, longer recovery and higher cost [Maher 2010]. There are no randomised trials comparing ASC to ULS or to transvaginal mesh procedures. Given the prolonged recovery and unique complications associated with laparotomy, many surgeons reserve sacrocolpopexy for patients with apical prolapse thought to be of high risk of failure from a vaginal approach, often considering such factors as age, comorbidities, history of previous prolapse surgery, and vaginal length. [Toozs-Hobson 1998; Shull 1999; Maher 2004; Brubaker 2005; Weber 2005] Unfortunately, there is little published data to allow an evidence-based decision about which patient with POP will be best served by an ASC relative to other techniques.

Some surgeons have attempted to decrease mesh complications of ASC by using biological materials instead of synthetic mesh. However, the current evidence suggests that biologic materials whether allograft or xenograft have inferior anatomic outcomes to synthetic mesh, particularly polypropylene, without decreased graft-related complications. Level 1 evidence supports the superiority of polypropylene mesh to fascia lata for objective anatomic support following ASC [Culligan 2005; Tate 2010]. A randomised trial of 106 women undergoing ASC compared polypropylene mesh to cadaveric fascia lata and found superior anatomic outcomes in those who received polypropylene at one year [success 91% vs. 68%, p = .007] and five years after surgery [93% vs. 62%, p =.02] [Culligan 2005; Tate 2010]. There were no differences in graft related complications overall between the two groups. Several retrospective case series support these data [FitzGerald 1999, Flynn 2005, Gregory 2005]. Similarly, Level 3 evidence suggests that use of xenografts such as porcine dermis and small intestinal submucosa also have inferior anatomic success rates compared with polypropylene mesh with similar rates of graft-related complications [Quiroz 2008; Deprest 2009; Claerhout 2010].

Beyond mesh erosion, reported complications of ASC are generally consistent with other major open pelvic surgeries. The systematic review by Nygaard et al reported that wound complications occurred in 4.6% [range 0.4% to 19.8%], hemorrhage or transfusion in 4.4% [.2% to 16.9%], cystotomy in 3.1% [0.4% to 15.8%], ureteral injury in 1.0% [0.8% to 1.9%] and bowel injury in 1.6% [0.4% to 2.5%] [Nygaard 2004]. One in 20 women in the CARE trial experienced significant gastrointestinal morbidity after sacrocolpopexy. Of 322 women in the study, 19 had symptoms of possible ileus or small bowel obstruction; of these, 4 had reoperation for small bowel obstruction, 11 were readmitted for medical management, and 4 had a prolonged initial hospitalisation for gastrointestinal symptoms [Whitehead 2007].

b) Abdominal sacral colpopexy (ASC) versus sacrospinous ligament suspension (SSLS)

To date, there are three RCTs that directly compare ASC to SSLS.[Benson 1996; Lo 1998; Maher 2004] The Cochrane review on the surgical management of POP by Maher et al summarises these studies and concludes that these trials provide level 1 evidence that there were no statistically significant differences in objective failure at any site [any pelvic organ prolapse RR 0.77, 95% CI 0.39 to 1.53], subjective failure [RR 0.53, 95%CI 0.25 to 1.09], reoperation for POP [RR 1.46, 95% CI 0.19 to 1.11] or patient satisfaction [RR 0.82, 95% CI 0.32 to 2.06] [Maher 2010]. However, ASC was superior to SSLS for the following outcomes: Prolapse < Stage 2 [RR 0.29, 95% CI 0.09 to 0.97], recurrent vault prolapse [RR 0.23, 95% CI 0.07 to 0.77] post-operative stress urinary incontinence [RR 0.55, 95% CI 0.32 to 0.95] and less post-operative dyspareunia RR 0.39, 95% CI 0.18 to 0.86]. In contrast, ASC was associated with a longer operating time (Weighted Mean Difference [WMD] 21 minutes, 95% CI 12 to 30), longer time to recover [WMD 8.3 days, 95% CI 3.9 to 12.7] and was more expensive [WMD US $1334, 95% CI 1027 to 1641) than SSLS [Maher 2010].

c) Laparoscopic Sacral Colpopexy (LSC)

The laparoscopic approach of sacral colpopexy has been adopted by many surgeons over the last decade as an alternative to ASC with the hopes of

Table 15. Abdominal Sacral Colpopexy outcomes*

Author	Year	Number of patients, (number lost to follow-up, if known)	Follow –up (months)	Success rate (%)	Criteria for success#	Comments
Addison(Addison 1985)	1985	56 (2)	39	96	Good vaginal vault suspension in a normal axis	Fascia lata was graft material used for patient with early recurrence 1 patient unimproved as a presacral hemorrhage prevented successful completion of the procedure
Baker(Baker 1990)	1990	59 (6)	6	100	No complaint of protrusion from the vagin	51/59 patients had postoperative records available, at which time all patients had a well- supported vagina
Snyder(Snyder 1991)	1991	147 (15)	43	93 (108/116)	Lack of major long- term postoperative complications, restoration of functional vagina in the proper axis, and no recurrence of presenting symptoms with at least 6 months of follow-up	Graft attached to the entire length of the vagina in the rectovaginal septum
Imparato (Imparato 1992)	1992	71 (8)	NS	78	Excellent, well- suspended vault on exam	50 had direct attachment of the vaginal apex to the anterior sacrum
				16	Good vault suspension, but asymptomatic vaginal "relaxation"	
Timmons(Timmons 1992)	1992	163	33	99	Good vaginal vault support	The range of success is due to 4 different techniques which were compared
van Lindert(van Lindert 1993)]	1993	61	32	97	No recurrent vaginal prolapse	8 patients had preservation of the uterus
Grunberge(Grunberger 1994)[1]	1994	62 (14)	75.6	94	No moderate vaginal vault prolapse on exam	42 patients had direct attachment of the vagina to the sacral promontory 12 had permanent "suture bridges" 8 had lyodura loops
Lecuru(Lecuru 1994)**	1994	203	32.5	86.7-100	Anatomically good results	
				53.3-80.5	Functionally good results	
Brubaker(Brubaker 1995)	1995	65 (0)	3	71	No anterior or apical prolapse	63/65 patients had abdominal anterior compartment repair at the time of the sacrocolpopexy
de Vries(de Vries 1995)	1995	101 (29)	48	32	Fully cured (patient satisfaction based upon questionnaire)	Questionnaires sent to patients to evaluate pain, prolapse-related complaints and functional disorders. Patients indicated symptoms before surgery, >1 year after surgery, and >1 year after surgery
				39	Considerable improvement	
				29	No improvement	
Benson(Benson 1996)	1996	40	60	58 (another 26% of patients had"satisfactor y" outcomes)	Patient asymptomatic, vaginal apex supported above the levator plate, no protrusion beyond the hymen	All patients had sacrocolpopexy and paravaginal repair. Results are from a RCT comparing sacrocolpopexy to sacrospinous suspension.
Hardiman(Hardiman 1996)	1996	80	47	99	No recurrent vault prolapse	
Sullivan(Sullivan 2001)	2001	236 (31)	64	100	No recurrence of vaginal or rectal prolapse	Total pelvic mesh repair involved attachment mesh strip between the perineal body and the sacrum, and then attaching two additional strips laterally to the pubis to support the vagina and bladder
				34%	Very satisfied	
				38%	Satisfied	
Occelli(Occelli 1999)]**	1999	271 (54)	66	97.7	Cured for prolapse	
Patsner(Patsner 1999)	1999	175 (0)	≥ 12	97	No "mesh failures"	
Sze (Sze 1999)	1999	56 (9)	23	81	No recurrent prolapse to or beyond the hymen	All 9 patients with recurrent prolapse were Symptomatic
Lo(Lo 1998)	1998	52 (not clear)	25	94	No prolapse > Stage II	Results are from a RCT comparing sacrocolpopexy to sacrospinous ligament suspension.
Collopy(Collopy 2002)	2002	89 (0)	56.7	100	No recurrence of rectal or vaginal vault prolapse	All had concomitant culdoplasty
Culligan(Culligan 2002)	2002	245	61.2	85	Any POP-Q point ≥ 2	No apical failures observed
Lefranc(Lefranc 2002)	2002	85 (0)	126 (median)	90.6	No relapse of any prolapse	All patients without preoperative SUI had a prophylactic Burch procedure done
Lindeque(Lindeque 2002)	2002	262 (0)	≥ 16	99	No vaginal vault prolapse	1/3 failures due to graft detachment from vagina
Medina(Medina 2002)	2002	97 (1)	19	90	< Grade I prolapse	Etiology of 1 failure was graft detachment from the vagina (etiology of other 4 unknown)
Brizzolara(Brizzolara 2003)	2003	124	36		No recurrent vault prolapse	
Podratz(Podratz 1995)	1995	50(6)			Asymptomatic (including no incontinence) and durable repair by exam	
Hilger(Hilger 2003)	2003	69(31)			Subsequent POP operation or a positive response to question 5 on the PFDI***	
Maher(Maher 2004)	2004	47 (1)			Objective: No POP beyond halfway point Subjective: No symptoms of POP	Results are from a RCT comparing sacrocolpopexy to sacrospinous ligament suspension.
Higgs (Higgs 2005)	2005	148			No recurrent vault prolapse	24% required recurrent SUI surgery
					< Grade 1 prolapse	
					No prolapse symptoms	
Brubaker(Brubaker 2008)	2008	322 (302)			< Stage 2 prolape	CARE Trial 2 year follow-up; Reoperations for prolapse occurred in 6 (2%)
				98	≤ Stage 2 prolapse	
					POPQ point C within 2 cm of TVL	
Jeon(Jeon 2009)	2009	57			< Stage 2 prolapse	Major complication requring reoperation or intensive care developed in 12 (21%)
Huebner(Huebner 2009)	2009	78 (53)	NS		< Stage 2 prolapse	
Tate(Tate 2010)	2010	100 (58)			< Stage 2 prolapse	5 year follow-up of RCT comparing polypropylene to cadavaric fascia. Polypropylene demonstated supperior anatomic results (93% vs 62%, p =.02) but no difference in symptomatic outcomes
					Symptoms of prolapse or bulging	

**Prospective and Retrospective cohorts with n > 50 published since 1985, ASC arms of 3 RCTs comparing ASC to sacrospinous ligament suspension. #POP staging systems, if used, are indicated as 'grade' for Baden-walker{ or 'stage' for POPQ*

NS = not stated;SUI = stress urinary incontinence; RPU = retropubic urethropexy; RCT=randomised clinical trial

***Only abstract reviewed (paper not in English)*

****Question 5 on the Pelvic Floor Distress Inventory – "Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?"*

reproducing the high success rate of the ASC while decreasing the morbidity and delayed recovery associated with laparotomy. Multiple prospective and retrospective case series demonstrate good short to mid-term success rates with mean objective success rate of 90.5% [range 60 -100%, subjective success rates of 79-98%[Higgs 2005; Rivoire 2007; Sarlos 2008] and mean reoperation rate of 5.9% (**Table 16**). Recently, several prospective studies have been published that demonstrate significant improvements in pelvic symptoms and quality of life after LSC [Sergent ; Maher 2011; Paraiso 2011]. To date, no randomised trials have compared LSC to ASC, however three retrospective comparisons have been published [Paraiso 2005; Hsiao 2007; Klauschie 2009]. While results vary somewhat between studies, in general, LSC is associated with shorter hospital stay, less blood loss with conflicting data on operating time. Objective outcomes appear to be similar between the groups. Well designed high quality clinical trials are necessary to establish independently the effectiveness and safety of the LSC relative to ASC.

There is Level 1 evidence that LSC provides superior outcomes to total vaginal mesh procedure for women with symptomatic Stage 2-4 vaginal vault prolapse as described above. There are currently no comparative studies, randomised or not, evaluating the relative safety and efficacy of LSC and native tissue [non-mesh] vaginal POP repair.

A recent retrospective study assessed the complications rates in 402 LSC cases.[Stepanian 2008] This study compared patients who received concurrent laparoscopically-assisted vaginal hysterectomy with those that had previous hysterectomy. They showed no differences in intra- or perioperative complications and similar rates of mesh erosion between the two groups.[Stepanian 2008] Overall the complication rates for this cohort were 0.75% for hematoma, 2.2% for ileus or small bowel obstruction, 1.5% for bladder injury, 0.75% for bowel injury and 0.25% ureteric injury. At 1 year, the overall mesh erosion rate was 1.2%. In contrast, Tan-Kim et al reported on a retrospective series of 188 minimally invasive sacrocolpopexy and found a significantly higher mesh exposure rate in those who received concurrent total vaginal hysterectomy [TVH] [23%] compared with those who were post-hysterectomy (5%) or received a supracervical hysterectomy [5%].[Tan-Kim 2011] TVH was found to be an in independent risk factor for mesh erosion on multivariable regression analysis in this study [OR 5.67; 95% CI 2.88-17.10].

Table 16. Describes outcomes for laparoscopic sacral colpopexy trials reporting greater 12 months review.

Authors, year	*n (mesh)*	*Success Rate*	*f.u. months*	*Total reoperation rate*	*Reoperation rate for recurrence*	*Reoperation rate for complication*	*Vaginal mesh exposure*	*Spondylodiscitis*	*de novo dyspareunia*
Maher, 2011 [11]	53 (PP)	41/53	24	3/53	0/53	1/53	1/53	0/53	MD
Price, 2011 [25]	84(PP)	84/84	24	7/84	4/84	3/84	5/84	0/84	MD
Sergent, 2011 [26]	124 (PE)	103/116	34	10/124	MD	3/124	4/116	1/124	1/85
Paraiso 2011	29	21/23	12	0/29	0/29	0/29	0/29	0/29	MD
Sabbagh, 2010 [27]	186 (PPS)	122/132	60	8/186	2/186	6/186	5/132	0/132	9/170
Akladios 2010	48(PP)	46/48	16	8/48	0/48	2/48	1/48	0/48	MD
Granese, 2009 [28]	138 (PP)	131/138	43	1/138	0/138	0/138	0/138	0/138	2/138
Sarlos, 2008 [29]	101 (PP)	98/101	12	4/101	1/101	1/101	1/101	0/101	1/101
Deprest, 2009 [30]	39 (PD) 65 (PP)	20/39 43/65	32 (PD) 33 (PP)	7/39 (PD) 7/65 (PP)	6/39 (DP) 0/65 (PP)	1/39 (PD) 7/65 (PP)	2/39 7/65	0/39 0/65	MD
Claerhout, 2009 [46]	132(PP)	127/132	12	9/132	0/132	9/132	6/132	0/132	10/53
North 2009	22(PP)	22/22	27.5	1/22	0/22	1/22	1/22	0/22	0/12
Stepanian, 2008 [31]	402 (PP)	380/402	12	14/402	0/402	11/402	5/402	0/402	4/402
Agarwala, 2007 [34]	74 (PP)	74/74	24	2/74	0/74	2/74	1/74	MD	1/74
Rivoire, 2007 [35]	114 (PE) 12 (PP) 5 (PPM)	118/133	33	14/133	7/133	7/114 (PE) 0/17 (PP) 0/5 (PPM)	7/133	1/133	0/133
Paraiso, 2005 [36]	56 (PP)	MD	13	3/56	1/56	2/56	2/56	0/56	MD
Rozet, 2005 [37]	363 (PE)	348/363	14	13/363	7/363	6/363	3/363	1/363	MD
Ross, 2005 [39]	51(PP)	48/53	60	10/51	3/51	4/51	4/51	0/51	4/51
Higgs 2005	103 (PP)	39/66	60	15/103	11/103	4/103	6/103	0/103	MD
Gadonneix, 2004 [40]	46 (PE)	38/46	24	0/46	0/46	0/46	o/46	0/46	MD
Antiphon, 2004 [41]	108 (MD)	75/100	16	10/108	5/108	0/108	0/108	1/108	MD
Cosson, 2002 [42]	83 (PE)	78/83	11	2/83	1/83	1/83	1/83	0/83	MD
Total-	**-**	**2056/2271 (90.5%)**	**-**	**132/2337 (5.9%)**	**37/2192 (1.75%)**	**67/2340 (2.86%)**	**56/2275 (2.46%)**	**4/2179(0.18%)**	**33/1219 (2.65%)**

95% CI for 90.5% (89.3-91.7), 5.9% (4.9-6.9), 1.75% (1.20-2.30), 2.86% (2.18-3.54), 2.46% (1.82-3.10), 0.18% (0-0.36) and 2.65% (1.75-3.55)

Abreviations : PD, porcine dermis ; MD, missing data ; PE, polyester ; PP, monofilament polypropylene ; PPM, polypropylene multifilament ; PPPE, polypropylene + polyester ; PPS, monofilament polypropylene-dimethyl siloxane (silicone) ; PTFE, polytetrafluoroethylene.

Despite the clinical advantages of a laparoscopic approach, adoption of LSC has been relatively limited probably because of the steep learning curve associated with attaining laparoscopic suturing and knot tying skills that are required to attach the mesh to the vagina and sacrum. Claerhout et al evaluated their learning curve in the first 206 cases performed by a single surgeon.[Claerhout 2009] Operating times declined rapidly during the first 30 procedures in this series and reached steady state (175 minutes) after 90 cases. Using a cumulative sum [CUSUM] approach to evaluate operative time and failures (laparotomy, complication or anatomic failures) they found that adequate learning occurred after 60 cases.[Claerhout 2009] Complication rates remained unchanged throughout this series. Akladios et al found that there was a steady decrease in LSC operative time in a series of the first 48 cases performed but that a turning point was observed after 18-24 cases.[Akladios 2010] Complication rates were also low throughout this series.

d) Robotic Sacral Colpopexy(RSC)

Because of the relatively long learning curve required for LSC, many surgeons have turned to robotic-assisted surgery in order to offer patients a minimally invasive approach to sacrocolpopexy. Robotic surgical systems have been developed with the goal of facilitating technically difficult procedures by improving the surgeon's vision, dexterity and ergonomics. No data has been published on the learning curve for RSC however expert opinion suggests that the learning curve is shorter for RSC compared to the laparoscopic approach.

The currently available data for RSC are relatively limited and consist primarily of uncontrolled cases series, but meta-analysis suggests anatomic outcomes similar to that of ASC and LSC with objective success rates reported at 60-100% [mean 93%], subjective success of 91-94% and mean mesh erosion rate 5%.(**Table 17**) To date, there are only two

Table 17. Robotic Sacral Colpopexy (RSC)

Author	Year	Number of patients	Mean Follow –up months	Objective Success rate (%)	Subjective Success rate (%)	Criteria for Objective (O) and Subjective (S) success*	Mesh erosion (%)	Comments
Paraiso (Paraiso 2011)	2011	38 LSC	12	91	NR	O: Stage < 2	0	RCT comparing LSC to RSC. No significant differences noted in anatomic or quality of life outcomes between groups at 12 months
		40 RSC	12	35/40 (88)	NR		2/40(6)	
Shariati(Shariati 2008)	2008	77	7	76/77 (99)	94	O: Stage < 2 S: Satisfaction	3/77(4)	
Kramer(Kramer 2009)	2009	21	25.2	20/21 (95)	NR	O: No Apical failure	NR	12/20 subjects required repeat surgery for cystocele, rectocele or UI and 5 await additional surgery
Akl(Akl 2009)	2009	80	4.8	78/80 (96)	NR	O: No "recurrence" of POP	5/80 (6)	
Chan(Chan 2011)	2011	36	29	33/36 (91)	91	O: Stage < 2 S: Satisfied with procedure	0/36 (0)	
Geller (Geller 2011)	2011	28	14.8	17/28 (60)	NR	O: No POP to or beyond the hymen	2/28 (7)	Significant improvments in quality of life and sexual function seen using validated questionnaires.
Mereno (Moreno 2011)	2011	33	24.5	33/33 (100)	NR	O: No "recurrence" of POP	NR	
Total				**292/315 (93%)**			**12/261 (5%)**	

*Retrospective and Prospective cohorts RSC with n > 20 follow-up greater than 3 months. *POP staging systems, if used, are indicated as 'grade' for Baden-walker{ or 'stage' for POPQ*

Author	Year	Number of patients	Mean Follow –up months	Objective Success rate (%)	Subjective Success rate (%)	Criteria for Objective (O) and Subjective (S) success*	Mesh erosion (%)	Comments
Paraiso	2011	38 LSC	12	91	NR	O: Stage < 2	0	RCT comparing LSC to RSC. No significant differences noted in anatomic or quality of life outcomes between groups at 12 months
		40 RSC	12	35/40 (88)	NR		2/40(6)	
Shariati	2008	77	7	76/77 (99)	94	O: Stage < 2 S: Satisfaction	3/77(4)	
Kramer	2009	21	25.2	20/21 (95)	NR	O: No Apical failure	NR	12/20 subjects required repeat surgery for cystocele, rectocele or UI and 5 await additional surgery
Akl	2009	80	4.8	78/80 (96)	NR	O: No "recurrence" of POP	5/80 (6)	
Chan(Chan 2011)	2011	36	29	33/36 (91)	91	O: Stage < 2 S: Satisfied with procedure	0/36 (0)	
Geller(Geller 2011)	2011	28	14.8	17/28 (60)	NR	O: No POP to or beyond the hymen	2/28 (7)	Significant improvments in quality of life and sexual function seen using validated questionnaires.
Mereno(Moreno 2011)	2011	33	24.5	33/33 (100)	NR	O: No "recurrence" of POP	NR	
Total				**292/315 (93%)**			**12/261 (5%)**	

published studies that provide comparative data for the RSC. Geller et al retrospectively compared 73 patients who received RSC to 105 who received ASC [Geller 2008]. RSC was associated with less blood loss, longer operative time, shorter length of stay and a higher incidence of fever [4.1% vs. 0%] Anatomic outcomes 6 weeks after surgery were similar between groups [Geller 2008].

In the only randomised comparison of RSC to date, Paraiso et al recently published a clinical trial that provides level 1 evidence that RSC results in longer operating time and increased pain and cost compared with LSC.[Paraiso 2011] This single-centre, blinded randomised trial compared RSC [n = 40] to LSC [n=38] in women with stage 2-4 post-hysterectomy vaginal prolapse. Total operative time was chosen as the primary outcome for this study serving as a proxy measure for surgical efficiency. Total operative time was significantly longer in the robotic group compared with the laparoscopic group (+67-minute difference; 95% confidence interval [CI] 43-89; P<.001).[Paraiso 2011] Anesthesia time, total time in the operating room, total sacral colpopexy time, and total suturing time were all significantly longer in the robotic group. Participants in the robotic group also had significantly higher pain at rest and with activity during weeks 3 through 5 after surgery and required longer use of nonsteroidal anti-inflammatory drugs (median, 20 compared with 11 days, P<.005). The robotic group incurred greater cost than the laparoscopic group (mean difference +$1,936; 95% CI $417-$3,454; P=.008).[Paraiso 2011] Both groups demonstrated significant improvement in vaginal support and functional outcomes 1 year after surgery with no differences between groups. It is worth noting that the surgeons in this study had considerable experience with LSC.

A meta-analysis of observational studies on robotic gynaecological surgery, found that the currently available evidence shows that for most gynaecological procedures studied robotic surgery achieved a shorter hospital stay and less blood loss than open surgery.[Reza 2010] However, no clinically significant improvements were noted when robotic surgery is compared with conventional laparoscopic surgery in benign gynaecological procedures.[Reza 2010] The current evidence, while limited, suggests that these conclusions are also applicable for RSC (**Table 18**). RSC probably has a shorter learning curve than LSC and thus may be more generalisable however published evidence for this is currently lacking. In surgeons with advanced laparoscopic skills, RSC offers no clinical benefit when compared to LSC and results in longer operating times, greater cost and greater postoperative pain.

8. OBLITERATIVE PROCEDURES: LEFORT COLPOCLEISIS, TOTAL COLPOCLEISIS

Obliterative surgery, such as total colpocleisis (also called colpectomy/colpocleisis) or the Le-Fort partial colpocleisis, corrects POP by reducing the pelvic viscera back into the pelvis and closing off the vaginal canal either in part or whole.[FitzGerald 2006] Obliterative procedures are less commonly performed in the Europe, Asia, and Australia compared to the United States, and are usually reserved for women who are elderly, medically compromised, and no longer sexually active.[Jelovsek 2007] The purported advantages of obliterative surgery in this population are decreased operative time, decreased perioperative morbidity, and an extremely low prolapse recurrence risk. The obvious disadvantage is the elimination of the potential for vaginal intercourse. Preoperative counseling is essential when choos-

Table 18. Compares abdominal (ASC), laparoscopic (LSC) and robotic sacral clopopexy (RSC)

Author		*No. patients*	*Operating time mins*	*Blood loss mls*	*Inpatient Days*	*Objective Success rate (%)*	*Complications (%)*	*Mesh exposure (%)*
Paraiso 2005	ASC	61	218*	234	4	95	28	1.6
	LSC	56	269	172*	1.8*	89	36	3.6
	RSC							
Hsaio 2007	ASC	22	185	195	3.3	95	MD	9
	LSC	25	219	87	1.2*	100	MD	10
	RSC							
Klauschie 2008	ASC	41	168	139	2.6	78	21	2
	LSC	43	183	104*	1.5*	86	32	2
	RSC							
Geller 2008	ASC	105	225*	255	2.7	100	19	0
	LSC							
	RSC	73	328	103*	1.3*	100	15	0
Paraiso# 2011	ASC							
	LSC	38	199*		1.4	91	18*	0
	RSC	40	257		1.8	88	71	6

*MD, missing dara #Randomised trial, all other studies are retrospective comparisons; *indicates statistically significant result that is superior to the comparator*

ing between the obliterative and reconstructive options. A systematic review of colpocleisis published in 2006 noted colpocleisis appears to be nearly 100% effective for correcting pelvic organ prolapse, however until recently little was known about postoperative functional or quality of life outcomes.[FitzGerald 2006] In the last few years a number of reports evaluating symptom improvement and changes in quality of life after colpocleisis have been reported.[Barber 2007; Hullfish 2007; Fitzgerald 2008; Gutman 2009] Overall, these series have found high rates of patient satisfaction and significant functional improvement with low rates of regret for loss of sexual function.[Barber 2007; Hullfish 2007; Fitzgerald 2008] Barber et al reported results from a multicentre study of obliterative surgery using a prospective cohort design with a concurrent control group of age-matched women undergoing vaginal reconstructive surgery.[Barber 2007] Despite permanent alterations in sexual function, significant improvements in bladder, bowel and prolapse symptoms as well as body image were noted after surgery with no differences between those who received colpocleisis and those who underwent reconstructive surgery. Additionally, significant and clinically important improvements were noted in bodily pain, vitality, social functioning, role-emotional, and mental health summary scales of the SF-36.[Barber 2007] Similarly, a retrospective cohort of women over age 65 by Murphy et al comparing women who underwent colpocleisis [n=45] and similar group women who underwent reconstructive surgery with transvaginal mesh (Prolift, Ethicon Women's Health and Urology) found that improvements in condition-specific quality of life and postoperative patient satisfaction were comparable between the two treatment groups.[Murphy 2008].

The Pelvic Floor Disorders Network has reported on a large series of women undergoing colpocleisis [n=153] with one year follow-up.[Fitzgerald 2008]. All pelvic symptom scores and related bother significantly improved at 3 and 12 months, and 125 [95%] patients said they were either 'very satisfied' or 'satisfied' with the outcome of their surgery.[Fitzgerald 2008] Bothersome stress and urge incontinence were present before surgery in 54% and 41% of subjects respectively. Forty percent of subjects received a concurrent mid-urethral sling at the time of their colpocleisis and the rates of bothersome stress and urge incontinence one year after surgery was 14% and 15% respectively. Similarly, bothersome bowel symptoms were present in 77% of subjects at baseline. One year after surgery, the majority of bothersome bowel symptoms resolved, particularly obstructive and incontinence symptoms, and development of new bowel symptoms was uncommon [0-14%].[Gutman 2009].

While obliterative procedures are predominantly performed in elderly, frail women who often have multiple co-morbidities, the rate of serious adverse events after this procedure appears to be low. In general, major complications due to performance of surgery on the elderly (e.g. cardiac, pulmonary and cerebrovascular complications) occur at a rate of approximately 2%.[FitzGerald 2006] Major complications due to the surgery itself (e.g. pyelonephritis, blood transfusion) occur at a rate of approximately 4%.[FitzGerald 2006] A systematic review of published series of colpocleisis from 1966 to 2004 reported a surgical mortality rate of approximately 1 in 400 cases.[FitzGerald 2006] One complication that appears to be uniquely associated with obliterative surgery is development de novo rectal prolapse after surgery.[von Pechmann 2003; Collins 2007] Collins et al in a retrospective cohort of 916 women undergoing vaginal POP surgery at one institution and found that the incidence of postoperative full-thickness rectal prolapse in women who were > or = 65 years old who underwent obliterative surgery was 3 of 74 [4.1%; 95% CI, 1.4-11], with an estimated odds ratio of 22 [95% CI, 2.3-196; P < .002] compared with women who were > or = 65 years old who underwent reconstructive surgery.[Collins 2007].

Conclusions Apical prolapse

- Level 1 evidence suggest ASC has a higher success rate as compared to sacrospinous colpopexy with less SUI and post-operative dyspareunia. ASC had greater morbidity including operating time, inpatient stay, slower return to activities of daily living and higher cost. (**Grade A**)
- ASC has the lowest inpatient cost as compared to LSC and RSC. LSC has lower inpatient cost than RSC (**Grade B**)
- In single RCT's the RSC had longer operating time than both ASC and LSC (**Grade B**). In small trials objective outcomes appear similar although postoperative pain was greater in RSC.
- LSC as effective as ASC with reduced blood loss and admission time. (**Grade C**). The data relating to operating time are conlicting
- ASC performed with polypropylene mesh has superior outcomes to fascia lata (**Level I**) and porcine dermis and small intestine submucosa (**Level 3**) (**Grade B**)
- In a single RCT, LSC had a superior objective and subjective success rate and lower reoperation rate compared to polypropylene transvaginal mesh for vault prolapse (**Grade B**).
- Level three evidence suggest vaginal uterosacral ligament suspension, McCall culdoplasty, Iliococcygeus fixation and colpocleisis are relatively safe and effective interventions (**Grade C**)

VII. SURGERY FOR POSTERIOR VAGINAL WALL PROLAPSE

The prevalence of rectocele in women ranges from 12.9-18.6% and the average annual incidence is estimated to be 5.7 cases per 100 women years [Hendrix 2002; Handa 2004]. Approximately 225,000 operations are performed every year in the United States for pelvic organ prolapse and repair of posterior vaginal wall is performed in between 40-85% [Olsen 1997; Boyles 2003; Whiteside 2004].

Terms used to describe the supportive tissue utilised for posterior wall prolapse repair date back to a publication by Jeffcote in 1961 [Francis WJA 1961]. The concept of site-specific repair stems from observations by Richardson who felt that discrete defects in what he termed rectovaginal fascia should be addressed by a directed repair of the defect thus producing a more anatomical repair in his opinion [Richardson 1993]. In recent years there has been a clearer understanding of the anatomy of the posterior vaginal wall and its support however surgical studies in this area continue to utilise terms that are not anatomically based. The goal of this review will be to provide a brief overview regarding current understanding of the anatomy of the support of the posterior vaginal wall, discuss various anatomic defects that can clearly contribute to posterior vaginal wall prolapse, and finally update the previous ICI report by citing the various studies that have reported outcomes for the surgical correction of posterior vaginal wall prolapse.

1. ANATOMY OF THE POSTERIOR VAGINAL WALL

Historically pelvic organ support as it relates to the anterior and posterior vaginal wall compartments has been described in relation to supportive tissues termed endopelvic fascia. In the anterior segment this has been called pubocervicovesical fascia and in the posterior segment this has been called rectovaginal fascia. Histological studies have noted that what has previously been termed fascia is actually vaginal muscularis in both the anterior and posterior segments.[Farrell 2001] With respect to the rectovaginal fascia it is now well appreciated that there is no such layer between the posterior vaginal wall and the anterior wall of the rectum. At the level of the mid vagina histological assessment of the posterior vaginal wall from the lumen of the vagina to the lumen of the rectum notes the following layers; vaginal epithelium, the lamina propria of the vagina, fibro muscular wall of the vagina (smooth muscle cells, elastin, and type II collagen) adventitia, outer muscular wall of the rectum, inner muscular wall of the rectum, lamina propria of the rectum, and rectal mucosa.

Delancey et el performed cross-sections on nulliparous and multiparous cadavers and noted that the support of the posterior compartment was maintained by a complex interaction of connective tissue and levator ani muscle [DeLancey 1999]. He went on to note that the support of the posterior vaginal wall was best divided into 3 separate and distinct levels of support. Level III support being the most distal portion of the vagina is provided by the perineal membrane and the rectovaginal septum. This level of support has strong attachments to the levator ani complex and is thus less susceptible to pelvic pressure transmission that may cause prolapse. Level II or the mid vagina is supported by its attachments of the vaginal muscularis laterally to the fascia of the levator ani muscles. Level I support or the upper vagina is supported by the cardinal-uterosacral ligament complex.

This same group of investigator's recently discussed posterior vaginal wall anatomy in a review article and likened it to an open container. The front wall of the container would be formed by the posterior vaginal wall while the bottom of the container is made up of the perineal body and anal sphincters. The levator ani muscles form the lateral sides of the container and the levator plate where the muscles decussate behind the rectum to create the iliococcygeal raphe form the back wall of the container. The uppermost portion of the container would be that created by the attachment of the posterior vaginal wall to the uterosacral ligament which extend below the peritoneum All of these boundaries are subject to defects that can give rise to different structural failures.[Lewicky-Gaupp 2009]

2. ANATOMIC DEFECTS THAT MAY CONTRIBUTE TO PROLAPSE OF THE POSTERIOR VAGINAL WALL

The patient who presents with prolapse of the posterior vaginal wall either in isolation or in conjunction with prolapse of other segments of the pelvic floor could potentially have a posterior enterocele, a rectocele, or a sigmoidocele.[Fenner 1996] These 3 conditions can occur in isolation or in conjunction with each other and will commonly be accompanied by a perineal defect and or a widened genital hiatus. While it is beyond the scope of this article to discuss clinical and radiographic mechanisms that can be used to differentiate these various defects suffice it to say that they can all result in descent of the posterior vaginal wall in various degrees.

The published literature continues to classify posterior vaginal repairs into what has been termed a "traditional technique" which implies that the repair has been supplemented with a levator ani muscle plication in the midline or a "site specific technique" which implies that discreet defects in the rectovaginal fascia are identified and repaired and no levator plication is performed. To date we are unaware of any studies that have addressed how often a posterior enterocele and or sigmoidocele coexist with a rectocele and how the presence of these defects impacts on ultimate surgical out-

comes. Based on our current understanding of the anatomy of the posterior vaginal wall and perineum it is clear that the defect specific repairs involve plication of the fibromuscular layer of the posterior vaginal wall and based on the initial level of dissection this tissue may be found on the anterior wall of the rectum or may have to be mobilised off the vaginal epithelium to allow an appropriate tension free plication. In patients with advanced prolapse and a widened genital hiatus the only way to address the gaping vagina is to routinely perform a distal levatorplasty. In the authors opinion future surgical studies assessing outcomes of prolapse repair involving the posterior vaginal wall should take into consideration these points, and realise that these procedures are not mutually exclusive and a combination of the techniques, especially in cases of advanced prolapse is commonly required. Other type of repairs that have been reported include transanal repairs, transperineal mesh (biologic or synthetic) augmented repairs, and abdominal sacral colpopexy in which the mesh attachment is extended down to the distal portion of the posterior vaginal wall and or perineum. The authors have also observed that aggressive reattachment of the uppermost portion of the full thickness of the posterior vaginal wall (level III support) to the uterosacral ligament provides significant support to the posterior vaginal wall in patients with high rectoceles or rectoceles in conjuction with a posterior enterocele.

3. MIDLINE PLICATION OR TRADITIONAL POSTERIOR COLPORRAPHY

The mean reported anatomic success rates with this type of repair is 83% (range 76-96%) with mean post-operative dyspareunia rate of 18%(range 5-45%) and 26% using vaginal digitation to defecate. (**Table 19**)

4. SITE SPECIFIC DEFECT REPAIR

This technique is similar to traditional post repair in terms of dissection. The aim of the repair is for the surgeon to indentify and individually correct breaks in the rectovaginal septum. Tradition levatoroplasty is avoided. The mean anatomic success rate is 83% (range 56-100%) with 18% postoperatively needing vaginal digitation to defecate and 18% experiencing post-operative dyspareunia (**Table 20**).

Abramov et al retrospectively compared the midline fascial plication and discrete site specific repair for rectoceles [Abramov 2005]. They noted a significantly higher recurrence rate of rectoceles following the discrete site-specific repair (32%) as compared to 13% following the midline fascial plication [P=0.015]. The correction of the rectovaginal fascia defect that allows entrapment of feces on straining in significant rectoceles maybe to large to be repaired with the discrete approach [Kenton 1999] and appears to be corrected by the more robust midline fascial plication.

Table 19. Midline plication or traditional posterior colporrhaphy

Study (year)	N	Review Months	Anatomic Cure (%)	Vaginal Bulge (%)	Vaginal Digitation (%)	Defecatory Dysfunction (%)	Dyspareunia (%)
Arnold et al(Arnold MW 1990) Preoperative Postoperative	 29 24		 19/24(80)		 20	 9/24(36)	 6/24(23)
Mellgren et al.(Mellgren 1995) Preoperative Postoperative	 25 25	 12	 24/25(96)	 21 4	 50 0/25 (0)	 8 2/25(8)	 2/25(8)
Kahn et al(Kahn MA 1997) Preoperative Postoperative	 231 171	 42	 130/171(76)	 64 31	 56/171(33)	 4 19/171(11)	 27/171(16)
Weber et al (Weber 2000). [15] Preoperative Postoperative	 53 53	 12					 14/53(26)
Sand et al.(Sand 2001) [16] Preoperative Postoperative	 70 67	 12	 67/70(90)				
Maher et al.(Maher CF 2002) Preoperative Postoperative	 38 38	 12	 33/38(87)	 100 5	 100 6/38(16)	 3 6/38 (16%)	 37 2/38(5)
Abramov et al.(Abramov Y 2003) Preoperative Postoperative	 183 183	 >12	 150/183(82)	 100 4		 17 33/183 (18)	 8 31/183 (17)
Paraiso et al.(Paraiso 2011) Preoperative Postoperative	 37 28	 17.5	 24/28 (86%)			 80 9/28 (32)	 56 13/28(45)
Total			**447/539 (83%)**		**61/234 (26%)**	**78/469 (17%)**	**95/522 (18%)**

Table 20. Site-specific posterior vaginal repair

Study (year)	N	Review (Mo)	Anatomic Cure (%)	Vaginal Bulge (%)	Vaginal Digitation (%)	Defecatory Dysfunction (%)	Dyspareunia (%)
Cundiff et al. (Cundiff 1998) Preoperative Postoperative	 69 61	 12	 50/61 (82%)	 100 11/61(18)	 39 11/61(18)	 13 5/61(8)	 29 12/61(19)
Porter et al(Porter WE 1999) Preoperative Postoperative	 125 72	 6	 59/72 (82)	 38 10/72(14)	 24 15/72/(21)	 24 15/72(21)	 67 33/72(46)
Kenton et al.(Kenton 1999) Preoperative Postoperative	 66 46	 12	 41/46 (90)	 86 4/46(9)	 30 7/46(15)	 30	 28 4/46(8)
Glavind and Madsen(Glavind 2000) Preoperative Postoperative	 67 67	 3	 67/67 (100)				 12 2/67(3)
Singh et al.(Singh 2003) Preoperative Postoperative	 42 33	 18	 30/33(92)	 78 2/33(7)		 9 2/33(5)	 31 5/33(15)
Abramov et al.(Abramov 2005) Preoperative Postoperative	 124 124	 >12	 69/124 (56)	 100 14/124(11)		 15 24/124(19)	 8 20/124(16)
Paraiso et al.(Paraiso 2006) Preoperative Postoperative	 37 27	 17.5	 21/23 (78)		 58 6/27(21)		 48 8/27(28)
Sung et al(Sung 2012) Preoperative Postoperative	 80 70	 12	 63/70 (90)	 4/58(7%)	 9/58 (15.5%)	 12/57 (21)	 4/57 (7)
Total			**410/496 (83%)**	**45/394 (11.4%)**	**48/264 (18%)**	**58/347 (17%)**	**88/487 (18%)**

In a randomised control trial Paraiso et al compared three techniques for rectocele repair in a prospective randomized trial [Paraiso 2006]. Patients were randomized to receive either a traditional repair [N=37], a site specific repair [N=37] or a site-specific repair augmented with porcine small intestine mucosa [N=32]. All patients preoperatively had Stage II or greater posterior vaginal wall prolapse. The objective anatomic failure rate was highest in the graft augmented group [12 to 26] at 1 year which was statistically significantly worse then results in the site specific group [6 of 27] and traditional repair [4 of 28]. There was no significant difference in subjective symptoms (worsening prolapse or colorectal symptoms) or dyspareunia between the three groups.

Recently Sung et al reported on a double blind multicentre randomised control trial comparing native tissue repair [70] or native tissue porcine subintestine submucosal (SIS) graft [67] for symptomatic grade 2 rectocele [Sung 2012]. The native tissue repair involved either a midline plication or site specific repair with majority undergoing site-specific repair. In the graft group this repair was augmented with porcine SIS overlay. At one year there was no difference between the groups in objective and subjective success rates or in resolution of defecatory symptoms. Post operative dyspareunia rates were not significantly different at 7% in the native tissue group and 12.5% graft group.

In a single trial Vijaya (Abstract #52, ISC 2011 Glasgow) reported at 6 months follow up superior support of the posterior vaginal wall was attained after the fascial plication as compared to levator ani repair. Block randomisation was performed with 26 women randomised to each operation. Allocation concealment, power analysis, and status of reviewers was not reported. Anatomic outcomes were reported via Pop-Q point AP and a variety of quality of life assessments were performed without reporting the data.

5. TRANSANAL REPAIR OF RECTOCELE

Three trials have evaluated transanal vs transvaginal repairs of rectoceles [Kahn MA 1999; Nieminen 2004; Farid 2010]. Each trial had slightly different inclusion criteria. Kahn included women who had symptoms of prolapse or impaired rectal evacuation with incomplete emptying on isotope defaecography and normal compliance on anorectal manometry [Kahn MA 1999]. Nieminen's included women with symptomatic rectoceles not responding to conservative therapy. Importantly women with compromised anal sphincter function and other symptomatic genital prolapse were excluded. In both trials the vaginal repair was performed by gynaecologists and the transanal repair by colorectal surgeons. In Kahn's trial the posterior vaginal wall repair was performed using levator plication and in Nieminen's trial the rectovaginal fascia was plicated. Farid's inclusion criteria required women to have a rectocele

larger than 2 cm on defaecography with symptoms including digitation, incomplete evacuation, excessive straining and dyspareunia. Women with a compromised anal sphincter complex or recurrent prolapse, rectal prolapse, intussusception, or anismus were excluded. The surgery was performed within the surgery department and blinded examiners utilised defecography, anal manometry, and a modified obstructed defecation syndrome patient questionnaire to report outcomes.

Based on these three trials we can conclude that the results for transvaginal repair of rectocele are superior to transanal repair of rectocele, in terms of subjective and objective outcomes. In women with rectocele alone recurrent rectocele occurred in 2 out of 39 women in the vaginal group and 7 out of 48 following the transanal repair, a difference that did not reach statistical significance. Post-operative enterocele was however significantly less common following vaginal surgery as compared to the transanal group.

Farid [Farid 2010] reported on outcomes of three types of rectocele repair comparing transperineal repair to levatorplasty to transanal repair and noted conclusions similar to the two previously discussed trials. The size of the rectocele on defecography was significantly smaller in the transperineal group (with or without levatorplasty) as compared to the transanal repair. Also functional outcome based on a modified obstruction defecation syndrome patient questionnaire was better after transperineal repair compared to transanal repair.

Puigdollers et al reported results from a prospective cohort of women with rectocele and constipation who underwent surgery via either endorectal or a transperineal approach based on surgeon preference[Puigdollers 2007]. At the end of one year the overall subjective improvement in constipation was reported in 43% [p<0.001] and the need to splint decreased in 52% [p=0.001].

Thornton et al [Thornton 2005] reported in a single non-randomised study outcomes for a cohort of women with symptomatic rectocele who were treated laparoscopically [N=40] vs transanally [N=40]. Level 2B evidence from this study supports the superiority of the transanal approach for symptom relief (55% vs 28%, p<0.02) but lower post-operative dyspareunia rates (22% vs 36%) with the laparoscopic approach.

van Dam et al [van Dam 2000] performed a combined transvaginal and transanal repair in 89 women who were evaluated at a follow up of 52 months. The anatomic success rate was 71% (defined as no persistent or recurrent rectocele on defaecography at 6 months). However de novo dyspareunia was reported in 41% of women and there was a deterioration of fecal maintenance in 7 patients.

6. GRAFT AUGMENTED RECTOCELE

Sand et al [Sand 2001] compared posterior repair with and without mesh and noted rectocele recurrence appeared equal with and without polyglactin (vicryl) mesh augmentation [7 out of 67 vs 6 out of 65]. Neither Paraiso et al or Sung et al noted any benefit to augmenting a native tissue repair with a porcine subintestine submocosal graft overlay [Paraiso 2006; Sung 2012]. Mesh exposure was not reported in these trials. Altman et al reported on a prospective evaluation of insertion of a 7x4cm porcine dermis graft at three years and found a 40% recurrence rate on examination and while there was a significant decrease in rectal emptying difficulties as compared to preoperatively less than 50% reported cure of rectal emptying issues [Altman 2006]. There was no change in the rate of anal incontinence or dyspareunia post-intervention.

7. MODIFIED SACROCOLPOPEXY

The abdominal route has been employed in the correction of posterior vaginal wall prolapse when a co-existing apical defect requires surgery. The technique is a modification of sacrocolpopexy with extension of the posterior mesh down to the distal posterior vaginal wall and or the perineal body. The procedure has been reported completely abdominally or as a combined abdominal and vaginal approach. **Table 21** summarises a series of studies that have reported on extended posterior fixation of sacrocolpopexy mesh.

Summary

- Transvaginal Repair of Posterior Vaginal Wall prolapse continues to be reported as either a traditional repair with levatorplasty, midline fascial plication without levatorplasty or site-specific repair. Level one and two evidence suggest midline plication posterior repair without levatorplasty has superior objective outcomes as compared to site-specific posterior repair. (**Grade B**)
- Higher dyspareunia rate reported when levatorplasty is employed. (**Grade C**)
- Transvaginal approach is superior to the transanal approach for repair of posterior wall prolapse (**Level 1 Grade A**)
- To date no study has shown any benefit to mesh overlay or augmentation of a suture repair for posterior vaginal wall prolapse. (**Grade B**)
- While modified abdominal sacrocolpopexy results have been reported, data on how these results would compare to traditional transvaginal repair of posterior vaginal wall prolapse is lacking.

Table 21. Abdominal Repair (Posterior extension of Colpopexy Mesh)

Author	N	Follow Up	Success	Dyspareunia Pre-op	Post-op
Baessler K（Baessler 2001）	33	26 months	45%	39%	13%
Fox S. (Fox 2000)	29	14 months	90%	38%	17%
Su K (Su 2007)	122	12 months	90%	-	-
Lyons (Lyons 1997)	20	12 months	80%	-	-
Marinkovic (Marinkovic 2003)	12	39 months	91%	29%	None

VIII. PELVIC ORGAN PROLAPSE SURGERY AND BLADDER FUNCTION

In women with stage II POP about 55% have concurrent stress urinary incontinence (SUI). This prevalence decreases with increasing POP stages to 33% in women with stage IV POP [Slieker-ten Hove 2009]. However, if the prolapse is reduced digitally or with the help of a pessary, sponge holder or speculum, SUI might be demonstrated in a further 10% to 80%. [Haessler 2005; Reena 2007; Sinha 2007; Ellstrom Engh 2010] This type of SUI is termed occult, masked or latent SUI and is present when stress urinary incontinence is only demonstrable with the prolapse reduced in otherwise continent women. The importance of this finding remains ambiguous [Visco 2008]: the test itself is not optimal [Visco 2008] as it does not necessarily mimic prolapse surgery and may obstruct or put undue tension on the urethra. Although different techniques to reduce the prolapse have been described, a gold-standard has not been established. [Visco 2008; Ellstrom Engh 2010] Neither the speculum nor the pessary test to reduce the prolapse had acceptable positive predictive values to identify women in need of a concomitant continence procedure. The negative predictive values however were 92.5% [95%CI 90.3–1.00] and 91.1% [95%CI 88.5–99.7], respectively. Therefore, women with negative tests for occult SUI preoperatively are at low risk of developing SUI postoperatively. [Ellstrom Engh 2010; Chughtai 2011] Women with occult SUI are at risk of developing SUI after POP repair. Reducing the prolapse may also restore normal voiding function during urodynamics.[Romanzi 1999] These findings demonstrates the importance of testing bladder function in continent women with and without the prolapse reduced.

The Cochrane review on surgical management of POP found that new or denovo SUI symptoms were reported by 187 of 1280 women (15%) after prolapse surgery. [Maher 2010] The term de novo stress urinary incontinence is used to describe stress incontinence that develops following surgical correction of the prolapse, amongst women who were continent prior to surgery. De novo SUI might develop because POP surgery has unkinked the previously obstructed urethra.[Kenton 2005; Mueller 2007] De novo stress urinary incontinence is clearly disappointing to women and this outcome measure is considered in this review.

A third of women with stage II or more POP experience difficulties emptying the bladder.[Slieker-ten Hove 2009] Voiding difficulties might disappear postoperatively because the obstruction caused by the prolapse has been corrected.[Romanzi 1999] In contrast, they might develop because of kinking of the urethra due the surgical technique.

This section of the chapter assesses the effect of POP surgery on bladder function including stress urinary incontinence, overactive bladder and voiding dysfunction. In order to optimally evaluate pre and postoperative bladder symptoms, only studies with standardised or validated pre and postoperative outcome measures, more than 20 operated women and a follow up time of at least 12 months are included and summarised in Table 22. The follow up time of 12 months does not apply to studies assessing voiding dysfunction. We will evaluate the evidence surrounding common clinical scenarios.

1. CONTINENT WOMEN UNDERGOING POP SURGERY. WHAT IS THE RISK OF DE NOVO SUI AND IS CONTINENCE SURGERY REQUIRED?

For symptomatically and clinically dry women an anterior native tissue repair yields lower rates of de novo SUI than transobturator anterior mesh procedures. The overall cumulative de novo SUI rate after anterior repairs is 9% [44/481]. In five RCT´s [Hiltunen 2007; Sivaslioglu 2008; Altman 2011; Sokol 2011; Withagen 2011] de novo SUI was found in 31/377 (8%) women and in 13/104 (12%) women in two prospective studies [Hung 2004; Ellstrom Engh 2010]. After armed-mesh repairs the overall cumulative rate is significantly higher at 14% [134/951; p=0.017, chi-square] with a rate of 17% [101/584] in six RCT [Hiltunen 2007; Sivaslioglu 2008; Halaska 2010; Altman 2011; Sokol 2011; Withagen 2011] and 9% [33/367] in eight prospective trials [Sentilhes 2007; Ek 2010; Fayyad 2010; Feiner 2010; Sergent 2010; Takahashi 2010; Kuribayashi 2011; Liang 2011].

Five RCT´s directly compared anterior colporrhaphy and transobturator mesh procedures [mesh kits or self-fashioned] and reported 12-months results [Hiltunen 2007; Sivaslioglu 2008; Altman 2011; Sokol 2011; Withagen 2011]. Anterior native tissue repair significantly reduced the risk of de novo SUI (RR

0.64 95%CI 0.42, 0.97; **Figure 4**). Although all these trials employed quality of life and symptom questionnaires, different instruments were used and meta-analysis was not able to be performed.

In a longer term follow up of Hiltunen ´s trial [Hiltunen 2007], subsequently more women developed new SUI after anterior repair resulting in similar SUI rates after three years of 17% after both anterior repair [15/86] and transobturator mesh procedure [15/84]. [Nieminen 2010].

Similar rates of de novo SUI occurred if the anterior compartment prolapse was repaired using a polypropylene transobturator mesh 2% [2/96] or a porcine dermis graft 1% [1/94].[Natale 2009] In a single RCT de novo SUI was significantly more common after sacrospinous fixation and vaginal repairs compared with abdominal sacral colpopexy [8/24, 33% versus 2/22, 9% in a single RCT][Maher 2004], however, these data need to be reviewed cautiously as in the sacral colpopexy group continent women pre-operatively received paravaginal repairs which may be effective in limiting de novo SUI postoperatively.

In the large multicentre randomised controlled CARE trial (Colpopexy and urinary reduction efforts), preoperatively continent women were randomly allocated to undergo sacral colpopexy with [n=157] or without colposuspension [n=165]. Brubaker et al. demonstrated at 2 years that Burch colposuspension, performed concomitantly with an abdominal sacrocolpopexy significantly reduced the risk of de novo SUI. Subjective SUI was reported by 38/147 (26%) after additional Burch colposuspension and by 63/155 women (41%) after sacrocolpopexy alone. However, objective testing yielded similar findings in the two groups: 11/116 (9%) and 9/134 women (7%), respectively, demonstrated SUI. The study was terminated prematurely because of the high postoperative SUI rate in women who did not receive concomitant Burch colposuspension and as a result of early termination was underpowered. Unfortunately, irregularities in study design create uncertainty for the reader regarding the study findings. Firstly, different and complicated definitions were used to categorise stress continence prior to and after the interventions that made it more difficult to be classified as stress continent post intervention than prior to the intervention. Thirty-nine percent of women classified as stress continent prior to surgery would have been classified as stress incontinent using the post-intervention definition! Secondly, while surgery was standardised for colposuspension neither the paravaginal repair nor sacral colpopexy was standardised with significant variations in use of suture type and graft materials: in 17% biological grafts, in 43% Mersilene, in 39% polypropylene and in 6% Gore-tex was utilised.[Brubaker 2006; Brubaker 2008] which may have impacted on the continence results.

After a follow up of 8 years, Costantini et al. in another smaller RCT reported contrary results with 9/31 women (29%) developing SUI after additional Burch colposuspension compared to 5/31 (16%) after sacrocolpopexy alone.[Costantini 2007; Costantini 2010].

Figure 5 summarises these two RCT´s in a meta-analysis.[Brubaker 2008; Costantini 2010] Because of contrary outcomes resulting in significant heterogeneity, a random-effects model was used. According to this model, women do not benefit from Burch colposuspension in addition to abdominal sacral colpopexy. This is true for subjective de novo SUI [RR 0.96 95%CI 0.35, 2.62] and objective rates of de novo SUI [RR 1.56 95%CI 0.82, 2.95].

2. POP SURGERY AND STRESS URINARY INCONTINENT WOMEN

In women with SUI undergoing prolapse surgery, what kind of prolapse procedure and which continence surgery is required concomitantly in order to reduce postoperative SUI rates? The cumulative success rate for SUI after anterior colporrhaphy in two randomised trial arms was 48% [19/40][Colombo 2000; Hviid 2010]. Colombo et al.[Colombo 2000] compared to Burch colposuspension and anterior repair for the treatment of women with anterior vaginal wall prolapse and SUI. While women benefited more from Burch colposuspension with regards to SUI [cure of SUI 30/35, 86% versus 17/33, 52%], anterior repair better corrected the anterior prolapse [cure of cystocele 23/35 versus 32/33].[Colombo 2000].

Prospective POP surgery studies employing transobturator mesh without additional continence surgery show a cumulative SUI success rate of 61% [81/132]

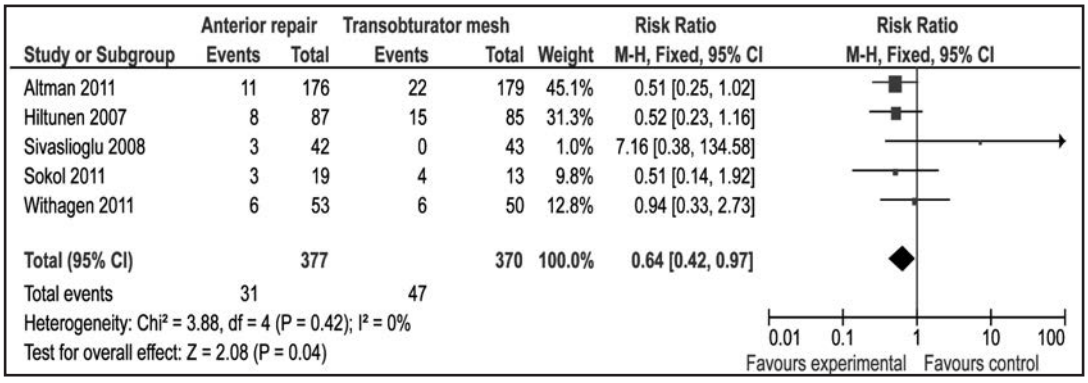


Figure 4. De novo SUI: Forrest plot of five RCT´s comparing anterior repair and transobturator mesh repairs.

[Sentilhes 2007; Sergent 2009; Sergent 2010]. Success rates improve considerably if a suburethral tape is performed concomitantly [cumulative rate 235/237, 99%]. [Hung 2004; Fayyad 2010; Feiner 2010; Takahashi 2010] Persisting or worsening SUI was described in 9/15 (60%) by Fayyad et al.[Fayyad 2010] who prospectively evaluated the role of transobturator polypropylene mesh without any concomitant surgery in the management of recurrent prolapse.

Whether a suburethral tape (TVT) is inserted concomitantly or after three months did not result in significantly different success rates based on an "on-treatment" analysis of Borstad et al. [83/87, 95% versus 47/53, 89% three months later].[Borstad 2010] Twenty-seven/94 (29%) women were cured of SUI after prolapse surgery alone and did not receive a TVT three months later.[Borstad 2010].

Costantini et al. 2008 compared abdominal sacrocolpopexy or sacrohysteropexy with and without concomitant Burch colposuspension in women with POP and SUI.[Costantini 2008] Similarly to their randomised trial in continent women, Burch colposuspension increased the postoperative SUI rate: 13/24 (54%) versus 9/23 (39%) were incontinent.[Costantini 2008].

3. SHOULD WOMEN UNDERGOING POP SURGERY WITH OCCULT SUI IDENTIFIED PREOPERATIVELY UNDERGO CONTINENCE SURGERY AT TIME OF POP SURGERY?

Three randomised trials addressed this issue [Meschia 2004; Schierlitz 2007; Wei 2011] and found that after the addition of TVT to vaginal prolapse repairs (mainly anterior and posterior colporrhaphy) significantly fewer women complained of SUI [21/116, 18% versus 64/125, 51%]. The meta-analysis of these three trials calculated that a concomitant TVT reduced the risk of postoperative SUI significantly [RR 0.54, 95%CI 0.41, 0.72; **Figure 6**]. In two trials, including women who tested positive for SUI after the POP was reduced (occult SUI) [Meschia 2004; Schierlitz 2007], whereas in Wei et al. study (OPUS trial) only 34% demonstrated occult incontinence. [Wei 2011] However, they reported data separately for women with a positive stress test after reduction of the prolapse: 41/57 women without and 16/54 with an additional TVT were stress incontinent at three months follow up (**Figure 6**).

In a retrospective trial of 60 women who tested negative for occult SUI on preoperative urodynamic studies, 15 (25%) developed SUI after vaginal mesh surgery.[Kasturi 2011] However, 12% [7/60] had preoperative symptomatic SUI.

4. OVERACTIVE BLADDER (OAB) SYMPTOMS

OAB symptoms may be associated with POP.[Slieker-ten Hove 2009] Therefore, prolapse surgery may cure or improve OAB but it may also result in new OAB symptoms. The current Cochrane review on the surgical management of POP [Maher 2010; Maher 2011] calculated that new overactive bladder symptoms developed in 103/854 [12%] women in nine trials with various prolapse surgery.[Bump 1996; Colombo 1996; Colombo 1997; Maher 2004; Meschia 2004; Brubaker 2006; de Tayrac 2008; Natale 2008; Natale 2009] Whether women have been treated with anticholinergics e.g. postoperatively is not at all clear and numbers might in fact be higher. The cumulative rate of de novo OAB in women who underwent transobturator anterior mesh procedure

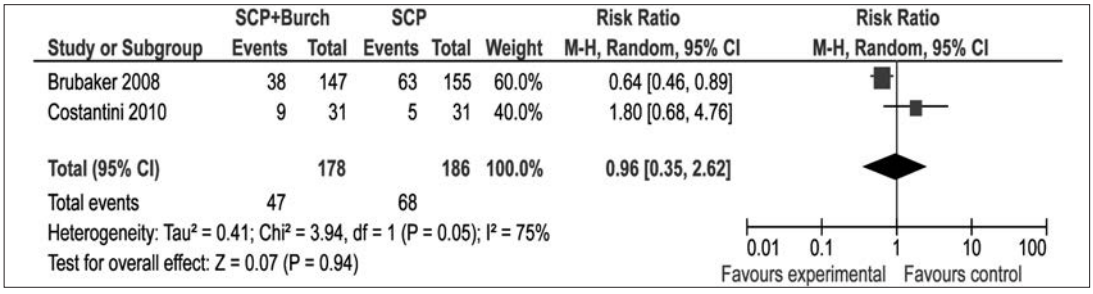


Figure 5. Meta-analysis of two RCT´s looking at the effect of Burch colposuspension in addition to sacrocolpopexy. Presented are subjective rates of de novo SUI

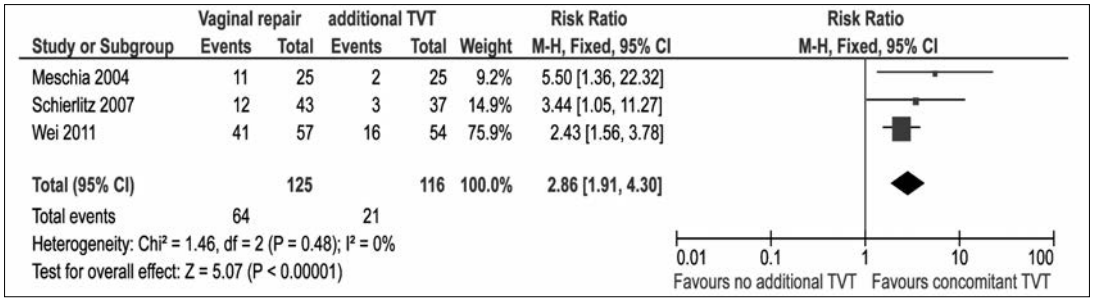


Figure 6. The addition of a suburethral sling to vaginal prolapse repairs in women without symptomatic SUI

is 7% [39/557], [Sentilhes 2007; Moore 2009; Fayyad 2010; Feiner 2010; Halaska 2010; Liang 2011] whereas it is 10% [7/71] in the few studies reporting data after anterior repair with or without suburethral tape.[Meschia 2004; Foster 2007] This difference is not statistically significant [p=0.4].

In a new RCT, Halaska et al. reported de novo overactive bladder in 7/97 [7%] after anterior Prolift, in 7/34 (21%) after anterior Prolift and sacrospinous fixation, in 8/84 (9%) after total Polypropylene mesh repair and in 1/98 (1%) after posterior Prolift only. [Halaska 2010] In another RCT, after vaginal sacrospinous fixation 6/29 women complained of OAB whereas after sacrocolpopexy 11/33 developed symptoms.[Maher 2004]. Sacrocolpopexy with or without Burch colposuspension resulted in similar rates of de novo OAB [3/34 versus 2/32][Costantini 2007]. Similarly, after vaginal POP surgery with or without TVT OAB rates were not different [3/25 versus 1/25].[Meschia 2004].

In 22/48 (46%) of women with several different prolapse operations urgency incontinence resolved, whereas it persisted in 26/48 (54%) and developed de novo in 3 (12%).[Foster 2007].

5. VOIDING PROBLEMS

The Cochrane review noted new voiding dysfunction in 56/476 (12%) women in six randomised trials with various prolapse surgeries with or without continence procedures [Bump 1996; Colombo 1996; Colombo 1997; Maher 2004; Natale 2007; de Tayrac 2008]. However, variation in defining and reporting voiding problems makes meta-analysis is unfeasible.

After anterior repair, voiding dysfunction ranges from 0% to 37%.[Colombo 2000; Meschia 2004; Gandhi 2005; Meschia 2007; Stekkinger 2011; Withagen 2011]

In their RCT Withagen et al. described significantly different temporary urinary retention rates in 5/97 (5%) compared with 15/93 (16%) after transobturator mesh repair [p=0.008]. Normal micturition was restored in all women within 14 days. [Withagen 2011] Anterior repair with or without concomitant vaginal POP surgery resulted in postvoid residuals exceeding 150 ml in 27/126 (21%) in an RCT comparing transurethral and suprapubic catheterisation.[Stekkinger 2011]

After anterior mesh repair, voiding difficulties occur between 5% and 42%.[Maher 2004; Feiner 2010; Steinberg 2010; Withagen 2010; Feiner 2011; Maher 2011; Withagen 2011] One study looked at postoperative urinary retention defined as the need to discharge the patient with an indwelling catheter because of a failed trial of void.[Steinberg 2010] Voiding dysfunction ranged from 34% [10/29] after isolated anterior mesh repair to 42% [30/71] cases after combined anterior and posterior repairs. After isolated posterior repair 8/42 (19%) developed urinary retention. At the 3-months follow up, there were no more voiding complaints.[Steinberg 2010]

If there are postoperative voiding problems with residuals exceeding 150 ml, clean intermittent catherisation is superior to an indwelling catheter for three days with regards to bacteriuria, urinary tract infection and length of required catheterisation according to one RCT [Hakvoort 2011] and intermittent transurethral catheterisation is equivalent to a suprapubic catheter regimen.[Stekkinger 2011] Insertion of a suprapubic catheter however resulted in more related complications including dislodgment or blockage of the catheter and haematuria.[Stekkinger 2011].

Another RCT [Huang 2010] reported on the duration of postoperative urethral catheterisation between two and four days after anterior repair and found no differences in voiding dysfunction. This was confirmed by an RCT comparing two and five days of routine postoperative indwelling catheter placement. Longer hospital stay and more urinary tract infections were associated with the five days protocol.[Weemhoff 2011] Patients do not seem to benefit from postoperative urethral catherisation beyond two days.[Huang 2010; Weemhoff 2011].

Summary

Assessed trials were considerably heterogeneous regarding inclusion and exclusion criteria, clinical testing for stress urinary incontinence and operations performed. Also, the lack of separate reports of bladder symptoms account for a difficult interpretation of outcomes.

Continent women undergoing anterior compartment POP surgery have a lower rate of de novo SUI after anterior repair than armed mesh procedures. (**Grade A**)

Data are conflicting on whether colposuspension should be performed prophylactically in continent women undergoing sacral colpopexy. (**Grade C**)

In continent women undergoing POP surgery with occult SUI the addition of continence surgery reduces the rate of postoperative SUI (**Grade A**).

In women with POP and SUI prolapse procdures alone (transobturator mesh and anterior repair) are associated with low success rates for SUI. Concomitant continence procedures reduce the risk of postoperative SUI .

No clear conclusion can be made regarding the management of continent women undergoing POP surgery without occult SUI.

Preoperative bladder overactivity may resolve in 40% undergoing POP surgery and denovo bladder overactivity occurres 12%.

No valid conclusions regarding voiding dysfunction following POP surgery can be drawn from the available data.

Level 1 evidence demonstrates there is no need to leave an indwelling catheter beyond two days and a suprapubic catheter yields similar outcomes to clean intermittent self catheterisation however is associated with more complications.

Table 22. Studies reporting on de novo stress urinary incontinence (SUI) or cured SUI

Author, year	Study design / LoE	Operations	Follow up months	SUI status preop	De novo SUI	Cured SUI	Persistent SUI	De novo OAB
Altman et al 2011(Altman 2011)	RCT	Anterior colporrhaphy	12	continent 176/189	11/176 (6%).			
	LoE 1	Anterior Prolift	12	continent 179/200	22/179 (12%)			
Halaska et al. 2010(Halaska 2010)	RCT	Anterior Prolift	12+	?continent, no concomitant SUI-procedures	26/97 (27%)			7/97 (7%)
	LoE 2	Anterior Prolift + sacrospinous fixation			6/34 (18%)			7/34 (21%)
		total Prolift			22/84 (26%)			8/84 (9%)
		Posterior Prolift			9/98 (9%)			1/98 (1%)
Ek et al. 2010* (Ek 2010)	RCT	Anterior colporrhaphy	12	3/25 pos. stress test	2/25 (8%)			
	LoE 1	Anterior Prolift	12	1/22 pos. stress test	7/22 (32%)			
Sivaslioglu 2008(Sivaslioglu 2008)	RCT	Anterior colporrhaphy	mean 12	continent	3/42 (7%)			
	LoE 2	4-armed ant. Mesh	mean 12		0/43			
Natale 2009(Natale 2009)	RCT	Anterior tension-free 2-armed PP mesh repair	24	continent	2/96 (2%)			
	LoE 2	Anterior 2-armed porcine dermis graft repair (self-cut)	24		1/94 (1%)			
Hviid et al. 2010(Hviid 2010)	RCT	Anterior repair	12	7/29 (24%)	?	2/7 (29%)		
	LoE 2	Pelvicol graft inlay fixed with Vicryl	12	10/28 (36%)	?	4/10 (40%)		
Borstad 2010(Borstad 2010)	RCT	Any vag. POP surgery + TVT	12	All SUI	n/A	83/87 (95%)		
	LoE 1	Any vag. POP surgery TVT 3 months later				47/53 (89%) on treatment analysis--- 72/94 (77%) ITT		
Colombo 2000 (Colombo 2000)	RCT	Burch colposuspension	12	SUI		30/35 (86%)		
	LoE 2	Anterior repair	12			17/33 (52%)		
Sokol 2011(Sokol 2011)	RCT	conventional vaginal repairs, USLP or sacrospinous fix.	12		3/19 (16%)			
	LoE 2	Prolift	12		4/13 (31%)			
Whithagen 2011(Withagen 2011)	RCT	Conventional vaginal repair (anterior repair=58)	12	continent and incontinent	8/88 (9%); only anterior repair 6/53			
	LoE 2	Prolift (Prolift in ant. compartment=56)	12		8/81 (10%); only ant. Prolift 6/50			
Meschia 2004(Meschia 2004)	RCT	Anterior repair + TVT	26	occult SUI	1/25 (4%) subj 2/25 (8%) obj			3/25 (12%)
	LoE 2	Anterior repair +plication urethrovesical junction	24		9/25 (36%) subj 11/25 (44%) obj			1/25 (4%)
Schierlitz 2007	RCT	vaginal POP repair	median 21	occult SUI	USI 6 months 12/43 (28%)			
	LoE 2	vaginal POP repair + TVT	median21		USI 6 months 3/37 (8%)			
Wei 2011	RCT	vaginal POP repair	12	symptomatically continent, 34% occult SUI	74/172 (43%)			
	Abstract, LoE 2	vaginal POP +TVT	12		45/165 (27%)			
Nieminen 2010 3yrs FU(Nieminen 2010)	RCT	anterior repair	36	continent	15/86 (17%)			
		anterior repair+4-armed self-cut mesh	36		15/84 (17%)			
Ramanah 2011	Prospective comparative follow up	laparoscopic sacralcolpopexy	median 30		11/87 (13%)			1 1%
	LoE 2	vaginal porcine dermis transobturator hammock with sacrospinous fixation	median 34		15/64 (23%)			3 5%
Kuribayashi 2011	Prospective follow up	self-cut Prolift (TVM)	3	did not need continence procedure	5/46 (11%)			
Alcalay et al. 2010(Alcalay 2011)	Prospective	Trocarless mesh attached near SSL and laterally	12		2/20 (10%)			
Ek et al. 2010(Ek 2010)	Prospective follow up	Anterior Prolift	12		9/52 (17%)		39/57 68% persistent 32/57 worsend	
Fayyad et al. 2010(Fayyad 2011)	Prospective follow up	Anterior Prolift	24+		5/21 (24%)	4/15 (27%)	9/15 (60%)	1/22 (5%)
Feiner et al. 2010(Feiner 2010)	Prospective follow up	Prolift + sacrospinous ligament fixation + TVT-O for SUI	12	SUI 21/94 (22%)	2/73 (3%)	20/21 with TVT-O (95%)		7/84 (8%)
Ellstroem 2010	Prospective follow up	anterior repair +-post rep, hyst, apical procedures	12	subjectively continent, occult SUI in 10%	8/74 (11%) subj 4/8 (50%) obj.			
Groutz 2010(Groutz 2001)	Prospective follow up	vaginal ant.+post. repairs +TOT	12+	occult USI	2/92 (2%) subj 13/92 (14%) obj			4 7%
Takahashi 2010(Takahashi 2010)	Prospective follow up	TVM (Gynemesh cut like Prolift, transobt) +- TOT for SUI in 208 (67%)	12		7/102 TVM alone (7%)	207/208 TVM+TOT (99%)	0/303	1 (TVM alone) 1 TVM+TOT
Sergent et al. 2010 Int JGO	Prospective follow up	transobturator/infracocc. Mesh (Ugytex) - no SUS for SUI	12+	SUI 26/52 (50%)	?	12/26 (46%)		
Sergent et al. 2009 Female Urology	Prospective follow up	transobturator/infracocc. Mesh (Ugytex) - no SUS for SUI	12+	100% SUI	n/a	53/74 (72%) cured 11/74 (15%) improved		
Moore 2009	Prospective follow up	Perigee +- TOT	24	Nm	Nm	nm	nm	4/114 (4%)
Sentilhes 2007	Prospective follow up	transobturator/infracocc. Mesh (Surgipro-Ugytex) - no SUS for SUI	12	17/44 (39%)	0/27	12/17 (71%)	5/17 (29%)	2/29 (7%)
Hung 2004	Prospective follow up	anterior repair+ four-corner anchored PP mesh +TVT for SUI	12+	8/38 SUI occult or overt	5/30 (17%)	8//8		
Liang Ching 2011	Retrospective with standardised workup pre-post	self-shaped ant. mesh with 2 arms positioned retropubically and under cystocele +TOT if overt SUI	12	USI 24/100 24%	Na	23/24 (96%)	1/24 (4%)	3/93 (3%): 3-6 months postop
				Continent n=46	5/46 (11%)	Na		
				Occult n=30	5/30 (17%)			

** urodynamic evaluation of Altman 2011, SUS = suburethral sling; ant.= anterior, post.= posterior, USLP = uterosacral ligament plication, OAB= overactive bladder*

IX. COMPLICATIONS AND METHODS OF PREVENTION

Pelvic reconstructive surgery for genital prolapse, with or without mesh, results in improved prolapse related symptoms and quality of life improvement in most of the cases [Jia 2008; Iglesia 2010; Maher 2010] (Level 1). While the use of non-absorbable synthetic mesh in the anterior compartment subjectively and objectively decreases the rate of anterior vaginal wall prolapse recurrence in comparison to native tissue repair Cochrane 2012(Level 1) however, short term improvement of quality of life or reduced reoperation rates have yet to be demonstrated [Jia 2008; Iglesia 2010; Maher 2010; Altman 2011]. Furthermore, the use of non-absorbable synthetic mesh exposes patient to moderate to severe specific complications.

The first objective of this section is to report non specific and specific complications related to pelvic reconstructive surgery for genital prolapse with mesh, in comparison to surgery with no mesh. The second objective is to describe the recognised methods of prevention of these complications.

1. CLASSIFICATION OF COMPLICATIONS

Recently, the IUGA (International Urogynecological Association) and the ICS (International Continence Society) have published a specific classification of complications related to pelvic reconstructive surgery [Haylen 2011]. That classification has been developed to be sensitive to all possible physical complications involving the use of a prosthesis or graft in a female pelvic floor surgical procedure. Both insertion complications (e.g trocar related) and healing abnormalities are covered. Whilst this creates a large number of possible complication scenarios, appropriate organisation has still been possible by category (C), time (T) and site (S). A key advantage of a standardised classification is that all parties involved in female pelvic floor surgery will be referring to the same clinical issue. It is anticipated that in time this classification will significantly add to clarity in reporting mesh related complications.

2. REOPERATION AFTER VAGINAL MESH SURGERY

Table 23 shows the reoperation rates after vaginal mesh surgery for both non specific (linked to surgical dissection) and specific (linked to the mesh) complications. Only randomised trials have been used for analysis. Although meta-analysis shows a decreased rate of anatomical recurrences after mesh surgery, the total reoperation rate is increased after transvaginal mesh surgery (8.5%) as compared to surgical procedures using native

Table 23. Reoperation rates after Polypropylene and porcine dermis vaginal surgery from randomised control trials

Author	Year	Mesh	Technique	f.u. (months)	Total except SUT without vs with mesh ***	SUT without vs with mesh	Recurrence without vs with mesh	Mesh complication ****
Altman 2011	2011	PP*	4 arms TO	12	1/189 vs 8/200	0/189 vs 5/200 (p=0.06)	1/189 vs 0/200 (p=0.49)	6/200 (3%)
Maher 2011	2011	PP*	4 arms TO	24	†	†	†	9/55 (16%)
Withagen 2011	2011	PP*	4 arms TO	12	5/97 vs 5/93	MD	4/97 vs 0/93 (p=0.14)	5/93 (5%)
Vollebregt 2011	2011	PP*	4arm TO	12	4/58 vs 5/56	1/58 vs 2/56		2/56 (4%)
Iglesia 2010	2010	PP*	4 arms TO	9	0/33 vs 5/32	MD	0/33 vs 2/32 (p=0.45)	3/32 (9%)
Nieminen 2010	2010	PP*	4 arms non TO	36	8/96 vs 20/104	9/96 vs 5/104 (p=0.32)	1/96 vs 6/104 (p=0.15)	14/104 (13%)
Nguyen 2008	2008	PP*	4 arms TO	12	1/38 vs 2/38	MD	MD	2/38 (5%)
Sivaslioglu 2008	2008	PP*	4 arms TO	12	0/42 vs 3/43	MD	MD	3/43 (7%)
Total (PP)	-	-	-	-	18/553 (3.2%) vs 48/566 (8.5%) (p=0.01)	10/ 343vs 12/360 (0.85)	6/512 vs 8/534 (p=0.86)	44/621 (7.1%)
Hviid 2010	2010	PD**	free SBP	12	0/31 vs 1/30 (PD)	1/31 vs 1/31	2/31 vs 3/31	1/30 (PD)
Natale 2009	2009	PD** PP*	free SBP	24	0/94 (PD) vs 6/96 (PP)	MD	0/94 vs 0/96	0/94 (PD) 6/96 (PP)
Meschia 2007	2007	PD**	free SBP	15	0/103 vs 1/98 (PD)	MD	MD	1/98 (PD)
Total (PD)	-	-	-	-	0/228 (0%) vs 2/128 (1.6%) (p=0.72)	-	-	2/222 (1%)

** Different mesh weight, ** Different porcin dermis graft, *** Comparative studies anterior colporraphy vs mesh, or biologic graft vs synthetic mesh (procedures for de novo SUI were excluded), **** Procedures for vaginal exposition, infection or painful contraction† Comparative studies between two synthetic meshes or vaginal vs abdominal mesh*

Abreviations : SUT, sub urethral tape ; SBM, sub bladder mesh; PD, porcin dermis ; CF, cadaver fascia ; MD, missing data ; GT, goretex ; PE, polyester ; PP, monofilament polypropylene ; PPM, polypropylene multifilament ; PPPE, polypropylene + polyester ; PPS, monofilament polypropylene-dimethyl siloxane (silicone) ; PTFE, polytetrafluoroethylene.

tissues (3.2%)(Level 1). The rate of reoperation for prolapse is similar in both the transvaginal mesh group and native tissue repair. Altman, 2011 #137} [Maher 2004; Meschia 2007; Nguyen 2008; Sivaslioglu 2008; Natale 2009; Hviid 2010; Nieminen 2010; Withagen 2011] (Level 1). Denovo apical or posterior compartment prolapse surgery is significantly more frequent after anterior compartment polypropylene mesh (17.7%) as compared to native tissue repair (9.5%)[Nieminen 2010; Vollebregt 2011].

Similarly, a meta-analysis from Diwadkar et al, including prospective or retrospective observational studies with at least 50 patients and a minimum follow-up of 3-months, has shown an increased rate of reoperation after vaginal mesh surgery in comparison to native tissue repair. (8.5% versus 5.7%) [Diwadkar 2009].

In the only randomised trial that has compared vaginal mesh surgery to laparoscopic sacrocolpopexy with a mean follow-up of 2-year Maher et al has also shown a increased rate of reoperation after vaginal mesh surgery (22% versus 5%, p=0.006) [Maher 2004] (Level 2). Nieminen et al demonstrated a 24% [25/104] rate or reoperation after self styled polypropylene anterior compartment mesh at 3 years [Nieminen 2010].

A recent retrospective study on 524 patients who received a Prolift mesh with a median follow-up of 38 months [range, 15-63], has reported a global reoperation rate of 11.6% including postoperative urinary incontinence (6.9%), mesh-related complications (3.6%), and prolapse recurrence (3%) [de Landsheere 2011].

3. REOPERATION AFTER ABDOMINAL SURGERY

Mean rates of reoperation for prolapse recurrence and for de novo stress urinary incontinence after open abdominal sacral colpopexy are 4% and 5%, respectively [Nygaard 2004; Culligan 2005; Elneil 2005; Handa 2007; Meschia 2007; Jeon 2009].

Table 16 demonstrates the total reoperation rate for laparoscopic sacrocolpopexy is 5.9%. with 2.9% representing complications and 1.7% representing reoperations for prolapse. [Agarwala 2007; Maher 2007; Sarlos 2008; Stepanian 2008; Deprest 2009; Granese 2009; Sabbagh 2010; Price 2011; Sergent 2011].

The rate of reoperation for recurrences after laparoscopic sacrocolpopexy is significantly higher with the use of porcine dermis grafts in comparison to polypropylene mesh [Deprest 2009] (Level 3).

Tijdink et al [Tijdink 2011] reported on the surgical management of 60 mesh complications following mesh prolapse surgery. Twelve followed sacral colpopexy and 48 vaginal mesh surgeries. Most women reported more than one complication however the principle presentation requiring surgical intervention was pain in 77% (vaginal pain, dyspareunia or other chronic pain buttock, abdomen or thighs). They detected a distinct difference in symptoms related to mesh complications following transvaginal mesh and ASC. Vaginal pain and dyspareunia were the most commonly reported symptoms necessitating surgical intervention following transvaginal mesh and vaginal discharge and bleeding following ASC. Previous mesh excision procedures had been performed in 29% and complete mesh excision was required in 37% of cases. Peri-operative complications occurred more frequently in those requiring complete excision of mesh. Furthermore perioperative complications were more common in those who had undergone ASC as compared to vaginal mesh surgery (23% versus 1% p=0.001). Finally, recurrence of prolapse was significantly more likely if complete excision of the mesh was required and occurred in 29% as compared to 5% after partial excision of mesh. Resolution of preoperative symptoms was reported in 92% who underwent surgical management of mesh complications.

4. VAGINAL MESH EXPOSURE

It is difficult to know the exact rate of vaginal mesh exposure, as the definition of exposure is variable between studies and meshes used are different. **Table 24** shows the rate of exposures after vaginal mesh surgeries in the current available randomised controlled trials. In these trials, the mean rate of exposure was 13.1% [Meschia 2007; Nguyen 2008; Sivaslioglu 2008; Natale 2009; Hviid 2010; Iglesia 2010; Lopes 2010; Nieminen 2010; Altman 2011; Maher 2011; Vollebregt 2011; Withagen 2011](Level 1).

Abreviations : RCT, randomised controlled trial; L, Level; SBM, sub bladder mesh; PD, porcine dermis ; CF, cadaver fascia ; MD, missing data ; GT, goretex ; PE, polyester ; PP, monofilament polypropylene ; PPM, polypropylene multifilament ; PPPE, polypropylene + polyester ; PPS, monofilament polypropylene-dimethyl siloxane (silicone) ; PTFE, polytetrafluoroethylene.

95% CI for 13.1% [10.4-15.8] for PP and 0.9% [0-2.1] for PD

The mean rate of vaginal mesh exposure after open sacrocolpopexy was 3% [Nygaard 2004; Culligan 2005; Elneil 2005; Wu 2006; Handa 2007; Jeon 2009]. **Table 16** shows the rate of exposures after laparoscopic sacrocolpopexy is 2.5% [Cosson 2002; Antiphon 2004; Gadonneix 2004; Maher 2004; Paraiso 2005; Ross 2005; Rozet 2005; Agarwala 2007; Rivoire 2007; Sarlos 2008; Stepanian 2008; Claerhout 2009; Deprest 2009; Granese 2009; Sabbagh 2010; Price 2011; Sergent 2011] Paraiaso(Level 2).

Table 24. Rate of vaginal exposure after vaginal graft surgery from randomised control trials

Author	Year	Total sample size	Number of mesh procedure	Number of vaginal exposure	Rate of vaginal Exposure	f.u. (months)	Mesh
Altman	2011	389	183	21	11.5%	12	PP
Maher	2011	108	55	5	13%	24	PP
Withagen	2011	190	93	16	17%	12	PP
Vollebregt	2011	120	56	2	4%	12	
Iglesia	2010	65	32	5	15%	10	PP
Lopes	2010	32	14	5	35%	12	PP
Nieminen	2010	202	105	20	19%	24	PP
Nguyen	2008	76	37	2	5%	12	PP
Sivaslioglu	2008	90	45	3	7%	12	PP
Total (PP)	-	-	**620**	**81**	**13.1% 95% CI 10.4-15.8)**	-	-
Hviid	2010	61	30	1	3%	12	PD
Natale	2009	190	96	0	0%	24	PD
Meschia	2007	201	98	1	1%	15	PD
Total (PD)	-	-	**224**	**2**	**0.9% 95%CI (0-2.1)**	-	-

Abreviations : RCT, randomised controlled trial; L, Level; SBM, sub bladder mesh; PD, porcine dermis ; CF, cadaver fascia ; MD, missing data ; GT, goretex ; PE, polyester ; PP, monofilament polypropylene ; PPM, polypropylene multifilament ; PPPE, polypropylene + polyester ; PPS, monofilament polypropylene-dimethyl siloxane (silicone) ; PTFE, polytetrafluoroethylene. 95% CI for 13.1% (10.4-15.8) for PP and 0.9% (0-2.1) for PD

Maher et al, have shown a non significant increased rates of vaginal mesh exposure and reoperation for vaginal mesh exposure after vaginal mesh surgery in comparison to laparoscopic sacrocolpopexy (13% vs 2%, p=0.07 and 9% vs 2%, p=0.11, respectively) [Maher 2004] (Level 2). However, that was not the primary endpoint of the study, and that study was underpowered for this parameter.

5. VISCERAL (BLADDER, RECTUM) MESH EXPOSURE

There was no visceral mesh exposure reported in the randomised controlled trials after vaginal mesh surgeries, but follow-up were short [Nguyen 2008; Sivaslioglu 2008; Carey 2009; Iglesia 2010; Nieminen 2010; Altman 2011]. Late bladder or ureteric and rectal exposure were reported after both sacrocolpopexy [Nicolson 2009; Paine 2010] and vaginal surgery [Huffaker 2009 ; Karateke 2010]. The rate of late visceral exposure after laparoscopic sacral colpopexy is between 0.5 and 1% [Sabbagh 2010] (Level 4).

6. INFECTION, ABSCESS, CELLULITIS, SPONDYLODISCITIS

There is no clear definition of bacterial colonisation around a mesh or mesh infection. Consequently, the rate of infection is currently unknown [Jia 2010]. Some studies have reported up to 80% bacterial mesh colonisation [Boulanger 2008; Vollebregt 2009]. However, the rate of relevant clinical infection (abscess, cellulitis, spondylodiscitis) does not seem to be more than 1%, after both sacrocolpopexy (Level 4) [Akl 2009; Donnez 2009; Walid 2009; de Tayrac 2011], or vaginal mesh surgery (Level 4) [Chen 2009; Lewicky-Gaupp 2009]. In a cohort of 684 polypropylene mesh implanted vaginally (TVM procedure), the rates of pelvic abscess and cellulitis have been reported to occur in only 0.29% and 0.15%, respectively [Caquant 2008] (Level 4).

7. PAINFUL MESH CONTRACTION

Feiner et al defined mesh contraction as an adverse outcome following armed polypropylene mesh repair in which patients experience vaginal pain with movement and dyspareunia and on examination have localised areas of prominent, tense and tender mesh under the vaginal epithelium[Feiner 2010]. They reported a case series of 17 painful meshes and in that series, 90% of the patients have been improved by a reoperation for partial mesh removal, however in three patients a second reoperation with wider excision of the mesh was required. The rate of polypropylene mesh-related pain reported ranged between 4 and 11% according to the definition used (Level 3) [Caquant 2008; Nguyen 2008; Sivaslioglu 2008; Lunardelli 2009; Feiner 2010; Iglesia 2010; Lopes 2010; Moore 2010; Nieminen 2010; Withagen 2011].

Maher et al have reported a rate of reoperation for mesh contraction significantly greater after vaginal mesh surgery than after laparoscopic sacrocolpopexy (7% vs 0%, p=0.05) [Maher 2004] (Level 2). Ridgeway et al [Ridgeway 2008] reported a cases series of 19 polypropylene mesh complications that underwent a variety of vaginal and abdominal procedures to partially remove mesh. Six underwent excision for severe pain and one had residual pain following partial excision.

In the 2011 American FDA report regarding transvaginal mesh, vaginal pain and dyspareunia

were the most common adverse event reported and vaginal pain and dyspareunia were also the most common indications for reoperation following transvaginal mesh in the report by Tijdink et al.[Tijdink 2011] These reports contrast with the common perception in the literature that mesh exposure is the commonnest complication associated with transvaginal meshes and requires ongoing evaluation.

8. OTHER COMPLICATIONS

Other rare but severe complications have been described after mesh surgery, such as massive haemorrage after a trans-obturator mesh procedure, major vessel injury during sacrocolpopexy, trocar hernia, bowel obstruction, ureteric complications, thrombo-embolism.

9. METHODS OF PREVENTION

a) Influence of non specific factors on mesh-related complications (obesity, smoking, age, sexual activity)

Concerning vaginal mesh surgery, obesity (BMI>30 kg/m², OR=10.1) and smoking [OR=3.7] are independent risk factors for mesh exposure [Araco 2009] (Level 3). With regard to sacrocolpopexy, smoking [OR=5.2 ; IC95% 1.7-16] is also an independent risk factor for vaginal mesh exposure [Cundiff 2008] (Level 3). Although there is no specific study in prolapse surgery, to demonstrate the cessation of smoking prior to surgery will decrease the post-operative complication rate (healing problems) in many other surgical specialties these data exist (Level 2).

Current data on the impact of aging on mesh complications are conflicting and no conclusion can be drawn. [de Tayrac 2006; Cundiff 2008; Araco 2009; Ganj 2009; Nosti 2009; Kaufman 2011].

Sexual activity has been reported to be a risk factor for vaginal mesh exposure after vaginal mesh surgery [Letouzey 2010 ; Kaufman 2011] (Level 3) however this could simply reflect that those who are sexually active are more likely to identify a mesh exposure than those who are not.

No study has shown that the following are significantly associated with mesh exposure : diabetes mellitus, corticosteroid use, immunosuppressive therapy, previous pelvic irradiation, history of previous mesh exposure, vaginal atrophy. However, many studies have shown in other surgical specialties that poorly controlled diabetes mellitus is a risk factor for post-operative infection.

b) Oestrogen therapy

Although some authors report routine use of local oestrogen therapy for the pre and post-operative course of prolapse surgery in post-menopausal women [Altman 2011], others did not give any details on such prescription, and there is no comparative study. In multivariate analysis, local oestrogen therapy has no protective effect of vaginal erosion, after vaginal mesh surgery [Guillibert 2009] (Level 3), or after sacrocolpopexy [Kohli 1998] (Level 4).

c) Antibiotic prophylaxis

There is not specific study on the use of antibiotic prophylaxis at the time of mesh reconstructive surgery for prolapse. However, most of studies report their use during surgery [Withagen 2011] [Hiltunen 2007; Carey 2009].

There are no data on the need to identify a urinary tract infection in the preoperative course, nor to perform a vaginal bacteriological test or to use antiseptic or antibiotic meshes.

Prolonged post-operative bladder catheterisation increases the risk of lower urinary tract infection. [Liang 2009].

d) Mesh implantation and visceral injury

Although there is no comparative study, most of authors would consider the use of mesh after a rectal injury during dissection as a contraindication to mesh insertion, due to a perceived higher risk of mesh infection and subsequent recto-vaginal fistula [Jacquetin 2010] (Level 4).

In the anterior compartment, a small series of five cases of recognised intra-operative bladder injury (out of 704 Trans-Vaginal Mesh procedures) has shown that mesh surgery was feasible without subsequent complications after appropriate bladder repair [Popovic 2007] (Level 4). These data are limited and further evaluation is required.

e) Surgeon training

Regarding sacral colpopexy, a learning curve has been shown, with a reduction of operative time and laparoconversion over the first 80 procedures [Claerhout 2009] (Level 3). However, the incidence of severe complications does not seem to be related to the learning curve [Claerhout 2009] [Akladios 2010].

The data regarding the impact of the learning curve for transvaginal meshes on the incidence of post-operative complications is conflicting. Some authors have reported that learning has a significant effect on the complication rate [Dwyer 2004] while others did not [Fatton 2007] [Sentilhes 2007] (Level 3).

10. VAGINAL MESH SURGERY

a) Choose the right mesh for vaginal surgery

For vaginal mesh surgery, the use of non-absorbable synthetic meshes was associated with a reduced rate of short-term recurrences in comparison to the use of absorbable biological or synthetic meshes, for both primary and recurrent cases [Jia 2008] [Iglesia 2010] [Maher 2010] [Altman 2011] [Withagen 2011] [Nieminen 2010] [Natale 2009] (Level 1). Contrarily, the use of

absorbable biological or synthetic meshes is associated with a lower risk of vaginal mesh exposure and re-operation in comparison to non-absorbable synthetic meshes [Jia 2008] [Natale 2009] (Level 1).

Concerning the type of non-absorbable synthetic mesh, the use of polyester is associated with an increased risk of vaginal exposure in comparison to polypropylene [33.3% vs 8.8%, p<0.03] [Sentilhes 2008] (Level 4). Furthermore, the use of multifilament polypropylene is associated with an increased risk of vaginal exposure than monofilament polypropylene [Sentilhes 2008] [Deffieux 2009] (Level 4), and the use of microporous monofilament polypropylene is associated with an increased risk of vaginal exposure than macroporous monofilament polypropylene [Baessler 2005] [Guillibert 2009] (Level 4). Composite polypropylene/ polyglactin meshes do not seem to reduce the vaginal exposure rate [7.2% vs 6.9%, p=0.4] [Achtari 2005] (Level 4). Finally, lower-weight meshes, titanium or collagen-coated meshed have currently shown a significant reduction rate of vaginal mesh exposure rates [de Tayrac 2007; Deffieux 2007 ; Milani 2008; Cervigni 2011] [Sergent 2011] (Level 4). However, comparative studies would be necessary to compared new ultra-light-weight or composite to existing meshes.

b) Interest in mesh kits

The rate of intra-operative complications does not seem to be reduced by the use of a mesh kit rather than a self-prepared mesh [Caquant 2008] (Level 4). However, the rate of vaginal mesh exposure was shown to be reduced by the use of the same mesh in a kit format (4.5% versus 11%, p=0.048), in a retrospective study where the same surgeons had the experience of the technique with the self-prepared mesh before to use the kit [Caquant 2008] (Level 4).

Only one small randomised controlled trial has compared commercial transvaginal mesh kits to self styled mesh, however the techniques used where different (the kit only was trans-obturator) [Finamore 2010] (Level 2).

c) Concomitant hysterectomy

Several studies have shown an increased rate or vaginal mesh exposure with concomitant vaginal hysterectomy [Ganj 2009] [Guillibert 2009)] [de Tayrac 2007] [Cervigni 2011] [Collinet 2006] [Lowman 2008], while others did not find any differences [Deffieux 2007] [Sentilhes 2008] [Achtari 2005] **Table 25**. Meta-analysis demonstrates demonstrates that the addition of hysterectomy to a transvaginal mesh surgery significantly (p<0.001) increases the risk of mesh exposure from 7.3% (98% CI 4.1 to 9.6) without hysterectomy as compared to 19.2% [98% CI 15.8 to 22.7] with hysterectomy.

d) Surgical incision

Although some authors recommend avoiding sagittal or inverted T colpotomy and trimming of excessive vaginal epithelium in order to reduce the rate of vaginal mesh exposure [Fatton 2007], this has not been evaluated by other authors.

11. ABDOMINAL SACROCOLPOPEXY

a) Choice of surgical route for sacrocolpopexy

Laparoscopic sacrocolpopexy is as efficient as open abdominal sacrocolpopexy, with a reduced rate of intra-operative bleeding, hospitalisation and wound complications [Paraiso 2005] [Klauschie 2009] [Hsiao 2007] (Level 3).

The risk of vaginal mesh exposure is higher if the mesh is sutured vaginally during sacrocolpopexy [Higgs 2005] [Visco 2001; Tan-Kim 2011] (Level 4).

Although the feasibility of robotic-assisted and single-port sacrocolpopexy have been demonstrated there is currently not enough evidence to determine if these interventions will have an impact on complication rates.[Xylinas 2010; Paraiso 2011].

b) Choose the right mesh for abdominal surgery

In a retrospective comparative study of open abdominal sacrocolpopexy, Quiroz et al have shown that the short-term mesh-related complication rate was significantly higher with polypropylene than with porcine dermis [24/102 vs 12/134, p=0.003] [Quiroz 2008] (Level 3), however the prolapse recurrence rate using porcine dermis was higher [7/93 vs 0/105, p = 0.004]. Another study comparing fascia lata and polypropylene meshes with 5-year review, has shown a long-term increased recurrence rate, but

Table 25. Compares mesh exposure rate at transvaginal polypropylene mesh surgery with and without hysterectomy

Author	Year	Number	Review months	Surgical technique	Mesh exposure hysterectomy	Mesh exposure no hysterectomy	*p value*
Deffieux	2007	138	32	Polypropylene gynemesh	20/103	7/35	
Ganj	2009	127	18	Polypropylene mesh	6/21	7/106	
De Tayrac	2007	143	10	Low weight polypropylene coated Sofradim France	6/57	3/86	
Collinet	2006	277	2	Polypropylene mesh	30/164	4/113	
Guillilbert	2009	208	36	Polypropylene mesh awaiting raw data	24/77	7/40	
Chu	2011	91	9	Perigee & apogee Polypropylene mesh	5/39	2/52	
Neuman	2007	79	29	Posterior intravaginal slingplasty	6/44	4/35	
Total					97/505 (19.2%)	34/467 (7.3%)	<0.001

with no differences in the rate of complication (Tate) (Level 2). Concerning laparoscopic sacrocolpopexy, in a prospective comparative non randomised study, Deprest et al have shown that recurrences at the level of anterior and apical compartment occur significantly more often when using a biograft, in comparison to polypropylene [21% vs 3%, p<0.01 and 36% vs 19%, p <0.05, respectively] [Deprest 2009] [Level 3]. Partially absorbable composite meshes (polyglactin + polypropylene) also seems to increase the risk of short-term recurrences [Granese 2009] (Level 4).

The risk of vaginal mesh exposure seems to be higher with the use of polytetrafluoroethylene than with polypropylene meshes at ASC If you are going to abbreviate you must do it throughout or not at all [15% vs 0%, p=0.03] [Jeon 2009] (Level 4) and 19% vs 5% [Cundiff 2008] (Level 2). Similar results were observed with the use of silicon-coated polyester (19% vs 0%, p<0.05) [Govier 2005] (Level 4).

c) Choose the right fixation to the promontory, vaginal wall and levator ani

Most of authors perform a direct fixation to the vaginal wall using absorbable or non-absorbable sutures, and to the promontory using non-absorbable sutures [Agarwala 2007] [Rozet 2005] [Ross 2005] [Gadonneix 2004] [Antiphon 2004].

Fewer authors use staples for the mesh fixation, both to the vaginal wall and to the levator ani muscle [Cheret 2001] [Claerhout 2009], or tackers to the promontory [Maher 2004], with no specific reported complications. Several cases of spondylodiscitis were reported after the use of tackers to the promontory [Cosson 2001] however this complication also occurs if sutures are utilised. [Sergent 2011] [Rivoire 2007] [Ross 2005] [Antiphon 2004]. Whatever the fixation material use for the vaginal wall, the main method to prevent the occurrence of vaginal mesh exposure seems to avoid breaching the vaginal epithelium. [Paraiso 2005] [Cheret 2001] (Level 4).

d) Concomitant hysterectomy

The risk of vaginal mesh exposure is significantly increased in cases of sacrocolpopexy associated with concomitant total hysterectomy (8.6%), in comparison to 2.2% in those with previous hysterectomy [Wu 2006] [Stepanian 2008] [Cundiff 2008] [Nosti 2009] [Quiroz 2008] (Level 4), 1.5% at sacral hysteropexy and 1.7% subtotal hysterectomy [Jeon 2009] [Costantini 2005] [Bensinger 2005] (Level 4) (**Table 8 and10**).

12. PERITONEAL CLOSURE

Most of authors close the peritoneum after a sacrocolpopexy, both after open [Culligan 2005] [Wu 2006] [Stepanian 2008] [Maher 2004; Brubaker 2006] or laparoscopic approach [Maher 2011] [Rivoire 2007] [Rozet 2005] [Antiphon 2004].

13. TREATMENT OF VAGINAL MESH EXPOSURE

Vaginal mesh exposure, both after vaginal mesh surgery or sacrocolpopexy is usually associated with vaginal discharge, and sometimes pain, dyspareunia, vaginal infection, and rarely abscess or cellulitis [Deffieux 2007] [Costantini 2011] (Level 3).

The choice of treatment has to take into account the type of mesh implanted (need to obtain previous surgical records), clinical symptoms, location and size of exposure.

All cases with abscess or cellulitis need a immediate reoperation to withdraw the maximum (if possible all) of the foreign material.

In cases of mesh exposure after vaginal mesh surgery, if there is no abscess or cellulitis, medical treatment is usually undertaken using local oestrogens and/or local antiseptic. However, medical treatment efficacy is low at 23.5% as seen **Table 26**. [Withagen 2011] [Feiner 2010] [Moore 2010] [Achtari 2005] [Cervigni 2011] [Collinet 2006] After failure of medical treatment, a reoperation under local or general anesthesia is generally performed, in order to remove the exposed portion of the mesh and to close the vaginal epithelium.

In cases of mesh exposure after sacrocolpopexy, most of authors report a reoperation by the vaginal approach as first line [Wu 2006] [Stepanian 2008] [Claerhout 2009] [Kohli 1998] [Bensinger 2005] [Begley 2005], because of the risk of spondylodiscitis and of the very low success rate of medical treatment (<15%) [Price 2011] [Stepanian 2008] [Cundiff

Table 26. Efficacy of medical treatment for vaginal mesh exposure after vaginal mesh surgery

Author, Year	Mesh	Efficacy of medical treatment
Cervigni Natale, 2011	PP coated collagen (AVAULTA)	3/21
Withagen, 2011	PP (PROLIFT)	3/14
Long, 2011	PP	3/14
Moore, 2010	PP (PERIGEE)	1/12
Feiner, 2010	PP (PROLIFT)	6/10
Collinet, 2006	PP	9/34
Deffieux, 2006	PP (GYNEMESH ou GYNEMESH Soft)	7/34
Achtari, 2005	PP	4/14
Total		**36/153 (23.5%)**

Abbreviation: PP, polypropylene

2008] [Lowman 2008]. When recurrence occurs after vaginal mesh excision, or in case of associated pelvic infection, total mesh removal by laparoscopy or laparotomy has been described [Quiroz 2008] (Level 4).

Conclusion

The use of mesh for pelvic reconstructive surgery is associated with a risk of specific complications, whatever the surgical approach and whatever type of mesh (**Level 1**).

Preoperatively, patients must be informed of these risks and give their consent for the use of a mesh. Patients must also be informed of conservative and alternative surgical techniques.

PROPOSED RECOMMENDATIONS TO REDUCE THE RATE OF COMPLICATIONS

Grade A

Transvaginal mesh have a higher re-operation rate than native tissue vaginal repairs.(grade A)

Grade B

Concerning Vaginal Surgery:

- If a synthetic mesh is placed by the vaginal route, it is recommended that a macroporous polypropylene monofilament mesh should be used.
- Polyester mesh is not recommended.

Concerning Sacral Colpopexy:

- It is recommended that the mesh should not be introduced or sutured by vaginal route when a sacral colpopexy is performed.
- The use of silicone-coated polyester, porcine dermis, fascia lata, and polytetrafluoroethylene meshes is not recommended.
- It is recommended to avoid total hysterectomy

Grade C

Whatever the Surgical Route:

- There is no evidence to recommend routine local or systemic oestrogen therapy before or after prolapse surgery using mesh.
- The first cases should be undertaken with the guidance of an experienced surgeon in the relevant technique.

Concerning Sacrocolpopexy:

- Laparoscopic approach is recommended for sacral colpopexy
- The use of polyester (without silicone coating) or polypropylene meshes is recommended.
- Suture of the meshes to the promontory can be performed using thread/needle or tacker.
- Reperitonealisation is recommended to cover the meshes.

.Expert opinion

Whatever the Surgical Route:

- As with any surgery, cessation of smoking preoperatively is recommended.
- It is recommended to comply with the prevention of nosocomial infections.
- Antibiotic prophylaxis is recommended, regardless of the approach.
- It is recommended that pre-operative urinary tract infections are identified and treated.
- It is recommended that the type and commercial name of mesh used in the operative report .

Concerning Vaginal Surgery:

- It is recommended that a non-absorbable synthetic mesh should not be inserted into the rectovaginal septum when a rectal injury occurs.
- The placement of a non-absorbable synthetic mesh into the vesicovaginal septum may be considered after a bladder injury has been repaired if the repair is considered to be satisfactory.
- It is possible to perform a hysterectomy in association with the introduction of a non-absorbable synthetic mesh inserted vaginally but this is not recommended routinely .
- It is recommended to minimise the excision of vaginal tissue.
- Currently, there are not sufficient data to recommend the use of a mesh kit rather a self-prepared mesh.

X. PELVIC ORGAN PROLAPSE AND SEXUAL FUNCTION

Sexual health is an essential component of a women's well-being. Female sexual dysfunction is defined as a sexual desire, sexual arousal, orgasm and /or sexual pain disorder which causes personal distress [Basson 2000]. Up to 64% of sexually active women attending a Urogynecology clinic suffer from female sexual dysfunction [Pauls 2006]. The data on sexual function after prolapse surgery are conflicting although in most cases sexual function will improve or remain the same.

Apart from anatomical outcome, clinicians increasingly understand the importance of functional data after POP surgery. To measure sexual function, validated questionnaires on sexual function

are necessary. Some validated quality of life and symptom questionnaires are inclusive of sexual function[Baessler 2010] or there are dedicated questionnaires specific to sexual function that provide a discreet and reproducible method for evaluating sexual health. The Pelvic Organ Prolapse/Incontinence Sexual Questionnaire (PISQ)[Rogers 2001] and the Female Sexual Function Index(FSFI) [Rosen 2000] are two questionnaires frequently used.

1. SEXUAL FUNCTION AFTER PROLAPSE SURGERY WITHOUT MESH

Overall, sexual function improves after prolapse surgery without mesh[Ghielmetti 2006; Rogers 2006; Komesu 2007]. In two randomized controlled trials, sexual function was measured after sacrospinous hysteropexy and vaginal hysterectomy. No differences were found between the two groups [Jeng 2005; Dietz 2010]. No validated questionnaires were used.

2. SEXUAL FUNCTION AFTER PROLAPSE SURGERY WITH MESH

Increasing data on sexual function after mesh repair are becoming available. Excellent randomised controlled trials on efficacy of mesh prolapse surgery have been published and while most have not utilised validated questionnaires regarding sexual function most do include data on dyspareunia. Data from level 1 studies comparing transvaginal mesh and native tissue repairs are summarised in **Table 27**. When comparing sexual function in the anterior compartment with or without mesh, no differences in de novo dyspareunia, post-operative dyspareunia or PISQ scores were found [Nguyen 2008; Sivaslioglu 2008; Carey 2009; Nieminen 2010; Altman 2011; Milani 2011; Vollebregt 2011]. Most women improved or remained the same. In one study by Vollebregt [Vollebregt 2011], baseline dyspareunia disappeared more often after anterior colporrhaphy than after mesh implant [80% vs 20%, p=0.018]. Natale et al showed that the use of Porcine dermis graft (Pelvicol), compared to polypropylene mesh (Gynemesh) in the anterior compartment, was associated with an improvement in the PISQ scores[Natale 2009]. Possibly, porcine dermis allows more flexibility to the anterior wall resulting is less pain, however this requires further evaluation.

In the posterior compartment, fewer RCT's have been performed comparing native tissue repairs to mesh repairs. Paraiso et al compared three techniques (posterior colporrhaphy, site- specific repair and use of porcine small intestine sub mucosa) [Paraiso 2006]. No differences in sexual outcome were found between the groups and PISQ scores improved after surgery in all three groups. Trials which analysed anterior and posterior mesh together also reported no differences in sexual outcome between native tissue and mesh repairs.[Iglesia 2010; Milani 2011; Withagen 2011]. Overall, after mesh surgery in the anterior and/or posterior compartment, de novo dyspareunia ranged from 5-28% of women [Nguyen 2008; Sivaslioglu 2008; Carey 2009; Vollebregt 2011; Withagen 2011]. Data on the apical compartment using mesh showed less dyspareunia after abdominal sacral colpopexy as compared to vaginal sacrospinous colpopexy [Benson 1996; Maher 2004; Maher 2010].

Meta-analyses from all RCT comparing transvaginal mesh and native tissue repairs shown in **Table 25** demonstrated no difference in the rate of denovo dyspareunia (mesh 10.6% versus 11.8% native tissue),

Table 27 Meta-analysis sexual function data from randomized controlled trials comparing transvaginal mesh to native tissue repairs

Author		**de novo dyspareunia**		**Post operative dyspareunia**		**Post operative PISQ score**	
RCT		Vaginal Mesh	Native tissue	Mesh	Native tissue	Mesh	Native tissue
Altman	2011			8/110	2/101	33.1±6.7 35.1(1.4)	32.2±7.2 35.0(1.4)
Vollebregt	2011	3/20	2/21				
Carey	2009	5/18	5/12	12/30	13/33	change -6,9	change -7,8
Sivasliogly	2008	2/43	0/42				
Ngyuyen	2008	2/22	4/26	2/23	2/23	33±3 34±6	32±4 33±3
Sokol	2011	1/11	3/14			31/34	32/35
Milani	2011	3/37	3/29	9/53	12/51	35±5.7 34.0±6.7	31.5±7.2 34.7±5.7
TOTAL		**16/151 (10.6%)**	**17/144 (11.8%)**	**31/216 (14.4%)**	**26/207 (12.5%)**	**0.09 [-0.17, 0.36] No difference**	

post-operative dyspareunia (14.4% versus 12.5%), and PISQ scores (WMD 0.09 95% CI -0.17 to 0.36).

Although data from RCT's is valuable, sexual function was a secondary outcome measurement and most studies are underpowered to detect differences in sexual function. Therefore, reports from Level 3 cohort studies on the use of mesh were evaluated. The rate of de novo dyspareunia after anterior and/or posterior mesh in these cohort studies was comparable to the RCT's mentioned before and varied between 21-43% (**Table 28**) [Fayyad 2011; Milani 2011]. Milani et al stated that mesh should be abandoned because of high scores on dyspareunia [20% more dyspareunia after anterior mesh and 63% more dyspareunia after posterior Mesh)(Milani 2005]. However, when measuring sexual function with questionnaires, the impact of transvaginal meshes was variable with some demonstrating poorer sexual outcomes [Altman 2009; Su 2009; Wetta 2009][lower PISQ scores] and some improved outcomes or no change following surgery. [Moore ; Sentilhes ; Milani 2011; Sayer 2011]. Altman et all showed lower scores on sexual function one year after mesh surgery (anterior repair and posterior repair), however this was related to behavioral-emotional function and partner related items, not to physical function [Altman 2009]. Pain and dyspareunia before surgery with mesh was a risk factor for pain and dyspareunia after mesh surgery [Withagen 2011]. There is some evidence that light meshes, partly absorbable meshed or non anchored meshes have less negative side effects on sexual function, however comparitive studies or RCT's on this subject have not been performed [de Tayrac 2007; Zyczynski 2010; Milani 2011].

Recommendations

Grade B

With regard to the anterior compartment, the use of mesh is neither associated with a worsening in sexual function nor with an increase of de novo dyspareunia compared to traditional anterior colporrhaphy.

Grade D

There is insufficient information to provide evidence based recommendation on sexual function after vaginal mesh in the posterior compartment.

There is insufficient information to provide evidence based recommendation on sexual function after new light of partially absorbable vaginal meshes.

It is essential to use validated questionnaires measuring sexual function in women before and after prolapse surgery. We also recommend reporting sexual activity and dyspareunia rates pre and post intervention in all patients.

Table 28. Meta-analysis sexual function from prospective evaluations transvaginal meshes

Author	Year	n*	*de novo* dyspareunia	f.u. (months)	Mesh	PISQ-12pre	PISQ-12 post
Withagen	2011	294	20/71 (28%)	12	PP		
Maher	2011	55	3/21 (14%)	24	PP		
Long	2011	60 (Perigee™) 48 (Prolift™)	10/60 (16%) 12/48 (25%)	6 6	PP PP		
Milani	2011	127	1/43 (2%)	12	PPlight	33.4±7.7	39.0±4.4
Sergent	2011	101	4/52 (8%)	57	Coated PP		
Sayer	2011	110	2/32(6%)	24	PP	32.2±6.2	36.8±5.5
Jacquetin	2010	90	5/35 (14%)	3	PP		No
Moore	2010	87	6/65 (9%)	24	PP	33.4±7.7	36.8±5.5
Fayyad	2010	36	7/16 (43%)	24	PP	NA	NA
Feiner	2010	117	4/51 (8%)	12	PP	NA	NA
Wetta	2009	50		12	PP	20.2±4.9	16.2±6.0
Milina	2009	46	2/11(18%)	1	PP		
Altman	2009	69		12	PP	15.5±8.0	11.7±6.7
Su	2009	33		6	PP	29.5±9.0	19.3±14.7
Lowman	2008	57	6/36(17%)	12	PP	NA	NA
Hinoul	2008	48	3/20 (15%)	12	PP	NA	NA
Sentilhes	2008	83	6/37 (16%)	1	PP	33.4±7.8	35.5±7.3
de Tayrac	2007	143	10/78 (12.8%)	10	Coated PP		No
Total	**-**	**-**	**102/680 (15.0%)**	**-**	**-**	**-**	**-**

XI. ECONOMIC EVALUATION

Vaginal prolapse is an increasingly common problem affecting approximately 3-6% [Bradley 2008; Lawrence 2008] of community dwelling American women and the lifetime risk of surgery for pelvic organ prolapse varies between 6-19%. [Olsen 1997; Smith 2010]The need for pelvic organ prolapse surgery increases with age and it has been conservatively estimated that the surgical workload related to pelvic organ prolapse will increase by 46% over the next 4 decades as our population ages [Wu 2009]. Despite the high prevalence and frequency of surgery for POP, there is a little information on costs of medical care for this condition. A study in the United States (US) estimated that the direct costs of POP surgery were substantial accounting for $1012 million (95% confidence interval $775, 1251 million) for a total of 226,000 in patient surgical procedures during 1997[Subak 2001].

A European study showed that the number (rate) of admissions for POP surgery was 36,854/ 0.87 per 1000 women) in Germany, 36,679 (1.14 per 1000 women) in France, and 28,959 (1.13 per 1000 women) in England during the year 2005[Subramanian 2009]. The total costs were €144,236,557, €83,067,825, and €81,030,907 in Germany, France and England respectively which are also considered to be substantial and required more attention in order to decrease the burden on the countries studied.

Traditionally a Gynaecologists have based their decisions on surgical interventions upon the success rate, patient satisfaction, peri-operative morbidity and complications. With rising health care cost and in a setting of finite resources it is now imperative that clinicians include the financial costs of surgical interventions as a vital part of our decision making process. Despite considerable consumable costs there is a scarcity of cost effectiveness data on pelvic organ prolapse surgery.

Hullfish designed a study to compare the relative cost effectiveness of treatment decision alternatives for post-hysterectomy POP[Hullfish 2011]. The authors used a Markov decision analysis model to assess and compare the relative cost effectiveness of expectant management, use of a ring pessary, and Vaginal Reconstructive Surgery (VRS) and open or robotic sacral colpopexy for obtaining months of quality adjusted life over 1 year. Laparoscopy for prolapse and vaginal mesh kits were excluded as the authors do not utilise those two procedures at their institution and colpocleisis was excluded as the baseline case desired preservation of coital function. Only two decision alternatives were found to be cost-effective: pessary use and VRS. Pessary use achieved 10.4 quality-adjusted months at a cost of $10,000 per patient. This cost includes all events for patients initially assigned to pessary use including costs for those patients who eventually underwent to surgery within the 12-month time frame. The VRS alternative obtained 11.4 quality-adjusted months, at $15,000 per patient. Each of the other alternatives achieved fewer quality-adjusted months at greater cost.

Abdominal sacral colpopexy (ASC), in rudimentary analysis of inpatient cost has been shown to be more expensive than vaginal sacrospinous colpopexy for vault prolapse mainly reflecting the longer operating time and inpatient stay for the ASC. Two cost-minimisation studies have evaluated the relative inpatient cost of robotic sacral colpopexy (RSC), laparoscopic sacral colpopexy (LSC) and ASC [Patel 2009; Judd 2010] with both finding the ASC was the least costly inpatient option. Patel reviewed 15 cases, 5 each of ASC, LSC and RSC performed in Connecticut USA in 2008 [Patel 2009]. Results showed that ASC was the least expensive at $13,149, LSC $19.308 and RSC most expensive at $24,161. Importantly in this model there were no differences in length of stay and all procedures had long operating time with the robotic procedure being over 2 hours quicker than the laparoscopic procedures which does not reflect common practice in the literature.

Judd et al, using a decision model, estimated the hospital cost of ASC at $5792, LSC at $7353 and RSC at $8508 (excluding the cost of the robotic system)[Judd 2010]. In this model, RSC and LSC became cost equivalent only when robotic operating times was reduced to 149 minutes, robotic disposables were reduced to $2132 or laparoscopic disposables were increased to $3413. Both models of analysis only included inpatient care and may not reflect other benefits of minimally invasive approach such as quicker recovery and possibly faster return to work.

As already reported in the apical prolapse section of this document Parasio et al [Paraiso 2011] performed a RCT comparing RSC [38] and LSC [40] for vault prolapse and reported cost analysis alongside the clinical outcomes which the authors of this document would prefer to see as the standard reporting requirements. The robotic group incurred significantly greater cost than the laparoscopic group [mean difference +$1,936; 95% CI $417-$3,454; P=.008]. Importantly in this study the authors were experienced laparoscopic surgeons who had also completed the learning phase of the RSC.

Over the last decade both clinical efficacy and cost efficiency of the suburethral tapes in continence surgery has been demonstrated. Transvaginal mesh kits have been introduced to prolapse surgery in an attempt to replicate this benefit for the community. Unfortunately a paucity of cost analysis data is available for review. A study on the analysis of the cost-effectiveness of tradition-

al anterior colporrhaphy (AC), non kit mesh and commercial mesh kit for anterior vaginal prolapse repair showed that commercial mesh kits are not cost effective [Murray 2011]. The authors included estimated cost of managing recurrent prolapse and extrusions in the analytic model after performing a meta-analysis of 18 papers relating to anterior compartment repair to determine operating and admission time, recurrence rate and mesh extrusion rate for the three groups. The cost of non kit mesh was $3,380, AC was $3,461 and mesh kit $4,678. Non kit mesh repair is cost-effective, compared with AC, if extrusion rates remain below 25%. One way cost sensitivity analysis demonstrates that when the reoperation rate for AC reached 28% the commercial mesh kits became cost effective. The balance of cost of AC and non-mesh kits depends significantly on recurrence and extrusion rates. Two-way cost sensitivity analysis demonstrated that if re-operation rate of AC is below 20%, AC is more cost effective even if extrusion rate is 0%. When reoperation rate of AC is 30% the non-mesh kit repair is the most effective option if the extrusion rate is less than 25%.

Recently, Maher et al reported a cost minimisation analysis of a RCT comparing total vaginal mesh [TVM n=55] and LSC [n=53] in the management of vault prolapse at 2 years[Maher 2011]. The clinical outcomes have been reported in this document previously. Similarly to Hullfish's model above the authors captured inpatient, consumable and direct reoperation cost within the two year period. Opportunity cost defined as economic cost to the women associated with recovery time were added to above cost to define total economic cost. Mean total economic costs were significantly lower in the LSC group as compared to the TVM ($4,013.07 95% CI 3107.77, 4918.37). Labour costs were significantly greater for the LSC reflecting that the operating time was twice as long as compared to the TVM procedure. These higher labour costs were offset by lower consumable, inpatient, opportunity? and reoperation costs for the LSC as compared to the TVM.

One way cost analysis for the LSC and TVM demonstrates that cost equivalence would be achieved once the consumable cost reduced to zero, or the reoperation rate was zero in the TVM group or the operating time in the LSC was 130 minutes longer than the TVM. The cost model reported by Maher et al would provide an excellent model that all clinicians could utilise in audit and authors when reporting prolapse outcomes, by simply substituting their own institutions and community cost. The reporting of such cost analysis data is urgently required so that we can deliver efficient and cost effective pelvic organ prolapse procedures that our community requires.

Conclusion

In conclusion, despite the high prevalence and frequency of surgery for POP, there is little information relating to cost. Our findings can be summarised as:

- Economic cost of POP surgeries annually is significant in United States and Europe and over the next decades will grow at twice the rate of population growth due to our aging population
- Programs aimed at reducing the burden of this disease are urgently needed.
- In a single institution study vaginal reconstructive surgery and pessary use were more cost-effective than expectant management, traditional abdominal sacral colpopexy (ASC) or robot-assisted sacral colpopexy (RSC) (**Grade C**).
- Two studies have demonstrated that ASC has lower inpatient cost than LSC or RSC (**Grade C**)
- Data from a single RCT demonstrated the LSC to have lower inpatient cost than RSC specifically relating to lower operating time in the LSC group (**Grade B**)
- Data from a single RCT demonstrated LSC to be a more effective cost minimising surgery than total vaginal mesh for vaginal vault prolapse.(Grade B)
- Data from a meta-analysis of anterior vaginal compartment prolapse operations demonstrated that commercial mesh kits for anterior repair are less cost-effective than non kit mesh and anterior colporrhaphy. (**Grade B**)

REFERENCES

http://www.fda.gov/downloads/MedicalDevices/Safety/AlertsandNotices/UCM262760.pdf.

http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm.

Abramov Y, Kwon C, et al. (2003). "Long-term anatomic outcome of discrete site-specific defect repair versus standard posterior colporraphy for the correction of advanced rectocele: A 1 year follow-up analysis." Neurourol Urodyn **22**(5): 520-521.

Abramov, Y., S. Gandhi, et al. (2005). "Site-specific rectocele repair compared with standard posterior colporrhaphy." Obstet Gynecol **105**(2): 314-318.

Achtari, C., R. Hiscock, et al. (2005). "Risk factors for mesh erosion after transvaginal surgery using polypropylene (Atrium) or composite polypropylene/polyglactin 910 (Vypro II) mesh." International Urogynecology Journal And Pelvic Floor Dysfunction **16**(5): 389-394.

Addison, W. A., C. H. Livengood, 3rd, et al., Eds. (1985). Abdominal sacral colpopexy with Mersilene mesh in the retroperitoneal position in the management of posthysterectomy vaginal vault prolapse and enterocele. Am J Obstet Gynecol. United States.

Addison, W. A. and M. C. Timmons (1993). "Abdominal approach to vaginal eversion." Clin Obstet Gynecol **36**(4): 995-1004.

Agarwala, N., N. Hasiak, et al. (2007). "Laparoscopic sacral colpopexy with Gynemesh as graft material--experience and results." J Minim Invasive Gynecol **14**(5): 577-583.

Akl, M. N., J. B. Long, et al. (2009). “Robotic-assisted sacrocolpopexy: technique and learning curve.” Surg Endosc **23**(10): 2390-2394.

Akl, M. N., J. B. Long, et al. (2009). “Robotic-assisted sacrocolpopexy: technique and learning curve.” Surgical endoscopy **23**(10): 2390-2394.

Akladios, C. Y., D. Dautun, et al. (2010). “Laparoscopic sacrocolpopexy for female genital organ prolapse: establishment of a learning curve.” Eur J Obstet Gynecol Reprod Biol **149**(2): 218-221.

Alcalay, M., M. Cosson, et al. (2011). “Trocarless system for mesh attachment in pelvic organ prolapse repair--1-year evaluation.” Int Urogynecol J Pelvic Floor Dysfunct **22**(5): 551-556.

Altman, D., C. Elmer, et al. (2009). “Sexual dysfunction after trocar-guided transvaginal mesh repair of pelvic organ prolapse.” Obstet Gynecol **113**(1): 127-133.

Altman, D. and C. Falconer (2007). “Perioperative morbidity using transvaginal mesh in pelvic organ prolapse repair.” Obstet Gynecol **109**(2 Pt 1): 303-308.

Altman, D., T. Vayrynen, et al. (2011). “Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse.” N Engl J Med **364**(19): 1826-1836.

Altman, D., J. Zetterstrom, et al. (2006). “A three-year prospective assessment of rectocele repair using porcine xenograft.” Obstetrics & Gynecology **107**(1): 59-65.

Amrute, K. V., E. R. Eisenberg, et al. (2007). “Analysis of outcomes of single polypropylene mesh in total pelvic floor reconstruction.” Neurourology And Urodynamics **26**(1): 53-58.

Amundsen, C. L., B. J. Flynn, et al. (2003). “Anatomical correction of vaginal vault prolapse by uterosacral ligament fixation in women who also require a pubovaginal sling.” J Urol **169**(5): 1770-1774.

Antiphon, P., S. Elard, et al. (2004). “Laparoscopic promontory sacral colpopexy: is the posterior, recto-vaginal, mesh mandatory?” Eur Urol **45**(5): 655-661.

Antosh, D. D., C. B. Iglesia, et al. (2011). “Outcome assessment with blinded versus unblinded POP-Q exams.” Am J Obstet Gynecol **205**(5): 489 e481-484.

Antovska, S. V. and D. G. Dimitrov (2006). “Vaginosacral colpopexy (VSC)--a new modification of the Mc Call operation using vaginosacral ligaments as autologous sliding grafts in posthysterectomy vault prolapse.” Bratislavske lekarske listy **107**(3): 62-72.

Araco, F., G. Gravante, et al. (2009). “The influence of BMI, smoking, and age on vaginal erosions after synthetic mesh repair of pelvic organ prolapses. A multicenter study.” Acta Obstet Gynecol Scand **88**(7): 772-780.

Arnold MW, Stewart WR, et al. (1990). “Rectocele repair. Four year’s experience.” Dis Colon Rectum **33**(684-7.).

Aronson, M. P., P. K. Aronson, et al., Eds. (2005). Low risk of ureteral obstruction with “deep” (dorsal/posterior) uterosacral ligament suture placement for transvaginal apical suspension. Am J Obstet Gynecol. United States.

Arthure, H. G. and D. Savage (1957). “Uterine prolapse and prolapse of the vaginal vault treated by sacral hysteropexy.” J Obstet Gynaecol Br Emp **64**(3): 355-360.

Ayhan, A., S. Esin, et al. (2006). “The Manchester operation for uterine prolapse.” Int J Gynaecol Obstet **92**(3): 228-233.

Baden, W. F. and T. A. Walker (1972). “Genesis of the vaginal profile: a correlated classification of vaginal relaxation.” Clin Obstet Gynecol **15**(4): 1048-1054.

Baessler, K., A. D. Hewson, et al. (2005). “Severe mesh complications following intravaginal slingplasty.” Obstet Gynecol **106**(4): 713-716.

Baessler, K., S. M. O’Neill, et al. (2010). “A validated self-administered female pelvic floor questionnaire.” Int Urogynecol J **21**(2): 163-172.

Baessler, K., S. M. O’Neill, et al. (2010). “A validated self-administered female pelvic floor questionnaire.” International Urogynecology Journal **21**(2): 163-172.

Baessler, K. and B. Schuessler (2001). “Abdominal sacrocolpopexy and anatomy and function of the posterior compartment.” Obstet Gynecol **97**(5 Pt 1): 678-684.

Bai, S. W., E. H. Kim, et al. (2005). “A comparison of different pelvic reconstruction surgeries using mesh for pelvic organ prolapse patients.” Yonsei Med J **46**(1): 112-118.

Baker, K. R., J. M. Beresford, et al. (1990). “Colposacropexy with Prolene mesh.” Surgery, gynecology & obstetrics **171**(1): 51-54.

Banu, L. F. (1997). “Synthetic sling for genital prolapse in young women.” Int J Gynaecol Obstet **57**(1): 57-64.

Barber, M. D. (2005). “Symptoms and outcome measures of pelvic organ prolapse.” Clin Obstet Gynecol **48**(3): 648-661.

Barber, M. D., C. L. Amundsen, et al. (2007). “Quality of life after surgery for genital prolapse in elderly women: obliterative and reconstructive surgery.” Int Urogynecol J Pelvic Floor Dysfunct **18**(7): 799-806.

Barber, M. D., L. Brubaker, et al. (2009). “Opterations and Pelvic Muscule Traning in the Management of Apical Support Loss Trial: Design and Methods.” Contemp Clin Trials **in press**.

Barber, M. D., L. Brubaker, et al. (2009). “Defining success after surgery for pelvic organ prolapse.” Obstet Gynecol **114**(3): 600-609.

Barber, M. D., M. N. Kuchibhatla, et al. (2001). “Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders.” Am J Obstet Gynecol **185**(6): 1388-1395.

Barber, M. D., A. G. Visco, et al. (2000). “Bilateral uterosacral ligament vaginal vault suspension with site-specific endopelvic fascia defect repair for treatment of pelvic organ prolapse.” Am J Obstet Gynecol **183**(6): 1402-1410; discussion 1410-1401.

Barber, M. D., M. D. Walters, et al. (2005). “Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7).” Am J Obstet Gynecol **193**(1): 103-113.

Barranger, E., X. Fritel, et al. (2003). “Abdominal sacrohysteropexy in young women with uterovaginal prolapse: long-term follow-up.” Am J Obstet Gynecol **189**(5): 1245-1250.

Basson, R., J. Berman, et al. (2000). “Report of the international consensus development conference on female sexual dysfunction: definitions and classifications.” J Urol **163**(3): 888-893.

Begley, J. S., S. P. Kupferman, et al. (2005). “Incidence and management of abdominal sacrocolpopexy mesh erosions.” Am J Obstet Gynecol **192**(6): 1956-1962.

Behnia-Willison, F., E. I. Seman, et al. (2007). “Laparoscopic paravaginal repair of anterior compartment prolapse.” J Minim Invasive Gynecol **14**(4): 475-480.

Benizri, E. J., P. Volpe, et al. (1996). “A new vaginal procedure for cystocele repair and treatment of stress urinary incontinence.” J Urol **156**(5): 1623-1625.

Bensinger, G., L. Lind, et al. (2005). “Abdominal sacral suspensions: analysis of complications using permanent mesh.” Am J Obstet Gynecol **193**(6): 2094-2098.

Benson, J. T., V. Lucente, et al. (1996). “Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with long-term outcome evaluation.” Am J Obstet Gynecol **175**(6): 1418-1421.

Borstad, E., M. Abdelnoor, et al. (2010). “Surgical strategies for women with pelvic organ prolapse and urinary stress incontinence.” Int Urogynecol J Pelvic Floor Dysfunct **21**(2): 179-186.

Borstad, E., M. Abdelnoor, et al. (2010). “Surgical strategies for women with pelvic organ prolapse and urinary stress incontinence.” Int Urogynecol J **21**(2): 179-186.

Boulanger, L., M. Boukerrou, et al. (2008). “Bacteriological analysis of meshes removed for complications after surgical management of urinary incontinence or pelvic organ prolapse.” Int Urogynecol J Pelvic Floor Dysfunct **19**(6): 827-831.

Boyles, S. H., A. M. Weber, et al. (2003). “Procedures for pelvic organ prolapse in the United States, 1979-1997.” Am J Obstet Gynecol **188**(1): 108-115.

Bradley, C. S., K. S. Kenton, et al. (2008). “Obesity and outcomes after sacrocolpopexy.” Am J Obstet Gynecol **199**(6): 690 e691-698.

Bradley, C. S. and I. E. Nygaard (2005). “Vaginal wall descensus and pelvic floor symptoms in older women.” Obstet Gynecol **106**(4): 759-766.

Brizzolara, S. and A. Pillai-Allen (2003). “Risk of Mesh Erosion With Sacral Colpopexy and Concurrent Hysterectomy.” Obstet Gynecol **102**(2): 306-310.

Brown, J. S., L. E. Waetjen, et al. (2002). “Pelvic organ prolapse surgery in the United States, 1997.” Am J Obstet Gynecol **186**(4): 712-716.

Brubaker, L., Ed. (1995). Sacrocolpopexy and the anterior compartment: support and function. Am J Obstet Gynecol. United States.

Brubaker, L. (2005). “Burch Colposuspension at the time of sacrocolpopexy in stress continent women reduces bothersome stress urinary symptoms: The CARE randomized trial.” J Pelvic Surg **11**(Supplement 1): S5.

Brubaker, L., G. W. Cundiff, et al. (2006). “Abdominal sacrocolpopexy with Burch colposuspension to reduce urinary stress incontinence.” N Engl J Med **354**(15): 1557-1566.

Brubaker, L., C. Glazener, et al. (2009). Surgery for Pelvic Organ Prolapse. Paris, Health Publication Ltd.

Brubaker, L., I. Nygaard, et al., Eds. (2008). Two-year outcomes after sacrocolpopexy with and without burch to prevent stress urinary incontinence. Obstet Gynecol. United States.

Brubaker, L., I. Nygaard, et al. (2008). “Two-year outcomes after sacrocolpopexy with and without burch to prevent stress urinary incontinence.” Obstet Gynecol **112**(1): 49-55.

Bruce, R. G., R. E. El Galley, et al. (1999). “Paravaginal defect repair in the treatment of female stress urinary incontinence and cystocele.” Urology **54**(4): 647-651.

Bump, R. C., W. G. Hurt, et al. (1996). “Randomized prospective comparison of needle colposuspension versus endopelvic fascia plication for potential stress incontinence prophylaxis in women undergoing vaginal reconstruction for stage III or IV pelvic organ prolapse. The Continence Program for Women Research Group.” Am J Obstet Gynecol **175**(2): 326-333; discussion 333-325.

Bump, R. C., A. Mattiasson, et al. (1996). “The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction.” Am J Obstet Gynecol **175**(1): 10-17.

Caquant, F., P. Collinet, et al. (2008). “Safety of Trans Vaginal Mesh procedure: retrospective study of 684 patients.” J Obstet Gynaecol Res **34**(4): 449-456.

Carey, M., P. Higgs, et al. (2009). “Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial.” BJOG **116**(10): 1380-1386.

Carey, M., M. Slack, et al. (2008). “Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device.” BJOG **115**(3): 391-397.

Cervigni, M., F. Natale, et al. (2007). “Transvaginal cystocele repair with polypropelene mesh using a tesion-free technique.” International Urogynecology Journal And Pelvic Floor Dysfunction **published online**(DOI 10.1007/soo192-0070-0486-6).

Cervigni, M., F. Natale, et al. “Transvaginal cystocele repair with polypropylene mesh using a tension-free technique.”

Cervigni, M., F. Natale, et al. (2011). “Collagen-coated polypropylene mesh in vaginal prolapse surgery: an observational study.” Eur J Obstet Gynecol Reprod Biol **156**(2): 223-227.

Chan, S. S., S. M. Pang, et al. (2011). “Laparoscopic sacrocolpopexy for the treatment of vaginal vault prolapse: with or without robotic assistance.” Hong Kong medical journal = Xianggang yi xue za zhi / Hong Kong Academy of Medicine **17**(1): 54-60.

Chen, G., B. Ling, et al. (2010). “Laparoscopic extraperitoneal uterine suspension to anterior abdominal wall bilaterally using synthetic mesh to treat uterovaginal prolapse.” J Minim Invasive Gynecol **17**(5): 631-636.

Chen, H. W., M. K. Guess, et al. (2009). “Ischiorectal abscess and ischiorectal-vaginal fistula as delayed complications of posterior intravaginal slingplasty: a case report.” J Reprod Med **54**(10): 645-648.

Cheret, A., P. Von Theobald, et al., Eds. (2001). [Laparoscopic promontofixation feasibility study in 44 patients]. J Gynecol Obstet Biol Reprod (Paris). France.

Chmielewski, L., M. D. Walters, et al., Eds. (2011). Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol. United States.

Chmielewski, L., M. D. Walters, et al. (2011). “Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success.” Am J Obstet Gynecol.

Chou, L. Y., D. Y. Chang, et al., Eds. (2010). Clinical outcome of transvaginal sacrospinous fixation with the Veronikis ligature carrier in genital prolapse. Eur J Obstet Gynecol Reprod Biol. Ireland.

Chu, L. C., F. C. Chuang, et al. “Comparison of short-term outcomes following pelvic reconstruction with Perigee and Apogee systems: hysterectomy or not?” Int Urogynecol J.

Chughtai, B., S. Spettel, et al. (2011). “Ambulatory pessary trial unmasks occult stress urinary incontinence.” Obstet Gynecol Int **2012**: 392027.

Chung, S. Y., M. Franks, et al. (2002). “Technique of combined pubovaginal sling and cystocele repair using a single piece of cadaveric dermal graft.” Urology **59**(4): 538-541.

Claerhout, F., D. De Ridder, et al. (2010). “Sacrocolpopexy using xenogenic acellular collagen in patients at increased risk for graft-related complications.” Neurourology and urodynamics **29**(4): 563-567.

Claerhout, F., J. P. Roovers, et al. (2009). “Implementation of laparoscopic sacrocolpopexy--a single centre’s experience.” Int Urogynecol J Pelvic Floor Dysfunct **20**(9): 1119-1125.

Claerhout, F., J. P. Roovers, et al. (2009). “Implementation of laparoscopic sacrocolpopexy--a single centre’s experience.” Int Urogynecol J Pelvic Floor Dysfunct **20**(9): 1119-1125.

Clemons, J. L., D. L. Myers, et al. (2003). “Vaginal paravaginal repair with an AlloDerm graft.” American Journal of Obstetrics and Gynecology **189**(6): 1612-1618.

Collinet, P., F. Belot, et al. (2006). “Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors.” International Urogynecology Journal And Pelvic Floor Dysfunction **17**(4): 315-320.

Collinet, P., F. Belot, et al. (2006). “Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors.” Int Urogynecol J Pelvic Floor Dysfunct **17**(4): 315-320.

Collins, S. A., J. E. Jelovsek, et al., Eds. (2007). De novo rectal prolapse after obliterative and reconstructive vaginal surgery for urogenital prolapse. Am J Obstet Gynecol. United States.

Collopy, B. T. and K. A. Barham (2002). “Abdominal colporectopexy with pelvic cul-de-sac closure.” Diseases of the colon and rectum **45**(4): 522-526; discussion 526-529.

Colombo, M., A. Maggioni, et al. (1997). “Surgery for genitourinary prolapse and stress incontinence: a randomized trial of posterior pubourethral ligament plication and Pereyra suspension.” Am J Obstet Gynecol **176**(2): 337-343.

Colombo, M., A. Maggioni, et al. (1996). “Prevention of postoperative urinary stress incontinence after surgery for genitourinary prolapse.” Obstet Gynecol **87**(2): 266-271.

Colombo, M. and R. Milani, Eds. (1998). Sacrospinous ligament fixation and modified McCall culdoplasty during vaginal hysterectomy for advanced uterovaginal prolapse. Am J Obstet Gynecol. United States.

Colombo, M. and R. Milani (1998). “Sacrospinous ligament fixation and modified McCall culdoplasty during vaginal hysterectomy for advanced uterovaginal prolapse.” Am J Obstet Gynecol **179**(1): 13-20.

Colombo, M., D. Vitobello, et al. (2000). “Randomised comparison of Burch colposuspension versus anterior colporrhaphy in

women with stress urinary incontinence and anterior vaginal wall prolapse." BJOG **107**(4): 544-551.

Comiter, C. V., S. P. Vasavada, et al. (1999). "Transvaginal culdosuspension: technique and results." Urology **54**(5): 819-822.

Cosson, M., P. Collinet, et al. (2001). "The vaginal patch plastron for vaginal cure of cystocele. Preliminary results for 47 patients." Eur J Obstet Gynecol Reprod Biol **95**(1): 73-80.

Cosson, M., R. Rajabally, et al. (2002). " Laparoscopic sacrocolpopexy, hysterectomy, and burch colposuspension: feasibility and short-term complications of 77 procedures." JSLS **6**(2): 115-119.

Costantini, E., M. Lazzeri, et al. (2008). "Burch colposuspension does not provide any additional benefit to pelvic organ prolapse repair in patients with urinary incontinence: a randomized surgical trial." J Urol **180**(3): 1007-1012.

Costantini, E., M. Lazzeri, et al. (2010). "Pelvic organ prolapse repair with and without prophylactic concomitant Burch colposuspension in continent women: a randomized, controlled trial with 8-year followup." J Urol **185**(6): 2236-2240.

Costantini, E., M. Lazzeri, et al. (2011). "Pelvic organ prolapse repair with and without prophylactic concomitant Burch colposuspension in continent women: a randomized, controlled trial with 8-year followup." J Urol **185**(6): 2236-2240.

Costantini, E., M. Lazzeri, et al. "Five-year outcome of uterus sparing surgery for pelvic organ prolapse repair: a single-center experience." Int Urogynecol J **22**(3): 287-292.

Costantini, E., R. Lombi, et al. (1998). "Colposacropexy with Gore-tex mesh in marked vaginal and uterovaginal prolapse." Eur Urol **34**(2): 111-117.

Costantini, E., L. Mearini, et al. (2005). "Uterus preservation in surgical correction of urogenital prolapse." Eur Urol **48**(4): 642-649.

Costantini, E., A. Zucchi, et al. (2007). "Must colposuspension be associated with sacropexy to prevent postoperative urinary incontinence?" Eur Urol **51**(3): 788-794.

Cruikshank, S. H. and M. Muniz, Eds. (2003). Outcomes study: A comparison of cure rates in 695 patients undergoing sacrospinous ligament fixation alone and with other site-specific procedures--a 16-year study. Am J Obstet Gynecol. United States.

Culligan, P. J., L. Blackwell, et al., Eds. (2005). A randomized controlled trial comparing fascia lata and synthetic mesh for sacral colpopexy. Obstet Gynecol. United States.

Culligan, P. J., L. Blackwell, et al. (2005). "A randomized controlled trial comparing fascia lata and synthetic mesh for sacral colpopexy." Obstet Gynecol **106**(1): 29-37.

Culligan, P. J., M. Murphy, et al. (2002). "Long-term success of abdominal sacral colpopexy using synthetic mesh." Am J Obstet Gynecol **187**(6): 1473-1480; discussion 1481-1472.

Cundiff, G. W., E. Varner, et al. (2008). "Risk factors for mesh/suture erosion following sacral colpopexy." Am J Obstet Gynecol **199**(6): 688 e681-685.

Cundiff, G. W., A. C. Weidner, et al. (1998). "An anatomic and functional assessment of the discrete defect rectocele repair." Am J Obstet Gynecol **179**(6 Pt 1): 1451-1456.

de Boer, T. A., A. L. Milani, et al. (2009). "The effectiveness of surgical correction of uterine prolapse: cervical amputation with uterosacral ligament plication (modified Manchester) versus vaginal hysterectomy with high uterosacral ligament plication." International urogynecology journal and pelvic floor dysfunction **20**(11): 1313-1319.

de Landsheere, L., S. Ismail, et al. (2011). "Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up." Am J Obstet Gynecol.

de Tayrac, R., X. Deffieux, et al. (2006). "Long-term anatomical and functional assessment of trans-vaginal cystocele repair using a tension-free polypropylene mesh." International Urogynecology Journal And Pelvic Floor Dysfunction **17**(5): 483-488.

de Tayrac, R., G. Devoldere, et al. (2007). "Prolapse repair by vaginal route using a new protected low-weight polypropylene mesh: 1-year functional and anatomical outcome in a prospective multicentre study." Int Urogynecol J Pelvic Floor Dysfunct **18**(3): 251-256.

de Tayrac, R., G. Devoldere, et al. (2007). "Prolapse repair by vaginal route using a new protected low-weight polypropylene mesh: 1-year functional and anatomical outcome in a prospective multicentre study." Int Urogynecol J Pelvic Floor Dysfunct **18**(3): 251-256.

de Tayrac, R., G. Devoldere, et al. (2006). "prolapse repair by the vaginal route using a new protected low-weight polypropelene mesh; 1-year functional and antomical outcome in prospective multicentre study." Int Urogynecol J Pelvic Floor Dysfunct **(epub ahead of print)**.

de Tayrac, R., G. Devoldere, et al. (2007). "Prolapse repair by vaginal route using a new protected low-weight polypropylene mesh: 1-year functional and anatomical outcome in a prospective multicentre study." International Urogynecology Journal And Pelvic Floor Dysfunction **18**(3): 251-256.

de Tayrac, R., A. l. Gervaise, et al. (2005). "Tension-free polypropylene mesh for vaginal repair of anterior vaginal wall prolapse." The Journal Of Reproductive Medicine **50**(2): 75-80.

de Tayrac, R. and V. Letouzey (2011). "Basic science and clinical aspects of mesh infection in pelvic floor reconstructive surgery." Int Urogynecol J Pelvic Floor Dysfunct **22**(7): 775-780.

de Tayrac, R., M. L. Mathe, et al. (2008). "Infracoccygeal sacropexy or sacrospinous suspension for uterine or vaginal vault prolapse." Int J Gynaecol Obstet **100**(2): 154-159.

de Tayrac, R., O. Picone, et al. (2006). "A 2-year anatomical and functional assessment of transvaginal rectocele repair using a polypropylene mesh." International Urogynecology Journal And Pelvic Floor Dysfunction **17**(2): 100-105.

de Vries, M. J., T. H. vanDessel, et al. (1995). "Short-term results and long-term patients' appraisal of abdominal colposacropexy for treatment of genital and vaginal vault prolapse. ." Eur J Obstet Gynecol Reprod Biol **59**(35-8).

Deffieux, X., R. de Tayrac, et al. (2007). "Vaginal mesh erosion after transvaginal repair of cystocele using Gynemesh or Gynemesh-Soft in 138 women: a comparative study." Int Urogynecol J Pelvic Floor Dysfunct **18**(1): 73-79.

Deffieux, X., D. Savary, et al. (2011). "[Prevention of the complications related to the use of prosthetic meshes in prolapse surgery: Guidelines for clinical practice - Literature review]." J Gynecol Obstet Biol Reprod (Paris) **40**(8): 827-850.

DeLancey, J. O. (1999). "Structural anatomy of the posterior pelvic compartment as it relates to rectocele." Am J Obstet Gynecol **180**(4): 815-823.

Delancey, J. O. (2002). "Fascial and muscular abnormalities in women with urethral hypermobility and anterior vaginal wall prolapse." Am J Obstet Gynecol **187**(1): 93-98.

Demirci, F., I. Ozdemir, et al. (2006). "Abdominal sacrohysteropexy in young women with uterovaginal prolapse: results of 20 cases." J Reprod Med **51**(7): 539-543.

Denman M, G. W., Boyles S, Smith V, Edwards R, Clark A. 2008;198:555 (2008). "Reoperation rate 10 years after surgically managed pelvic organ prolapse and urinary incontinence." Am J Obstet Gynecol **198**: 555.

Deprest, J., D. De Ridder, et al. (2009). "Medium term outcome of laparoscopic sacrocolpopexy with xenografts compared to synthetic grafts." J Urol **182**(5): 2362-2368.

Deprest, J., D. De Ridder, et al., Eds. (2009). Medium term outcome of laparoscopic sacrocolpopexy with xenografts compared to synthetic grafts. J Urol. United States.

Dietz, V., J. de Jong, et al. (2007). "The effectiveness of the sacrospinous hysteropexy for the primary treatment of uterovaginal prolapse." Int Urogynecol J Pelvic Floor Dysfunct **18**(11): 1271-1276.

Dietz, V., M. Huisman, et al. (2008). "Functional outcome after sacrospinous hysteropexy for uterine descensus." Int Urogynecol J Pelvic Floor Dysfunct **19**(6): 747-752.

Dietz, V., C. H. van der Vaart, et al. (2010). "One-year follow-up after sacrospinous hysteropexy and vaginal hysterectomy for uterine descent: a randomized study." Int Urogynecol J **21**(2): 209-216.

Dietz, V., C. H. van der Vaart, et al. (2010). “One-year follow-up after sacrospinous hysteropexy and vaginal hysterectomy for uterine descent: a randomized study.” Int Urogynecol J Pelvic Floor Dysfunct **21**(2): 209-216.

Digesu, G. A., V. Khullar, et al. (2005). “P-QOL: a validated questionnaire to assess the symptoms and quality of life of women with urogenital prolapse.” Int Urogynecol J Pelvic Floor Dysfunct **16**(3): 176-181; discussion 181.

Diwadkar, G. B., M. D. Barber, et al. (2009). “Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review.” Obstet Gynecol **113**(2 Pt 1): 367-373.

Diwan, A., C. R. Rardin, et al. (2006). “Laparoscopic uterosacral ligament uterine suspension compared with vaginal hysterectomy with vaginal vault suspension for uterovaginal prolapse.” Int Urogynecol J Pelvic Floor Dysfunct **17**(1): 79-83.

Dmochowski, R. R., P. E. Zimmern, et al. (1997). “Role of the four-corner bladder neck suspension to correct stress incontinence with a mild to moderate cystocele.” Urology **49**(1): 35-40.

Donnez, O., J. Squifflet, et al. (2009). “Complete mesh expulsion as a complication of vaginally assisted laparoscopic cervicosacropexy with subtotal hysterectomy: a case report.” J Minim Invasive Gynecol **16**(2): 212-215.

Doumouchtsis, S. K., A. Khunda, et al. (2011). “Long-term outcomes of modified high uterosacral ligament vault suspension (HUSLS) at vaginal hysterectomy.” Int Urogynecol J **22**(5): 577-584.

Dwyer, P. L. and B. Fatton (2008). “Bilateral extraperitoneal uterosacral suspension: a new approach to correct posthysterectomy vaginal vault prolapse.” International urogynecology journal and pelvic floor dysfunction **19**(2): 283-292.

Dwyer, P. L. and B. A. O’Reilly (2004). “Transvaginal repair of anterior and posterior compartment prolapse with Atrium polypropylene mesh.” BJOG: An International Journal of Obstetrics and Gynaecology **111**(8): 831-836.

Ek, M., D. Altman, et al. (2010). “Effects of anterior trocar guided transvaginal mesh surgery on lower urinary tract symptoms.” Neurourol Urodyn **29**(8): 1419-1423.

Ek, M., G. Tegerstedt, et al. (2010). “Urodynamic assessment of anterior vaginal wall surgery: a randomized comparison between colporraphy and transvaginal mesh.” Neurourol Urodyn **29**(4): 527-531.

Elkins. T, E., R. Chesson. R, et al. (2000). “Transvaginal paravaginal repair. A useful adjunctive procedure at pelvic relaxation surgery.” J Pelvic Surg **6**: 11-15.

Ellerkmann, R. M., G. W. Cundiff, et al. (2001). “Correlation of symptoms with location and severity of pelvic organ prolapse.” Am J Obstet Gynecol **185**(6): 1332-1337; discussion 1337-1338.

Ellstrom Engh, A. M., A. Ekeryd, et al. (2010). “Can de novo stress incontinence after anterior wall repair be predicted?” Acta Obstet Gynecol Scand **90**(5): 488-493.

Elneil, S., A. S. Cutner, et al. (2005). “Abdominal sacrocolpopexy for vault prolapse without burial of mesh: a case series.” BJOG **112**(4): 486-489.

Farid, M., K. M. Madbouly, et al. (2010). “Randomized controlled trial between perineal and anal repairs of rectocele in obstructed defecation.” World J Surg **34**(4): 822-829.

Farrell, S. A., T. Dempsey, et al. (2001). “Histologic examination of “fascia” used in colporrhaphy.” Obstet Gynecol **98**(5 Pt 1): 794-798.

Fatton, B., J. Amblard, et al. (2007). “Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (Prolift technique)--a case series multicentric study.” Int Urogynecol J Pelvic Floor Dysfunct **18**(7): 743-752.

Fatton, B., P. L. Dwyer, et al. (2009). “Bilateral extraperitoneal uterosacral vaginal vault suspension: a 2-year follow-up longitudinal case series of 123 patients.” International urogynecology journal and pelvic floor dysfunction **20**(4): 427-434.

Fayyad, A. M., C. North, et al. (2010). “Prospective study of anterior transobturator mesh kit (Prolift) for the management of recurrent anterior vaginal wall prolapse.” Int Urogynecol J **22**(2): 157-163.

Fayyad, A. M., C. North, et al. (2011). “Prospective study of anterior transobturator mesh kit (Prolift) for the management of recurrent anterior vaginal wall prolapse.” Int Urogynecol J Pelvic Floor Dysfunct **22**(2): 157-163.

Feiner, B., L. Gietelink, et al. (2010). “Anterior vaginal mesh sacrospinous hysteropexy and posterior fascial plication for anterior compartment dominated uterovaginal prolapse.” Int Urogynecol J Pelvic Floor Dysfunct **21**(2): 203-208.

Feiner, B., L. Gietelink, et al. (2010). “Anterior vaginal mesh sacrospinous hysteropexy and posterior fascial plication for anterior compartment dominated uterovaginal prolapse.” Int Urogynecol J **21**(2): 203-208.

Feiner, B. and C. Maher (2010). “Vaginal mesh contraction: definition, clinical presentation, and management.” Obstet Gynecol **115**(2 Pt 1): 325-330.

Feiner, B., P. O’Rourke, et al. (2011). “A prospective comparison of two commercial mesh kits in the management of anterior vaginal prolapse.” Int Urogynecol J.

Feldner, P. C., Jr., R. A. Castro, et al. (2010). “Anterior vaginal wall prolapse: a randomized controlled trial of SIS graft versus traditional colporrhaphy.” Int Urogynecol J Pelvic Floor Dysfunct **21**(9): 1057-1063.

Fenner, D. E. (1996). “Diagnosis and assessment of sigmoidoceles.” Am J Obstet Gynecol **175**(6): 1438-1441; discussion 1441-1432.

Finamore, P. S., K. T. Echols, et al. (2010). “Risk factors for mesh erosion 3 months following vaginal reconstructive surgery using commercial kits vs. fashioned mesh-augmented vaginal repairs.” Int Urogynecol J Pelvic Floor Dysfunct **21**(3): 285-291.

Fitzgerald, M. P., H. E. Richter, et al. (2008). “Pelvic support, pelvic symptoms, and patient satisfaction after colpocleisis.” Int Urogynecol J Pelvic Floor Dysfunct **19**(12): 1603-1609.

Fitzgerald, M. P., H. E. Richter, et al. (2008). “Pelvic support, pelvic symptoms, and patient satisfaction after colpocleisis.” International urogynecology journal and pelvic floor dysfunction **19**(12): 1603-1609.

FitzGerald, M. P., H. E. Richter, et al. (2006). “Colpocleisis: a review.” International urogynecology journal and pelvic floor dysfunction **17**(3): 261-271.

Flood, C. G., H. P. Drutz, et al. (1998). “Anterior colporrhaphy reinforced with Marlex mesh for the treatment of cystoceles.” Int Urogynecol J Pelvic Floor Dysfunct **9**(4): 200-204.

Foster, R. T., Sr., M. D. Barber, et al. (2007). “A prospective assessment of overactive bladder symptoms in a cohort of elderly women who underwent transvaginal surgery for advanced pelvic organ prolapse.” Am J Obstet Gynecol **197**(1): 82 e81-84.

Fox, S. D. and S. L. Stanton (2000). “Vault prolapse and rectocele: assessment of repair using sacrocolpopexy with mesh interposition.” BJOG **107**(11): 1371-1375.

Frances, W. and T. Jeffcoate (1961). “Dysparunia following vaginal operatons.” J Obstet Gynaecol Br Commonw **68**: 1-10.

Francis WJA and J. TNA. (1961). “Dyspareunia following vaginal operations.” J Obstet gynaecol Br Comnwlth **68**: 1-10.

Frederick, R. W. and G. E. Leach (2005). “CADAVERIC PROLAPSE REPAIR WITH SLING: INTERMEDIATE OUTCOMES WITH 6 MONTHS TO 5 YEARS OF FOLLOWUP.” The Journal of Urology **173**(4): 1229-1233.

Frick, A. C., M. D. Walters, et al. (2010). “Risk of unanticipated abnormal gynecologic pathology at the time of hysterectomy for uterovaginal prolapse.” Am J Obstet Gynecol **202**(5): 507 e501-504.

Gadonneix, P., A. Ercoli, et al. (2004). “Laparoscopic sacrocolpopexy with two separate meshes along the anterior and posterior vaginal walls for multicompartment pelvic organ prolapse.” J Am Assoc Gynecol Laparosc **11**(1): 29-35.

Gandhi, S., R. P. Goldberg, et al. (2005). “A prospective randomized trial using solvent dehydrated fascia lata for the prevention of recurrent anterior vaginal wall prolapse.” Am J Obstet Gynecol **192**(5): 1649-1654.

Ganj, F. A., O. A. Ibeanu, et al. (2009). “Complications of transvaginal monofilament polypropylene mesh in pelvic organ

prolapse repair." Int Urogynecol J Pelvic Floor Dysfunct **20**(8): 919-925.

Gardy, M., M. Kozminski, et al. (1991). "Stress incontinence and cystoceles." J Urol **145**(6): 1211-1213.

Geller, E. J., B. A. Parnell, et al., Eds. (2011). Pelvic floor function before and after robotic sacrocolpopexy: one-year outcomes. J Minim Invasive Gynecol. United States.

Geller, E. J., N. Y. Siddiqui, et al. (2008). "Short-term outcomes of robotic sacrocolpopexy compared with abdominal sacrocolpopexy." Obstetrics and gynecology **112**(6): 1201-1206.

Ghielmetti, T., P. Kuhn, et al. (2006). "Gynaecological operations: do they improve sexual life?" Eur J Obstet Gynecol Reprod Biol **129**(2): 104-110.

Giles, A. E. (1930). "The Effect of Hysteropexy upon a Subsequent Pregnancy, and of Pregnancy upon a Previous Hysteropexy." Proc R Soc Med **23**(8): 1170-1177.

Glavind, K. and H. Madsen (2000). "A prospective study of the discrete fascial defect rectocele repair." Acta Obstet Gynecol Scand **79**(2): 145-147.

Goldberg, R. P., S. Koduri, et al. (2001). "Protective effect of suburethral slings on postoperative cystocele recurrence after reconstructive pelvic operation." Am J Obstet Gynecol **185**(6): 1307-1312.

Gomelsky, A., D. C. Rudy, et al. (2004). "PORCINE DERMIS INTERPOSITION GRAFT FOR REPAIR OF HIGH GRADE ANTERIOR COMPARTMENT DEFECTS WITH OR WITHOUT CONCOMITANT PELVIC ORGAN PROLAPSE PROCEDURES." The Journal of Urology **171**(4): 1581-1584.

Govier, F. E., K. C. Kobashi, et al. (2005). "High complication rate identified in sacrocolpopexy patients attributed to silicone mesh." Urology **65**(6): 1099-1103.

Granese, R., M. Candiani, et al. (2009). "Laparoscopic sacrocolpopexy in the treatment of vaginal vault prolapse: 8 years experience." Eur J Obstet Gynecol Reprod Biol **146**(2): 227-231.

Grody. M, H., T,, Nyirjesy. P, et al. (1995). "Paraurethral fascial sling urethropexy and vaginal paravaginal defects cystopexy in the correction of urethrovesical prolapse." Int Urogynecol J Pelvic Floor Dysfunct **6**: 80-85.

Groutz, A., D. C. Chaikin, et al. (2001). "Use of cadaveric solvent-dehydrated fascia lata for cystocele repair--preliminary results." Urology **58**(2): 179-183.

Grunberger, W., V. Grunberger, et al. (1994). "Pelvic promontory fixation of the vaginal vault in sixty-two patients with prolapse after hysterectomy." Journal of the American College of Surgeons **178**(1): 69-72.

Guerette, N. L., T. V. Peterson, et al. (2009). "Anterior repair with or without collagen matrix reinforcement: a randomized controlled trial." Obstet Gynecol **114**(1): 59-65.

Guillibert, F., G. Chene, et al. (2009). "[Risk factors of mesh exposure after transvaginal repair of genital prolapse]." Gynecologie, Obstetrique & Fertilite **37**(6): 470-475.

Gustilo-Ashby, A. M., J. E. Jelovsek, et al. (2006). "The incidence of ureteral obstruction and the value of intraoperative cystoscopy during vaginal surgery for pelvic organ prolapse." Am J Obstet Gynecol **194**(5): 1478-1485.

Gutman, R. E., C. S. Bradley, et al. (2009). "Effects of colpocleisis on bowel symptoms among women with severe pelvic organ prolapse." Int Urogynecol J **21**(4): 461-466.

Haessler, A. L., L. L. Lin, et al. (2005). "Reevaluating occult incontinence." Curr Opin Obstet Gynecol **17**(5): 535-540.

Hakvoort, R. and J. Roovers (2011). "Comparing clean intermittent catheterisation and transurethral indwelling catheterisation for incomplete voiding after vaginal prolapse surgery: a multicentre randomised trial." Bjog **119**(1): 115-116.

Halaska, M., O. Sottner, et al. (2010). "[Prolene mesh comparing with sacrospinal fixation in the treatment of genital prolapse in women. Prospective multicentre randomized study]." Ceska Gynekol **75**(2): 126-132.

Handa, V. L., E. Garrett, et al. (2004). "Progression and remission of pelvic organ prolapse: a longitudinal study of menopausal women." Am J Obstet Gynecol **190**(1): 27-32.

Handa, V. L., H. M. Zyczynski, et al. (2007). "Sexual function before and after sacrocolpopexy for pelvic organ prolapse." Am J Obstet Gynecol **197**(6): 629.e621-626.

Handel, L. N., T. L. Frenkl, et al. (2007). "Results of Cystocele Repair: A Comparison of Traditional Anterior Colporrhaphy, Polypropylene Mesh and Porcine Dermis." The Journal of Urology **178**(1): 153-156.

Hardiman, P. J. and H. P. Drutz (1996). "Sacrospinous vault suspension and abdominal colposacropexy: success rates and complications." Am J Obstet Gynecol **175**(3 Pt 1): 612-616.

Hathaway, J. K. and J. M. Choe (2002). "Intact genetic material is present in commercially processed cadaver allografts used for pubovaginal slings." J Urol **168**(3): 1040-1043.

Haylen, B. T., R. M. Freeman, et al. (2011). "An International Urogynecological Association (IUGA) / International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) & grafts in female pelvic floor surgery." Int Urogynecol J **22**(1): 3-15.

Hefni, M., T. El-Toukhy, et al. (2003). "Sacrospinous cervicocolpopexy with uterine conservation for uterovaginal prolapse in elderly women: an evolving concept." Am J Obstet Gynecol **188**(3): 645-650.

Hefni, M. A. and T. A. El-Toukhy (2006). "Long-term outcome of vaginal sacrospinous colpopexy for marked uterovaginal and vault prolapse." Eur J Obstet Gynecol Reprod Biol **127**(2): 257-263.

Hefni, M. A. and T. A. El-Toukhy, Eds. (2006). Long-term outcome of vaginal sacrospinous colpopexy for marked uterovaginal and vault prolapse. Eur J Obstet Gynecol Reprod Biol. Ireland.

Hendrix, S. L., A. Clark, et al. (2002). "Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity."

Higgs, P., J. Goh, et al., Eds. (2005). Abdominal sacral colpopexy: an independent prospective long-term follow-up study. Aust N Z J Obstet Gynaecol. Australia.

Higgs, P. J., H. L. Chua, et al., Eds. (2005). Long term review of laparoscopic sacrocolpopexy. BJOG. England.

Hilger, W. S., M. Poulson, et al., Eds. (2003). Long-term results of abdominal sacrocolpopexy. Am J Obstet Gynecol. United States.

Hiltunen, R., K. Nieminen, et al. (2007). "Low-weight polypropylene mesh for anterior vaginal wall prolapse: a randomized controlled trial." Obstet Gynecol **110**(2 Pt 2): 455-462.

Hsiao, K. C., K. Latchamsetty, et al. (2007). "Comparison of laparoscopic and abdominal sacrocolpopexy for the treatment of vaginal vault prolapse." Journal of endourology / Endourological Society **21**(8): 926-930.

Hsu, Y., L. Chen, et al. (2008). "Anterior vaginal wall length and degree of anterior compartment prolapse seen on dynamic MRI." International urogynecology journal and pelvic floor dysfunction **19**(1): 137-142.

Huang, C. C., C. S. Ou, et al. (2010). "Optimal duration of urinary catheterization after anterior colporrhaphy." Int Urogynecol J **22**(4): 485-491.

Huang, K. H., F. C. Chuang, et al. "Polypropylene mesh as an alternative option for uterine preservation in pelvic reconstruction in patients with uterine prolapse." J Obstet Gynaecol Res.

Huebner, M., M. Krzonkalla, et al., Eds. (2009). Abdominal sacrocolpopexy--standardized surgical technique, perioperative management and outcome in women with posthysterectomy vaginal vault prolapse. Gynakol Geburtshilfliche Rundsch. Switzerland.

Huffaker, R. K., B. L. Shull, et al. (2009). "A serious complication following placement of posterior Prolift." Int Urogynecol J Pelvic Floor Dysfunct **20**(11): 1383-1385.

Hullfish, K. L., V. E. Bovbjerg, et al. (2007). "Colpocleisis for pelvic organ prolapse: patient goals, quality of life, and satisfaction." Obstet Gynecol **110**(2 Pt 1): 341-345.

Hullfish, K. L., E. R. Trowbridge, et al. (2011). "Treatment strategies for pelvic organ prolapse: a cost-effectiveness analysis." Int Urogynecol J **22**(5): 507-515.

Hung, M. J., F. S. Liu, et al. (2004). "Factors that affect recur-

rence after anterior colporrhaphy procedure reinforced with four-corner anchored polypropylene mesh." Int Urogynecol J Pelvic Floor Dysfunct **15**(6): 399-406; discussion 406.

Hviid, U., T. V. Hviid, et al. (2010). "Porcine skin collagen implants for anterior vaginal wall prolapse: a randomised prospective controlled study." Int Urogynecol J Pelvic Floor Dysfunct **21**(5): 529-534.

Hviid, U., T. V. Hviid, et al. (2010). "Porcine skin collagen implants for anterior vaginal wall prolapse: a randomised prospective controlled study." Int Urogynecol J **21**(5): 529-534.

Iglesia, C. B., A. I. Sokol, et al. (2010). "Vaginal mesh for prolapse: a randomized controlled trial." Obstet Gynecol **116**(2 Pt 1): 293-303.

Imparato, E., G. Aspesi, et al. (1992). "Surgical management and prevention of vaginal vault prolapse." Surg Gynecol Obstet **175**(3): 233-237.

Inoue, H., Y. Sekiguchi, et al. (2009). "Tissue fixation system (TFS) to repair uterovaginal prolapse with uterine preservation: a preliminary report on perioperative complications and safety." J Obstet Gynaecol Res **35**(2): 346-353.

Jacquetin, B., B. Fatton, et al. (2010). "Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 3-year prospective follow-up study." Int Urogynecol J **21**(12): 1455-1462.

Jelovsek, J. E. and M. D. Barber (2006). "Women seeking treatment for advanced pelvic organ prolapse have decreased body image and quality of life." Am J Obstet Gynecol **194**(5): 1455-1461.

Jelovsek, J. E., C. Maher, et al. (2007). "Pelvic organ prolapse." Lancet **369**(9566): 1027-1038.

Jeng, C. J., Y. C. Yang, et al. (2005). "Sexual functioning after vaginal hysterectomy or transvaginal sacrospinous uterine suspension for uterine prolapse: a comparison." J Reprod Med **50**(9): 669-674.

Jenkins, V. R., 2nd (1997). "Uterosacral ligament fixation for vaginal vault suspension in uterine and vaginal vault prolapse." Am J Obstet Gynecol **177**(6): 1337-1343; discussion 1343-1334.

Jeon, M. J., H. J. Jung, et al. (2008). "Is hysterectomy or the use of graft necessary for the reconstructive surgery for uterine prolapse?" Int Urogynecol J Pelvic Floor Dysfunct **19**(3): 351-355.

Jeon, M. J., Y. J. Moon, et al. (2009). "A long-term treatment outcome of abdominal sacrocolpopexy." Yonsei medical journal **50**(6): 807-813.

Jeon, M. J., Y. J. Moon, et al. (2009). "A long-term treatment outcome of abdominal sacrocolpopexy." Yonsei Med J **50**(6): 807-813.

Jia, X., C. Glazener, et al. (2010). "Systematic review of the efficacy and safety of using mesh in surgery for uterine or vaginal vault prolapse." Int Urogynecol J Pelvic Floor Dysfunct **21**(11): 1413-1431.

Jia, X., C. Glazener, et al. (2008). "Efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: systematic review and meta-analysis." BJOG **115**(11): 1350-1361.

Jo, H., J. W. Kim, et al. (2007). "Efficacy and outcome of anterior vaginal wall repair using polypropylene mesh (Gynemesh)." The Journal Of Obstetrics And Gynaecology Research **33**(5): 700-704.

Joshi, V. M. (1993). "A new technique of uterine suspension to pectineal ligaments in the management of uterovaginal prolapse." Obstet Gynecol **81**(5 (Pt 1)): 790-793.

Judd, J. P., N. Y. Siddiqui, et al., Eds. (2010). Cost-minimization analysis of robotic-assisted, laparoscopic, and abdominal sacrocolpopexy. J Minim Invasive Gynecol. United States.

Julian, T. M. (1996). "The efficacy of Marlex mesh in the repair of severe, recurrent vaginal prolapse of the anterior midvaginal wall." Am J Obstet Gynecol **175**(6): 1472-1475.

kahn MA, Stanton SL, et al. (1999). "Posterior colporrhaphy is superior to the transanal repair for treatment of posterior vaginal wall prolapse." Neurourol Urodyn **18**(4): 70-71.

Kahn MA, S. S. (1997). "Posterior colporrhaphy:its effects on bowel and sexual function." Br J Obstet Gynaecol **104**: 82-86.

Kalogirou, D., G. Antoniou, et al. (1996). "Comparison of surgical and postoperative complications of vaginal hysterectomy and Manchester procedure." Eur J Gynaecol Oncol **17**(4): 278-280.

Kapoor, D. S., M. Nemcova, et al. (2010). "Reoperation rate for traditional anterior vaginal repair: analysis of 207 cases with a median 4-year follow-up." International urogynecology journal **21**(1): 27-31.

Karateke, A., C. Cam, et al. (2010). "Unilateral hydroureteronephrosis after a mesh procedure." J Minim Invasive Gynecol **17**(2): 232-234.

Karram, M., S. Goldwasser, et al. (2001). "High uterosacral vaginal vault suspension with fascial reconstruction for vaginal repair of enterocele and vaginal vault prolapse." Am J Obstet Gynecol **185**(6): 1339-1342; discussion 1342-1333.

Kaufman, Y., S. S. Singh, et al. (2011). "Age and sexual activity are risk factors for mesh exposure following transvaginal mesh repair." Int Urogynecol J **22**(3): 307-313.

Kenton, K., M. P. Fitzgerald, et al. (2005). "Striated urethral sphincter activity does not alter urethral pressure during filling cystometry." Am J Obstet Gynecol **192**(1): 55-59.

Kenton, K., S. Shott, et al. (1999). "Outcome after rectovaginal fascia reattachment for rectocele repair." Am J Obstet Gynecol **181**(6): 1360-1363.

Klauschie, J. L., B. A. Suozzi, et al. (2009). "A comparison of laparoscopic and abdominal sacral colpopexy: objective outcome and perioperative differences." Int Urogynecol J Pelvic Floor Dysfunct **20**(3): 273-279.

Klauschie, J. L., B. A. Suozzi, et al. (2009). "A comparison of laparoscopic and abdominal sacral colpopexy: objective outcome and perioperative differences." International urogynecology journal and pelvic floor dysfunction **20**(3): 273-279.

Kobashi, K. C., G. E. Leach, et al. (2002). "Continued Multicenter Followup of Cadaveric Prolapse Repair With Sling." The Journal of Urology **168**(5): 2063-2068.

Komesu, Y. M., R. G. Rogers, et al. (2007). "Posterior repair and sexual function." Am J Obstet Gynecol **197**(1): 101 e101-106.

Koyama, M., S. Yoshida, et al. (2005). "Surgical reinforcement of support for the vagina in pelvic organ prolapse: concurrent iliococcygeus fascia colpopexy (Inmon technique)." Int Urogynecol J **16**(3): 197-202.

Kramer, B. A., C. M. Whelan, et al. (2009). "Robot-assisted laparoscopic sacrocolpopexy as management for pelvic organ prolapse." Journal of endourology / Endourological Society **23**(4): 655-658.

Krause, H. G., J. T. Goh, et al. (2006). "Laparoscopic sacral suture hysteropexy for uterine prolapse." Int Urogynecol J Pelvic Floor Dysfunct **17**(4): 378-381.

Kuribayashi, M., Y. Kitagawa, et al. (2011). "Postoperative voiding function in patients undergoing tension-free vaginal mesh procedure for pelvic organ prolapse." Int Urogynecol J **22**(10): 1299-1303.

Lane, F. (1962). "Repair of posthysterectomy vaginal-vault prolapse." Obstet Gynecol **20**: 72-77.

Lantzsch, T., C. Goepel, et al. (2001). "Sacrospinous ligament fixation for vaginal vault prolapse." Arch Gynecol Obstet **265**(1): 21-25.

Lawrence, J. M., E. S. Lukacz, et al. (2008). "Prevalence and co-occurrence of pelvic floor disorders in community-dwelling women." Obstet Gynecol **111**(3): 678-685.

Leboeuf L, Miles RA, et al. (2004). "Grade 4 cystocele repair using 4-defect repair and porcine xenograft acellular matrix (Pelvicol). Outcome measures using SEAPI. ." Urology **64**((2)): 282-286.

Leboeuf, L., R. A. Miles, et al. (2004). "Grade 4 cystocele repair using four-defect repair and porcine xenograft acellular matrix (Pelvicol): Outcome measures using SEAPI." Urology **64**(2): 282-286.

Lecuru, F., R. Taurelle, et al. (1994). "[Surgical treatment of genito-urinary prolapses by abdominal approach. Results in a continuous series of 203 operations]." Annales de chirurgie **48**(11): 1013-1019.

Lefranc, J. P., D. Atallah, et al., Eds. (2002). Longterm followup of posthysterectomy vaginal vault prolapse abdominal repair: a report of 85 cases. J Am Coll Surg. United States.

Leron, E. and S. L. Stanton (2001). "Sacrohysteropexy with synthetic mesh for the management of uterovaginal prolapse." BJOG **108**(6): 629-633.

Letouzey, V., X. Deffieux, et al. (2010). "Trans-vaginal cystocele repair using a tension-free polypropylene mesh: more than 5 years of follow-up." Eur J Obstet Gynecol Reprod Biol **151**(1): 101-105.

Lewicky-Gaupp, C., ., E. J. McGuire, et al. (2009). "Multiple perineal abscesses and sinus tracts as a complication of vaginal mesh." Int Urogynecol J Pelvic Floor Dysfunct **20**(9): 1137-1139.

Lewicky-Gaupp, C., C. Brincat, et al. (2009). "Racial differences in bother for women with urinary incontinence in the Establishing the Prevalence of Incontinence (EPI) study." Am J Obstet Gynecol **201**(5): 510 e511-516.

Liang, C. C., C. L. Lee, et al. (2009). "Postoperative urinary outcomes in catheterized and non-catheterized patients undergoing laparoscopic-assisted vaginal hysterectomy--a randomized controlled trial." Int Urogynecol J Pelvic Floor Dysfunct **20**(3): 295-300.

Liang, C. C., Y. H. Lin, et al. (2011). "Urodynamic and clinical effects of transvaginal mesh repair for severe cystocele with and without urinary incontinence." Int J Gynaecol Obstet **112**(3): 182-186.

Lin, T. Y., T. H. Su, et al. (2005). "Risk factors for failure of transvaginal sacrospinous uterine suspension in the treatment of uterovaginal prolapse." J Formos Med Assoc **104**(4): 249-253.

Lindeque, B. G. and W. S. Nel (2002). "Sacrocolpopexy--a report on 262 consecutive operations." South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde **92**(12): 982-985.

Lo, T. S. and A. C. Wang (1998). "Abdominal colposacropexy and sacrospinous ligament suspension for severe uterovaginal prolapse: a comparison." J Gynecol Surg **14**: 59-64.

Lopes, E. D., N. L. Lemos, et al. (2010). "Transvaginal polypropylene mesh versus sacrospinous ligament fixation for the treatment of uterine prolapse: 1-year follow-up of a randomized controlled trial." Int Urogynecol J Pelvic Floor Dysfunct **21**(4): 389-394.

Lovatsis, D. and H. P. Drutz (2002). "Safety and efficacy of sacrospinous vault suspension." International urogynecology journal and pelvic floor dysfunction **13**(5): 308-313.

Lowenstein, L., A. Fitz, et al., Eds. (2009). Transabdominal uterosacral suspension: outcomes and complications. Am J Obstet Gynecol. United States.

Lowman, J. K., P. J. Woodman, et al. (2008). "Tobacco use is a risk factor for mesh erosion after abdominal sacral colpoperineopexy." Am J Obstet Gynecol **198**(5): 561 e561-564.

Lunardelli, J. L., A. P. Auge, et al. (2009). "Polypropylene mesh vs. site-specific repair in the treatment of anterior vaginal wall prolapse: preliminary results of a randomized clinical trial." Rev Col Bras Cir **36**(3): 210-216.

Lyons, T. L. and W. K. Winer (1997). "Laparoscopic rectocele repair using polyglactin mesh." J Am Assoc Gynecol Laparosc **4**(3): 381-384.

Macer, G. A. (1978). "Transabdominal repair of cystocele, a 20 year experience, compared with the traditional vaginal approach." Am J Obstet Gynecol **131**(2): 203-207.

Maher, C., K. Baessler, et al. (2004). "Surgical management of pelvic organ prolapse in women." Cochrane Database Syst Rev(4): Cd004014.

Maher, C., K. Baessler, et al. (2007). "Surgical management of pelvic organ prolapse in women." Cochrane Database Of Systematic Reviews (Online)(3): CD004014.

Maher, C. and B. Feiner (2011). "Laparoscopic removal of intravesical mesh following pelvic organ prolapse mesh surgery." Int Urogynecol J **22**(12): 1593-1595.

Maher, C., B. Feiner, et al. (2010). "Surgical management of pelvic organ prolapse in women." Cochrane Database Syst Rev(4): CD004014.

Maher, C. and P. O'Rourke (2011). "Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial." Obstet Gynecol **117**(6): 1435-1436; author reply 1436-1437.

Maher CF, Qatwneh A, et al. (2002). "Midline rectovaginal fascial plication for repair of rectocele and obstructed defecation." Int Urogynecol J Pelvic Floor Dysfunct **13**(1): Abstract 166.

Maher, C. F., M. P. Carey, et al. (2001). "Laparoscopic suture hysteropexy for uterine prolapse." Obstet Gynecol **97**(6): 1010-1014.

Maher, C. F., M. P. Cary, et al. (2001). "Uterine preservation or hysterectomy at sacrospinous colpopexy for uterovaginal prolapse?" Int Urogynecol J Pelvic Floor Dysfunct **12**(6): 381-384; discussion 384-385.

Maher, C. F. and L. B. Connelly (2011). "Cost minimization analysis of laparoscopic sacral colpopexy and total vaginal mesh." Am J Obstet Gynecol.

Maher, C. F., B. Feiner, et al. (2011). "Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial." Am J Obstet Gynecol **204**(4): 360 e361-367.

Maher, C. F., C. J. Murray, et al. (2001). "Iliococcygeus or sacrospinous fixation for vaginal vault prolapse." Obstet Gynecol **98**(1): 40-44.

Maher, C. F., A. Qatawneh, et al. (2004). "Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse. A prospective randomized trial." Am J Obstet Gynecol **190**: 20-26.

Maher, C. F., A. M. Qatawneh, et al. (2004). "Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study." Am J Obstet Gynecol **190**(1): 20-26.

Maher, C. M., B. Feiner, et al. (2011). "Surgical management of pelvic organ prolapse in women: the updated summary version Cochrane review." Int Urogynecol J **22**(11): 1445-1457.

Mallipeddi, P. K., A. C. Steele, et al. (2001). "Anatomic and functional outcome of vaginal paravaginal repair in the correction of anterior vaginal wall prolapse." Int Urogynecol J Pelvic Floor Dysfunct **12**(2): 83-88.

Margulies, R. U., M. A. Rogers, et al. (2010). "Outcomes of transvaginal uterosacral ligament suspension: systematic review and metaanalysis." Am J Obstet Gynecol **202**(2): 124-134.

Marinkovic, S. P. and S. L. Stanton (2003). "Triple compartment prolapse: sacrocolpopexy with anterior and posterior mesh extensions." BJOG **110**(3): 323-326.

McDermott, C. D., C. L. Terry, et al. (2011). "Surgical outcomes following total Prolift: colpopexy versus hysteropexy." Aust N Z J Obstet Gynaecol **51**(1): 61-66.

Medina, C. and P. Takacs (2006). "Laparoscopic uterosacral uterine suspension: a minimally invasive technique for treating pelvic organ prolapse." J Minim Invasive Gynecol **13**(5): 472-475.

Medina, C. A., P. A. Pietro, et al. (2002). "The use of dura mater allografts for abdominal sacral colpopexy." J Pelvic Surg **8**: 247-251.

Meeks, G. R., J. F. Washburne, et al., Eds. (1994). Repair of vaginal vault prolapse by suspension of the vagina to iliococcygeus (prespinous) fascia. Am J Obstet Gynecol. United States.

Mellgren, A., B. Anzen, et al. (1995). "Results of rectocele repair. A prospective study." Dis Colon Rectum **38**(1): 7-13.

Menefee, S. A., K. Y. Dyer, et al. (2011). "Colporrhaphy Compared With Mesh or Graft-Reinforced Vaginal Paravaginal Repair for Anterior Vaginal Wall Prolapse: A Randomized Controlled Trial." Obstet Gynecol.

Meschia, M., F. Bruschi, et al. (1999). "The sacrospinous vaginal vault suspension: Critical analysis of outcomes." Int Urogynecol J Pelvic Floor Dysfunct **10**(3): 155-159.

Meschia, M., P. Pifarotti, et al. (2007). "Porcine skin collagen implants to prevent anterior vaginal wall prolapse recurrence: a multicenter, randomized study." J Urol **177**(1): 192-195.

Meschia, M., P. Pifarotti, et al. (2007). "Porcine skin collagen

implants to prevent anterior vaginal wall prolapse recurrence: a multicenter, randomized study." The Journal Of Urology **177**(1): 192-195.

Meschia, M., P. Pifarotti, et al. (2004). "A randomized comparison of tension-free vaginal tape and endopelvic fascia plication in women with genital prolapse and occult stress urinary incontinence." Am J Obstet Gynecol **190**(3): 609-613.

Miedel, A., G. Tegerstedt, et al. (2008). "A 5-year prospective follow-up study of vaginal surgery for pelvic organ prolapse." International urogynecology journal and pelvic floor dysfunction **19**(12): 1593-1601.

Migliari, R., M. De Angelis, et al. (2000). "Tension-free vaginal mesh repair for anterior vaginal wall prolapse." Eur Urol **38**(2): 151-155.

Migliari, R. and E. Usai (1999). "Treatment results using a mixed fiber mesh in patients with grade IV cystocele." J Urol **161**(4): 1255-1258.

Milani, A. L., W. M. Heidema, et al. (2008). "Vaginal prolapse repair surgery augmented by ultra lightweight titanium coated polypropylene mesh." Eur J Obstet Gynecol Reprod Biol **138**(2): 232-238.

Milani, A. L., P. Hinoul, et al. (2011). "Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1 year outcomes." Am J Obstet Gynecol **204**(1): 74 e71-78.

Milani, A. L., M. I. Withagen, et al. (2011). "Sexual function following trocar-guided mesh or vaginal native tissue repair in recurrent prolapse: a randomized controlled trial." J Sex Med **8**(10): 2944-2953.

Milani, A. L., M. I. Withagen, et al. (2011). "Sexual Function Following Trocar-guided Mesh or Vaginal Native Tissue Repair in Recurrent Prolapse: A Randomized Controlled Trial." J Sex Med.

Milani, R., S. Salvatore, et al. (2005). "Functional and anatomical outcome of anterior and posterior vaginal prolapse repair with prolene mesh." BJOG **112**(1): 107-111.

Miller, N. (1927). "A new method of correcting complete inversion of the vagina." Surg Gynecol Obstet **44**: 550-554.

Montella, J. M. and M. Y. Morrill (2005). "Effectiveness of the McCall culdeplasty in maintaining support after vaginal hysterectomy." International urogynecology journal and pelvic floor dysfunction **16**(3): 226-229.

Moore, R. D., R. D. Beyer, et al. "Prospective multicenter trial assessing type I, polypropylene mesh placed via transobturator route for the treatment of anterior vaginal prolapse with 2-year follow-up." International Urogynecology Journal **21**(5): 545-552.

Moore, R. D., R. D. Beyer, et al. (2010). "Prospective multicenter trial assessing type I, polypropylene mesh placed via transobturator route for the treatment of anterior vaginal prolapse with 2-year follow-up." Int Urogynecol J **21**(5): 545-552.

Moore, R. D., R. D. Beyer, et al. (2010). "Prospective multicenter trial assessing type I, polypropylene mesh placed via transobturator route for the treatment of anterior vaginal prolapse with 2-year follow-up." Int Urogynecol J Pelvic Floor Dysfunct **21**(5): 545-552.

Moore, R. D. and J. R. Miklos (2009). "Vaginal repair of cystocele with anterior wall mesh via transobturator route: efficacy and complications with up to 3-year followup." Adv Urol: 743831.

Moore, R. D., G. K. Mitchell, et al. (2012). "Single-incision vaginal approach to treat cystocele and vault prolapse with an anterior wall mesh anchored apically to the sacrospinous ligaments." Int Urogynecol J **23**(1): 85-91.

Moreno, S. J., O. E. Ortiz, et al. (2011). "Long-term outcomes after robotic sacrocolpopexy in pelvic organ prolapse: prospective analysis." Urol Int **86**: 414-418.

Morgan, D. M., M. A. Rogers, et al., Eds. (2007). Heterogeneity in anatomic outcome of sacrospinous ligament fixation for prolapse: a systematic review. Obstet Gynecol. United States.

Morley, G. W. and J. O. DeLancey (1988). "Sacrospinous ligament fixation for eversion of the vagina." Am J Obstet Gynecol **158**(4): 872-881.

Mueller, E. R., K. Kenton, et al. (2007). "Urodynamic prolapse reduction alters urethral pressure but not filling or pressure flow parameters." J Urol **177**(2): 600-603.

Murphy, M., G. Sternschuss, et al., Eds. (2008). Quality of life and surgical satisfaction after vaginal reconstructive vs obliterative surgery for the treatment of advanced pelvic organ prolapse. Am J Obstet Gynecol. United States.

Murray, S., R. M. Haverkorn, et al. (2011). "Mesh kits for anterior vaginal prolapse are not cost effective." Int Urogynecol J Pelvic Floor Dysfunct **22**(4): 447-452.

Natale, F., C. La Penna, et al. (2009). "A prospective, randomized, controlled study comparing Gynemesh, a synthetic mesh, and Pelvicol, a biologic graft, in the surgical treatment of recurrent cystocele." Int Urogynecol J Pelvic Floor Dysfunct **20**(1): 75-81.

Natale, F., C. La Penna, et al. (2010). "High levator myorraphy versus uterosacral ligament suspension for vaginal vault fixation: a prospective, randomized study." Int Urogynecol J Pelvic Floor Dysfunct **21**(5): 515-522.

Natale, F., C. La Penna, et al. (2008). "High levator myorrhaphy for transvaginal suspension of the vaginal apex: long-term results." J Urol **180**(5): 2047-2052; discussion 2052.

Natale, F., A. Mako, et al. (2007). "Prospective randomized controlled study between two different procedures to suspend the vaginal vault: high levator myorrhaphy and uterosacral vaginal vault suspension (Abstract number 6)." Neurourol Urodyn **26**(5): 608-609.

Natale. F, Marziali. S, et al. (2000). "Tension-free cystocele repair(TCR): Longterm follow-up." Int Urogynecol J Pelvic Floor Dysfunct **11**(supp 1): S51.

Nesbitt, R. E., Jr. (1989). "Uterine preservation in the surgical management of genuine stress urinary incontinence associated with uterovaginal prolapse." Surg Gynecol Obstet **168**(2): 143-147.

Neuman, M. and Y. Lavy (2007). "Conservation of the prolapsed uterus is a valid option: medium term results of a prospective comparative study with the posterior intravaginal slingoplasty operation." Int Urogynecol J Pelvic Floor Dysfunct **18**(8): 889-893.

Nguyen, J. N. and R. J. Burchette (2008). "Outcome after anterior vaginal prolapse repair: a randomized controlled trial." Obstetrics & Gynecology **111**(4): 891-898.

Nguyen, J. N. and R. J. Burchette (2008). "Outcome after anterior vaginal prolapse repair: a randomized controlled trial." Obstet Gynecol **111**(4): 891-898.

Nicita, G. (1998). "A new operation for genitourinary prolapse." J Urol **160**(3 Pt 1): 741-745.

Nicita, G., V. Li Marzi, et al. (2005). "Uterus-sparing vaginal surgery of genitourinary prolapse employing biocompatible material." Urol Int **75**(4): 314-318.

Nicolson, A. and D. Adeyemo (2009). "Colovaginal fistula: a rare long-term complication of polypropylene mesh sacrocolpopexy." J Obstet Gynaecol Res **29**(5): 444-445.

Nieminen, K., K. M. Hiltunen, et al. (2004). "Transanal or vaginal approach to rectocele repair: a prospective, randomized pilot study." Dis Colon Rectum **47**(10): 1636-1642.

Nieminen, K., R. Hiltunen, et al. (2010). "Outcomes after anterior vaginal wall repair with mesh: a randomized, controlled trial with a 3 year follow-up." Am J Obstet Gynecol **203**(3): 235 e231-238.

Nieminen, K., H. Huhtala, et al. (2003). "Anatomic and functional assessment and risk factors of recurrent prolapse after vaginal sacrospinous fixation." Acta Obstet Gynecol Scand **82**(5): 471-478.

Nosti, P. A., J. K. Lowman, et al. (2009). "Risk of mesh erosion after abdominal sacral colpoperineopexy with concomitant hysterectomy." Am J Obstet Gynecol **201**(5): 541 e541-544.

Nygaard, I. E., R. McCreery, et al. (2004). "Abdominal sacrocolpopexy: a comprehensive review." Obstet Gynecol **104**(4): 805-823.

Nygaard, I. E., R. McCreery, et al. (2004). "Abdominal sacrocolpopexy: a comprehensive review." Obstet Gynecol **104**(4): 805-823.

O'Brien, P. M. and J. Ibrahim (1994). "Failure of laparoscopic uterine suspension to provide a lasting cure for uterovaginal prolapse." Br J Obstet Gynaecol **101**(8): 707-708.

O'Reilly BA and D. PL. (2003). "Functional results of transvaginal surgery with atrium polypropylene mesh." Int Urogynecol J Pelvic Floor Dysfunct **Proceeds 28th International Urogynecology Meeting Buenos Aires**: Absract 90.

Occelli, B., F. Narducci, et al. (1999). "[Abdominal colposacroplexy for the treatment of vaginal vault prolapse with or without urinary stress incontinence]." Annales de chirurgie **53**(5): 367-377.

Olsen, A. L., V. J. Smith, et al. (1997). "Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence." Obstet Gynecol **89**(4): 501-506.

Paine, M., J. R. Harnsberger, et al. (2010). "Transrectal mesh erosion remote from sacrocolpopexy: management and comment." Am J Obstet Gynecol **203**(2): e11-13.

Paraiso, M. F., L. A. Ballard, et al. (1996). "Pelvic support defects and visceral and sexual function in women treated with sacrospinous ligament suspension and pelvic reconstruction." Am J Obstet Gynecol **175**(6): 1423-1430; discussion 1430-1421.

Paraiso, M. F., M. D. Barber, et al. (2006). "Rectocele repair: a randomized trial of three surgical techniques including graft augmentation." Am J Obstet Gynecol **195**(6): 1762-1771.

Paraiso, M. F., J. E. Jelovsek, et al. (2011). "Laparoscopic compared with robotic sacrocolpopexy for vaginal prolapse: a randomized controlled trial." Obstet Gynecol **118**(5): 1005-1013.

Paraiso, M. F., M. D. Walters, et al. (2005). "Laparoscopic and abdominal sacral colpopexies: a comparative cohort study." Am J Obstet Gynecol **192**(5): 1752-1758.

Paraiso, M. F. R., M. D. Barber, et al. (2006). "Rectocele repair: a randomized trial of three surgical techniques including graft augmentation." American Journal Of Obstetrics And Gynecology **195**(6): 1762-1771.

Pasley, W. W. (1995). "Sacrospinous suspension: a local practitioner's experience." Am J Obstet Gynecol **173**(2): 440-445; discussion 445-448.

Patel, M., D. O'Sullivan, et al. (2009). "A comparison of costs for abdominal, laparoscopic, and robot-assisted sacral colpopexy." International urogynecology journal and pelvic floor dysfunction **20**(2): 223-228.

Patsner, B., Ed. (1999). Abdominal sacral colpopexy in patients with gynecologic cancer: report of 25 cases with long-term follow-up and literature review. Gynecol Oncol. United States.

Pauls, R. N., J. L. Segal, et al. (2006). "Sexual function in patients presenting to a urogynecology practice." Int Urogynecol J Pelvic Floor Dysfunct **17**(6): 576-580.

Penalver, M., Y. Mekki, et al. (1998). "Should sacrospinous ligament fixation for the management of pelvic support defects be part of a residency program procedure? The University of Miami experience." Am J Obstet Gynecol **178**(2): 326-329.

Podratz, K. C., L. K. Ferguson, et al. (1995). " Abdominal sacral colpopexy for posthysterectomy vaginal vault descensus. ." J Pelvic Surg **1**: 18-23.

Popovic, I., P. Debodinance, et al. (2007). "Prosthetic reinforcements: how to manage bladder injuries?" International Urogynecology Journal And Pelvic Floor Dysfunction **18**(10): 1215-1217.

Porges RF and S. SW. (1994). "Long-term analysis of the surgical management of pelvic support defects." Am J Obstet Gynecol **1994**(171): 1518-1528.

Porter WE, Steele A, et al. (1999). "The anatomic and functional outcomes of defect-specific rectocele repair." Am J Obstet Gynecol **181**: 1353-1359.

Powell, C. R., A. J. Simsiman, et al. (2004). "Anterior Vaginal Wall Hammock With Fascia Lata for the Correction of Stage 2 or Greater Anterior Vaginal Compartment Relaxation." The Journal of Urology **171**(1): 264-267.

Price, N., S. R. Jackson, et al. (2006). "Development and psychometric evaluation of the ICIQ Vaginal Symptoms Questionnaire: the ICIQ-VS." Bjog **113**(6): 700-712.

Price, N., A. Slack, et al. (2011). "Laparoscopic sacrocolpopexy: an observational study of functional and anatomical outcomes." Int Urogynecol J **22**(1): 77-82.

Puigdollers, A., X. Fernandez-Fraga, et al. (2007). "Persistent symptoms of functional outlet obstruction after rectocele repair." Colorectal Dis **9**(3): 262-265.

Quiroz, L. H., R. E. Gutman, et al., Eds. (2008). Abdominal sacrocolpopexy: anatomic outcomes and complications with Pelvicol, autologous and synthetic graft materials. Am J Obstet Gynecol. United States.

Rane, A., J. Iyer, et al. (2011). "Prospective study of the Perigee system for treatment of cystocele - our five-year experience." Aust N Z J Obstet Gynaecol.

Rardin, C. R., E. A. Erekson, et al. (2009). "Uterosacral colpopexy at the time of vaginal hysterectomy: comparison of laparoscopic and vaginal approaches." The Journal of reproductive medicine **54**(5): 273-280.

Raz, S., C. G. Klutke, et al. (1989). "Four-corner bladder and urethral suspension for moderate cystocele." J Urol **142**: 712-715.

Raz, S., N. A. Little, et al. (1991). "Repair of severe anterior vaginal wall prolapse (grade IV cystourethrocele)." J Urol **146**(4): 988-992.

Reena, C., A. N. Kekre, et al. (2007). "Occult stress incontinence in women with pelvic organ prolapse." Int J Gynaecol Obstet **97**(1): 31-34.

Reza, M., S. Maeso, et al. (2010). "Meta-analysis of observational studies on the safety and effectiveness of robotic gynaecological surgery." Br J Surg **97**(12): 1772-1783.

Richardson, A. C. (1993). "The rectovaginal septum revisited: its relationship to rectocele and its importance in rectocele repair." Clin Obstet Gynecol **36**(4): 976-983.

Richardson AC, Lyon JB, et al. (1976). "A new look at pelvic relaxation." Am J Obstet Gynecol **126**: 568.

Richardson, A. C., P. B. Edmonds, et al. (1981). "Treatment of stress urinary incontinence due to paravaginal fascial defect." Obstet Gynecol **57**(3): 357-362.

Ridgeway, B., M. D. Walters, et al. (2008). "Early experience with mesh excision for adverse outcomes after transvaginal mesh placement using prolapse kits." Am J Obstet Gynecol **199**(6): 703 e701-707.

Rivoire, C., R. Botchorishvili, et al. (2007). "Complete laparoscopic treatment of genital prolapse with meshes including vaginal promontofixation and anterior repair: a series of 138 patients." J Minim Invasive Gynecol **14**(6): 712-718.

Rivoire, C., R. Botchorishvili, et al., Eds. (2007). Complete laparoscopic treatment of genital prolapse with meshes including vaginal promontofixation and anterior repair: a series of 138 patients. J Minim Invasive Gynecol. United States.

Robles, J. E., J. Rioja, et al. (2007). "Anterior compartment prolapse repair with a hybrid biosynthetic mesh implant technique." International Urogynecology Journal And Pelvic Floor Dysfunction **18**(10): 1191-1196.

Rodriguez, L. V., R. Bukkapatnam, et al. (2005). "Transvaginal paravaginal repair of high-grade cystocele central and lateral defects with concomitant suburethral sling: Report of early results, outcomes, and patient satisfaction with a new technique." Urology **66**(5, Supplement 1): 57-65.

Rogers, R. G., D. Kammerer-Doak, et al. (2006). "Does sexual function change after surgery for stress urinary incontinence and/or pelvic organ prolapse? A multicenter prospective study." Am J Obstet Gynecol **195**(5): e1-4.

Rogers, R. G., D. Kammerer-Doak, et al. (2001). "A new instrument to measure sexual function in women with urinary incontinence or pelvic organ prolapse." Am J Obstet Gynecol **184**(4): 552-558.

Romanzi, L. J., D. C. Chaikin, et al. (1999). "The effect of genital prolapse on voiding." J Urol **161**(2): 581-586.

Rooney, K., K. Kenton, et al. (2006). "Advanced anterior vaginal wall prolapse is highly correlated with apical prolapse." Am J Obstet Gynecol **195**(6): 1837-1840.

Roovers, J. P., J. G. van der Bom, et al. (2002). "Abdominal

versus vaginal approach for the management of genital prolapse and coexisting stress incontinence." Int Urogynecol J Pelvic Floor Dysfunct **13**(4): 224-231.

Roovers, J. P., C. H. van der Vaart, et al. (2004). "A randomised controlled trial comparing abdominal and vaginal prolapse surgery: effects on urogenital function." Bjog **111**(1): 50-56.

Rosen, D. M., A. Shukla, et al. (2008). "Is hysterectomy necessary for laparoscopic pelvic floor repair? A prospective study." J Minim Invasive Gynecol **15**(6): 729-734.

Rosen, R., C. Brown, et al. (2000). "The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function." J Sex Marital Ther **26**(2): 191-208.

Ross, J. W. and M. Preston (2005). "Laparoscopic sacrocolpopexy for severe vaginal vault prolapse: five-year outcome." J Minim Invasive Gynecol **12**(3): 221-226.

Rozet, F., E. Mandron, et al. (2005). "Laparoscopic sacral colpopexy approach for genito-urinary prolapse: experience with 363 cases." Eur Urol **47**(2): 230-236.

Sabbagh, R., ., E. Mandron, et al. (2010). "Long-term anatomical and functional results of laparoscopic promontofixation for pelvic organ prolapse." BJU Int **106**(6): 861-866.

Safir. M, H., E. Gousse. A, et al. (1999). "4-defect repair of grade 4 cystocele." J Urol **161**: 587-594.

Salomon, L. J., R. Detchev, et al. (2004). "Treatment of Anterior Vaginal Wall Prolapse with Porcine Skin Collagen Implant by the Transobturator Route: Preliminary Results." European Urology **45**(2): 219-225.

Salvatore S, Soligo M, et al. (2002). "Prosthetic surgery for genital prolapse: functional outcome." Neurourol Urodyn **21**(4): 296-297.

Samuelsson, E. C., F. T. Victor, et al. (1999). "Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors." Am J Obstet Gynecol **180**(2 Pt 1): 299-305.

Sand, P. K., S. Koduri, et al. (2001). "Prospective randomized trial of polyglactin 910 mesh to prevent recurrence of cystoceles and rectoceles." Am J Obstet Gynecol **184**(7): 1357-1362.

Sarlos, D., S. Brandner, et al. (2008). "Laparoscopic sacrocolpopexy for uterine and post-hysterectomy prolapse: anatomical results, quality of life and perioperative outcome-a prospective study with 101 cases." International urogynecology journal and pelvic floor dysfunction **19**(10): 1415-1422.

Sarlos, D., S. Brandner, et al. (2008). "Laparoscopic sacrocolpopexy for uterine and post-hysterectomy prolapse: anatomical results, quality of life and perioperative outcome-a prospective study with 101 cases." Int Urogynecol J Pelvic Floor Dysfunct **19**(10): 1415-1422.

Sayer, T., J. Lim, et al. (2011). "Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device." International urogynecology journal.

Sayer, T., J. Lim, et al. (2011). "Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device." Int Urogynecol J.

Schierlitz, L., P. Dwyer, et al. (2007). "A prospective randomised controlled study comparing vaginal prolapse repair with and without tension free vaginal tape (TVT) in women with severe pelvic organ prolapse and occult stress incontinence (Abstract number 114)." Neurourology and Urodynamics **26**(5): 743-744.

Scotti, R. J., A. D. Garely, et al. (1998). "Paravaginal repair of lateral vaginal wall defects by fixation to the ischial periosteum and obturator membrane." Am J Obstet Gynecol **179**(6 Pt 1): 1436-1445.

Sederl, J. (1958). "Zur operation des prolapses der blind endigenden sheiden." Geburtshilfe Frauenheilkd **18**: 824-828.

Sentilhes, L., A. Berthier, et al. (2008). "Sexual function in women before and after transvaginal mesh repair for pelvic organ prolapse." Int Urogynecol J Pelvic Floor Dysfunct **19**(6): 763-772.

Sentilhes, L., A. Berthier, et al. "Sexual function in women before and after transvaginal mesh repair for pelvic organ prolapse

Infracoccygeal sacropexy reinforced with posterior mesh interposition for apical and posterior compartment prolapse."

Sentilhes, L., F. Sergent, et al. (2007). "Midterm follow-up of high-grade genital prolapse repair by the trans-obturator and infracoccygeal hammock procedure after hysterectomy." Eur Urol **51**(4): 1065-1072.

Sergent, F., G. Gay-Crosier, et al. (2009). "Ineffectiveness of associating a suburethral tape to a transobturator mesh for cystocele correction on concomitant stress urinary incontinence." Urology **74**(4): 765-770.

Sergent, F., B. Resch, et al. (2011). "Transvaginal mesh repair of pelvic organ prolapse by the transobturator-infracoccygeal hammock technique: long-term anatomical and functional outcomes." Neurourol Urodyn **30**(3): 384-389.

Sergent, F., B. Resch, et al. "Mid-term outcome of laparoscopic sacrocolpopexy with anterior and posterior polyester mesh for treatment of genito-urinary prolapse

Pelvic floor function before and after robotic sacrocolpopexy: one-year outcomes

Supracervical robotic-assisted laparoscopic sacrocolpopexy for pelvic organ prolapse

Prevalence and risk factors for mesh erosion after laparoscopic-assisted sacrocolpopexy

Laparoscopic sacrocolpopexy: an observational study of functional and anatomical outcomes

Cost-minimization analysis of robotic-assisted, laparoscopic, and abdominal sacrocolpopexy

Laparoscopic sacrocolpopexy for female genital organ prolapse: establishment of a learning curve

Anatomic outcomes of vaginal mesh procedure (Prolift) compared with uterosacral ligament suspension and abdominal sacrocolpopexy for pelvic organ prolapse: a Fellows' Pelvic Research Network study

Laparoscopic sacrocolpopexy in the treatment of vaginal vault prolapse: 8 years experience

A prospective study of laparoscopic sacrocolpopexy for the management of pelvic organ prolapse

Short-term outcomes of robotic sacrocolpopexy compared with abdominal sacrocolpopexy

Will hysterectomy at the time of sacrocolpopexy increase the rate of polypropylene mesh erosion?

Laparoscopic sacrocolpopexy, hysterectomy, and burch colposuspension: feasibility and short-term complications of 77 procedures."

Sergent, F., J. Zanati, et al. (2010). "Perioperative course and medium-term outcome of the transobturator and infracoccygeal hammock for posthysterectomy vaginal vault prolapse." Int J Gynaecol Obstet **109**(2): 131-135.

Shariati, A., J. S. Maceda, et al. (2008). "Da Vinci assisted laparoscopic sacral colpopexy: surgcial tehcnique ona cohort of 77 patients." J Pelvic Surg **14**: 163-171.

Shull, B. L. (1999). "Pelvic organ prolapse: anterior, superior, and posterior vaginal segment defects." Am J Obstet Gynecol **181**(1): 6-11.

Shull, B. L., C. Bachofen, et al. (2000). "A transvaginal approach to repair of apical and other associated sites of pelvic organ prolapse with uterosacral ligaments." Am J Obstet Gynecol **183**(6): 1365-1373; discussion 1373-1364.

Shull, B. L. and W. B. Baden (1989). "A six-year experience with paravaginal defect repair for stress urinary incontinence." Am J Obstet Gynecol **160**: 1432-1440.

Shull, B. L., S. J. Benn, et al. (1994). "Surgical management of prolapse of the anterior vaginal segment :An analysis of support defects, operative morbidity, and anatomical outcome." Am J Obstet Gynecol **171**(1429-39).

Shull, B. L., C. V. Capen, et al. (1992). "Preoperative and postoperative analysis of site-specific pelvic support defects in 81 women treated with sacrospinous ligament suspension and pelvic reconstruction." Am J Obstet Gynecol **166**(6 Pt 1): 1764-1768; discussion 1768-1771.

Shull, B. L., C. V. Capen, et al. (1993). “Bilateral attachment of the vaginal cuff to iliococcygeus fascia: an effective method of cuff suspension.” American journal of obstetrics and gynecology **168**(6 Pt 1): 1669-1674; discussion 1674-1667.

Silva, W. A., R. N. Pauls, et al. (2006). “Uterosacral ligament vault suspension: five-year outcomes.” Obstetrics And Gynecology **108**(2): 255-263.

Simonds RJ, Homberg SD, et al. (1992). “Transmission of human immunodeficiency virus type 1 from seronegative organ tissue donar.” N Engl J Med **326**: 726-730.

Simsiman, A. J., K. M. Luber, et al. (2006). “Vaginal paravaginal repair with porcine dermal reinforcement: Correction of advanced anterior vaginal prolapse.” American Journal of Obstetrics and Gynecology **195**(6): 1832-1836.

Singh, K., E. Cortes, et al. (2003). “Evaluation of the fascial technique for surgical repair of isolated posterior vaginal wall prolapse.” Obstet Gynecol **101**(2): 320-324.

Sinha, D. and A. S. Arunkalaivanan (2007). “Prevalence of occult stress incontinence in continent women with severe genital prolapse.” J Obstet Gynaecol **27**(2): 174-176.

Sivaslioglu, A., E. Unlubilgen, et al. (2007). “A randomised comparison of polypropelene mesh surgery with site-specific surgery in treatment of cystocele.” International Urogynecology Journal And Pelvic Floor Dysfunction **published online**(19(4)): 467-471.

Sivaslioglu, A. A., E. Unlubilgin, et al. (2008). “A randomized comparison of polypropylene mesh surgery with site-specific surgery in the treatment of cystocoele.” Int Urogynecol J Pelvic Floor Dysfunct **19**(4): 467-471.

Slieker-ten Hove, M. C., A. L. Pool-Goudzwaard, et al. (2009). “The prevalence of pelvic organ prolapse symptoms and signs and their relation with bladder and bowel disorders in a general female population.” Int Urogynecol J Pelvic Floor Dysfunct **20**(9): 1037-1045.

Smith, F. J., C. D. Holman, et al. (2010). “Lifetime risk of undergoing surgery for pelvic organ prolapse.” Obstet Gynecol **116**(5): 1096-1100.

Snyder, T. E. and K. E. Krantz (1991). “Abdominal-retroperitoneal sacral colpopexy for the correction of vaginal prolapse.” Obstetrics and gynecology **77**(6): 944-949.

Sokol, A. I., C. B. Iglesia, et al. (2011). “One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse.” Am J Obstet Gynecol.

Sokol, A. I., Iglesia, C.B., Kudish, B.I., Gutman, R.E., Shveiky, and B. D., R., Sokol, E.R., (2011). “One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse.” American Journal of Obstetrics and Gynecology **doi: 10.1016/j.ajog.2011.08.003.**

Stanton, S. L., P. Hilton, et al. (1982). “Clinical and urodynamic effects of anterior colporrhaphy and vaginal hysterectomy for prolapse with and without incontinence.” Br J Obstet Gynaecol **89**(6): 459-463.

Steinberg, B. J., P. S. Finamore, et al. (2010). “Postoperative urinary retention following vaginal mesh procedures for the treatment of pelvic organ prolapse.” Int Urogynecol J **21**(12): 1491-1498.

Stekkinger, E. and P. J. van der Linden (2011). “A comparison of suprapubic and transurethral catheterization on postoperative urinary retention after vaginal prolapse repair: a randomized controlled trial.” Gynecol Obstet Invest **72**(2): 109-116.

Stepanian, A. A., J. R. Miklos, et al. (2008). “Risk of mesh extrusion and other mesh-related complications after laparoscopic sacral colpopexy with or without concurrent laparoscopic-assisted vaginal hysterectomy: experience of 402 patients.” J Minim Invasive Gynecol **15**(2): 188-196.

Stoesser, F. G. (1955). “Construction of a sacrocervical ligament for uterine suspension.” Surg Gynecol Obstet **101**(5): 638-641.

Su, K. C., M. F. Mutone, et al. (2007). “Abdominovaginal sacral colpoperineopexy: patient perceptions, anatomical outcomes, and graft erosions.” Int Urogynecol J Pelvic Floor Dysfunct **18**(5): 503-511.

Su, T. H., H. H. Lau, et al. (2009). “Short term impact on female sexual function of pelvic floor reconstruction with the Prolift procedure.” J Sex Med **6**(11): 3201-3207.

Subak, L. L., L. E. Waetjen, et al. (2001). “Cost of pelvic organ prolapse surgery in the United States.” Obstet Gynecol **98**(4): 646-651.

Subramanian, D., K. Szwarcensztein, et al. (2009). “Rate, type, and cost of pelvic organ prolapse surgery in Germany, France, and England.” Eur J Obstet Gynecol Reprod Biol **144**(2): 177-181.

Sullivan, E. S., C. J. Longaker, et al. (2001). “Total pelvic mesh repair: a ten-year experience.” Dis Colon Rectum **44**(6): 857-863.

Sung, V. W., C. R. Rardin, et al. (2012). “Porcine subintestinal submucosal graft augmentation for rectocele repair: a randomized controlled trial.” Obstet Gynecol **119**(1): 125-133.

Swain, J. (1897). “A Case of Ovarian Cystoma Associated with Prolapsus Uteri, Treated by Ovariotomy and Hysteropexy.” Br Med J **2**(1911): 399-400.

Swift, S., P. Woodman, et al. (2005). “Pelvic Organ Support Study (POSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects.” Am J Obstet Gynecol **192**(3): 795-806.

Swift, S. E. (2000). “The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care.” Am J Obstet Gynecol **183**(2): 277-285.

Swift, S. E., S. B. Tate, et al. (2003). “Correlation of symptoms with degree of pelvic organ support in a general population of women: what is pelvic organ prolapse?” Am J Obstet Gynecol **189**(2): 372-377; discussion 377-379.

Sze, E. H. and M. M. Karram (1997). “Transvaginal repair of vault prolapse: a review.” Obstet Gynecol **89**(3): 466-475.

Sze, E. H., N. Kohli, et al. (1999). “A retrospective comparison of abdominal sacrocolpopexy with Burch colposuspension versus sacrospinous fixation with transvaginal needle suspension for the management of vaginal vault prolapse and coexisting stress incontinence.” Int Urogynecol J Pelvic Floor Dysfunct **10**(6): 390-393.

Takahashi, S., D. Obinata, et al. (2010). “Tension-free vaginal mesh procedure for pelvic organ prolapse: a single-center experience of 310 cases with 1-year follow up.” Int J Urol **17**(4): 353-358.

Tan-Kim, J., S. A. Menefee, et al. (2011). “Prevalence and risk factors for mesh erosion after laparoscopic-assisted sacrocolpopexy.” Int Urogynecol J **22**(2): 205-212.

Tan, J. S., E. S. Lukacz, et al. (2005). “Predictive value of prolapse symptoms: a large database study.” Int Urogynecol J Pelvic Floor Dysfunct **16**(3): 203-209; discussion 209.

Tate, S. B., L. Blackwell, et al. “Randomized trial of fascia lata and polypropylene mesh for abdominal sacrocolpopexy: 5-year follow-up.” International Urogynecology Journal **22**(2): 137-143.

Tate, S. B., L. Blackwell, et al. (2010). “Randomized trial of fascia lata and polypropylene mesh for abdominal sacrocolpopexy: 5-year follow-up.” International urogynecology journal **22**(2): 137-143.

Thomas, A. G., M. L. Brodman, et al. (1995). “Manchester procedure vs. vaginal hysterectomy for uterine prolapse. A comparison.” J Reprod Med **40**(4): 299-304.

Thornton, M. J., A. Lam, et al. (2005). “Laparoscopic or transanal repair of rectocele? A retrospective matched cohort study.” Dis Colon Rectum **48**(4): 792-798.

Thys, S. D., A. Coolen, et al. “A comparison of long-term outcome between Manchester Fothergill and vaginal hysterectomy as treatment for uterine descent.” Int Urogynecol J **22**(9): 1171-1178.

Tijdink, M. M., M. E. Vierhout, et al. (2011). “Surgical management of mesh-related complications after prior pelvic floor reconstructive surgery with mesh.” Int Urogynecol J **22**(11): 1395-1404.

Timmons, M. C., W. A. Addison, et al. (1992). “Abdominal sacral colpopexy in 163 women with posthysterectomy vagi-

nal vault prolapse and enterocele. Evolution of operative techniques." The Journal of reproductive medicine **37**(4): 323-327.

Tipton, R. H. and P. F. Atkin (1970). "Uterine disease after the Manchester repair operation." J Obstet Gynaecol Br Commonw **77**(9): 852-853.

Toglia, M. R. and M. J. Fagan, Eds. (2008). Suture erosion rates and long-term surgical outcomes in patients undergoing sacrospinous ligament suspension with braided polyester suture. Am J Obstet Gynecol. United States.

Toozs-Hobson, P., K. Boos, et al. (1998). "Management of vaginal vault prolapse." Br J Obstet Gynaecol **105**(1): 13-17.

Toozs-Hobson, P., R. Freeman, et al. (2012). "An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for reporting outcomes of surgical procedures for pelvic organ prolapse." International Urogynecology Journal **23**(5): 527-535.

van Brummen, H. J., G. van de Pol, et al. (2003). "Sacrospinous hysteropexy compared to vaginal hysterectomy as primary surgical treatment for a descensus uteri: effects on urinary symptoms." Int Urogynecol J Pelvic Floor Dysfunct **14**(5): 350-355; discussion 355.

van Dam, J. H., W. M. Huisman, et al. (2000). "Fecal continence after rectocele repair: a prospective study." Int J Colorectal Dis **15**(1): 54-57.

van Lindert, A. C., A. G. Groenendijk, et al. (1993). "Surgical support and suspension of genital prolapse, including preservation of the uterus, using the Gore-Tex soft tissue patch (a preliminary report)." European journal of obstetrics, gynecology, and reproductive biology **50**(2): 133-139.

van Lindert, A. C., A. G. Groenendijk, et al. (1993). "Surgical support and suspension of genital prolapse, including preservation of the uterus, using the Gore-Tex soft tissue patch (a preliminary report)." Eur J Obstet Gynecol Reprod Biol **50**(2): 133-139.

Visco, A. G., L. Brubaker, et al. (2008). "The role of preoperative urodynamic testing in stress-continent women undergoing sacrocolpopexy: the Colpopexy and Urinary Reduction Efforts (CARE) randomized surgical trial." Int Urogynecol J Pelvic Floor Dysfunct **19**(5): 607-614.

Visco, A. G., A. C. Weidner, et al. (2001). "Vaginal mesh erosion after abdominal sacral colpopexy." Am J Obstet Gynecol **184**(3): 297-302.

Visco, A. G., A. C. Weidner, et al., Eds. (2001). Vaginal mesh erosion after abdominal sacral colpopexy. Am J Obstet Gynecol. United States.

Vollebregt, A., K. Fischer, et al. (2011). "Primary surgical repair of anterior vaginal prolapse: a randomised trial comparing anatomical and functional outcome between anterior colporrhaphy and trocar-guided transobturator anterior mesh." BJOG **118**(12): 1518-1527.

Vollebregt, A., A. Troelstra, et al. (2009). "Bacterial colonisation of collagen-coated polypropylene vaginal mesh: are additional intraoperative sterility procedures useful?" Int Urogynecol J Pelvic Floor Dysfunct **20**(11): 1345-1351.

von Pechmann, W. S., M. Mutone, et al., Eds. (2003). Total colpocleisis with high levator plication for the treatment of advanced pelvic organ prolapse. Am J Obstet Gynecol. United States.

Walid, M. S., N. Agarwala, et al. (2009). "Laparoscopic removal of infected mesh colposacropexy." Arch Gynecol Obstet **280**(1): 103-106.

Walter, S., K. P. Olesen, et al. (1982). "Urodynamic evaluation after vaginal repair and colposuspension." Br J Urol **54**(4): 377-380.

Ward, K. L. and P. Hilton (2008). "Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up." BJOG **115**(2): 226-233.

Ward, R. M., V. W. Sung, et al. (2007). "Vaginal paravaginal repair with an AlloDerm graft: Long-term outcomes." American Journal of Obstetrics and Gynecology **197**(6): 670.e671-670.e675.

Webb, M. J., M. P. Aronson, et al., Eds. (1998). Posthysterectomy vaginal vault prolapse: primary repair in 693 patients. Obstet Gynecol. United States.

Weber, A. M. and H. E. Richter (2005). "Pelvic organ prolapse." Obstet Gynecol **106**(3): 615-634.

Weber, A. M., M. D. Walters, et al. (2000). "Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence." Am J Obstet Gynecol **182**(6): 1610-1615.

Weber, A. M., M. D. Walters, et al. (2001). "Anterior colporrhaphy: a randomized trial of three surgical techniques." Am J Obstet Gynecol **185**(6): 1299-1304; discussion 1304-1296.

Weemhoff, M., M. M. Wassen, et al. (2011). "Postoperative catheterization after anterior colporrhaphy: 2 versus 5 days. A multicentre randomized controlled trial." Int Urogynecol J **22**(4): 477-483.

Wei, J. (2011). "A midurethral sling prevents incontinence among women undergoing vaginal prolapse repair-the OPUS trial (Abstract)." Neurourol Urodyn.

Wetta, L. A., K. A. Gerten, et al. (2009). "Synthetic graft use in vaginal prolapse surgery: objective and subjective outcomes." Int Urogynecol J Pelvic Floor Dysfunct **20**(11): 1307-1312.

Wheeler, T. L., 2nd, H. E. Richter, et al. (2006). "Outcomes with porcine graft placement in the anterior vaginal compartment in patients who undergo high vaginal uterosacral suspension and cystocele repair." American Journal Of Obstetrics And Gynecology **194**(5): 1486-1491.

White GR (1909). "Cystocele." JAMA **853**: 1707-1710.

White GR (1912). "An anatomic operation for the cure of cystocele." Am J Obstet Dis Women Children **65**: 286-290.

Whitehead, W. E., C. S. Bradley, et al., Eds. (2007). Gastrointestinal complications following abdominal sacrocolpopexy for advanced pelvic organ prolapse. Am J Obstet Gynecol. United States.

Whiteside, J. L., A. M. Weber, et al. (2004). "Risk factors for prolapse recurrence after vaginal repair." Am J Obstet Gynecol **191**(5): 1533-1538.

Williams, B. F. (1966). "Surgical treatment for uterine prolapse in young women." Am J Obstet Gynecol **95**(7): 967-971.

Withagen, M. I., A. L. Milani, et al. (2011). "Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial." Obstet Gynecol **117**(2 Pt 1): 242-250.

Withagen, M. I., M. E. Vierhout, et al. (2011). "Risk factors for exposure, pain, and dyspareunia after tension-free vaginal mesh procedure." Obstet Gynecol **118**(3): 629-636.

Withagen, M. I., M. E. Vierhout, et al. (2010). "Does trocar-guided tension-free vaginal mesh (Prolift) repair provoke prolapse of the unaffected compartments?" Int Urogynecol J Pelvic Floor Dysfunct **21**(3): 271-278.

Withagen, M. I., M. E. Vierhout, et al. (2010). "Does trocar-guided tension-free vaginal mesh (Prolift) repair provoke prolapse of the unaffected compartments?" Int Urogynecol J **21**(3): 271-278.

Wu, J. M., A. F. Hundley, et al. (2009). "Forecasting the prevalence of pelvic floor disorders in U.S. Women: 2010 to 2050." Obstet Gynecol **114**(6): 1278-1283.

Wu, J. M., E. C. Wells, et al. (2006). "Mesh erosion in abdominal sacral colpopexy with and without concomitant hysterectomy." Am J Obstet Gynecol **194**(5): 1418-1422.

Xylinas, E., I. Ouzaid, et al. (2010). "Robot-assisted laparoscopic sacral colpopexy: initial experience in a high-volume laparoscopic reference center." J Endourol **24**(12): 1985-1989.

Young, S. B., J. J. Daman, et al. (2001). "Vaginal paravaginal repair: one-year outcomes." Am J Obstet Gynecol **185**(6): 1360-1366.

Zyczynski, H. M., M. P. Carey, et al. (2010). "One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device." Am J Obstet Gynecol **203**(6): 587 e581-588.

Zyczynski, H. M., M. P. Carey, et al., Eds. (2010). One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol. United States.

Committee 16

Assessment and Conservative Management of Faecal Incontinence and Quality of Life in Adults

Chair

Bliss DZ (USA)

Members

Mellgren A (USA),

Whitehead WE (USA),

Chiarioni G (Italy),

Emmanuel A (UK),

Santoro GA (Italy),

Zbar A (Israel),

Peden-McAlpine C (USA),

Northwood M (Canada),

Slieker-ten Hove M (Netherlands),

Berghmans B (Netherlands),

Mimura T. (Japan)

CONTENTS

I. INTRODUCTION

II. CLINICAL ASSESSMENT

1. SEARCH STRATEGY
2. HISTORY
3. PHYSICAL EXAMINATION

III. SPECIALIZED TESTING

1. ANORECTAL MANOMETRY
2. ENDOANAL ULTRASOUND IMAGING
3. MAGNETIC RESONANCE IMAGING
4. DEFECOGRAPHY
5. CLINICAL NEUROPHYSIOLOGIC TESTING

IV. EDUCATION AND LIFESTYLE INTERVENTIONS

1. BACKGROUND
2. SEARCH
3. REVIEW OF EVIDENCE ON THE EFFECT OF EDUCATION AND LIFESTYLE CHANGES ON FAECAL INCONTINENCE

V. DIET AND FLUIDS

1. INTRODUCTION
2. LITERATURE SEARCH
3. REVIEW OF EVIDENCE ON DIET AND FLUIDS

VI. BOWEL MANAGEMENT AND RETRAINING PROGRAMMES

1. BACKGROUND
2. SEARCH
3. REVIEW OF EVIDENCE ON BOWEL MANAGEMENT AND RETRAINING PROGRAMMES

VII. TREATMENT WITH MEDICATION

1. GOALS
2. SEARCH
3. REVIEW OF EVIDENCE ON MEDICATIONS FOR FAECAL INCONTINENCE

VIII. PELVIC FLOOR MUSCLE EXERCISES, BIOFEEDBACK, AND ELECTRICAL STIMULATION

1. PELVIC FLOOR MUSCLE TRAINING
2. BIOFEEDBACK
3. ELECTRICAL STIMULATION
4. METHODS
5. SUMMARY OF ICI 2008 ASSESSMENT
6. UPDATE: REVIEW OF EVIDENCE FOR 2008-2012
7. SUMMARY OF EVIDENCE
8. RECOMMENDATIONS FOR PRACTICE
9. RECOMMENDATIONS FOR RESEARCH

IX. QUALITATIVE RESEARCH ON THE EXPERIENCE OF FAECAL INCONTINENCE AND QUALITY OF LIFE

1. BACKGROUND
2. CRITERIA FOR EVALUATION
3. SEARCH METHOD
4. REVIEW OF EVIDENCE ON THE EXPERIENCE OF FAECAL INCONTINENCE AND QUALITY OF LIFE
5. LIVING WITH FAECAL INCONTINENCE AND RELATIONSHIPS – SUMMARY OF EVIDENCE
6. LIVING WITH FAECAL INCONTINENCE AND TIME AND PLANNING – SUMMARY OF EVIDENCE
7. LIFE LIVING WITH FAECAL INCONTINENCE AND BODILY SYMPTOMS, SELF ESTEEM AND BODY IMAGE – SUMMARY OF EVIDENCE
8. LIVING WITH FAECAL INCONTINENCE AND SEXUALITY – SUMMARY OF EVIDENCE
9. LIVING WITH FAECAL INCONTINENCE AND DIET ISSUES – SUMMARY OF EVIDENCE

X. ALGORITHM

REFERENCES

Assessment and Conservative Management of Faecal Incontinence and Quality of Life in Adults

Bliss DZ

Mellgren A, Whitehead WE, Chiarioni G, Emmanuel A, Santoro GA, Zbar A, Peden-McAlpine C, Northwood M, Slieker-ten Hove M, Berghmans B, Mimura T.

I. INTRODUCTION

The definitions of anal incontinence and faecal incontinence, adopted at the previous consultations, [1] are maintained:

"Anal incontinence is the involuntary loss of flatus, liquid or solid stool that is a social or hygienic problem."

"Faecal incontinence is the involuntary loss of liquid or solid stool that is a social or hygienic problem."

There is no consensus on the best definition, anal incontinence or faecal incontinence, to use for an outcome in treatment trials or evidence to guide when one may be more appropriate; this impacts comparison and evaluation of study findings because different criteria for successful outcomes have been employed. The committee recommends that whichever outcome is used in studies and publications, the conceptual and operational definition be made explicit and used in a consistent manner. The terms anal incontinence and faecal incontinence are not synonymous. As the majority of intervention studies have focused on faecal incontinence rather than anal incontinence as an outcome measure, faecal incontinence is covered in this chapter, except where anal incontinence is specified.

This chapter addresses assessment and diagnosis, and conservative management, including medications, of faecal incontinence in adults and the impact of faecal incontinence on quality of life as assessed by qualitative methods. New to this chapter are the topics of faecal incontinence assessment and quality of life. The following related topics, some of which may have appeared in this chapter previously, are reviewed by other committees, often together with their urinary incontinence counterpart: epidemiology of faecal incontinence (Committee 1), faecal incontinence in frail or institutionalized older adults (Committee 11), faecal incontinence in persons with neurological disease or injury (Committee 10), faecal incontinence in children (Committee 9), surgical management of faecal incontinence (Committee 17), faecal incontinence management using technologies (e.g., products and devices) (Committee 20), and quality of life and faecal incontinence severity as measured by quantitative instruments of patient reported outcomes (Committee 5B), primary prevention of faecal incontinence (Committee 21). The one study of primary prevention of faecal incontinence (avoiding or delaying the initial occurrence) using conservative therapies [2] is included in this chapter.

As some knowledge gained in these specific groups may have applications to an adult population, the interested reader is encouraged to reviews the work of those committees. There is at present a relatively limited evidence base from high quality experimental trials of faecal incontinence, and it remains challenging to provide strong evidence for most interventions. However, expert consensus in this committee and the world literature is unanimous in recommending conservative interventions, singly or in combination, for the majority of patients with faecal incontinence as first-line management.

Conservative management is defined as a non-operative intervention designed to improve faecal incontinence incontinence or prevent deterioration. It includes pharmacological treatments. Reducing the severity and related complications of faecal incontinence are included from the view of conservative management outcomes rather than secondary and tertiary prevention. Patient selection for operative versus conservative management remains largely empirical. The committee recommends a trial of conservative management, in the vast majority of patients, before considering surgical options, because these conservative options are comparatively inexpensive and involve no significant morbidity (see algorithm). Exceptions would be patients with acute traumatic anal sphincter rupture or an endosonographically confirmed major defect in the external anal sphincter in the presence of gross faecal incontinence: these patients would be referred for surgical evaluation as first line treatment.

II. CLINICAL ASSESSMENT

Normal anorectal physiologic function is complex and relies on a several different factors, including

anatomic and neurology factors. Consequently, anorectal dysfunction may affect all ages [1] and symptoms necessitate careful clinical assessment and sometimes specialised tests to assess the background to patients' symptoms. Several different questionnaires and tests are used and they are frequently used in conjunction with each other, but the clinical utility is sometimes limited.[2, 3]

1. SEARCH STRATEGY

The following search terms were used for PubMed, Web of Science and Cochrane reviews: faecal incontinence, anal incontinence, symptoms, signs, clinical assessment, history, examination, digital examination, clinical features.

2. HISTORY

History gathering requires sensitivity in dealing with this taboo symptom, but also a willingness to ask direct questions about the complaint. Although there are questionnaires about the severity of faecal incontinence or anal incontinence and their impact on quality of life (See Chapter 5B), they are most often used in research and sometimes in clinical practice. Currently there are no uniform set of questions to elucidate the comprehensive set of factors involved in faecal incontinence, and recommended approaches of experts [3] and clinical experience continue to guide practice. In taking a history, the necessary first step is to determine the nature of the incontinence being experienced by the patient. The aim of a history and examination is to identify conditions that are amenable to management and to characterise symptoms so they might be reduced.

a) Type of incontinence

Additional characteristics of faecal incontinence or types of incontinence other than faecal and anal may be identified during assessment. *Passive faecal incontinence* is the involuntary soiling or leakage of faeces without forewarning of the patient. *Flatus incontinence* is the inability to control flatus. *Passive and flatus incontinence* are frequently related to internal anal sphincter dysfunction.[4] *Urge incontinence* is an inability to defer defecation once the urge is perceived, for long enough to find a toilet. *Soiling after defecation* can also occur, and is typically related to either a defect in the internal sphincter or poor "snapping shut" of the external sphincter after voiding.[5] It is also important to determine if the incontinence is for liquid stool only, and, if so, then the possibility of a colonic cause of diarrhoea needs to be considered.[6]

b) Etiology

The history of faecal incontinence should include questioning about its potential etiology:

- Dietary history - including intake of caffeine and sorbitol as they may stimulate GI transit or diarrhoea.[7] **(Recommendation Grade C)**
- Medical history – particularly anti-anginal and antihypertensive medications which may reduce sphincter tone and ferrous sulphate or antacids which may provoke diarrhoea.[8] **(Recommendation Grade C)**
- Presence of benign anal disease – haemorrhoids, fistula, anal warts.[9] **(Recommendation Grade B)**
- History of chronic straining or constipation.10 **(Recommendation Grade B)**
- Obstetric history[11] **(Recommendation Grade B**)- particularly with regard to number of vaginal deliveries, need for forceps or Ventouse, birth weights of all children, duration of second stage(s) of labour, episiotomy
- Perianal surgery history [12,13] **(Recommendation Grade B)** particularly:
- Anal fissure surgery (sphincterotomy or anal stretch), fistula surgery, rectal resection surgery
- History of pelvic radiation – due to risk of radiation proctitis (that can cause decreased rectal compliance) and internal anal sphincter radiation damage.[14] **(Recommendation Grade B)**
- Symptoms of other pelvic floor problems (urinary incontinence and pelvic organ prolapse), which have similar risk factors [15] **(Recommendation Grade C)**
- Cognitive assessment in appropriate patients [16] **(Recommendation Grade C)**

3. PHYSICAL EXAMINATION

a) General, perianal, and digital rectal exam

Examination is focused towards the detection of evidence of incontinence and identifying the cause of incontinence, if possible. Physical examination should include inspection of underclothing for soiling and staining by stool, pus, or mucus. Perianal skin should be examined for signs of irritation such as erythema, rash, and excoriation [17] **(Recommendation Grade C)**. Perianal inspection should also include attempts to identify a patulous anus or one which gapes on gentle traction of the anal verge and/or a "keyhole" deformity of the anal canal which suggests a persisting sphincter defect [18-20] **(Recommendation Grade B).** Inspection may reveal scars from previous episiotomies or obstetric tears. Abnormalities at the anal verge from previous surgery or a gaping anus suggestive of marked loss of function may be present. Perianal inspection or digital rectal examination should identify the following [14,18,20] **(all recommendations Grade C)**:

- Scars from previous surgery
- Perianal disease – prolapsing haemorrhoids, fistula, anal warts

- External prolapse at rest
- Absence of perineal body – suggestive of obstetric trauma; at its worst this may manifest as a cloacal deformity
- Inspection for sphincter asymmetry whilst patient contracts sphincter – suggestive of regional sphincter defect
- Function of the puborectalis muscle (palpable at the anorectal junction) -- assessed by asking the patient to squeeze the sphincter at which time the puborectalis should push the examiner's finger anteriorly.

Digital examination should also assess for [18-20] **(all recommendations Grade C)**:

- Rectal contents – if faecal impaction is present this could explain incontinence
- Resting tone – indicative of internal anal sphincter function
- Voluntary and reflex squeeze pressure – indicative of external anal sphincter function and potential function, respectively. The latter is elicited most commonly by asking the patient to cough while assessing sphincter tone – a cough causes a reflex near-maximal external sphincter contraction (analogous to the guarding reflex in the bladder)
- Regional sphincter defects – detected as asymmetry
- A thickened sphincter – suggestive of chronic straining and occult rectal mucosal prolapsed
- Paradoxical puborectalis contraction – this may be valuable in assessing constipated patients to identify paradoxical contraction as a cause of retained stool, and hence overflow incontinence

True faecal incontinence must be differentiated from conditions that cause seepage such as prolapsing external haemorrhoids, fistulas, low rectal or anal tumors, and poor perineal hygiene. Diagnostic administration of an enema may be useful in this respect; retention of the enema suggests that the patient does not have clinically significant faecal incontinence. This serves to both clarify the patient's history, but also begins to suggest the anatomical deficit causing the incontinence.

If suggested by earlier findings (history of straining, thickened sphincter), the patient should be asked to sit on a commode and attempt voiding – the perineum should then be inspected for evidence of a rectal mucosal or full thickness prolapsed on straining10 **(Recommendation Grade C)**.

b) Proctoscopy

Proctoscopy with a rigid instrument, or flexible sigmoidoscopy, is a bedside test of value in excluding potentially treatable causes of faecal incontinence: anal tumors or polyps, rectal cancers or adenoma [21] **(Recommendation Grade B)**, solitary rectal ulcer syndrome – a functional disorder of evacuation, in which repeated straining at stool and or rectal self-digitalization may result in an ulcerated area of the anterior rectal wall [22] **(Recommendation Grade B)**.

c) Vaginal examination

Vaginal examination using a Simms speculum may show a rectocele, cystocele and/or uterine prolapse, all of which may contribute to developing faecal incontinence [23] **(Recommendation Grade C)**. Physiological and complimentary radiological tests are used to confirm clinical suspicions and provide objective data on the function of the anorectum. Pelvic floor dysfunction is a complex problem and multiple tests may be needed based on the initial findings and complexity of the planned intervention.

d) Recommendations for practice

- Perform a baseline assessment including a focused medical history, a general physical examination, and an anorectal examination with inspection of perinanal skin. **(Recommendation Grade B-C)**
- Several conditions should be specifically assessed for in the history and physical examination, as they may be amenable to definitive treatment, including rectal prolapse, haemorrhoids, faecal loading, potentially treatable causes of diarrhoea (e.g., Inflammatory bowel disease and irritable bowel syndrome, infection, adenomas), acute anal sphincter injury, and acute disc prolapse/cauda equina syndrome. **(Recommendation Grade B)**
- Conduct a digital exam **(Recommendation Grade C)**
- Perform a proctoscopy **(Recommendation Grade B)**

e) Recommendations for research

- Assess inter-rater variability of digital rectal examination
- Assess positive and negative predictive value of digital rectal examination to diagnose pelvic floor diseases associated with faecal incontinence

III. SPECIALIZED TESTING

1. ANORECTAL MANOMETRY

a) Indications

Anorectal manometry measures the pressures in the anal canal and the distal rectum. This test

serves as one of the most accepted and used investigations to measure the function of the internal anal sphincter and the external anal sphincter. Evaluation of the sphincter function in patients with faecal incontinence is the primary indication for manometry [24-26] **(Evidence Level 2)**. However, preliminary evidence suggests that rectal sensation should be treated as well.[27]

b) Equipment and testing

Anorectal manometry can be performed with different types of catheters, including solid state, water perfused, air charged, or microballoon catheters. [28] The diameter of the probe should not exceed 5-6 mm and the probe usually includes sensors radially distributed to measure several pressures at each level. Any manipulation of the rectum, such as digital rectal examination or administration of enema prior to a test should be followed by a minimum of 5 minutes of rest to allow sphincter activity to return to baseline.

The stationary pull-through technique is today commonly used, since this technique avoids the reflex sphincter contraction caused by some dynamic techniques. The stationary pull-through measures the resting pressure and the squeeze increase at 6, 5, 4, 3, 2, and 1 cm from the anal verge by extracting the probe in increments of 1 cm from the rectum to the anal verge. Allowing a waiting period between each measurement minimizes artifacts.

c) Anal resting pressure

The anal resting tone is a composite pressure generated by the internal anal sphincter (55%), external anal sphincter (30%) and the anal cushions (15%). [29] There is some radial asymmetry in pressures in the different parts of the anal canal [30] and therefore the pressures in the four quadrants is usually averaged to account for this asymmetry.[25] New equipment provides a more precise measurement of radial asymmetry, but more complete evaluation of this high resolution technique is still lacking. The length of the functional anal canal or high pressure zone is defined as the length of the anal canal with resting pressures exceeding 30% of the rectal pressure.[31]

Patients with faecal incontinence usually have a lower anal resting tone than continent patients or normal controls **(Evidence Level 2)**. [24,32] The degree of faecal incontinence will however not only depend on the anal sphincter tone, since there are many other factors (i.e. stool consistency, rectal compliance, etc.) that play an important role. There is also a lack of defined values of what is the normal range for the anal resting tone.

d) Squeeze increase

The squeeze increase of the anal canal pressure is generated by contraction of the external anal sphincter and can be calculated as the increase in pressure from the anal canal resting tone during maximal anal squeeze. The squeeze increase is also usually measured at 6, 5, 4, 3, 2, and 1 cm from the anal verge with the stationary pull through technique. Decreased squeeze pressures are frequently correlated to injuries in the external anal sphincter, neurologic damage or just poor patient compliance/ voluntary control.

The fatigability of the external anal sphincter can be estimated by measuring the patients' ability to sustain the squeeze effort over time. The squeeze duration is often reduced in patients with incontinence. The squeeze durability may be measured as a fatigue index.[33]

e) Recto-anal inhibitory reflex

Rectal distension or attempted defecation results in an inhibition the tonic activity of the internal anal sphincter and relaxation of this muscle. Presence of an intact internal anal sphincter is dependent on an intact myenteric plexus and it is usually impaired in patients with severe constipation due to Hirschsprung's disease. The value of react-anal inhibitory reflex testing in patients with faecal incontinence is limited.

f) Rectal sensation and compliance

Rectal sensation (and rectal compliance) can be measured by intermittent balloon distension in the distal rectum and simultaneously monitoring the patient's response. The first sensation, the first urge and the maximal tolerable volume are usually recorded. Rectal compliance can also be assessed by measuring the pressure and volume relationship when a balloon is inflated in the rectum.

Reduced sensory threshold levels of the rectum (rectal hypersensitivity) in patients with faecal incontinence could indicate a presence of urge faecal incontinence and increased frequency of defecation [34,35] **(Evidence Level 3)**, whereas incontinent patients with increased sensory threshold levels (rectal hyposensitivity) may suffer from passive (overflow) incontinence [36] **(Evidence Level 3)**.

g) Recommendations for practice

- Anorectal manometry can objectively assess anal sphincter function in patients with faecal incontinence. **(Recommendation Grade C)**
- Focused expertise to perform manometry is required; each center/laboratory should establish its own control values for anorectal manometry and check for reproducibility of the test. **(Recommendation Grade B)**

h) Recommendations for research

- Assess normal values for rectal manometry in large healthy control samples spanning all ages to serve as comparisons for abnormalities in faecal incontinence

- Assess capability of an-rectal physiology testing results (anal pressure-rectal sensation-compliance) on predicting outcomes of medical and/ or surgical treatments for faecal incontinence
- Assess rectal manometry reproducibility in large control and patients samples
- Evaluate the utility of high definition and high resolution manometry in the assessment of patients with faecal incontinence

2. ENDOANAL ULTRASOUND IMAGING

a) Introduction

Endoanal ultrasound (EAUS) is established as am important part of a colorectal diagnostic work-up [37] and has been recommended as the gold standard investigation to identify anal sphincter injury by the International Urogynecological Association/ International Continence Society joint report.[38]

b) Endoanal ultrasonography technique

EAUS is usually performed with high multi-frequency (9-16 MHz), 360° rotational mechanical probe or radial electronic probe (frequency: 5-10 MHz). During examination, the patient may be placed in the dorsal lithotomy, in the left lateral or in the prone position. However, irrespective of the position, the transducer should be rotated so that the anterior aspect of the anal canal is superior (12 o'clock) on the screen, right lateral is left (9 o'clock), left lateral is right (3 o'clock), and posterior is inferior (6 o'clock). The length of recorded data should extend from the upper aspect of the PR to the anal verge.

Three-dimensional (3D) EAUS offers a synthesis of a high number of parallel transaxial 2D images and it is possible to analyze coronal, anterior-posterior, or posterior-anterior as well as sagittal right-left views, together with any oblique image plane. The 3D image can be rotated, tilted, and sliced to allow the operator to infinitely vary the different section parameters. Volume Render Mode (VRM) is a special feature that can be applied to high-resolution 3D data volume so information inside the cube is reconstructed to some extent. The volume-rendered image provides better visualization performance when there are not large differences in the signal levels of pathologic structures compared with surrounding tissues.[39]

With EAUS, the anal canal is divided into three levels of assessment. The upper level corresponds to the hyperechoic sling of the puborectalis muscle and the concentric hypoechoic ring of the internal anal sphincter. In males, the deep part of the external anal sphincter is also identified at this level. The middle level corresponds to the complete ring of the superficial external anal sphincter (concentric band of mixed echogenicity), the conjoined longitudinal layer, the complete ring of internal anal sphincter, and the transverse perinei muscles are visualized. The lower level corresponds to the subcutaneous part of the external anal sphincter.

c) Endoanal ultrasonography in faecal incontinence

EAUS has become the gold standard for the morphological assessment of the anal canal. It can differentiate between incontinent patients with intact anal sphincters and those with sphincter lesions (defects, scarring, thinning, thickening, and atrophy) due to vaginal delivery or anal surgery (i.e., hemorrhoidectomy, sphincterotomy, fistula surgery).[40]

Tears are defined by an interruption of the circumferential fibrillar echo texture. Scarring is characterized by loss of normal architecture, with an area of amorphous texture that usually has low reflectivity. The operator should identify if there is a combined lesion of the internal anal sphincter and external anal sphincter or if the lesion involves just one muscle. The majority of lesions of the internal anal sphincter are easily recognized given the prominent appearance of the internal anal sphincter in the mid anal canal, and they appear as hyperechoic breaks in the normally hypoechoic ring. The appearance of an external anal sphincter defect is a break in the circumferential integrity of the mixed hyperechoic band. A defect can have either a hypoechoic or a hyperechoic density pattern. This corresponds to replacement of the normal striated muscle with granulation tissue and fibrosis. A limitation of EAUS remains the identification of external anal sphincter atrophy in patients with idiopathic faecal incontinence because of the vague contours of the muscle ring.

The number, circumferential (radial angle in degrees or in hours of the clock site) and longitudinal (proximal, distal or full length) extension of the defect should be reported. In addition, 3D EAUS allows to measure length, thickness, area of sphincter defect in the sagittal and coronal planes and volume of sphincter damage.[40,41] Two scoring systems have been proposed to define the severity of the sphincter damage.[42,43] Both systems have demonstrated a good intraobserver and interoberver agreement in classifying anal sphincter defects. [41,44]

EAUS has an important role in detecting clinically occult anal sphincter injuries after vaginal delivery. [45,46] In another study, Oberwalder et al.[47] reported that faecal incontinence related to sphincter lesions is likely to occur even in an elderly population of women who experienced vaginal deliveries earlier in life. They found that 71% of women with late-onset faecal incontinence (median age 61.5 years) had occult sphincter defects on EAUS.

Ultrasonographic imaging is useful to evaluate the result of treatments. Dobben et al.[48] reported that patients with a persistent ultrasonographic external anal sphincter defects after sphincteroplasty had a worse clinical outcome than those without an external anal sphincter defect. Using 3D-EAUS, de la Portilla et al. [49] demonstrated that all the implants of silicone to treat faecal incontinence were properly located in the intersphincteric space three months after injection.

d) Alternative Ultrasound Modalities in Faecal Incontinence

1. Transperineal ultrasonography

Perineal ultrasound is performed with the patient placed in the dorsal lithotomy position. Conventional convex transducers (main frequency between 3 and 6 MHz, field of view at least 70°) are applied in the perineum between the mons pubis and the anal margin.[40,41] Perineal ultrasound provides sagittal, coronal and oblique sectional imaging, with the mid-sagittal plane the most commonly used as this gives an overall assessment of all anatomical structures (bladder, urethra, vaginal walls, anal canal and rectum) between the posterior surface of the symphysis pubis (SP) and the posterior part of the levator avulsion (LA). The imaging is usually performed at rest, on maximal Valsalva maneuver and on pelvic floor muscle contraction. The access to the mid-sagittal plane allows the following evaluation of the integrity of the perineal body, measurement of ARA, and dynamic assessment of the posterior compartment.

3D perineal ultrasound imaging may be performed with volumetric probes developed for obstetric imaging. The most important clinical application is the assessment of LA injuries. At these injuries, the muscle disconnects from its insertion on the inferior pubic ramus and the pelvic sidewall and is a common consequence of overstretching during the second stage of labor.[50,51]

2. Endovaginal Ultrasonography

Endovaginal ultrasound is performed with the patient placed in the dorsal lithotomy position. The most frequently used transducer for pelvic floor 3D transvaginal ultrasound is a high multi-frequency (9-16 MHz), 360° rotational mechanical probe. The pelvic floor is divided into four levels of assessment.[52] At level I, the bladder base is visualized on the screen in the 12 o'clock position and the inferior third of the rectum in the 6 o'clock position. Level II corresponds to the bladder neck, the intramural region of the urethra and to the anorectal junction. Level III: corresponds to the midurethra and to the upper third of the anal canal. Level IV corresponds to the perineal muscles, the perineal body, the distal urethra and the middle and distal third of the anal canal.

e) Summary of Evidence

- EAUS is considered as an integral part in the investigation of faecal incontinence. **(Evidence Level 2).**

f) Recommendations for practice

- EAUS is an important part in the assessment of patients with faecal incontinence, since the examination will define the possible presence of anal sphincter injuries. **(Recommendation Grade A)**
- Pelvic floor ultrasound may define conditions, for instance, rectal intussuception, and enterocele, which may play a role in patients' faecal incontinence symptoms. **(Recommendation Grade C)**

g) Recommendations for research

- Evaluate the role of levator ani damage, visualized with pelvic floor ultrasound, on faecal incontinence symptoms and therapy results
- Further characterize and standardize the utility of pelvic floor ultrasound in patients with faecel incontinence.

3. MAGNETIC RESONANCE IMAGING

a) Introduction

Recently, there has been evidence to show that magnetic resonance imaging (MRI) is accurate in detecting external anal sphincter defects potentially suitable for repair in patients presenting with faecal incontinence [53-66] **(Evidence Level 2)**. MRI can be performed with endoluminal MRI technology or surface phased-array antennas. MRI is an alternative, with relative accuracy in the detection of external anal sphincter defects, although there is reduced local spatial resolution using this technology and less experience in the specific assessment of external anal sphincter defects.[67-71] Recently, there has been evidence to show that the longer-term functional outcome following sphincteroplasty for obstetric-related external anal sphincter defects (the principal cause of clinical faecal incontinence in this population) is somewhat dependent upon the presence of attendant pudendal neuropathy [72-74] and that worse outcome is correlated with neuropathy-associated external anal sphincter atrophy. [75-77] This technique has also been shown to accurately identify external anal sphincter atrophy in comparison with endoanal ultrasound.[78,79]

b) Normal anal sphincter anatomy at MRI

The bulk of useful images are obtained with T2-weighting where contrast is described in relation to the surrounding structures, as there are no absolute values for tissue contrast (as there are, for example in computed tomography). In a series of 100 normal volunteers, age- and gender-related differences are demonstrable on endoanal MRI,[80] as women have a significantly shorter external anal sphincter than men.

c) Anal sphincter defects on MRI

External anal sphincter lesions are detected as alterations in the normal external anal sphincter anatomical integrity or as scarring, local atrophy, or a definitive defect. The full extent damage is best appreciated in a combined evaluation of the axial and longitudinal plane sequences. Secondary changes to the architecture of adjacent structures (longitudinal muscle, perianal fat) provide

supportive evidence of a sphincter tear. Variations in normal anatomy of the anal sphincter may be misdiagnosed as sphincter defects, with constitutive differences in the external anal sphincter being observed.

Internal anal sphincter defects are identified as either internal anal sphincter discontinuity or as replacement of the normal smooth muscle by fibrous tissue with concomitant muscle thinning. Internal anal sphincter defects are often found in combination with external anal sphincter defects, especially in women presenting with incontinence. Solitary internal anal sphincter defects are more common in iatrogenic cases of incontinence.

Several studies have evaluated the accuracy of endoanal MRI in detecting anal sphincter defects. Tears of both the internal anal sphincter and external anal sphincter are readily visualized, with an accuracy of 95% for external anal sphincter lesions.[56,58,63]

d) Anal sphincter atrophy at MRI

Recent publications on endoanal MRI imaging reemphasize the importance of external anal sphincter atrophy with its potential predictive clinical implications on sphincteroplasty outcome. [54,56,58,81]

e) Role of MRI in the assessment of faecal incontinence

EAUS can be used as a primary imaging technique, given the similar results when compared with endoanal MRI in detecting sphincter defects, the widespread availability of endoanal ultrasound, and the lower costs. There is no doubt, however, that endoanal MRI technology is accurate. Its role in defining and diagnosing external anal sphincter atrophy can both direct sphincter repair and provide some prognostic information.

f) Recommendations for practice

- The place for MRI assessment of anal sphincters is limited. **(Recommendation Grade D).**
- Patients with faecal incontinence after repeated anorectal surgeries may benefit from assessment with MRI. **(Recommendation Grade C)**
- Patients with possible, but not proven, external sphincter defect on ultrasound may benefit from further assessment with MRI. **(Recommendation Grade C)**

g) Recommendations for research

- MRI can define atrophy of the anal sphincter muscles. Study to assess the degree of atrophy influences the outcomes after treatment with surgical sphincter repair and sacral nerve stimulation.

4. DEFECOGRAPHY

a) Introduction

Defecography, also termed as evacuation proctography, is the radiological assessment of the voluntary rectal evacuation of semisolid contrast material, and provides information on anorectal structure and function. It is useful and widely used in the diagnosis and management of obstructed defecation, but the technique is less often utilized in the assessment of faecal incontinence. [82-84] Rao [85] did not include defecography in commonly performed diagnostic tests for faecal incontinence in an evidenced-based summary and American Gastroenterological Association medical position statement [86] concluded that defecography is not of established value in patients with faecal incontinence. Whitehead et al.[87] concluded that defecography is useful in the assessment of perineal descent, pelvic organ prolapse, rectocele, defecation and puborectalis contraction, but they did not include it in the algorithm for the diagnosis and management of faecal incontinence.

On the other hand, defecography was used by 56% of physicians in the routine diagnostic work-up of patients with faecal incontinence in a recent Dutch study.[88] There are several studies reporting that surgical correction of rectal intussusception [89-92] or rectocele [93,94] result in improved faecal incontinence.[93,94]

There is a suboptimal correlation between symptoms and defecographic findings. Abnormal findings of defecography can be seen in many normal subjects without any anorectal symptoms.[86,95-98] Another problem in performing defecography in patients with faecal incontinence is that those with weak anal sphincters have problems retaining the semisolid contrast material in the rectum when seated on a commode.

b) Examination technique

There are no universally consented standard methods of defecography. Usually, a viscous barium contrast material is injected into the rectum of the patient in the left decubitus position. The semi-solid contrast material can be made by mixing barium with flour, oatmeal or mashed potato. The volume of the injected material is either fixed at around 150ml or up to the volume at which the patient feels the urge to defecate. A radiopaque marker can be placed close to the anus to facilitate interpretation. Barium contrast in the vagina facilitates interpretation of enterocele and prolapse in the anterior and middle compartments.

The patient sits on a commode attached to the footboard of the fluoroscopy table and lateral views of the film are taken at rest and maximum squeeze before rapid film sequences are taken at one frame per second during evacuation, followed by a film taken after the completion of the evacuation at maximum straining. The sequential films is usually by a video recording; cinedefecography.

c) Parameters studied at defecography

The anorectal junction is the distally tapered point of the rectal contrast column caused by posterior impression of the puborectal muscle. The anorectal angle (ARA) is measured by the angle between the line along the anal canal and the axis of the rectum. Normal subjects should be able to evacuate more than two thirds of rectal contrast material within 30 seconds. In addition to assessing rectal evacuation, defecography can reveal rectal intussusception, rectocele, sigmoidocele and enterocele. Rectal intussusception is defined as the invagination of the rectal wall into itself and the degree of rectal intussusception can be classified by Oxford. [89] Rectocele is defined as the outpouching of the anterior rectal wall beyond the normally expected anterior rectal wall at straining. Sigmoidocele and enterocele are defined as the herniation of the lining of the peritoneum by the sigmoid colon or the small bowl, respectively, into the rectovaginal septum and may push on the anterior rectal wall.

Perineal descent may be a sign of the weak pelvic floor muscles and possible pudendal neuropathy. An obtuse ARA implies weakening of the puborectal muscle and possibly the entire pelvic floor muscles. In a study by Piloni et al.,[99] the mean ARA at rest differed significantly between patients with faecal incontinence and those without. The normal range of ARA, however, is wide and some patients with normal ARA are incontinent to stool, whilst some with abnormally obtuse ARA are continent.

Karasick[100] stated that the major indication for performing defecography in patients with faecal incontinence is to diagnose rectal intussusception **(Evidence Level 3)**. Collinson et al.[89] performed defecography in 40 patients whose faecal incontinence could not be explained by anorectal physiology and endoanal ultrasound, recto-anal intussusception was observed in 63% of the patients. Surgical correction of rectal intussusception has been shown to improve faecal incontinence, indicating a possibility that rectal intussusception can be a cause of faecal incontinence **(Evidence Level 3)**. Lazorthes et al.[90] performed defecography in 51 patients with faecal incontinence. Fourteen patients had a recto-anal intussusception and were operated with transabdominal rectopexy. Faecal incontinence improved in all 14 patients and completely resolved in 6 patients. When Collinson et al.[89] performed laparoscopic ventral rectopexy in 24 patients with rectal intussusception and a combination of obstructed defecation and faecal incontinence, incontinence symptoms significantly improved in 92% of the patients.

It is more controversial whether a rectocele can cause faecal incontinence **(Recommendation Grade C)**. Collinson el al.[89] claimed that one of its mechanisms is faecal trapping in the rectum that allows post-defaecatory leakage to occur.

d) Recommendations for practice

- Defecography is of limited value and not always utilized in the diagnosis and management of faecal incontinence. **(Recommendation Grade B)**
- Defecography can be useful in the diagnosis and management of faecal incontinence by measuring perineal descent and ARA, evaluating involuntary leakage of the contrast material as well as diagnosing rectal intussusception and rectocele. **(Recommendation Grade B)**
- Defecography might be useful in diagnosing the existence and extent of rectal intussusception and rectocele as a cause of faecal incontinence. **(Recommendation Grade B)**

e) Recommendations for research

- Identify and characterize the degree of rectal intussusception and prolapse at defecography and correlate this to treatment outcomes after ventral rectopexy.
- Defecography may be superseded by magnetic resonance imaging (MRI) defecography, which can visualize the pelvic floor and organs as well as avoids radiation exposure.[101-103] The latter technique is, however not widely available at present, because of higher cost and most equipment does not allow examination in the sitting position.[83,104] Further investigation is needed to determine whether an open-magnet unit of MRI may solve this postural problem.

5. CLINICAL NEUROPHYSIOLOGIC TESTING

a) Introduction

The clinical use of neurophysiologic testing in patients presenting with incontinence has a long history, but appears to be diminishing in practice because of improvements in clinical sphincter imaging and as a result of the understanding that some neurophysiologic parameters have only minimal influence on decision-making.[105,106] Despite the rise of sacral neuromodulation (SNS) in the selective management of incontinent patients, there is no clear guideline for specific predictive neurophysiologic testing,[107,108] relegating its specific use in complicated cases of incontinence secondary to particular neurological diseases and following spinal injury.

b) Types of neurophysiologic testing for faecal incontinence

Neurophysiologic testing for faecal incontinence incorporates a range of different testing modalities, including somatic motor testing, somatosensory testing, determination of clinical reflexes, and autonomic nervous system (ANS) testing. Somatic

motor testing assesses the somatic nervous system responsible for skeletal muscle motor innervation plus sensory innervation from cutaneous sites to the muscle spindles. This testing incorporates all forms of electromyography (EMG), including pudendal terminal motor latency studies (PNTML), motor nerve conduction studies, and motor evoked potentials. Somatosensory testing includes somatosensory evoked potentials and sensory neurography. ANS testing: assesses the ANS which provides motor innervation to the viscera and other end-organs and which assess its visceral afferent pathways at peripheral, spinal and supraspinal levels

c) Elelectromyography

The specific use of this EMG technology in faecal incontinence in the past was for the differentiation of those patients with potential voluntary sphincter defects from those without sphincter defects thought to be reparable but who had an attendant presumptive neurological cause for their incontinence. Concentric needle electromyography (CN-EMG) is performed with single- use needles used at multiple sites. Inherent differences exist at rest in sphincter musculature when compared with peripheral (non-sphincteric) musculature showing basal resting activity whereas non-sphincter musculature is electrically silent. [109,110] Denervation is diagnosed as a reduction in the number of continuously firing low-threshold MUPs. CN-EMG has disappeared with improved accurate sphincter imaging; however, it may have a specific place in those patients where ultrasonography and/or MR imaging is equivocal. Single Fibre EMG (SF-EMG) has a smaller recording surface with a pickup of activity from a smaller muscle volume than that recorded with CN-EMG, recording generally 1-3 single muscle fibres from the same MU.

d) Pudendal nerve conduction testing

Pudendal nerve conduction testing measures the nerve conduction velocity in the pudendal nerve. There is a customized (Dantec Electronic Tonsbaaken 16-18 DK-2740 Skovlunde, Denmark) St. Mark's electrode that has been designed. Prolongation of the pudendal nerve terminal motor latency (PNTML) is common after vaginal delivery and with aging. [111-113] It has been suggested that the delay in PNTML is associated with a worse overall prognosis of external anal sphincter repair for patients presenting with faecal incontinence, [75-77] although there is little available evidence to suggest that PNTML measurement alters specific surgical decision-making. [114] There is little available evidence that the presence or extent of a pudendal neuropathy correlates with objective incontinence[106] or with the specific response to biofeedback therapy with or without the presence of an external anal sphincter defect. [115]

e) Sensory system testing

Anorectal sensitivity plays a significant role in the defecation process and in maintaining faecal continence. Variation in anorectal sensibility is also important in pain disorders and in irritable bowel syndrome. Basic sensory testing of light touch and pinprick and sensation of bladder filling is standard. The ano-cutaneous sensation of the perianal area and in the anal canal below the dentate line is conveyed by the efferent fibers of the pudendal nerve (S2-S4).[116]

f) Anal mucosal electrosensitivity

Anal mucosal electrosensitivity (MES) testing was originally described independently by Roe et al.[117] and Siegel [118] using two electrodes with a constant square wave of current with variable intensity. It is unknown precisely which receptors are involved in this standardized and reproducible response.[119] Incontinent patients invariably have a high MES whereas patients with anal sphincter defects, (with or without faecal incontinence), show an increased MES with the highest values found in patients with a combined internal anal sphincter and external anal sphincter sphincter defect.

g) Recommendations for practice

- Neurophysiologic testing is of limited value in the assessment of patients with faecal incontinence. **(Recommendation Grade C)**
- PNTML may be useful in the preoperative assessment of patients before sphincteroplasty or sacral nerve stimulation. **(Recommendation Grade C)**
- PNTML may be useful in the assessment of patients with possible pudendal neuralgia. **(Recommendation Grade D)**
- CN-EMG may have a specific role when ultrasonography and/or MR imaging is equivocal. **(Recommendation Grade D)**

h) Recommendations for research

- Assess reproducibility of testing of anorectal sensation on predicting outcome of surgical and medical treatment for faecal incontinence in large patient samples

IV. EDUCATION AND LIFESTYLE INTERVENTIONS

1. BACKGROUND

Most patients with faecal incontinence do not know how the bowel works and what might improve bowel function. Many patients also have attitudes toward defaecation that are influenced by stigma and taboos present in their particular family and their wider cultural group within a society.[120] Expert opinion supports the use of general health education, patient teaching about bowel function and advice on lifestyle modification,[121,122] but the evidence

base is small. Little is known about whether interventions designed to modify lifestyle factors might improve faecal incontinence.

2. SEARCH

Because a small number of studies on these topics were identified in past reviews, two independent searches using their own search strategy were conducted to maximize yield. The following databases were searched: EBSCOhost® databases including Academic Search Premier, Alt HealthWatch, Health Source: Nursing/Academic Edition, CINAHL 2008-November, 2011 MEDLINE 2008- Nov, 2011 and EMBASE 2008- Nov, 2011. The Cochrane library and a recent systematic review of the epidemiology and prevention of urinary and faecal incontinence was also reviewed.[123]

Searches included both Medical Subjects Heading (MeSH) terms that were exploded and text searches. The following terms were searched: anal, anorectal, bowel, faecal, faecal, f?ecal, feces, rectal, stool and continent$ or incontinent$, or diarrhea, diarrhoea, diarrh?a; and the relevant lifestyle or intervention term: education, educat*, health education; exercise, exercise*, exercis*, exercise therapy, exercise movement techniques, physical exertion; primary prevention, prevent*, preventive health services, preventive health services for older people; weight loss, diet+, diet low carbohydrate, diet fat-restricted, diabetic diet, macrobiotic diet, restricted diet+, diet gluten-free, diet reducing; irrigat$ and rectal, rectum, anal, transanal; smoking, tobacco smoke pollution, tobacco use disorder, tobacco, tobacco$, cigarette$, smok$, smoking cessation; toileting, toilet$, toilet facilities; herbal medicine, plant extracts, drugs, Chinese herbal, plant preparations, plants, medicinal, medicine, Chinese traditional; carer, caregiver, spouse, family, families, famil*, parent$, caregiver burden, caregiver support, and nursing or care. All seemingly relevant abstracts were reviewed, then salient articles were retrieved and reviewed, and the reference lists searched for further studies. Results of the two searches were virtually identical.

3. REVIEW OF EVIDENCE ON THE EFFECT OF EDUCATION AND LIFESTYLE CHANGES ON FAECAL INCONTINENCE

a) Weight loss

Obesity has been proposed as a risk factor for faecal incontinence but the evidence is inconsistent. In 2008, one study of the effect of weight loss after bariatric surgery on faecal incontinence was identified with positive results. In the current review, results of two new studies are included, one using surgery; neither showed a benefit for decreasing faecal incontinence. The effect of a weight loss (i.e., dieting) versus a control (i.e., education) intervention, on reducing faecal incontinence, was compared in a subgroup analysis of 80 women with dual (faecal and urinary) incontinence who participated in a study examining the ability of weight loss to improve UI.[124]

There was no significant difference in the Faecal Incontinence Severity Index (faecal incontinenceSI) or faecal incontinence type (i.e., consistency) between the weight loss and control groups. The 6 month intervention focusing on dietary intake was not correlated with a decrease in faecal incontinence. Women who showed improvement in faecal incontinence had a lower weight at baseline (89 kg) than those with no improvement in faecal incontinence or no faecal incontinence (97 kg). In one study of women who underwent bariatric surgery for morbid obesity (mean (sd) body mass index (BMI) = 48.9 (7.2) kg/m2), there was a decrease in the prevalence of faecal incontinence of solid or liquid stool from 19.4% preoperatively to 8.6% at 12 months (p=.018; 95% CI= 2.1–19.4%).[125] In a later study of 193 morbidly obese patients, bariatric surgery was not beneficial in reducing faecal incontinence.[126]

Faecal incontinence was worse two years after gastric bypass or gastric banding surgery than before surgery despite an average 48 kg weight loss in more than half of the patients. Worsened faecal incontinence was attributed to diarrhoea that occurred postoperatively. When men and women were analyzed together, liquid stool was significantly more common after gastric bypass than gastric banding surgery, a finding not seen when either gender was analyzed separately.

b) Smoking

Nicotine is thought to slow upper gut motility and increase total transit time,[127] but it seems that it can speed recto-sigmoid transit,[128] and this stimulation of distal colonic motility may exacerbate a tendency to faecal urgency. This fits with many anecdotal reports that smoking a cigarette facilitates initiation of defaecation. No association has been found between antenatal smoking and postnatal faecal incontinence.[129] In a survey of 271 pairs of identical twin sisters, smoking was not significantly related to faecal incontinence or flatus incontinence.[130] In a longitudinal observational study of community-living elderly men and women, smoking was not predictive of prevalent or incident faecal incontinence.[131] No new or intervention studies were identified in the current literature search.

c) Medication side-effects

Medication used specifically to treat faecal incontinence is covered in section 6 below. A vast number of drugs have direct or indirect effects on the gastrointestinal system, tending to cause constipation, diarrhoea, or either in different people. A case report was found reporting that a combination of olestra in the diet and orlistat given to treat obesity led to symptoms of faecal incontinence, which resolved when the olestra was stopped.[132] Patients reporting soiling while on treatment with orlistat for obesity

have been found to have pre-existing impaired anorectal function, thus predisposing them to symptom development.[133] It is beyond the scope of this chapter to review drug effects in detail, and prescribers should be aware of the possible unintended side-effect of faecal incontinence. A careful drug history (including all over the counter or "herbal" preparations) should be taken in each person with faecal incontinence. No studies were identified that evaluated the benefits of patient or provider education regarding the gastrointestinal side-effects of medications in the past or current literature search.

d) Toilet facilities

An environment with physical or social obstacles may impair the ability to maintain continence. This is particularly relevant to individuals who have physical or mental disabilities. Environmental obstacles include toilet facilities that are physically inaccessible, too few, or distant, require obtaining a key or money to access, or are restricted to the public altogether; they also include clothes that are difficult to manipulate in a hurry and a variety of other fac¬tors which vary with abilities of the individual. The toilet itself may be too high, leaving the feet dangling and thus making abdominal straining difficult. The toilet may be too low, making sitting and rising difficult for those with immobile hips. Commode use is reviewed in by Committee 20.

Public laws, such as those in some U.S. states that require businesses in public spaces that have toilet facilities to make them accessible for public use, reduce environmental obstacles to continence.[134]

There are many adaptations that can be made to a toilet to facilitate access and stability in use.[135] Effective bowel evacuation is helped by sitting well-supported, with feet slightly raised upon a small step stool if needed to enable appropriate use of abdominal effort, and leaning forward slightly.[136] Horizontal grab rails assist pushing up from a seated position, while vertical ones can enable pulling up. A raised seat or foot blocks can adjust the height as needed. For lateral transfer from a wheelchair, both seats need to be at the same height. Where it proves impossible for a person to use the toilet, alternative commodes or chemical toilets are available with appropriate features for the individual's needs. No studies were found examining the effect of modifying the physical or social environment for toileting to manage faecal incontinence in the previous or current literature search.

e) Patient and care-giver education and attitudes

The strongest data on education and lifestyle comes from a single RCT identified in the previous review. The study compared nurse-led education and advice about conservative faecal incontinence management (e.g., advice on diet, medication titration, and bowel retraining) alone or as part of a combined intervention that added exercises and/or biofeedback.[137] The education and advice group showed reduced frequency of faecal incontinence and was as effective as the combination therapies.[137] Other support for the benefits of patient education comes from a study reported in abstract form [138] which showed that education and standard medical care, when provided systematically to a group of faecal incontinence patients, who had failed prior attempts at medical management, led to a successful outcome in 38%. Success in this trial was defined as a patient's report that they had experienced adequate relief of bowel symptoms.

An RCT of a nurse-led education-focused intervention for bowel problems, in 146 stroke patients found that a single educational visit with a detailed information booklet increased patients' help-seeking from their family practitioner for bowel problems, demonstrating a heightened awareness of the possibility of treatment.[139] Education also changed diet and fluid behaviour, up to one year later, compared to controls who received routine care. However, there was no difference in the rates of faecal incontinence between the intervention and control groups. No new studies using an education focused intervention to reduce faecal incontinence were identified in the current literature search.

For people with dementia or other severe intellectual impairments, expert opinion holds that the attitude and management methods adopted by care providers are as important as bowel function in maintaining continence.[139] An assessment checklist of toileting difficulties in individuals with intellectual disabilities, has been developed to identify the need for intervention, and guide its focus, was identified in the current literature search.[140] No controlled studies on managing faecal incontinence in this population were found. One quasi-experimental study examined care-givers' knowledge and compliance before and after an educational intervention.[141]

Forty home care-givers of people with dementia, over half of whom had some degree of faecal incontinence, completed a study-specific questionnaire before and after receiving a videotape and information booklet entitled, "A practical approach to maintaining bowel control in people with dementia." Ninety percent of the care-givers accessed the information and there was an improvement in post-intervention knowledge scores, measured on a 55-point scale, with the mean score increasing from 23 pre-test to 32 post-test ($p=<0.001$). However, it is not known if this improved knowledge translates into improved care or reduced faecal incontinence.

f) Complementary therapies

There have been no studies of the use of acupuncture, reflexology, homeopathy or any other complimentary therapeutic approach identified in the previous or current literature search. The use of cognitive therapy for managing incontinence has been proposed but not studied.[142]

g) Summary of evidence on education and lifestyle interventions in faecal incontinence

There is at present limited evidence for any lifestyle intervention for faecal incontinence.

- Educating patients and caregivers about their bowel function and faecal incontinence can improve faecal incontinence **(Evidence Level 5)**
- Obesity: no benefit from weight loss without surgery **(Evidence Level 5)** and conflicting evidence about the effect of weight loss after bariatric surgery for morbid obesity **(Evidence Level 3)**
- Smoking: No association with faecal incontinence **(Evidence Level 3)**; no studies of effects of smoking cessation on faecal incontinence
- Medication side effects may cause faecal incontinence related to diarrhoea **(Evidence Level 4)**
- Environmental modifications in public facilities or private homes to reduce faecal incontinence **(Evidence Level 4)**

h) Recommendations for practice

- Medication side effects: consider alternatives if causing diarrhoea **(Recommendation Grade C)**
- Ensure appropriate toilet facilities and convenient access especially for people with disabilities **(Recommendation Grade C)**
- Improvement in education of patient **(Recommendation Grade B/C)**, and of carer **(Recommendation Grade C)**
- Complementary therapies cannot be recommended: no evidence **(Recommendation Grade D)**

There is insufficient evidence to recommend or discourage most lifestyle modifications either for the prevention or treatment of faecal incontinence. The committee recommends patient education about the causes of faecal incontinence and a systematic effort to remove barriers to effective toileting, as an intervention that is likely to be beneficial, based on the consensus of experts **(Evidence Level 3 evidence)**. This may be provided at relatively low cost and involves no significant risk to the patient.

i) Recommendations for research

- Based on encouraging preliminary reports that patient education, combined with conservative management, can reduce the frequency of faecal incontinence, we recommend further research. An RCT may not be possible, due to the challenge of identifying a suitable control for expectancy and attention, but a study which demonstrates a sustained benefit from a limited educational intervention (provided to patients or caregivers), would provide useful guidance for clinical management.
- Further investigation of the benefits for faecal incontinence of weight reduction, especially in moderately obese patients, using non-surgical interventions
- Exercise programmes, when incorporated into a multi-component intervention, have produced promising preliminary results and should be tested further. Such trials should differentiate between constipation-associated faecal incontinence and diarrhoea-associated faecal incontinence, as exercise may be more beneficial to the former group.
- Evaluation of the incremental or additive value of different lifestyle interventions in the patient pathway.
- Research on the contribution of complementary therapies.

V. DIET AND FLUIDS

1. INTRODUCTION

Community-living adults and elderly individuals, especially women, report that they manipulate their diet and eating patterns as a strategy for managing their faecal incontinence.[143-145] Dietary manipulation is employed by the approximately 20% of patients with irritable bowel syndrome (IBS) who also have faecal incontinence [122,146] and by the approximately 19% to 40% of patients with inflammatory bowel disease who have faecal incontinence.[122,147-151] Empirical observations of a suspected relationship between diet and changes in bowel pattern are not limited to faecal incontinence but have been reported by, individuals with constipation, those with IBS with constipation (IBS-C) and some healthy individuals, and together with physiological principles of gastrointestinal (GI) function, supported an investigation of the evidence and discussion of possible mechanisms.

2. LITERATURE SEARCH

The following databases were searched for studies to include in this review of dietary interventions for faecal incontinence management: EBSCOhost® databases including Academic Search Premier, Alt HealthWatch, Health Source: Nursing/Academic Edition, CINAHL 2008-November, 2011 MEDLINE 2008-Nov, 2011, and EMBASE 2008-Nov, 2011. The Cochrane library and a recent systematic review of the epidemiology and prevention of urinary and faecal incontinence [140] was also reviewed.

The following terms were searched: anal, anorectal, bowel, faecal, faecal, rectal, stool, continent or

incontinent, with diarrhea, diarrhoea, digestive or digestive disease with : alcohol, ethanol, alcoholism, alcoholic beverages, ethanol, drinking; beverages, fluid, fluid intake; liquid, water; coffee, caffeine, cola; diet, dietary therapy, diet, eat, intake, consum and fat or lipid, diet+, diet low carbohydrate, diet fat-restricted, diabetic diet, macrobiotic diet, restricted diet+, diet gluten-free; dietary fibre, fiber, fibre and also with constipation; lactose, lactose intolerance, lactose tolerance, lactose tolerance test, lactose factors, lactose synthase, dairy, dairy products, milk; prebiotic, probiotic, symbiotic; oligofructose, oligofructose, oligosaccharides, fructans, fructose, fos, fructooligosaccharide; sorbitol, glucitol, isosorbide, meglumine; spice, spicy, hot; yogurt, bifidibacteria, Bifidobacterium, Lactobacillius acidophilus, acidophil. All seemingly relevant abstracts were reviewed; then salient articles were retrieved and reviewed, and the reference lists of these articles searched for further studies.

a) Criteria for considering studies for this review

• Types of studies

Only studies in the English language were reviewed. Systematic reviews and meta-analyses of randomised controlled trials and full-length manuscripts reporting individual studies published in a peer-reviewed journal were considered.

• Types of study participants

Studies that involved people who were 18 years or older, had faecal incontinence, and received a dietary intervention were included. People who were tube-fed or had an intestinal ostomy of any type were ineligible.

• Types of dietary interventions

A dietary intervention was defined as any type of food, supplement, dietary product, or fluid that is purposefully consumed or restricted, limited or avoided to manage faecal incontinence. Studies were excluded if it was not possible to distinguish any direct effect of the dietary intervention from other interventions introduced simultaneously. For example, a study was excluded if it combined pelvic floor muscle training and a dietary intervention and compared it to another intervention such as drug therapy making it impossible to determine the effect of the dietary intervention alone.

• Types of outcome measures

A change in faecal incontinence was required to be a primary outcome measure of the studies. Studies which focused primarily on the outcomes of stool consistency or form, stool amount, volume or bulk, defecation frequency, diarrhoea, or constipation, without including any measure of faecal incontinence, were excluded.

• Method of review

The reviewers examined the list of citations and abstracts yielded from the electronic search strategy. Potentially relevant papers were retrieved in full text. The reviewers were not blind to the journal titles, authors' names or their institutional affiliations.

3. REVIEW OF EVIDENCE ON DIET AND FLUIDS

a) Diet modification

Studies of diet modification primarily used observational survey or qualitative research methods and provide background and rationale for examining the effects of diet. One new descriptive study with a large sample size was identified in the current literature search. Findings support those of earlier studies. A survey about faecal incontinence and self-care practices, administered to 1,352 community-living elderly people, showed that many of the respondents changed their diet and skipped meals as a management strategy for faecal incontinence. Changing diet was a significantly more common practice among women (35.4%) compared to men (12.5%).[144]

A qualitative interview of 10 women with faecal incontinence revealed that some avoided eating anything on days they were going to be away from home or restricted the amount eaten while out in public. [145] Many also restricted foods that they thought worsened faecal incontinence (for example, fried or spicy foods or caffeinated beverages and chocolate), or foods that increased flatus (for example, cabbage, onions); a few purposely ate certain foods as a therapy to decrease faecal incontinence (for example, yogurt). Using a trial and error approach, women with faecal incontinence often modified their diet based on recommendations for other gastrointestinal problems (e.g., lactose intolerance and IBS) that were available in the professional or lay literature. [145] Interviews of 189 community living men and women showed similarities with previous reports regarding aggravating types of foods that are restricted to lessen faecal incontinence. [152] In order of frequency these were: vegetables, spicy foods, fruits, fatty or greasy foods, caffeine containing foods, and dairy. More women (40%) than men (18%, p=.008) avoided foods. There were also differences by age. Younger adults were likely to report that fatty foods and alcohol worsened their faecal incontinence. Individuals with faecal incontinence also modified how they prepared food preferring blander and baked foods.

The effectiveness of these diet modifications was unmeasured and described as variable. Concerns of diet manipulation are nutritional deficiencies and subsequent poor health. However, Bliss et al. [7] found few significant differences in the nutritional composition of usual diets of persons with faecal incontinence compared to the usual diets of age and gender matched controls with normal bowel function.

Those faecal incontinence had a greater intake of carbohydrates, manganese, and vitamin B1.

b) Fluids

Faecal incontinence occurs in association with faecal impaction or constipation, mainly in elderly residents in long-term care institutions.[153,154] General clinical recommendations for faecal incontinence management in these cases are for an adequate intake of fluid to prevent hard stool consistency and constipation (See Chapter 11). Some community-living individuals report increasing fluid intake especially when faecal incontinence is loose or liquid to replace additional fluid lost.[145] However, there are no research-based data to support the recommendation of increased fluids either for constipation or for faecal incontinence, and there is no evidence that the diets of patients with faecal incontinence or constipation are deficient in fluids.

c) Lactose, yogurt, sorbitol, fructose, caffeine, and alcohol

Certain dietary components such as lactose, sorbitol, fructose, caffeine, and alcohol may cause loose stools that can potentially aggravate faecal incontinence. A deficiency of the intestinal enzyme, lactase, prevents hydrolysis of the disaccharide lactose and its absorption. The presence of lactose creates an osmotic shift of intestinal water into the small intestine and speeds transit. In the large intestine, fermentation of lactose by colonic bacteria may result in flatulence, distension, diarrhoea, and cramps. However, the majority of adults who have lactase deficiency can tolerate a small amount of lactose in foods.[155] Yogurt is usually well tolerated by lactose maldigesting individuals because the lactose is partially digested by the beta-galactosidase of the bacteria used to ferment the yogurt. However, yogurt has not been found to aid the digestion or tolerance for additional lactose simultaneously consumed with it.[156]

Due to its prevalence in approximately two-thirds of the world's population, hypolactasia is currently regarded as a normal physiological pattern rather than a disease.[157] The prevalence ranges from highs of nearly 100% in some Asian countries and 70% in Italy to lows of 2% in Scandinavia and 15% in U.S. Whites.[158] Malabsorption of fructose and sorbitol results in osmotic diarrhoea and adverse symptoms, similar to lactose. A diet, reduced in fructose and sorbitol content, is suggested for some patients with irritable bowel syndrome to reduce adverse GI symptoms.[159] No studies in the current literature search on the effect of modification of intake of lactose, sorbitol, or fructose, on faecal incontinence were found.

Caffeine, of which coffee is a popular source, induces a desire to defecate.[160-164] Caffeine has also been observed to stimulate defaecation urgency in some patients with faecal incontinence.[131] However, regular consumption of coffee was not associated with prevalent or incident faecal incontinence in elderly men and women.[131] No studies were found on caffeine restriction to improve faecal incontinence.

Chronic consumption of alcohol has been associated with accelerated gastric emptying and small bowel transit in animal studies whereas a single large dose has an inhibitory effect on these parameters.[165-167] Excessive alcohol consumption leads to damage to the duodenal and upper jejunal mucosa and inhibition of sodium and water absorption. There is an increased prevalence of bacterial overgrowth in the small intestine of alcoholics, which may contribute to loose stools, diarrhoea, incontinence, and other GI symptoms.[168] No studies were found in which alcohol restriction was reported to reduce faecal incontinence.

d) Prebiotics, probiotics, and synbiotics

A prebiotic is a general term describing a food ingredient that is not digested in the human small intestine and thus stimulates the growth and/or activity of one or more types of bacteria in the colon that have the potential to improve the health of the host. Because of its ability to stimulate growth of bacteria in the colon, dietary fibre can be considered a prebiotic. Fructo-oligosaccharides and galacto-oligosaccharides are popular prebiotics. A probiotic is a food supplement containing live non-pathogenic and non-toxic microbes that have the potential to affect the balance of colonic microbes and thereby improve the host's health. Bifidobacteria and lactobaccilli are the most commonly used probiotics, and yogurt which has active microbial cultures can be considered a probiotic. A synbiotic refers to a product that combines a prebiotic and probiotic. Probiotics have been investigated for their ability to prevent or reduce diarrhoea associated with antibiotics, Clostridium difficile infection, ulcerative colitis, acute infant dehydration due to diarrhoea and in treating Heliobacter pylori infections.[169,170] However, there are no published data on the use of probiotics or synbiotics to treat faecal incontinence.

e) Dietary fibre

1. Background

Dietary fibre is the non-starch, polysaccharide component of plant cell walls and lignin that resists digestion by human intestinal enzymes.[171] In a recent study of weight loss for incontinent and overweight women, analysis of a subsample of 55 women with faecal incontinence showed that those with faecal incontinence were 2.5 times as likely to have a low fibre intake (≤ 10 g/d) than those without faecal incontinence.[124] Moreover, persons with normal bowel function, who had diarrhoea induced by administration of phenolphthalein, reported that they had fewer days with urgency to defaecate, or fear of faecal incontinence, when they ingested the soluble fibre psyllium compared to wheat bran, cal-

cium polycarbophil, or placebo in an unblinded manner.[172] On the other hand, there are reports that dietary fibre may exacerbate faecal incontinence in some patients. It has been observed that some patients with faecal incontinence benefit from moderating their intake of foods containing largely insoluble fibre, such as whole grain breads and cereals, nuts, beans, fruits and vegetables with skin, and sweet corn.[173] Moreover, one clinical letter reported that treating constipation in elderly immobile people with a supplement of insoluble fibre and bran, resulted in faecal incontinence in half of them.[174] Thus, fibre supplements appear to benefit diarrhoea-associated but not constipation-associated faecal incontinence. Larger studies are needed to determine the indications and overall efficacy of dietary supplements for faecal incontinence.

Adverse gastrointestinal (GI) symptoms are a potential problem mediating tolerance of dietary intervention, including dietary fibre supplementation,[175] but few studies have examined this outcome systematically. In a recent secondary analysis of a larger trial that compared the symptoms associated with supplementation of 16g of fiber from psyllium, gum arabic, or CMC supplements to placebo among 189 community living adults living with faecal incontinence, the severity of symptoms in all groups was minimal.[176] Adjusting for study segment and day, a greater feeling of fullness in the psyllium group was the only symptom that differed from symptoms in the placebo group. However, subjects with greater symptom severity, especially a feeling of fullness or bloating, were more likely to request a reduction in the amount of fibre to be ingested or withdraw from the study, across groups. There was a positive association between symptom severity and being emotionally upset.

2. Review of evidence on dietary fibre

There are four studies investigating the effect of dietary fibre for managing faecal incontinence.[177-180] Two are RCTs [177,178] and were included in the previous review (**Table 1**). The methods and findings of these previously reported studies differed. In three of the four studies of dietary fibre for faecal incontinence in this review, dietary fibre was adjunctive to other therapies.[177,179,180] In two of those studies, dietary fibre was the initial treatment of a staged intervention [179,180] and, in the third study, dietary fibre was added to antimotility medication in an RCT design.[177] In the fourth study,[178] supplementation with one of two soluble dietary fibres of, moderate (psyllium) or high fermentability (gum arabic), was compared to placebo in an RCT design.

In one RCT,[178] subjects were community-living adults living in the United States with incontinence of loose or liquid stools. The intervention was supplementation with one of two soluble dietary fibres of moderate (psyllium) or high fermentability (gum arabic) compared to placebo. This study provided Evidence Level 1 evidence suggesting that dietary fibre can reduce the percentage of incontinent stools. The percentage of stools that had a loose/liquid consistency was also significantly lower in the fibre groups.[178]

Lauti et al.[177] investigated two combination treatments consisting of an antimotility medication, a diet advice sheet for a high or low fibre diet, and a fibre supplement or placebo in an RCT design. Subjects were outpatients of a colorectal service in Australia who were incontinent of mucus, liquid, or solid stools (i.e., this study was not limited to patients with faecal incontinence of loose or liquid stools). Results showed no additional benefit of a dietary fibre supplement and advice for a high vs.low fibre diet, over use of the antimotility medication, loperamide, for reducing incontinence of flatus, mucus or solid or liquid stool.[177] This study had a low level of control of threats to internal validity and intervention fidelity.

Two studies included dietary fibre as part of a staged intervention and used a non-randomized design. [179,180] In one study using a tailored staged intervention,[179] female outpatients with faecal incontinence of either liquid or solid faeces, who agreed to follow the intervention, were instructed to consume one heaped tablespoon of methylcellulose twice per day that could be increased to two heaped tablespoons as needed. If faecal incontinence did not cease within two weeks, the women were instructed to add one capsule of loperamide twice a day that could be increased up to two capsules three times per day as needed. Fluid intake was also regulated by subgroups: those with solid stool were instructed to drink 60 ml per day (doesn't seem much!) and those with liquid stool were to avoid drinking 30 minutes before and after every meal. The control group was comprised of women who did not agree to follow the intervention but who agreed to report follow-up data. faecal incontinence was cured in 46% of women in the intervention group and none in the control group.[179]

In another study, 50 consecutive patients (41 men) who had faecal soiling and normal sphincter function were recruited from two clinics in the Netherlands, and 47 completed the protocol.180 For two months, patients consumed 3.25 g psyllium fibre per day and a fibre rich diet. Patients with persistent faecal soiling added rectal irrigation using 500 ml of tap water daily for two months. Patients whose faecal soiling continued added 4 g of cholestyramine daily. Faecal soiling resolved completely in 79% (37/47) of patients. In 12 patients (24%), soling resolved after psyllium supplementation alone. Of the 37 who added rectal irrigation to psyllium supplementation, 24 (48% of 50) resolved soiling. Of the remaining 11 who added cholestyramine to psyllium supplementation rectal irrigation, 2 (2% of 50) resolved soiling.

One study of institutionalized frail elderly showed that treating faecal impaction or constipation using

Table 1: Randomised Trials Using Dietary Fibre to Manage Faecal Incontinence

Study	Design and sample	Intervention and Outcomes	Findings	Strengths	Limitations
Bliss et al.[178]	Randomised, parallel-group, placebo-controlled, single blind trial Subjects, statistician, lab technician, and subjects' clinicians were blinded. 39 adults (79% female) completed study Subjects had faecal incontinence of loose or liquid stool at least weekly. A block scheme resulted in equal numbers (n=13) in each group. Groups' characteristics were comparable at baseline.	Intervention was one of the following soluble fibre supplements mixed into fruit juices: 7.1g of psyllium/d, 21.5 g of gum arabic/d, or placebo (0.2 g pectin/d). Supplements taken for 31 days in addition to usual diet Subjects reported faecal inconti-nence daily on a stool diary for 8 d in each period Primary measure was the proportion of incontinent stools. Secondary clinical measures were stool consistency and frequency, and flatulence reported daily. Secondary lab measures were stool wet and dry weights, % of water, pH, total fibre content, water-holding capacity of stool solids, and faecal short chain fatty acids.	Proportion of incontinent stools in psyllium or gum arabic groups was significantly lower than placebo. Percent of loose/unformed or liquid stools in psyllium or gum arabic groups was significantly lower than placebo. The water-holding capacity of stool solids was highest for the psyllium group. No significant differences among the groups in other measures.	The inclusion and exclusion criteria were reported. Sample size was based on a power analysis. Data collection interval during the baseline and intervention was equal. There were attempts to control concomitant treatments, e.g., no subject was also doing biofeed-back. Supplements were pre-mixed and ready-to-take. 95% of subjects completed the study and reasons for attrition were reported. Standard lab measures were used.	Details of the procedures for random assignment and allocation concealment were not provided. Although adequately powered, small group sizes reduce generalizability of findings.
Lauti et al.[177]	Double-blind, randomized, cross-over design using blocks of 10 63 adults with inconti-nence of mucus, or liquid or formed stools. started study: Treatment A = 31 and B = 32 49 crossed-over Treatment A = 27 and B = 22 47 subjects (91% female) completed the study	Treatment A: self-titrated dose of loperamide (starting at 2 mg twice/d), 1 teaspoon of a food thickener containing starch, maltodextrin, and locust bean gum twice/d, and a diet advice sheet about a low-fibre residue diet. Treatment B: same self-titrated dose of loperamide, one teaspoon of psyllium fibre in water twice/d, and a diet advice sheet about a high and low fiber residue diet. Treatments were for 6 weeks each Primary measure was self-reported anal incontinence for the last 4 weeks of each treatment using a faecal incontinence severity index (FISI). Secondary clinical measures were faecal incontinence quality of life (FIQL) and SF-36, a measure of general health.	67% of treatment A fibre and 73% of treatment B fibre were taken. The mean difference in the FISI score between treatments was not statistically significant.	A power analysis was used for sample size calculation. Independent pharmacists dispensed the treatments. The interval for data collection during both treatments was the same. 75% of subjects completed the study protocol and reasons for attrition were reported.	Period and sequence effects were not reported prior to combining all subjects on Treatments A or B for analysis. Attrition resulted in low statistical power. There was no theoretical or physiological rationale for use of dietary fibre for leakage of mucus or solid stools. Subjects mixed their own fibre supplements and intake was uncontrolled. Doses of the anti-motility medication and supposito-ries for constipation were uncontrolled.

lactulose, a nondigestible sugar with osmotic properties, and a laxative or enema did not reduce faecal incontinence, [181] but no studies were found treating faecal incontinence associated with constipation in non-institutionalized adults.

3. Summary of evidence

Patients consider diet a factor affecting the severity of their faecal incontinence and they use diet modification as a self-care strategy **(Evidence Level 3)**. Dietary fibre supplementation appears to be a safe and tolerable intervention that reduces faecal incontinence of loose stools **(Evidence Level 1)**. However, findings about its effectiveness when added to an anti-motility medication differ **(Evidence Level 2)**. Dietary fibre as an adjuvant to rectal irrigation can reduce faecal incontinence **(Evidence Level 3)**.

4. Recommendations for practice

- Soluble dietary fibre is recommended for the management of faecal incontinence especially when stool consistency is loose or liquid. **(Recommendation Grade B)**.
- Soluble dietary fibre is recommended as part of a combination therapy involving rectal irrigation **(Recommendation Grade B).**
- No recommendations about the use of dietary fibre as an adjuvant to antimotility medications can be made because evidence is conflicting and study methods vary in quality. **(Recommendation Grade B)**
- The effectiveness of food restrictions, timing of eating schedules, and modifications of eating patterns and food preparation on reducing faecal incontinence should be evaluated for their usefulness. **(Recommendation Grade C)**
- Patients should be asked about dietary restrictions and meal skipping to assess nutritional impact especially in groups who may be at higher risk for malnutrition. **(Recommendation Grade C)**

5. Recommendations for research

Further studies on the effect of dietary fibre and other diet modifications on faecal incontinence are encouraged to build a greater body of evidence:

- Determine the optimal type and amount of fibre to use for faecal incontinence as dietary fibres differ in their chemical composition and properties
- Determine the extent to which a dietary intervention can augment other behavioural interventions, such as pelvic floor muscle exercises or bowel training, needs further study.
- Assess the effect of modifying usual diet and eating pattern as a management strategy for faecal incontinence
- Assess the role of specific foods, caffeine, and alcohol in the management of faecal incontinence
- Assess ability of fibre and fluid in relieving constipation related faecal incontinence

There are several recommendations for methodological rigour in future studies. Theory-based, adequately powered, controlled trials are sought. Studies should control for variability in an individual's baseline severity of incontinence and any adjuvant therapies. In staged interventions, the effect of the order of dietary fibre and other components, should be assessed. Monitoring adherence to the dietary intervention and intervention fidelity are recommended. A common set of outcome measures that includes tolerance to diet interventions is recommended. Reporting outcomes of faecal incontinence in addition to those of anal incontinence (which incorporates flatus incontinence) is recommended.

VI. BOWEL MANAGEMENT AND RETRAINING PROGRAMMES

1. BACKGROUND

Bowel management programmes are used by individuals with constipation and although constipation is a risk factor for faecal incontinence in children and older people, it has not been found to be a consistent risk factor for faecal incontinence in adults of other ages. Committees 9 and 11 have reviewed the evidence for bowel retraining programmes in children and older adults, respectively. Bowel management after spinal cord injury also involves other bowel problems in addition to faecal incontinence, such as constipation or incomplete evacuation; therefore, combinations of therapies for both faecal incontinence and constipation are common. Few bowel management approaches have been tested for their effectiveness for faecal incontinence only in adults with non-neurogenic faecal incontinence. Any studies found which addressed bowel management or training for multiple bowel problems in adults with non-neurogenic faecal incontinence that did not separate results for faecal incontinence, were excluded from this review.

2. SEARCH

The following keywords were searched: anal, anorectal, bowel, faecal, faecal, rectal, stool and continent or incontinent, or diarrhea, diarrhoea and the relevant lifestyle or intervention term: bowel and train or retrain; digital and stimulat); crede or massage; enema; and suppository, toileting, toile, toilet facilitiest. The following databases were searched: EBSCOhost® databases including Academic Search Premier, Alt HealthWatch, Health Source: Nursing/ Academic Edition, CINAHL 2008-November, and 2011 MEDLINE 2008- Nov, 2011 The Cochrane library and a recent systematic review of the epidemiology

and prevention of urinary and faecal incontinence was also reviewed.[123]

All seemingly relevant abstracts were reviewed, after which salient articles were retrieved and reviewed, and the reference lists searched for further studies. Studies that included patients with a variety of bowel disorders, but did not report results of bowel management/retraining for patients with faecal incontinence separately, were excluded. Studies in which results of retrograde irrigation were not reported separately from those of antegrade irrigation were also excluded.

3. REVIEW OF EVIDENCE ON BOWEL MANAGEMENT AND RETRAINING PROGRAMMES

a) Bowel habit and toileting

Expert opinion supports the importance of attempting to establish a regular, predictable pattern of bowel evacuation by patient teaching and adherence to a routine.[121,182] Because peristaltic contractions of the colon, that are associated with defaecation, increase in frequency following awakening from sleep and following meals,[183,184] the period after breakfast is the best time for scheduled defaecation. No studies of bowel habit training or regular toileting in non-institutionalised adults with mobility or cognitive limitations, or with normal cognitive function, were found in the current literature search.

b) Resisting urgency

The strong sensation of urgency to defecate is frequently associated with diarrhoea, and it is a recognized risk factor for faecal incontinence in adults.[185] In contrast to urinary incontinence, particularly the overactive bladder syndrome (Committee 14), for which a body of knowledge has developed on the efficacy of bladder training techniques (i.e., voiding at specific intervals rather than in response to urge and deferment techniques), the possibility of bowel retraining for resisting urgency to defaecate is relatively unexplored. Some biofeedback protocols focus on altering rectal sensory thresholds as discussed below.

In the previous review, one RCT[173] that compared patients who received education, including urgency resistance techniques and dietary advice, to a group of patients who received the same training plus anal sphincter exercises with or without home or clinic biofeedback showed no significant difference in outcomes.[137] No new studies of resisting urgency to reduce faecal incontinence were identified in the current search.

c) Evacuation training

A common factor in the genesis of pelvic floor problems may be chronic straining with perineal descent from constipation; this may lead to pelvic floor damage (direct or neurological),[186,187] and may be associated with pelvic organ prolapse or UI or faecal incontinence. In one small study, women who reported straining were more likely to develop urogynaecologic symptoms such as prolapse and stress urinary incontinence.[188] However, straining has not been shown to be a risk factor for faecal incontinence. No studies were identified in the previous or current search that examined the effect of decreasing straining on preventing or treating faecal incontinence in non-institutionalised adults.

Clinically, many patients with faecal incontinence are taught evacuation techniques or are encouraged to use laxatives, suppositories or enemas in an attempt to ensure that the rectum remains empty most of the time, thus giving less chance of faecal incontinence. This is known to improve continence in children (Committee 9) and elderly patients (Committee 11). One RCT of a combination treatment package for faecal incontinence in adults included training on evacuation techniques and noted that patients reported improved ease of evacuation after treatment.[137] No separate data on faecal incontinence were presented. No new studies were found utilising specific evacuation training to treat faecal incontinence in younger adults in the current literature search.

Committee 10 has reviewed the evidence for digital rectal stimulation and manual evacuation in patients with neurogenic faecal incontinence. The use of these techniques to assist complete evacuation in non-neurological populations has not been evaluated.

d) Rectal irrigation

Irrigation of the lower bowel has been used for many years to manage both faecal incontinence and constipation by patients with spinal cord damage (Committee 10). Surgical construction of a portal for antegrade irrigation is covered by Committee 17. Various equipment has been used for retrograde irrigation, including a stoma irrigation cone held in place manually against the anus;[189,190] a mechanical pump[191] and specifically designed anal irrigation equipment.[192,193] Rectal irrigation for faecal incontinence secondary to spina bifida is common.[192]

Five studies that investigated rectal irrigation for faecal incontinence and met the criteria were found in the current literature review. Three of the studies examined the effect of rectal irrigation in patients whose faecal incontinence did not improve after using other conservative therapies.[194-196] Three studies had an observational design [180,194,197] and two studies reported results of one group before and after using rectal irrigation.[196,198] One study included rectal irrigation as part of a staged intervention along with dietary fibre,[180] and two studies allowed addition of other therapies such as laxatives or dietary fibre on an uncontrolled basis.[196,198] Sample sizes were small in all studies and none used a randomized between groups design.

The effects of rectal irrigation using tap water for a mean duration of 18 months to treat faecal incontinence were reported in one study of 32 patients who had faecal soiling (n=16) or faecal incontinence (n=16) (the distinction between the two conditions was not defined).[197] Overall, approximately half (57%) of subjects reported improvement of faecal incontinence on a questionnaire; improvement was less in those with faecal incontinence (38%) compared to those with faecal soiling (79%). Ten patients discontinued rectal irrigation after 1 month due to lack of benefit, adverse symptoms or time required.

In a survey of patients with a variety of different bowel disorders, retrograde colonic irrigation was observed as being effective in reducing soiling in 41% of 32 individuals and reducing faecal incontinence in 47% of 71 persons.[194] However, irrigation was discontinued by 67% of those with soiling and 17% of those with faecal incontinence despite a benefit. Reasons for discontinuation included the time required, difficulties with the irrigating procedure, and incontinence of irrigation fluid later in the day.

One prospective study followed 18 patients with faecal incontinence who used a rectal irrigation pump and tap water. Subjects could add soap to the irrigation fluid and take laxatives or dietary fibre as needed.198 Six patients added psyllium dietary fire and three added medications. Compared to baseline Parks incontinence scores (3.6 (0.50 SD)), faecal incontinence significantly decreased at 3 months (2.3 (1.03)), 6 months (2.7 (1.3)) and one year (1.6 (.92)). Eleven patients (61%) were considered “pseudo” continent at 3 months.

A prospective study of a nurse practitioner-led rectal irrigation program for adult and pediatric patients (age = 52 (5-85 mean (range) years)) with functional bowel disorders included 51 adult patients with predominant faecal incontinence.[196] faecal incontinence symptoms were reported on a non-validated linear analogue scale at the start and after an average of 42 months using rectal irrigation with water, plus laxatives if needed. faecal incontinence symptom scores improved in the faecal incontinence only group from 7.5 (6.5-8.5 range) before to 4.9 (3.5-6.4) after the rectal irrigation program.

Rectal irrigation was included as part of a staged intervention for faecal incontinence in an already mentioned, study of 50 consecutive patients (41 men) who had faecal soiling and normal sphincter function were recruited.[180] For two months, all patients consumed 3.25 g psyllium fibre per day and a fibre rich diet. Patients with persistent faecal soiling added rectal irrigation using 500 ml of tap water for two months. Patients whose faecal soiling continued added 4 g of cholestyramine daily; 47 patients completed the protocol. Faecal soiling resolved in 12 patients (24% of 50) consuming psyllium alone, 24 of 37 (48% of 50 patients) who added rectal irrigation to psyllium supplementation, and 2 of 11 (2% of 50 patients) who added cholestyramine to psyllium supplementation rectal irrigation.

e) Combinations of therapies

It is recognised that in many people, the symptom of faecal incontinence is the result of a complex combination of disordered anatomy and physiology, stool consistency and gut motility, emotional and psychological status and restricted access to toilet facilities, amongst other factors (see Committee 5). Hence in clinical practice many patients use a combined approach, for example, adjusting diet, medications, lifestyle, muscle function and bowel habit simultaneously, depending on the result of an initial assessment. [199,200] Studies of combinations of education, diet or fluid, and behavioural therapies, which have been identified in this review, are included by topic of the intervention in the respective section above. A limitation of these studies is that the contribution of the individual components to the overall effect, or the effect of the order of components, has not been determined and remains unknown.

f) Summary of evidence on bowel management and retraining programs

There is limited evidence on many topics in this area. In particular there are no studies on effects of bowel habit training, scheduled toileting, resisting urgency, and rectal evacuation in adults with faecal incontinence. However, rectal irrigation can reduce faecal incontinence when first-line conservative therapies fail **(Evidence Level 2)**.

g) Recommendations for practice

- Rectal irrigation is recommended for patients who do not respond to other conservative therapies and as part of a combined approach of therapies **(Recommendation Grade C)**
- Attempt to establish a bowel routine **(Recommendation Grade C)**
- Urgency resistance training is possibly useful for urgency. **(Recommendation Grade D)**
- No recommendation on toileting methods is given due to lack of evidence. **(Recommendation Grade D)**

h) Recommendations for research

- Randomized clinical trials of rectal irrigation are needed.
- Research is needed in all other areas of bowel training.

VII. TREATMENT WITH MEDICATION

1. GOALS

With the recognition that severity is subjective, treatment should be allocated according to symptom

profile and patient lifestyle. The goals of this section are to identify the drugs and other medical interventions that have been used to treat faecal incontinence and to evaluate the evidence regarding their efficacy (**See Table 2**). Drugs can be combined for synergistic effect, helping reduce individual doses; loperamide plus codeine phosphate, and loperamide plus amitriptyline are examples. Conservative management of faecal incontinence has focused exclusively on three mechanisms:

- Reduction of diarrhoea. Diarrhoea is consistently found to be a strong risk factor for faecal incontinence.
- Increasing resting anal canal pressure. Low resting anal canal pressure is a risk factor for passive faecal incontinence, and is commonly seen following some types of anorectal surgery (e.g., ileal pouch procedures, sphincterotomy, abdominoperineal pull-through for imperforate anus).
- Treatment or prevention of constipation. Constipation is frequently found to be a risk factor for faecal incontinence, especially in children and the elderly.

2. SEARCH METHODS

The Medline database and the Cochrane reviews [201,202] were searched for studies in any language and any year through October 2011 which matched the following search terms: “Faecal incontinence” OR “anal incontinence” AND “drug” OR “medical management” OR “medical treatment;” “Faecal incontinence” OR “anal incontinence” AND “loperamide” OR “diphenoxylate;” “Faecal incontinence” OR “anal incontinence” AND “laxative” OR “polyethylene;” “Faecal incontinence” OR “anal incontinence” AND “phenylephrine gel.” Additional articles were identified by examining systematic reviews.[202-204]

3. REVIEW OF EVIDENCE ON MEDICATIONS FOR FAECAL INCONTINENCE

a) Treatment of diarrhoea-associated faecal incontinence with antidiarrhoeal drugs

1. Loperamide and diphenoxylate

The most extensively tested drug treatment for diarrhoea-associated faecal incontinence is loperamide. We identified 7 studies in adult subjects [177,205-209] and 3 studies in children.[210-212] These studies all have methodological weaknesses including small sample sizes, use of crossover designs, or they are case series. Loperamide is a synthetic opioid with μ-agonist activity and coincidental calcium channel blocking actions. By slowing gut transit, increasing fluid reabsorption and reducing secretion, loperamide thickens stool consistency and reduces stool frequency. It also has direct sphincter actions, attenuating the anorectal inhibitory reflex and increasing resting anal pressure. It is at least as effective as codeine, and superior to diphenoxylate in chronic diarrhoea, with a tendency to reduce faecal incontinence more effectively than the other agents. The availability of a syrup formulation offers the opportunity of titrating the dose more finely to avoid the side-effect of constipation. Some authors advocate using the drug before meals to reduce postprandial bowel urgency. Tolerance does not seem to develop with chronic administration, and the safety profile is excellent with both regular and as-required use.

Diphenoxylate, a natural opioid, is usually combined with atropine to reduce abuse potential. It crosses the blood–brain barrier to produce central nervous system side-effects and, when combined with atropine, can cause anticholinergic effects. It is less effective than loperamide. Codeine phosphate is another opiate derivative, with side-effects of nausea, tolerance and dependence. Its clinical effects are similar to those of loperamide, but it is harder to titrate and adverse effects become prominent with time.

Studies generally support the efficacy of loperamide for decreasing diarrhoea-associated faecal incontinence. The most important of these studies are briefly summarized below: Palmer and colleagues[205] compared loperamide (average of 4.6 mg per day) to codeine (average of 103 mg per day) and diphenoxylate (average of 12.5 mg per day) in 30 patients with diarrhoea, of whom 19 had faecal incontinence prior to treatment. However, change in faecal incontinence was not the primary outcome measure. Loperamide was superior to diphenoxylate and similar to codeine with respect to decreased stool frequency, improved stool consistency, and reduced side-effects. Although not statistically significant, there was a trend for less faecal incontinence while taking loperamide compared to diphenoxylate.

Fox and colleagues [209] tested different doses of loperamide against placebo in a double-blind crossover study of 10 obese subjects who were soiling as a result of taking orlistat for weight control. These 10 subjects were selected for study because they had previously been found to soil while taking orlistat. In this study, loperamide decreased soiling and faecal incontinence and increased resting anal canal pressure. Lauti’s group [177] compared loperamide plus fibre supplementation to loperamide with a low fibre diet and placebo fibre supplement in the first adequately powered study. This was a double-blind crossover study with order of treatments counterbalanced. Results showed a significant improvement in continence relative to baseline in both groups, but the addition of fibre to loperamide did not increase benefit.

Sze and Hobbs [179] investigated the additional benefit of loperamide over methylcellulose in an unblended study of 69 patients. Forty-six percent of patients were “cured” by the combined treatment, although loperamide had a tendency to cause constipation, which

Table 2: Effectiveness of Drug Therapy

Citation	Sample	Study Design	Major Findings	Adverse Events	Comments
Guillemot et al.[228]	24 patients (16 biofeedback (BF) treated and 8 anti-diarrhoeal and enema treated), mixed aetiology. 12 controls. 30 month follow-up	Unblinded RCT	At 30 months, non-significant change in Wexner score in both BF-treated (17.8 to 14.4) and medical-treated (17.0 to 18.0) groups. More marked BF change at 6 months.	Nil significant	Low quality study.
Santoro et al.[213]	18 patients and 24 controls (latter for anal physiology measurements)	Open study of 20 mg amitriptyline for 4 weeks	Faecal incontinence scores reduced from median 16 (maximum 18) pre-treatment to 3. Treatment reduced amplitude and frequency of rectal contractions and improved sphincter pressure.	Dry mouth or drowsiness in 4 patients (22%) nil withdrew	Effects suggested to be mediated by anti-muscarinic slowing of transit, and improved ano-rectal coordination.
Demirci et al.[229]	Two stage study. Stage I: 287 tertiary referred patients. Multiple aetiologies (including transit disorders), mixed treatments based on consensus algorithm. Stage II: 36 patients, mixed aetiology including transit disorders outcomes measured at median of 2 months after treatment.	Stage I: intention to assess proportion of patients suitable for medical treatment. Quantified by Pescatori scale. Stage II: uncontrolled trial of efficacy of medical therapy – unclear duration of treatment. Wexner score outcome	Stage I: 44% recommended drug treatment (anti-diarrhoeal, laxatives, enemas or anti-depressants), 18% biofeedback and 35% surgery. Stage II: 22% "cured," 39% improved, 39% unchanged (non-compliance 11%, untreatable transit issues 17%, faecal incontinence despite "normalising" transit 11%).	None reported	Low quality – time lapse of many years between stages, not clear algorithm applied prospectively in all subjects. Stage II – small numbers, no attrition rate details
Lauti et al.[177]	63 randomised (49 completed both phases of cross-over) consecutive referrals to specialist centre.	Double-blind randomized cross-over trial, each treatment was 6 weeks. Treatment A = low-residue diet sheet, placebo fibre and loperamide Treatment B = psyllium fibre, low and high residue diet sheet and loperamide.	Faecal incontinence severity index (FISI) scores fell from baseline 31 to 18 for treatment A and 19 for treatment B. No differences between treatments in terms of faecal incontinence severity or quality of life (FIQL).	Nil major – palatability of supplements caused 1 patient (3%) to withdraw	Marked inter-individual variation, hence importance of tailoring fibre to individual symptom profile.
Remes-Troche et al.[230]	21 patients with faecal incontinence treated with cholestyramine plus biofeedback and matched cohort of 21 with faecal incontinence who underwent biofeedback alone.	Prospectively collected data which was retrospectively compared between groups. Median cholestyramine dose 4gm	Improved stool frequency and consistency with cholestyramine only, not biofeedback. faecal incontinence symptoms and global satisfaction similar in both groups. Physiological measures improved in both groups.	Side effects in 7 (33%), constipation 4 (19%), bloating (9%) and headache 1 (5%).	Poor palatability side effects improved with dose reduction.
Sze & Hobbs[179]	59 patients and 10 controls (latter recruited if declined active treatment). Outcomes: overall improvement and Pescatori score at 8 weeks.	Prospective unblinded controlled study of methyl-cellulose with or without loperamide.	27 patients (46%) "cured" by intervention, equally whether solid or liquid stool incontinence.	Constipation with loperamide, relieved by dose alteration.	40 of 59 used loperamide. Power calculation aimed to detect 46% difference in open study.
Bharucha et al.[217]	12 women with urge-predominant faecal incontinence and mixture of sphincter integrity. Outcomes: diary data, faecal incontinence symptom severity score, faecal incontinence QoL, anorectal physiology	Open label, uncontrolled study of 4 weeks clonidine via patch (0.2mg/day).	Clonidine reduced stool frequency and proportion of patients with >50% reduction of faecal incontinence episodes (9 of 12, 75%) and faecal incontinence days (8 of 12, 67%). No changes manometry, but slight increased rectal capacitance with clonidine.	6 (50%) had adverse effects. 5 (42%) had skin reaction, 3 (25%) fatigue, 2 (16%) postural hypotension and 2 (16%) dry mouth.	Unclear whether effects most marked in those with baseline looser stool

was modified by dose reduction. Taken together, these studies suggest that loperamide may be more effective than fibre supplementation alone for the treatment of diarrhoea-associated faecal incontinence. An earlier study by Bliss et al.,[178] which is reviewed in Section 16.5, showed that fibre supplementation with either psyllium or gum arabic improved diarrhoea associated faecal incontinence, more than placebo.

2. Other antidiarrhoeal drugs

Santoro and colleagues [213] carried out an uncontrolled study of the tricyclic antidepressant, amitriptyline, given 20 mg at bedtime, in 18 patients with faecal incontinence; diarrhoea was not required. Thirteen of 18 became continent and 3 reported improvement. The authors attributed the benefits to increased anal resting pressure and decreased numbers of "rectal motor complexes." This study suggests that amitriptyline and other tricyclic antidepressants are of possible benefit for treating faecal incontinence. Sucralfate is a formulation of aluminium hydroxide used primarily for the treatment of duodenal ulcers; it has the property of coating the stomach lining. An early study suggested that sucralfate might reduce diarrhoea secondary to radiation proctitis in patients receiving radiotherapy for pelvic cancer.[214] However, subsequent large randomized controlled trials have shown no significant benefit for diarrhoea [215] and a worsening of faecal incontinence [216] in this patient population. Bharucha et al.[217] undertook a 4 week trial of a clonidine patch. There was a modest reduction of stool frequency and improvement of continence.

3. Mechanism of action

Three possible mechanisms of action have been identified in these studies of the drug treatment of diarrhoea-related faecal incontinence: loperamide, diphenoxylate, amitriptyline and clonidine appear to work in part by decreasing bowel movement frequency through an effect on motility and absorption. Fibre supplements (reviewed in Section 4 above), on the other hand, work by binding more water into the stools. Resting anal canal pressures were reported to be increased in response to loperamide [206,207] and amitriptyline.[213]

b) Drugs for increasing anal canal pressure in patients with passive faecal incontinence

A subgroup of patients with faecal incontinence has passive incontinence, defined as faecal incontinence that is not preceded by a sensation of urgency to defecate and that occurs without awareness. This is believed to be related to decreased resting pressure in the anal canal, due to an impaired internal anal sphincter and/or to decreased sensation for rectal distension. A specific aetiology for passive faecal incontinence is the patient with a colectomy (usually for ulcerative colitis) with a surgically constructed ileal reservoir connected to the anal canal.[218]

1. Phenylephrine gel

Phenylephrine gel, an alpha-1 adrenergic agonist, has been investigated for the treatment of passive faecal incontinence in several studies.[219-223] In an initial study of 36 patients with intact sphincters, no significant benefit was seen.[223] Two subsequent studies [219,222] suggested a benefit of phenylephrine gel, but a recent randomized controlled trial in 35 patients with passive incontinence secondary to low anterior resection failed to show a benefit.[221] Thus, the clinical utility of phenylephrine gel (if any) may be limited to patients with passive incontinence associated with ileal pouches.L-erythro methoxamine gel, an alpha-1 adrenoreceptor agonist similar to phenylephrine, has also been shown in two proof-of-concept studies to increase internal anal sphincter resting pressure,[224,225] although no clinical trial data are available as yet.

2. Valproate sodium

The gamma-amino butyric acid transaminase inhibitor, valproate sodium, also increases anal canal resting pressure. It was compared to placebo in a double-blind, randomised crossover study [226] in 17 patients with diarrhoea-related faecal incontinence secondary to colectomy and ileoanal anastamosis. The drug decreased faecal incontinence episodes and stool frequency relative to baseline and increased anal canal pressure, whereas placebo did not have these effects. In a second randomized controlled trial by the same investigators [227] patients with ileal pouches were treated with valproate sodium or placebo. There was a significant improvement in anal canal pressures, pouch capacity, and continence. Therefore, valproate sodium is of possible benefit in this population.

c) Drug treatment of constipation-associated faecal incontinence

Constipation-associated faecal incontinence, sometimes referred to as "overflow incontinence." It is more common in children, nursing home residents, and in patients with spinal cord injury. The proportion of faecally incontinent nursing home residents whose faecal incontinence is attributable to "overflow constipation" is not known. No studies of treating constipation-associated faecal incontinence in adults, outside these groups, were found.

1. Summary of evidence on medication and faecal incontinence

- Loperamide is useful for diarrhoea-associated faecal incontinence. There is some evidence that the loperamide may be superior to diphenoxylate **(Evidence Level 2).**

2. Recommendations for practice

- Treat faecal incontinence with diarrhoea with anti-diarrhoeal medication **(Recommendation**

Grade C); titrate the dose to individual response. **(Recommendation Grade C)**

- We are unable to recommend sphincter modifying drugs. **(Recommendation Grade D)**

3. Recommendations for research

- Additional, well-designed studies are needed to validate the common clinical practice of using laxatives to treat constipation-associated faecal incontinence.
- There is a need for further research on preparations, doses and combination therapies for all types of faecal incontinence and all patient subgroups
- The potential for topical treatments is high, but there will need to be formal clinical trials of such agents.

VIII. PELVIC FLOOR MUSCLE EXERCISES, BIOFEEDBACK, AND ELECTRICAL STIMULATION

Pelvic floor muscle training (PFMT), biofeedback, and electrical stimulation are distinctly different therapeutic techniques for treating faecal incontinence; see descriptions below. These techniques are compared to each other or combined in some studies (e.g., biofeedback combined with electrical stimulation).

1. PELVIC FLOOR MUSCLE TRAINING

Pelvic floor muscle training (PFMT) is also called Kegel exercise training, after its developer. [231] The patient is instructed to contract the pelvic floor muscles including the external anal sphincter and puborectalis while keeping abdominal wall muscles relaxed and to do this multiple times each day with the goal of strengthening pelvic floor muscles. In a typical protocol, the patient may be instructed to squeeze for 10 seconds while continuing to breathe deeply so that the abdominal wall muscles do not also contract. Ten to 20 such 10-sec squeezes are separated by 20 second periods of pelvic floor relaxation. Often patients are instructed to squeeze 10-20 times in a block and to repeat this block of exercises 3-5 times a day. The patient may be taught how to perform this exercise using only verbal or written instructions,[232] or they may be given verbal feedback on their performance by the therapist during a digital rectal examination.[233,234] However, electronic or mechanical devices are not often used to amplify the sensory information available to the patient on how well they are performing the exercises.

2. BIOFEEDBACK

Biofeedback training is distinguished from PFMT by the use of electronic or mechanical devices to augment the intrinsic sensory information available to the patient on how well they are contracting their pelvic floor muscles. The purpose of this type of training is to ensure that patients learn the appropriate way to contract the pelvic floor muscles while keeping abdominal wall muscles relaxed. Such training is intended to strengthen pelvic floor muscles and it is usually combined with instructions to practice PFMT at home between clinic visits. Another feature of many biofeedback training protocols is sensory training or coordination training. As a consequence of neurological injuries, many patients lose the ability to recognize sensations associated with the movement of stool into the rectum and may fail to contract the pelvic floor muscles in order to avoid stool leakage. In sensory training, a balloon-tipped catheter is introduced into the rectum and distended with varying volumes of air to help the patient learn to recognize weaker distensions. Coordination training is a variant of sensory training and refers to having the patient practice contracting pelvic floor muscles in response to any sensation of rectal distention until this becomes a well-practiced habit.[138]

3. ELECTRICAL STIMULATION

Electrical stimulation from probes placed in the anal canal or from electrodes on the perineum adjacent to the anus has also been used to treat faecal incontinence. In typical applications, stimulation is performed daily at home using a battery operated electrical pulse generator connected to the anal electrodes. [234] Different theories have been advanced to account for how this might facilitate continence. [234] In the earliest applications, electrical stimulation was used at intensities that triggered a contraction of the pelvic floor muscles, and patients were encouraged to try to augment the contractions produced by electrical stimulation or to try to reproduce these contractions. [234] Others have suggested that the stimulation of afferent nerves by lower intensities of electrical stimulation may help by increasing the sprouting of synapses peripherally or the size of the receptive fields for these nerves in the brain. [235] Electrical stimulation is sometimes combined with biofeedback. [236]

4. METHODS

The effectiveness of PFMT, biofeedback, and electrical stimulation was assessed by this committee in 2008. In this review, we summarize the recommendations made in the Fourth International Consultation on Incontinence [173] and update the recommendations for PFMT, biofeedback, and electrical stimulation from non- implanted devices by reviewing in detail articles published between January 2008 and January 2012. The faecal incontinence surgery committee (Committee 17) updated the review on electrical stimulation. Databases searched were PubMed, Web of Science,

Cochrane Reviews, and (for drug treatment) EMBASE. These searches were limited to studies in which the subjects were adult humans. No restrictions were placed on language of publication. The search terms were: (Faecal incontinence OR Anal incontinence) AND (Biofeedback OR Neuromuscular conditioning OR Pelvic floor exercise OR Kegel exercise OR Neuromodulation OR Drug treatment OR Antidiarrheal OR Loperamide OR Laxative OR Nifedipine OR Phenylephrine OR Cholestyramine OR Clonidine). In addition, the following individual authors were searched: A Bharucha, C Norton, B Southwell, SS Rao, M Kamm, A Wald, F Azpiroz, P Enck, M Crowell, and R Mittal. The bibliographies of identified studies were also searched for additional references.

This search identified 665 references which were reviewed by title and abstract for relevance and the relevant ones were assigned to the following 4 sets. Minor overlap between lists was allowed and reviews were included to allow us to check for additional references. The reference sets were (1) Biofeedback (69 references), (2) Pelvic floor exercise (9 references), (3) Electrical stimulation without implanted device (13 references), and (4) Drug treatment (25 references). These reference sets were assigned to separate reviewers and read carefully to identify randomized controlled trials (RCTs), cohort studies with appropriate comparison groups, and a few uncontrolled cohort studies which were included because they addressed key issues such as long-term maintenance of treatment effects. After eliminating duplicate references and studies containing fewer than 10 patients per treatment condition, 6 studies published since January 2008 met inclusion criteria (**Table 3**).

5. SUMMARY OF ICI 2008 ASSESSMENT

a) ICI 2008 assessment of pelvic floor muscle exercises

The review of the literature in the previous ICI report [173] identified several RCTs in which PFMT was used as a control condition to determine whether the addition of biofeedback to PFMT yielded greater improvements, but only one RCT which attempted to isolate the contribution of PFMT by comparing education and advice alone to education and advice plus PFMT. [137] This study (described above) was well designed and adequately powered. No greater benefit was observed for PFMT compared to advice. Based on this evidence, the reviewers in 2008 concluded that PFMT may be as effective as biofeedback and that advice alone may be as effective as PFMT.

b) ICI 2008 assessment of biofeedback therapy [173]

In the last International Consultation on Incontinence [173] the working committee concluded that, "In contrast to the mostly favourable outcomes reported in uncontrolled studies, randomized controlled trials have generally found no additional benefit when biofeedback was added to either a comprehensive behavioural and medical management program, or to digitally taught sphincter exercises" [page 1358]. The reviewers noted that very few studies have reported process measures, such as pre-post changes in sphincter strength or rectal sensory thresholds, which are targeted by biofeedback therapy, and presumed to account for any improvements in continence, and they questioned whether this should be required, before a biofeedback treatment protocol can be said to be responsible for an improvement in faecal incontinence. The committee concluded that biofeedback "…is possibly effective but currently unproven" [page 1359]. Only the following three RCTs were available for review in 2008:

Heymen et al. [237] randomized 40 patients with faecal incontinence to one of 4 groups: (a) EMG biofeedback during clinic visits, (b) EMG biofeedback plus sensory training with a balloon during clinic visits, (c) EMG biofeedback in the clinic plus use of an EMG biofeedback trainer at home, and (d) EMG biofeedback plus sensory training in the clinic plus daily use of an EMG biofeedback trainer at home. There were no significant differences between groups, but the study was underpowered with only 10 patients per group.

Norton et al. [137] randomized 171 patients to one of 4 groups: (a) education and management advice provided by a nurse clinical specialist; (b) advice plus PFMT taught verbally and by digital rectal exam; (c) advice, PFMT, and instrumented biofeedback which included both sensory and strength training; and (d) advice, PFMT, biofeedback, and daily home practice with an EMG biofeedback unit. There were up to nine 40-60 minute sessions in each group (median number of sessions completed was 5). There were no significant differences between groups in subjective rating of improvement, change in Vaizey Continence Scale scores, or change in frequency of faecal incontinence. Specifically, there was no greater rate of improvement in the biofeedback group (53% improved) compared to the advice and education only group (54% improved). A limitation of the study was that 49% of patients rated their incontinence severity as "minor" at baseline, and the median frequency of incontinence before treatment was only once per week.

Solomon et al. [233] randomized 120 patients with mild to moderate faecal incontinence to one of three groups: (a) manometric biofeedback, (b) trans-anal ultrasound biofeedback in which the ultrasound image was visible to the patient in real time, and (c) PFMT taught by a therapist who provided verbal feedback during digital rectal exami-

nation. There were no differences between groups on the Pescatori or St. Mark's incontinence severity scales, subjective ratings of improvement, quality of life, or manometrically measured squeeze pressures. However, there were significant differences from pre-treatment to post-treatment on most outcome measures.

c) ICI 2008 assessment of tibial nerve transcutaneous electrical stimulation from non-implantable devices

In the previous ICI report, [173] studies of tibial nerve transcutaneous electrical stimulation were reviewed by the faecal incontinence surgery committee. [238] In the absence of any controlled studies, this committee concluded that tibial nerve stimulation was an investigational technique and did not endorse it for clinical use.

6. UPDATE: REVIEW OF EVIDENCE FOR 2008-2012

Five studies published between January 2008 and January 2012 met criteria for review (**Table 3**). Two studies were RCTs comparing manometric biofeedback to PFMT, [232,239] a third RCT compared different methods of performing PFMT, [240] and the last evaluated the effects of PFMT vs. no PFMT on the prevention of anal incontinence (i.e., inclusion of flatus incontinence) during pregnancy and post-partum. [241] Another large cohort study [242] was included because it addresses the duration of biofeedback effects by following subjects until 60 months.

The Heymen et al. study [232] is important because of its novel design: All patients were first treated for 4 weeks with a conservative treatment protocol that emphasized patient education and normalization of stool consistency with fibre or non-prescription medication. This run-in protocol included only what is considered standard care for faecal incontinence, but the educational component was enhanced by (a) using schematics of the anatomy of the pelvic floor and images from defaecography to teach them why they were incontinent, and (b) having patients keep diaries of bowel accidents and stool consistency. At the end of 4 weeks, patients were asked whether they had experienced "adequate relief" of faecal incontinence, and the 21% who answered affirmatively were excluded from the rest of the trial. The remaining patients who did not report adequate relief had been randomly assigned before the run-in period to either biofeedback plus PFMT or PFMT alone. These interventions were presented in such a way that there were no differences between groups in the expectation of benefit. The biofeedback intervention combined strength training with sensory and coordination training, and was delivered in 5 one-hour sessions spaced approximately 2 weeks apart. PFMT was taught by verbal instruction, not with the benefit of digital rectal examination. The primary assessment was at 3 months follow-up as determined a priori, and patients who reported adequate relief at 3 months were followed up again at 12 months. All patients not reporting adequate relief at 3 months were assumed to be non-responders at 12 months.

An intent-to-treat analysis at 3 months showed that significantly more patients in the biofeedback group reported adequate relief compared to the PFMT-only group (76% vs. 41%). Continence (zero faecal incontinence episodes in the previous month) was achieved by 44% of biofeedback-treated patients compared to 21% of PFMT-only patients. Scores on the validated Faecal Incontinence Severity Index [243] confirmed significantly greater improvement in the biofeedback patients compared to the PFMT-only patients at 3 months and again at 12 months follow-up. Heymen et al. [232] also showed that biofeedback-treated patients increased their anal canal squeeze pressures and decreased their abdominal wall tension during pelvic floor contractions significantly more than PFMT-treated patients, but changes in sensory thresholds were not significantly different.

The results of Heymen et al. [232] suggest that biofeedback plus PFMT is superior to PFMT alone in patients with moderate to severe faecal incontinence. They also show that treatment benefits for both biofeedback and PFMT are not explained by nonspecific treatment effects of conservative management such as education and normalization of stool consistency. Furthermore, these data provide evidence that PFMT is more effective than conservative management alone.

Bols et al. [239] reported an RCT which also compared manometric biofeedback plus PFMT to PFMT alone. Eighty patients with moderate to severe faecal incontinence were randomized to these two conditions. Up to 12, 35-minute training sessions were provided, and the primary outcome was the Vaizey Incontinence Severity Score. There was no significant difference between groups, although there was a trend favouring manometric biofeedback: 82.5% of the manomeric group vs. 66% of the PFMT-only group improved by more than one point on the Vaizey scale. Limitations of this study were lack of power, only 75% of the numbers calculated beforehand as needed for adequate power were enrolled, and the fact that the intervention was provided by 25 different physiotherapists in private practice settings.

Bartlett et al.[240] compared exercise regimens, i.e., whether the patients were trained to perform fast twitch exercises (1 sec duration contractions) in addition to slow contractions (10 second squeezes) or they only performed slow contractions (10 second squeezes). The 72 patients enrolled in this

Table 3: Studies of Biofeedback, Pelvic Floor Muscle Training, and Electrical Stimulation from Surface Electrodes

Reference Country	Population	Intervention	Control	Outcome	Comments
Heymen et al.[232] USA	108 patients with faecal incontinence, Mean age=59.6 years, 77% females. Patients excluded if they responded to run-in of medical management. Patients randomized to groups prior to run-in	Manometric biofeedback (**BF)** taught in 6 biweekly sessions of 60 min each. Patients taught to coordinate sphincter contraction with sensation of balloon distention. Also performed pelvic floor muscle exercises (**PFME**) daily. Only difference from control was BF.	**PFME** taught by verbal instruction. Instructed to squeeze 100X/day. Returned for biweekly sessions to review diary and receive further instructions. Matched to BF group on therapist contact time and expectancy.	Groups comparable at baseline. At 3 mo. follow-up, BF showed greater decrease in FISI than PFME. 76% of BF reported adequate relief at 3 mo vs. 41% PFME. Greater improvement maintained at 12 mo follow-up. Complete continence in 44% of BF vs. 21% of PFE.	Strengths: Exclusion of subjects responding to medical management and use of intent to treat analysis. Weakness: Most assessments not performed by blinded assessor. No differences in quality of life improvement.
Bols et al.[239] Netherlands	80 FI patients with Vaizey severity score >12 (possible range 0-24). Excluded patients with absent squeeze pressure, chronic diarrhea, overflow incontinence, rectal prolapse, and soiling only. Mean age 60; 90% females	**Rectal balloon training (RBT) + PFME**. RBT was individualized: For insensitive rectum, patient was trained to respond to smaller volumes; for hypersensitive rectum, patient was trained to tolerate larger volumes using progressive distension and urge resistance. All patients received coordination training. PFME training was individualized with goal of improving strength and duration of squeeze. Sessions were 45 min.	**PFME** training was individualized with goal of improving strength and duration of squeeze. In both arms patients received up to 12 sessions in 9-week period. Sessions were 35 min. long.	Primary outcome was Vaizey severity score which was not significantly different between groups. 82.5% of RBT group and 66% of PFME-only group improved >1 on Vaizey scale. Some secondary outcomes favoured RBT.	Limitations: Lack of power: only 75% of required sample size for adequate power was included. The use of 25 different physiotherapists from private practice may have resulted in inconsistent treatment.
Bartlett et al. [240] Australia	72 patients with onset of faecal incontinence following colorectal cancer surgery were randomized to two groups. Mean age 62 years; 73.6% female	All patients received 4 weekly manometric **BF** sessions plus **PFME** training in sustained, 10 sec squeezes. The experimental group received additional practice of **1/sec rapid maximal contractions**.	Equivalent number and type of BF sessions combined with **PFME** training of **sustained, 10 sec contractions**. The only difference was no rapid exercises.	Both groups improved with no difference between groups. Attrition rate was 22-29%.	Major limitation: Heterogeneity of population and small sample sizes (type 2 error
Bo et al.[241] Norway	105 sedentary primiporous women without history of faecal incontinence	**PFME** taught as part of group exercise class 2X/week for 12 wks. Patients performed 3 sets of 12 maximal contractions per class. Only group verbal instructions provided.	Controls received usual care.	No difference in number of women reporting flatus or faecal incontinence during pregnancy or at 6 wks. post-partum.	Study was underpowered.
Lacima et al.[242] Spain	Cohort of 95 patients incontinent of solid stool referred for BF. Mean age 61 years; 85% females. Excluded patients with recent obstetric injury, cloaca defect, and rectal prolapse	**Manometric BF** combined strength training, sensory training, and coordination training for five 45-min.sessions. Daily **PFME** were also prescribed.	**No treatment.** Cohort of 40 patients referred to the same clinic for evaluation but BF was not recommended and no treatment for faecal incontinence was prescribed.	At **60 months follow-up** 86% of the BF group were continent or had >75% reduction in faecal incontinence frequency compared to 26% of untreated controls.	Strength: 60 month follow-up. Weakness: patients were not randomized to treatment. The BF group had greater average faecal incontinence severity than controls at baseline.

study had an onset of faecal incontinence following colorectal cancer therapy. Both groups improved with no difference between groups.

Lacima et al. [242] followed a cohort of 95 patients whom he treated with biofeedback and PFMT and followed up 60 months later. What makes this study worth including is that the authors showed that even at 60 months following training, 86% of the biofeedback/PFMT group were continent or had at least a 75% reduction in the frequency of faecal incontinence.

7. TIBIAL NERVE PERCUTANEOUS STIMULATION

There has been persisting interest in the use of tibial nerve stimulation for the treatment of faecal incontinence, reflected by the publication of several uncontrolled case series. [244,245] The theory behind this treatment derives from traditional Chinese medicine which identifies the posterior tibial nerve as an acupuncture point where stimulation can inhibit bladder contraction. Stimulation is done either using surface electrodes applied over the tibial nerve at the level of the ankle or by inserting a needle electrode into the region of the tibial nerve. Published case series [244,245] show a modest benefit for approximately half of patients tested, and in the absence of controlled studies, this technique must still be regarded as investigational.

Another variation of electrical stimulation is transabdominal electrical stimulation accomplished by passing electric current between an electrode on the abdominal wall and one on the back. This has so far been used only in children with slow transit constipation, [246] many of whom have encopresis. Reports show improved transit time, [247] improved quality of life, [244] and reduced encopresis. [245] This technique may find application in adults with overflow faecal incontinence but is currently regarded as investigational.

8. SUMMARY OF EVIDENCE

- Manometric biofeedback training is possibly effective. A new high quality study provides support for the hypothesis that biofeedback, when provided by an experienced therapist, is more effective than pelvic floor exercises alone, but the variability between studies suggests that results may be dependent on the training and experience of the therapist. (**Evidence Level 1**)
- PFMT is possibly effective for the treatment of faecal incontinence. New evidence shows that PFMT alone significantly improves outcomes for patients who have not responded to conservative management. [232] (**Evidence Level 2**)
- There is no support for the hypothesis that adding “fast twitch” contractions to PFMT improves continence outcomes. (**Evidence Level 2**)
- There is no support for the addition of electric stimulation from non-implanted devices in the treatment of faecal incontinence. (**Evidence Level 2**)

9. RECOMMENDATIONS FOR PRACTICE

- PFM exercises are recommended as an early intervention in the treatment of faecal incontinence as part of a conservative management bundle of interventions, based upon low cost and morbidity and weak evidence suggesting efficacy. (**Recommendation Grade B**).
- The use of biofeedback as a treatment for faecal incontinence is recommended after other behavioural and medical management has been tried, if adequate symptom relief is not obtained, given the numerous positive outcomes from uncontrolled trials, limitations in the current RCTs and low morbidity associated with its application. (**Recommendation Grade B**).
- Based on currently available evidence it is not possible to recommended electrical stimulation for faecal incontinence. (**Recommendation Grade C**)

10. RECOMMENDATIONS FOR RESEARCH

- There is a need to conduct further RCTs to determine whether specific biofeedback and pelvic floor muscle exercise protocols can alter physiological parameters of ano-rectal function with concomitant changes in bowel control.
- Clear description of modalities and evaluation of different elements of biofeedback
- Adherence monitoring
- Standardisation of outcome measures
- Long term follow up
- Robust patient-focused outcome measures
- Understanding of physiological effect and relationship to symptom change
- Work on clinically meaningful improvement and distinguishing cure from improvement rates
- The exploration of possible synergies between urinary and faecal incontinence interventions and evaluations should be considered in study designs.

IX. QUALITATIVE RESEARCH ON THE EXPERIENCE OF FAECAL INCONTINENCE AND QUALITY OF LIFE

1. BACKGROUND

The experience of faecal incontinence has been studied from a qualitative perspective since 1999 and tied with quality of life. Qualitative methods focus on

the intensive investigation of the particular, and the meaning of a phenomenon, in this case, faecal incontinence. Because qualitative studies generate large amounts of quality text data small purposeful sample sizes are used to accomplish their aims. These studies focus on studying the context or experience of a phenomena rather than measurement of variables. Sample sizes in the 14 studies included in this review ranged from 9 to 100 for qualitative phenomenological, grounded theory and descriptive studies, to 186 participants in an open ended questionnaire interview, for a total of 462 participants. Three studies received a grade of C but were included in the review because the evidence was relevant and substantiated by other quality studies.

The studies below have used a number of qualitative methods to explore the experiences of quality of life using phenomenological, grounded theory and qualitative descriptive designs using in-depth interviews, one study used one question with a rating scale, and one study used a semi-structured interview questionnaire. A thematic analysis was completed on the content of the quality of life studies, and the following five themes were derived and used as categories for the review of content: issues relating to relationships, time, body, sexuality and diet. Of the twelve studies reviewed on faecal incontinence, 4 studies focused on community living women, one study of women in a nursing home with pelvic floor dysfunction, one study of community living men, 4 studies of community living adults, and studies of specific diseases causing faecal incontinence including spinal bifida and multiple sclerosis.

2. CRITERIA FOR EVALUATION

Over the last 25 years there has been an extensive debate about the best methods and criteria to evaluate qualitative research studies. Criteria for the evaluation of qualitative research was synthesized using the most recent literature on quality and rigor, and is included here. These criteria were used to critique studies, strengths and limitations were noted, and a grade was given for practice recommendation.

In the last 10 years new ideas and criteria have been designed and are now being applied to evaluate qualitative studies.[248-257] The qualitative research studies on faecal incontinence (faecal incontinence) and quality of life, related to faecal incontinence, will be analyzed according to these new criteria summarized below. The strength of the evidence provided by an individual study depends upon the individual study design to maximize application to practice. A grading procedure has been developed here to rate studies for their applicability to practice from A to C.

a) Type of study – The qualitative evidence pyramid

1) Qualitative metasynthesis

2) Interpretive designs including phenomenology, grounded theory, ethnography.

3) Descriptive qualitative designs using content analysis (including inductive and deductive content analysis approaches, analysis of focus group data, photovoice, participatory action research, single or multiple case studies).

4) Surveys with semi-structured open-ended questions.

b) Criteria for evaluation of qualitative studies

1) There is a set of discernable research purposes or questions that are suitable for qualitative inquiry.

2) The purpose or questions are linked with a critical review of the literature and key studies are included identifying a gap or misunderstanding of the phenomenon.

3) There is a guiding frame of reference for the study that fits the target phenomenon.

4) There is congruence between the method and the research purpose.

5) The sampling plan is purposeful and fits the purpose and method.

6) The sample size and configuration fit the purpose and sampling strategy.

7) Inclusion and exclusion criteria are described and appropriate for the purpose.

8) Data collection techniques and sources fit the purpose, method and sample.

9) The analysis plan fits the purpose and method.

10) Data are sufficiently analyzed and interpreted, data is re-represented and category or thematic meaning is apparent. The interpretation or description is distinguishable from the original data collected.

11) The participants' voices are heard through examples highlighting the categories or themes of the findings.

12) Concepts and ideas are well developed and linked to each other and to the data.

13) The results offer new insight into the phenomenon studied and transferability of findings is evident.

14) Reflexivity is addressed within the context of the study.

15) Evidence of an audit trail of how key decisions were made is clear. Strategies to achieve rigor are described.

16) Study specific limitations are summarized.

17) Ethical considerations are attended to and described.

c) Levels of evidence

Level 1: A study would include all criteria. Excellent evidence leads to a practice recommendation.

Level 2: A study should include criteria numbered 1, 4 - 13, 17. Moderate evidence leads to a possible practice recommendation (more evidence is needed).

Level 3: A study does not include the majority of criteria for evaluation. Poor evidence that does not lead to a practice recommendation.

d) Grades of recommendation

Grade A recommendation: Grade A recommendation includes studies with evidence levels 1-2 (the qualitative evidence pyramid).

Grade B. Grade B recommendation includes studies with evidence levels 2-3.

Grade C. Grade C recommendation includes studies with evidence levels 3 or lesser quality.

3. SEARCH METHOD

In order to gain a deeper understanding of the experience of having faecal incontinence from the perspective of the client, the PUBMED database (from 2000 to 2011) was searched using the following subject headings and key words: qualitative research; anal, bowel, faecal and incontinence; quality of life and faecal incontinence; and quality and rigor in qualitative research. Additional articles were identified by examining reference lists from articles, articles in press by the authors and other systematic reviews. This search yielded over 600 studies of which only 16 used qualitative methods and 11 were used for evaluation of qualitative methods. These articles included topics on the experience of faecal incontinence from the perspectives of men and women, faecal incontinence and colorectal cancer, incontinence and sexuality, quality of life and faecal incontinence, pelvic floor dysfunctions and frail elderly women, diet strategies to manage faecal incontinence, goals of faecal incontinence management, life with post-natal faecal incontinence, and spina bifida.

4. REVIEW OF EVIDENCE ON THE EXPERIENCE OF FAECAL INCONTINENCE AND QUALITY OF LIFE

The review of the evidence on the experience of faecal incontinence and quality of life begins with a study review including the study purpose, design and critique of the design and the evidence level. The findings were overlapping for most studies so that the study findings are summarized in a following section using five categories of experience/quality of life that were identified: relationships, time, bodily symptoms, sexuality, and diet.

A descriptive qualitative study conducting unstructured interviews of 20 women's experiences of faecal incontinence from Britain focused on the assessment of symptoms of incontinence, coping strategies and the provision of continence aids.[258] The quality of the study was fair to good. Details of the analysis procedure were not clear and participant's voices were not included in the report. Additionally reflexivity concerns were not addressed.

The purpose of a descriptive qualitative study in the United Kingdom was to identify question items for a quality symptom and quality of life assessment for individuals with anal incontinence.[259] Three substudies addressed the purpose. First, seven clinical experts were asked to characterize symptom items of anal incontinence, second,[284] free text comments from patients involved in a treatment intervention trial were collected, and third, 31 qualitative interviews were conducted with people with anal incontinence. The study design was strong and inclusive of clinicians and patients. A grounded study method was mentioned as the study design but no substantive theory was developed and reflexivity was not addressed.

Another descriptive qualitative study in Sweden explored faecal incontinence in adults with spina bifida.[260] Using semi-structured interviews with 11 subjects, themes were generated using content analysis. The rigor of this study was good with insightful findings and powerful quotations used to illustrate the interpretations of the participants' experiences. Specifics of the analysis process were not given which was a weakness. The concept of reflexivity was not addressed.

A phenomenological study using 10 community dwelling women was conducted on dietary issues in the US.[145] The study was a secondary analysis of the dataset collected in a larger study by Peden-McAlpine, Bliss, and Hill.[261] Content focused specifically on diet and the meaning of the role of diet and food related to faecal incontinence. Narrative interviews were conducted with the women and the design of the study was strong with few limitations although reflexivity was not mentioned.

A descriptive qualitative study, conducted in the US on frail elderly women, with pelvic floor dysfunction, in nursing homes, interviewed 25 women ages 65-96.[262] The purpose of the study was to increase understanding of the views of frail elderly women in residential care related to quality of life, and values and preferences for pelvic floor care. The study design was strong and used NVIVO as a tool to identify representative categories. The categories derived were not specifically related to the aims. One limitation was that the criterion of reflexivity was not addressed.

A study in the U.S.[263] interviewed clients about their goals for faecal incontinence management as part of a RCT on dietary fibre. The main purpose and source of data in this study was not an interpretive qualitative

exploration. A semi-structured interview questionnaire was used to elicit goals from 189 people with faecal incontinence. The study design was methodologically sound and the overall quality was excellent.

A phenomenological study on community living women was conducted in the USA to investigate the lived experience of women managing faecal incontinence.[261] The study used in-depth narrative interviews with women between the ages of 37 and 78. The study design was excellent although issues of reflexivity were not mentioned.

A phenomenological study on 11 community living men, between the ages of 48-85, was conducted in the USA to investigate the lived experience of men managing faecal incontinence.264 The study used in-depth narrative interviews with men between the ages of 37-78. The study design was excellent although issues of reflexivity were not mentioned.

A study from England was conducted to explore the impact of incontinence on an individual's sexuality and to identify the impact of health interventions for the management of incontinence on sexuality.[265] A quota sample of 27 subjects who were being successfully managed and those being unsuccessfully managed were interviewed. The study design was strong although the inclusion/exclusion criteria used for quota sampling was not specific and reflexivity and limitations were not addressed.

One study from Denmark explored how post-partum women experience and cope with faecal incontinence. [266] In-depth unstructured interviews were conducted with 9 women ages 28-50 and analyzed with a grounded theory analysis technique for analysis. This study was of good quality however reflexivity, ethical considerations, and limitations were not noted.

A qualitative analysis was conducted on letters sent to the Multiple Sclerosis Society in the UK after a letter regarding constipation was printed in the Society's newsletter.[267] More than 100 letters and emails were received from Society members discussing their bowel problems and were analyzed using a qualitative approach. The study quality was good however the detail of the analysis was lacking.

A study in the UK investigated aspects of distress, expressed by colorectal cancer patients, to produce a more detailed account of the illnesses' impact on their identities and self-understanding.[268] Thirty-nine men and women participated in in depth interviews from across the UK. The sample included 19 men and 20 women ranging from 33 to 87 at the time of the interview. The study design was strong and the findings portrayed a powerful experience of these participants. No report of reflexivity was noted.

A qualitative descriptive study conducted unstructured interviews with 10 women who had flatal or faecal incontinence, post-vaginal delivery, with a view to improve an existing quality of life scale for faecal incontinence.[269] The authors came to interesting conclusions about relevant parameters to measure in younger women with faecal incontinence, but it is not clear if these concepts are reflective of the participants' voices. The collection technique, analysis and concept development were not explained.

A qualitative descriptive study completed guided interviews with 22 community living adults with faecal incontinence.[270] The aims of the study were to explore the participants' experiences of faecal incontinence on lifestyle, quality of life and how they adapted management strategies. Another aim was to learn about their disclosures and reasons for seeking help from health professionals. Grounded theory was stated as the method although a substantive theory was not produced in the findings. The findings were not well interpreted and linked together. Some insightful information was learned from the study, about faecal incontinence, that was corroborated by other quality studies.

A descriptive qualitative study was conducted in Britain to validate a draft questionnaire measuring quality of life issues with community living women with faecal incontinence.[271] Twenty-seven women with longstanding faecal incontinence problems were invited to participate in one of 2 focus groups. The mean age of the women was 51. No specific procedures for data analysis were included and reflexivity and ethical issues were not mentioned. Study findings were similar to those of other quality studies.

5. LIVING WITH FAECAL INCONTINENCE AND RELATIONSHIPS – SUMMARY OF EVIDENCE

- Men and women found that faecal incontinence was a perceived threat to their social acceptability, privacy and relationships. [258,261,262,264,265,269] **(Evidence Level 1)**
- Who to tell about the faecal incontinence problem and when was a matter of great concern. Usually family, close trusted friends and coworkers were told because it could not be kept a total secret,[258,261,264] **(Evidence Level 1)**
- Discussing the problems with others who suffered from faecal incontinence was comforting and allowed conversation about how to manage the problem.[261,264] **(Evidence Level 1)**
- Humor was used as a resource to avoid humiliation and embarrassment in dealing with daily symptoms of faecal incontinence and relationships, even though feelings of shame and humiliation persisted.[259, 261, 264] **(Evidence Level 1)**
- Men and women spoke about their discomfort in being with 'mixed company' and their concerns about a possible accident. Gender was an issue in relation to perceived social risk [261,264] **(Evidence Level 1)**

- Men and women described trying to protect themselves from the unpredictability of their symptoms and kept up a façade to keep the secret of faecal incontinence from others. [259] **(Evidence Level 2)**

- Support from spouses was noted to be very important for men and women.[258, 261, 264, 266] **(Evidence Level 1)**

- Relationships with healthcare providers were not helpful in providing advice concerning symptom management and control. Misinformation or no information was commonly given.[258-261, 264] **(Evidence Level 2)**

- Women reported feeling embarrassed and humiliated by having their faecal incontinence problem minimized or trivialized by rude or blaming health care providers leading, to the feeling of marginalization.[259,261] **(Evidence Level 1)**

- Women had concerns about entering into new relationships and there was an expressed concern about fear and shame of having to disclose their bowel problems.[259] **(Evidence Level 2)**

- Anxiety was present in both men and women who suffered from the uncertainty of social isolation because of faecal incontinence. [145,258-261,264,266] **(Evidence Level 2)**

a) Recommendations for practice

- Health care providers need to acknowledge the problem of faecal incontinence compassionately, and initiate the assessment and discussion of faecal incontinence symptoms, so they can be properly managed. The stigma, embarrassment and sensitivity associated with faecal incontinence compel clinicians to refrain from giving dismissive or blaming responses that may retard future care seeking and contribute to the under reporting of faecal incontinence. **(Recommendation Grade A)**

- Health care professionals can facilitate gender sensitive support groups and sharing of practical knowledge of faecal incontinence symptom management. **(Recommendation Grade A)**

- Primary care/generalists should refer patients to incontinence specialists when unable to provide therapeutic advice or treatment. **(Grade B)**

b) Recommendations for research

- Investigate the use of humour as a therapeutic coping strategy for dealing personally with the symptoms of faecal incontinence

- Defining the attitudes and treatment goals of health professionals treating faecal incontinence would be helpful to the identify some of the barriers to effective treatment.

- Assess the value of gender sensitive support groups to facilitate sharing of practical management strategies for faecal incontinence symptom management.

6. LIVING WITH FAECAL INCONTINENCE AND TIME AND PLANNING – SUMMARY OF EVIDENCE

- Participants describe spending a significant amount of time planning for and worrying about accidents.[261,264] **(Evidence Level 1)**

- Men and women perceived that their symptoms of faecal incontinence grew worse with aging in relationship to severity, onset and duration.[261,264] **(Evidence Level 1)**

- Men and women had symptoms for months or years before seeking help for the condition. [261,264] **(Evidence Level 1)**

- Women reported that the frequency of stool leakage was unpredictable and because of this, they needed to be vigilant and prepared for the unexpected. [259,261] **(Evidence Level 2)**

- Planning and management strategies of faecal incontinence to avoid an accident included: morning bathroom rituals, changing the location of their workstation (relative to the bathroom), altering eating habits (foods and timing), taking a fibre supplement, or using anti-diarrheal products.[258-261,264] **(Evidence Level 2)**

- Many women discussed packing 'kits' of absorbent products, cleansing supplies, extra clothing as a routine part of planning to leave their home.[258,261] **(Evidence Level 2)**

- Women postponed business meetings because of the faecal incontinence.[261] **(Evidence Level 1)**

- Women reported the frequency of stool leakage was unpredictable and because of this they needed to be vigilant and prepared for the unexpected.[258,261] **(Evidence Level 2)**

- Space was experienced as a measure of risk exposure for faecal incontinence and personal space shrank inward or expanded related to perceived comfort or lack of perceived social safety.[258, 260, 261, 264, 265, 268, 272] **(Evidence Level 2)**

- Seeking out the location and availability of a bathroom was a major consideration in all dimensions of space outside the home.[258-262,264,267] **(Evidence Level 2)**

- Travel was limited to places that felt comfortable and significant planning was done to prevent an accident. faecal incontinence limited travel for the family.[254,261,264,266] **(Evidence Level 2)**

- Women and men experienced heightened anxiety about faecal incontinence symptoms

and the risk of accidents in public spaces. [258,260,261,264] **(Evidence Level 2)**

- Work life presented complicated situations for both men and women and limited some people's ability to engage in productive work outside the home.[261,264,268] **(Evidence Level 2)**

- Symptoms related to faecal incontinence were a common reason for early retirement for both men and women.[268,261,264] **(Evidence Level 2)**

a) Recommendations for practice

- Recommend that clinicians share findings of practical management strategies, such as preparing cleansing kits and locating public restrooms, with other patients who have faecal incontinence to help them self-manage their experiences better. **(Recommendation Grade A)**

- Recommend coaching clients on how to plan for and reduce unpredictable incontinence accidents and/or their embarrassment; teach patients strategies to go to social situations and into public more confidently by supporting self-efficacy (this could include education on products, packing a change of clothes, disposable wipes, using a bowel diary to plan schedules, etc.). **(Recommendation Grade B)**

b) Recommendations for research

- Study interventions that promote enhanced self-efficacy

- Evaluate effectiveness of using a bowel diary or keeping a routine schedule to reduce incontinence accidents in public

- Evaluate effect of public education campaigns on normalizing elimination and raising awareness that incontinence is a treatable condition

7. LIFE LIVING WITH FAECAL INCONTINENCE AND BODILY SYMPTOMS, SELF ESTEEM AND BODY IMAGE – SUMMARY OF EVIDENCE

- Across all studies feelings of shame and embarrassment related to faecal incontinence were noted. **(Evidence Level 1)**

- Women felt stigmatized because of the faecal incontinence problem and stigmatized themselves.[258,261,266] **(Evidence Level 2)**

- Men and women reported that their emotional life and self-confidence was undermined because of the faecal incontinence and embarrassment.[258,261,264,266] **(Evidence Level 2)**

- Men and women reported changes in body image and self esteem as a result of their inability to control the symptoms of faecal incontinence. [259,261,264] **(Evidence Level 2)**

- Not talking about the problem and denying the faecal incontinence was a coping mechanism used to protect themselves from a threat to self-esteem and to prevent public embarrassment.[266] **(Evidence Level 2)**

- faecal incontinence caused women to view themselves as shameful, impure, or unworthy. [260,266] **(Evidence Level 2)**

- Some women reported the need for psychological consultations because of the feeling of being insufficient and vulnerable.[259,266] **(Evidence Level 2)**

- Unpredictability of the type and timing of an faecal incontinence event and its magnitude were key issues discussed by men and women.[145,261] **(Evidence Level 2)**

- faecal incontinence was a consequence of exercise, heavy chores, and lifting.[260] **(Evidence Level 2)**

- Bodily sensations associated with the symptoms included sensations in the intestines, itching, burning, cramping, feelings of incomplete bowel movements, and odour associated with flatus. Other symptoms discussed included leaking stool without feeling the need to defecate and false abrupt and urgent sensations usually indicative of defecation. Men lost confidence in symptoms to alert them to faecal incontinence due to the unpredictability of faecal incontinence.[260,261,264] **(Evidence Level 2)**

- Skin excoriation around the anus was reported, because of frequent bowel movements, soiling and excessive cleaning.[261] **(Evidence Level 2)**

- Women were attentive to their body image and dressed carefully to conceal pads and wore dark clothing when outside the home to hide stains if an accident should happen. [259,261,265] **(Evidence Level 2)**

- Men and women wore only small disposable pads that were not obvious through their clothing. Large diaper like, pads were avoided because of their visibility beneath clothing. [259,261,264] **(Evidence Level 2)**

- The essential theme in the phenomenological study of men managing faecal incontinence was 'secret resignation' where men came to accept that the consequences of faecal incontinence were normal for them.[264] **(Evidence Level 1)**

- The essential theme in the phenomenological study of women managing faecal incontinence was 'controlling the body out of control' as women tried to control all aspects of their life in relationship to the faecal incontinence and avoiding accidents.[264] **(Evidence Level 2)**

- Major goals of people experiencing faecal incontinence were to have fewer dietary restrictions, eliminate faecal leakage especially during exercise, less reliance on public toilet accessibility, more confidence in controlling faecal incontinence symptoms and a normal daily routine.[263] **(Evidence Level 2)**

- A sense of mastery and new self-confidence was perceived by some after years of successfully dealing with the symptoms of faecal incontinence.[270] **(Evidence Level 2)**

a) Recommendations for practice

- Acknowledge and provide empathy for the common feelings of shame and embarrassment **(Recommendation Grade B)**

- Raise awareness with clients and general public that faecal incontinence can often improve with conservative treatment and is not something that must be "put up with" in private **(Recommendation Grade A)**

- Recommend that conservative symptom management for faecal incontinence includes education about causes of faecal incontinence, diet modifications including fibre supplements, behavioural strategies such as pelvic floor muscles exercises and biofeedback, anti-motility medications, and use of absorbent products such as pads and briefs. **(Recommendation Grade A)**

- Recommend that health care professionals share positive coping strategies identified by participants, with other people managing the symptoms of faecal incontinence, that include privacy issues in the bathroom, counselling, restricting activity, carrying a change of clothes, humour, knowing the location of toilets when out, care of diet, choosing clothes carefully, careful cleansing and use of pads. **(Recommendation Grade B)**

- Recommend that clinicians consider patient's goals when developing a plan for faecal incontinence. **(Recommendation Grade A)**

- Requesting that people complete a daily stool diary is recommended when accurate information of faecal incontinence severity is important. **(Recommendation Grade A)**

- Appropriate referral to psychologists should be made to manage issues of self-efficacy, self-esteem and depression. **(Recommendation Grade B)**

b) Recommendations for research

- Determine how goal setting and tailoring interventions for faecal incontinence is effective in promoting adherence to a management plan.

- Evaluate whether training to pay attention to body sensations might reduce incontinence accidents.

- Studies of the effectiveness of interventions to promote a positive body image and increase self-esteem despite faecal incontinence are needed,

- Future studies should focus on the phenomenon of secret resignation as a method of coping by men, and effective techniques for treating these attitudes to assist them with improved communication with healthcare providers and care seeking.

- Studies are needed on approaches to educate and support men and women in adopting practices for managing faecal incontinence, the associated odour and urgency symptoms as well as to evaluate the successfulness of their practices.[264]

8. LIVING WITH FAECAL INCONTINENCE AND SEXUALITY – SUMMARY OF EVIDENCE

- Although asked about sexuality and intimacy women were reticent to discuss their sexuality or the effect of their symptoms on their sexual functioning.[259,261] **(Evidence Level 2)**

- Some women felt there were no changes in their sexual drive.[266] **(Evidence Level 2)**

- Women arranged timing of sex to meet their needs and the needs of their husbands in relation to the symptoms of faecal incontinence. [266] **(Evidence Level 2)**

- Women reported a range of psychosocial issues including lack of sexual arousal or a desire for abstinence.[259,260,265] **(Evidence Level 2)**

- Choice of clothing was an outward expression of sexuality and faecal incontinence and UI restricted clothing to wearing patterned materials in order to avoid people detecting an accident. [265] **(Evidence Level 2)**

- Men and women reported continually washing themselves to avoid smelling.[272] **(Evidence Level 2)**

- There was a lack of discussion of sexual concerns by health care providers after surgeries that affected sexual functioning.[265,268] **(Evidence Level 2)**

a) Recommendations for practice

- Recommend that clinicians ask directly about the impact of faecal incontinence on clients' sexuality. **(Recommendation Grade B)**

- Recommend that clinicians establish a comfortable, stigma-free climate in order to elucidate

the impact on sexuality and teach practical strategies. **(Recommendation Grade A)**

b) Recommendations for research

- Interventions that minimize stool leakage during intercourse, such as pelvic floor muscle therapy
- Develop and test intervention s to improve sexuality altered by faecal incontinence

9. LIVING WITH FAECAL INCONTINENCE AND DIET ISSUES – SUMMARY OF EVIDENCE

- Men and women discussed fasting or not eating for a number of hours or days as a strategy to deal with faecal incontinence symptoms outside the home.[145,259,261,264,266] **(Evidence Level 2)**
- Altering the timing of meals to avoid an accident was a common management strategy for faecal incontinence.[145,258,261,264] **(Evidence Level 2)**
- Restricting foods noted to lead to faecal incontinence, included sweets, alcohol, onions.[145] **(Evidence Level 2)** chocolate, rich and spicy foods, caffeine, fruits, greasy, fat, fried foods, and dairy products [145] **(Evidence Level 2)**
- Limiting portion or meal size was a strategy to limit faecal incontinence.[145,261] **(Evidence Level 2)**
- Avoiding gas producing foods such as pea soup, onions, cabbage, cauliflower and dairy products, was used as a treatment for flatus. [145,254,261,264] **(Evidence Level 2)**
- Increasing fluids was another practice used as a management technique for constipation. [145,261] **(Evidence Level 2)**
- Some women reported using protracted voluntary constipation as a management technique for leakage for up to 1 month.[260] **(Evidence Level 2)**
- Increasing dietary fibre and taking fibre supplements along with digestive enzymes and yogurt were noted as treatments for faecal incontinence.[145,261,264] **(Evidence Level 2)**
- Women reported eating foods they enjoyed at home and then dealt with the consequences of faecal incontinence symptoms.[145,261,269] **(Evidence Level 2)**
- Women lacked therapeutic guidance regarding diet modifications and adapted recommendations from other gastrointestinal disorders such as IBS and lactose intolerance or approached diet modification by trial and error.[145,261] **(Evidence Level 2)**

a) Recommendations for practice

- Diet is an important self-care strategy for faecal incontinence. Recommend that clinicians include teaching of successful strategies including timing of food intake, restricting food amounts to minimize leakage, avoiding aggravating foods, increasing water intake, and increasing the consumption of yogurt, high fibre foods or a fibre supplement. **Recommend Grade B**
- Recommend clinicians ask about dietary restrictions, as not all strategies employed by clients with faecal incontinence are helpful or evidence-based. **(Recommendation Grade B)**

b) Recommendations for research

- Determine the effectiveness of diet restrictions and supplementation and modifications in food preparation in reducing faecal incontinence
- Assess the effect of timing of food intake in a bowel management program

X. ALGORITHM

A revised algorithm for the initial management of faecal incontinence has been developed based on a review of new evidence in the literature within the context of previous evidence and consensus of an international group of experts on faecal incontinence. (See summary of the recommendations and algorithms at the end of this book.)

REFERENCES

1. Norton C, Whitehead WE, Blizz DZ, Metsola P, Tries J. Conservative and pharmacological management of faecal incontinence in adults. *Int Incontinence Soc*. 2005:1521-1563.

2. Bols E, Hendriks E, de Bie R, Baeten C, Berghmans B. Predictors of a favorable outcome of physiotherapy in faecal incontinence: Secondary analysis of a randomized trial. *Neurourol Urodyn*. 2012.

3. Norton C, Chelvanayagam S. A nursing assessment tool for adults with faecal incontinence. *J Wound Ostomy Continence Nurs*. 2000;27(5):279-91.

4. Engel AF, Kamm MA, Bartram CI, Nicholls RJ. Relationship of symptoms in faecal incontinence to specific sphincter abnormalities. *Int J Colorectal Disease*. 1995;10(3):152-155.

5. Wall LL. The muscles of the pelvic floor. *Clin Obstet Gynecol*. 1993;36(4):910-925.

6. Hill J, Corson RJ, Brandon H, Redford J, Faragher EB, Kiff ES. History and examination in the assessment of patients with idiopathic faecal incontinence. *Dis Colon Rectum*. 1994;37(5):473-477.

7. Bliss DZ, McLaughlin J, Jung HJ, Lowry A, Savik K, Jensen L. Comparison of the nutritional composition of diets of persons with faecal incontinence and that of age- and gender-matched controls. *J Wound Ostomy Continence Nurs*. 2000;27(2):90-97.

8. Jorge JM, Wexner SD. Etiology and management of faecal incontinence. *Dis Colon Rectum*. 1993;36(1):77-97.

9. Holzheimer RG. Hemorrhoidectomy: Indications and risks. *Eur J Med Res*. 2004;9(1):18-36.

10. Parmentier H, Damon H, Henry L, Barth X, Mellier G, Mion F. Frequency of anal incontinence and results of pelvic viscerography in 291 women with pelvic organ prolapse. *Gastroenterol Clin Biol*. 2004;28(3):226-30.

11. Sultan AH, Kamm MA, Talbot IC, Nicholls RJ, Bartram CI. Anal endosonography for identifying external sphincter defects confirmed histologically. *Br J Surg*. 1994;81(3):463-5.

12. Kamm MA. Faecal incontinence. *Bmj*. 2003; 327(7427): 1299-300.

13. Chatoor DR, Taylor SJ, Cohen CRG, Emmanuel AV. Faecal incontinence. *Br J Surg*. 2007;94(2):134-44.

14. Kushwaha RS, Hayne D, Vaizey CJ, Wrightham E, Payne H, Boulos PB. Physiologic changes of the anorectum after pelvic radiotherapy for the treatment of prostate and bladder cancer. *Dis Colon Rectum*. 2003;46(9):1182-8.

15. Jackson SL, Weber AM, Hull TL, Mitchinson AR, Walters MD. Faecal incontinence in women with urinary incontinence and pelvic organ prolapse. *Obstet Gynecol*. 1997;89(3):423-7.

16. Maloney C, Cafiero M. Implementing an incontinence program in long-term care settings. A multidisciplinary approach. *J Gerontol Nurs*. 1999;25(6):47-52.

17. Gray M, Beeckman D, Bliss DZ, et al. Incontinence-associated dermatitis: A comprehensive review and update. *J Wound Ostomy Continence Nurs*. 2012;39(1):61-74.

18. Cooper ZR, Rose S. Faecal incontinence: A clinical approach. *Mt Sinai J Med*. 2000;67(2):96-105.

19. Kaushal JN, Goldner F. Validation of the digital rectal examination as an estimate of anal sphincter squeeze pressure. *Am J Gastroenterol*. 1991;86(7):886-7.

20. Hallan RI, Marzouk DE, Waldron DJ, Womack NR, Williams NS. Comparison of digital and manometric assessment of anal sphincter function. *Br J Surg*. 1989;76(9):973-5.

21. Henry MM. Pathogenesis and management of faecal incontinence in the adult. *Gastroenterol Clin North Am*. 1987;16(1):35-45.

22. Vaizey CJ, van den Bogaerde JB, Emmanuel AV, Talbot IC, Nicholls RJ, Kamm MA. Solitary rectal ulcer syndrome. *Br J Surg*. 1998;85(12):1617-23.

23. Soligo M, Salvatore S, Emmanuel AV, et al. Patterns of constipation in urogynecology: Clinical importance and pathophysiologic insights. *Am J Obstet Gynecol*. 2006;195(1):50-5.

24. Hiltunen KM, Matikainen M. Anal manometric findings in symptomatic hemorrhoids. *Dis Colon Rectum*. 1985;28(11):807-9.

25. Bharucha AE. Faecal incontinence. *Gastroenterology*. 2003;124(6):1672-85.

26. Chaliha C, Sultan AH, Emmanuel AV. Normal ranges for anorectal manometry and sensation in women of reproductive age. *Colorectal Dis*. 2007;9(9):839-44.

27. Chiarioni G, Bassotti G, Stanganini S, Vantini I, Whitehead WE. Sensory retraining is key to biofeedback therapy for formed stool faecal incontinence. *Am J Gastroenterol*. 2002;97(1):109-117.

28. Rao SSC, Azpiroz F, Diamant N, Enck P, Tougas G, Wald A. Minimum standards of anorectal manometry. *Neurogastroenterol Motil*. 2002;14(5):553-9.

29. Lestar B, Penninckx F, Kerremans R. The composition of anal basal pressure. an in vivo and in vitro study in man. *Int J Colorectal Dis*. 1989;4(2):118-22.

30. Williams N, Barlow J, Hobson A, Scott N, Irving M. Manometric asymmetry in the anal canal in controls and patients with faecal incontinence. *Dis Colon Rectum*.1995;38(12):1275-80.

31. Lowry AC, Simmang CL, Boulos P, et al. Consensus statement of definitions for anorectal physiology and rectal cancer. *ANZ J Surg*. 2001;71(10):603-5.

32. McHugh SM, Diamant NE. Anal canal pressure profile: A reappraisal as determined by rapid pullthrough technique. *Gut*. 1987;28(10):1234-41.

33. Telford KJ, Ali ASM, Lymer K, Hosker GL, Kiff ES, Hill J. Fatigability of the external anal sphincter in anal incontinence. *Dis Colon Rectum*. 2004;47(5):746-52.

34. Sun WM, Read NW, Miner PB. Relation between rectal sensation and anal function in normal subjects and patients with faecal incontinence. *Gut*. 1990;31(9):1056-61.

35. Chan CLH, Ponsford S, Scott SM, Swash M, Lunniss PJ. Contribution of the pudendal nerve to sensation of the distal rectum. *Br J Surg*. 2005;92(7):859-65.

36. Gladman MA, Scott SM, Chan CLH, Williams NS, Lunniss PJ. Rectal hyposensitivity: Prevalence and clinical impact in patients with intractable constipation and faecal incontinence. *Dis Colon Rectum*. 2003;46(2):238-46.

37. Groenendijk AG, Birnie E, Boeckxstaens GE, Roovers JW, Bonsel GJ. Anorectal function testing and anal endosonography in the diagnostic work-up of patients with primary pelvic organ prolapse. *Gynecologic Obstetric Investigation*. 2009;67(3):187-94.

38. Haylen BT, de Ridder D, Freeman RM, et al. An international urogynecological association (IUGA)/International continence society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol J*. 2010;21(1):5-26.

39. Santoro GA, Fortling B. The advantages of volume rendering in three-dimensional endosonography of the anorectum. *Dis Colon Rectum*. 2007;50(3):359-68.

40. Santoro GA, Wieczorek AP, Dietz HP, et al. State of the art: An integrated approach to pelvic floor ultrasonography. *Ultrasound in Obstet Gynecol*. 2011;37(4):381-96.

41. Dietz HP, Lanzarone V. Levator trauma after vaginal delivery. *ObstetGynecology*. 2005;106(4):707-12.

42. Starck M, Bohe M, Valentin L. Results of endosonograph-

ic imaging of the anal sphincter 2-7 days after primary repair of third- or fourth-degree obstetric sphincter tears. *Ultrasound in Gynecol*. 2003;22(6):609-15.

43. Norderval S, Dehli T, Vonen B. Three-dimensional endoanal ultrasonography: Intraobserver and interobserver agreement using scoring systems for classification of anal sphincter defects. *Ultrasound in Obstet Gynecol*. 2009;33(3):337-43.

44. Voyvodic F, Rieger NA, Skinner S, et al. Endosonographic imaging of anal sphincter injury: Does the size of the tear correlate with the degree of dysfunction? *Dis Colon Rectum*. 2003;46(6):735-41.

45. Dobben AC, Terra MP, Deutekom M, Bossuyt PMM, Felt-Bersma RJF, Stoker J. Diagnostic work-up for faecal incontinence in daily clinical practice in the Netherlands. *Netherlands J Med*. 2005;63(7):265-9.

46. Sultan AH, Kamm MA, Hudson CN, Thomas JM, Bartram CI. Anal-sphincter disruption during vaginal delivery. *New Engl J Med*. 1993;329(26):1905-11.

47. Oberwalder M, Dinnewitzer A, Baig MK, et al. The association between late-onset faecal incontinence and obstetric anal sphincter defects. *Arch Surg*. 2004;139(4):429-32.

48. Dobben AC, Terra MP, Deutekom M, et al. The role of endoluminal imaging in clinical outcome of overlapping anterior anal sphincter repair in patients with faecal incontinence. *Am J Roentgenol*. 2007. 189(2):W70-7.

49. de la Portilla F, Vega J, Rada R, et al. Evaluation by three-dimensional anal endosonography of injectable silicone biomaterial (PTQ) implants to treat faecal incontinence: Long-term localization and relation with the deterioration of the continence. *Techniques in Coloproctology*. 2009;13(3):195-9.

50. DeLancey JOL, Kearney R, Chou Q, Speights S, Binno S. The appearance of levator ani muscle abnormalities in magnetic resonance images after vaginal delivery. *Obstet Gynecol*. 2003;101(1):46-53.

51. Lien K, Mooney B, DeLancey JOL, Ashton-Miller JA. Levator ani muscle stretch induced by simulated vaginal birth. *Obstet Gynecol*. 2004;103(1):31-40.

52. Santoro GA, Wieczorek AP, Stankiewicz A, Wozniak MM, Bogusiewicz M, Rechberger T. High-resolution three-dimensional endovaginal ultrasonography in the assessment of pelvic floor anatomy: A preliminary study. *Int Urogynecol J*. 2009;20(10):1213-22.

53. Cuesta MA, Meijer S, Derksen EJ, Boutkan H, Meuwissen SG. Anal sphincter imaging in faecal incontinence using endosonography. *Dis Colon Rectum*. 1992;35:59–63.

54. deSouza NM, Hall AS, Puni R, Gilderdale DJ, Young IR, Kmiot WA. High resolution magnetic resonance imaging of the anal sphincter using a dedicated endoanal coil: Comparison of magnetic resonance imaging with surgical findings. *Dis Colon Rectum*. 1996;39:926–934.

55. deSouza NM, Puni R, Gilderdale DJ, Bydder GM. Magnetic resonance imaging of the anal sphincter using an internal coil. *Magn Reson Q*. 1995;11:45–56.

56. deSouza NM, Puni R, Zbar A, Gilderale DJ, Coutts GA, Krausz T. MR imaging of the anal sphincter in multiparous women using an endoanal coil: Correlation with in vitro anatomy and appearances in faecal incontinence. *Am J Roentgenol (AJR)*. 1996;167:1465–1471.

57. Deen KI, Kumar D, Williams JG, Olliff J, Keighley MR. Anal sphincter defects: Correlation between endoanal ultrasound and surgery. *Ann Surg*. 1993;218:201–205.

58. Briel JW, Zimmerman DD, Stoker J, et al. Relationship between sphincter morphology on endoanal MRI and histopathological aspects of the external anal sphincter. *Int J Colorectal Dis*. 2000;15(2):87-90.

59. Hussain SM, Stoker J, Zwamborn AW, et al. Endoanal MRI of the anal sphincter complex: Correlation with cross-sectional anatomy and histology. *J Anat*. 1996;189:677–682.

60. Malouf AJ, Norton CS, Engel AF, Nicholls RJ, Kamm MA. Long-term results of overlapping anterior anal-sphincter repair for obstetric trauma. *Lancet*. 2000;355:260–265.

61. Meyenberger C, Bertschinger P, Zala GF, Buchmann P. Anal sphincter defects in faecal incontinence: Correlation between endosonography and surgery. *Endoscopy*. 1996;28:217–224.

62. Nielsen MB, Hauge C, J.F. P, Christiansen J. Endosonographic evaluation of patients with anal incontinence: Findings and influence on surgical management. *Am J Roentgenol (AJR)*. 1993;160:771–775.

63. Rociu E, Stoker J, Zwamborn AW, Lameris JS. Endoanal MR imaging of the anal sphincter in faecal incontinence. *RadioGraphics*. 1999;19 [suppl]:S171–S177.

64. Rociu E, Stoker. J, Eijkemans MJ, Schouten WR, Lameris JS. Faecal incontinence: Endoanal US versus endoanal MR imaging. *Radiol*. 1999;212:453–458.

65. Van Beers BE, Kartheuser A, Delos MA, et al. MRI of the anal canal; correlation with histologic examination. *Magn Reson Imaging*. 1996;14:151–156.

66. Williams AB, Malouf AJ, Bartram CI, Halligan S, Kamm MA, Kmiot WA. Assessment of external anal sphincter morphology in idiopathic faecal incontinence with endocoil magnetic resonance imaging. *Dig Dis Sci*. 2001;46:1466–1471.

67. Beets-Tan RG, Beets GL, van der Hoop AG, et al. High-resolution magnetic resonance imaging of the anorectal region without an endocoil. *Abdom Imaging*. 1999;24(6):576-81.

68. Beets-Tan RG, Morren GL, Beets GL, et al. Measurement of anal sphincter muscles: Endoanal US, endoanal MR imaging, or phased-array MR imaging? A study with healthy volunteers. *Radiol*. 2001;220(1):81-9.

69. Fletcher JG, Busse RF, Riederer SJ, et al. Magnetic resonance imaging of anatomic and dynamic defects of the pelvic floor in defecatory disorders. *Am J Gastroenterol*. 2003;98(2):399-411.

70. Morren GL, Beets-Tan RG, van Engelshoven JM. Anatomy of the anal canal and perianal structures as defined by phased-array magnetic resonance imaging. *Br J Surg*. 2001;88(11):1506-12.

71. Terra MP, Beets-Tan RGH, van Der Hulst VPM, et al. Anal sphincter defects in patients with faecal incontinence: Endoanal versus external phased-array MR imaging. *Radiol*. 2005;236(3):886-95.

72. Kiff ES, Swash M. Slowed conduction in the pudendal nerves in idiopathic (neurogenic) faecal incontinence. *Br J Surg*. 1984;71(8):614-6.

73. Kiff ES, Swash M. Normal proximal and delayed distal conduction in the pudendal nerves of patients with idiopathic (neurogenic) faecal incontinence. *J Neurol, Neurosurg Psychiatry*. 1984;47(8):820-3.

74. Jacobs PP, Scheuer M, Kuijpers JH, Vingerhoets MH. Obstetric faecal incontinence. role of pelvic floor denervation and results of delayed sphincter repair. *Dis Colon Rectum*. 1990;33(6):494-7.

75. Chen AS, Luchtefeld MA, Senagore AJ, Mackeigan JM, Hoyt C. Pudendal nerve latency. does it predict outcome of anal sphincter repair? *Dis Colon Rectum*. 1998;41(8):1005-9.

76. Gilliland R, Altomare DF, H. M,Jr, Oliveira L, Gilliland JE, Wexner SD. Pudendal neuropathy is predictive of failure following anterior overlapping sphincteroplasty. *Dis Colon Rectum*. 1998;41(12):1516-22.

77. Sangwan YP, Coller JA, Barrett RC, et al. Unilateral pudendal neuropathy. impact on outcome of anal sphincter repair. *Dis Colon Rectum*. 1996;39(6):686-9.

78. Malouf AJ, Williams AB, Halligan S, Bartram CI, Dhillon S, Kamm MA. Prospective assessment of accuracy of endoanal MR imaging and endosonography in patients with faecal incontinence. *Am J Roentgenol*. 2000;175(3):741-5.

79. West RL, Dwarkasing S, Briel JW, et al. Can three-dimensional endoanal ultrasonography detect external anal

sphincter atrophy? A comparison with endoanal magnetic resonance imaging. *Int J Colorectal Dis*. 2005;20(4):328-33.

80. Rociu E, Stoker J, Eijkemans MJ, Lameris JS. Normal anal sphincter anatomy and age- and sex-related variations at high-spatial-resolution endoanal MR imaging. *Radiol*. 2000;217(2):395-401.

81. Briel JW, Stoker J, Rociu E, Lameris JS, Hop WC, Schouten WR. External anal sphincter atrophy on endoanal magnetic resonance imaging adversely affects continence after sphincteroplasty. *Br J Surg*. 1999;86(10):1322-7.

82. McNevin MS. Overview of pelvic floor disorders. *Surg Clin North America*. 2010;90(1):195-205.

83. Terra MP, Stoker J. The current role of imaging techniques in faecal incontinence. *Eur Radiol*. 2006;16(8):1727-36.

84. Harvey CJ, Halligan S, Bartram CI, Hollings N, Sahdev A, Kingston K. Evacuation proctography: A prospective study of diagnostic and therapeutic effects. *Radiol*. 1999;211(1):223-7.

85. Rao SSC. Advances in diagnostic assessment of faecal incontinence and dyssynergic defecation. *Clin Gastroenterol Hepatol*. 2010;8(11):910-9.

86. Diamant NE, Kamm MA, Wald A, Whitehead WE. AGA technical review on anorectal testing techniques. *Gastroenterol*. 1999;116(3):735-60.

87. Whitehead WE, Bharucha AE. Diagnosis and treatment of pelvic floor disorders: What's new and what to do. *Gastroenterol*. 1235;138(4):1231-5.

88. Dobben AC, Terra MP, Slors JFM, et al. External anal sphincter defects in patients with faecal incontinence: Comparison of endoanal MR imaging and endoanal US. *Radiology*. 2007;242(2):463-71.

89. Collinson R, Cunningham C, D'Costa H, Lindsey I. Rectal intussusception and unexplained faecal incontinence: Findings of a proctographic study. *Colorectal Dis*. 2009;11(1):77-83.

90. Lazorthes F, Gamagami R, Cabarrot P, Muhammad S. Is rectal intussusception a cause of idiopathic incontinence? *Dis Colon Rectum*. 1998;41(5):602-5.

91. Rex DK, Lappas JC. Combined anorectal manometry and defecography in 50 consecutive adults with faecal incontinence. *Dis Colon Rectum*. 1992;35(11):1040-5.

92. Silvis R, Gooszen HG, van Essen A, de Kruif AT, Janssen LW. Abdominal rectovaginopexy: Modified technique to treat constipation. *Diseases of the Colon & Rectum*. 1999;42(1):82-8.

93. Abbas SM, Bissett IP, Neill ME, Macmillan AK, Milne D, Parry BR. Long-term results of the anterior delorme's operation in the management of symptomatic rectocele. *Dis Colon Rectum*. 2005;48(2):317-22.

94. Ayabaca SM, Zbar AP, Pescatori M. Anal continence after rectocele repair. *Dis Colon Rectum*. 2002;45(1):63-9.

95. Shorvon PJ, McHugh S, Diamant NE, Somers S, Stevenson GW. Defecography in normal volunteers: Results and implications. *Gut*. 1989;30(12):1737-49.

96. Turnbull GK, Bartram CI, Lennard-Jones JE. Radiologic studies of rectal evacuation in adults with idiopathic constipation. *Dis Colon Rectum*. 1988;31(3):190-7.

97. Bartram CI, Turnbull GK, Lennard-Jones JE. Evacuation proctography: An investigation of rectal expulsion in 20 subjects without defecatory disturbance. *Gastrointestinal Radiol*. 1988;13(1):72-80.

98. Wald A, Caruana BJ, Freimanis MG, Bauman DH, Hinds JP. Contributions of evacuation proctography and anorectal manometry to evaluation of adults with constipation and defecatory difficulty. *Dig Dis Sci*. 1990;35(4):481-7.

99. Piloni V, Fioravanti P, Spazzafumo L, Rossi B. Measurement of the anorectal angle by defecography for the diagnosis of faecal incontinence. *Int J Colorectal Dis*. 1999;14(2):131-5.

100. Karasick S. Defecography for the diagnosis of abnormalities in patients with faecal incontinence. Am J Roentgenol. 2006;186(6):E20.

101. Bharucha AE, Fletcher JG. Recent advances in assessing anorectal structure and functions. *Gastroenterol*. 2007;133(4):1069-74.

102. Hetzer FH, Andreisek G, Tsagari C, Sahrbacher U, Weishaupt D. MR defecography in patients with faecal incontinence: Imaging findings and their effect on surgical management. *Radiol*. 2006;240(2):449-57.

103. Woodfield CA, Krishnamoorthy S, Hampton BS, Brody JM. Imaging pelvic floor disorders: Trend toward comprehensive MRI. *Am J Roentgenol*. 2010;194(6):1640-9.

104. Bertschinger KM, Hetzer FH, Roos JE, Treiber K, Marincek B, Hilfiker PR. Dynamic MR imaging of the pelvic floor performed with patient sitting in an open-magnet unit versus with patient supine in a closed-magnet unit. *Radiol.* 2002;223(2):501-8.

105. Rosato GO, Lumi CM, Miguel AM. Anal sphincter electromyography and pudendal nerve terminal motor latency assessment. *Seminars Colon Rectal Surg*. 1992;3(2):68-74.

106. Rosato GOP, Lumi CM. Neurophysiology in pelvic floor disorders. In: Wexner SD, Zbar AP, Pescatori M, eds. *Complex anorectal disease: Investigation and management.* Springer Verlag; 2005:153-69.

107. Amend B, Matzel KE, Abrams P, de Groat WC, Sievert K. How does neuromodulation work. *Neurourol Urodynam*. 2011;30(5):762-5.

108. Dudding TC, Pares D, Vaizey CJ, Kamm MA. Predictive factors for successful sacral nerve stimulation in the treatment of faecal incontinence: A 10-year cohort analysis. *Colorectal Dis*. 2008;10(3):249-56.

109. Podnar S, Vodusek DB. Protocol for clinical neurophysiologic examination of the pelvic floor. *Neurourol Urodynam*. 2001;20(6):669-82.

110. Podnar S, Mrkaic M, Vodusek DB. Standardization of anal sphincter electromyography: Quantification of continuous activity during relaxation. *Neurourol Urodynam*. 2002;21(6):540-5.

111. Ryhammer AM, Laurberg S, Hermann AP. Long-term effect of vaginal deliveries on anorectal function in normal perimenopausal women. *Dis Colon Rectum*. 1996;39(8):852-9.

112. Swash M, Snooks SJ. Electromyography in pelvic floor disorders. In: Henry MM, Swash M, eds. *Coloproctology and the pelvic floor: Pathophysiology and management.* London: Butterworths; 1992:252-6.

113. Laurberg S, Swash M. Effects of aging on the anorectal sphincters and their innervation. *Dis Colon Rectum*. 1989;32(9):737-42.

114. Barnett JL, Hasler WL, Camilleri M. American gastroenterological association medical position statement on anorectal testing techniques. american gastroenterological association. *Gastroenterol*. 1999;116(3):732-60.

115. Leroi AM, Dorival MP, Lecouturier MF, et al. Pudendal neuropathy and severity of incontinence but not presence of an anal sphincter defect may determine the response to biofeedback therapy in faecal incontinence. *Dis Colon Rectum*. 1999;42(6):762-9.

116. Rogers J. Rectal and anal sensation. In: MM SMaH, ed. *Coloproctology and the pelvic floor.* Oxford: Butterworth Heinemann; 1992:54-60.

117. Roe AM, Bartolo DC, Mortensen NJ. New method for assessment of anal sensation in various anorectal disorders. *Br J Surg*. 1986;73(4):310-2.

118. Sigel H. Cutaneous sensory threshold stimulation with high frequency square-wave current. I. the relationship of electrode dimensions to the sensory threshold. *J Investigative Dermatol*. 1952;18(6):441-5.

119. Vierck CJ, Greenspan JD, Ritz LA, Yeomans DC. The spinal pathways contributing to the ascending conduction and descending modulations of pain sensations and reactions. In: Yaksh TL, ed. *Spinal afferent processing.* New York: Plenum Press; 1986:275-329.

120. Norton C. Nurses, bowel continence, stigma, and taboos. *J Wound Ostomy Continence Nurs*. 2004;31(2):85-94.

121. Norton C, Chelvanayagam S, eds. *Bowel continence nursing.* Beaconsfield, Bucks, UK: Beaconsfield Publishers Ltd; 2004.

122. Whitehead WE, Wald A, Norton NJ. Treatment options for faecal incontinence. *Dis Colon Rectum*. 2001;44(1):131-42.

123. Shamliyan T, Wyman J, Bliss DZ, Kane RL, Wilt TJ. Prevention of urinary and faecal incontinence in adults. . 2007;Contract No. 290-02-0009 Prepared for Agency for Healthcare Research and Quality.

124. Markland AD, Richter HE, Burgio KL, Bragg C, Hernandez AL, Subak LL. Faecal incontinence in obese women with urinary incontinence: Prevalence and role of dietary fiber intake. *Am J Obstet Gynecol*. 2009;200(5):566.e1-566.e6.

125. Burgio KL, Richter HE, Clements RH, Redden DT, Goode PS. Changes in urinary and faecal incontinence symptoms with weight loss surgery in morbidly obese women. *Obstet Gynecol*. 2007;110(5):1034-1040. doi: 10.1097/01.AOG.0000285483.22898.9c.

126. Roberson EN, Gould JC, Wald A. Urinary and faecal incontinence after bariatric surgery. *Dig Dis Sci*. 2010;55(9):2606-2613.

127. Scott AM, Kellow JE, Eckersley GM, Nolan JM, Jones MP. Cigarette smoking and nicotine delay postprandial mouth-cecum transit time. *Dig Dis Sci*. 1992;37(10):1544-1547.

128. Rausch T, Beglinger C, Alam N, Gyr K, Meier R. Effect of transdermal application of nicotine on colonic transit in healthy nonsmoking volunteers. *Neurogastroenterol Motil*. 1998;10(3):263-270.

129. Chaliha C, Kalia V, Stanton SL, Monga A, Sultan AH. Antenatal prediction of postpartum urinary and faecal incontinence. *Obstet Gynecol*. 1999;94(5 Pt 1):689-694.

130. Abramov Y, Sand PK, Botros SM, et al. Risk factors for female anal incontinence: New insight through the evanston-northwestern twin sisters study. *Obstet Gynecol*. 2005;106(4):726-732.

131. Ostbye T, Seim A, Krause KM, et al. A 10-year follow-up of urinary and faecal incontinence among the oldest old in the community: The canadian study of health and aging. *Can J Aging*. 2004;23(4):319-331.

132. Heck AM, Calis KA, McDuffie JR, Carobene SE, Yanovski JA. Additive gastrointestinal effects with concomitant use of olestra and orlistat. *Ann Pharmacother*. 2002;36(6):1003-1005.

133. Fox M, Thumshirn M, Menne D, Stutz B, Fried M, Schwizer W. The pathophysiology of faecal spotting in obese subjects during treatment with orlistat. *Aliment Pharmacol Ther*. 2004;19(3):311-321.

134. Minnesota statute 325E.60. RESTROOM ACCESS. . 2008;325E.60.

135. White H. Making toilets more accessible for individulas with a disability. *Bowel Continence Nursing*. 2004.

136. Chiarelli P, Markwell S. Let's get things moving: Overcoming constipation. *Neen Healthcare*. 1992.

137. Norton C, Chelvanayagam S, Wilson-Barnett J, Redfern S, Kamm MA. Randomized controlled trial of biofeedback for faecal incontinence. *Gastroenterol*. 2003;125(5):1320-1329.

138. Heymen A, Jones KR, Ringel Y, Scarlett Y, Drossman DA, Whitehead WE. Biofeedback for faecal incontinence and constipation: The role of medical management and education. *Gastroenterol*. 2001;120(Suppl 1):A397.

139. Harari D, Norton C, Lockwood L, Swift C. Treatment of constipation and faecal incontinence in stroke patients: Randomized controlled trial. *Stroke*. 2004;35(11):2549-2555.

140. Matson JL, Tureck K, Rieske R. The questions about behavioral function (QABF): Current status as a method of functional assessment. *Res Dev Disabil*. 2012;33(2):630-634.

141. Clemesha L, Davies E. Educating home carers on faecal incontinence in people with dementia. *Nursing Standard*. 2004;18(34):33.

142. Dowd T, Dowd ET. A cognitive therapy approach to promote continence. *J Wound Ostomy Continence Nurs*. 2006;33(1):63-68.

143. Bliss DZ, Johnson S, Savik K, Clabots CR, Gerding DN. Faecal incontinence in hospitalized patients who are acutely ill. *Nurs Res*. 2000;49(2):101-8.

144. Bliss DZ, Fischer LR, Savik K. Managing faecal incontinence: Self-care practices of older adults. *J Gerontol Nurs*. 2005;31(7):35-44.

145. Hansen JL, Bliss DZ, Peden-McAlpine C. Diet strategies used by women to manage faecal incontinence. *J Wound Ostomy Continence Nurs*. 2006;33(1):52-61.

146. Chrysos E, Athanasakis E, Tsiaoussis J, et al. Rectoanal motility in crohn's disease patients. *Dis Colon Rectum*. 2001;44(10):1509-13.

147. Drossman DA, Sandler RS, Broom CM, McKee DC. Urgency and faecal soiling in people with bowel dysfunction. *Dig Dis Sci*. 1986;31(11):1221-5.

148. Kangas E, Hiltunen KM, Matikainen M. Anorectal function in crohn's disease. *Ann Chir Gynaecol*. 1992;81(1):43-47.

149. Buchmann P, Mogg GA, Alexander-Williams J, Allan RN, Keighley MR. Relationship of proctitis and rectal capacity in crohn's disease. *Gut*. 1980;21(2):137-140.

150. Farthing MJ, Lennard-jones JE. Sensibility of the rectum to distension and the anorectal distension reflex in ulcerative colitis. *Gut*. 1978;19(1):64-69.

151. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. prevalence, sociodemography, and health impact. *Dig Dis Sci*. 1993;38(9):1569-80.

152. Croswell E, Bliss DZ, & Savik K. Diet and eating pattern modifications used by community living adults to manage their faecal incontinence. *J Wound Ostomy Continence Nurs*. 2010;37(6):677-682.

153. Chassagne P, Landrin I, Neveu C, et al. Faecal incontinence in the institutionalized elderly: Incidence, risk factors, and prognosis. *Am J Med*. 1999;106(2):185-90.

154. Read NW, Abouzekry L, Read MG, Howell P, Ottewell D, Donnelly TC. Anorectal function in elderly patients with faecal impaction. *Gastroenterol*. 1985;89(5):959-966.

155. Aurisicchio LN, Pitchumoni CS. Lactose intolerance. recognizing the link between diet and discomfort. *Postgrad Med*. 1994;95(1):113-6, 119-20.

156. Martini MC, Kukielka D, Savaiano DA. Lactose digestion from yogurt: Influence of a meal and additional lactose. *Am J Clin Nutr*. 1991;53(5):1253-1258.

157. Inman-Felton AE. Overview of lactose maldigestion (lactase nonpersistence). *J Am Diet Assoc*. 1999;99(4):481-9.

158. Vesa TH, Marteau P, Korpela R. Lactose intolerance. *J Am Coll Nutr*. 2000;19(2 Suppl):165S-175S.

159. Ledochowski M, Widner B, Bair H, Probst T, Fuchs D. Fructose- and sorbitol-reduced diet improves mood and gastrointestinal disturbances in fructose malabsorbers. *Scand J Gastroenterol*. 2000;35(10):1048-1052.

160. Brown SR, Cann PA, Read NW. Effect of coffee on distal colon function. *Gut*. 1990;31(4):450-3.

161. Dennish GW, Castell DO. Caffeine and the lower esophageal sphincter. *Am J Dig Dis*. 1972;17(11):993-996.

162. Debas HT, Cohen MM, Holubitsky IB, Harrison RC. Caffeine-stimulated acid and pepsin secretion: Dose-response studies. *Scand J Gastroenterol*. 1971;6(5):453-457.

163. Wald A, Back C, Bayless TM. Effect of caffeine on the human small intestine. *Gastroenterol*. 1976;71(5):738-742.

164. Acquaviva F, DeFrancesco A, Andriulli A, et al. Effect of regular and decaffeinated coffee on serum gastrin levels. *J Clin Gastroenterol*. 1986;8(2):150-153.

165. Izbeki F, Wittmann T, Csati S, Jeszenszky E, Lonovics J. Opposite effects of acute and chronic administration of alcohol on gastric emptying and small bowel transit in rat. *Alcohol Alcohol*. 2001;36(4):304-308.

166. Bujanda L. The effects of alcohol consumption upon the gastrointestinal tract. *Am J Gastroenterol*. 2000;95(12):3374-3382.

167. Bode C, Bode JC. Effect of alcohol consumption on the gut. *Baillieres Best Pract Res Clin Gastroenterol*. 2003;17(4):575-592.

168. Jairath V, Langmead L. Acute gastroenterology. *Clin Med*. 2007;7(3):262-266.

169. Bengmark S. Pre-, pro- and synbiotics. *Curr Opin Clin Nutr Metab Care*. 2001;4(6):571-579.

170. Eddins C, Gray M. Are probiotic or symbiotic preparations effective for the management of clostridium difficile-associated or radiation-induced diarrhea? *J Wound Ostomy Continence Nurs*.. 2008;35(1):571-579.

171. Cho S, DeVries JW, Prosky L. Dietary fiber analysis and applications. . 1997.

172. Eherer AJ, Santa Ana CA, Porter J, Fordtran JS. Effect of psyllium, calcium polycarbophil, and wheat bran on secretory diarrhea induced by phenolphthalein. *Gastroenterol*. 1993;104(4):1007-12.

173. Norton C, Whitehead WE, Bliss DZ, Harari D, Lang J. Conservative and pharmacological management of faecal incontinence in adults. In: Abrams P, Cardoza L, Khoury S, Wein A, eds. *Incontinence.* 4th ed. London: Health Publication Ltd.; 2009:1321-1386.

174. Ardon M, Main A. Management of constipation. *British medical journal*. 2004:114-131.

175. Livesey G. Tolerance of low-digestible carbohydrates: A general view. *Br J Nutr*. 2001;85 Suppl 1:S7-16.

176. Bliss DZ, Savik K, Jung HJ, Whitebird R, Lowry A. Symptoms associated with dietary fiber supplementation over time in individuals with faecal incontinence. *Nurs Res*. 2011;60(3 Suppl):S58-67. 177. Lauti M, Scott D, Thompson-Fawcett MW. Fibre supplementation in addition to loperamide for faecal incontinence in adults: A randomized trial. *Colorectal Dis*. 2008;10(6):553-562.

178. Bliss DZ, Jung HJ, Savik K, et al. Supplementation with dietary fiber improves faecal incontinence. *Nurs Res*. 2001;50(4):203-213.

179. Sze EH, Hobbs G. Efficacy of methylcellulose and loperamide in managing faecal incontinence. *Acta Obstet Gynecol Scand*. 2009;88(7):766-771.

180. van der Hagen SJ, Soeters PB, Baeten CG, van Gemert WG. Conservative treatment of patients with faecal soiling. *Tech Coloproctol*. 2011;15(3):291-295.

181. Chassagne P, Jego A, Gloc P, et al. Does treatment of constipation improve faecal incontinence in institutionalized elderly patients? *Age Ageing*. 2000;29(2):159-164.

182. Doughty D. A physiologic approach to bowel training. *J Wound Ostomy Continence Nurs*. 1996;23(1):46-56.

183. Narducci F, Bassotti G, Gaburri M, Morelli A. Twenty four hour manometric recording of colonic motor activity in healthy man. *Gut*. 1987;28(1):17-25.

184. Bassotti G, Crowell MD, Cheskin LJ, Chami TN, Schuster MM, Whitehead WE. Physiological correlates of colonic motility in patients with irritable bowel syndrome. *Z Gastroenterol*. 1998;36(9):811-817.

185. Bharucha AE, Zinsmeister AR, Locke GR, et al. Prevalence and burden of faecal incontinence: A population-based study in women. *Gastroenterol*. 2005;129(1):42-9.

186. Snooks SJ, Barnes PR, Swash M, Henry MM. Damage to the innervation of the pelvic floor musculature in chronic constipation. *Gastroenterol*. 1985;89(5):977-981.

187. Lubowski DZ, Swash M, Nicholls RJ, Henry MM. Increase in pudendal nerve terminal motor latency with defaecation straining. *Br J Surg*. 1988;75(11):1095-1097.

188. Spence-Jones C, Kamm MA, Henry MM, Hudson CN. Bowel dysfunction: A pathogenic factor in uterovaginal prolapse and urinary stress incontinence. *Br J Obstet Gynaecol*. 1994;101(2):147-152.

189. Crawshaw AP, Pigott L, Potter MA, Bartolo DC. A retrospective evaluation of rectal irrigation in the treatment of disorders of faecal continence. *Colorectal Dis*. 2004;6(3):185-190.

190. Crawshaw A, Marshall J. Rectal irrigation for enduring bowel dysfunction. the results of a nurse-led, two-centre cross-over trial. measuring the efficacy and acceptability of two methods of delivering rectal irrigation. *World Counc Enterostom Therapists J*. 2010;30(1):45-46.

191. Gardiner A, Marshall J, Duthie G. Rectal irrigation for relief of functional bowel disorders. *Nurs Stand*. 2004;19(9):39-42.

192. Shandling B, Gilmour RF. The enema continence catheter in spina bifida: Successful bowel management. *J Pediatr Surg*. 1987;22(3):271-273.

193. Christensen P, Bazzocchi G, Coggrave M, et al. A randomized, controlled trial of transanal irrigation versus conservative bowel management in spinal cord-injured patients. *Gastroenterology*. 2006;131(3):738-747.

194. Gosselink MP, Darby M, Zimmerman DD, et al. Long-term follow-up of retrograde colonic irrigation for defaecation disturbances. *Colorectal Dis*. 2005;7(1):65-69.

195. Koch SM, Melenhorst J, Uludag O, et al. Sacral nerve modulation and other treatments in patients with faecal incontinence after unsuccessful pelvic floor rehabilitation: A prospective study. *Colorectal Dis*. 2010;12(4):334-341.

196. Whitehouse PA, McWilliams D, Katte C, Bearn PE. Peristeen rectal irrigation for functional bowel disorders: Which patients benefit? *Gastrointestinal nursing*. 2010;8(2):40-46.

197. Briel JW, Schouten WR, Vlot EA, Smits S, van Kessel I. Clinical value of colonic irrigation in patients with continence disturbances. *Dis Colon Rectum*. 1997;40(7):802-805.

198. Koch SM, Melenhorst J, van Gemert WG, Baeten CG. Prospective study of colonic irrigation for the treatment of defaecation disorders. *Br J Surg*. 2008;95(10):1273-1279.

199. Norton C, Chelvanayagam S. Methodology of biofeedback for adults with faecal incontinence: A program of care. *J Wound Ostomy Continence Nurs*. 2001;28(3):156-68.

200. Doughty D. Urinary and faecal incontinence. Nursing management. 2000.

201. Brazzelli M, Griffiths PV, Cody JD, Tappin D. Behavioural and cognitive interventions with or without other treatments for the management of faecal incontinence in children. *Cochrane Database Syst Rev*. 2011;12:CD002240.

202. Cheetham M, Brazzelli M, Norton C, Glazener CM. Drug treatment for faecal incontinence in adults. *Cochrane Database Syst Rev*. 2003;(3)(3):CD002116. 2

203. Scarlett Y. Medical management of faecal incontinence. *Gastroenterol*. 2004;126(1 Suppl 1):S55-63.

204. Ehrenpreis ED, Chang D, Eichenwald E. Pharmacotherapy for faecal incontinence: A review. *Dis Colon Rectum*. 2007;50(5):641-649.

205. Palmer KR, Corbett CL, Holdsworth CD. Double-blind cross-over study comparing loperamide, codeine and diphenoxylate in the treatment of chronic diarrhea. *Gastroenterol*. 1980;79(6):1272-1275.

206. Read M, Read NW, Barber DC, Duthie HL. Effects of loperamide on anal sphincter function in patients complaining of chronic diarrhea with faecal incontinence and urgency. *Dig Dis Sci*. 1982;27(9):807-14.

207. Hallgren T, Fasth S, Delbro DS, Nordgren S, Oresland T, Hulten L. Loperamide improves anal sphincter function and continence after restorative proctocolectomy. *Dig Dis Sci*. 1994;39(12):2612-2618.

208. Sun WM, Read NW, Verlinden M. Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhoea and faecal incontinence. *Scand J Gastroenterol*. 1997;32(1):34-38.

209. Fox M, Stutz B, Menne D, Fried M, Schwizer W, Thumshirn M. The effects of loperamide on continence problems and anorectal function in obese subjects taking orlistat. *Dig Dis Sci*. 2005;50(9):1576-1583.

210. Kekomaki M, Vilkki P, Gordin A, Salo H. Loperamide as a symptomatic treatment in pediatric surgery: A double-blind cross-over study. *Z Kinderchir*. 1981;32(3):237-243.

211. Arnbjornsson E, Breland U, Kullendorff CM, Okmian L. Effect of loperamide on faecal control after rectoplasty for high imperforate anus. *Acta Chir Scand*. 1986;152:215-216.

212. Pena A, Guardino K, Tovilla JM, Levitt MA, Rodriguez G, Torres R. Bowel management for faecal incontinence in patients with anorectal malformations. *J Pediatr Surg*. 1998;33(1):133-137.

213. Santoro GA, Eitan BZ, Pryde A, Bartolo DC. Open study of low-dose amitriptyline in the treatment of patients with idiopathic faecal incontinence. *Dis Colon Rectum*. 2000;43(12):1676-81; discussion 1681-2.

214. Henriksson R, Franzen L, Littbrand B. Effects of sucralfate on acute and late bowel discomfort following radiotherapy of pelvic cancer. *J Clin Oncol*. 1992;10(6):969-975.

215. Kneebone A, Mameghan H, Bolin T, et al. Effect of oral sucralfate on late rectal injury associated with radiotherapy for prostate cancer: A double-blind, randomized trial. *Int J Radiat Oncol Biol Phys*. 2004;60(4):1088-1097.

216. Martenson JA, Bollinger JW, Sloan JA, et al. Sucralfate in the prevention of treatment-induced diarrhea in patients receiving pelvic radiation therapy: A north central cancer treatment group phase III double-blind placebo-controlled trial. *J Clin Oncol*. 2000;18(6):1239-1245.

217. Bharucha AE, Seide BM, Zinsmeister AR. The effects of clonidine on symptoms and anorectal sensorimotor function in women with faecal incontinence. *Aliment Pharmacol Ther*. 2010;32(5):681-688.

218. McIntyre PB, Pemberton JH, Wolff BG, Beart RW, Dozois RR. Comparing functional results one year and ten years after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Dis Colon Rectum*. 1994;37(4):303-307.

219. Badvie S, Andreyev HJ. Topical phenylephrine in the treatment of radiation-induced faecal incontinence. *Clin Oncol (R Coll Radiol)*. 2005;17(2):122-126.

220. Cheetham MJ, Kamm MA, Phillips RK. Topical phenylephrine increases anal canal resting pressure in patients with faecal incontinence. *Gut*. 2001;48(3):356-359.

221. Park JS, Kang SB, Kim DW, Namgung HW, Kim HL. The efficacy and adverse effects of topical phenylephrine for anal incontinence after low anterior resection in patients with rectal cancer. *Int J Colorectal Dis*. 2007;22(11):1319-1324.

222. Carapeti EA, Kamm MA, Nicholls RJ, Phillips RK. Randomized, controlled trial of topical phenylephrine for faecal incontinence in patients after ileoanal pouch construction. *Dis Colon Rectum*. 2000;43(8):1059-1063.

223. Carapeti EA, Kamm MA, Phillips RK. Randomized controlled trial of topical phenylephrine in the treatment of faecal incontinence. *Br J Surg*. 2000;87(1):38-42.

224. Nisar PJ, Gruss HJ, Bush D, Barras N, Acheson AG, Scholefield JH. Intra-anal and rectal application of L-erythro methoxamine gel increases anal resting pressure in healthy volunteers. *Br J Surg*. 2005;92(12):1539-1545.

225. Nisar PJ, Gruss HJ, Bush D, Acheson AG, Scholefield JH. Intra-anal application of L-erythro methoxamine gel increases anal resting pressure in patients with incontinence. *Br J Surg*. 2007;94(9):1155-1161.

226. Kusunoki M, Shoji Y, Ikeuchi H, Yamagata K, Yamamura T, Utsunomiya J. Usefulness of valproate sodium for treatment of incontinence after ileoanal anastomosis. *Surg*. 1990;107(3):311-315.

227. Shoji Y, Kusunoki M, Yanagi H, Sakanoue Y, Utsunomiya J. Effects of sodium valproate on various intestinal motor functions after ileal J pouch-anal anastomosis. *Surg*.1993;113(5):560-563.

228. Guillemot F, Bouche B, Gower-Rousseau C, et al. Biofeedback for the treatment of faecal incontinence. long-term clinical results. *Dis Colon Rectum*. 1995;38(4):393-397.

229. Demirci S, Gallas S, Bertot-Sassigneux P, Michot F, Denis P, Leroi AM. Anal incontinence: The role of medical management. *Gastroenterol Clin Biol*. 2006;30(8-9):954-960.

230. Remes-Troche JM, Rao SSC. Neurophysiological testing in anorectal disorders. *Expert rev*. 2008;2(3):323-35.

231. Kegel AH. Progressive resistance exercise in the functional restoration of the perineal muscles. *Am J Obstet Gynecol*. 1948;56(2):238-248.

232. Heymen S, Scarlett Y, Jones K, Ringel Y, Drossman D, Whitehead WE. Randomized controlled trial shows biofeedback to be superior to pelvic floor exercises for faecal incontinence. *Dis Colon Rectum*. 2009;52(10):1730-1737.

233. Solomon MJ, Pager CK, Rex J, Roberts R, Manning J. Randomized, controlled trial of biofeedback with anal manometry, transanal ultrasound, or pelvic floor retraining with digital guidance alone in the treatment of mild to moderate faecal incontinence. *Dis Colon Rectum*. 2003;46(6):703-710.

234. Norton C, Gibbs A, Kamm MA. Randomized, controlled trial of anal electrical stimulation for faecal incontinence. *Dis Colon Rectum*. 2006;49(2):190-196.

235. Hosker G, Cody JD, Norton CC. Electrical stimulation for faecal incontinence in adults. *Cochrane Database Syst Rev*. 2007(3).

236. Schwander T, Konig IR, Heimerl T, et al. Triple target treatment (3T) is more effective than biofeedback alone for anal incontinence: The 3T-AI study. *Dis Colon Rectum*. 2010;53:1007-1016.

237. Heymen S, Wexner SD, Vickers D, Nogueras JJ, Weiss EG, Pikarsky AJ. Prospective, randomized trial comparing four biofeedback techniques for patients with constipation. *Dis Colon Rectum*. 1999;42(11):1388-1393.

238. Madoff R, Laurberg S, Matzel K, et al. Surgery for faecal incontinence. in: Abrams P, Cardozo L, Khoury S, Wein A, eds. In: *Incontinence: 4th International consultation on incontinence.* Paris: Health Publications Ltd; 2009:1387-1417.

239. Bols E, Berghmans B, De Bie R, et al. Rectal baloon

training as add-on therapy to pelvic floor muscle training in adults with faecal incontinence: A randomized controlled trial. *Neurourol Urodynam*. 2011.

240. Bartlett LM, Sloots K, Nowak M, Ho YH. Biofeedback therapy for faecal incontinence: A rural and regional perspective. *Rural Remote Health*. 2011;11:1630.

241. Bø K, Hagen. Is pelvic floor muscle training effective when taught in a general fitness class in pregnancy? A randomised controlled trial. *Physiotherapy*. 2011;97(3):190-195.

242. Lacima G, Perma M, Amador A, Escaramis G, Pique J. Long-term results of biofeedback treatment for faecal incontinence: A comparative study with untreated controls. *Colorectal Dis*. 2010;12:742-749.

243. Rockwood TH, Church JM, Fleshman JW, et al. Patient and surgeon ranking of the severity of symptoms associated with faecal incontinence: The faecal incontinence severity index. *Dis Colon Rectum*. 1999;42(12):1525-32.

244. Clarke MC, Chase JW, Gibbs S, Hutson JM, Southwell BR. Improvement of quality of life in children with slow transit constipation after treatment with transcutaneous electrical stimulation. *J Pediatric Surg*. 2009;44:1268-1272.

245. Leong LC, Yik YI, Catto-Smith AG, Robertson VJ, Hutson JM, Southwell BR. Long-term effects of transabdominal electrical stimulation in treating children with slow-transit constipation. *J Pediatric Surg*.. 2011;46:2309-2312.

246. Siproudhis L, Pigot F, Godeberge P, Damon H, Soudan D, Bigard MA. Defecation disorders: A french population survey. *Dis Colon Rectum*. 2006;49(2):219-227.

247. Clarke MC, Chase JW, Bibbs S, et al. Decreased colonic transit time after transcutaneous interferential electrical stimulation in clidren with slow transit constipation. *J Pediatric Surg*.. 2009;44:408-412.

248. Beck CT. Critiquing qualitative research. *AORN J*. 2009;90(4):543-554.

249. Caelli, K., Ray, L., Mill, J. 'Clear as mud': Toward greater clarity in generic qualitative research. *Int J Qual Methods*. 2003;2(2):1-13.

250. Koro-Ljungberg M. Validity and validation in the making in the context of qualitative research. *Qual Health Res*. 2008;18(7):983-989.

251. Polit, D. F., & Beck, C. T. *Nursing research: Generating and assessing evidence for nursing practice* 8th ed. Lippincott Williams & Wilkins.; 2008.

252. Stige B, Malterud K, Midtgarden T. Toward an agenda for evaluation of qualitative research. *Qual Health Res*. 2009;19(10):1504-1516.

253. Joanna Briggs Institute. http://www.joannabriggs.edu.au/services/sumari.php. Updated 2001.

254. Cohen DJ, Crabtree BF. Evaluative criteria for qualitative research in health care: Controversies and recommendations. *Ann Fam Med*. 2008;6(4):331-339.

255. Hannes K, Lockwood C, Pearson A. A comparative analysis of three online appraisal instruments' ability to assess validity in qualitative research. *Qual Health Res*. 2010;20(12):1736-1743.

256. Meyrick J. What is good qualitative research? A first step towards a comprehensive approach to judging rigour/quality. *J Health Psychol*. 2006;11(5):799-808.

257. Sandelowski, M., & Barroso, J. Reading qualitative studies. *International Journal of Qualitative Methods*. 2002;1(1):93.

258. Collings S, Norton C. Women's experiences of faecal incontinence: A study. *Br J Community Nurs*. 2004;9(12):520-523.

259. Cotterill N, Norton C, Avery KN, Abrams P, Donovan JL. A patient-centered approach to developing a comprehensive symptom and quality of life assessment of anal incontinence. *Dis Colon Rectum*. 2008;51(1):82-87.

260. Johnsen V, Skattebu E, Aamot-Andersen A, Thyberg M. Problematic aspects of faecal incontinence according to the experience of adults with spina bifida. *J Rehabil Med*. 2009;41(7):506-511.

261. Peden-McAlpine C, Bliss DZ, Hill J. The experience of community-living women managing faecal incontinence. *West J Nurs Res*. 2008;30(7):817-835.

262. O'Dell KK, Jacelon C, Morse AN. 'I'd rather just go on as I am'--pelvic floor care preferences of frail, elderly women in residential care. *Urol Nurs*. 2008;28(1):36-47.

263. Manthey A, Bliss DZ, Savik K, Lowry A, Whitebird R. Goals of faecal incontinence management identified by community-living incontinent adults. *West J Nurs Res*. 2010;32(5):644-661.

264. Peden-McAlpine, C., Bliss D., Sherman S., Becker, B. The experience of community living men with faecal incontinence. *J Rehabilitation Nurs. 2012;* doi/10.1002/rnj.38/pdf.

265. Roe B, May C. Incontinence and sexuality: Findings from a qualitative perspective. *J Adv Nurs*. 1999;30(3):573-579.

266. Rasmussen JL, Ringsberg KC. Being involved in an everlasting fight--a life with postnatal faecal incontinence. A qualitative study. *Scand J Caring Sci*. 2010;24(1):108-115.

267. Norton C, Chelvanayagam S. Bowel problems and coping strategies in people with multiple sclerosis. *Br J Nurs*. 2010;19(4):220, 221-6.

268. Rozmovits L, Ziebland S. Expressions of loss of adulthood in the narratives of people with colorectal cancer. *Qual Health Res*. 2004;14(2):187-203.

269. Cockell SJ, Oates-Johnson T, Gilmour DT, Vallis TM, Turnbull GK. Postpartum flatal and faecal incontinence quality-of-life scale: A disease- and population-specific measure. *Qual Health Res*. 2003;13(8):1132-1144.

270. Wilson M. The impact of faecal incontinence on the quality of life. *Br J Nurs*. 2007;16(4):204-207.

271. Chelvanayagam S, Norton C. Quality of life with faecal continence problems. *Nurs Times*. 2000;96(31 Suppl):15-17.

272. Roe B, Flanagan L, Jack B, et al. Systematic review of the management of incontinence and promotion of continence in older people in care homes: Descriptive studies with urinary incontinence as primary focus. *J Adv Nurs*. 2011;67(2):228-250.

Committee 17

Surgery For Faecal Incontinence

Chair

R. D. Madoff (Usa)

Members

S. Laurberg (Denmark)

P. Lehur (France)

K. E. Matzel (Germany)

A.F. Mellgren (Usa)

T. Mimura (Japan)

P. R. O'connell (Ireland)

M. G. Varma (Usa)

CONTENTS

I. INTRODUCTION

II. SURGERY FOR ADULT FAECAL INCONTINENCE

1. SPHINCTER REPAIR
2. SPHINCTEROPLASTY
3. POST-ANAL REPAIR
4. NON-STIMULATED MUSCLE TRANSPOSITION
5. STIMULATED MUSCLE TRANSPOSITION
6. ARTIFICIAL ANAL SPHINCTER
7. SACRAL NERVE STIMULATION
8. POSTERIOR TIBIAL NERVE STIMULATION
9. INJECTABLE BIOMATERIALS
10. COLOSTOMY
11. PUBORECTAL SLING

III. SURGERY FOR PAEDIATRIC FAECAL INCONTINENCE

1. ANORECTAL MALFORMATIONS
2. OTHER CAUSES OF FAECAL INCONTINENCE
3. OTHER OPERATIONS

IV. CONCLUSIONS

1. SPHINCTER REPAIR (GRADE B)
2. SPHINCTEROPLASTY (GRADE B)
3. POST-ANAL REPAIR (GRADE C)
4. NON-STIMULATED MUSCLE TRANSPOSITION (GRADE C)
5. STIMULATED MUSCLE TRANSPOSITION (GRADE C)
6. ARTIFICIAL ANAL SPHINCTER (GRADE B)
7. SACRAL NERVE STIMULATION (GRADE B)
8. POSTERIOR TIBIAL NERVE STIMULATION (GRADE D)
9. INJECTABLE BIOMATERIALS (GRADE C)
10. COLOSTOMY (GRADE C)
11. PUBORECTAL SLING (GRADE D)
12. SURGERY FOR PAEDIATRIC FAECAL INCONTINENCE (GRADE C)

V. RESEARCH PRIORITIES

1. BASIC SCIENCE AND PATHOPHYSIOLOGY
2. CELLULAR THERAPY
3. OUTCOME MEASURES
4. CLINICAL TRIALS
5. DECISION AND COST-BENEFIT ANALYSIS
6. TREATMENT DELIVERY

REFERENCES

Surgery For Faecal Incontinence

R. D. Madoff

S. Laurberg, P. Lehur, K. E. Matzel, A.F. Mellgren, T. Mimura, P. R. O'connell, M. G. Varma

I. INTRODUCTION

Therapy for faecal incontinence is readily divided into non-surgical and surgical therapy. Selection of specific therapy is based upon a number of considerations, including the severity of incontinence and structural integrity of the anal sphincter.

Conservative therapy is most applicable to relatively mild cases of incontinence. Biofeedback retraining can be attempted for incontinence of any cause or severity, as the therapy is painless and risk-free. These treatments are discussed in detail elsewhere in this monograph.

The most widely accepted surgical therapy for faecal incontinence is overlapping sphincteroplasty. Typical of other well-established therapies, the evidence base supporting this approach is paradoxically less robust than that supporting more recent treatment options. Sphincteroplasty is useful only in cases in which there is an anatomic sphincter defect, and it has been reported to provide satisfactory results in many case series. However, several recent studies have now shown that results of sphincteroplasty deteriorate with time [1,2].

A number of operations were developed in the early to mid 20th century to provide a treatment option for patients whose native sphincter was either intact but weak or not reparable. Muscle transposition procedures using either gluteus maximus or gracilis were devised to create a functional biological neosphincter, but the approach did not gain widespread popularity. The Parks postanal repair was devised in 1975 to treat patients with incontinence due to pelvic neuropathy [3].

Dissatisfaction with available operations for faecal incontinence led to development of a variety of novel procedures during the last 20 years. The stimulated (dynamic) graciloplasty and the artificial anal sphincter were devised as salvage procedures for patients who had failed or were not candidates for standard therapy. A more recent approach is the use of sacral nerve stimulation, which was adopted for this purpose from its previously better-defined role in detrusor overacitivity incontinence and idiopathic urinary retention. Moreover, there has also been a trend towards development of minimally invasive approaches to faecal incontinence, such as the use of injectable biomaterials.

Several important caveats apply to interpretation of the results of surgery for faecal incontinence reported in the literature. First, the vast majority of reports are uncontrolled case series. Randomised controlled studies are rare, and those reported include only small numbers of patients [4]. Second, numerous quantitative measures have been used to report outcomes, but only recently have any of these been validated, such as the Faecal Incontinence Quality of Life (FIQL) instrument. Third, criteria for "successful" outcomes have been variable and often arbitrary. Fourth, the quality of data reported is variable, though it has generally improved with the passage of time. Chart review has been supplanted by patient questionnaires and interviews by independent data auditors; daily continence diaries, the most stringent form of data collection, have become increasingly commonplace (though not routine). Despite the fact that studies using lax data collection are certain to report better results than those using methodology that is more stringent, of necessity, composite reviews of surgical results include studies using various methods of data collection. Finally, results are not always reported on an intention to treat basis, particularly in the implantable device literature.

Search Methods

Pubmed search was conducted to identify studies published on the use of surgery for faecal incontinence in children and adults. Keywords used were faecal incontinence and surgery. Full text copies of studies deemed to be potentially relevant were obtained. Priority was given to systematic reviews, randomised controlled trials, and controlled clinical trials; if those were unavailable or inadequate, comparative observational studies, case series, case reports and narrative reviews were also included. Reviewers were not blinded to the names of studies' authors, institutions or publications. In view of the nature of the guideline, priority was given to the

reports with large number of patients and long follow-ups assessing efficacy of surgical interventions. Particular emphasis was placed on those reporting techniques and functional outcome including quality of life after an operation.

Non-English language papers were noted but excluded from the review unless they contained an English-language abstract providing sufficient information.

II. SURGERY FOR ADULT FAECAL INCONTINENCE

1. SPHINCTER REPAIR

Anal sphincter repair is the term used to describe primary repair of the anal sphincter mechanism following direct trauma. The most common indication is following childbirth and repair in this situation is usually performed by the attending obstetrician. Colorectal surgeons are more commonly involved in primary repair of injury that is the result of blunt or penetrating trauma. Occasionally, the anal sphincter mechanism is damaged during anorectal surgery for other anal pathology particularly surgery for anal fistula.

In Western obstetric practice, the incidence of overt anal sphincter injury (grade 3 or 4 tear) is low, 3- 5% following primiparous delivery and 0.5-1% following second and subsequent deliveries [5]. When prospectively looked for with endoanal ultrasound, the actual incidence of anal sphincter injury is higher [6,7]. A meta-analysis of 717 vaginal deliveries found an incidence of new anal sphincter defects of 27% in primiparous and 9% in multiparous women using 2D endoanal ultrasound [8]. 3D ultrasonography suggests that the incidence is somewhat less, perhaps 11%, following primiparous delivery [9]. The risk factors for sphincter injury include instrumental vaginal delivery, prolonged second stage of labor, fetal macrosomia, and a persistent occipital position of the fetal head [7,10-12]. Midline episiotomy is associated with higher incidence of anal sphincter injury and the angle of mediolateral episiotomy may also influence perineal outcome [13]. A policy of restrictive use of episiotomy may reduce the incidence of anal sphincter injury [14].

Obstetric injury of the perineum is classified as a first degree tear if confined to vaginal epithelium and skin, second degree if the perineal muscles are torn, third degree if the anal sphincter muscles (external: EAS; internal: IAS) are torn, (3a: less than 50% EAS torn; 3b: more than 50% EAS torn; 3c: IAS torn) or fourth degree if both EAS and IAS and rectal or anal mucosa are torn [15]. Primary repair of an obstetrical tear is correctly termed anal sphincter repair and is usually performed by the obstetrician immediately after delivery, most commonly in the delivery room under local or epidural anaesthetic. However recent guidelines issued by the Royal College of Obstetricians and Gynaecologists in the UK recommend that all such repairs should be performed in an operating room with adequate exposure, lighting and adequate anaesthesia [16]. By tradition, the technique of repair has been a direct oppositional repair of the severed EAS, however an overlapping technique, as commonly used in secondary repair (vide infra), has been recommended as it obligates identification and adequate mobilization of the severed ends of the EAS [17]. The IAS, if damaged, is difficult to identify separately and is usually repaired en block with the anal canal mucosa in a complete or 4th degree tear. Mahoney et al [18] however have shown that persistence of an IAS defect is adversely associated with continence outcome following repair of a 3rd or 4th degree tear, while Roos et al [19] have found that women with major tears (grade 3c or 4) were significantly more likely to have ultrasound evidence of a persisting IAS or combined IAS and EAS defect following obstetric repair. Such women were more likely to have poor functional outcomes. Separate repair of the IAS has been advocated [17]; however as with overlapping EAS repair, separate repair of the IAS requires good anatomical knowledge and meticulous technique and it is probable that these factors are reflected in the improved outcomes reported, rather than the actual technique used. Thus, McNicol et al [20] have reported full continence in 39/45 (86%) women who underwent primary repair using a standardized overlapping repair without separate identification and repair of the IAS.

There have been six randomised clinical trials [17,21-25], one meta-analysis [26], and a systematic review [27] that have investigated different techniques of immediate primary anal sphincter repair following obstetric injury. Four trials have found no difference between the overlapping and end-to-end repairs. One trial found the overlapping procedure superior and one found the end-to-end procedure to be superior. Thus it appears inappropriate to favor one type of repair over another [26]. **[LEVEL OF EVIDENCE: 1**] However, all studies were small and it is difficult to control for the skill of the individual obstetrician performing the repair. With regard to the suture material used in repair, a randomised trial found no difference in outcomes between braided and monofilament absorbable sutures with 12 months follow-up [22], while Parnell et al [28] found no difference in outcome in a case series of patients between absorbable and permanent sutures. [**LEVEL OF EVIDENCE: 2**]

As colorectal surgeons are in general more familiar with the anatomy of the anal canal, it has been suggested that primary anal sphincter repair might be best performed by a colorectal surgeon than an obstetrician [29]. Nordenstam et al [30] concluded, in a single institution study of 165 women, that technique and expertise impact on the outcome of pri-

mary repair and that if needed, the repair could be safely delayed until such expertise was available. In a similar study, Soerensen et al [31] found no adverse outcome with delayed primary repair; thus, repair can be safely delayed until adequate expertise is available. Co-operation between obstetric and colorectal surgical colleagues can result in much improved outcomes [20], while a structured training programme for obstetric trainees also improves clinical outcomes [32]. [**LEVEL OF EVIDENCE: 2**]

There have been two randomised trials of post-operative management of the bowel after primary anal sphincter repair. These have shown benefit in use of a laxative rather than a constipating regimen but no advantage to the addition of a stool bulking agent [33,34]. [**LEVEL OF EVIDENCE: 1**]

Alteration in faecal continence occurs in approximately 13 - 17% of women following primiparous vaginal delivery, even in the absence of a recognised sphincter tear [6,35,36]. The prevalence is greater if urgency of defaecation is included as a symptom [7]. MacArthur et al [37] found flatal incontinence in 27% of 7,879 women surveyed 12 weeks after delivery. [**LEVEL OF EVIDENCE: 2**] Fenner et al [38] found that women who had sustained third and fourth degree tears were more likely to have bowel incontinence than women without anal sphincter injury 6 months following delivery. This was more pronounced in women with a history of 4th degree tear. Samarasekera et al [39] have found long-term effects on anal continence and quality of life following postpartum anal sphincter injury. Oom et al [40] have suggested that concomitant injury to the pelvic floor may be an associated determinant of outcome in addition to adequacy of sphincter repair. [**LEVEL OF EVIDENCE: 2**]

Management of subsequent labor following a previous anal sphincter tear must take account of obstetric risk factors, symptoms of incontinence and patient preferences. Harkin et al [12] found an approximately 5 fold increase in the incidence of recurrent sphincter tear compared to the incidence of first sphincter injury during second labor. Fynes et al [41] found that women with altered continence after first vaginal delivery were at risk of deterioration if delivered vaginally on their second pregnancy. Cesarean delivery before the onset of the second stage of labor was found to be protective [42]; however, Nelson et al [43] in a systematic review found that pregnancy rather than delivery was a more important in predicting post partum continence. Recently, Scheer et al [44] have confirmed that subsequent vaginal delivery is reasonable in asymptomatic women after a previously repaired third degree tear. [**LEVEL OF EVIDENCE: 3**]

A number of studies have looked at long-term outcomes after repair of a 3rd or 4th degree tears and all have shown an increasing prevalence of continence disorders with age. These findings parallel those of the general population of parous women who have not had a recognised tear [45-47]. Eogan et al [48] found in a study of women, 10, 20 and 30 years following delivery that onset of menopause was the most significant determent of symptoms, whereas Mous et al [49] found the incidence of incontinence increased with age irrespective of menopausal status. Fornell et al [50] found that subjective and objective anal function after anal sphincter injury deteriorates with time and subsequent deliveries. A persistent defect in the IAS was also found to be an important determinant, an observation supported by Mahony et al [18]. [**LEVEL OF EVIDENCE: 3**] There is some evidence that hormone replacement therapy may be of value in women who develop symptoms post menopause [51]. [**LEVEL OF EVIDENCE: 2**]

2. SPHINCTEROPLASTY

The term anal sphincteroplasty is used to describe secondary or delayed reconstruction of the anal sphincter musculature, injury to which has either not been recognised at the time of injury or the outcome of primary repair has been unsatisfactory. Anterior sphincteroplasty is the most common type of reconstruction performed because of the association with obstetric injury. In this situation, the anal sphincter muscles and perineal body have separated leaving a horseshoe type configuration to the anal sphincter mechanism, with a large defect in the anterior quadrant. Occasionally, the defect is such that the anal and vaginal mucosa have healed to form a cloacal defect. Anal sphincter defects related to previous anal fistula surgery or direct trauma are usually less complex and are not associated with a deficient perineum.

The decision to perform anal sphincteroplasty is based on an assessment of symptoms and the anatomical extent of the sphincter defect [52] . In assessing symptoms one of several continence scores should be used. The two most commonly applied are the Cleveland Clinic Continence Score [53] and the St Mark's Continence Score [54]. In addition a quality of life instrument should be applied [55] . Endoanal ultrasound is helpful in defining the extent of anal sphincter injury. 3D endo anal ultrasonography may provide further information [9]. Pelvic floor assessment using fMRI [56] or multiple contrast defeacating proctography [57] are valuable in the assessment of a more global pelvic floor injury. The American Society of Colon and Rectal Surgeons considers as surgical indication those symptomatic patients with localized defects, without defining exactly the minimum size of the injury detected as indication for this surgery [58]. [**LEVEL OF EVIDENCE: 4**]

Other causes of disordered continence should be excluded e.g. inflammatory bowel disease, colorectal cancer and neurological lesions. Patients with background IBS are more likely to be symptomatic

than those more predictable bowel habit and equivalent anal sphincter defects [59] . Pelvic floor electrophysiological assessment, while not essential, if performed, should be comprehensive and not confined to measurement of pudendal nerve terminal motor latency [60].

For symptomatic patients with a less than one quadrant anal sphincter defect, a trial of dietary modification, stool regulating drugs and physiotherapy is appropriate. There are limited data regarding the role of biofeedback with or without electrical augmentation [61,62], however a recent Cochrane review concluded there were insufficient data to allow definitive assessment [63]. [**LEVEL OF EVIDENCE: 2**]

For patients with a more than one quadrant anal sphincter defect, anal sphincteroplasty is appropriate [4,15,52]. Preoperative counseling should identify post operative wound healing as the most common difficulty. The majority of patients can expect significant improvement in continence after the procedure with a mean of 66% reporting excellent of good results in the short term [52]. Concomitant repair of a cloacal defect or vaginal fistula should be undertaken [64-66]. There is no evidence that a defunctioning colostomy improves outcome. The results of anal sphincteroplasty in recent series reporting more than 50 patients are given in **Table 1** [1,2,52,67-84].

Anal sphincteroplasty is usually performed in the lithotomy position although adequate exposure can be obtained in the prone jack-knife position. Full bowel preparation is not needed, although most would give a cleansing enema pre-operatively. The conventional incision is an inverted 'V' that may be closed as an inverted 'Y' as described by Parks [85]. If anterior levatorplasty or rectocele repair is contemplated, a posterior fourchette incision with the patient in lithotomy may have advantages [76]. The external anal sphincter is usually repaired using an overlapping technique without separate identification and repair of the IAS [15], however, Maslekar et al [82] attribute their good long term results to a selective policy of separate repair of the IAS. There has been one small randomised trial of direct versus overlapping sphincteroplasty which showed similar outcomes [86]. Occasionally the EAS defect is not full thickness and overlapping repair in such circum-

Table 1. Published results of anal sphincteroplasty since 1990, including series with 50 or more

Authors (ref)	Year	Number of patients	Follow–up months	Continent % (excellent / good)
Fleshman et al [67]	1991	55	12	72
Engel et al [68]	1994	55	15	79
Londono-Schimmer et al [69]	1994	94	60	50
Oliveira et al [70]	1996	55	29*	71
Gilliland et al [71]	1998	77	24*	55$
Young et al [72]	1998	54	18*	86$
Malouf et al [1]	2000	55	77	49
Karoui et al [73]	2000	74	40	47
Osterberg et al [74]	2000	51	12	58
Morren et al [75]	2001	55	40	56
Tan et al [76]	2001	50	28	50
Halverson and Hull [2]	2002	71	69	25
Bravo Gutierrez et al [77]	2004	130+	120	6
Madoff# [52]	2004	891		66
Norderval et al [78]	2005	71	27	41
Zorcolo et al [79]	2005	93	70*	55
Trowbridge et al [80]	2006	86	67	11
Barisic et al [81]	2006	65	80*	48
Maslekar et al [82]	2007	64	84*	80
Oom et al [83]	2009	120	111*	38
Gleason et al [84]	2011	74	32	77

 # metanalysis
** Median follow-up*
+ 130/190 available for 10 year follow-up
$ defined as "successful"

stances would require division of the residual intact fibres to facilitate overlap. Oberwalder et al [87] have found in a small series of patients that imbrication of the EAS in such cases is associated with outcomes similar to formal overlapping sphincteroplasty.

Initial success of sphincteroplasty is related to whether the anal sphincter defect is corrected [68,88]. Early failure is usually associated with a persisting defect identifiable using endoanal ultrasound [89]. This may be amenable to a further attempt at repair [88,90,91]. There is however increasing evidence that continence outcomes deteriorate with long-term follow-up [15,52,92]. Zutshi et al [93] found in a cohort of 31 patients followed for 10 years after overlapping sphincteroplasty that continence deteriorates over time. Mevik et al [94] also identified significant deterioration over time while Bravo Gutierrez et al [77] found that only 6% of patients retained full continence 10 years following anal sphincteroplasty. The effect of age at time of operation on long-term function is controversial [93,95,96], however long-term effects of aging and menopause coupled with atrophy of the sphincters may be relevant [15,97]. [**LEVEL OF EVIDENCE: 3**]

Pre-operative physiologic testing is helpful in the overall management of patients with faecal incontinence, however the value of anal manometry and pelvic floor electrophysiological assessment as prognostic indicators for outcome following sphincteroplasty is controversial [98]. There are no established parameters that reliably predict outcome following sphincteroplasty [82,99]. Patients with an unsatisfactory clinical outcome follow sphincteroplasty may be considered, if sufficiently symptomatic, for adjunctive sacral neuromodulation (vide infra) [100]. [**LEVEL OF EVIDENCE: 4**]

3. POST-ANAL REPAIR

Post-anal repair was first reported by Sir Alan Parks in 1975 [3]. This procedure was designed to increase the length of the anal canal, restore the ano-rectal angle and re-create the flap valve mechanism, which at the time was thought essential for maintaining faecal continence. Success rates ranged from 15% to 83%, depending on the definition of the success, the length of follow-up, and possibly the cause of incontinence. The published studies regarding post-anal repair include three systematic reviews of randomised controlled trials (level 1) [4,101,102], two randomised controlled trials (level 1 [103] and 2 [104]), two non-randomised cohort studies (level 2) [105,106], 8 case series of good quality (level 3) [107-114] and 11 case series of poor quality (level 4) [3,115-124]. The results of post-anal repair are shown in **Table 2** [3,103-124].

Table 2. Postanal repair for faecal incontinence

Authors (ref)	Year	Number of patients (female)	Median or mean follow-up: months (range)		Outcomes		Evidence level
					Continent to Solid and Liquid (%)	Symptomatic improvement	
Parks [3]	1975	75 (68)	ns	(180 or less)	83%	ns	4
Browning and Parks [107]	1983	42 (36)	ns	(1or less)	81%	ns	3
Keighley [115]	1984	89 (ns)	ns	(6 or more)	63%	84%	4
Ferguson [116]	1984	9 (8)	ns	(ns)	67%	ns	4
van Vroonhoven and Schouten[117]	1984	16	ns	(3 or more)	63%	75%	4
Henry and Simson [118]	1985	242 (193)	11	(0.5 - 27)	60%	ns	4
Habr-Gama et al [119]	1986	42 (39)	12	(12)	52%	ns	4
Womack et al [105]	1988	16 (14)	26	(15 or more)	38%	88%	2
Scheuer et al [108]	1989	39 (ns)	ns	(ns)	15%	70%	3
Yoshioka and Keighley [109]	1989	116 (?)	60	(ns)	24%	81%	3
Rainey et al [120]	1990	42 (37)	42	(6 - 95)	31%	71%	4
Scott et al [121]	1990	62 (56)	ns	(ns)	45%	82%	4
Laurberg et al [122]	1990	28 (28)	ns	(ns)	32%	75%	4
Orrom et al [106]	1991	17 (ns)	15	(ns)	59%	ns	2
Deen et al [103]	1993	PAR: 12 (12)	24	(22 - 28)	42%	42%	1
		ALP: 12 (12)	22		33%	50%	
		TPFR:12 (12)	28		67%	83%	
Engel et al [110]	1994	38 (34)	43	(15 - 126)	21%	50%	3
Jameson et al [111]	1994	36 (33)	6	(6)	50%	83%	3
			25	(6 - 72)	28%	53%	
Setti-Carraro et al [112]	1994	34 (34)	73	(61 - 95)	26%	82%	3
Rieger et al [123]	1997	19 (ns)	96	(24 - 120)	37%	58%	4
van Tets et al [104]	1998	PAR: 11 (11)	3	(3)	27%	45%	2
		TPFR: 9 (9)	3	(3)	22%	33%	
Matsuoka et al [113]	2000	20 (20)	36	(12 - 90)	35%	35%	3
Abbas et al [114]	2005	44 (44)	36	(24 - 216)	23%	68%	3
Mackey et al [124]	2010	57 (53)	109	(26 - 224)	26%	79%	4

ns: not stated; PAR: postanal repair; ALP: anterior levatorplasty; TPFR: total pelvic floor repair

Subsequent observational studies with a median follow-up of more than 5 years revealed that continence deteriorated with time. Despite 60% to 80% of patients reporting persisting symptomatic improvement, only one-third were actually continent to liquid or solid stool [109,112,114,123]. Even in the most recent study reporting the long-term outcome of post-anal repair [124], only 26% reported none to minimal incontinence, with the Cleveland Clinic incontinence score being between 0 and 5, while 79% improved symptomatically with a mean follow-up of 9.1 years. Possible explanations for deterioration of continence following initial improvement included unrecognised denervation and/or muscular injury of the sphincter and pelvic floor musculature, and the presence of occult anal sphincter disruption, particularly in the studies reported before endoanal ultrasonography or magnetic resonance imaging were available. Moreover, physiological and radiological evaluations before and after postanal repair have not demonstrated consistent changes in anal canal length, resting pressure, voluntary contraction pressure, anorectal sensitivity and movement of the ano-rectal angle [104-107,125]. These reports of increasingly poor outcomes have diminished the popularity of this procedure significantly.

Deen et al [103] in a randomised controlled trial, comparing three procedures in 36 women with neuropathic faecal incontinence, found that complete continence was achieved in 42% of patients after post-anal repair, 33% after anterior levatorplasty and 67% after total pelvic floor repair. In contrast, van Tets et al [104] conducted a randomised controlled trial comparing post-anal repair and total pelvic floor repair in 20 women with neurogenic faecal incontinence. Complete continence to solid or liquid stool was achieved in 27% of patients after post-anal repair and in 22% after total pelvic floor repair.

4. NON-STIMULATED MUSCLE TRANSPOSITION

A variety of muscle transposition procedures have been devised for the treatment of faecal incontinence. Early efforts focused upon the use of transposed skeletal muscle to supplement the function of a weak or disrupted anal sphincter. Early in the 20th century, a number of surgeons utilized gluteus maximus muscle, transposed in a variety of configurations, to create a neosphincter [126,127]. In 1952, Pickrell et al [128] described the use of transposed gracilis muscle to create a neosphincter for incontinent children.

Published series of gracilis transposition are uncontrolled and demonstrate variable success rates [129-138]. [**LEVEL OF EVIDENCE: 3**] One study reviewed the functional results of graciloplasty longitudinally in 22 patients followed for a median 63 months [139]. 18 patients (81%) were improved at 6 months, though only one regained normal continence. Results deteriorated in 5 patients during subsequent follow up. Bilateral gracilis transposition has been used successfully in several small series [130,140].

Success rates following gluteus transposition have likewise been variable [141-145]. [**LEVEL OF EVIDENCE: 3**] A prospective randomised trial in women with post-obstetric neuropathic incontinence showed similar significant degrees of improvement following both gluteus maximus transposition and total pelvic floor repair [146]. A recent retrospective review of 25 gluteoplasty patients reported restoration of continence in 18 patients (72%) and partial restoration in an additional 4 patients (16%). Donor-site and peri-rectal complications occurred in 16 patients (64%) [147].

5. STIMULATED MUSCLE TRANSPOSITION

The transposition of the gracilis muscle to reconstruct the anal sphincter was first performed in children in 1952 [128]. The blood supply is primarily from a single proximal artery that allows excellent mobility for transposition [148]. Successful electrical stimulation of a previously transposed gracilis muscle was first reported in 1988 [149], and case series from 2 independent centers were simultaneously reported in 1991 [150,151]. Baeten et al [150] showed improved continence in 8 of 10 patients; Williams et al [151] in 12 of 20.

Even after successful muscle transposition, functional outcomes are limited by two physiological factors. First, patients are unable to consciously maintain tonic contraction of their neosphincters over long periods of time. Furthermore, even if patient volition were not a problem, gracilis muscle is poorly suited to tonic contraction. While the external anal sphincter comprises predominantly slow-twitch, fatigue-resistant type I fibres, the gracilis muscle comprises predominantly type II, fast-twitch fibres that are rapidly fatigable [152]. Graded electrical stimulation transforms type II into type I muscles fibres [153], and use of an implantable electrical pulse generator has been shown to convert transposed gracilis to a muscle with predominantly type I fibres [150-152]. The gracilis muscle is well suited to electrical stimulation due to the relatively constant proximal location of the neurovascular bundle, which is easily identified at surgery [154].

The results of stimulated graciloplasty are shown in **Table 3** [155-165]. [**LEVEL OF EVIDENCE: 2**] In 1995, Baeten reported his results in 52 patients, with 38 (72%) becoming continent after surgery [155]. In a subsequent paper by this group published in 2003, 200 patients followed for a median of 261 weeks were reported [163].

Table 3. Dynamic Graciloplasty: General measures of continence

Authors (ref)	Year	Number of patients	Follow-up	Percentage continent*
Baeten et al [155]	1995	52	25.2 months (mean)	73
Geerdes et al [156]	1996	67	32.4 months (mean)	78
Cavina et al [157]	1998	31	37.8 months (mean)	85
Madoff et al [158]	1999	131	24 months (median)	66
Mander et al [159]	1999	64	16 months (median)	69
Baeten et al [160]	2000	123	23 months (mean)	74
Wexner et al [162]	2002	83	24 months	53
Rongen et al [163]	2003	200	16.3 months (median)	72
Pennickx et al [164]	2004	60	48 months (median)	55
Tillin et al [165]	2006	49	43 months (median)	70
Hassan et al [169]	2010	31	67 months (median)	71

** variable definitions; does not necessarily denote perfect continence. Issues of divergence in technique arose from these studies, each of which has seen increasing consensus in the literature despite a lack of randomised trial data. Thus, intramuscular (vs. epineural) electrodes are now universally employed, and diverting stomas and 'vascular delay' prior to muscle transposition are no longer utilized.*

The overall success rate was 72%. Patients with incontinence due to trauma had the best results (82% success), while patients with incontinence due to congenital anorectal malformation had the worst results (52% success). 138 complications were reported, including disturbed evacuation in 32 patients (16%), infection in 24 (12%), pain in 16 (8%) and pulse generator displacement in 12 (6%). Ten patients (5%) had anorectal perforations, 7 of whom eventually obtained a successful outcome. Rosen et al [166] reported restoration of continence in 9 of 10 patients treated by dynamic graciloplasty using a "split-sling" wrap configuration. Sielezneff et al [167] treated 16 patients and 13 had improved continence. However, 8 patients suffered morbidity, resulting in 33 subsequent admissions and 23 reoperations.

Three multicenter prospective trials of dynamic muscle plasty have been performed to date [158-160]. In each of these studies, patients served as their own controls. No randomised prospective trials have been performed.

Madoff et al [158] studied 139 patients from 12 centers, 128 of whom had gracilis wraps and 11 gluteus wraps. Of those patients, 104 were treated for faecal incontinence, and 35 underwent total anorectal reconstruction following abdominoperineal resection for cancer. Success rates for graciloplasty were 71% for patients with acquired incontinence and 50% for those with incontinence due to a congenital abnormality. There were a total of 138 complications for the entire group. Wound complications (41 major and 35 minor) were both the most prevalent and the most consequential. Other complications included pain in 28 patients (22%), hardware problems in 14 (11%) and tendon detachment in 4 (3%). Centers with significant prior experience with the procedure had substantially fewer major wound complications (17.4 vs. 33.1%) and significantly higher success rates (80% vs. 47%).

Mander et al [159] reported the results of dynamic graciloplasty in 64 patients with refractory faecal incontinence treated at 7 centers. There were 24 infectious complications, 5 of which involved perineal wound breakdown and 3 of which required reoperation. 44 (69%) patients became continent to solid stool 1 month following stoma closure. Evacuation problems developed in 16 patients (25%), and this lead to failure in 14. At a median of 10 months follow-up, 29 patients had a good functional result.

Baeten et al [160] reported the results of dynamic graciloplasty in 123 patients treated at 20 centers as part of the Dynamic Graciloplasty Therapy Study Group (DGTSG). The aims of this study were

to assess both the safety and efficacy of this treatment; 189 adverse events occurred in 91 patients, including one death due to pulmonary embolism. There were 18 major and 31 minor infectious complications. There were 42 instances of therapy-associate pain, occurring variably in the donor leg, at the anal canal, or at the device site. There were 11 lead dislodgements but no problems with lead breakage or pulse generator malfunction. A follow-up study showed full or partial recovery from these complications in 87% of patients. [161] This study, in contrast to others, was based upon data from daily continence diaries. A successful result (defined as a 50% or greater decrease in incontinent events in patients without pre-existing stomas) was achieved in 63% of patients after one year. Another follow-up of this patient cohort demonstrated stable success rates at 18 months (55%) and 24 months (56%) [162]. Statistically significant improvements in the physical and social function scales of the SF-36 were also recorded at 12 months.

A multicenter retrospective trial from Belgium using dynamic graciloplasty treated 60 patients with 27 failures [164]. Continence was achieved in 78% of the group. However, more than half (26 patients) required the use of antegrade continence enemas or other measures to maintain continence. Seven patients had a permanent stoma constructed. Seventy-five complications occurred with 61 total reoperations. Loss of muscle stimulation occurred in 22 patients; 10 were due to issues specific to the stimulator and leads, 4 were due to technical failure of the muscle wrap. Functional outcome was directly associated with a maintenance of stimulation and initiation of stimulation within 50 days of surgery.

Very few studies have examined the long term results with dynamic muscle wraps. Thornton et al [168] reported on the 5-year follow up of 38 patients who had undergone dynamic graciloplasty. Of the 33 patients available for follow-up by telephone interview, obstructive defaecation was a problem for 11% of the cohort and 16% had been converted to a permanent colostomy. Of those with a functioning graciloplasty (22 patients) who reported a faecal incontinence score of less than 12 (range 0-24), 50% reported problems with obstructive defaecation and 64% felt their bowel habits had negatively impacted their quality of life. Long-term complications were primarily related to stimulator issues; ten patients required 15 operations to replace stimulator components. However, 72% of patients reported pain, swelling or paresthesias of the donor leg and 27% reported sexual dysfunction. Hassan et al [169] reported follow-up of 31 patients who underwent gracilis muscle transposition with periodic electrical stimulation and postoperative supplement of biofeedback. Twenty-two patients (71%) reported improvement at five-years. Nine patients (29%) were deemed failure requiring further surgical intervention (colostomy formation, contralateral dynamic gracilis muscle transposition, implantation of artificial bowel sphincter). Six patients developed perineal wound infections (5 resolved with antibiotics, 1 required surgical drainage), and 2 patients had evacuation difficulties requiring regular enemas. Those who underwent operation due to traumatic injury to sphincters had better outcome (82% improvement) compared to patients with congenital faecal incontinence (55%).

Tillin et al [165] performed a prospective case-comparison study of 49 patients who had a dynamic graciloplasty and 87 patients who either refused the surgery or were not offered the surgery. The primary outcomes evaluated were symptoms, quality of life, anxiety, and depression. Of the treated group, the procedure failed completely in 15 patients. At two year follow-up, two-thirds of patients were either never or rarely incontinent to liquid or solid stool. Up to 50% of patients with a satisfactory outcome reported disordered evacuation and 8 other patients were deemed failures due to this problem. However, in comparison to the 87 patients who did not undergo treatment, there were significantly more patients in the dynamic graciloplasty group who reported a greater than 20% improvement in their incontinence scores. However, the treated group also had a significantly worse pain as assessed on a validated pain scale.

Chapman et al [170] performed a systematic review of dynamic graciloplasty for faecal incontinence on behalf of the Australian Safety and Efficacy Register of New Interventional Procedures- Surgical (ASERNIP-S). The authors reviewed 37 original articles published between 1991 and October 2000. All of the papers were judged to be of low-evidence quality, as all but one paper were case series, and the sole comparative study utilized historical controls. Mortality excluding cancer deaths was 1% (95% confidence interval 1-3%) and morbidity 1.12 (95% CI 0.14 - 2.08) events per patient. Success was variably defined between studies, but was reported as ranging from 42-58%. The ASERNIP-S Review Group determined that “the safety of the procedure cannot be determined at the present time due to an incomplete and/or poor-quality evidence base” and that “efficacy is established.” Tan et al [171] examined three treatments for faecal incontinence including dynamic graciloplasty, artificial bowel sphincter and end stoma. They concluded that the most cost effective intervention was an end stoma, the artificial bowel sphincter was most cost-effective after 10 years and that dynamic graciloplasty should only be considered as an alternative in highly specialized centers.

6. ARTIFICIAL ANAL SPHINCTER

Artificial sphincters can be defined as any kind of implanted device intending to replace or reinforce the sphincteric mechanism that normally closes the bowel end. They aim to be a substitute to the normal sphincters. As such, it is necessary that they be efficient for both terminal bowel functions: continence and evacuation; that their implantation be safe and reproducible, with a limited need for patient/medical

intervention and follow-up after implantation; and finally that they be cost effective.

There is active laboratory research at a preclinic phase for new artificial devices. Different parts of the world are involved, including China with a novel electro-magnetic anal sphincter with sensor feedback currently tested on animals [172-174], US with bioengineered tissue designed to mimic the function of the internal anal sphincter [175,176], and Germany with a new version of the previously described "German artificial sphincter system" (GASS), now consisting of an inflatable cuff connected to a combined implantable micropump, fluid reservoir and microprocessor [177]. These various prototypes have not been implanted yet in humans but clinicians have to be aware of any development of these innovations.

Artificial sphincters currently used in humans are silicone-made, pressure-regulated devices restoring continence through an inflatable cuff placed around the lower rectum or upper anal canal. Three models have been proposed on the market. Over the 5 last years, no publication has reported any results from the implantation of two of them: the prosthetic bowel sphincter (PBS) developed by Finlay in UK and the Agency for Medical Innovations (AMI) soft anal band system once popular in Germany and Austria. The only currently available data concern the Acticon Neosphincter (American Medical Systems, AMS) artificial bowel sphincter (ABS).

The ABS, a modified model of the AMS 800 artificial urinary sphincter has been in use since 1996 for faecal incontinence management. In short, it comprises a fluid-filled cuff that encircles and compresses the anal canal. A pressure-regulating balloon is implanted in the retropubic space of Retzius. The system is controlled by a pump placed in the labia majora or scrotum which is accessible to the patient. To initiate defaecation, squeezing the pump empties the cuff by a fluid transfer into the balloon, allowing for the passage of stool. The cuff then refills automatically from pressure built up in the balloon.

The role of the ABS in the treatment of faecal incontinence has been confirmed in reports from different groups [178-182]. [**LEVEL OF EVIDENCE: 2**] ABS use has been supported in the current recommendations of both the United Kingdom's National Institute for Health and Clinical Excellence (NICE) and the American Society of Colon and Rectal Surgeons (ASCRS) [58,183]. The ABS is especially indicated for patients with "severe end-stage faecal incontinence," especially those with major sphincter disruptions that preclude direct sphincter repair, or those in whom sphincter repair has failed. For many of these patients, creation of a permanent end colostomy is the only remaining therapeutic alternative. However, generalizability of the published results remains doubtful as the majority of the series come from expert centers that have developed particular expertise in the implantation of artificial sphincters.

a) Functional Results of ABS

The artificial bowel sphincter provides good restoration of continence for solid and liquid stool in patients who retain the device, with all studies reporting almost similar data (**Table 4**) [179-181,184,185]. Implantation of an ABS was successful in 27 out of 33 patients in a Dutch series with a significant improvement in Williams faecal continence score at 17 month follow-up [180]. In a series from France, a new transvaginal approach to implant the cuff has been tested [178]. It was successful in 23 out of 32 patients (71.9%), with a device that remained activated for a mean follow-up of 41 (range 18-75) months, resulting in a significant decrease in Wexner incontinence score from 18.4 to 6.8 and no dyspareunia in sexually active patients [179]. Long term data from Spain reported a final success with an activated ABS in 9 out of 17 cases (53%) allowing for a decrease in CCF score from a median of 17.5 preoperatively to 10 at 66 month follow-up and a significant improvement in QOL [184]. In the report of a large single-center experience of ABS implantations, including 52 patients (46 women) implanted over the past 10

Table 4. Artificial anal sphincter for faecal incontinence with Acticon Neosphincter®

Authors (ref)	year	No of pts	mean or median Follow-up (mo)	No (%) of functioning device	Overall Complication (%)	"Success" in patients with a functioning device	Evidence level
Michot et al [179]	2010	32	41 (range,18-75)	23 (71.9)	28.1	CCF-FI from 18.4 to 6.8	2
Melenhorst et al [180]	2008	33	17.4 (0.8-106.3)	26 (81)	21	Williams score from 4.8 (4–5) to 2.1	2
Wexner et al [181]	2009	47	39 ± 28 (range, 3-108)	16 (34)	41.2	CCF-FI from 18.4 to ns	2
Ruiz Carmona et al [184]	2009	17	68 (range, 3-133)	9 (53)	100	CCF-FI from 17.5 to 10	2
Wong et al [185]	2011	52	64.3 ± 46.5	35 (67.3)	50	CCF-FI from 16.7 (range, 12–20) to 5.6 (range, 0–17)	2

CCF-FI:Cleveland Clinic Florida Fecal Incontinence (0: full continence - 20: worst incontinence); ns: not stated.
"Success" is defined as "continence to solid and liquid stool without significant obstructed defaecation, otherwise defined in each study"

years with 85 devices and a mean follow-up of 64.3 ± 46.5 months, 35 patients (67.3%) had a functioning device at review. A significant improvement in both CCF (P < 0.0001) and FIQL (P = 0.0286) was observed [185]. Some patients of this study with an activated ABS were matched to a group of successful SNS patients to compare their respective functional outcomes. Although this study had several limitations, it showed that the ABS achieved significantly better control of continence, albeit at the expense of more symptoms of outlet obstruction postoperatively and a similar quality of life for the 2 groups of 15 patients each [186]. [**LEVEL OF EVIDENCE: 2**] This risk of constipation after implantation of an ABS is a real concern as the cuff, even when opened, can narrow enough the anal canal to prevent a complete and easy evacuation. It has been well measured in a series of 44 patients with 55% of them expressing some sort of constipation or outlet obstruction [187].

b) Surgical Risks and Postoperative Complications of ABS

Besides an evident beneficial effect in treating severe faecal incontinence, the above-mentioned studies have confirmed the high risk of failure after implantation due to infection and mechanical failure. However severe morbidity is rare and no mortality has been ever reported. Explantation of the device generally solves the problems without long term sequelae.

The primary concern with ABS implantation is infection. In the report from the Cleveland Clinic 23 of 51 (41.2%) implantations became infected [181]. Among these, 18 (35.3%) developed as an early-stage (before ABS activation) and 5 (5.9%) a late-stage infection. On multivariable analysis the authors found that the time between ABS implantation and first bowel movement and a history of perineal sepsis were independent risk factors for early-stage infection. This may explain some variations in infection rate when compared to European reports where great care is taken in bowel preparation before device implantation. Series from France and Holland each reported a 21% infection rate [179,180].

Mechanical failure is now a well-recognised complication after ABS implantation. The most common cause is microperforation at the folds of the cuff membrane, which leads to a loss of fluid and pressurization of the system. Cuff perforation is easily perceived by the patient as both a return to incontinence and development of a non-functioning control pump. Cuff perforation reflects intrinsic wear-and-tear of the device components over time and contributes to the number of revision procedures, especially in patients with satisfactory functional ABS results. Revision rate is directly proportional to the length of follow up. With a mean follow-up of more than 5 years, half of a series of 52 patients required revision surgery after a mean of 57.7 ± 35.0 months, with 73.1% due to a leaking cuff [185]. Although ABS reimplantation is usually easy in the encapsulated area of the previous device, the risks of infection and impaired function are real and account for some long-term failures. Furthermore, the need for reimplantation increases the overall treatment costs. These concerns suggest that an appropriate component upgrade by the manufacturer might lead to improved long term results and a lower cost basis for this therapy.

Cost issues have been assessed in a complex health economics study [188]. The authors aimed to assess cost-effectiveness of ABS, dynamic graciloplasty and end-stoma in the treatment of faecal incontinence. Based on an assessment of incremental cost-effectiveness ratio (ICER), they concluded from published data and expert opinion that the all three procedures were cost-effective with the end-stoma most cost-effective over a 5-year period (ICER GB£4,719 /QALY) and the ABS most cost-effective over a 10 year period (GB£5,387/QALY).

Careful patient selection and sound operative technique are critical components of success for artificial sphincter implantation. Exclusion criteria include morbid obesity, insulin-dependent diabetes mellitus, Crohn's disease, pelvic sepsis and radiation proctitis. Individuals who practice anoreceptive intercourse are not candidates for the procedure. It is also vital to ensure that all patients are adequately motivated and have sufficient manual dexterity to operate the device independently.

At present, ABS is not commercially available due to a manufacturing hold by the FDA. This situation is especially difficult for those waiting for revision surgery.

Studied in small trials, but not yet clinically available, the magnetic anal sphincter (MAS) (FENIX™; Torax Medical, Inc., Shoreview, MN - US) is a novel device designed to augment the native anal sphincter. It consists of a series of titanium beads with magnetic cores hermetically sealed inside. The beads are interlinked with independent titanium wires to form a flexible ring that rests around the external anal sphincter in a circular fashion. The device is manufactured in different lengths based on the number of beads (14 to 20) necessary to accommodate the variation in anal canal circumferences.

One of the advantages of this still investigational device over the previous artificial sphincters is that it begins working immediately once implanted, without the need for further manipulation by either the patient or surgeon. The procedure for implantation is also substantially simpler than the ABS because access to the perineum alone is required. The device is place under fluoroscopic guidance.

A recent multicenter feasibility study demonstrated good short-term restoration of continence with limited complications [189]. In a subsequent non-randomised comparative cohort study assessing results of the magnetic anal sphincter and the ABS,

it was shown that the 2 devices were similarly effective in restoring continence and quality of life, without any difference in morbidity [190]. [**LEVEL OF EVIDENCE: 3**] Further comparative studies with other innovative treatments of faecal incontinence such as SNS are getting underway.

Based on these results, FENIX™ has been granted CE mark on November 2011 and its commercial use has started in selected centers in Europe. Further reports from more centers are expected.

Presently the place of the magnetic anal sphincter in the treatment algorithm of faecal incontinence remains to be determined. It appears to be a promising innovation as it offers a less invasive and simpler alternative of anal reinforcement than the ABS. However, with only short-term follow-up available, it remains to be seen if the MAS can withstand the test of time.

7. SACRAL NERVE STIMULATION

Sacral nerve stimulation (SNS) was first applied for the treatment of faecal incontinence in 1994 by Matzel et al [191] in patients with functional deficits of the anal sphincter but no morphologic defect. The concept of recruiting residual function of an inadequate anorectal continence organ by electrostimulation of its peripheral nerve supply, i.e. the sacral spinal nerves, was adapted from the field of urology in the early 1990s [192], where it has been used since 1981 [193]. The rationale for applying SNS to faecal incontinence was based on both clinical observations and anatomic considerations (from the former, the beneficial effect on bowel habits and anorectal continence function and increased anorectal angulation and anal canal closure pressure seen in urologic patients; from the latter, the demonstration by dissection of a dual peripheral nerve supply of the striated pelvic floor muscles that govern these functions [192], with the sacral spinal nerves being the most distal common location of this dual nerve supply). It was hypothesized that stimulating the sacral spinal nerves could both enhance physiologic function and improve the symptoms of faecal incontinence.

a) Technique

SNS has become a minimally invasive technique with low morbidity. The surgical technique can be divided into two stages:

As no other predictors of SNS outcome exist at present, patients are uniformly selected for operative implantation of a permanent neurostimulation device on the basis of clinical improvement during test stimulation. This first stage, termed percutaneous nerve evaluation (PNE), is used to confirm a satisfactory neural response and then to evaluate the clinical effect of stimulation before implantation of a permanent device. Therapeutic trial stimulation is performed for one to three weeks, a period sufficient to prove its therapeutic effect--commonly considered a decrease in the frequency of incontinence episodes (documented by bowel-habit diary) by at least 50% and reversibility after discontinuation. Two technical options are used for PNE: a temporary, percutaneously placed, unipolar test stimulation lead (or multiple leads) that will be removed at the end of this phase; or operative placement of a quadripolar lead, the so-called “foramen electrode,” close to a target nerve. This electrode can stay in place and be used for permanent stimulation if the trial is effective. Today most commonly a minimally invasive technique places this foramen electrode with a modified anchoring device, the so-called “tined lead,” through a trochar. For screening, both types of leads are connected to an external pulse, the tined lead with a percutaneous extension cable.

The second stage is implantation of a permanent electrode and neurostimulator if screening is successful. Patients with a temporary lead require simultaneous implantation of the pulse generator and the quadripolar lead, most commonly as a tined lead procedure. Those with a foramen electrode already in place for screening will undergo removal of the percutaneous extension before placement of the pulse generator (so-called “two-stage implant”) [194]. Bilateral placement of foramen electrodes remains the exception, based either on improved outcome of bilateral stimulation during the screening phase [195] or on conceptual considerations [196]. The pulse generator is placed subcutaneously, usually in the gluteal area or under certain circumstances in the abdominal wall. It is activated and stimulation parameters are set early after surgery by telemetry; it can be deactivated by the patient with a small, handheld device commonly referred to as a “patient programmer.”

A small retrospective study, comparing the earlier use of an open electrode placement technique to the current tined lead placement demonstrated no difference in outcome [197]. The infection rate was slightly higher in patients undergoing open electrode placement (11% vs. 8%). Although responses to temporary stimulation and the permanent device are comparable, therapeutic outcome for permanent SNS appears to be best when both sensory/anal motor and toe flexion responses are achieved during test stimulation [198].

b) Patient Selection and Indications

Today, a variety of causes leading to faecal incontinence can be treated with SNS. During the initial SNS experience, only patients presenting with deficient function but no morphologic defect of the striated anal sphincter and levator ani were eligible [192,199,200]. However, because of the high predictive value of the test stimulation, a more pragmatic, trial-and-error approach to patient selection evolved. Patients are now selected for SNS based upon PNE results rather than conceptual considerations of the potential mechanism of action. Test stimulation is in-

dicated, not by an underlying physiologic condition, but by the existence of an anal sphincter with reduced or absent voluntary squeeze function and existing reflex activity, indicating an intact nerve-muscle connection (confirmed by intact anocutaneous reflex activity or by muscular response to pudendal stimulation with the St. Mark's electrode) [199].

At present, the test stimulation is the only reliable mode for selecting patients who will likely benefit from permanent therapeutic stimulation. Various studies have focused on potential predictors of success of SNS. In a study by Gourcerol et al [201], age was the only variable related to success of temporary stimulation. In patients with a permanent implant, neurologic disorders, delay of the left bulbocavernosus reflex and a prolonged or absent bulbocavernosus reflex were more frequent in patients with successful outcome. In another cohort analysis, the need for repeated temporary procedures was associated with failure during the screening in univariate and multivariate analysis [202]. A low threshold to obtain motor response during temporary lead placement was revealed to be associated with improved outcome only in univariate, but not in multivariate, analysis. Evidence of anal sphincter injury was related to a greater risk of failure during temporary testing, but not with permanent implant.

In a large single-center study comprising 245 patients with test stimulation and 169 patients with permanent implant, Govaert et al [203] determined in univariate analysis that older age (>70 years), presence (but not size) of an external sphincter defect, and the need for repeated procedures after initial failure were significantly related to failure of test stimulation. In multivariate regression analysis presence of an external sphincter defect and need for repeated procedures remained significant. The permanent implant was successful in 76.9% of the patients, but no predictor was found to be significantly related. In a cohort of 55 patients with permanent SNS, Brouwer and Duthie [100] demonstrated that continence scores did not differ significantly in those with a defect, pudendal neuropathy, or previous sphincter repair. Melenhorst et al [204] found no difference in outcome with chronic SNS in patients after sphincter repair and those with an external sphincter lesion of up to 33% of the circumference; they concluded that a morphologically intact sphincter is not a prerequisite for successful SNS. In 244 patients undergoing test stimulation with a success rate of 78.3%, Maeda et al [205] determined that low amplitude of the sensory threshold during PNE and lead placement anterior to the sacral cortex are positive predictors of PNE outcome. No other demographic, physiologic or morphologic variable was a negative predictive factor. In a cohort of 200 patients with permanent SNS from 6 centers [206] only loose stool consistency, a history of diarrhoea management by medical treatment, and low stimulation intensity were associated with improved medium-term outcome. Multivariate regression analysis confirmed that stool consistency and stimulation intensity were independent predictive factors of success or failure of SNS.

In a cohort of 45 consecutive patients, temporary stimulation was successful in 32 (71%). At a median follow-up of 33 months, the neurostimulator remained in place in 25 (55%) and active in 23 (51%). No statistically significant differences were found in the characteristics (including anorectal physiological workup) of the 32 patients who underwent implantation and the 13 who did not or in those 23 with a functioning stimulator [207].

Altomare et al [208] in a comparative study of 48 patients demonstrated in univariate and multivariate analysis that quadripolar electrode use for test stimulation leads to better clinical outcome than a unipolar electrode.

In summary, none of the variables usually considered in a preoperative workup are of any help in selecting the appropriate patient for chronic SNS. [**LEVEL OF EVIDENCE: 3**]

Contraindications to SNS include pathologic conditions of the sacrum preventing adequate electrode placement (such as spina bifida), skin disease at the area of implantation, anal sphincter damage requiring a sphincter substitute (e.g. artificial bowel sphincter, dynamic graciloplasty), trauma sequelae with micturition disorders or low bladder capacity, pregnancy, bleeding complications, psychological instability, low mental capacity, limited cognitive function that interferes with the operation of the neurostimulation device, need for magnetic resonance imaging, and the presence of an implantable defibrillator or a cardiac pacemaker. A case series has shown the relative safety of the use of SNS in the presence of a cardiac pacemaker when monitored intraoperatively. If the distance between the devices is greater than eight inches, interference is unlikely [209].

c) Mechanism of Action

The mechanism of action of SNS remains uncertain. Clinical outcome has been seen to correlate with results of anorectal physiology studies, but the effect of chronic stimulation varies greatly among published reports [199,200]. Data are in part contradictory and inconclusive and sometimes not reproducible. The effect appears to be somatomotor [210-217], somatosensory [210], autonomic nervous system-based [210,212,218], and mediated by somatovisceral reflexes [219,220]. The effects appear not to be limited to the continence organ per se, but also to the central nervous system: corticoanal excitability in patients with faecal incontinence was found to be reduced with SNS [221]; in successfully treated

patients cerebral somatosensory evoked potential (SEP) latencies were higher at baseline than in the normal population, whereas they were normal in patients with SNS failure. Success was also associated with a fall of the SEP latency to the normal range after one month of SNS at 40 Hz [222]. SNS induces changes in anal representation on the primary somatosensory cortex [223]. The central nervous effect induced by SNS changes during its course: at its initiation, changes are seen in the contralateral frontal cortex, reflecting focus attention; subsequent changes are found in the ipsilateral caudate nucleus, an area related to learning [224].

Qualitative (or quantitative?)changes are seen in anal, rectal and colonic motility, such as reduction of spontaneous rectal motility complexes [225,226], spontaneous anal sphincter relaxation [225], reduction of antegrade transport from the ascending colon and increased retrograde transport from the descending colon at defaecation [227], increase rectal perception thresholds [228,229] and improve pelvic floor contraction during SNS [229]. The findings on rectal capacity with SNS have been inconsistent: unaltered [230-232] or increased [225,233]. No changes in gastric retention, gastric emptying, small bowel transit or colonic passage were seen with scintigraphic measurements during SNS [234].

An effect on mucosal neurochemistry during SNS has also been shown, with elevation of Substance P and TRPV1 levels [235], although the relevance of each of these has not been proven in specific pathophysiological conditions. The mechanism of action is most likely multifactorial and dependent on the underlying condition. [**LEVEL OF EVIDENCE: 4**]

d) Outcome

The results of permanent SNS after pragmatic, trial-and-error, patient selection are shown in **Table 5** [100,206,207,210-213,235-251]. Most studies have encompassed patients with heterogeneous pathophysiologic conditions, and they vary with regard to design and patient number, but there is general agreement regarding the test stimulation for selection for permanent implant. Most commonly, clinical outcome is reported as an improvement in the number of incontinence episodes or days with incontinence during the period of observation, changes in the Cleveland Clinic Incontinence Score, and quality of life.

In a first multicenter prospective trial of SNS adherent to the initial, confined spectrum of indications, Matzel et al [238] reported 37 patients, 34 of whom underwent a permanent implant. Not only were the frequency of incontinence episodes and the CCIS score improved significantly, so too was the ability to postpone defaecation. These effects were attained immediately.

Leroi et al [240] reported a double-blind, cross-over multicenter study in 34 patients with faecal incontinence treated with SNS. Three months after implantation, patients were randomised in a double-blind manner to on- or off-stimulation for a 2-month period, with reversal of the activation mode after 1 month. Of these, 24 of 27 randomised patients completed the 2-month trial. A significant decrease in median frequency of faecal incontinence episodes was noted during the on-stimulation period. No significant change was observed between on- and off-stimulation for frequency of urgency episodes, delay in postponing defaecation, or median number of bowel movements per week (10.2 and 11.1 for on and off, respectively). There was a trend towards greater improvement in the Cleveland Clinic Incontinence Score during on-stimulation (8.5 vs. 10.5; ns). A total of 24 patients (89%) considered that they had improved during the on period compared with 17 (63%) during the off period.

Melenhorst et al [213] published the largest mid-term follow-up, single-center study, with 100 patients undergoing permanent SNS. Late failure occurred in 21 patients as defined by a relapse of symptoms to less than 50% improvement over baseline, implementation of another therapy for faecal incontinence, or patient dissatisfaction. The mean time for definitive failure was 13.6 months (range 3–42.4). There was no evidence of technical failure such as lead migration or lead breakage.

A report by Rosen et al [210] highlights the effect of SNS in a cohort of patients of whom 75% suffered from faecal incontinence of neurologic origin. Frequency of incontinence episodes/week was reduced from 6 to 2 at 15 months' follow-up.

In a recent larger multicenter study Wexner et al [247] confirmed the efficacy of SNS in reducing symptoms of faecal incontinence: of 112 patients with permanent SNS followed for a mean of 28 months (2-69), 83% experienced a ≥50% improvement, including 41% who gained complete continence (at 12 months).

Mellgren et al [251] reported the same cohort after a mean follow-up of 3.1 years (0.2 – 6.1 years). With a complete or partial data set available in 64% of the patients, a ≥ 50% reduction of incontinence episodes was seen in 86%, with 40% achieving perfect continence. Symptom improvement resulted in improved quality of life, which was stable over follow-up. If a "last observation carried forward analysis" is performed, the 50% reduction of symptoms at 3 years is a 78% success rate; in a "modified worst-case analysis"--with all missing data classified as failure--the success rate at 3 years is 59%.

The findings of sustained symptomatic improvement with extended follow-up are in accordance with several other series focusing on long-term outcome: a sustained effect was seen in 74% of 52 patients after 5 years [245]; in 84% after a median follow-up of 7.1 years (5.6-8.7) [252]; and in 6/9 with follow-up of 7 – 14 years [253].

Table 5. Sacral nerve stimulation (SNS) for faecal incontinence

Authors (ref)	Year	No. of patients	Follow-up (months)	Incontinence episodes per week		Incontinence Score (CCIS*)		
				Before SNS (base-line)	SNS (last FU)	Before SNS (base-line)	SNS (last FU)	
HETEROGENOUS ETIOLOGIES †								
Rosen et al [210]	2001	16	15‡	6	2	ns	ns	
Ganio et al [211]	2001	16	15.5	5.8	0	ns	ns	
Rippetti et al [235]	2002	4	24	12	2	12.2	9.8	
Matzel et al [236]	2003	16	32.5	ns	ns	16	2	
Altomare et al [237]	2004	14	14‡	7	0.5	15	2	
Matzel et al [238]	2004	34	24‡	16.4	2.0	ns	ns	
Jarret et al [212]	2004	46	12‡	7	1	14	6	
Rasmussen et al [239]	2004	34	6	ns	ns	18	7	
Leroi et al [240]	2005	34	7‡	3.5‡	0.5‡	16‡	10‡	
Kenefick et al [241]	2006	19	24‡	12	0	ns	ns	
Holzer et al [242]	2007	29	35‡	2.3	0.67	ns	ns	
Hetzer et al [243]	2007	37	13	ns	ns	14	5	
Tan et al [244]	2007	53	12	9.5	3.1	16	1.2	
Melenhorst et al [213]	2007	100	25.5	10.4	1.5	nr	nr	
Vallet et al [207]	2008	32	37	ns	ns	16.1	4.9	
Altomare et al [245]	2009	60	74	3.5	0.7	15	5	
El-Gazzaz et al [246]	2009	24	28‡	4.5	1.5	12	4.7	
Wexner et al [247]	2010	120	28	9.4	1.4	ns	ns	
Michelsen et al [248]	2010	126	24	8.3	0.6	16	10	
Brouwer et al [100]	2010	55	18	ns	ns	15‡	5.2	
Gallas et al [206]	2010	200	12‡	4‡	ns	14‡	6.5‡	
Hollingshead et al [249]	2011	86	33‡	8.5	1.3	15	9	
Lim et al [250]	2011	41	51	ns	ns	11.5‡	8.0‡	
Mellgren et al [251]	2011	83	37.2	9.4	1.7	ns	ns	
SPHINCTER LESIONS								**Defect size** (degree)
Melenhorst et al [204]	2008	20	22.6	8.3	1.4	ns	ns	EAS: 17–33
Jarrett et al [257]	2008	8	26.5‡	5.5	1.5	15‡	9.5‡	EAS: 30–150
Vitton et al [258]	2008	5	14‡	ns	ns	15‡	6‡	EAS: 45–180
Chan et al [259]	2008	21	12	13.8	5	15.7	1	EAS: 90–120
Boyle et al [260]	2009	15	nr	7.5‡	1.5‡	12	9	EAS: 90–180
Ratto et al [261]	2010	10	33	25.6	0.8	18	10	IAS: 60-180 EAS:30-170
Dudding et al [262]	2010	8	46	9.9	1	ns	ns	IAS defect
Brouwer et al [100]	2010	20	20	ns	ns	15‡	7‡	EAS, extent nr
DISTINCT CONDITIONS								
Jarrett et al [263]	2005	2	12	9.8	1	ns	ns	Post rectal resection
Ratto et al [196]	2005	4	19.5	12	2.5	16.3	4.5	Post rectal resection ± chemoradiation
De Miguel et al [264]	2010	15	12‡	ns	ns	19.2	6.2	Post rectal resection ± chemoradiation
Jarrett et al [265]	2005	4	12	12.2	2	ns	ns	Post rectal prolapse
Robert-Yap et al [266]	2010	9	36‡	3‡	1‡	15‡	5‡	Post rectal prolapse
Jarrett et al [267]	2005	12	12‡	9.2	2.4	ns	ns	Spinal cord injury
Holzer et al [242]	2007	29	35‡	2.3	0.67	ns	ns	Neurogenic
Duelund-Jakobsen et al [268]	2011	91	46‡	6.3‡	0.8‡	ns	ns	Idiopathic incontinence

**CCIS: Cleveland Clinic Faecal Incontinence Score: 0 = fully continent, 20 = worst incontinence;*
†Limited to studies reporting incontinence episodes/week and/or CCIS at last follow-up
‡Denotes median; otherwise all data are presented as mean. ns: not stated; FU, follow-up

In most studies, quantitative measures are used to describe the clinical benefit, such as days with incontinence episodes or absolute numbers of incontinence episodes per period of observation, ability to postpone defaecation (in minutes), and percentage of improvement. Even though published reports differ with regard to patient population, a general pattern of outcome can be observed: when compared with baseline status, the clinical outcome is significantly improved.

The majority of studies report the outcome based on a per protocol approach (PP): the outcome reporting is limited to those patients with a permanent implant after successful testing. The infrequently used intention-to-treat protocol (ITT) approach analyses all patients considered for the therapy and undergoing PNE test. Thus, those are included who failed PNE, who are lost for follow-up or who died. In one study with 245 patients undergoing PNE and 176 patients subsequently being implanted, 132 patients were treated with SNS for a median follow up of 33 months (ITT 53.9%, PP. 75.0%). Outcome was good or acceptable in 103 patients (ITT: 42,1%, PP: 58.5%), limited or reduced requiring additional or alternative treatment in 20 patients (ITT: 11.8 %, PP: 16.5%) [254].

In a meta-analysis of publications from 2000-2008 comprising 790 patients, 28 studies compared incontinence episodes per week before and with SNS, and 14 studies compared incontinence scores. Both outcome criteria were significantly decreased. Another nine studies documented the ability to postpone defaecation, and this criterion also was significantly improved [255]. [**LEVEL OF EVIDENCE: 2**]

An increasing body of evidence indicates that SNS may also be a treatment option for patients with sphincter defects, unrepaired or after attempted anatomic reconstruction. The presence of an internal anal sphincter defect on endoanal sonography is reportedly unrelated to the success of permanent SNS [202]. Since the first report that three of five patients with ultrasound evidence of sphincter disruption measuring 25–33% of the circumference benefited from chronic SNS [256], several studies have been published (**Table 5**) [100,204,257-262]. The origins and morphologic findings regarding the extent of the sphincter gap differ in these studies, but lesions up to 180° have been treated. It appears that outcome is not dependent on the radial extent [257,260]. A significant improvement in clinical function, measured either as frequency of incontinence episodes or Cleveland Clinic Incontinence Score, has been seen in a substantial number of patients in all studies [100,204,257-262]. Follow-up is still limited.

Melenhorst et al showed that the primary use of SNS in patients with a sphincter gap 17-33% of the circumference appeared to result in an outcome similar to its use after failed sphincter repair [204]. In another study, SNS in 6 of 8 patients with faecal incontinence related to obstetric full-thickness anal sphincter lesions of >30-150º resulted in improved frequency of incontinence episodes (from 5.5 to 1.5 per week), improved ability to postpone bowel emptying, and improved FIQL quality-of-life scores at a median follow-up of 26.5 months [257]. No correlation between improvement and the radial extent of the sphincter defect was seen. In patients with internal and external sphincter disruption owing to Crohn's disease SNS was demonstrated to be beneficial in one study [258].

In a comparative cohort study [259], the effect of permanent SNS was reported in 53 patients with either an intact external anal sphincter (N= 32 (37.5% after sphincter repair)) or an external anal sphincter lesion (N=21 (81% after prior sphincter repair)) of <90° (N=11) or 90-120° (N=10). Improvement in symptoms and quality of life was achieved, and outcome after 12 months was not statistically significantly different between both groups. [**LEVEL OF EVIDENCE: 3**]

The therapeutic potential of SNS has also been demonstrated in some, mostly small, case series and individual case reports of patients with distinct pathological conditions or well defined anorectal physiology findings (**Table 5**) [196,242,263-268]: e.g. muscular dystrophy [269], proctocolectomy with ileoanal J-Pouch reconstruction for colitis [270], neurologic dysfunction including spinal disc prolapse [267], rectal prolapse repair [265,266], and rectal resection for cancer [263] with or without neoadjuvant chemoradiation [196,264,271], and after neoadjuvant and adjuvant chemoradio/radiotherapy for endometrial and anorectal cancer [272,273]. [**LEVEL OF EVIDENCE: 4**]

In a randomised controlled trial Tjandra et al [274] compared the effect of SNS for severe faecal incontinence with supervised optimal medical therapy that comprised pelvic floor exercises, bulking agents, and dietary manipulation. Permanent SNS in 53 patients was significantly better than conservative treatment in 60 patients: Cleveland Clinic Continence Score 1.2 vs. 14.1; incontinence episodes/week 3.1 vs. 9.4; days with incontinence/week 1 vs. 3.3; lifestyle 3.31 vs. 2.31; coping/behavior 2.68 vs. 1.86; depression/self-perception 3.25 vs. 2.64; embarrassment 2.76 vs. 1.78. [**LEVEL OF EVIDENCE: 2**]

e) Quality of Life

As with indications, outcome assessment has also evolved, and aspects of quality of life have been added to the evaluation (Cleveland Clinic Continence Scoring System, SF-36 and FIQL Score.) The therapeutic impact of SNS is most evident when a disease-specific quality-of-life instrument, the FIQL scale, is applied.

In the first study to apply this instrument, the multicenter clinical trial by Matzel el al [238], FIQL score was significantly increased in all 4 scales; SF-36

scores improved in 7 of 8 scales, the greatest being social functioning and mental health, but only the former reached statistical significance. A similar result was published by Leroi et al [240] with the French version of the FIQL: at the final follow-up visit, improvements in lifestyle, coping behavior, depression, and self-perception and embarrassment were significant. Hetzer et al [243] demonstrated a significant improvement of the median Gastrointestinal Quality of Life Index score with permanent SNS from a baseline of 96 (range 47–128) to 107 (range: 36–128) at 6 months post-implantation.

In most studies on outcome, quality-of-life evaluation is a secondary endpoint [196, 200, 210, 238, 240, 242, 243, 249 - 252, 259, 263, 265, 267, 274, 275]. When used, the finding of improved quality of life is consistently related to symptom relief and remains stable with longer follow-up [245, 251, 252, 276].

In a meta-analysis [255] of 34 studies with 790 patients, SF-36 score data were analysed from 7 studies with 98 to 102 patients and ASCRS FIQL data from 9 studies comprising 199 patients: SF-36 outcome was significantly increased in all categories (physical functioning, social functioning, role physical, role emotional, mental health, vitality, general health) with one exception (bodily pain). FIQL outcome was significantly increased in all categories (lifestyle, coping/behavior, depression/self-perception, embarrassment).

In a two-center study of patients with permanent SNS for a median of 46 months (11-122), 108 of 127 patients responded to questionnaires regarding bowel habits and quality of life. Using a non-validated score, 75.8% reported satisfaction, which in most was related to clinical improvement. However, at last follow-up 11 of 23 patients who had failed to achieve a 50% reduction in incontinence episodes reported satisfaction, and 6 of these had more incontinence episodes than at baseline [268]. [**LEVEL OF EVIDENCE: 2**]

f) Cost Benefit

Permanent SNS is expensive; however, its cost-effectiveness has been demonstrated in several European nations. Hetzer et al [277] compared the costs of SNS with those of conservative treatment, anterior sphincteroplasty, dynamic graciloplasty, and stoma creation in 34 consecutive patients. The 5-year cumulative cost for SNS was €19,333, compared with €35,965 for a stoma (with annual costs of €5,339) and €34,953 for dynamic graciloplasty (annual costs €1,659). The equivalent cost for conservative treatment was €3,895, and the overall median real cost for an anterior sphincteroplasty was €5,327. Muñoz-Duyos et al [276] analysed the direct medical costs of SNS in a series of 47 patients undergoing 57 PNEs and the consequent 29 patients with a permanent unilateral implant for a median follow-up of 34.7 (2.3-81.2) months. The cost totaled €371,434, including €31,7791 for the devices. In patients without anal sphincter damage SNS provided 0.34 incontinence-free life-years and entailed additional costs of €1,054, which generates a cost-effectiveness ratio of €16,181 per quality-adjusted life-year (QALY). The nationally accepted threshold is around €30,000/QALY. The economic impact of the introduction of SNS would be to add 0.07-0.1% to the care of these patients.

In a decision-analysis model based on prospectively collected data in 70 patients undergoing test stimulation and implantation of the permanent SNS device, incontinence episodes/week were reduced from 6 at baseline to 0.5. Dudding et al [278], based on direct medical and non-medical costs, found an incremental cost-effectiveness ratio (ICER) for SNS of GB£25,070 per QALY gained. It cost GB£1,038 per year to achieve a median reduction of 238 incontinence episodes, equal to GB£3.61 per reduced episode. The ICER of GB£25,070 per QALY was within the nationally accepted GB£30,000 per QALY threshold.

In a similarly designed study based on published reports and expert opinion, Indinnimeo et al [279] found that the ICER is €28,285 per QALY gained in patients with a structurally deficient anal sphincter and €30,662 per QALY in patients with an intact anal sphincter. Both are below the national threshold of €40,000 per QALY gained. Budget-impact analysis demonstrated that the implementation of SNS would have an estimated impact of 0.56% over a 5-year period on the budget allocated for faecal incontinence treatment. [**LEVEL OF EVIDENCE: 3**]

g) Safety

SNS is a relatively safe procedure [247,280]. A recent meta-analysis [255] is in accordance with earlier reports, which describe a relatively low late of complications [199,200] and a need for device removal in only approximately 5% because of loss of effect, symptom deterioration, pain from lead dislocation, or infection. The results of the meta-analysis, which covered the period 2000 – 2008 and included patients undergoing the more invasive, open-approach electrode placement technique, found a complication rate of less than 15% in 665 patients with a permanently implanted device. In only 3% did the device need to be removed. In patients in whom infection has necessitated removal, re-implantation at a later date has reportedly been successful [274].

In a recent FDA study with strict monitoring of adverse events, 334 were reported in 99 patients at three-year follow-up; 67% occurred in the first year, and most required no or minimal intervention. The adverse events included pain at the implant site (28%), paresthesia (15%), change in the sensation of stimulation (12%), implant site infection (10%) [247], urinary incontinence (6%), diarrhoea (6%), and leg pain (6%). Half of the infections required surgical intervention with removal of the device in 5 of 6 patients [251]. A single report with a consecutive series of 87 patients over a mean follow-up of 48.5

months describes the need for revisional surgery in 41%, one-third for device-related failure, including 24% for removal [281]. In a French multicenter study comprising 200 consecutive patients with a mean follow-up of 12 months, the rate of device-related adverse events was 24.5% [206].

Major complications are rare: one case report of a life-threatening haemorrhage after elective tined lead electrode removal has been published [282].

A recent review of 48 cohort studies (45 for faecal incontinence and 3 for constipation) documented the postoperative issues in the 1661 patients with test stimulation and 1600 patients with a permanent SNS implant [283]: it found that the incidence of suboptimal outcome was 12.1%, pain 13%, and infection 3.9%. The most common problem during test stimulation was lead dislodgement (5.3%). The reported incidence rate for suboptimal outcome – loss of efficacy or lack of efficacy – ranged between 0% and 27%. Systematic literature review suggests a possible underreporting of suboptimal outcome and adverse events. In one single study, the rate of adverse event reached up to 85.2% in patients with a median follow-up of 11 months: loss or lack of efficacy and pain or discomfort accounting for 88.5% of these [254]. [**LEVEL OF EVIDENCE: 3**]

8. POSTERIOR TIBIAL NERVE STIMULATION

a) Introduction

Posterior tibial nerve stimulation has it origin in pain treatment as transcutaneous electrical stimulation (TENS). Its use for the treatment of faecal incontinence (first published in 2003 [284]) is an adaptation of its successful application in the field of urology, stemming from the early 1980s [285-287]. Only recently, based on the therapeutic success of sacral nerve stimulation, has there been an increasing interest in this alternative approach of neuromodulation. The number of publications is still limited and the evidence low; however, several clinical trials are currently ongoing. Larger patient studies are awaited.

b) Techniques

Two different techniques are used: percutaneous stimulation with a needle electrode [288] and transcutaneous stimulation with surface adhesive electrodes [289]. In both techniques current is delivered by positioning the active electrode close to the posterior tibial nerve proximal to the medial malleolus. Adequate placement is confirmed by inducing digital plantar flexion, and the ground pad is placed in the proximity. Both systems are powered by a portable pulse generator. The stimulation parameter are set arbitrarily, mostly to 0.2 ms, a current below the threshold for motor response ranging between 0.5-9.0 mA, and a frequency usually to 10 – 20 Hz.

Although the stimulation parameters themselves are fairly uniform, there is no general agreement regarding the protocol: duration and pattern of stimulation; interval between sessions; basic or “top-up” treatment (**Table 6**) [289-295].

c) Patient Selection and Indications

Indications vary substantially among the proof-of-principle studies. A prospective observational design

Table 6. Tibial nerve stimulation for faecal incontinence

Authors (ref)*	Year	Nr. of patients	Follow-up (months)	Incontinence episodes per week		Incontinence Score (CCIS)		Treatment
				Before PTNS (baseline)	PTNS (last FU)	Before PTNS (baseline)	PTNS (last FU)	
PERCUTANEOUS STIMULATION								
de la Portilla et al [290]	2006	16	9	ns	ns	13.2	7.4	4 weeks 30 min/ week
Govaert et al [291]	2009	22	12	ns	ns	11.5	5.9	6 weeks 30 min/week
Boyle et al [292]	2010	31	9*	ns	ns	13*	7*	12 weeks 30 min / 3-4 d
Hotouras et al [293]	2011	15 passive	6	4.0	3.0	11.5	9.4	6 -12 weeks 1-2 x 30 min/week
Hotouras et al [293]	2011	25 urge	6	4.0	0.0	11.0	8.3	6 -12 weeks 1-2 x 30 min/week
Hotouras et al [293]	2011	60 mixed	6	5.0	1.0	12.8	9.1	6 -12 weeks 1-2 x 30 min/week
TRANSCUTANEOUS STIMULATION								
Queralto et al [289]	2006	10	4	ns	ns	11.4	5.4	4 weeks 20 min/d
Vitton et al [294]	2009	12	3	ns	ns	13.1	12.3	12 weeks 20 min/d
Eléouet et al [295]	2010	32	6	ns	ns	14.5†	11.4†	4 weeks 20 min/d

** limited to studies with ≥ 10 patients included*

†, denotes median, otherwise all data are presented as mean; ns: not stated; FU, follow-up

CCIS: Cleveland Clinic Faecal Incontinence Score: 0 = fully continence, 20 = worst incontinence

predominates, with mostly single-center trials and a limited number of patients. Inclusion criteria range from idiopathic faecal incontinence [289,290,292] and incontinence owing to inflammatory bowel disease [294], to faecal incontinence with internal or external sphincter lesions or a combination of both, some after obstetric trauma [290,292,296]. PTNS has been applied for passive, urgency, and mixed incontinence [293]. Symptom improvement has been demonstrated with PTNS for faecal incontinence after partial spinal injury in two cases [297].

d) Mechanism of Action

No studies have been performed to elucidate distinctly the effect of PTNS on symptoms of faecal incontinence. Several hypotheses of a potential mechanism of action have evolved based on the experience of the use of PTNS in urology and on an analogy drawn from findings of physiological changes with sacral nerve stimulation, but none of these hypotheses has been systematically explored. In one study significant changes in maximal squeeze pressure only was seen after 6 months [290]; others demonstrated no changes in physiological measurements [289]. An improvement in rectal sensory threshold and resting and squeeze pressures was reported in two patients after partial spinal injury [297]. In another study the clinical efficacy of PTNS was found to be independent of damage to the anal sphincter [298]. [**LEVEL OF EVIDENCE: 4**]

e) Outcome

All studies demonstrate an improvement in outcome measures, although outcome is not described uniformly (**Table 6**). Most commonly, clinical efficacy is monitored with the Wexner Incontinence Score and/or the recording of faecal incontinence episodes. Where incontinence episodes per month were reported and differentiated by stool consistency, in a study of 13 patients, reduction at 3 months was significant for all categories: wind, baseline 6 (0-17.5) vs. 0 (0-0) episodes/month; liquid, 10 (5-29.5) vs. 0 (0-4); and solid, 18 (0-30) vs. 0 (0-0) [290].

In all studies outcome reporting is limited to short-term follow-up. Postponement of defaecation was found to be significantly increased at 6 weeks and sustained at 12 months [291]. In one study the median increase in the ability to defer was 3 minutes (0-26) in patients suffering from urge incontinence [292]. [**LEVEL OF EVIDENCE: 4**]

f) Quality of Life.

If measured, instruments of quality-of-life recording also demonstrate an improvement with therapy [291]. Comparisons between success and failure, however, have not depicted conditions predictive of symptomatic improvement [291,295]. In patients with subjective improvement, quality of life was significantly better after 3 and 6 months' follow-up [295,296]. [**LEVEL OF EVIDENCE: 4**]

g) Safety

Reports on safety are limited, but none of the studies found relevant side effects. Mild, procedure-related reversible adverse events, such as gastrodynia and numbness in the leg for 2 hours, were reported in one study [291]. [**LEVEL OF EVIDENCE: 4**]

9. INJECTABLE BIOMATERIALS

Injection of bulk-enhancing agents into the anal canal to treat faecal incontinence has continued to gain popularity since the last review. Although injectable agents for urinary incontinence (UI) have had variable success, they offer the benefit of performing an outpatient procedure without anesthesia and with minimal morbidity. This has resulted in their continued use for urinary incontinence [299,300], as well as in more research on different injectable agents for use in faecal incontinence. The ideal agent for injection should be biocompatible, non-allergenic, non-immunogenic, easy to inject, and should not migrate within the tissues. No agent currently has all these properties. Agents that have a diameter of 80 mm are felt to be less prone to migration, but agents with a larger particle size require a larger bore needle to inject, which put them at a higher risk for leakage from the injection site. The results of all injectable biomaterials used for faecal incontinence to date are shown in **Table 7** [301-324].

Injectable agents for faecal incontinence were first used in 1993 when Shafik [301] treated 11 patients with injections of polytetrafluoroethylene paste into the anal submucosa. After 18-24 months of follow-up, 64% reported complete cure and 36% had partial improvement. Shafik [302] subsequently treated 14 patients with autologous fat injections with a reported 100% success rate at 2-3 months and all patients who lost continence to gas or stool became continent after repeat injections. There were no complications using either agent. However, other reports of autologous fat injection have resulted in death from pulmonary fat embolism [325], and a randomised clinical trial using fat for UI demonstrated no efficacy over placebo; thus, it is currently not used for faecal incontinence [325].

Other agents used for injection in the past, that have not achieved widespread use include micro balloons, bovine dermal collagen, and polyacrylamide hydrogel (Bulkamid). A series of six patients injected with self-detaching cross-linked silicone micro balloons with a biocompatible filler material demonstrated fairly good results, with Browning-Parks incontinence scores for the group decreasing from 16 to 5 (range 0-20) [305]. However, sterilization issues have prevented the ongoing use of this product.

The first reported injections of glutaraldehyde cross-linked synthetic bovine dermal collagen (Contigen) for faecal incontinence included 17 patients [303], 11 (65%) of whom showed marked

Table 7. Injectable biomaterials

Authors (ref)	Year	Agent	# Pts.	Injection technique	# Sites	Volume	Success
Shafik [301]	1993	Polytetrafluoroethylene paste	11	Transanal	2	0.5ml	64%
Shafik [302]	1995	Autologous fat	14	Transanal	2	50-60ml	100%
Kumar et al [303]	1998	Glutaraldehyde cross-linked synthetic bovine dermal collagen	17	Transanal	1-3	Up to 2ml	65% pts improved
Malouf et al [304]	2001	PTQ implants	10		1-4	5-11.5ml	60% initial improvement, 20% long-term
Feretis et al [305]	2001	Microballoons with biocompatible hydrogel	6	Transanal	3-5	0.9ml in balloon	Browning-Parks Incontinence score 16 to 5
Davis et al [306]	2003	Carbon-coated zirconium oxide beads	18	Transanal	1-4	1.28ml	83% pts improved CCF-FIS 11.9 to 8.1
Tjandra et al [307]	2004	PTQ implants	82	Intrasphincteric with and without ultrasound	4	2.5ml	CCF-FIS w US: 14.5 to 3 Without US: 14.5 to 11
Stojkovic et al [308]	2006	Glutaraldehyde cross-linked synthetic bovine dermal collagen	73	Transanal	3	1.7ml	63% improved CCF-FIS 10 to 6
Dehli et al [309]	2007	Zuidex	4	Transanal to Submucosal	4	1.4ml	St Marks Incontinence score 19.25 to 15.75, 75% pts impr
Siproudhis et al [310]	2007	Polydimethylsilozane elastomer silicone biomaterial	22	Intrasphincteric	3	2.5ml	No difference in CCF-FIS: 13.8 to 11.7 PMDS, 14.6 to 11.4 placebo
de la Portilla et al [311]	2008	PTQ implants	20	Transsphincteric	3	2.5 ml	CCF-FIS 13.5 to 4.5
Altomare et al [312]	2008	Carbon-coated zirconium oxide beads	33	Transsphincteric	4	8.8ml	CCF-FIS 12 to 8 AMS 89 to 73
Maeda et al [313]	2008	Cross-linked porcine dermal collagen	5	Transsphincteric	3	9ml	St Marks Incontinence score 15 to 12.5
		Polyacrylamide hydrogel	5	Transsphincteric	3	15ml	St Marks Incontinence score 15 to 12.5
		Saline	22				
Ganio et al [314]	2008	Calcium Hydroxylaptatite Ceramic Microspheres	10	Transphincteric to submucosal site	4	1ml	FISS 85.6-28 FIQL impr $^{3}/_{4}$ subsc
Soerensen et al [315]	2009	PTQ silicone biomaterial	33	Transsphincteric to Intrasphincteric	3	2.5ml	CCF-FIS score 12.7 to10.4 18% pts sig impr
Tjandra et al [316]	2009	PTQ	20	Intrasphincteric	4	2.5ml	No complications, more pts with >50% improvement CCF-FIS 11.45 to 3.8 sig impr FIQL and SF12
		Durasphere	20	Submucosal	4	2.5ml	More complications CCF-FIS 11.45 to 7 No change FIQL andSF12
Bartlett & Ho [317]	2009	PTQ	74	Intrasphincteric	4	2.5ml	70% continent CCF-FIS=0 30% CCF-FIS 20 to 3.5
Aigner et al [318]	2009	Durasphere	11	Intrasphincteric to submucosa	3-4	Avg. 2.82ml	CCF-FIS 12.7 to 4.91, FIQL 2/4 subscl improved
Oliveira et al [319]	2009	Silicone PTQ	35	Transsphincteric to intrasphincteric site	3	2.5ml	CCF-FIS 11 to 3.5
Danielson et al [320]	2009	NASHA	34	Transanal to submucosa	4	1ml	# episodes/4wks 22 to 9
Beggs et al [321]	2010	Durasphere	23	Intersphincteric	4	2.8ml	CCF-FIS 18.7 to 10.9 FIQL impro
Stephens et al [322]	2010	Ethylene Vinyl Alcohol EVOH	21	Intrasphincteric	Max 8	1-2ml	FISI 32.8 to 22 CCF-FIS 11 to 6.9 FIQL 2/4 subs impr
Ratto et al [323]	2011	Polyacrylonitrile cylinder	14	Transdermal to intrasphincteric	4	NA	CCF-FIS 12.7 to 5.1 FIQL and SF36 impr
Graf et al [324]	2011	NASHA	136	Transanal submucosal	4	1ml	52% vs. 31% had >50% reduction in incont episodes No difference in CCF-FIS:14 to 2.5 NASHA Dx ,13 to 1.7 placebo
		Placebo	70				

US: endoanal ultrasound guidance
CCF-FIS: Cleveland Clinic Florida Faecal Incontinence Score
FISS: Faecal Incontinence Scoring System
AMS: American Medical Systems score
FISI: Faecal Incontinence Severity Index

symptomatic improvement at 8 months. A much larger series of 73 patients was then reported [308] in which subjects received injections of 1.7 ml of collagen transanally into the rectal submucosa in three separate areas just proximal to the anal canal. Overall, 63% reported an improvement in their incontinence and the 49 patients with idiopathic incontinence (no sphincter defect and no pudendal neuropathy) had a significant decrease in their Wexner Faecal Incontinence Score (CCF-FIS, range 0-20). The disadvantages of using synthetic collagen are its potential to be allergenic and degrade over time. Furthermore, its success in urinary incontinence has been limited [299].

A pilot study conducted in 2008 examined two other products, cross-linked porcine dermal collagen (Permacol), and polyacrylamide hydrogel (Bulkamid) [313]. Ten patients with passive faecal incontinence to liquid or solid stool who had failed conventional treatments were prospectively randomised to receive either of the two products. The needle was first inserted into the skin 2 cm from the anal margin and the product was then injected trans-sphincterically. The median volume to achieve closure of the anal canal under direct vision was 9 ml for Bulkamid and 15 ml for Permacol. The St Mark's incontinence score decreased at 6 weeks for both groups, but this decrease was sustained at 6 months only for the Bulkamid group. This pilot study lacked power to determine if these two treatments for faecal incontinence differed significantly. Unfortunately, no other follow-up studies have been reported.

Several other injectables have been used for faecal incontinence with variable results. In one of the few adequately powered, randomised controlled trials using injectables, 44 patients were randomised to receive transdermal injections of polydimethylsilozane elastomer silicone biomaterial (PDMS) or saline into the intersphincteric space [310]. Three 2.5ml injections were performed using local anesthesia. Only the patients were blinded to the treatment. There was no difference in the percentage of patients in the two groups who had a successful treatment, defined as having a CCF-FIS score <8 or the decrease in CCF-FIS scores post treatment. The saline group tolerated treatment better and had fewer adverse effects overall. Thus, the study concluded that the use of PDMS should not be recommended.

Three smaller studies using other products have shown some promise although the testing was much less rigorous. In one of these studies, calcium hydroxylaptatite ceramic microspheres (Coaptite) were injected transphincterically to four submucosal sites using 1ml at each site with the patient under local anesthesia. The average Faecal Incontinence Scoring System (FISS) score for 10 patients decreased from 85.6 to 28 at 12 months (p=0.008) and the lifestyle, coping and behavior/embarrassment subscales of the Faecal Incontinence Quality of Life Scale (FIQL) showed improvements (p<0.05). Anorectal manometry also showed better resting pressures (40 to 47 mmHg, p=0.018). There were no complications, but one patient experienced leakage of product from the injection site that required another injection [314]. In the second of these smaller studies, 21 patients received ethylene vinyl alcohol (EVOH) injections with 1-2 ml in up to 8 sites in the intersphincteric space under general or local anesthesia. At 12 months, Faecal Incontinence Severity Index (FISI) scores dropped from 32.8 to 22 and CCF-FIS scores decreased from 11 to 6.9. Two subscales of the FIQL improved significantly and repeat anorectal manometry demonstrated some increase in anal canal length and resting pressures [302]. The third and most recent of these small studies reported on 14 patients who received transdermal injections of polyacrylonitrile cylinders (Gatekeeper prosthesis) into the intersphincteric space. The CCF-FIS score decreased from 12.7 to 5.1(p<0.01) and there were no complications. Location of the prostheses was documented by ultrasound and no dislodgement was seen at 1 year [323].

The two most common injectables used to treat faecal incontinence are silicone biomaterial (Macroplastique, Bioplastique, PTQ implants) and pyrolytic carbon-coated zirconium oxide beads (Durasphere). Injectable silicone biomaterial has been used extensively for urinary incontinence. It consists of polydimethylsiloxane particles suspended in a bioexcretable carrier hydrogel of polyvinylpyrrolidone. Two pilot studies using Bioplastique for faecal incontinence in 2001 and 2002 [304,326] led to increased use of this product in Europe and it was renamed PTQ implants (PTP implants in Australia). Malouf et al [304] studied 10 patients with passive incontinence who received circumferential or single site injections of Bioplastique. At six weeks, six patients showed either marked improvement or complete cessation of leakage and an additional patient improved after a second injection. However, after six months, only two of seven patients had maintained marked improvement. Complications included anal pain and ulceration at the injection site. In the largest study of PTQ injection to date [307] 82 patients with severe faecal incontinence were randomised to receive PTP implants either with or without endoanal ultrasound guidance for injection. All patients had a significant improvement in their CCF-FIS. At 12 months, this score decreased from 14.5 to 3 in the ultrasound guidance group and from 14.5 to 11 in the non-ultrasound group. Six patients, two from the ultrasound guidance group, complained of pain at the injection sites. There were no other complications. The ultrasound guidance group had more significant improvement in resting pressures and quality of life scores. The same investigators injected PTQ into seven patients with passive incontinence after haemorrhoidectomy and found significant improvement CCF-FIS and quality of life scores in all patients [327].

Several other series have been reported PTQ use for faecal incontinence [311,315,317,319]. In all of them, 2.5ml of product was injected into 3-4 sites in the intersphincteric space and CCF-FIS decreased significantly. In one study of 20 patients, the CCF-FIS decreased significantly from 13.5 to 4.5 at one month and slowly increased to 9.4 at two years, which was a still a significant improvement from the baseline score. Quality of life scores also improved, but there was no effect on resting and squeeze pressures measured at baseline and 3 months after injection. Seventy percent of patients experienced pruritus ani and one patient developed an infection at an injection site [311]. In a study of 33 patients, CCF-FIS decreased from 12.7 to 10.4 at one year, yet quality of life was not improved [315]. Both of these studies examined implant migration and 63-84% of patients had detectable implants at the site of injection by ultrasound, though this did not seem to affect clinical response. The largest of these studies is notable for its sample size of 74 patients and that half of these subjects were men. It found that 70% of patients reported complete satisfaction with their continence (post-treatment CCF-FIS =0) and in the remaining 30%,CCF-FIS decreased from 12 to 3.5 at 33 months with associated improvements in quality of life measures. All patients, but especially those who became continent, had significant improvements in mean resting pressures, squeeze pressure and mean anal canal length. Worse results were seen in women with pudendal neuropathy or those for whom biofeedback had already failed [317]. Another study specifically compared the anorectal manometry of patients injected with PTQ with that of normal controls and found that after injection in the symptomatic patients there was a similar decrease in CCF-FIS with associated improvements in FIQL scores. The symptomatic patients had lower resting and squeeze pressures than controls at baseline and these pressures did not improve with injection. However, these patients did have elongation of their high pressure zone, as well as improvements in the asymmetry index, indicating that morphologic but not physiologic changes had occurred with injection [319]. The only report of long-term results for injectable agents was for Bioplastique [328].The 5-year outcome for 6 patients injected with Bioplastique in 1999 included a median St. Mark's incontinence score that was essentially unchanged from 11 to 13 (range 9-20). One patient had undergone a colostomy, but four of the five remaining patients reported subjective improvement in their incontinence and better quality of life scores.

The other commonly used injectable, Durasphere, is non-reactive and not biodegradable. However, the beads are known to migrate within the tissues and require a large bore needle to inject the substance. The injected substance is placed in the submucosal plane using either a transanal or intersphincteric approach. The initial trial [306] assessed the short and long-term efficacy in 18 patients with an internal anal sphincter defect refractory to conservative management. About 1.3ml was injected in the submucosal plane at the site of the sphincter defect in 1-4 sites until adequate anal sphincter symmetry was restored. At 12 months, CCF-FIS and patient satisfaction scores were significantly improved. Fifteen of 18 patients reported improvement in their incontinence. An abstract presented by Weiss et al [329] also demonstrated improvement in ten patients who were only followed for 3 months. In a larger study, 33 patients with minor or medium severity faecal incontinence (CCF-FIS < 14 and/or American Medical Systems (AMS) score < 89) received injections (mean of 8.8 ml (range 2-19 ml) of Durasphere into the submucosa at the level of the dentate line using an 18-gauge needle at four different sites [312]. After a mean follow-up period of 21 months, the CCF-FIS for the group decreased significantly from 12 to 8 and the AMS score from 89 to 73 but the faecal incontinence specific quality of life measures did not change. Resting and squeeze pressures also increased 12 months after injection. Adverse events included anal pain in two patients, asymptomatic leakage of material in one patient, and distal migration of product in two patients. A study of 11 patients in which about 2.8ml of Durasphere was injected into 3-4 sites in the submucosal space reported a decrease in CCF-FIS from 12.7 to 4.9 at 2 years with improvements in the coping and embarrassment subscales of the FIQL at 6 months. Although manometry pressures did not change initially, the resting and cough pressures were higher at 2 years than at 1 year [318].

The most recent study using Durasphere injected the product using a slightly different approach. In all 23 subjects, the product was injected into the intersphincteric space in four sites. Again, about 2.8ml of product was injected at each site. At 12 months, patients had a decrease in the CCF-FIS from 18.7 to 10.9 and an increase in FIQL score from 46 to 55.8. Mean squeeze pressures on anorectal manometry increased significantly at 12 months. Adverse complications included prolonged pain in one patient and a sterile perianal fluid collection in another [321].

Only one trial compared the safety and efficacy of PTQ and Durasphere [316]. Sample size was calculated to detect a 50% reduction in the CCF-FIS post injection. Thus, 40 patients with faecal incontinence (mean CCF-FIS 11.45) were randomised to receive either PTQ or Durasphere. Both groups were similar in terms of age, medical history, faecal incontinence severity and quality of life scores, as well as anorectal manometry results. Although the Durasphere group had a more significant reduction in CCF-FIS at 2 weeks (11.45 to 8.25 vs. 11.45 to 10.9), the PTQ group had a greater reduction in CCF-FIS at 6 weeks, 6 months and 12 months (4.6,2.95 and 3.8 vs. 7.65, 6.2 and 7), and had no complications. The Durasphere group had several complications including anal pain (5%), mucosal erosion (10%),

arthritis and skin rashes (5%). Furthermore, the PTQ group demonstrated significant improvements in general and faecal-incontinence-specific quality of life scores that were not seen in the Durasphere group. Thus, the conclusion was that PTQ was safer and more effective than Durapshere for the treatment of faecal incontinence [316].

The newest injectable agent to be used for faecal incontinence is dextranomer- hyaluronic acid co-polymer (Zuidex, NASHA Dx). Dextranomer microspheres are suspended in non-animal stabilized hyaluronic acid. As with other injectable agents, Zuidex has been used to treat urinary incontinence [330] and a pilot study of four patients reported no adverse events and a median decrease in St Marks incontinence score of 3.5 points(19.25 to 15.75) [309]. In a subsequent study of 34 patients who received transanal injections into the submucosa just above the dentate line (about 1ml of product was injected into four sites), the median number of incontinent episodes in a four-week period dropped from 22 to 9 [320]. When response was defined as a 50% or greater decrease in number of incontinent episodes, 56% of patients were defined as responders at 12 months. No adverse events were reported. These findings led to a randomised double-blinded sham-controlled trial of 206 patients randomised in a 2:1 fashion to receive NASHA Dx or placebo injection [324]. The patients and the evaluating investigators were blinded to the treatment. More patients in the treatment group had 50% or greater reduction in the number of incontinence episodes (52% versus 31% of controls; p=0.009), but the change in CCF-FIS did not differ after treatment between groups (14 to 2.5 in the treatment group vs. 13 to 1.7 in placebo group). The FIQL was only significantly improved compared to placebo for the coping and behavior subscale. Both groups had a high retreatment rates: 82% of patients in the NASHA Dx group received reinjection of product and 87% of patients in the control group had repeat sham injection. The NASHA Dx group had significantly more adverse events, including proctalgia, rectal bleeding, pruritus, diarrhoea, constipation, fever, and two serious complications of rectal abscess and prostatic abscess. The control group had more injection site bleeding [324]. The most recent study of NASHA Dx was reported in an abstract of 21 patients who received injections of 1ml of product in four sites of submucosa. There were no adverse events and 61% of patients had a significant decrease in incontinence episodes at 3 months and 56% had a sustained improvement at 22 months. The CCF-FIS decreased from 16.8 to 12.3 but was not significant. Improvement in FIQL scores were noted [331].

In summary, studies of injectable biomaterials comprise several small case series that in general show short-term efficacy and only three randomised trials, two of which compared PMDS and NASHA Dx to placebo, and a third that compared PTQ to Durasphere. These trials indicated that PMDS should not be used, PTQ appears to be better than Durasphere in terms of both safety and efficacy, and that NASHA Dx has some evidence of efficacy compared to placebo. Two systematic reviews [332,333] and a Cochrane review [334] have been published recently that review the data for all injectable agents for faecal incontinence. Due to the poor methodology and small sample sizes of most of these studies, none of these reviews could establish adequate evidence to support the efficacy of any of these agents. However, one review did find that in a multivariate analysis, use of the intersphincteric, instead of transanal or trans-sphincteric routes of injection, was associated with a higher complication rate. Furthermore, PTQ and Coaptite were significant predictors of short-term outcome and use of local anesthesia was associated with a lower likelihood of success [332]. [**LEVEL OF EVIDENCE: 3**]

10. COLOSTOMY

A permanent colostomy is usually formed as a last resort for severe faecal incontinence when all other interventions have failed. Because colostomy is generally regarded as a failure of treatment, its effectiveness, perioperative complications, and impact on the quality of life have never been properly evaluated except for patients with functional bowel disorders after spinal cord injury [335,336]. For a specific role of colostomy for these patients, please refer to the specific chapter. Not only for patients with spinal cord injury, but also for general population with severe faecal incontinence, colostomy is a frequently successful management strategy that restores dignity and allows them to regain social function.

No randomised controlled trials or non-randomised cohort studies have been reported regarding colostomy for faecal incontinence, and only one systematic review (level 4) [188], one case control study (level 4) [337] and two case series (level 4) [338,339] were identified.

Colquhoun et al [337] conducted a cross-sectional postal survey, comparing quality of life between 71 patients with faecal incontinence and 39 with a colostomy created for rectal cancer, complicated colonic diverticular disease or faecal incontinence. Analysis of the Short Form 36 General Quality of Life Assessment revealed significantly higher social function score in the colostomy group than in the faecal incontinence group (0 vs. -0.6, p=0.022). An age- and gender-adjusted regression analysis of the Faecal Incontinence Quality of Life score revealed significantly higher scores in the coping (2.7 vs. 2.0, p=0.005), embarrassment (2.7 vs. 2.2, p=0.014), and lifestyle scales (3.2 vs. 2.7, p=0.14) in the colostomy group compared to the faecal incontinence group. The authors concluded that a colostomy is a viable option for patients who suffer from severe faecal incontinence and offers a definitive cure with improved quality of life.

Tan et al [188] performed a systematic review, specifically comparing the cost-effectiveness between end stoma (ES), artificial anal sphincter (AAS) and

dynamic graciloplasty (DG). The quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER) were compared between the three procedures, by obtaining the probability estimates for patients with faecal incontinence from published data, with being supplemented by expert opinion. The end stoma was the most cost-effective therapy at 5 years, with a QALY gain of 3.45 for GB£16,280 and an ICER of GB£4,719 /QALY, compared to AAS (4.38 for GB£23,569; GB£5,387 /QALY) and DG (4.00 for GB£25,035; GB£6,257/QALY). After 10 years, AAS became the most cost-effective surgical intervention, with a QALY gain of 8.384 for GB£32,397 and an ICER of GB£3,864/QALY, compared to ES (6.9 for GB£27,910; GB£4,046 /QALY) and DG (7.678 for GB£35,165; GB£4,580 /QALY). The results of this study, however, must be interpreted with great caution, because it is not an interventional study but a systematic review with a rather complicated methodology and a variety of possible biases.

Norton et al [338] examined patients' view of a colostomy by conducting a questionnaire study of patients who had a colostomy created to manage their faecal incontinence. Sixty-nine people (58 women) responded. When patients were asked to rate their ability to live with their stoma now on a scale of 0-10, the median score was 8 (range 0 – 10). The majority (83%) felt that the stoma, within the past month, restricted their life "a little" or "not at all". Eighty-four percent answered that they would "probably" or "definitely" choose to have the stoma again. When they were asked the question "compared to when you were incontinent, how much change has having a stoma made to your overall quality of life?" on the scale of -5 (much worse) to +5 (much better), the median rating was +4.5 (range -5 to +5). The authors concluded that health care professionals should discuss the option of a stoma with incontinent patients because of the overwhelming positive outcomes.

An end sigmoid colostomy without proctectomy is usually recommended as a procedure of choice for patients who elect colostomy for the management of their refractory faecal incontinence. Creating such a colostomy, however, does not always solve all the problems of patients with faecal incontinence. Catena et al [339] reported a retrospective chart review of 44 patients (35 women) who underwent elective end sigmoid colostomy for faecal incontinence of various etiologies. After colostomy formation 19 patients (43%) were asymptomatic, while the other 25 experienced such problems with their rectal stump as diversion colitis and mucus leakage. Of the 25 patients, 12 (27% of the total) underwent a secondary proctectomy due to the rectal stump problems sufficient to warrant the operation. Histological examination revealed diversion colitis in 6 patients. The factor associated with proctectomy was age, with younger patients being more likely to require rectal excision. The authors concluded that data are insufficient to recommend primary proctectomy in patients with severe faecal incontinence warranting permanent end sigmoid colostomy.

11. PUBORECTAL SLING

The puborectal sling operation was first reported by O'Rourke in 1974 [340]. In this procedure, an artificial sling is routed behind the anorectal junction and its two ends are fixed to the pubic bone, pulling the anorectal junction up forward with some tension. Similar to the postanal repair, the rationale of this operation is the restoration of the anorectal angle normally maintained by puborectal muscle. For the treatment of female urinary stress incontinence, a similar procedure, called tension free vaginal tape (TVT), has been performed with a reasonable success rate of 81-93% [341].

No systematic reviews, non-randomised cohort studies or case control studies have been reported regarding puborectal sling operation for faecal incontinence, whilst one prospective comparative study (level 2) [342], one case series of good quality (level 3) [343] and three case series of low quality (level 4) [340,344,345] were identified. Results of the puborectal sling operation are shown in **Table 8** [340,342-345].

O'Rourke [340] first reported the sling operation using Dacron mesh for the treatment of 3 patients with full rectal prolapse as well as 4 with mucosal partial rectal prolapse and faecal incontinence. Two patients developed a sinus or sinus discharge at the site of the insertion of the sling, and the sling was removed in one. Out of the 4 patients with faecal incontinence and partial prolapse, 3 were reported to have "benefited considerably" from the procedure although a formal evaluation of the faecal incontinence was not performed and the follow-up period was not documented.

Table 8. Puborectal sling

Authors (ref)	year	Study design	Material used	No of pts	mean or median follow-up (mo)	No (%) of functioning slings	Overall Complication	"Success" in patients with a functioning sling	"Success" in intention to treat	Evidence level
O'Rourke [340]	1974	case series	Dacron band sling	4	ns	4 (100%)	25%	75%	75%	4
O'Rourke & Egerton [344]	1985	case series	rolled mersilene mesh	2	ns	ns	ns	ns	ns	4
Shafik [345]	1991	case series	Teflon sling	31	24-48	31 (100%)	3%	84%	84%	4
Yamana et al [343]	2004	case series	polyester mesh sling	8	6	7 (88%)	25%	100%	88%	3
Shafik & Shafik [342]	2009	PCS	two fascia lata slings	22	12	22 (100%)	9%	64%	69%	2
			one fascia lata sling	22	12	22 (100%)	0%	36%	69%	
PCS: prospective comparative study ; ns: not stated										

O'Rourke and Egerton [344] reviewed 24 patients in whom the sling operation was performed using a strip of rolled mersilene mesh. This procedure, however, was performed mainly for the treatment of rectal prolapse, while it was conducted because of faecal incontinence alone only in two out of the 24 patients, and the outcomes regarding the continence were not formally evaluated.

Shafik [345] reported another sling operation called puborectoplasty utilizing a Teflon sling for faecal incontinence. Out of the 31 patients who had been incontinent to solid stool and underwent this procedure, "good results" were achieved in 26 patients (84%) after a follow-up period of between 2 and 4 years: 20 became continent to solid and liquid stool as well as flatus; 6 to solid and liquid stool but not to flatus; 4 to solid stool only; and only one remained incontinent to solid stool. Postoperative complications included a wound infection only in one patient, which responded to antibiotics without requiring the sling removal.

Shafik and Shafik [342] conducted a prospective study comparing two fascia lata slings (double loop) in 22 patients and one fascia lata sling (single loop) in 22 for the treatment of faecal incontinence. After 12 months follow-up, "good results" were achieved in 14 (63%) and 8 (36%) by the double loop and the single loop, respectively, and its difference was statistically significant. Postoperative complications included superficial infection in two patients of single loop, which responded to antibiotics without requiring the sling removal.

Yamana et al [343] performed the perineal puborectalis sling operation in 8 patients with passive faecal incontinence using polyester mesh sling. A wound infection developed in one patient which responded to antibiotics, while a rectal ulcer developed in one requiring the sling removal. In the 6 month evaluation of the remaining 7 patients, all reported some extent of improvement of their faecal incontinence. Both the Faecal Incontinence Severity Index and the Cleveland Clinic Faecal Incontinence Score significantly improved from 27 to 9 and from 13 to 5, respectively. Moreover, all parameters in Faecal Incontinence Quality of Life Scale significantly improved: lifestyle from 2.1 to 3.6; coping/behavior from 1.5 to 3.4; depression/self perception from 2.3 to 3.7; and embarrassment from 2 to 3.6.

III. SURGERY FOR PAEDIATRIC FAECAL INCONTINENCE

Faecal incontinence is common in children who have anorectal malformations, spinal problems and surgery for Hirschsprung's disease. Despite advances in technique for anatomic corrective surgeries, many patients continue to suffer from persistent incontinence. This guideline mainly focuses on anorectal malformations and corrective surgeries along with their results and subsequent management in case of persistent incontinence. Other surgical interventions used less frequently were also reviewed.

1. ANORECTAL MALFORMATIONS

Anorectal malformations occur once in every 3000-5000 live births. Although the severity of malformation varies, it is invariably associated with defaecatory problems including incontinence. The surgical advances have been most prominent in last few decades, particularly with the advent of posterior sagittal approach. [**LEVEL OF EVIDENCE: 3**] This technique has enabled surgeons to visualise the anatomy under direct vision and perform corrective surgeries more accurately [346,347]. In brief, a mid-sagittal incision is performed and the sphincter mechanism is completely divided in the midline. The rectum is separated from the genitourinary tract and moved down to the perineum. The most challenging aspect of the operation is the separation of the rectum from the vaginal or urinary tract, which effectively requires creating two walls out of one septum without damaging each structure. This approach can also used for reoperation in anorectal malformations [348] and can also be applied for reconstruction of severe perineal trauma [349].

For both male and female babies, urethral-perineal fistula is the simplest fistula to correct. These require the so-called 'minimal posterior sagittal approach' which enlarges the stenotic orifice and relocates the rectal orifice posteriorly within the limits of the sphincter complex. For males with recto-urethral-bulbar fistula or recto-urethral-prostatic fistula and females with recto-vestibular fistula or cloaca with short (less than 3cm) common channel, posterior sagittal approach is the main operation performed. For males with higher fistulas such as recto-bladder neck fistula and other complex and unusual defects and females with cloaca with long (greater than 3cm) common channel and complex defects, the posterior sagittal approach needs to be coupled with abdominal access which can be either laparoscopy or laparotomy [350]. There has been no robust evidence to suggest superiority of laparoscopy in terms of outcome [351,352] though better visualisation and assessment of fistula have been advocated as an advantage of this approach [353,354].

Cloacal repair is the most challenging amongst the corrective surgeries for anorectal malformations. A recent operative advance in cloacal repair is a maneuver called total urogenital mobilization whereby the rectum is separated from the vagina and both vagina and urethra are then mobilized together. The advantage of this technique is to avoid separating rectum, vagina and urethra completely which is not feasible all the time and risks damaging these structures during the procedure. This technique avoids the risk of urethrovaginal fistula and vaginal stricture previously reported as complications in 10% of the cloacal repair and also gives enough mobilization to allow more than 50% of all cloacal repairs without opening the abdomen [355,356].

Functional outcomes depend on the severity of the malformations. A review of more than 1000 anorec-

tal malformation cases showed 100% of babies who had perineal fistula repair achieved continence. Approximately 55% of patients who had been operated for recto-vestibular fistula had bowel control. Any malformations more complicated resulted in only up to 30% achieving continence. All patients who had recto-bladder neck fistula repair were incontinent. In cloacal repair the length of the common channel, shorter or longer than 3cm, appears to be the distinct prognostic factor in terms of functional outcome [357]. Overall it is estimated that nearly 40% will have voluntary bowel movement and no soiling but some of them may still lose bowel control in case of severe diarrhoea and 25% of all repairs will result in total incontinence [358].

For the group of patients with persistent incontinence following the corrective surgery, the next aim will be to keep the colon clean to avoid unpleasant accidents and improve quality of their life. A good option is implementation of a bowel management programme whereby the patient and family are instructed in the use of daily enema, manipulation of diet and medication to remain clean [359]. This is also a good treatment for constipation, which is the most common difficulty after corrective surgery [360].

Although most young children accept their parents administering enemas, when they get older they want privacy and rectal enemas on daily basis becomes an unpleasant routine. In such cases, continent appendicostomy is a feasible option, whereby a conduit for the administration of an antegrade continence enema (ACE) is created. First described by Malone [361] it has become an important option in paediatric surgery for functional bowel disorder.

According to the initial description by Malone, appendicostomy was created by dividing the appendix at its base and reimplanting by a reverse manner into the cecum, which was then exteriorized through the right lower quadrant. Malone later revised it and the reimplantation of appendix is no longer considered necessary [362]. Levitt et al [363] introduced utilizing the appendix in situ and added caecal plication to prevent reflux of stool and exteriorizing through umbilicus fold rendering it less noticeable. This appears to yield good long-term results [364] though a recent study has shown that caecal fixation and wrap may be unnecessary for appendicostomy [365]. The benefit of a variation called orthotopic continent appendiceal stoma is not clear [366]. However, construction of appendicostomy with burial of the appendiceal tip appears to help avoid problems of exposed mucosa such as bleeding and mucus discharge. From this perspective, a few techniques have been suggested such as V-Y flap [362] and Y-appendicoplasty [367]. For patients without an appendix, a neoappendix could be formed from ileum or cecum [368-370]. Laparoscopic antegrade continence enema procedure has been reported to yield as good result as open procedure [371-374].

This procedure is not a cure to the problem but a more acceptable method for many children to engage in a bowel management programme without the need for rectal enemas. Success rate is variable between 61-96% [362,368,375-379] with older children benefiting more [380]. Satisfaction with the treatment is reported to be as high as 93% [363,381,382]. [**LEVEL OF EVIDENCE 3**]

As with any operation, there are known complications associated with antegrade continence enema. Stomal stenosis is the most common complication and the use of ACE stopper will prevent it in the short-term [383]. Leakage of stool from appendicostomy is another common complication. These complications cause 10-33% of patients to undergo revision of the appendicostomy [358,384]. Stoma prolapse, pressure sore, wound infection, anastomotic leak, stomal granulation, caecal-flap necrosis and caecal volvulus are less common complications reported after ACE [385-387].

2. OTHER CAUSES OF FAECAL INCONTINENCE

Some children with Hirschsprung's disease following pull-through operations and severe constipation may also present with symptoms of incontinence [388]. Patients with spinal problems often lack bowel control due to paralysis and absence of sensation; 50% of the children with spina bifida suffer from incontinence [389]. The majority of these cases can be successfully managed with above mentioned bowel management programme including appendicostomy although wheelchair-bound children with spinal neuropathy is a predictive factor for poorer outcome with ACE [377].

The mechanism of incontinence after an operation for Hirschsprung's disease, anorectal malformations and severe constipation is thought to be due to impaired bowel motility. Impaired bowel motility causes faecal impaction, which can lead to development of a dilated segment of bowel called 'megarectosigmoid'. This can subsequently lead to overflow incontinence due to incomplete evacuation [390]. Once the rectum is dilated it is refractory to conservative management, and resection of megarectum or megasigmoid has been associated with improvement [390-392]. A small minority of patients (5%) who fail these options may need colostomy [393].

3. OTHER OPERATIONS

Sphincter augmentation by either palmaris longus transposition, gluteus muscle transposition, graciloplasty or levatorplasty has been used for children with faecal incontinence albeit in small series [394-403]. Dynamic graciloplasty has also been piloted and 50% of patients achieved complete continence although the study only contained four patients [404]. Sacral nerve stimulation has been used in a small open label study with nearly 80% of positive response [405]. [**LEVEL OF EVIDENCE: 4**]

IV. CONCLUSIONS

Data regarding the surgical treatment of faecal incontinence are generally weak. Randomised, controlled studies are few, and practical considerations make the likelihood of such studies improbable. The quality of data reported in older studies was often poor. Problems included heterogeneous patient populations; variable definitions of “continence,” “incontinence,” “success,” and “failure”; non-standardized and non-validated continence scales; underreporting of validated symptom-specific quality of life measures; variable patient follow up and lack of independent assessment of continence outcomes. However, there has been a notable improvement in the quality of studies reported in the past decade.

The spectrum of surgery for faecal incontinence is broad and expanding. Interventions range from simple outpatient procedures to major reconstructive surgery. As the reported outcomes of these various operations are often similar, a sound general principle is to proceed first with the simplest and least invasive procedure. Major operations associated with more profound morbidity should be restricted to patients who have failed simpler measures.

1. SPHINCTER REPAIR (GRADE B)

Sphincter repair is indicated for patients with acute traumatic sphincter disruption, such as following obstetrical injury, but many patients experience persisting symptoms.

2. SPHINCTEROPLASTY (GRADE B)

Overlapping sphincteroplasty can be offered to patients with significant faecal incontinence and a documented sphincter defect. Most patients improve after sphincteroplasty, but outcomes deteriorate over time.

3. POST-ANAL REPAIR (GRADE C)

Post-anal repair can be performed with modest success in carefully selected patients. However, this procedure is now rarely performed due to the advent of newer treatments.

4. NON-STIMULATED MUSCLE TRANSPOSITION (GRADE C)

Non-stimulated muscle transposition repair can be performed with modest success in carefully selected patients, notably in children. However, this procedure is now rarely performed due to the advent of newer treatments.

5. STIMULATED MUSCLE TRANSPOSITION (GRADE C)

Stimulated muscle transposition has been shown to have reasonable success but is associated with significant morbidity. It remains a useful technique in selected patients with significant perineal tissue loss or in those who have failed other treatments.

6. ARTIFICIAL ANAL SPHINCTER (GRADE B)

Artificial anal sphincter has been shown to have reasonable success but is associated with significant morbidity. It remains a useful technique in carefully selected patients, particularly those who have failed other treatments.

7. SACRAL NERVE STIMULATION (GRADE B)

SNS is an effective therapy for most patients with clinically significant incontinence who fail conservative management. The technique is safe, minimally invasive, and has the unique advantage of allowing a therapeutic trial prior to permanent stimulator implantation.

8. POSTERIOR TIBIAL NERVE STIMULATION (GRADE D)

Posterior tibial nerve stimulation is an investigational technique with few available data regarding efficacy and outcome.

9. INJECTABLE BIOMATERIALS (GRADE C)

Most series of injectable biomaterials report reasonable success rates. However, the optimal injectable bulking agent and the technique for its insertion have not been established.

10. COLOSTOMY (GRADE C)

Formation of an end colostomy is a reasonable treatment option for patients with refractory faecal incontinence who are able to accept the associated alteration in body image. Colostomy provides restoration of a more normal lifestyle and improves quality of life. It also could be the most cost-effective in the short to medium term, compared to more complicated surgical procedures such as artificial anal sphincter and dynamic graciloplasty. Colostomy should not be regarded as a treatment failure but rather a reasonable treatment option for patients whose lives are restricted by faecal incontinence that is not amenable to other therapies. An end sigmoid colostomy alone, without proctectomy, is recommended. The minority of patients who develop significant symptoms from their retained rectal stump may eventually require proctectomy as a secondary procedure.

11. PUBORECTAL SLING (GRADE D)

The puborectal sling operation seems promising because it is a simple procedure and yielded reasonably good results so far with low complication rate, although the number of patients was small with a short follow-up period. More prospective studies of larger number of patients with a longer follow-up period are warranted. They are expected to closely evaluate complications such as sling infection, erosion and rectal ulcer that might require the removal of the sling.

12. SURGERY FOR PAEDIATRIC FAECAL INCONTINENCE (GRADE C)

Anorectal malformations should undergo surgical repair, most commonly by a posterior sagittal repair.

An antegrade continence enema procedure can be considered for children with persistent or refractory faecal incontinence.

V. RESEARCH PRIORITIES

Despite steady progress in the clinical management of faecal incontinence, including the development of novel treatment methods since the last International Consultation, there remain numerous areas where additional research is needed.

1. BASIC SCIENCE AND PATHOPHYSIOLOGY

Several animal models of faecal incontinence have now been developed that are capable of provided interesting insights into the physiology of normal continence and the pathophysiology of faecal incontinence [223,406-412]. Further use of these and other animal models can be expected to yield valuable information about pathophysiology and treatment, and is strongly encouraged.

2. CELLULAR THERAPY

There is a body of basic research on the use of stem or precursor cells of different tissue of origin (muscle, fat, bone marrow) in supplementation of urinary continence [413]. Recently, Frudinger and colleagues[414] have reported successful treatment of faecal incontinence using autologous myoblasts cultured from a pectoralis muscle biopsy, harvested, and injected into the external anal sphincter defect using ultrasound guidance. Further research relating to the tissue of origin, harvesting and processing of graft cells, the technique of implantation and clinical outcomes is urgently needed.

3. OUTCOME MEASURES

While there is general agreement that patient-based outcome measures are most appropriate for studies of faecal incontinence, standardization of the optimal instrument or combination of instruments remains a central challenge in clinical incontinence research. These instruments should be selected based upon eight general criteria and applied to the specific field of faecal incontinence: appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility [415].

It is unknown if the main outcome measure following incontinence treatment ought to be incontinence severity, incontinence-related quality of life, or a combination of these factors. The FIQL is a well-validated quality outcome measure but it yields separate scores on 4 individual scales. It is desirable that a single score outcome be developed. Furthermore, quantitative changes in FIQL have not been anchored to the corresponding impact on patient quality of life and thus remain rather abstract. Additional studies, for example using time trade-off techniques, are needed to understand the clinical meaning of a given change in FIQL.

The FISI severity score is not as broadly used as the FIQL, and it appears to require additional validation work. Continence diaries have been considered to be the gold standard measurement, but these are highly influenced by the patient's willingness to stray from a nearby toilet. Standard definitions are needed for such terms as seepage and leakage, and a standardized measure of faecal urgency should be developed. Additional validation work is needed to assess the potential effect of recall bias in recall-based scoring systems such as the Wexner and Vaizey scales. The International Consultation on Incontinence Bowel module (ICIQ-B) has recently been developed, but additional experience with this instrument is required [416].

4. CLINICAL TRIALS

There remains a paucity of randomized, controlled trials in the field of faecal incontinence. Proof of efficacy of novel therapies, numerous in the field of faecal incontinence therapy, is best demonstrated using a randomized trial design, and these types of studies are strongly encouraged.

Long-term outcomes following sphincteroplasty have demonstrated a substantial fall-off in function over many years. Similar long-term data are not available for other therapies, including especially the more recently developed ones such as SNS and injection therapies. Prospective trials funded for long-term follow-up and creation of treatment specific registries are needed.

Much recent research has been industry funded and designed to assess the efficacy of a specific novel therapy. There have been very few studies prospectively comparing different treatments, and randomized comparative treatment trials are urgently needed. The Committee has in particular noted the need for a randomized trial of SNS versus sphincteroplasty for individuals with faecal incontinence associated with a sphincter injury.

5. DECISION AND COST-BENEFIT ANALYSIS

Given the broad range of potential treatments for faecal incontinence and the usual costly proposed devices, additional research is needed in the areas of decision analysis and cost-benefit analysis. In severe faecal incontinence a comparison against stoma care cost would be appropriate.

6. TREATMENT DELIVERY

While there is ongoing research on the epidemiology of faecal incontinence, little is known about the true number of patients who have had treatment, who have access to treatment, or who have adequate knowledge to seek treatment. Research should be directed to identify current treatment needs, improve the accessibility of treatment, and improve the transmission and distribution of information about acceptable treatment options.

REFERENCES

1 Malouf AJ, Norton CS, Engel AF, Nicholls RJ, Kamm MA: Long-term results of overlapping anterior anal-sphincter repair for obstetric trauma. Lancet 2000;355:260-265.

2 Halverson AL, Hull TL: Long-term outcome of overlapping anal sphincter repair. Dis Colon Rectum 2002;45:345-348.

3 Parks AG: Royal society of medicine, section of proctology; meeting 27 november 1974. President's address. Anorectal incontinence. Proc R Soc Med 1975;68:681-690.

4 Brown SR, Nelson RL: Surgery for faecal incontinence in adults. Cochrane Database Syst Rev 2007:CD001757.

5 Fitzpatrick M, Cassidy M, O'Connell PR, O'Herlihy C: Experience with an obstetric perineal clinic. Eur J Obstet Gynecol Reprod Biol 2002;100:199-203.

6 Sultan AH, Kamm MA, Hudson CN, Thomas JM, Bartram CI: Anal-sphincter disruption during vaginal delivery. N Engl J Med 1993;329:1905-1911.

7 Donnelly V, Fynes M, Campbell D, Johnson H, O'Connell PR, O'Herlihy C: Obstetric events leading to anal sphincter damage. Obstet Gynecol 1998;92:955-961.

8 Oberwalder M, Connor J, Wexner SD: Meta-analysis to determine the incidence of obstetric anal sphincter damage. Br J Surg 2003;90:1333-1337.

9 Williams AB, Bartram CI, Halligan S, Spencer JA, Nicholls RJ, Kmiot WA: Anal sphincter damage after vaginal delivery using three-dimensional endosonography. Obstet Gynecol 2001;97:770-775.

10 Zetterström JP, López A, Anzén B, Dolk A, Norman M, Mellgren A: Anal incontinence after vaginal delivery: A prospective study in primiparous women. Br J Obstet Gynaecol 1999;106:324-330.

11 Fitzpatrick M, McQuillan K, O'Herlihy C: Influence of persistent occiput posterior position on delivery outcome. Obstet Gynecol 2001;98:1027-1031.

12 Harkin R, Fitzpatrick M, O'Connell PR, O'Herlihy C: Anal sphincter disruption at vaginal delivery: Is recurrence predictable? Eur J Obstet Gynecol Reprod Biol 2003;109:149-152.

13 Eogan M, Daly L, O'Connell PR, O'Herlihy C: Does the angle of episiotomy affect the incidence of anal sphincter injury? BJOG 2006;113:190-194.

14 Clemons JL, Towers GD, McClure GB, O'Boyle AL: Decreased anal sphincter lacerations associated with restrictive episiotomy use. Am J Obstet Gynecol 2005;192:1620-1625.

15 Dudding TC, Vaizey CJ, Kamm MA: Obstetric anal sphincter injury: Incidence, risk factors, and management. Ann Surg 2008;247:224-237.

16 Royal college of obstetricians and gynaecolgists. third- and fourth-degree perineal tears, management (green-top 29), 2008;

17 Fernando RJ, Sultan AH, Kettle C, Radley S, Jones P, O'Brien PM: Repair techniques for obstetric anal sphincter injuries: A randomized controlled trial. Obstet Gynecol 2006;107:1261-1268.

18 Mahony R, Behan M, Daly L, Kirwan C, O'Herlihy C, O'Connell PR: Internal anal sphincter defect influences continence outcome following obstetric anal sphincter injury. Am J Obstet Gynecol 2007;196:217 e211-215.

19 Roos AM, Thakar R, Sultan AH: Outcome of primary repair of obstetric anal sphincter injuries (oasis): Does the grade of tear matter? Ultrasound Obstet Gynecol 2010;36:368-374.

20 McNicol FJ, Bruce CA, Chaudhri S, Francombe J, Kozman E, Taylor BA, Tighe MJ: Management of obstetric anal sphincter injuries--a role for the colorectal surgeon. Colorectal Dis 2010;12:927-930.

21 Fitzpatrick M, Behan M, O'Connell PR, O'Herlihy C: A randomized clinical trial comparing primary overlap with approximation repair of third-degree obstetric tears. Am J Obstet Gynecol 2000;183:1220-1224.

22 Williams A, Adams EJ, Tincello DG, Alfirevic Z, Walkinshaw SA, Richmond DH: How to repair an anal sphincter injury after vaginal delivery: Results of a randomised controlled trial. Bjog 2006;113:201-207.

23 Garcia V, Rogers RG, Kim SS, Hall RJ, Kammerer-Doak DN: Primary repair of obstetric anal sphincter laceration: A randomized trial of two surgical techniques. Am J Obstet Gynecol 2005;192:1697-1701.

24 Farrell SA, Gilmour D, Turnbull GK, Schmidt MH, Baskett TF, Flowerdew G, Fanning CA: Overlapping compared with end-to-end repair of third- and fourth-degree obstetric anal sphincter tears: A randomized controlled trial. Obstet Gynecol 2010;116:16-24.

25 Rygh AB, Körner H: The overlap technique versus end-to-end approximation technique for primary repair of obstetric anal sphincter rupture: A randomized controlled study. Acta Obstet Gynecol Scand 2010;89:1256-1262.

26 Fernando R, Sultan AH, Kettle C, Thakar R, Radley S: Methods of repair for obstetric anal sphincter injury. Cochrane Database Syst Rev 2006;3:CD002866.

27 Farrell SA: Overlapping compared with end-to-end repair of third and fourth degree obstetric anal sphincter tears. Curr Opin Obstet Gynecol 2011;23:386-390.

28 Parnell BA, Whitehead WE, Geller EJ, Jannelli ML, Connolly A: Overlapping anal sphincteroplasty: Impact of suture selection on bowel symptoms. J Reprod Med 2011;56:187-191.

29 Cook TA, Mortensen NJ: Is there a role for the colorectal team in the management of acute severe third-degree vaginal tears? Colorectal Dis 1999;1:263-266.

30 Nordenstam JF, Zetterstrom J, Lopez A, Johansson C, Anzen B, Parker S, Mellgren A: Operative technique and expertise influence outcome after primary repair for obstetric sphincter injury [abstract]. Dis Colon Rectum 2006;49:729.

31 Soerensen MM, Bek KM, Buntzen S, Hojberg KE, Laurberg S: Long-term outcome of delayed primary or early secondary reconstruction of the anal sphincter after obstetrical injury. Dis Colon Rectum 2008;51:312-317.

32 Andrews V, Thakar R, Sultan AH: Structured hands-on training in repair of obstetric anal sphincter injuries (oasis): An audit of clinical practice. Int Urogynecol J Pelvic Floor Dysfunct 2009;20:193-199.

33 Mahony R, Behan M, O'Herlihy C, O'Connell PR: Randomized, clinical trial of bowel confinement vs. Laxative use after primary repair of a third-degree obstetric anal sphincter tear. Dis Colon Rectum 2004;47:12-17.

34 Eogan M, Daly L, Behan M, O'Connell PR, O'Herlihy C: Randomised clinical trial of a laxative alone versus a laxative and a bulking agent after primary repair of obstetric anal sphincter injury. Bjog 2007;114:736-740.

35 Faltin DL, Boulvain M, Irion O, Bretones S, Stan C, Weil A: Diagnosis of anal sphincter tears by postpartum endosonography to predict fecal incontinence. Obstet Gynecol 2000;95:643-647.

36 Abramowitz L, Sobhani I, Ganansia R, Vuagnat A, Benifla JL, Darai E, Madelenat P, Mignon M: Are sphincter defects the cause of anal incontinence after vaginal delivery? Results of a prospective study. Dis Colon Rectum 2000;43:590-596; discussion 596-598.

37 MacArthur C, Glazener CM, Wilson PD, Herbison GP, Gee H, Lang GD, Lancashire R: Obstetric practice and faecal incontinence three months after delivery. Bjog 2001;108:678-683.

38 Fenner DE, Genberg B, Brahma P, Marek L, DeLancey JO: Fecal and urinary incontinence after vaginal delivery with anal sphincter disruption in an obstetrics unit in the united states. Am J Obstet Gynecol 2003;189:1543-1549; discussion 1549-1550.

39 Samarasekera DN, Bekhit MT, Wright Y, Lowndes RH, Stanley KP, Preston JP, Preston P, Speakman CT: Long-term anal continence and quality of life following postpartum anal sphincter injury. Colorectal Dis 2008;10:793-799.

40 Oom DM, Steensma AB, Zimmerman DD, Schouten WR: Anterior sphincteroplasty for fecal incontinence: Is the outcome compromised in patients with associated pelvic floor injury? Dis Colon Rectum 2010;53:150-155.

41 Fynes M, Donnelly V, Behan M, O'Connell PR, O'Herlihy C: Effect of second vaginal delivery on anorectal physiology and faecal continence: A prospective study. Lancet 1999;354:983-986.

42 Fynes M, Donnelly VS, O'Connell PR, O'Herlihy C: Cesarean delivery and anal sphincter injury. Obstet Gynecol 1998;92:496-500.

43 Nelson RL, Westercamp M, Furner SE: A systematic review of the efficacy of cesarean section in the preservation of anal continence. Dis Colon Rectum 2006;49:1587-1595.

44 Scheer I, Thakar R, Sultan AH: Mode of delivery after previous obstetric anal sphincter injuries (oasis)--a reappraisal? Int Urogynecol J Pelvic Floor Dysfunct 2009;20:1095-1101.

45 Nygaard IE, Rao SS, Dawson JD: Anal incontinence after anal sphincter disruption: A 30-year retrospective cohort study. Obstet Gynecol 1997;89:896-901.

46 Faltin DL, Otero M, Petignat P, Sangalli MR, Floris LA, Boulvain M, Irion O: Women's health 18 years after rupture of the anal sphincter during childbirth: I. Fecal incontinence. Am J Obstet Gynecol 2006;194:1255-1259.

47 Bollard RC, Gardiner A, Duthie GS, Lindow SW: Anal sphincter injury, fecal and urinary incontinence: A 34-year follow-up after forceps delivery. Dis Colon Rectum 2003;46:1083-1088.

48 Eogan M, O'Brien C, Daly L, Behan M, O'Connell PR, O'Herlihy C: The dual influences of age and obstetric history on fecal continence in parous women. Int J Gynaecol Obstet 2011;112:93-97.

49 Mous M, Muller SA, de Leeuw JW: Long-term effects of anal sphincter rupture during vaginal delivery: Faecal incontinence and sexual complaints. Bjog 2008;115:234-238.

50 Fornell EU, Matthiesen L, Sjodahl R, Berg G: Obstetric anal sphincter injury ten years after: Subjective and objective long term effects. Bjog 2005;112:312-316.

51 Donnelly V, O'Connell PR, O'Herlihy C: The influence of oestrogen replacement on faecal incontinence in postmenopausal women. Br J Obstet Gynaecol 1997;104:311-315.

52 Madoff RD: Surgical treatment options for fecal incontinence. Gastroenterology 2004;126:S48-54.

53 Jorge JM, Wexner SD: Etiology and management of fecal incontinence. Dis Colon Rectum 1993;36:77-97.

54 Maeda Y, Pares D, Norton C, Vaizey CJ, Kamm MA: Does the st. Mark's incontinence score reflect patients' perceptions? A review of 390 patients. Dis Colon Rectum 2008;51:436-442.

55 Rothbarth J, Bemelman WA, Meijerink WJ, Stiggelbout AM, Zwinderman AH, Buyze-Westerweel ME, Delemarre JB: What is the impact of fecal incontinence on quality of life? Dis Colon Rectum 2001;44:67-71.

56 Mortele KJ, Fairhurst J: Dynamic mr defecography of the posterior compartment: Indications, techniques and mri features. Eur J Radiol 2007;61:462-472.

57 Altringer WE, Saclarides TJ, Dominguez JM, Brubaker LT, Smith CS: Four-contrast defecography: Pelvic «Floor-oscopy». Dis Colon Rectum 1995;38:695-699.

58 Tjandra JJ, Dykes SL, Kumar RR, Ellis CN, Gregorcyk SG, Hyman NH, Buie WD, Surgeons SPTFoTASoCaR: Practice parameters for the treatment of fecal incontinence. Dis Colon Rectum 2007;50:1497-1507.

59 Donnelly VS, O'Herlihy C, Campbell DM, O'Connell PR: Postpartum fecal incontinence is more common in women with irritable bowel syndrome. Dis Colon Rectum 1998;41:586-589.

60 Fitzpatrick M, O'Brien C, O'Connell P R, O'Herlihy C: Patterns of abnormal pudendal nerve function that are associated with postpartum fecal incontinence. Am J Obstet Gynecol 2003;189:730-735.

61 Fynes MM, Marshall K, Cassidy M, Behan M, Walsh D, O'Connell PR, O'Herlihy C: A prospective, randomized study comparing the effect of augmented biofeedback with sensory biofeedback alone on fecal incontinence after obstetric trauma. Dis Colon Rectum 1999;42:753-758; discussion 758-761.

62 Mahony RT, Malone PA, Nalty J, Behan M, O'Connell P R, O'Herlihy C: Randomized clinical trial of intra-anal electromyographic biofeedback physiotherapy with intra-anal electromyographic biofeedback augmented with electrical stimulation of the anal sphincter in the early treatment of postpartum fecal incontinence. Am J Obstet Gynecol 2004;191:885-890.

63 Norton C, Cody JD, Hosker G: Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults. Cochrane Database Syst Rev 2006;3:CD002111.

64 Hull TL, Bartus C, Bast J, Floruta C, Lopez R: Multimedia article. Success of episioproctotomy for cloaca and rectovaginal fistula. Dis Colon Rectum 2007;50:97-101.

65 Kaiser AM: Multimedia article. Anovaginal reconstruction with bilateral x-flaps and sphincteroplasty for cloaca-like deformity after obstetrical injury. Dis Colon Rectum 2007;50:1707.

66 Kaiser AM: Cloaca-like deformity with faecal incontinence after severe obstetric injury--technique and functional outcome of ano-vaginal and perineal reconstruction with x-flaps and sphincteroplasty. Colorectal Dis 2008;10:827-832.

67 Fleshman JW, Peters WR, Shemesh EI, Fry RD, Kodner IJ: Anal sphincter reconstruction: Anterior overlapping muscle repair. Dis Colon Rectum 1991;34:739-743.

68 Engel AF, Kamm MA, Sultan AH, Bartram CI, Nicholls RJ: Anterior anal sphincter repair in patients with obstetric trauma. Br J Surg 1994;81:1231-1234.

69 Londono-Schimmer EE, Garcia-Duperly R, Nicholls RJ, Ritchie JK, Hawley PR, Thomson JP: Overlapping anal sphincter repair for faecal incontinence due to sphincter trauma: Five year follow-up functional results. Int J Colorectal Dis 1994;9:110-113.

70 Oliveira L, Pfeifer J, Wexner SD: Physiological and clinical outcome of anterior sphincteroplasty. Br J Surg 1996;83:502-505.

71 Gilliland R, Altomare DF, Moreira H, Jr., Oliveira L, Gilliland JE, Wexner SD: Pudendal neuropathy is predictive of failure following anterior overlapping sphincteroplasty. Dis Colon Rectum 1998;41:1516-1522.

72 Young CJ, Mathur MN, Eyers AA, Solomon MJ: Successful overlapping anal sphincter repair: Relationship to patient age, neuropathy, and colostomy formation. Dis Colon Rectum 1998;41:344-349.

73 Karoui S, Leroi AM, Koning E, Menard JF, Michot F, Denis P: Results of sphincteroplasty in 86 patients with anal incontinence. Dis Colon Rectum 2000;43:813-820.

74 Osterberg A, Edebol Eeg-Olofsson K, Graf W: Results of surgical treatment for faecal incontinence. Br J Surg 2000;87:1546-1552.

75 Morren GL, Hallbook O, Nystrom PO, Baeten CG, Sjodahl R: Audit of anal-sphincter repair. Colorectal Dis 2001;3:17-22.

76 Tan M, O'Hanlon DM, Cassidy M, O'Connell PR: Advantages of a posterior fourchette incision in anal sphincter repair. Dis Colon Rectum 2001;44:1624-1629.

77 Bravo Gutierrez A, Madoff RD, Lowry AC, Parker SC, Buie

WD, Baxter NN: Long-term results of anterior sphincteroplasty. Dis Colon Rectum 2004;47:727-731; discussion 731-722.

78 Norderval S, Oian P, Revhaug A, Vonen B: Anal incontinence after obstetric sphincter tears: Outcome of anatomic primary repairs. Dis Colon Rectum 2005;48:1055-1061.

79 Zorcolo L, Covotta L, Bartolo DC: Outcome of anterior sphincter repair for obstetric injury: Comparison of early and late results. Dis Colon Rectum 2005;48:524-531.

80 Trowbridge ER, Morgan D, Trowbridge MJ, Delancey JO, Fenner DE: Sexual function, quality of life, and severity of anal incontinence after anal sphincteroplasty. Am J Obstet Gynecol 2006;195:1753-1757.

81 Barisic GI, Krivokapic ZV, Markovic VA, Popovic MA: Outcome of overlapping anal sphincter repair after 3 months and after a mean of 80 months. Int J Colorectal Dis 2006;21:52-56.

82 Maslekar S, Gardiner AB, Duthie GS: Anterior anal sphincter repair for fecal incontinence: Good longterm results are possible. J Am Coll Surg 2007;204:40-46.

83 Oom DM, Gosselink MP, Schouten WR: Anterior sphincteroplasty for fecal incontinence: A single center experience in the era of sacral neuromodulation. Dis Colon Rectum 2009;52:1681-1687.

84 Gleason JL, Markland A, Greer WJ, Szychowski JM, Gerten KA, Richter HE: Anal sphincter repair for fecal incontinence: Effect on symptom severity, quality of life, and anal sphincter squeeze pressures. Int Urogynecol J 2011;22:1587-1592.

85 Parks AG, McPartlin JF: Late repair of injuries of the anal sphincter. Proc R Soc Med 1971;64:1187-1189.

86 Tjandra JJ, Han WR, Goh J, Carey M, Dwyer P: Direct repair vs. Overlapping sphincter repair: A randomized, controlled trial. Dis Colon Rectum 2003;46:937-942; discussion 942-933.

87 Oberwalder M, Dinnewitzer A, Nogueras JJ, Weiss EG, Wexner SD: Imbrication of the external anal sphincter may yield similar functional results as overlapping repair in selected patients. Colorectal Dis 2008;10:800-804.

88 Pinedo G, Vaizey CJ, Nicholls RJ, Roach R, Halligan S, Kamm MA: Results of repeat anal sphincter repair. Br J Surg 1999;86:66-69.

89 Nielsen MB, Dammegaard L, Pedersen JF: Endosonographic assessment of the anal sphincter after surgical reconstruction. Dis Colon Rectum 1994;37:434-438.

90 Giordano P, Renzi A, Efron J, Gervaz P, Weiss EG, Nogueras JJ, Wexner SD: Previous sphincter repair does not affect the outcome of repeat repair. Dis Colon Rectum 2002;45:635-640.

91 Vaizey CJ, Norton C, Thornton MJ, Nicholls RJ, Kamm MA: Long-term results of repeat anterior anal sphincter repair. Dis Colon Rectum 2004;47:858-863.

92 Johnson E, Carlsen E, Steen TB, Backer Hjorthaug JO, Eriksen MT, Johannessen HO: Short- and long-term results of secondary anterior sphincteroplasty in 33 patients with obstetric injury. Acta Obstet Gynecol Scand 2010;89:1466-1472.

93 Zutshi M, Tracey TH, Bast J, Halverson A, Na J: Ten-year outcome after anal sphincter repair for fecal incontinence. Dis Colon Rectum 2009;52:1089-1094.

94 Mevik K, Norderval S, Kileng H, Johansen M, Vonen B: Long-term results after anterior sphincteroplasty for anal incontinence. Scand J Surg 2009;98:234-238.

95 Hull T: Invited editorial. Dis Colon Rectum 2004;47:731-732.

96 Evans C, Davis K, Kumar D: Overlapping anal sphincter repair and anterior levatorplasty: Effect of patient's age and duration of follow-up. Int J Colorectal Dis 2006;21:795-801.

97 O'Connell PR: The effects of age and menopause on anal sphincter function. Dis Colon Rectum 2012; (in press).

98 Zutshi M, Salcedo L, Hammel J, Hull T: Anal physiology testing in fecal incontinence: Is it of any value? Int J Colorectal Dis 2010;25:277-282.

99 Gearhart S, Hull T, Floruta C, Schroeder T, Hammel J: Anal manometric parameters: Predictors of outcome following anal sphincter repair? J Gastrointest Surg 2005;9:115-120.

100 Brouwer R, Duthie G: Sacral nerve neuromodulation is effective treatment for fecal incontinence in the presence of a sphincter defect, pudendal neuropathy, or previous sphincter repair. Dis Colon Rectum 2010;53:273-278.

101 Bachoo P, Brazzelli M, Grant A: Surgery for faecal incontinence in adults. Cochrane Database Syst Rev 2000:CD001757.

102 Brown SR, Wadhawan H, Nelson RL: Surgery for faecal incontinence in adults. Cochrane Database Syst Rev 2010:CD001757.

103 Deen KI, Oya M, Ortiz J, Keighley MR: Randomized trial comparing three forms of pelvic floor repair for neuropathic faecal incontinence. Br J Surg 1993;80:794-798.

104 van Tets WF, Kuijpers JH: Pelvic floor procedures produce no consistent changes in anatomy or physiology. Dis Colon Rectum 1998;41:365-369.

105 Womack NR, Morrison JF, Williams NS: Prospective study of the effects of postanal repair in neurogenic faecal incontinence. Br J Surg 1988;75:48-52.

106 Orrom WJ, Miller R, Cornes H, Duthie G, Mortensen NJ, Bartolo DC: Comparison of anterior sphincteroplasty and postanal repair in the treatment of idiopathic fecal incontinence. Dis Colon Rectum 1991;34:305-310.

107 Browning GG, Parks AG: Postanal repair for neuropathic faecal incontinence: Correlation of clinical result and anal canal pressures. Br J Surg 1983;70:101-104.

108 Scheuer M, Kuijpers HC, Jacobs PP: Postanal repair restores anatomy rather than function. Dis Colon Rectum 1989;32:960-963.

109 Yoshioka K, Keighley MR: Critical assessment of the quality of continence after postanal repair for faecal incontinence. Br J Surg 1989;76:1054-1057.

110 Engel AF, van Baal SJ, Brummelkamp WH: Late results of postanal repair for idiopathic faecal incontinence. Eur J Surg 1994;160:637-640.

111 Jameson JS, Speakman CT, Darzi A, Chia YW, Henry MM: Audit of postanal repair in the treatment of fecal incontinence. Dis Colon Rectum 1994;37:369-372.

112 Setti Carraro P, Kamm MA, Nicholls RJ: Long-term results of postanal repair for neurogenic faecal incontinence. Br J Surg 1994;81:140-144.

113 Matsuoka H, Mavrantonis C, Wexner SD, Oliveira L, Gilliland R, Pikarsky A: Postanal repair for fecal incontinence--is it worthwhile? Dis Colon Rectum 2000;43:1561-1567.

114 Abbas SM, Bissett IP, Neill ME, Parry BR: Long-term outcome of postanal repair in the treatment of faecal incontinence. ANZ J Surg 2005;75:783-786.

115 Keighley MR: Postanal repair for faecal incontinence. J R Soc Med 1984;77:285-288.

116 Ferguson EF, Jr.: Puborectalis sphincteroplasty for anal incontinence. South Med J 1984;77:423-425.

117 van Vroonhoven TJ, Schouten WR: Postanal repair in the treatment of faecal incontinence. Neth J Surg 1984;36:160-162.

118 Henry MM, Simson JN: Results of postanal repair: A retrospective study. Br J Surg 1985;72 Suppl:S17-19.

119 Habr-Gama A, Alves PA, da Silva e Souza AH, Femenia Viera MJ, Brunetti-Netto C: Treatment of faecal incontinence by postanal repair; Coloproctology 8, 1986, pp 244-246.

120 Rainey JB, Donaldson DR, Thomson JP: Postanal repair: Which patients derive most benefit? J R Coll Surg Edinb 1990;35:101-105.

121 Scott AD, Henry MM, Phillips RK: Clinical assessment and anorectal manometry before postanal repair: Failure to predict outcome. Br J Surg 1990;77:628-629.

122 Laurberg S, Swash M, Henry MM: Effect of postanal repair on progress of neurogenic damage to the pelvic floor. British Journal of Surgery 1990;77:519-522.

123 Rieger NA, Sarre RG, Saccone GT, Hunter A, Toouli J: Postanal repair for faecal incontinence: Long-term follow-up. Aust N Z J Surg 1997;67:566-570.

124 Mackey P, Mackey L, Kennedy ML, King DW, Newstead GL, Douglas PR, Lubowski DZ: Postanal repair--do the long-term results justify the procedure? Colorectal Dis 2010;12:367-372.

125 Yoshioka K, Hyland G, Keighley MR: Physiological changes after postanal repair and parameters predicting outcome. Br J Surg 1988;75:1220-1224.

126 Chetwood CH: Plastic operation for restoration of the sphicter ani with a report of a case. Med Rec 1902;61:529.

127 Schoemaker J: Un nouveau procédé opératoire pour la reconstitution du sphincter anal. Sem Med 1909;29:160.

128 Pickrell KL, Broadbent TR, Masters FW, Metzger JT: Construction of a rectal sphincter and restoration of anal continence by transplanting the gracilis muscle; a report of four cases in children. Annals of Surgery 1952;135:853-862.

129 Raffensperger J: The gracilis sling for fecal incontinence. J Pediatr Surg 1979;14:794-797.

130 Brandesky G, Holschneider AM: Operations for the improvement of faecal incontinence. Prog Pediatr Surg 1976;9:105-114.

131 Schwedler T, Erichsen K: [gracilis-muscle transplant for the treatment of fecal incontinence (author's transl)]. Langenbecks Arch Chir 1975;339:451-457.

132 Holschneider AM, Hecker WC: Smooth muscle reverse plasty. A new method to treat anorectal incontinence in infants with high anal and rectal atresia. Results after gracilis plasty and free muscle transplantation. Prog Pediatr Surg 1984;17:131-145.

133 Corman ML: Gracilis muscle transposition for anal incontinence: Late results. Br J Surg 1985;72 Suppl:S21-22.

134 Leguit P, Van Baal JG, Brummelkamp WH: Gracilis muscle transposition in the treatment of fecal incontinence. Long-term follow-up and evaluation of anal pressure recordings. Dis Colon Rectum 1985;28:1-4.

135 Scharli AF: Anorectal incontinence: Diagnosis and treatment. J Pediatr Surg 1987;22:693-701.

136 Yoshioka K, Keighley MRB: Clinical and manometric assessment of gracilis muscle transplant for fecal incontinence. Diseases of the Colon & Rectum 1988;31:767-769.

137 Sielezneff I, Bauer S, Bulgare JC, Sarles JC: Gracilis muscle transposition in the treatment of faecal incontinence. Int J Colorectal Dis 1996;11:15-18.

138 Kotobi H, Forin V, Larroquet M, Khairouni A, Loc'h P, Grapin C, Audry G: [pickrell intervention in children for anal incontinence secondary to anorectal malformation]. Ann Chir 2000;125:954-960.

139 Faucheron JL, Hannoun L, Thome C, Parc R: Is fecal continence improved by nonstimulated gracilis muscle transposition? Dis Colon Rectum 1994;37:979-983.

140 Kumar D, Hutchinson R, Grant E: Bilateral gracilis neosphincter construction for treatment of faecal incontinence. Br J Surg 1995;82:1645-1647.

141 Prochiantz A, Gross P: Gluteal myoplasty for sphincter replacement: Principles, results and prospects. J Pediatr Surg 1982;17:25-30.

142 Christiansen J, Hansen CR, Rasmussen O: Bilateral gluteus maximus transposition for anal incontinence. Br J Surg 1995;82:903-905.

143 Guelinckx PJ, Sinsel NK, Gruwez JA: Anal sphincter reconstruction with the gluteus maximus muscle: Anatomic and physiologic considerations concerning conventional and dynamic gluteoplasty. Plast Reconstr Surg 1996;98:293-302; discussion 303-294.

144 Devesa JM, Madrid JM, Gallego BR, Vicente E, Nuno J, Enriquez JM: Bilateral gluteoplasty for fecal incontinence. Dis Colon Rectum 1997;40:883-888.

145 Pearl RK, Prasad ML, Nelson RL, Orsay CP, Abcarian H: Bilateral gluteus maximus transposition for anal incontinence. Diseases of the Colon & Rectum 1991;34:478-481.

146 Yoshioka K, Ogunbiyi OA, Keighley MR: A pilot study of total pelvic floor repair or gluteus maximus transposition for postobstetric neuropathic fecal incontinence. Dis Colon Rectum 1999;42:252-257.

147 Hultman CS, Zenn MR, Agarwal T, Baker CC: Restoration of fecal continence after functional gluteoplasty: Long-term results, technical refinements, and donor-site morbidity. Ann Plast Surg 2006;56:65-70; discussion 70-61.

148 George BD, Williams NS, Patel J, Swash M, Watkins ES: Physiological and histochemical adaptation of the electrically stimulated gracilis muscle to neoanal sphincter function. Br J Surg 1993;80:1342-1346.

149 Baeten C, Spaans F, Fluks A: An implanted neuromuscular stimulator for fecal continence following previously implanted gracilis muscle: Report of a case. Dis Colon Rectum 1988;31:134-137.

150 Baeten CG, Konsten J, Spaans F, Visser R, Habets AM, Bourgeois IM, Wagenmakers AJ, Soeters PB: Dynamic graciloplasty for treatment of faecal incontinence. Lancet 1991;338:1163-1165.

151 Williams NS, Patel J, George BD, Hallan RI, Watkins ES: Development of an electrically stimulated neoanal sphincter. Lancet 1991;338:1166-1169.

152 Konsten J, Baeten CGMI, Havenith MG, Soeters PB: Morphology of dynamic graciloplasty compared with the anal sphincter. Dis Colon Rectum 1993;36:559-563.

153 Salmons S, Vrbova G: The influence of activity on some contractile characteristics of mammalian fast and slow muscles. Journal of Physiology 1969;201:535-549.

154 Patel J, Shanahan D, Williams N, Sinnatamby C, George B, Watkins E: The anatomy of the anterior division of the obdurator nerve in relation to the electrically stimulated gracilis neoanal sphincter [abstract]. Clin Anat 1991;4:385.

155 Baeten GM, Geerdes BP, Adang EM, Heineman E, Konsten J, Engel GL, Kester ADM, Spaans F, Soeters PB: Anal dynamic graciloplasty in the treatment of intractable fecal incontinence. N Engl J Med 1995;332:1600-1605.

156 Geerdes BP, Heineman E, Konsten J, Soeters PB, Baeten CG: Dynamic graciloplasty. Complications and management. Dis Colon Rectum 1996;39:912-917.

157 Cavina E, Seccia M, Banti P, Zocco G: Anorectal reconstruction after abdominoperineal resection. Experience with double-wrap graciloplasty supported by low-frequency electrostimulation. Dis Colon Rectum 1998;41:1010-1016.

158 Madoff RD, Rosen HR, Baeten CG, LaFontaine LJ, Cavina E, Devesa M, Rouanet P, Christiansen J, Faucheron JL, Isbister W, Kohler L, Guelinckx PJ, Pahlman L: Safety and efficacy of dynamic muscle plasty for anal incontinence: Lessons from a prospective, multicenter trial. Gastroenterology 1999;116:549-556.

159 Mander BJ, Wexner SD, Williams NS, Bartolo DC, Lubowski DZ, Oresland T, Romano G, Keighley MR: Preliminary results of a multicentre trial of the electrically stimulated gracilis neoanal sphincter. Br J Surg 1999;86:1543-1548.

160 Baeten CG, Bailey HR, Bakka A, Belliveau P, Berg E, Buie WD, Burnstein MJ, Christiansen J, Coller JA, Galandiuk S, LaFontaine LJ, Lange J, Madoff RD, Matzel KE, Pahlman L, Parc R, Reilly JC, Seccia M, Thorson AG, Vernava AM, 3rd, Wexner S: Safety and efficacy of dynamic graciloplasty for fecal incontinence: Report of a prospective, multicenter trial. Dynamic graciloplasty therapy study group. Dis Colon Rectum 2000;43:743-751.

161 Matzel KE, Madoff RD, LaFontaine LJ, Baeten CG, Buie WD, Christiansen J, Wexner S: Complications of dynamic graciloplasty: Incidence, management, and impact on outcome. Dis Colon Rectum 2001;44:1427-1435.

162 Wexner SD, Baeten C, Bailey R, Bakka A, Belin B, Belliveau P, Berg E, Buie WD, Burnstein M, Christiansen J, Coller J, Galandiuk S, Lange J, Madoff R, Matzel KE, Pahlman L, Parc R, Reilly J, Seccia M, Thorson AG, Vernava AM, 3rd: Long-term efficacy of dynamic graciloplasty for fecal incontinence. Dis Colon Rectum 2002;45:809-818.

163 Rongen MJ, Uludag O, El Naggar K, Geerdes BP, Konsten J, Baeten CG: Long-term follow-up of dynamic graciloplasty for fecal incontinence. Dis Colon Rectum 2003;46:716-721.

164 Penninckx F: Belgian experience with dynamic graciloplasty for faecal incontinence. Br J Surg 2004;91:872-878.

165 Tillin T, Gannon K, Feldman RA, Williams NS: Third-party prospective evaluation of patient outcomes after dynamic graciloplasty. Br J Surg 2006;93:1402-1410.

166 Rosen HR, Novi G, Zoech G, Feil W, Urbarz C, Schiessel R: Restoration of anal sphincter function by single-stage dynamic graciloplasty with a modified (split sling) technique. Am J Surg 1998;175:187-193.

167 Sielezneff I, Malouf AJ, Bartolo DC, Pryde A, Douglas S: Dynamic graciloplasty in the treatment of patients with faecal incontinence. Br J Surg 1999;86:61-65.

168 Thornton MJ, Kennedy ML, Lubowski DZ, King DW: Long-term follow-up of dynamic graciloplasty for faecal incontinence. Colorectal Dis 2004;6:470-476.

169 Hassan MZ, Rathnayaka MM, Deen KI: Modified dynamic gracilis neosphincter for fecal incontinence: An analysis of functional outcome at a single institution. World J Surg 2010;34:1641-1647.

170 Chapman AE, Geerdes B, Hewett P, Young J, Eyers T, Kiroff G, Maddern GJ: Systematic review of dynamic graciloplasty in the treatment of faecal incontinence. Br J Surg 2002;89:138-153.

171 Tan EK, Vaizey C, Cornish J, Darzi A, Tekkis PP: Surgical strategies for faecal incontinence--a decision analysis between dynamic graciloplasty, artificial bowel sphincter and end stoma. Colorectal Dis 2008;10:577-586.

172 Huang ZH, Shi FJ, Chen F, Liang FX, Li Q, Yu JL, Li Z, Han XJ: In vitro and in vivo assessment of an intelligent artificial anal sphincter in rabbits. Artif Organs 2011;35:964-969.

173 Zan P, Yang BH, Shao Y, Yan GZ, Liu H: Electromagnetic effects on the biological tissue surrounding a transcutaneous transformer for an artificial anal sphincter system. J Zhejiang Univ Sci B 2010;11:931-936.

174 Zan P, Yang B, Zhang JY, Shao Y: Research on a novel artificial anal sphincter for human incontinence. J Med Eng Technol 2010;35:386-392.

175 Raghavan S, Miyasaka EA, Hashish M, Somara S, Gilmont RR, Teitelbaum DH, Bitar KN: Successful implantation of physiologically functional bioengineered mouse internal anal sphincter. Am J Physiol Gastrointest Liver Physiol 2010;299:G430-439.

176 Raghavan S, Gilmont RR, Miyasaka EA, Somara S, Srinivasan S, Teitelbaum DH, Bitar KN: Successful implantation of bioengineered, intrinsically innervated, human internal anal sphincter. Gastroenterology 2011;141:310-319.

177 Ruthmann O, Richter S, Seifert G, Karcz W, Goldschmidboing F, Lemke T, Biancuzzi G, Woias P, Schmidt T, Schwarzbqch S, Vodermayer B, Hopt U, Schrag HJ: The first teleautomatic low-voltage prosthesis with multiple therapeutic applications: A new version of the german artificial sphincter system. Artif Organs 2010;34:635-641.

178 Michot F, Tuech JJ, Lefebure B, Bridoux V, Denis P: A new implantation procedure of artificial sphincter for anal incontinence: The transvaginal approach. Dis Colon Rectum 2007;50:1401-1404.

179 Michot F, Lefebure B, Bridoux V, Gourcerol G, Kianifard B, Leroi AM, Tuech JJ: Artificial anal sphincter for severe fecal incontinence implanted by a transvaginal approach: Experience with 32 patients treated at one institution. Dis Colon Rectum 2010;53:1155-1160.

180 Melenhorst J, Koch SM, van Gemert WG, Baeten CG: The artificial bowel sphincter for faecal incontinence: A single centre study. Int J Colorectal Dis 2008;23:107-111.

181 Wexner SD, Jin HY, Weiss EG, Nogueras JJ, Li VK: Factors associated with failure of the artificial bowel sphincter: A study of over 50 cases from cleveland clinic florida. Dis Colon Rectum 2009;52:1550-1557.

182 Chittawatanarat K, Koh DC, Seah AA, Cheong WK, Tsang CB: Artificial bowel sphincter implantation for faecal incontinence in asian patients. Asian J Surg 2010;33:134-142.

183 Nice clinical guideline 49: Faecal incontinence: The management of faecal incontinence in adults. http://www.Nice.Org.Uk/cg049. Accessed january 30, 2012.,

184 Ruiz Carmona MD, Alós Company R, Roig Vila JV, Solana Bueno A, Pla Martí V: Long-term results of artificial bowel sphincter for the treatment of severe faecal incontinence. Are they what we hoped for? Colorectal Dis 2009;11:831-837.

185 Wong MT, Meurette G, Wyart V, Glemain P, Lehur PA: The artificial bowel sphincter: A single institution experience over a decade. Ann Surg 2011;254:951-956.

186 Meurette G, La Torre M, Regenet N, Robert-Yap J, Lehur PA: Value of sacral nerve stimulation in the treatment of severe faecal incontinence: A comparison to the artificial bowel sphincter. Colorectal Dis 2009;11:631-635.

187 Gallas S, Leroi AM, Bridoux V, Lefebure B, Tuech JJ, Michot F: Constipation in 44 patients implanted with an artificial bowel sphincter. Int J Colorectal Dis 2009;24:969-974.

188 Tan EK, Vaizey C, Cornish J, Darzi A, Tekkis PP: Surgical strategies for faecal incontinence--a decision analysis between dynamic graciloplasty, artificial bowel sphincter and end stoma. Colorectal Dis 2008;10:577-586.

189 Lehur PA, McNevin S, Buntzen S, Mellgren AF, Laurberg S, Madoff RD: Magnetic anal sphincter augmentation for the treatment of fecal incontinence: A preliminary report from a feasibility study. Dis Colon Rectum 2010;53:1604-1610.

190 Wong MT, Meurette G, Stangherlin P, Lehur PA: The magnetic anal sphincter versus the artificial bowel sphincter: A comparison of 2 treatments for fecal incontinence. Dis Colon Rectum 2011;54:773-779.

191 Matzel KE, Stadelmaier U, Hohenfellner M, Gall FP: Electrical stimulation of sacral spinal nerves for treatment of faecal incontinence. Lancet 1995;346:1124-1127.

192 Matzel KE, Schmidt RA, Tanagho EA: Neuroanatomy of the striated muscular anal continence mechanism. Implications for the use of neurostimulation. Dis Colon Rectum 1990;33:666-673.

193 Thon WF, Baskin LS, Jonas U, Tanagho EA, Schmidt RA: Neuromodulation of voiding dysfunction and pelvic pain. World Journal of Urology 1991;9:138-141.

194 Janknegt RA, Weil EH, Eerdmans PH: Improving neuromodulation technique for refractory voiding dysfunctions: Two-stage implant. Urology 1997;49:358-362.

195 Matzel KE, Stadelmaier U, Bittorf B, Hohenfellner M, Hohenberger W: Bilateral sacral spinal nerve stimulation for fecal incontinence after low anterior rectum resection. Int J Colorectal Dis 2002;17:430-434.

196 Ratto C, Grillo E, Parello A, Petrolino M, Costamagna G, Doglietto GB: Sacral neuromodulation in treatment of fecal incontinence following anterior resection and chemoradiation for rectal cancer. Dis Colon Rectum 2005;48:1027-1036.

197 Dudding TC, Parés D, Vaizey CJ, Kamm MA: Comparison of clinical outcome between open and percutaneous lead insertion for permanent sacral nerve neurostimulation for the treatment of fecal incontinence. Dis Colon Rectum 2009;52:463-468.

198 Govaert B, Melenhorst J, van Gemert WG, Baeten CG: Can sensory and/or motor reactions during percutaneous nerve evaluation predict outcome of sacral nerve modulation? Dis Colon Rectum 2009;52:1423-1426.

199 Matzel KE, Stadelmaier U, Hohenberger W: Innovations in fecal incontinence: Sacral nerve stimulation. Dis Colon Rectum 2004;47:1720-1728.

200 Tjandra JJ, Lim JF, Matzel K: Sacral nerve stimulation: An emerging treatment for faecal incontinence. ANZ J Surg 2004;74:1098-1106.

201 Gourcerol G, Gallas S, Michot F, Denis P, Leroi AM: Sacral nerve stimulation in fecal incontinence: Are there factors associated with success? Dis Colon Rectum 2007;50:3-12.

202 Dudding TC, Parés D, Vaizey CJ, Kamm MA: Predictive factors for successful sacral nerve stimulation in the treatment of faecal incontinence: A 10-year cohort analysis. Colorectal Dis 2008;10:249-256.

203 Govaert B, Melenhorst J, Nieman FH, Bols EM, van Gemert WG, Baeten CG: Factors associated with percutaneous nerve evaluation and permanent sacral nerve modulation outcome in patients with fecal incontinence. Dis Colon Rectum 2009;52:1688-1694.

204 Melenhorst J, Koch SM, Uludag O, van Gemert WG, Baeten CG: Is a morphologically intact anal sphincter necessary for success with sacral nerve modulation in patients with faecal incontinence? Colorectal Dis 2008;10:257-262.

205 Maeda Y, Norton C, Lundby L, Buntzen S, Laurberg S: Predictors of the outcome of percutaneous nerve evaluation for faecal incontinence. Br J Surg 2010;97:1096-1102.

206 Gallas S, Michot F, Faucheron JL, Meurette G, Lehur PA, Barth X, Damon H, Mion F, Rullier E, Zerbib F, Sielezneff I, Ouaïssi M, Orsoni P, Desfourneaux V, Siproudhis L, Mathonnet M, Menard JF, Leroi AM, NEMO C: Predictive factors for successful sacral nerve stimulation in the treatment of faecal incontinence: Results of trial stimulation in 200 patients. Colorectal Dis 2011;13:689-696.

207 Vallet C, Parc Y, Lupinacci R, Shields C, Parc R, Tiret E: Sacral nerve stimulation for faecal incontinence: Response rate, satisfaction and the value of preoperative investigation in patient selection. Colorectal Dis 2010;12:247-253.

208 Altomare DF, Rinaldi M, Lobascio P, Marino F, Giuliani RT, Cuccia F: Factors affecting the outcome of temporary sacral nerve stimulation for faecal incontinence. The value of the new tined lead electrode. Colorectal Dis 2011;13:198-202.

209 Wallace PA, Lane FL, Noblett KL: Sacral nerve neuromodulation in patients with cardiac pacemakers. Am J Obstet Gynecol 2007;197:94.e91-93.

210 Rosen HR, Urbarz C, Holzer B, Novi G, Schiessel R: Sacral nerve stimulation as a treatment for fecal incontinence. Gastroenterology 2001;121:536-541.

211 Ganio E, Ratto C, Masin A, Luc AR, Doglietto GB, Dodi G, Ripetti V, Arullani A, Frascio M, BertiRiboli E, Landolfi V, DelGenio A, Altomare DF, Memeo V, Bertapelle P, Carone R, Spinelli M, Zanollo A, Spreafico L, Giardiello G, de Seta F: Neuromodulation for fecal incontinence: Outcome in 16 patients with definitive implant. The initial italian sacral neurostimulation group (gins) experience. Dis Colon Rectum 2001;44:965-970.

212 Jarrett ME, Varma JS, Duthie GS, Nicholls RJ, Kamm MA: Sacral nerve stimulation for faecal incontinence in the uk. Br J Surg 2004;91:755-761.

213 Melenhorst J, Koch SM, Uludag O, van Gemert WG, Baeten CG: Sacral neuromodulation in patients with faecal incontinence: Results of the first 100 permanent implantations. Colorectal Dis 2007;9:725-730.

214 Ganio E, Luc AR, Clerico G, Trompetto M: Sacral nerve stimulation for treatment of fecal incontinence: A novel approach for intractable fecal incontinence. Dis Colon Rectum 2001;44:619-629; discussion 629-631.

215 Kenefick NJ, Vaizey CJ, Cohen RC, Nicholls RJ, Kamm MA: Medium-term results of permanent sacral nerve stimulation for faecal incontinence. Br J Surg 2002;89:896-901.

216 Matzel KE, Stadelmaier U, Hohenfellner M, Hohenberger W: Chronic sacral spinal nerve stimulation for fecal incontinence: Long-term results with foramen and cuff electrodes. Dis Colon Rectum 2001;44:59-66.

217 Leroi AM, Michot F, Grise P, Denis P: Effect of sacral nerve stimulation in patients with fecal and urinary incontinence. Dis Colon Rectum 2001;44:779-789.

218 Kenefick NJ, Emmanuel A, Nicholls RJ, Kamm MA: Effect of sacral nerve stimulation on autonomic nerve function. Br J Surg 2003;90:1256-1260.

219 Gourcerol G, Vitton V, Leroi AM, Michot F, Abysique A, Bouvier M: How sacral nerve stimulation works in patients with faecal incontinence. Colorectal Dis 2011;13:e203-211.

220 Vitton V, Abysique A, Gaigé S, Leroi AM, Bouvier M: Colonosphincteric electromyographic responses to sacral root stimulation: Evidence for a somatosympathetic reflex. Neurogastroenterol Motil 2008;20:407-416.

221 Sheldon R, Kiff ES, Clarke A, Harris ML, Hamdy S: Sacral nerve stimulation reduces corticoanal excitability in patients with faecal incontinence. Br J Surg 2005;92:1423-1431.

222 Giani I, Novelli E, Martina S, Clerico G, Luc AR, Trompetto M, Malaguti S, Nicholls J, Ganio E: The effect of sacral nerve modulation on cerebral evoked potential latency in fecal incontinence and constipation. Ann Surg 2011;254:90-96.

223 Griffin KM, Pickering M, O'Herlihy C, O'Connell PR, Jones JF: Sacral nerve stimulation increases activation of the primary somatosensory cortex by anal canal stimulation in an experimental model. Br J Surg 2011;98:1160-1169.

224 Lundby L, Møller A, Buntzen S, Krogh K, Vang K, Gjedde A, Laurberg S: Relief of fecal incontinence by sacral nerve stimulation linked to focal brain activation. Dis Colon Rectum 2011;54:318-323.

225 Vaizey CJ, Kamm MA, Turner IC, Nicholls RJ, Woloszko J: Effects of short term sacral nerve stimulation on anal and rectal function in patients with anal incontinence. Gut 1999;44:407-412.

226 Uludağ O, Koch SM, van Gemert WG, Dejong CH, Baeten CG: Sacral neuromodulation in patients with fecal incontinence: A single-center study. Dis Colon Rectum 2004;47:1350-1357.

227 Michelsen HB, Christensen P, Krogh K, Rosenkilde M, Buntzen S, Theil J, Laurberg S: Sacral nerve stimulation for faecal incontinence alters colorectal transport. Br J Surg 2008;95:779-784.

228 Abdel-Halim MR, Crosbie J, Engledow A, Windsor A, Cohen CR, Emmanuel AV: Temporary sacral nerve stimulation alters rectal sensory function: A physiological study. Dis Colon Rectum 2011;54:1134-1140.

229 Otto SD, Burmeister S, Buhr HJ, Kroesen A: Sacral nerve stimulation induces changes in the pelvic floor and rectum that improve continence and quality of life. J Gastrointest Surg 2010;14:636-644.

230 Uludag O, Morren GL, Dejong CH, Baeten CG: Effect of sacral neuromodulation on the rectum. Br J Surg 2005;92:1017-1023.

231 Michelsen HB, Buntzen S, Krogh K, Laurberg S: Rectal volume tolerability and anal pressures in patients with fecal incontinence treated with sacral nerve stimulation. Dis Colon Rectum 2006;49:1039-1044.

232 Roman S, Tatagiba T, Damon H, Barth X, Mion F: Sacral nerve stimulation and rectal function: Results of a prospective study in faecal incontinence. Neurogastroenterol Motil 2008;20:1127-1131.

233 Ganio E, Masin A, Ratto C, Altomare DF, Ripetti V, Clerico G, Lise M, Doglietto GB, Memeo V, Landolfi V, Del Genio A, Arullani A, Giardiello G, de Seta F: Short-term sacral nerve stimulation for functional anorectal and urinary dis-

turbances: Results in 40 patients: Evaluation of a new option for anorectal functional disorders. Dis Colon Rectum 2001;44:1261-1267.

234 Damgaard M, Thomsen FG, Sørensen M, Fuglsang S, Madsen JL: The influence of sacral nerve stimulation on gastrointestinal motor function in patients with fecal incontinence. Neurogastroenterol Motil 2011;23:556-e207.

235 Ripetti V, Caputo D, Ausania F, Esposito E, Bruni R, Arullani A: Sacral nerve neuromodulation improves physical, psychological and social quality of life in patients with fecal incontinence. Tech Coloproctol 2002;6:147-152.

236 Matzel KE, Bittorf B, Stadelmaier U, Hohenberger W: [sacral nerve stimulation in the treatment of faecal incontinence]. Chirurg 2003;74:26-32.

237 Altomare DF, Rinaldi M, Petrolino M, Monitillo V, Sallustio P, Veglia A, De Fazio M, Guglielmi A, Memeo V: Permanent sacral nerve modulation for fecal incontinence and associated urinary disturbances. Int J Colorectal Dis 2004;19:203-209.

238 Matzel KE, Kamm MA, Stösser M, Baeten CG, Christiansen J, Madoff R, Mellgren A, Nicholls RJ, Rius J, Rosen H: Sacral spinal nerve stimulation for faecal incontinence: Multicentre study. Lancet 2004;363:1270-1276.

239 Rasmussen OO, Buntzen S, Sørensen M, Laurberg S, Christiansen J: Sacral nerve stimulation in fecal incontinence. Dis Colon Rectum 2004;47:1158-1162; discussion 1162-1153.

240 Leroi AM, Parc Y, Lehur PA, Mion F, Barth X, Rullier E, Bresler L, Portier G, Michot F, Group S: Efficacy of sacral nerve stimulation for fecal incontinence: Results of a multicenter double-blind crossover study. Ann Surg 2005;242:662-669.

241 Kenefick NJ: Sacral nerve neuromodulation for the treatment of lower bowel motility disorders. Ann R Coll Surg Engl 2006;88:617-623.

242 Holzer B, Rosen HR, Novi G, Ausch C, Hölbling N, Schiessel R: Sacral nerve stimulation for neurogenic faecal incontinence. Br J Surg 2007;94:749-753.

243 Hetzer FH, Hahnloser D, Clavien PA, Demartines N: Quality of life and morbidity after permanent sacral nerve stimulation for fecal incontinence. Arch Surg 2007;142:8-13.

244 Tan JJ, Chan M, Tjandra JJ: Evolving therapy for fecal incontinence. Dis Colon Rectum 2007;50:1950-1967.

245 Altomare DF, Ratto C, Ganio E, Lolli P, Masin A, Villani RD: Long-term outcome of sacral nerve stimulation for fecal incontinence. Dis Colon Rectum 2009;52:11-17.

246 El-Gazzaz G, Zutshi M, Salcedo L, Hammel J, Rackley R, Hull T: Sacral neuromodulation for the treatment of fecal incontinence and urinary incontinence in female patients: Long-term follow-up. Int J Colorectal Dis 2009;24:1377-1381.

247 Wexner SD, Coller JA, Devroede G, Hull T, McCallum R, Chan M, Ayscue JM, Shobeiri AS, Margolin D, England M, Kaufman H, Snape WJ, Mutlu E, Chua H, Pettit P, Nagle D, Madoff RD, Lerew DR, Mellgren A: Sacral nerve stimulation for fecal incontinence: Results of a 120-patient prospective multicenter study. Ann Surg 2010;251:441-449.

248 Michelsen HB, Thompson-Fawcett M, Lundby L, Krogh K, Laurberg S, Buntzen S: Six years of experience with sacral nerve stimulation for fecal incontinence. Dis Colon Rectum 2010;53:414-421.

249 Hollingshead JR, Dudding TC, Vaizey CJ: Sacral nerve stimulation for faecal incontinence: Results from a single centre over a 10-year period. Colorectal Dis 2011;13:1030-1034.

250 Lim JT, Hastie IA, Hiscock RJ, Shedda SM: Sacral nerve stimulation for fecal incontinence: Long-term outcomes. Dis Colon Rectum 2011;54:969-974.

251 Mellgren A, Wexner SD, Coller JA, Devroede G, Lerew DR, Madoff RD, Hull T, Group SS: Long-term efficacy and safety of sacral nerve stimulation for fecal incontinence. Dis Colon Rectum 2011;54:1065-1075.

252 Uludağ O, Melenhorst J, Koch SM, van Gemert WG, Dejong CH, Baeten CG: Sacral neuromodulation: Long-term outcome and quality of life in patients with faecal incontinence. Colorectal Dis 2011;13:1162-1166.

253 Matzel KE, Lux P, Heuer S, Besendörfer M, Zhang W: Sacral nerve stimulation for faecal incontinence: Long-term outcome. Colorectal Dis 2009;11:636-641.

254 Maeda Y, Lundby L, Buntzen S, Laurberg S: Suboptimal outcome following sacral nerve stimulation for faecal incontinence. Br J Surg 2011;98:140-147.

255 Tan E, Ngo NT, Darzi A, Shenouda M, Tekkis PP: Meta-analysis: Sacral nerve stimulation versus conservative therapy in the treatment of faecal incontinence. Int J Colorectal Dis 2011;26:275-294.

256 Conaghan P, Farouk R: Sacral nerve stimulation can be successful in patients with ultrasound evidence of external anal sphincter disruption. Dis Colon Rectum 2005;48:1610-1614.

257 Jarrett ME, Dudding TC, Nicholls RJ, Vaizey CJ, Cohen CR, Kamm MA: Sacral nerve stimulation for fecal incontinence related to obstetric anal sphincter damage. Dis Colon Rectum 2008;51:531-537.

258 Vitton V, Gigout J, Grimaud JC, Bouvier M, Desjeux A, Orsoni P: Sacral nerve stimulation can improve continence in patients with crohn's disease with internal and external anal sphincter disruption. Dis Colon Rectum 2008;51:924-927.

259 Chan MK, Tjandra JJ: Sacral nerve stimulation for fecal incontinence: External anal sphincter defect vs. Intact anal sphincter. Dis Colon Rectum 2008;51:1015-1024; discussion 1024-1015.

260 Boyle DJ, Knowles CH, Lunniss PJ, Scott SM, Williams NS, Gill KA: Efficacy of sacral nerve stimulation for fecal incontinence in patients with anal sphincter defects. Dis Colon Rectum 2009;52:1234-1239.

261 Ratto C, Litta F, Parello A, Donisi L, Doglietto GB: Sacral nerve stimulation is a valid approach in fecal incontinence due to sphincter lesions when compared to sphincter repair. Dis Colon Rectum 2010;53:264-272.

262 Dudding TC, Parés D, Vaizey CJ, Kamm MA: Sacral nerve stimulation for the treatment of faecal incontinence related to dysfunction of the internal anal sphincter. Int J Colorectal Dis 2010;25:625-630.

263 Jarrett ME, Matzel KE, Stösser M, Christiansen J, Rosen H, Kamm MA: Sacral nerve stimulation for faecal incontinence following a rectosigmoid resection for colorectal cancer. Int J Colorectal Dis 2005;20:446-451.

264 de Miguel M, Oteiza F, Ciga MA, Armendáriz P, Marzo J, Ortiz H: Sacral nerve stimulation for the treatment of faecal incontinence following low anterior resection for rectal cancer. Colorectal Dis 2011;13:72-77.

265 Jarrett ME, Matzel KE, Stösser M, Baeten CG, Kamm MA: Sacral nerve stimulation for fecal incontinence following surgery for rectal prolapse repair: A multicenter study. Dis Colon Rectum 2005;48:1243-1248.

266 Robert-Yap J, Zufferey G, Rosen H, Lechner M, Wunderlich M, Roche B: Sacral nerve modulation in the treatment of fecal incontinence following repair of rectal prolapse. Dis Colon Rectum 2010;53:428-431.

267 Jarrett ME, Matzel KE, Christiansen J, Baeten CG, Rosen H, Bittorf B, Stösser M, Madoff R, Kamm MA: Sacral nerve stimulation for faecal incontinence in patients with previous partial spinal injury including disc prolapse. Br J Surg 2005;92:734-739.

268 Duelund-Jakobsen J, van Wunnik B, Buntzen S, Lundby L, Baeten C, Laurberg S: Functional results and patient satisfaction with sacral nerve stimulation for idiopathic faecal incontinence. Colorectal Dis 2011

269 Buntzen S, Rasmussen OO, Ryhammer AM, Sorensen

M, Laurberg S, Christiansen J: Sacral nerve stimulation for treatment of fecal incontinence in a patient with muscular dystrophy: Report of a case. Dis Colon Rectum 2004;47:1409-1411.

270 Meurette G, Wong M, Paye F, Parc Y, Tiret E, Lehur PA: Sacral nerve stimulation for the treatment of faecal incontinence after ileal pouch anal anastomosis. Colorectal Dis 2011;13:e182-183.

271 Holzer B, Rosen HR, Zaglmaier W, Klug R, Beer B, Novi G, Schiessel R: Sacral nerve stimulation in patients after rectal resection--preliminary report. J Gastrointest Surg 2008;12:921-925.

272 Maeda Y, Høyer M, Lundby L, Buntzen S, Laurberg S: Temporary sacral nerve stimulation for faecal incontinence following pelvic radiotherapy. Radiother Oncol 2010;97:108-112.

273 Schiano di Visconte M, Munegato G: The value of sacral nerve stimulation in the treatment of faecal incontinence after pelvic radiotherapy. Int J Colorectal Dis 2009;24:1111-1112.

274 Tjandra JJ, Chan MK, Yeh CH, Murray-Green C: Sacral nerve stimulation is more effective than optimal medical therapy for severe fecal incontinence: A randomized, controlled study. Dis Colon Rectum 2008;51:494-502.

275 Malouf AJ, Vaizey CJ, Nicholls RJ, Kamm MA: Permanent sacral nerve stimulation for fecal incontinence. Ann Surg 2000;232:143-148.

276 Muñoz-Duyos A, Navarro-Luna A, Brosa M, Pando JA, Sitges-Serra A, Marco-Molina C: Clinical and cost effectiveness of sacral nerve stimulation for faecal incontinence. Br J Surg 2008;95:1037-1043.

277 Hetzer FH, Bieler A, Hahnloser D, Löhlein F, Clavien PA, Demartines N: Outcome and cost analysis of sacral nerve stimulation for faecal incontinence. Br J Surg 2006;93:1411-1417.

278 Dudding TC, Meng Lee E, Faiz O, Parés D, Vaizey CJ, McGuire A, Kamm MA: Economic evaluation of sacral nerve stimulation for faecal incontinence. Br J Surg 2008;95:1155-1163.

279 Indinnimeo M, Ratto C, Moschella CM, Fiore A, Brosa M, Giardina S: Sacral neuromodulation for the treatment of fecal incontinence: Analysis of cost-effectiveness. Dis Colon Rectum 2010;53:1661-1669.

280 Leroi AM, Damon H, Faucheron JL, Lehur PA, Siproudhis L, Slim K, Barbieux JP, Barth X, Borie F, Bresler L, Desfourneaux V, Goudet P, Huten N, Lebreton G, Mathieu P, Meurette G, Mathonnet M, Mion F, Orsoni P, Parc Y, Portier G, Rullier E, Sielezneff I, Zerbib F, Michot F, NEMO C: Sacral nerve stimulation in faecal incontinence: Position statement based on a collective experience. Colorectal Dis 2009;11:572-583.

281 Faucheron JL, Voirin D, Badic B: Sacral nerve stimulation for fecal incontinence: Causes of surgical revision from a series of 87 consecutive patients operated on in a single institution. Dis Colon Rectum 2010;53:1501-1507.

282 Faucheron JL, Herault MC: Life threatening haemorrhage after electrode removal: A severe complication following sacral nerve stimulation procedure for the treatment of faecal incontinence. Colorectal Dis 2011

283 Maeda Y, Matzel K, Lundby L, Buntzen S, Laurberg S: Postoperative issues of sacral nerve stimulation for fecal incontinence and constipation: A systematic literature review and treatment guideline. Dis Colon Rectum 2011;54:1443-1460.

284 Shafik A, Ahmed I, El-Sibai O, Mostafa RM: Percutaneous peripheral neuromodulation in the treatment of fecal incontinence. Eur Surg Res 2003;35:103-107.

285 McGuire EJ, Zhang SC, Horwinski ER, Lytton B: Treatment of motor and sensory detrusor instability by electrical stimulation. J Urol 1983;129:78-79.

286 Nakamura M, Sakurai T, Tsujimoto Y, Tada Y: [transcutaneous electrical stimulation for the control of frequency and urge incontinence]. Hinyokika Kiyo 1983;29:1053-1059.

287 Vandoninck V, Van Balken MR, Finazzi Agró E, Petta F, Caltagirone C, Heesakkers JP, Kiemeney LA, Debruyne FM, Bemelmans BL: Posterior tibial nerve stimulation in the treatment of urge incontinence. Neurourol Urodyn 2003;22:17-23.

288 Stoller ML: Afferent nerve stimulation for pelvic floor dysfunction (abstract). Eur Urol 1999;35:16.

289 Queralto M, Portier G, Cabarrot PH, Bonnaud G, Chotard JP, Nadrigny M, Lazorthes F: Preliminary results of peripheral transcutaneous neuromodulation in the treatment of idiopathic fecal incontinence. Int J Colorectal Dis 2006;21:670-672.

290 de la Portilla F, Rada R, Vega J, González CA, Cisneros N, Maldonado VH: Evaluation of the use of posterior tibial nerve stimulation for the treatment of fecal incontinence: Preliminary results of a prospective study. Dis Colon Rectum 2009;52:1427-1433.

291 Govaert B, Pares D, Delgado-Aros S, La Torre F, Van Gemert WG, Baeten CG: A prospective multicentre study to investigate percutaneous tibial nerve stimulation for the treatment of faecal incontinence. Colorectal Dis 2010;12:1236-1241.

292 Boyle DJ, Prosser K, Allison ME, Williams NS, Chan CL: Percutaneous tibial nerve stimulation for the treatment of urge fecal incontinence. Dis Colon Rectum 2010;53:432-437.

293 Hotouras A, Thaha MA, Boyle D, Allison ME, Currie A, Knowles CH, Chan CL: Short-term outcome following percutaneous tibial nerve stimulation (ptns) for faecal incontinence: A single-centre prospective study. Colorectal Dis 2011 Dec 6;[Epub ahead of print]

294 Vitton V, Veronique V, Damon H, Henri D, Roman S, Sabine R, Mion F, François M: Transcutaneous electrical posterior tibial nerve stimulation for faecal incontinence: Effects on symptoms and quality of life. Int J Colorectal Dis 2010;25:1017-1020.

295 Eléouet M, Siproudhis L, Guillou N, Le Couedic J, Bouguen G, Bretagne JF: Chronic posterior tibial nerve transcutaneous electrical nerve stimulation (tens) to treat fecal incontinence (fi). Int J Colorectal Dis 2010;25:1127-1132.

296 Findlay JM, Yeung JM, Robinson R, Greaves H, Maxwell-Armstrong C: Peripheral neuromodulation via posterior tibial nerve stimulation - a potential treatment for faecal incontinence? Ann R Coll Surg Engl 2010;92:385-390.

297 Mentes BB, Yuksel O, Aydin A, Tezcaner T, Leventoglu A, Aytac B: Posterior tibial nerve stimulation for faecal incontinence after partial spinal injury: Preliminary report. Tech Coloproctol 2007;11:115-119.

298 Hotouras A, Thaha MA, Allison ME, Currie A, Scott SM, Chan CL: Percutaneous tibial nerve stimulation (ptns) in females with faecal incontinence: The impact of sphincter morphology and rectal sensation on the clinical outcome. Int J Colorectal Dis 2012 Jan 25; [Epub ahead of print]

299 Keegan PE, Atiemo K, Cody J, McClinton S, Pickard R: Periurethral injection therapy for urinary incontinence in women. Cochrane Database Syst Rev 2007:CD003881.

300 Kotb AF, Campeau L, Corcos J: Urethral bulking agents: Techniques and outcomes. Curr Urol Rep 2009;10:396-400.

301 Shafik A: Polytetrafluoroethylene injection for the treatment of partial fecal incontinence. Int Surg 1993;78:159-161.

302 Shafik A: Perianal injection of autologous fat for treatment of sphincteric incontinence. Dis Colon Rectum 1995;38:583-587.

303 Kumar D, Benson MJ, Bland JE: Glutaraldehyde cross-linked collagen in the treatment of faecal incontinence. Br J Surg 1998;85:978-979.

304 Malouf AJ, Vaizey CJ, Norton CS, Kamm MA: Internal anal sphincter augmentation for fecal incontinence

using injectable silicone biomaterial. Dis Colon Rectum 2001;44:595-600.

305 Feretis C, Benakis P, Dailianas A, Dimopoulos C, Mavrantonis C, Stamou KM, Manouras A, Apostolidis N, Androulakis G: Implantation of microballoons in the management of fecal incontinence. Dis Colon Rectum 2001;44:1605-1609.

306 Davis K, Kumar D, Poloniecki J: Preliminary evaluation of an injectable anal sphincter bulking agent (durasphere) in the management of faecal incontinence. Aliment Pharmacol Ther 2003;18:237-243.

307 Tjandra JJ, Lim JF, Hiscock R, Rajendra P: Injectable silicone biomaterial for fecal incontinence caused by internal anal sphincter dysfunction is effective. Dis Colon Rectum 2004;47:2138-2146.

308 Stojkovic SG, Lim M, Burke D, Finan PJ, Sagar PM: Intra-anal collagen injection for the treatment of faecal incontinence. Br J Surg 2006;93:1514-1518.

309 Dehli T, Lindsetmo RO, Mevik K, Vonen B: [anal incontinence--assessment of a new treatment]. Tidsskr Nor Laegeforen 2007;127:2934-2936.

310 Siproudhis L, Morcet J, Lainé F: Elastomer implants in faecal incontinence: A blind, randomized placebo-controlled study. Aliment Pharmacol Ther 2007;25:1125-1132.

311 de la Portilla F, Fernandez A, Leon E, Rada R, Cisneros N, Maldonado VH, Vega J, Espinosa E: Evaluation of the use of ptq implants for the treatment of incontinent patients due to internal anal sphincter dysfunction. Colorectal Dis 2008;10:89-94.

312 Altomare DF, La Torre F, Rinaldi M, Binda GA, Pescatori M: Carbon-coated microbeads anal injection in outpatient treatment of minor fecal incontinence. Dis Colon Rectum 2008;51:432-435.

313 Maeda Y, Vaizey CJ, Kamm MA: Pilot study of two new injectable bulking agents for the treatment of faecal incontinence. Colorectal Dis 2008;10:268-272.

314 Ganio E, Marino F, Giani I, Luc AR, Clerico G, Novelli E, Trompetto M: Injectable synthetic calcium hydroxylapatite ceramic microspheres (coaptite) for passive fecal incontinence. Tech Coloproctol 2008;12:99-102.

315 Soerensen MM, Lundby L, Buntzen S, Laurberg S: Intersphincteric injected silicone biomaterial implants: A treatment for faecal incontinence. Colorectal Dis 2009;11:73-76.

316 Tjandra JJ, Chan MK, Yeh HC: Injectable silicone biomaterial (ptq) is more effective than carbon-coated beads (durasphere) in treating passive faecal incontinence--a randomized trial. Colorectal Dis 2009;11:382-389.

317 Bartlett L, Ho YH: Ptq anal implants for the treatment of faecal incontinence. Br J Surg 2009;96:1468-1475.

318 Aigner F, Conrad F, Margreiter R, Oberwalder M, Group CW: Anal submucosal carbon bead injection for treatment of idiopathic fecal incontinence: A preliminary report. Dis Colon Rectum 2009;52:293-298.

319 Oliveira LC, Neves Jorge JM, Yussuf S, Habr-Gama A, Kiss D, Cecconello I: Anal incontinence improvement after silicone injection may be related to restoration of sphincter asymmetry. Surg Innov 2009;16:155-161.

320 Danielson J, Karlbom U, Sonesson AC, Wester T, Graf W: Submucosal injection of stabilized nonanimal hyaluronic acid with dextranomer: A new treatment option for fecal incontinence. Dis Colon Rectum 2009;52:1101-1106.

321 Beggs AD, Irukulla S, Sultan AH, Ness W, Abulafi AM: A pilot study of ultrasound guided durasphere injection in the treatment of faecal incontinence. Colorectal Dis 2010;12:935-940.

322 Stephens JH, Rieger NA, Farmer KC, Bell SW, Hooper JE, Hewett PJ: Implantation of ethylene vinyl alcohol copolymer for faecal incontinence management. ANZ J Surg 2010;80:324-330.

323 Ratto C, Parello A, Donisi L, Litta F, De Simone V, Spazzafumo L, Giordano P: Novel bulking agent for faecal incontinence. Br J Surg 2011;98:1644-1652.

324 Graf W, Mellgren A, Matzel KE, Hull T, Johansson C, Bernstein M, Group NDS: Efficacy of dextranomer in stabilised hyaluronic acid for treatment of faecal incontinence: A randomised, sham-controlled trial. Lancet 2011;377:997-1003.

325 Lee PE, Kung RC, Drutz HP: Periurethral autologous fat injection as treatment for female stress urinary incontinence: A randomized double-blind controlled trial. J Urol 2001;165:153-158.

326 Kenefick NJ, Vaizey CJ, Malouf AJ, Norton CS, Marshall M, Kamm MA: Injectable silicone biomaterial for faecal incontinence due to internal anal sphincter dysfunction. Gut 2002;51:225-228.

327 Chan MK, Tjandra JJ: Injectable silicone biomaterial (ptq) to treat fecal incontinence after hemorrhoidectomy. Dis Colon Rectum 2006;49:433-439.

328 Maeda Y, Vaizey CJ, Kamm MA: Long-term results of perianal silicone injection for faecal incontinence. Colorectal Dis 2007;9:357-361.

329 Weiss E, Efron J, Nogueras J, Wexner S: Submucosal injection of carbon-coated beads is a successful and safe office-based treatment of fecal incontinence [abstract]. Dis Colon Rectum 2002;45:A46.

330 Stenberg AM, Larsson G, Johnson P: Urethral injection for stress urinary incontinence: Long-term results with dextranomer/hyaluronic acid copolymer. Int Urogynecol J Pelvic Floor Dysfunct 2003;14:335-338; discussion 338.

331 Schwandner O, Brunner M, Dietl O: Quality of life and functional results of submucosal injection therapy using dextranomer hyaluronic acid for fecal incontinence. Surg Innov 2011;18:130-135.

332 Hussain ZI, Lim M, Stojkovic SG: Systematic review of perianal implants in the treatment of faecal incontinence. Br J Surg 2011;98:1526-1536.

333 Luo C, Samaranayake CB, Plank LD, Bissett IP: Systematic review on the efficacy and safety of injectable bulking agents for passive faecal incontinence. Colorectal Dis 2010;12:296-303.

334 Maeda Y, Laurberg S, Norton C: Perianal injectable bulking agents as treatment for faecal incontinence in adults. Cochrane Database Syst Rev 2010:CD007959.

335 Branagan G, Tromans A, Finnis D: Effect of stoma formation on bowel care and quality of life in patients with spinal cord injury. Spinal Cord 2003;41:680-683.

336 Randell N, Lynch AC, Anthony A, Dobbs BR, Roake JA, Frizelle FA: Does a colostomy alter quality of life in patients with spinal cord injury? A controlled study. Spinal Cord 2001;39:279-282.

337 Colquhoun P, Kaiser R, Jr., Efron J, Weiss EG, Nogueras JJ, Vernava AM, 3rd, Wexner SD: Is the quality of life better in patients with colostomy than patients with fecal incontience? World J Surg 2006;30:1925-1928.

338 Norton C, Burch J, Kamm MA: Patients' views of a colostomy for fecal incontinence. Dis Colon Rectum 2005;48:1062-1069.

339 Catena F, Wilkinson K, Phillips RK: Untreatable faecal incontinence: Colostomy or colostomy and proctectomy? Colorectal Dis 2002;4:48-50.

340 O'Rourke DA: An anorectal sling in the treatment of rectal prolapse and incontinence. Aust N Z J Surg 1974;44:144-146.

341 Novara G, Ficarra V, Boscolo-Berto R, Secco S, Cavalleri S, Artibani W: Tension-free midurethral slings in the treatment of female stress urinary incontinence: A systematic review and meta-analysis of randomized controlled trials of effectiveness. Eur Urol 2007;52:663-678.

342 Shafik IA, Shafik A: Double-loop puborectoplasty: Novel technique for the treatment of fecal incontinence. Surg Technol Int 2009;18:103-108.

343 Yamana T, Takahashi T, Iwadare J: Perineal puborectalis sling operation for fecal incontinence: Preliminary report. Dis Colon Rectum 2004;47:1982-1989.

344 O'Rourke DA, Egerton WM: A puborectal sling in the management of anal incontinence and rectal prolapse. Aust N Z J Surg 1985;55:493-495.

345 Shafik A: Puborectoplasty: New technique for the repair of fecal incontinence. Dig Surg 1991;8:181-186.

346 deVries PA, Peña A: Posterior sagittal anorectoplasty. J Pediatr Surg 1982;17:638-643.

347 Peña A, Devries PA: Posterior sagittal anorectoplasty: Important technical considerations and new applications. J Pediatr Surg 1982;17:796-811.

348 Brain AJ, Kiely EM: Posterior sagittal anorectoplasty for reoperation in children with anorectal malformations. Br J Surg 1989;76:57-59.

349 Applebaum H, Atkinson JB: The posterior sagittal approach for reconstruction of severe rectovaginal injuries. J Pediatr Surg 1991;26:856-857.

350 Bischoff A, Levitt MA, Peña A: Laparoscopy and its use in the repair of anorectal malformations. J Pediatr Surg 2011;46:1609-1617.

351 Bailez MM, Cuenca ES, Di Benedetto V, Solana J: Laparoscopic treatment of rectovaginal fistulas. Feasibility, technical details, and functional results of a rare anorectal malformation. J Pediatr Surg 2010;45:1837-1842.

352 Bailez MM, Cuenca ES, Mauri V, Solana J, Di Benedetto V: Outcome of males with high anorectal malformations treated with laparoscopic-assisted anorectal pull-through: Preliminary results of a comparative study with the open approach in a single institution. J Pediatr Surg 2011;46:473-477.

353 Vick LR, Gosche JR, Boulanger SC, Islam S: Primary laparoscopic repair of high imperforate anus in neonatal males. J Pediatr Surg 2007;42:1877-1881.

354 Yang J, Zhang W, Feng J, Guo X, Wang G, Weng Y, Sun X, Yu D: Comparison of clinical outcomes and anorectal manometry in patients with congenital anorectal malformations treated with posterior sagittal anorectoplasty and laparoscopically assisted anorectal pull through. J Pediatr Surg 2009;44:2380-2383.

355 Peña A: The surgical management of persistent cloaca: Results in 54 patients treated with a posterior sagittal approach. J Pediatr Surg 1989;24:590-598.

356 Peña A: Total urogenital mobilization--an easier way to repair cloacas. J Pediatr Surg 1997;32:263-267; discussion 267-268.

357 Peña A, Levitt MA, Hong A, Midulla P: Surgical management of cloacal malformations: A review of 339 patients. J Pediatr Surg 2004;39:470-479; discussion 470-479.

358 Peña A, Hong A: Advances in the management of anorectal malformations. Am J Surg 2000;180:370-376.

359 Bischoff A, Levitt MA, Bauer C, Jackson L, Holder M, Peña A: Treatment of fecal incontinence with a comprehensive bowel management program. J Pediatr Surg 2009;44:1278-1283; discussion 1283-1274.

360 Rintala R, Lindahl H, Marttinen E, Sariola H: Constipation is a major functional complication after internal sphincter-saving posterior sagittal anorectoplasty for high and intermediate anorectal malformations. J Pediatr Surg 1993;28:1054-1058.

361 Malone PS, Ransley PG, Kiely EM: Preliminary report: The antegrade continence enema. Lancet 1990;336:1217-1218.

362 Griffiths DM, Malone PS: The malone antegrade continence enema. J Pediatr Surg 1995;30:68-71.

363 Levitt MA, Soffer SZ, Peña A: Continent appendicostomy in the bowel management of fecally incontinent children. J Pediatr Surg 1997;32:1630-1633.

364 Herndon CD, Rink RC, Cain MP, Lerner M, Kaefer M, Yerkes E, Casale AJ: In situ malone antegrade continence enema in 127 patients: A 6-year experience. J Urol 2004;172:1689-1691.

365 Koivusalo A, Pakarinen M, Rintala RJ: Are cecal wrap and fixation necessary for antegrade colonic enema appendicostomy? J Pediatr Surg 2006;41:323-326.

366 Goepel M, Sperling H, Stöhrer M, Otto T, Rübben H: Management of neurogenic fecal incontinence in myelodysplastic children by a modified continent appendiceal stoma and antegrade colonic enema. Urology 1997;49:758-761.

367 Tam PK: Y-appendicoplasty: A technique to minimize stomal complications in antegrade continence enema. J Pediatr Surg 1999;34:1733-1735.

368 Rangel SJ, Lawal TA, Bischoff A, Chatoorgoon K, Louden E, Peña A, Levitt MA: The appendix as a conduit for antegrade continence enemas in patients with anorectal malformations: Lessons learned from 163 cases treated over 18 years. J Pediatr Surg 2011;46:1236-1242.

369 Squire R, Kiely EM, Carr B, Ransley PG, Duffy PG: The clinical application of the malone antegrade colonic enema. J Pediatr Surg 1993;28:1012-1015.

370 Yerkes EB, Rink RC, Cain MP, Casale AJ: Use of a monti channel for administration of antegrade continence enemas. J Urol 2002;168:1883-1885; discussion 1885.

371 Lawal TA, Rangel SJ, Bischoff A, Peña A, Levitt MA: Laparoscopic-assisted malone appendicostomy in the management of fecal incontinence in children. J Laparoendosc Adv Surg Tech A 2011;21:455-459.

372 Lynch AC, Beasley SW, Robertson RW, Morreau PN: Comparison of results of laparoscopic and open antegrade continence enema procedures. Pediatr Surg Int 1999;15:343-346.

373 Nanigian DK, Kurzrock EA: Intermediate-term outcome of the simplified laparoscopic antegrade continence enema procedure: Less is better. J Urol 2008;179:299-303.

374 Webb HW, Barraza MA, Crump JM: Laparoscopic appendicostomy for management of fecal incontinence. J Pediatr Surg 1997;32:457-458.

375 Curry JI, Osborne A, Malone PS: How to achieve a successful malone antegrade continence enema. J Pediatr Surg 1998;33:138-141.

376 Dey R, Ferguson C, Kenny SE, Shankar KR, Coldicutt P, Baillie CT, Lamont GL, Lloyd DA, Losty PD, Turnock RR: After the honeymoon--medium-term outcome of antegrade continence enema procedure. J Pediatr Surg 2003;38:65-68; discussion 65-68.

377 Shankar KR, Losty PD, Kenny SE, Booth JM, Turnock RR, Lamont GL, Rintala RJ, Lloyd DA: Functional results following the antegrade continence enema procedure. Br J Surg 1998;85:980-982.

378 Tackett LD, Minevich E, Benedict JF, Wacksman J, Sheldon CA: Appendiceal versus ileal segment for antegrade continence enema. J Urol 2002;167:683-686.

379 Yerkes EB, Cain MP, King S, Brei T, Kaefer M, Casale AJ, Rink RC: The malone antegrade continence enema procedure: Quality of life and family perspective. J Urol 2003;169:320-323.

380 Wilcox DT, Kiely EM: The malone (antegrade colonic enema) procedure: Early experience. J Pediatr Surg 1998;33:204-206.

381 Kiely EM, Ade-Ajayi N, Wheeler R: Antegrade continence enemas in the management of intractable faecal incontinence. J R Soc Med 1995;88:103P-104P.

382 Wong AL, Kravarusic D, Wong SL: Impact of cecostomy and antegrade colonic enemas on management of fecal incontinence and constipation: Ten years of experience in pediatric population. J Pediatr Surg 2008;43:1445-1451.

383 Lopez PJ, Ashrafian H, Clarke SA, Johnson H, Kiely EM: Early experience with the antegrade colonic enema stopper to reduce stomal stenosis. J Pediatr Surg 2007;42:522-524.

384 Siddiqui AA, Fishman SJ, Bauer SB, Nurko S: Long-term follow-up of patients after antegrade continence enema procedure. J Pediatr Gastroenterol Nutr 2011;52:574-580.

385 Driver CP, Barrow C, Fishwick J, Gough DC, Bianchi A, Dickson AP: The malone antegrade colonic enema procedure: Outcome and lessons of 6 years' experience. Pediatr Surg Int 1998;13:370-372.

386 Hensle TW, Reiley EA, Chang DT: The malone antegrade continence enema procedure in the management of patients with spina bifida. J Am Coll Surg 1998;186:669-674.

387 Kokoska ER, Herndon CD, Carney DE, Lerner M, Grosfeld JL, Rink RC, West Kw KW: Cecal volvulus: A report of two cases occurring after the antegrade colonic enema procedure. J Pediatr Surg 2004;39:916-919; discussion 916-919.

388 Catto-Smith AG, Coffey CM, Nolan TM, Hutson JM: Fecal incontinence after the surgical treatment of hirschsprung disease. J Pediatr 1995;127:954-957.

389 Malone PS, Wheeler RA, Williams JE: Continence in patients with spina bifida: Long term results. Arch Dis Child 1994;70:107-110.

390 Peña A, el Behery M: Megasigmoid: A source of pseudoincontinence in children with repaired anorectal malformations. J Pediatr Surg 1993;28:199-203.

391 Hallows MR, Lander AD, Corkery JJ: Anterior resection for megarectosigmoid in congenital anorectal malformations. J Pediatr Surg 2002;37:1464-1466.

392 Lee SL, DuBois JJ, Montes-Garces RG, Inglis K, Biediger W: Surgical management of chronic unremitting constipation and fecal incontinence associated with megarectum: A preliminary report. J Pediatr Surg 2002;37:76-79.

393 Peña A, Guardino K, Tovilla JM, Levitt MA, Rodriguez G, Torres R: Bowel management for fecal incontinence in patients with anorectal malformations. J Pediatr Surg 1998;33:133-137.

394 Chen YL, Zhang XH: Reconstruction of rectal sphincter by transposition of gluteus muscle for fetal incontinence. J Pediatr Surg 1987;22:62-64.

395 Danielson J, Karlbom U, Graf W, Wester T: Long-term outcome after free autogenous muscle transplantation for anal incontinence in children with anorectal malformations. J Pediatr Surg 2010;45:2036-2040.

396 Hakelius L, Olsen L: Free autogenous muscle transplantation in children. Long-term results. Eur J Pediatr Surg 1991;1:353-357.

397 Han SJ, Park HJ, Kim CB, Hwang EH: Long-term follow-up of gracilis muscle transposition in children. Yonsei Med J 1995;36:372-377.

398 Kottmeier PK, Velcek FT, Klotz DH, Coren CV, Hansbrough F, Price AP: Results of levatorplasty for anal incontinence. J Pediatr Surg 1986;21:647-650.

399 Leguit P, van Baal JG, Brummelkamp WH: Gracilis muscle transposition in the treatment of fecal incontinence. Long-term follow-up and evaluation of anal pressure recordings. Dis Colon Rectum 1985;28:1-4.

400 Meehan JJ, Hardin WD, Georgeson KE: Gluteus maximus augmentation for the treatment of fecal incontinence. J Pediatr Surg 1997;32:1045-1047; discussion 1047-1048.

401 Puri P, Nixon HH: Levatorplasty: A secondary operation for fecal incontinence following primary operation for anorectal agenesis. J Pediatr Surg 1976;11:77-82.

402 Skef Z, Radhakrishnan J, Reyes HM: Anorectal continence following sphincter reconstruction utilizing the gluteus maximus muscle: A case report. J Pediatr Surg 1983;18:779-781.

403 Sonnino RE, Reinberg O, Bensoussan AL, Laberge JM, Blanchard H: Gracilis muscle transposition for anal incontinence in children: Long-term follow-up. J Pediatr Surg 1991;26:1219-1223.

404 Rückauer KD: Dynamic graciloplasty in children with fecal incontinence: A preliminary report. J Pediatr Surg 2001;36:1036-1039.

405 Haddad M, Besson R, Aubert D, Ravasse P, Lemelle J, El Ghoneimi A, Moscovici J, Hameury F, Baumstarck-Barrau K, Hery G, Guys JM: Sacral neuromodulation in children with urinary and fecal incontinence: A multicenter, open label, randomized, crossover study. J Urol 2010;184:696-701.

406 Congilosi SM, Johnson DR, Medot M, Tretinyak A, McCormick SR, Wong WD, Rothenberger DA, Madoff RD: Experimental model of pudendal nerve innervation of a skeletal muscle neosphincter for faecal incontinence. Br J Surg 1997;84:1269-1273.

407 Healy CF, O'Herlihy C, O'Brien C, O'Connell PR, Jones JF: Experimental models of neuropathic fecal incontinence: An animal model of childbirth injury to the pudendal nerve and external anal sphincter. Dis Colon Rectum 2008;51:1619-1626; discussion 1626.

408 Salcedo L, Damaser M, Butler R, Jiang HH, Hull T, Zutshi M: Long-term effects on pressure and electromyography in a rat model of anal sphincter injury. Dis Colon Rectum 2010;53:1209-1217.

409 Møller FV, Buntzen S, Rijkhoff NJ, Laurberg S: Pelvic nerve stimulation evokes nitric oxide mediated distal rectal relaxation in pigs. Dis Colon Rectum 2008;51:1261-1267.

410 Banahan M, Peirce C, Buffini M, O'Herlihy C, O'Connell PR, Jones JF: Atrophy of the sphincters of continence in an experimental model. Colorectal Dis 2010;12:e153-157.

411 Griffin KM, O'Herlihy C, O'Connell PR, Jones JF: Combined ischemic and neuropathic insult to the anal canal in an animal model of obstetric-related trauma. Dis Colon Rectum 2012;55:32-41.

412 Zutshi M, Salcedo LB, Zaszczurynski PJ, Hull TL, Butler RS, Damaser MS: Effects of sphincterotomy and pudendal nerve transection on the anal sphincter in a rat model. Dis Colon Rectum 2009;52:1321-1329.

413 Smaldone MC, Chancellor MB: Muscle derived stem cell therapy for stress urinary incontinence. World J Urol 2008;26:327-332.

414 Frudinger A, Kölle D, Schwaiger W, Pfeifer J, Paede J, Halligan S: Muscle-derived cell injection to treat anal incontinence due to obstetric trauma: Pilot study with 1 year follow-up. Gut 2010;59:55-61.

415 Fitzpatrick R, Davey C, Buxton MJ, Jones DR: Evaluating patient-based outcome measures for use in clinical trials. Health Technol Assess 1998;2:i-iv, 1-74.

416 Cotterill N, Norton C, Avery KN, Abrams P, Donovan JL: Psychometric evaluation of a new patient-completed questionnaire for evaluating anal incontinence symptoms and impact on quality of life: The iciq-b. Dis Colon Rectum 2011;54:1235-1250.

Committee 18

Fistula

Chair

Dirk De Ridder (Belgium)

Members

Obstetrical fistula*

Paul Abrams (UK)

Catherine De Vries (USA)

Suzy Elneil (UK)

Alice Emasu (Uganda)

Gloria Esegbono (UK/Nigeria)

Serigne Gueye (Senegal)

Rahmat Mohammad (Nigeria)

Sherif Mourad (Egypt)

Mulu Muleta (Ethiopia)

Non-obstetrical fistula

Paul Hilton (UK)

Sherif Mourad (Egypt)

Robert Pickard (UK)

Edward Stanford (USA)

Consultant

Eric Rovner (USA)

***The obstetrical fistula part contains the scientific summary of the ICI meeting held in Marrakech, Marocco 2010. The full text of all obstetrical fistula chapters will be published as a separate volume.**

CONTENTS

GENERAL INTRODUCTION

A. Obstetrical fistula

I. INTRODUCTION

II. WOMEN, FISTULA SURGEONS, NGOS AND GOVERNMENTS

1. EPIDEMIOLOGY OF VVF
2. PREVENTION OF VVF
3. UNMET NEEDS IN VVF
4. MANAGEMENT OF NEW AND ESTABLISHED VVFS
5. CLASSIFICATION OF VVF
6. MANAGEMENT OF THE COMPLICATIONS OF VVF
7. SOCIAL RE-INTEGRATION OF TREATED WOMEN

B. Non-obstetrical fistula

I. INTRODUCTION

II. EPIDEMIOLOGY

1. POST-GYNAECOLOGICAL SURGERY
2. ONCOLOGICAL FISTULA
3. CANCER SURGERY
4. RADIATION FISTULA
5. CHEMOTHERAPY
6. COMBINATION THERAPIES

III. URETERIC FISTULA

IV. FISTULA INVOLVING THE GI TRACT

V. DIAGNOSIS OF FISTULA

1. CLINICAL DIAGNOSIS
2. DIAGNOSIS OF GI FISTULA
3. RECOMMENDATIONS

VI. MANAGEMENT OF VESICO-VAGINAL FISTULA

1. CONSERVATIVE MANAGEMENT
2. SURGICAL MANAGEMENT
3. POST-OPERATIVE MANAGEMENT
4. MANAGEMENT OF RADIATION FISTULA

VII. MANAGEMENT OF GI FISTULA

1. LITERATURE REVIEW
2. NON-SURGICAL MANAGEMENT
3. SURGICAL MANAGEMENT
4. RECOMMENDATIONS

VIII. MANAGEMENT OF URETERIC FISTULA

1. GENERAL PRINCIPLES
2. EVIDENCE QUALITY
3. EVIDENCE SUMMARY
4. RECOMMENDATIONS

IX. MANAGEMENT OF URETHRO-VAGINAL FISTULA

1. INTRODUCTION
2. AETIOLOGY
3. DIAGNOSIS
4. SURGICAL REPAIR
5. COMPLICATIONS
6. FOLLOW UP

REFERENCES

Fistula

Dirk De Ridder

Obstetrical fistula: *Paul Abrams, Catherine De Vries, Suzy Elneil, Alice Emasu, Gloria Esegbono, Serigne Gueye, Rahmat Mohammad, Sherif Mourad*

Non-obstetrical fistula: *Paul Hilton, Sherif Mourad, Robert Pickard, Edward Stanford*

Consultant

Eric Rovner

GENERAL INTRODUCTION

In the developing world fistula are often a consequence of poor peri-natal care. The epidemiology, aetiology, diagnosis, treatment and prevention have been described in detail during the recent International Consultations on Incontinence.[1, 2]

In contrast to the field of obstetrical fistula where the numbers of patients are high, the prevalence of non-obstetrical fistula seems to be much lower. The published series deal with small numbers, are usually retrospective and have a low level of evidence. The published obstetrical series show impressive numbers and demonstrate the level of skill that many of the fistula surgeons have obtained while working in difficult and isolated situations.

In this consultation the main focus has been put on iatrogenic fistula in the developed world. An entirely new chapter was compiled on this subject.

Despite the fact that the main focus was to write a chapter on iatrogenif fistula, in this edition the scientific summary of the International Consultation on Vesicovaginal fistula in the developing world, which was held in Marrakech, Marocco in 2010 was added to the text.

Both committees are convinced that obstetric fistula surgeons in the developing world and reconstructive pelvic surgeons in the developed countries can learn a lot from each other. Combining the obstetrical and iatrogenic fistula into one chapter will facilitate interaction and exchange of knowledge and ideas in this difficult field of fistula repair.

A. Obstetrical fistula

I. INTRODUCTION

The First ICUD-SIU Consultation on Vesico-Vaginal Fistula was held at the SIU meeting in Marrakech, Morocco, October 13th – 16th 2010. The recommendations are evidence-based, following a thorough review of the available literature and the opinion of recognised experts serving on the six committees. The individual committee reports were developed and peer-reviewed by open presentation and comment. Review of the literature showed no Level 1 evidence in that there were no randomised controlled trials. All evidence was confined to case series and observational data: Level 3 and 4 evidence. Hence, all recommendations were Grade B and C.

The Scientific Committee includes the chairmen of the six committees, who refined the final recommendations. These recommendations published in 2011, will be periodically re-evaluated in the light of clinical experience, technological progress and research. These recommendations are taken from the full versions of the six Consultation chapters, from Epidemiology through to Social Reintegration. These chapters provide the full documentation of the existing scientific literature on the six topic areas.

II. WOMEN, FISTULA SURGEONS, NGOS AND GOVERNMENTS

The effect on a woman, in the developing world, of having a VVF resulting from obstructed labour, is disastrous from her point of view, the family perspective and for her society. It is estimated that there are two million women, in developing countries, mainly in sub-Saharan Africa, the Indian sub-continent and South- East Asia, who have either undetected or untreated VVFs. New fistulas are probably occurring at the rate of 82,000 new cases per year, yet only 10,000 operations for fistula closure are being done annually. Hence, this leaves a huge unmet need.

VVF, in itself, is bad enough, but it is also inextricably linked with high maternal mortality rate and high infant death rate. Hence the solution to fistula is similar to the solutions that will drive down the maternal mortality rate and the infant death rate. The solutions are not only medical, but also social and political.

At present, women in developing countries are often dependent on donations that reach their country

through non-governmental organisations (NGOs) and charities. The relationship between the NGOs and the fistula surgeons are critical. The fistula surgeons are the experts and those to whom fistula women turn for help. Hence, it is vital that the NGOs allow themselves to be guided by the fistula surgeons as to the priorities within their sphere of work. The vital role of the NGOs is to provide financial and logistical support. Support is also essential to allow the fistula surgeons to write up their work. This is often a considerable problem, as their commitment to the women means that their academic time is restricted. Nevertheless, the data the fistula surgeons generate is their intellectual property, and it is vital that they retain primary authorship of all published material.

There are an enormous number of committed and dedicated individuals from both within the developing countries and from developed countries who have committed themselves to the cause of helping women with this dreadful condition. However, the long-term solution must see the responsibilities for women's and children's health passing to the governments of the individual countries. Nevertheless, in the meantime, those many dedicated individuals will continue to strive to help as many women as possible return to a life in their own community.

1. EPIDEMIOLOGY OF VVF

Epidemiological studies on obstetric fistula are inadequate.

- They are mainly institutionally-based, retrospective cases series, often written from the perspective of a single fistula surgeon
- The geographical coverage of epidemiological reports is uneven
- However, better and more relevant information is emerging.

The incidence of fistula is expressed per 1,000 deliveries and would appear to be between 0.1% rising to 1.5 per 1,000 pregnancies in rural areas.

The major risk factors appear to be age at first marriage, short stature, pregnancy with a male child rather than a female child, failure to attend antenatal care, low socio-economic status, low social class, lack of employment and illiteracy.

The consequences of obstetric fistula include divorce (16-92%), social isolation, worsening poverty, malnutrition, sexual dysfunction and mental illness (including anxiety/depression), insomnia, general ill health and thoughts of worthlessness and suicide.

There are few detailed reports documenting these women's obstructed labours. The time of onset of labour is rarely recorded and reports from delivery locations may disregard the fact that the woman has laboured at home for days prior to attending the delivery location. The reason for the woman not receiving help rarely differentiates between the absence of health-seeking behaviour and the lack of services. The only observational study showed no substantial difference between VVF patients and women who delivered without fistula, both in terms of their use of orthodox health care services and more traditional forms of support before childbirth.

Recommendations

1. Community-based epidemiological studies using standardised and validated collection tools with acceptable sensitivity and specificity are highly recommended.
2. A validated standardised collection tool should be developed and used in national surveys to facilitate the collection and comparison of data when assessing the regional, continental and global magnitude of VVF and the distribution of fistula world-wide.
3. Prospective longitudinal community-based studies are needed to estimate the incidence of obstetric fistula.
4. Observational studies are needed, utilising advanced epidemiological analyses for:
   - Risk factors (multivariate analysis controlling potential biases)
   - Impacts and consequences of VVF
   - Determining health-seeking behaviour
5. Research that identifies the different profiles of women who manage to overcome the obstacles and successfully access health care, compared to those who do not, is recommended.
6. The contribution of other factors, such as ethnic background and malnutrition, needs to be researched and understood.
7. It is recommended that there is long-term follow up of patients following fistula repair to understand their ongoing quality of life and any long-term sequelae and their ongoing needs.

2. PREVENTION OF VVF

VVF is a characteristic of abject poverty, a clear marker of failure of political, social and health systems to protect and promote women's health and their rights. Prevention of VVF is ultimately linked to prevention of maternal and infant mortality and is a requirement of MDG5 of 2000.

Prevention, from the medical and public health point of view, mitigates the effect of VVF in the overall burden of pain and suffering the condition imposes, not just on the patient herself, but her family and the entire community. History has shown that improvements in the functioning of local health services dramatically reduce the incidence of maternal death, infant mortality and vesico-vaginal fistula. The following areas of health system improvement and capacity building need to be considered:

- Enhancing professionalism among health care workers to make the system work better.
- Massive infrastructural developments through strengthening existing government health facilities, and advocacy, to maximise the benefits that a political environment sensitive to the needs of these women, is required.
- Ensuring that facilities are properly equipped, monitored and supervised with an emphasis on quality as well as quantity of service provision.

Systematic improvements are required to address the social and economic inequalities, such as the low status of women, lack of education for girls, early marriages and pregnancy, malnutrition, poverty, inadequate health and transportation infrastructure, and harmful traditional practices, such as female genital mutilation.

Health and maternal care are inextricably linked to the availability of financial resources, to the individual in the community and within the country as a whole: as economic conditions improve, the risk of VVF diminishes.

Another key stratagem, in preventing VVF, is the empowerment of women and their spouses, to develop birth preparedness plans, within the context of family planning. Family planning in wealthy regions is available according to the choice of the individual, whilst in other developing areas, such as China, it is actively encouraged, or even enforced. Other components of public health care, such as addressing the special nutritional needs of girl children and the requirements of improving their physical health, in order to improve their physical growth and maturity, are also very important.

Education of the community is vital so that young women understand what VVF is, are made aware of the need to engage in the ante-natal care process, and plan for their delivery, including making transportation plans for use when they go into labour.

Prevention strategies can be considered in public health terms as primary, secondary or tertiary:

- Primary prevention addresses many of the indirect causes which are essential the root causes of fistula. It attempts to reduce or eliminate the risk of the disease and by, amongst other actions, reducing the high levels of illiteracy among women. It also seeks to widen the cadre of care workers by involving, for instance, traditional birth attendants (TBA)
- Secondary prevention attempts to limit the severity of the disease by detecting it at its earliest stages.
- Tertiary prevention aims to mitigate the effects of the existing disease, for example by effective treatment.

The work of Haddon and Maine in the Haddon Matrix and Maine's Three Delays provide documented approaches to the problems.

Maine's Three Delays:

- The first delay: the decision to seek care is influenced by the socio-economic and cultural factors in that woman's environment. These can include the need to obtain permission from a husband or male family member to seek care, or the community perception that only weak women need assistance with delivery and that strong women can manage delivery on their own.
- The second delay is delayed arrival at the health facility. Once the first delay has occurred, the second delay becomes more serious. Road conditions, transportation and communication deficiencies may conspire to delay the woman's arrival at a hospital or birthing centre.
- The third delay is the delayed provision of adequate care at the facility, and may be due to lack of staff, supplies, or electricity. If the lights are out and there is no back-up generator or fuel, a caesarean section cannot be done. If there is no way to reach a doctor or medical officer because there are no telephones, or if equipment hasn't been sterilised, then timely surgery cannot be performed.

These three stages of delay disproportionately affect the world's poor and, in particular, those women living in rural areas.

Table 1. Categories of Prevention Strategies: The Haddon Matrix

Primary Prevention	Secondary Prevention	Tertiary Prevention
• Nutrition • Education of girl child and engagement of TBAs • Delayed marriage • Training of medical staff/midwives • Roads, ambulance, functioning health facilities • Communication • Adequate facilities, equipment and staff • Electricity	• Transportation • Maternity waiting houses • Field surveys • Partographs • Low gynaecological age • Caesarean section (Symphysiotomy) • Foley catheter drainage	• Treatment /repairs (surgery) • Physical / social / economic rehabilitation and re-integration • Media campaigns

Recommendations

1. Strong community support is required to develop solidarity groups which include village volunteers working with trained, skilled and traditional birth attendants, depending on the local customs and resources.
2. The components of the three delays need to be identified and targeted in order to minimise the effect of obstructed labour. By this process there will be other benefits for maternal and child health.
3. There should be provision of adequate health facilities and birthing centres to which women move either as soon as they go into labour, or if labour is delayed. Such facilities must provide emergency obstetric care, including caesarean section.
4. National policies for maternity care should be developed for all countries whether or not VVF is a common complication of childbirth
5. Data collection by local, national and regional bodies should help to define the incidence of birth complications, and factors leading to the "3 Delays".
6. The components of the "Three Delays" need to be identified and targeted for each community where there is a high prevalence of complications of childbirth.
7. Girls, women and communities should be educated about normal and abnormal labour, and facilities such as waiting houses should be available for pregnant women at risk for complicated deliveries.
8. Solidarity groups including local volunteers and skilled and trained traditional birth attendants should be developed for maternal care.
9. Birthing centres with the capability for caesarean section should be accessible and sufficiently affordable for women to use.
10. Funding should be made available to retain adequate trained staff for waiting houses and birthing centres.
11. Partographs should be employed to track the progress of delivery in order to identify problems and for data collection.

3. UNMET NEEDS IN VVF

There is unmet need at every level of the healthcare service in those developing countries where VVF is a significant problem. These needs span from family planning through obstetric care, the availability of emergency obstetric services and the provision for dealing with maternal and infant post-partum problems.

Unmet need has not clearly been defined, although the increasing gulf between the prevalence and incidence of fistula and its prevention and treatment is exceedingly worrying.

In low resource countries there is a need for stable and enduring collaboration and partnerships between governments and non-governmental organisations (NGOs), such as, UNFPA, Engenderhealth, WHO and MSF. These partnerships will go some way to identifying unmet need and ensuring that unmet need is reduced.

One of the most important aspects of the unmet needs in fistula surgery training has been the lack of standardization. In order that the recommendations below can even be partially met, there has to be a global strategy in developing training, education, and ancillary support for the surgeons and their associated teams. This will be partially met by the creation of the global competency-based fistula surgical training manual, created by the International Federation for Gynaecology and Obstetrics (FIGO) with International Society of Fistula Surgeons (ISOFS). The purpose of this manual is to enable health care providers to acquire the required knowledge, skill and professionalism to prevent fistula and provide holistic care to fistula patients that includes medical, psychosocial and surgical care. A multi-disciplinary team-based approach is encouraged in the training of each doctor and his/her team nurses, physiotherapists and other health professionals. The course is structured at three levels: standard, advanced and expert levels of fistula training.

The manual is made up of several components:

- Curriculum Modules

Each module has an outline of the course content, that the trainee is expected to be aware of. It needs to be used in conjunction with recommended references, and in some cases with specific Performance Based Assessments (PBAs). There are 7 modules that need to be undertaken.

- Logbooks of Competency

These are records of the work carried out by each trainee. Each must be signed off by each trainer, who will determine if the trainee has observed a procedure, has assisted with a procedure or is able to work independently. The trainer will determine if the trainee needs further training in a particular area.

- Performance Based Assessment (PBA)

Each aspect of surgical training will be assessed separately and specifically. The trainees will complete each PBA to a standard, advanced or expert level and ideally need the signature of two or more trainers, from two or more training centres. It is expected that each trainee will undergo a prolonged period of fistula training at one or more centres. There are 15 PBA to be completed before a fistula surgeon would be deemed to be an expert, and will often require the full 24 months of training. However, this is a competency-based training manual and each trainee will require different lengths of time to achieve each level of expertise.

This structured approach of the competency-based manual will attempt to standardise and support surgical training in fistula repair. In the process of achieving this aim, it is envisaged that there will eventually

be an increase in the number of training centres accredited for training and eventually surgeons trained.

Recommendations

1. Unmet need has to be defined in each country, and within each country, in each geographical region.
2. The unmet need in ante-natal services needs to be rectified urgently in order to minimise the number of new fistulae occurring.
3. The need for education and training has to be addressed for birth attendants, community nursing and fistula surgeons.
4. Training centres for fistula surgeons need to be identified and new ones established, according to population matrix. Training should be systematic and structured, using assessment tools such as those developed by FIGO with ISFOS.
5. Audit and research must be developed in order to ensure that quality and advances in treatment methods are ensured.
6. National strategies need to be developed to empower individual nations to take charge of the women's and children's services in their country.

4. MANAGEMENT OF NEW AND ESTABLISHED VVFS

Management of VVF depends on whether the fistula is diagnosed within two or three months of its occurrence or whether the woman presents late with an established fistula. There is evidence that early catheter care will result in the cure of a significant minority of VVFs. Algorithm 1 (**Figure 1**) describes the management of women who have both early fistulas, defined as those that have occurred within 75 days of presentation, and established fistulas, that is those that are discovered more than 75 days after obstructed labour.

5. CLASSIFICATION OF VVF

The Consultation believes that fistula audit research is considerably hampered by the plethora of VVF classification systems, of which we believe there are 32. The Consultation feels that the fistula system that is able to relate its classification to outcome is the classification that should be used in the next few years. The Waaldijk Classification is the only one that has been used to document sufficient numbers of patients from diagnosis to follow-up (**Figure 2**). **Figure 2** shows the Waaldijk Classification which involves precise measurements of the distances between the external urinary meatus and the distal edge of the fistula, together with the widest diameter of the fistula. Fistulas are classified into types 1, 2 and 3. Type 3 fistulas are those fistulas other than vesico-vaginal fistulas and include recto-vaginal fistulas and uretero-vaginal fistulas. The Waaldijk Classification of Types 1 and 2 is illustrated in **Figure 3** and described below.

If catheter drainage fails, then fistula repair will be necessary. There are certain principles behind fistula repair:

- Necrotic tissue must be removed prior to fistula repair.
- Fistula repair must only be undertaken by a properly trained surgeon.
- Adequate post-operative care is essential.
- Proper follow-up should be arranged.

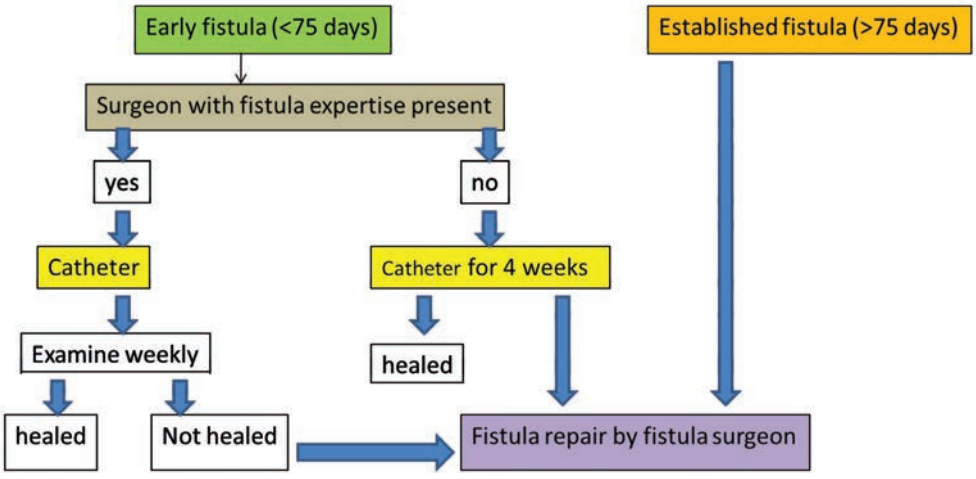


Figure 1. Algorithm to describe the management of fistula detected early (less than 75 days after obstructed labour) or later

Table 2 indicates the type of fistula closure that should be used depending on the type of fistula.

Bladder / urethra direction of closure Pubocervical fascia / urethral support Ant vagina wall closure

Recommendations

1. The comprehensive use of an indwelling catheter with free urinary drainage should be instituted for all patients who have undergone either an emergency caesarean section or a traumatic vaginal delivery after obstructed labour.
2. When fistula surgery is necessary the woman must be assured of the surgeon's competence to carry out her procedure.
3. It is recommended that further research is needed into the classification of fistula, not only to further validate the Waaldijk Classification, but also if other classifications are proposed for development.
4. There is a need to compare different surgical approaches to fistula within the context of randomized controlled trials, using the Waaldijk Classification to precisely describe the fistulas.
5. Long-term follow up of fistula patients is recommended in order to study the outcome of both conservative and surgical management and, in particular, to determine its effect on quality of life.

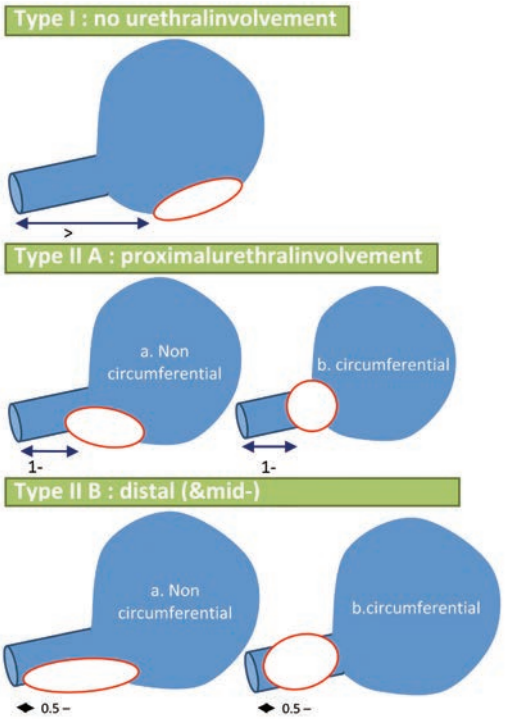


Figure 3. The Waaldijk Classification for Vesico-Vaginal Fistulas

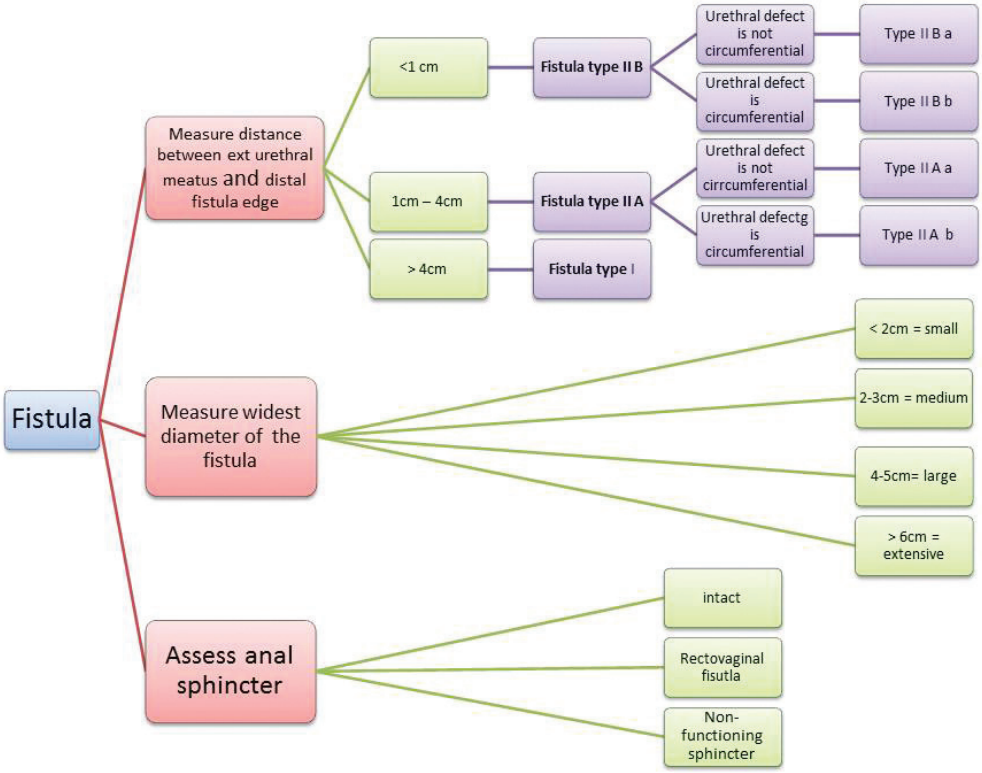


Figure 2. The Waaldijk Classification for Fistula

6. When reporting the outcome after fistula repair, authors should make a clear distinction between fistula closure rates and post-operative incontinence rates, specifying the time at which follow-up was carried out.

6. MANAGEMENT OF THE COMPLICATIONS OF VVF

The complications of Vesico-vaginal fistula are many but include:

- Persistence or recurrence of urinary incontinence
- Persistence of lower urinary tract symptoms or occurrence of new lower urinary tract symptoms, including overactive bladder
- Urinary tract infections
- Upper urinary tract symptoms, including loin pain
- Dyspareunia and sexual dysfunction
- Infertility
- Neurological symptoms
- Psychological problems and mental illness

Recommendations

1. A care programme for failed repairs with persisting incontinence after a successful repair, needs to be in place.
2. It is recommended that surgical treatment of post-operative stress incontinence should only be considered six months after fistula repair.
3. Autologous material should be used when a graft or sling is required and there is no place for synthetic sling material.
4. In order to prevent new fistulas in women who become pregnant after a fistula repair, waiting homes should be provided to ensure that each woman is able to have an elective caesarean section when she goes into labour.
5. In recurrent identifiable fistula make sure of the size and number and this kind of fistula is better repaired by a well experienced fistula surgeon. It is important to use tissue interposition like a Martius flap or fibrin glue.
6. With urinary tract infections or abscess formation, antibiotics must be given before and after the repair, according to culture and sensitivities.
7. Patients complaining of persistent leakage due to urgency incontinence may try antimuscarinics, botulinum toxin injection or even augmentation cystoplasty in small contracted or poorly compliant bladders.
8. Those with a shortened or disrupted urethra, before or after repair, must be treated with urethral reconstruction, autologous slings or injection of bulking agents, delivered trans or peri –urethrally.
9. In cases with unilateral or bilateral ureteric ligation or injury, the early diagnosis is life saving. Patients must be promptly treated by endoscopic ureteral stenting, PCN or ureteric reimplantation.
10. Patients complaining of contracted vagina and dysparunea with sexual dysfunction may use local estrogen, vaginal dilatation or may require the surgical creation of vaginal flaps to augment the vagina.
11. Patients who develop dropped foot may respond to physiotherapy or require tibialis tendon transfer. Women with neurogenic OAB may benefit from detrusor muscle botulinum injections if antimuscarinic drugs fail.
12. Psychological trauma, social isolation and depression is best treated by counselling and psychological rehabilitation.

Table 2. Surgical Techniques for the Closure of Type I and Type II VVFs

	Bladder / urethra direction of closure	**Pubocervical fascia / urethral support**	**Ant vagina wall closure**
Type I	Any according to common sense	No special measure	Approximate vag edges
Type IIAa	Transverse	Transverse repair (+ fixation) / sling	Transverse adaptation
Type IIAb	Circumferential end-to-end	Refixation / sling	Transverse adaptation
Type IIBa	Longitudinal (+ transverse) urethra tissue	Fixation / sling	Flap
Type IIBb	Longitudinal + circumferential non-urethra tissue	Refixation / sling	Flap

Table 3. Social Re-integration Matrix

ELEMENT	LEVEL		
	Facility	Community	Political
Physical Improved physical health	Early detection Rehabilitation Skilled surgeon Timely repair Designated space	Outreach Health education Follow up	Allocate funds for treatment
Psychological Improved mental health	Psychosocial therapy e.g. stigmatisation	Advocacy and sensitisation Follow up	Raise awareness on issues of counselling
Socio-economic Increased social connection	Vocational skill training Linkage with Existing programmes	Microcredit or finance Follow up	Link up with ongoing national poverty alleviation programmes

7. SOCIAL RE-INTEGRATION OF TREATED WOMEN

Social integration is defined as appropriate interventions that help women with obstetric fistula overcome physical, psychological and socio-economic challenges, freely identified by themselves, in order to enhance their return to the communities and social networks of their choosing, such that the risk of them presenting with another fistula is minimized.

The aim of social re-integration is to break the fistula recurrence/occurrence cycle in which the woman's physical state is inextricably connected to her mental state and her socio-economic situation.

Social re-integration should be seen as happening from the time the leaking of urine becomes manifest, and every subsequent intervention should have the re-integration of the woman, back into her community, as the primary goal. So, social re-integration is the responsibility of everyone who cares for the woman.

Social re-integration can be usefully looked at within a matrix, as shown in **Table 3** where the three elements of physical, psychological and socio-economic status are looked at in terms of the facility for treating the patient within her community and the political environment.

Recommendations

1. Social re-integration is important for all women with obstetric fistula. It is the process by which women are helped to overcome physical, psychological and socioeconomic challenges, freely identifiedby themselves, in order to enhance their level of social functioning in communities and social networks of their choosing, so that the risk of will presenting with another fistula is minimised.

2. Social re-integration should be used for all women. However this series of interventions can be performed by any trained care worker, providing it focuses on making the woman part of her social fabric again, and commences from the time leaking of urine becomes manifest.

3. Social re-integration should be designed to break the fistula recurrence cycle in which the woman's physical state is inextricably connected to her mental state and her socio-economic situation.

4. Early successful surgical repair or catheter management is highly recommended and is likely to be the only thing needed for social re-integration. Surgery should be performed as soon as possible by a skilled surgeon, and preferably within 3 months of developing the fistula, as this is likely to limit the length of time the woman is seen as abnormal by her family or community and thus perceived as an outcast.

5. Social re-integration should start in a designated space where women can recuperate, perhaps within the repair facility or nearby, rather than going home and encountering the risk of behaviours which may make it likely that a recurrence of fistula occurs, due to an exacerbating physical event such as early sexual intercourse or heavy work. Also, peer counselling is more likely to be available in this space.

6. Surgeons and other care workers should consider social re-integration as not just a social tool but also as a means of ensuring that adequate follow-up of the postsurgical improvement in quality of life is done and reported on. At the least, there should be a review of individually defined success of surgery and surgical outcomes, including continence and return to fertility and/or sexual life, as desired by the woman.

7. Appropriate counselling messages about the risk factors and causes associated with fistula should be targeted at family members (including husbands) and the community, as this can help to overcome the stigma, discrimination and misconceptions surrounding the condition and enhance her community inclusion. It is then an opportunity to make changes so that

the woman does not present with another fistula in the future.

8. Counselling should be seen as an opportunity for health providers to understand the socioeconomic, psychological and physical experiences that are faced by girls and women living with fistula, before and after surgery, so that they may give meaningful help. This will also help to generate knowledge on social re-integration processes and will help in the planning of a broader range of outcomes for women living with fistula.

9. Social re-integration should include assistance with education and life skills, and encouragement of private initiatives through vocational skills development and microcredit support. If this is freely chosen, it will not keep a woman away from her community unduly, and will help her regain or improve her previous economic status and enhance her self-sufficiency and community inclusion.

10. Social re-integration should include vocational skills training with the aim of providing women with alternative ways to generate income, without jeopardising their recuperation, by teaching them a trade which is economically viable within their community.

11. Institutional re-integration services should be incorporated into existing community activities or programmes directed to empower women (e.g. education, skills training, income generation, self-esteem).

12. Re-integration programmes should develop criteria to determine where support with socioeconomic interventions should be given, as funds may be limited and fistula consequences can vary dramatically by country and region. They should also be careful not to increase the burden of stigma and therefore inadvertently impede re-integration. Of particular concern should be women who are still incontinent, those who are deemed incurable, those who have no children and those who have lived with fistula for a long period of time.

13. Social re-integration programmes need to consider the potential ethical dilemmas in re-integration such as providing targeted financial support or high value goods to women with fistula in poor communities, other than as part of a community approach.

14. Social re-integration should seek to involve women who have been successfully re-integrated into their communities. These women can be termed motivational mobilisers and can contribute to community mobilisation movements for safe motherhood, fistula case mapping and referrals for treatment. Women should have a choice as to whether they wish to be involved in such advocacy activities.

15. Social re-integration programmes should be monitored and evaluated in order to collect correlates of success and failure and to help understand socio-cultural backgrounds, so that a context specific approach can be used to design and deliver effective, feasible reintegration programmes.

Below is set out the committee structure for the Consultation, within whose chapters full details of each committee's work can be found.

Scientific Committees for 1st Consultation on VVF (Chairpersons in bold)

1. Epidemiology

AHMED, aifuddin (USA)
ARROWSMITH, Steve (USA)
MULETA, Mulu (Ethiopia)
KISERUD,Torvid (Norway)

2. Prevention Strategy

BANGSER, Maggy (Tanzania)
COCHRAN, Seth (USA)
EMASU, Alice (Uganda) –Co-chair
LENGMANG, Sunday (Nigeria)
LUSI, Lyn (Congo)
KIRYA, Fred (Uganda)
DE VRIES, Catherine (USA)

3. UnmetNeeds

ELNEIL, Suzy (UK)
GAME, Xavier (France)
PATEL, Naren (UK)
RUSHWAN, Hamid (UK)
RUMINJO,Joseph (USA)

4. Surgery for Fistula

ABUBAKAR, Kabiru (Nigeria)
RAASSEN, Tom (Kenya)
DE RIDDER, Dirk (Belgium)
WAALDIJK, Kees (Nigeria)

5. Complex Fistulae and the Complications after Fistula Surgery

HILTON, Paul (UK)
MOURAD, Sherif (Egypt)
MWANJE HARUNA, Moses (Uganda)
SHAKER, Hassan (Egypt)
VASAN, Sirini (India)

6. Social Integration

AKHTER, Sayeba (Bangladesh)
BROWNING, Andrew (Ethiopia)
ESEGBONA, Gloria (UK/Nigeria)
ISAH, Adamu (Nigeria)
KAONGA, Taonga (Malawi)
MOHAMMAD, Rahmat (Nigeria) – Co-chair

B. Non-obstetrical fistula

I. INTRODUCTION

Iatrogenic urogenital fistulae are known complications of pelvic surgery and oncological treatments such as radiotherapy. For example a high quality population-based case-control study from Sweden found that the risk of urogenital fistula was 25 times higher amongst women undergoing hysterectomy (n=180,000) compared to an age matched control population (n=525,826) without hysterectomy. The risk appeared to be highest for laparoscopic hysterectomy and lowest for sub-total hysterectomy but absolute numbers were small with a number needed to harm of 5,700.[3]

This section is based on electronic searches of Medline, EMBASE (from 1980 to November 2011), the Cochrane Database of Systematic Reviews, Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Database of Health Technology Assessments, and Database of NHS Economic Evaluations, and the NICE website (all accessed November 2011); references included in identified systematic and non-systematic reviews were evaluated separately. Hand searching of recent (Jan-December 2011) issues of major American, European and British journals in urology, gynaecology and urogynaecology was undertaken, to capture recent publications not yet included in the online databases. ICS, IUGA, AUA, AUGS and SGS conference proceedings for 2011 were also reviewed. It was assumed that studies and trials presented earlier than this would be in press if they were of sufficient quality and maturity to justify inclusion; hence older abstracts have not been considered.Papers offering any relevant data were considered. This included systematic reviews, randomised and quasi-randomised trials, non-randomised cohort studies, case controlled studies, longitudinal studies and case series or reports. Those papers considered for inclusion were assessed for quality where relevant, in terms of sequence generation, allocation concealment, blinding, and handling of incomplete data, selective reporting and freedom from other biases. An evidence level [EL] was then assigned to all included studies according to the ICUD modified version of the Oxford Centre for Evidence-based Medicine system. [4) Where quality was considered to be poor – as in most of the studies included in these sections – the evidence level was reduced accordingly. Recommendations (graded A-D) were made on the basis of consistent or 'majority evidence' identified.[4]

II. EPIDEMIOLOGY

1. POST-GYNAECOLOGICAL SURGERY

Fistulae involving the lower urinary tract can occur following any surgical procedure or traumatic event to the female reproductive tract, bladder, or rectum. In developing countries, the most common aetiology of fistulae involving the lower urinary tract is clearly obstetric trauma. [5] In most developed countries in which antenatal and intrapartum care is more readily available, obstetrical fistulae are relatively rare and the majority of fistulae are related togynaecological surgery. The ratio of obstetric to gynaecological fistula appears to be consistent at about 10:90 in developed countries. [6] In some developing countries, as gynaecological procedures to treat benign and malignant conditions of the female reproductive tract are more commonly performed, the rate of iatrogenic fistulae is increasing (e.g. Pakistan). [7]

The types of fistulae associated with gynaecological procedures may include communication between any reproductive organ (uterus, cervix, Fallopian tube, vagina), intestinal tract (colon, rectum), genitourinary organ (bladder, ureter, urethra), and cutaneous system (abdominal wall, perineum). The combinations, locations, and severity of gynaecological fistulae vary with each patient. In general, vesicovaginal fistulae (VVF) are the most common type. The most common causes of VVF as a consequence of surgery, in developed countries isan injury injury to the urinary tract during hysterectomy for benign conditions (60-75%), followed by hysterectomy for malignant conditions (30%), caesarean section (6%), and obstetric injuries (1%). [8][9] At the ZekaiTahirBurakcentre in Turkey 25,998 gynaecologic and obstetric operations were performed over a 3-year period. The bladder was the most frequently injured organ. Urinary tract injury rates were reported to be 0.49% for the bladder and 0.24% for the ureter in gynaecological operations, and 0.18% for the bladder and 0.01% for the ureter in obstetric operations.[10] Overall, the risk of pelvic organ fistula following hysterectomy has been reported to be between 0.1 and 4%. [11]. It is important to recognize that most urinary tract injuries do not result in a fistula.

The prevalence of genitourinary injury and fistulae vary slightly from centre to centre. In one US retrospective study from the Mayo clinic, gynaecologic surgery was responsible for 82% of the fistulas, obstetric procedures for 8%, and various forms of irradiation for 6%, and trauma or fulguration for 4%. The majority of fistulae followed treatment for benign conditions. [12] The relative proportions of the types of urinary fistula have changed with urethral fistulae having increased from 6 to 13%, while ureteral, bladder and/ or urethral fistulae having dropped from 20 to 16 and 11 to 7%. [2]

Given the various indications for, and types of hysterectomies, it is important to have an understanding of the type of hysterectomy since genitourinary or colonic fistula is reported with all of these procedures. The overall incidence of hysterectomy complications is estimated to be <2%, with bladder injury (1.3%) and ureteral injury (<1%) being most commonlyreported. [13] Traditionally, the most common route used to

remove the uterus for benign and malignant gynaecological conditions is abdominal (open incision, laparotomy); referred to commonly as total abdominal hysterectomy (TAH). The types of hysterectomies also include total vaginal (TVH), laparoscopically-assisted vaginal (LAVH), total laparoscopic (TLH), and subtotal or supracervical abdominal (SCH) or laparoscopic (LSH). Laparoscopic procedures may be done using traditional laparoscopic techniques, robotic assistance, and more recently, the single-site umbilical technique.

Benign and malignant conditions confined to the uterus are usually treated with a simple hysterectomy using any of the methods mentioned above. More advanced malignant conditions are usually treated with a radical hysterectomy in which parametrial and/or vaginal dissection and removal may be involved. In rarer cases, exenterative procedures to remove the bladder or colon may be required if malignant extension to these organs is found. In some centres, robotic radical hysterectomies have been more commonly employed to treat gynaecological malignancies. The rate of urogenital fistula associated with simple abdominal hysterectomy for benign disease is often described as being of the order of 1 in 1000. In a national study from Sweden the rate of women undergoing any fistula surgery was reported as 0.26% in women having had a hysterectomy compared to 0.0007% in those not exposed to hysterectomy, with the 'number needed to harm' being estimated at 5700.[14] From Finland the rate of vesicovaginal fistula was reported to be 1 in 1250 after all hysterectomies, 1 in 455 after laparoscopic, 1 in 1000 after total abdominal, and 1 in 5000 after vaginal hysterectomy.[15] The publicly available tables from the national hospital database in England give similar figures of 1 in 600 after total abdominal hysterectomy, and 1 in 5000 after vaginal hysterectomy.[16, 17] More detailed longitudinal analysis of patient-level information from the same dataset suggests a rate of 1 in 788 for all types of hysterectomy, 1 in 540 for abdominal hysterectomy for benign disease, 1 in 896 following vaginal hysterectomy for benign disease (excluding prolapse), and 1 in 3861 following vaginal hysterectomy for prolapse.[18]

Naturally, caesarean hysterectomy is a recognised cause of fistula,[19]and, with the increase in the number of caesarean deliveries there have been more fistulae related to obstetricsurgical trauma. [2]

The degree of bladder injury appears to be a major factor in iatrogenic fistula formation. In one study, 1,317 benign hysterectomies were reviewed (46% abdominal, 48% vaginal, and 6% laparoscopically assisted vaginal) with reference to risk factors for VVF following intraoperative injury to the urinary tract. In all, 34 cystotomies occurred with 4 (11.7%) developing a VVF. Patients who developed a VVF were more likely to have a large cystotomy and these individuals trended toward greater tobacco use, larger uterine size, and more operative blood loss. [20] Another study involving 3,076 vaginal hysterectomies with or without additional gynaecological procedures, one ureteral injuryand 54 bladder lacerations were noted yielding a total of 4 VVF. The bladder lacerations occurred during the hysterectomy portion of the surgery in 61% of cases and during the additional procedures in 39%. [21](see **Table 1**)

VVFs associated with hysterectomy may require ureteral reimplantation in as many as one-third of the cases. [22]Ureteric trauma should be considered in any hysterectomy or operative obstetric procedure regardless of the difficulty but certainly in more difficult cases.[23] Iatrogenic ureteric injury may occur after less common procedures such as ureteroscopy, lumbar sympathectomy, abdominal trauma, and iliac vessel ligation.[24]

Altered intraabdominal anatomy such as that due to previoussurgery, extensive endometriosis and pelvic inflammatory disease have previously been thought to lead to an altered operative field increasing the risk for genitourinary injury; recent evidence from a cohort of over 300,000 women having hysterecomy for a variety of indications suggests that this may not be the case. [18]

The overall rate of ureteric injury from 4998 procedures in these studies was 1.5%; the overall sensitivity was 96.1%, specificity 99.5%, positive predictive value (PPV) 74%, and negative predictive value 99.9%. The modest PPV related to 21 cases in one study where cystoscopic examination revealed abnormal (sluggish or absent) flow of indigo–carmine dye through one or both ureteric

Table 1. Categories of Prevention Strategies: The Haddon Matrix

Author	Date	Total procedures		Cystotomies		Fistulae	
			N	*n*	%	*n*	%
Mathevet et al	2001	Vaginal hysterectomy	3076	54	1.8%	4	7%
Hadley et al	1994	Vaginal surgery		12		0	0%
Mehra et al	1996	Laparoscopic hysterectomy	300	3	1.0%	2	67%
Doung et al	2011	Hysterectomy	5698	102	1.8%	6	6%
			9074	171	1.9%	12	7%
			Confidence interval		1%		30%

orifices, but subsequent findings failed to confirm injury. For every 200 cystoscopies undertaken at gynaecological surgery therefore one might expect to diagnose three otherwise unsuspected ureteric injuries but at the expense of one false positive 'injury' that would ultimately be shown to be normal.

Visco et al. using a decision analysis model concluded that the cost-effectiveness of routine intraoperative cystoscopy depends on the rate of ureteric injury; if the rate exceeds 1.5% for abdominal hysterectomy and 2% for vaginal or laparoscopically-assisted vaginal hysterectomy, then routine cystoscopy is cost-effective. These data would suggest that whilst the routine cystoscopy might be considered clinically and cost-effective at the time of prolapse and incontinence surgery, its place at hysterectomy is less clear.

2. ONCOLOGICAL FISTULA

This section considers, where the literature permits, the epidemiology of fistula relating to malignant disease and its treatment by surgery, radiotherapy and chemotherapy. The literature relating to fistula of oncological aetiology is limited both in quantity and quality. Seventy-six papers of possible relevance were identified, of which only 52 contained any relevant material. Only one randomised trial was directly identified from the literature searches,[25] although one non-systematic review of relevance,[26] and two systematic reviews were found;[27, 28] each of the latter contained only one further randomised trial. One national cohort study, and one non-randomised cohort study, are included,[18, 29] but all other identified material comprised case series or case reports, and represent level 3or lower evidence. Two cases of duplicate publication (i.e. the same paper in two journals) were found.

In the oncological context, fistulae may occur as a result of primary or recurrent malignancy, or as a consequence of cancer treatment by surgery, radiotherapy, chemotherapy, or a combination of therapies.

Traditionally, malignancies involving the uterus, cervix, vagina, or ovaries are often treated with hysterectomy, bilateral oophorectomy, and pelvic lymph node dissection. In many cases, a radical hysterectomy is performed in which the uterus, cervix, and upper vagina are removed. It is generally accepted that the more advanced the cancer, the more radical the surgical dissection will necessarily be. With cervical and uterine carcinoma, oophorectomy is performed when indicated. Pelvic lymphadenectomy is done when invasive carcinoma is suspected or diagnosed. In one study, 536 women underwent a radical hysterectomy for invasive cervical cancer. More advanced stage of disease, obesity, diabetes, and postoperative surgical infection were predisposing factors to urinary tract complications. In this study, ureteral injury occurred in 1.32%, bladder injury in 1.49% with VVF forming in 2.61% and ureterovaginal fistula in 2.43% of cases, respectively. [30] In a similar report, 1,092 women with cervical cancer underwent a radical hysterectomy with obligatory pelvic lymphadenectomy. A VVF occurred in 0.3% and a ureterovaginal fistula occurred in 1.4%. [31] The rate of GU injury likely varies between centres. For example, in one report of 479 women undergoing different methods of radical hysterectomy for cervical cancer over a 15 year period, 52 (10.8 per cent) had urological complications (17 bladder and ureter injuries, 35 fistulae and strictures). [32] In contrast, one institution reported that , with modifications and careful dissection, ureteric and bladder injury have almost been eliminated.[33]

In two recently published case series, one of fistulae specifically associated with gynaecological cancers,[26] and one of urogenital fistula from all causes,[17] those relating directly to primary cancer were uncommon, (2/20=10%)[26] and (2/348=0.6% - 2/66=3% of the oncological cases in this series),[17] respectively. Fistulae associated with cancer surgery (3/20=15% and 30/348=8.6% - 30/66=45% of the oncological cases in this series) or radiotherapy (15/20=75% and 34/348=9.8% - 34/66=52% of the oncological cases in this series) made up a much larger proportion of both series.

Immune-deficiency may be a further contributory factor, and enterovesical fistula has previously been reported in association with non-Hodgkin's lymphoma in HIV-AIDS,[34] and vesicovaginal fistula has been seen in association with classical Hodgkin's affecting the vagina in a long-term pessary user.[35]

3. CANCER SURGERY

It is likely that all operations carried out in the pelvis can be complicated by genital tract fistula in some circumstances.[17] Operations carried out with the intention of curing malignant disease will inevitably carry a higher risk of subsequent fistula formation, as compared to those undertaken with less radical intent.

Following radical hysterectomy for cervical cancer (Wertheim-Meigs procedure] the rate of fistula formation reported from case series is between 0.6% and 4.4%.[30, 36-41]It should be noted that these data are very heterogeneous, some reporting all types of fistula together, i.e. intestinogenital plus urogenital fistula, and some reporting these separately; some report all urogenital fistulae together, and some separating vesicovaginal and ureterovaginal. Where they are reported separately, the rates of vesicovaginal and ureterovaginal fistula appear to be of the same magnitude with both being reported in between 0.9% and 2.5%. of cases [30, 42, 43] The data from UK

cited above suggests a urogenital fistula rate of 1 in 95 following radical abdominal hysterectomy in women with malignant disease as compared to 1 in 540 for total (simple) abdominal hysterectomy for benign disease, and 1 in 2041 for vaginal hysterectomy for all benign disease (including prolapse).[18] Overall, the rate of urogenital fistula appears to be approximately 9 times higher following radical hysterectomy in women with malignant disease as compared to that following simple hysterectomy (abdominal or vaginal) in women with benign conditions.[18]

The risk of visceral injury or subsequent fistula formation following radical hysterectomy undertaken in pregnancy, or immediately following Caesarean section isnot obviously increased over those carried out electively in non-pregnant individuals; Monk &Montz described inadvertent cystotomy followed by vesicovaginal fistula in one of 21 women operated on during or immediately after pregnancy.[44]

Several modifications to the conventional Wertheim-Meig's procedure of radical hysterectomy have been described in an effort to reduce the associated morbidity. The Miami modification includes vaginal reconstruction and closure using bladder and rectosigmoid serosa, retroperitoneal drainage through abdominal suction catheters, and suspension of the denuded ureters with the ipsilateral obliterated hypogastric artery. One prospective study of 978 women treated by this procedure reported a urinary fistula rate of 1.4% compared to 4.4% from a literature survey following the conventional procedure.[36] The Ohkawa procedure involves peritoneal sheathing of the ureters; Blythe et al. undertook a non-randomised comparison with retroperitoneal suction drainage, and found the conventional method to be associated with fewer ureteric complications (0/34 vs. 4/26 (15.4%)).[45] Similarly, Bostofte&Serup found no benefit in operative or postoperative morbidity following the application of the Okabayashi procedure for radical hysterectomy.[32]

Given the increased risk associated with radical surgery for malignancy, it is intuitive that the risks would increase with the stage of disease and with the extent of the surgery undertaken. There are few published reports of fistula following exenterative surgery. One study noted a 16% vesicovaginal fistula rate in 19 women following exenteration for vulvar carcinoma;[46] while another describes a 15% bowel fistula rate and an 8% urinary fistula rate from a series of 75 exenterations for recurrent cervical cancer.[47] In contrast, Ungar et al. describe only one ureterovaginal fistula and one pouch–vaginal fistula in 212 women undergoing exenteration out of a total of 2540 women treated for cervix cancer in one centre over a 13 year period (0.9%).[48]

Harkki-Siren et al. found the rate of vesicovaginal fistula to be over twice as high following laparoscopic hysterectomy compared to abdominal hysterectomy, and the rate of ureteric injury to be some 35 times higher.[15] The introduction of laparoscopic surgery within oncology is seen to have considerable advantages in terms of patient recovery; the risk of operative injury to bowel and the urinary tract, and subsequent fistula formation may however remain a concern in such cases. Although some studies, both case series and non-randomised cohorts, describe similar rates of injury to those described following open radical surgery,[29, 42, 43, 49, 50] others have reported injury or fistula rates several times higher following laparoscopic radical hysterectomy.[37, 51] A single non-randomised cohort study found that the risks of both injury to the urinary tract and of subsequent fistula formation were higher following laparoscopically-assisted radical hysterectomy as compared to that following laparoscopically-assisted radical trachelectomy (Dargent's operation).[29]

The risk of urinary tract injury from minor surgical interventions is in general low, although the use of repeat procedures may confer a significant increase in risk. Vesicovaginal fistula has been reported following repeated use of CO2 laser for vaporisation of vaginal condylomata,[52] and following cone biopsy of the cervix.[53] In one personal series of 370 urogenital fistulae, 4 were associated with large loop excision of the transformation zone (LLETZ) of cervix, 3 of which followed a second LLETZ procedure (Hilton, personal communication).

Rarely, localised malignancies have been associated with VVF. One example is a primary mixed mullerian vaginal tumour reported in a 48-year female. [54] The mechanism for fistula formation is likely to be direct invasion into the bladder.

4. RADIATION FISTULA

Pelvic irradiation can be delivered by external beam as well as locally (intracavitary/brachytherapy). Fistula formation appears to be slightly higher for postoperative external radiation (1.9%) compared to intravaginal brachytherapy (0.8%). [55] It does not appear that pre-treatment factors accurately predict those who will develop fistula related to radiotherapy. [56]

The literature in this area is particularly heterogeneous in nature, with wide variation in (and some lack of clarity over) the tumour type and stage being treated, the form of radiation and the site and dose delivered. In a series of urogenital fistulae from the UK, 34/348 or 9.8% were associated with previous radiotherapy; of those related to gynaecological cancer, 34/66 or 52% had undergone radiotherapy.[17] In a further series of cases specifically related to gynaecological malignancy, 15/20 or 75% had undergone previousradiotherapy.[26] In both series most cases followed radiation used

for the treatment of cervical cancer, although, 5/34 or 15% followed treatment of endometrial cancer, and 1/34 or 3% followed treatment of a multifocal gynaecological cancer in one series. [17] Amongst a series of 216 radiation-induced fistulae, the time to diagnosis of the fistula was made between 3 months and 10 years (mean 21 months) following radiation.[57] In other series fistulae have been reported to develop or present up to 30 years after the 'causative' influence.[17, 58](**Figure 1a** and **1b**)

The incidence of any deleterious clinical impact on the gastrointestinal and urinary tracts following radiation varies in the literature between 1% and 12%,[28, 59-65] with fistula rates of 1% to 5%.[26, 66]. In a retrospective review of 2096 patients treated for cervical cancer over a 10-year period using unspecified regimen/s of radiotherapy, 38 patients (1.8%) were found to have developed fistulae, all of whom had stage IIIa/b or IV disease at presentation.[62] Of these cases, approximately 3/4 involved the rectum, with 1/3 being combined rectovaginal and vesicovaginal fistulae; 1/4 were vesicovaginal only.[62]

Following a clearly defined regimen of external beam radiation plus brachytherapy for the treatment of primary squamous cell carcinoma of vagina in 91 women, de Crevoisier et al. reported 10.0% grade 2-3 urinary tract toxicity (using the Franco-Italian glossary)[67] and 12.1% grade 2-3 gastrointestinal toxicity.[60] Unsurprisingly, they found anterior tumour location to be correlated with increased risk of bladder toxicity and decreased rectal toxicity. Two women in this series developed rectovaginal fistulae (2%), and one ureterovaginal fistula (1%).[60]

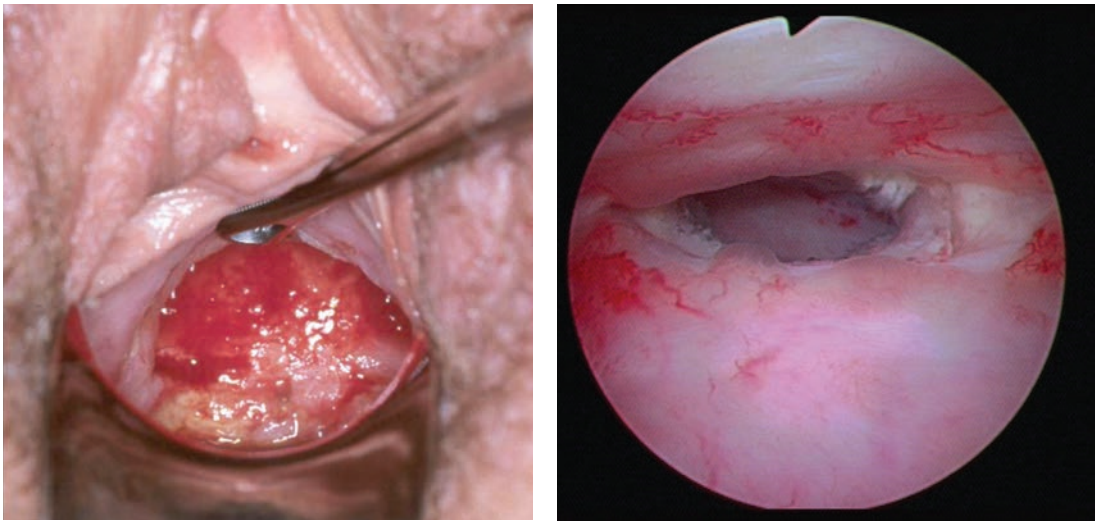


Figure 1a. Left: Acute radiation fistula; Right: fistula 20 years after radiotherapy, both for cervixcarcinoma

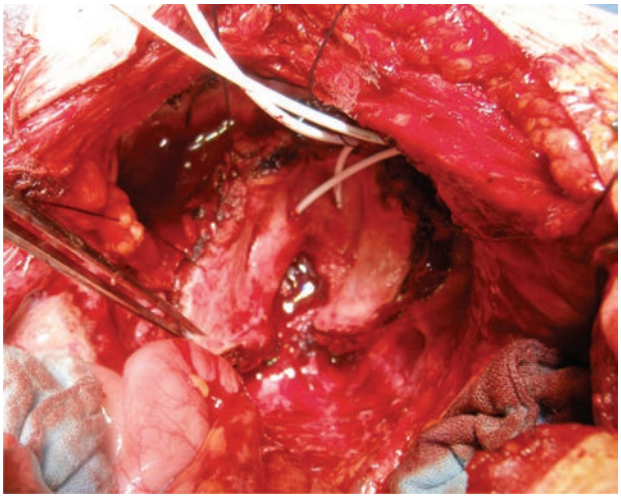


Figure 1b.Supratrigonal vesico-perineal radiation fistula in a small contracted bladder that occurred 22 years after cobalt irradiation for a gynaecological tumour.

In a series of 10,709 women treated by telebrachytherapy (67.5 Gy) for a range of gynaecological cancers in one centre over a 22 year period, 133 (1.2%) developed urological complications of which 35 (0.3%) developed fistulae.[64]

In a series of 28 women treated by brachytherapy for recurrent corpus or cervix cancer, four patients developed chronic morbidities related to treatment. Three fistulae were reported in two patients (7.1%): one combined rectovaginal and vesicovaginal fistula and one ureterointestinal fistula; a further patient developed a ureteric stricture and small bowel obstruction requiring resection.[65]

These data tend to suggest a higher rate of fistula formation following the application of radiotherapy in locally recurrent disease than in primary disease. From a small series of urological complications following radiotherapy for gynaecological cancers, 14 had developed vesicovaginal fistula; of these 4 (29%) had evidence of tumour recurrence.[63] In the series reported by Jones at al. 326/1161 (28%) developed urological complications over a 20 year period; 46 developed fistulae (4%), of whom 33 (72%) had evidence of active malignant disease.[39]

When a fistula occurs after radiotherapy, it is considered good clinical practice to exclude tumour recurrence before attempting a fistula closure.

5. CHEMOTHERAPY

There are few reports of fistula formation in association with the use of chemotherapy. One case report described a patient who developed a vesicovaginal fistula having undergone abdominal hysterectomy for atypical endometrial hyperplasia whilst taking tamoxifen following a previousmodified radical mastectomy. Surgical repair of the fistula was initially unsuccessful, although after discontinuing the tamoxifen and continued bladder drainage, healing occurred.[68] It was hypothesised that the impaired healing was a result of the administration of the hormone therapy.

6. COMBINATION THERAPIES

Adjuvant or neoadjuvant therapies are used to increase the efficacy of the primary treatment, compared to its use in isolation. It might be anticipated that this would also increase the range and magnitude of adverse effects.

In a case control study examining the urinary tract complications of radical hysterectomy only a single vesicovaginal fistula was seen in 50 patients (2%) – in a patient receiving preoperative irradiation (45-50 Gy).[69] A small case series found 2/20 or a 20% rate of urinary fistulae following preoperative irradiation and radical hysterectomy in a heterogeneous group of 'high risk' cervix cancers.[70] A further case series described the impact of combined external whole pelvic irradiation (50 Gy) and intravaginal cone boost (20-26 Gy) following radical hysterectomy in 108 women. The overall rate of fistula formation was 3.7%, 2.2% following 'prophylactic' radiation, and 10.5% in 'salvage' cases where recurrent disease was present.[71]

Modarress et al. reported a randomised comparison of preoperative combined chemoradiation (cisplatin plus external beam therapy) and neoadjuvant chemotherapy (cisplatin plus vincristine) followed by radical hysterectomy in stage IB-IIB bulky cervical cancer.[25]Four patients developed hydronephrosis (3 in the chemoradiation group – 13.3%) and two vesicovaginal fistula (both in the chemoradiation group – 6.7%).[25] Two further case series reported 2/36 or a 5.6% rate of fistulae following preoperative chemoradiation (cisplatin plus brachytherapy) followed by radical hysterectomy,[72] and 4/46 or 8.7% rate of fistulae following the use of neoadjuvant and postoperative chemotherapy using irinotecan, cisplatin and nedaplatin.[73]

III. URETERIC FISTULA

A large prospective case series from Finland found an incidence of ureteric injury associated with hysterectomy for benign pathology of 0.2% [10/5279] with the lowest rate associated with vaginal hysterectomy and no difference between open and laparoscopic abdominal hysterectomy.[74] The incidence of immediate and delayed ureteric injury during radical hysterectomy was found to be 1.3% [7/536] and 2.4% [13/536] respectively in a series from Serbia; injuries appeared more common after prolonged surgery and in patients with diabetes, obesity or wound infection. [75] A registry study from the United States found an overall incidence of ureteric injury during radical hysterectomy of 0.8%.[76] Case series from referral centres in India, Pakistan, and Egypt showed that the proportion of urinary tract injuries resulting from obstetric or gynaecological surgical trauma that primarily affected the ureter varied from 1% to 23%.[77-80]

IV. FISTULA INVOLVING THE GI TRACT

The literature relating to non-obstetric fistula involving the gastro-intestinal tract is sparse and of poor quality. Although literature searching identified 78 papers of possible relevance, less than half of these contained any useful material; no randomised trials or truly systematic reviews were identified. One case controlled study is included, but all other identified material comprised case series or single case reports, and is considered to represent level 3- evidence.

It should be recognised that, whilst in most papers the term 'enterovesical' is used to describe fistulae between small bowel and bladder, and 'colo/recto-vesical/vaginal' to describe those between

large bowel and bladder/vagina, in some reports 'enterovesical' appears to be employed generically to include all fistulae involving the gastrointestinal tract. In this chapter, the term 'intestinovesical' will be used in circumstances where the generic term is clearly more appropriate.

Whilst occasionally reported congenitally,[81] the most common non-obstetric causes of fistula involving the gastro-intestinal tract are diverticular disease, Crohn's disease, and malignant disease or its treatment. There are few data on the incidence of fistula formation in these conditions, although published estimates are in the range 2-6% in Crohn's disease,[82-84] and 20% in diverticular disease.[85]

Intestinal fistulae in Crohn's disease most typically involve the small bowel, although communication with urinary tract and large bowel are also found; involvement of the bladder was reported in 27% and of the colon in 14% in one series.[86] Two large series examining the urological complications in association with Crohn's disease reported that whilst a majority of patients were female, the most serious complications were seen in males; most significantly, 13/14 or 93% of the ileo-vesical fistulae (described in these series were in men.[82, 87]

Whilst clearly diverticular disease involves the large bowel primarily in all cases, diverticular fistulae have been reported to communicate withthe bladder in 65% of cases, the vagina or uterus in 28% and small bowel in 7%.[85] Diverticular disease is the most common cause of colovesical fistula in most reports, accounting for up to 75% of cases,[88-95] with colon cancer, bladder cancer, radiotherapy and Crohn's disease accounting for the remainder.

Although there are no direct comparisons between racial groups, the distribution of these causes may vary between populations. Malignancy and/or previousradiotherapy account for 53-93% of cases of colovesical fistula reported from China,[96, 97] presumably reflecting the previously low prevalence of inflammatory bowel disease.[98]

Previoushysterectomy appears to be a significant factor in the incidence of fistula associated with diverticular disease.[99] In a national case controlled study from Sweden, involving a total of 783,245 women over a 30 year period,the risk of undergoing fistula surgery increased four-fold in hysterectomised women without diverticulitis (hazard ratio (HR) 4.0 (95% confidence interval (CI) 3.5 to 4.7)), seven-fold in women with diverticulitis without hysterectomy (HR 7.6 (95% CI 4.8 to 12.1)) and 25-fold in hysterectomised women with diverticulitis (HR 25.2 (95% CI 15.5 to 41.2)).[100] Another study described previous hysterectomy in 50% of colovesical and 83% of colovaginal fistulae associated with diverticular disease.[85]

Evidence statements epidemiology

Urogenital fistula are more frequent in women who have undergone hysterectomy	2
The risk of injury to the bowel or urinary tract and of subsequent fistula formation is higher in women with malignant disease undergoing radical surgery than in women with benign disease undergoing simple surgical procedures	2
Several modifications to conventional radical hysterectomy have been described, although they have not consistently been shown to mitigate the risk of urinary fistula postoperatively.	3
Data on exenterative surgery are inconsistent, although the risk of fistula formation may be higher following exenteration for recurrent disease as compared to that following radical hysterectomy for the primary treatment of malignancy	3
The rate of visceral injury and fistula formation is inconsistently reported following laparoscopically assisted radical hysterectomy, but may be somewhat higher than following open surgery	3
Local ablative treatments applied in gynaecological oncology, whilst apparently relatively low risk as single treatments, may carry considerable risk for fistula formation when repeated.	3
The rate of fistula formation following radiotherapy for gynaecological cancer appears to be of the same order as that following surgical treatment	4
The risk of fistula formation following radiotherapy for locally recurrent malignancy is higher than following its use in primary disease	2
The use of neoadjuvant or adjuvant therapies is likely to be associated with a greater risk of fistula development than the primary treatment alone	2
The most common non-obstetric causes of fistula involving the gastro-intestinal tract are diverticular disease, Crohn's disease, malignancy and radiotherapy.	2
The causative factors may vary in different populations, with malignancy being more commonly reported in association with enterovesical fistula in China than in other countries	3

Recommendations

The development of fistula following radiotherapy for primary treatment should trigger a search for evidence of tumour recurrence	D

V. DIAGNOSIS OF FISTULA

1. CLINICAL DIAGNOSIS

Leakage of stool, urine, or possibly both is the hallmark sign of a fistula.The leakage is usually painless, may be intermittent if it is position dependent, or may be constant. Unfortunately, intraoperative diagnosis of a GU or GI injury is made in only about half of the cases that result in fistula. [101]In one study, 36% of VVF presented within 1 week of a laparoscopic hysterectomy and 50% in the second week. Most of the patients after trans-abdominal hysterectomies had leakage in the second week (90%). [102] As discussed above, more extensive dissection is a factor when lower urinary tract injury results in a fistula. However, other than a frank injury such as ureteric transection, not all injuries result in the formation of a fistula. With laparoscopic or abdominal dissection, ureteral injury may occur anywhere along the retroperitoneal ureter usually below the pelvic brim. Since the injury may not be recognised during surgery, post-operative pain is a key symptom. The cause of vesicovaginal fistulae after hysterectomy varies with the extent of surgery and the amount of damage that has occurred. In an attempt to determine causative factors of post-operative fistulae, the records of 12 patients who had developeda vesicovaginal fistula after TAH were compared with 12 consecutive TAH patients without fistula formation. Most of the patients who developed VVF had excessive postoperative abdominal pain, distension or paralytic ileus, or both. Haematuria, symptoms of irritability of the bladder, prolonged postoperative fever, and increased white blood cell count were also noted more often in the fistula group. In contrast, the postoperative course wasusually uncomplicated in the non-fistula group. The clinical course observed in many of the patients with vesicovaginal fistulas suggests that the patient has an unrecognized or recognized injury to the bladder resulting in urinary extravasation. [103] It may be possible to abort the development of many vesicovaginal fistulae by early recognition and treatment of an unsuspected bladder injury. It is suggested that patients with severe abdominal pain, distension, paralytic ileus, haematuria or symptoms of severe irritability of the bladder after abdominal hysterectomy should be investigated early for a possible genitourinary injury.

Another possible etiology of VVF in the setting of laparoscopic procedures is trocar insertion injury. To prevent this the bladder should be emptiedby intermittent or continuous bladder drainage prior to inserting the abdominal and pelvic trocars. During the laparoscopic procedure, gaseous distention of the urinary drainage bag may become evident indicating a hole in the bladder.This intraoperative sign however, has not been associated with fistula formation.[104]

The diagnosis of VVF usually requires clinical assessment often in combination with appropriate imaging or laboratory studies. Direct visual inspection (office evaluation or exam under anaesthesia) may confirm the presence of a fistula however it may not reveal the extent, location, or course of the fistula. Some fistulae are not readily visible. This is particularly true with iatrogenic fistula in which the fistula may be high in the vagina and may involve the ureter, bladder, or both. Therefore, most physicians rely on adjunctive tools for the diagnosis of VVF. This may include imaging studies in combination with other modalities such as cystoscopy. A simple approach in the office setting to confirm that a fistula is present is to fill the bladder retrograde with a coloured fluid. This could bea milky fluid such as baby formula or vital dye-tinted water or saline (methylene blue, indigo carmine). Direct visualisation of dye extravasation or placement of a tampon into the vagina to identify staining may facilitate the diagnosis of a VVF. (**Figure 2**) A double-dye test

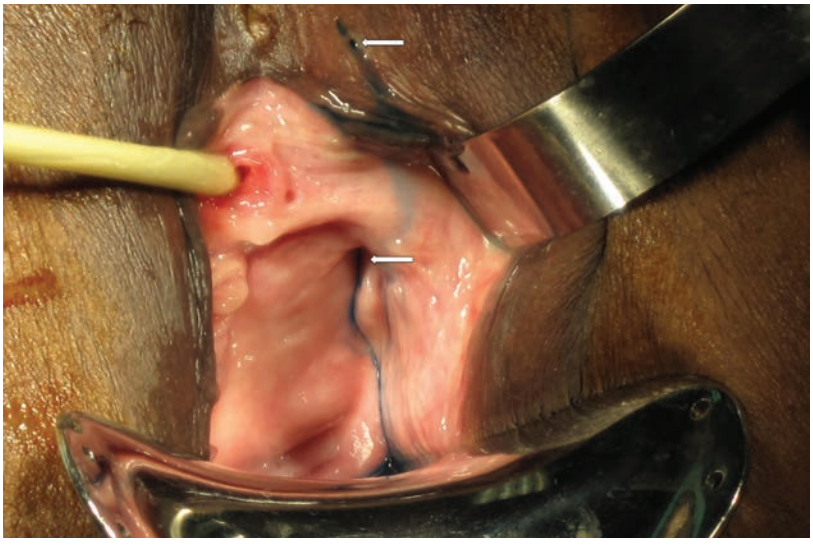


Figure 2. Methylene blue introduced intravesically, demonstrating complex vesico-vagino-vulval fistula following pelvic fracture (arrows indicate external openings)

to differentiate between an ureterovaginal and VVF may be useful in some cases. The patient is given phenazopyridine orally which will stain the urine orange while the bladder is filled with blue fluid. Blue tinting of the tampon leads to the presumptive diagnosis of a VVF while orange staining is suspicious for an ureterovaginal fistula. [105]

a) The role of cystoscopy in preventing and diagnosing VVF

A number of studies have investigated the role of routine cystoscopy in avoiding/detecting urinary tract injury at pelvic surgery; Indraratna et al. have recently reviewed these.[106]

Gilmour et al. undertook a systematic review of urinary tract injuries at benign gynaecological surgery including all studies of >500 patients reported between 1966 and 1998. [107] The overall rate of ureteric injury from 17 studies where cystoscopy was not undertaken (mostly hysterectomy) was 168⁄107,068=0.16%. In 10 studies where cystoscopy was undertaken routinely (mainly colposuspension or pelvic floor reconstruction), the rate of ureteric injury was 20/3235=0.62%. The corresponding rates of bladder injury were 0.26% (without cystoscopy) and 1.04% (with cystoscopy). Although the rates of detected urinary tract injury were approximately four-fold higher in those studies where cystoscopy was undertaken as a routine, it should be noted that none of these studies was randomised, and routine cystoscopy was undertaken predominantly during those procedures with intuitively the highest risk of injury. Summary statistics for available studies evaluating the place of routine cystoscopy (with or without intravenous indigo-carmine) at gynaecological surgery are given in **Table 2**.

Cystourethroscopy may provide direct visualisation of the fistula. In several series using cystoscopy (mostly with IV indigo-carmine) the sensitivity and specificity in detecting ureteric injury intra-operatively were >95%. Depending upon availability, radiologic studies (cystography, urography, intravenous urography, and CT urography) may be useful. Ultrasonography and colour Doppler have been used by some, although their use in routine practice remains to be established. [108][109]

Urine may extravasate externally or internally. Creatinine levels in the urinte are higher than serum levels. Therefore, in the setting of a suspected fisula, testing the creatinine level in either the extravasated fluid or the accumulated ascites and comparing this value to the the serum creatinine levels will confirm urinary leakage but not the location of the fistula. Likewise, testing potassium levels will show higher levels compared to serum levels. [110]

b) Imaging

An unstructured review by Narayanan et al. suggested that magnetic resonance imaging, particular with T2 weighting, provided optimal diagnostic information regardingfistula associated with pelvic malignancy, with contrast-enhanced CT with late excretory phase an acceptable alternative.[111] These newer modalities were considered to be superior to other X-ray contrast techniques and ultrasound.

2. DIAGNOSIS OF GI FISTULA

Pneumaturia, dysuria and/or recurrent UTI's are symptoms of a colovesical fistula but may be due to other causes as well.Accepting the limitations of small case series in this regard, a number of studies have investigated the value of a range of investigative techniques in the detection and evaluation of enterovesical or colovesical fistulae.[90, 92, 93, 97, 112-116]Since in each study the authors have presented only results on patients known to have fistulae, sensitivity (true positive/true positive + false negative) may be estimated, however, specificity (true negative/true negative + false positive), positive predictive value, (true positive/true positive + false positive) and negative predictive value (true negative/true negative + false negative) cannot (see **Table 3**). No test was shown to have consistent reliability; excluding those investigations for which only a single report was identified, CT (53%), cystoscopy (48%), and in the case of colovesical fistula, barium enema (38%) were perhaps the most useful; intravenous urography and sigmoidoscopy or colonoscopy appear to have limited utility in the diagnosis of GI fistula.

Table 2. Data from studies examining the reliability of intra-operative cystoscopy in detecting ureteric injury

Author	Date	Procedures	Method of detection	*N*	total	incidence	detected	sensitivity	specificity	PPV	NPV
Harris et al	1997	Urogynaecological surgery	IV indigo-carmine	224	6	2.68%	6	100.0%	100.0%	100.0%	100.0%
Gilmour et al	1999	Major gynaecological surgery*	Cystoscopy	3235	20	0.62%	19	95.0%	100.0%	95.0%	100.0%
Gustilo-Ashby et al	2006	Prolapse surgery	IV indigo-carmine	700	36	5.14%	34	94.4%	99.8%	91.9%	99.7%
Ibeanu et al	2009	Hysterectomy (all types)	IV indigo-carmine	839	15	1.79%	15	100.0%	97.4%	40.5%	100.0%
		All benign pelvic surgery	Cystoscopy +/- dye	4998	77	1.54%	74	96.1%	99.9%	74.0%	99.9%
						Confidence interval		3.0%	1.3%	27.4%	0.2%

* Data from Gilmour represent a metaanalysis of 10 studies published between 1990 & 1999 involving mainly colposuspension and pelvic floor reconstruction

Table 3: Data from studies examining the sensitivity of various investigations in the diagnosis of intestino-vesical fistulae.

Author	Date	n	Ba enema			Cystography			Sigmo/colonoscopy			Me blue			Charcoaluria			Bourne test			DTPA			Cystoscopy			CT			US			IVU		
Amendola et al	1984	28	10	20	50%	8	26	31%	4	24	17%	5	6	83%	1	1	100%	9	10	90%															
Bernstine et al	2002	1																			1	1	100%											
Garcea et al	2006	90	15	70	21%				0	77	0%													26	55	47%	5	45	11%	0	18	0%			
Jarrett et al	1995	9	0	5	0%	1	5	20%	0	4	0%													3	8	38%	8	9	89%				0	5	0%
Kavanagh et al	2005	30	4	8	50%				6	11	55%													14	16	88%	12	15	80%						
Kulman	1990	19																									25	25	###						
Liu et al	1999	41			63%			60%																		54%									
McBeath et al	1984	76						44%																		60%									
Pollard et al	1987	66	30	53	57%	2	5	40%	3	41	7%													14	40	35%									
Totals/mean		360	59	156	40%	11	36	39%	13	157	16%	5	6	83%	1	1	100%	9	10	90%	1	1	100%	57	119	54%	50	94	70%	0	18	0%	4	49	5%
Sensitivity					38%			31%			8%			83%			100%			90%			100%			48%			53%			0%			8%

3. RECOMMENDATIONS

CT and cystoscopy appear more consistent in the confirmation and location of possible intestino-vesical fistulae, than other investigations	C
Level 3 evidence indicates that the routine use of cystoscopy with dye testing at gynaecological surgery has high sensitivity, specificity and negative predictive value in the detection of ureteric injury, although false positive tests do occur. The clinical and cost-effectiveness of routine cystoscopy remains to be established	C

VI. MANAGEMENT OF VESICO-VAGINAL FISTULA

The literature relating to surgical fistula is extensive, but of limited quality. 356 papers of possible relevance were identified, of which only 173 contained any relevant material. Three systematic reviews were identified (albeit one only as a protocol),[117-119] although none contained information of direct relevance. Six randomised trials were identified including one on causation,[120] one on prevention of urinary tract injury at surgery,[121] two on antibiotic prophylaxis at the time of reparative surgery,[122, 123], and two on surgical techniques applied to obstetric fistulae.[124, 125] There was also one quasi-randomised study of relevance.[126] Four non-randomised cohort studies,[127-130] and one cost-effectiveness study,[131] were also identified. All other identified material comprised case series [99] and individual case reports or procedure descriptions [52], and represent level 3or 4 evidence. Three examples of duplicate publication were identified.

1. CONSERVATIVE MANAGEMENT

a) Immediate management by catheterisation or defunctionalizing

Before epithelialisation is complete an abnormal communication between viscera will tend to close spontaneously, provided that the natural outflow is unobstructed. Normal continence mechanisms, however, involve the physiological contraction and intermittent relaxation of urethral and anal sphincters. As a result, although completely spontaneous closure of genital tract fistulae does occur, it is the exception rather than the rule. Bypassing the sphincter mechanisms, or diverting flow around the fistula, for example by urinary catheterisation, percutaneous nephrostomy or defunctionalizing colostomy, may however encourage closure. Bazi reported a non-systematic review of papers including information on the spontaneous fistula closure of vesicovaginal fistulae; whilst the data quality of all was poor, he identified 30 studies from which 12 could be included; these included cases that were almost exclusively of surgical aetiology; it should be noted that in 9 of these 12 studies the sample size was less than 5 patients.[132] Few studies described catheter drainage in large fistulae, although it seemed that

Table 4. Data from studies including rates of spontaneous closure of surgical vesico-vaginal fistulae. n.b. table includes studies considered by Bazi,(132) but only those of known surgical aetiology.

Authors	Date	*N*	Spontaneous closure	%
Latzko	1942	39	9	23%
Falk & Orkin	1957	10	0	0%
Frang et al	1983	15	3	20%
Gorrea et al	1985	1	1	100%
Davits & Miranda	1991	4	4	100%
Tancer	1992	3	3	100%
Chittacharoen & Theppissai	1993	4	3	75%
Soong & Lim	1997	1	0	0%
Dogra & Nabi	2001	1	0	0%
Milicic et al	2001	21	0	0%
Mathevet et al	2001	4	2	50%
Lentz	2005	7	1	14%
Hilton	2011	238	19	8%
		348	45	13%
		Confidence interval		23%

those of less than 1cm diameter were most likely to heal spontaneously. The time between the insult and institution of drainage in cases of non-surgical closure varied widely, although in most cases this was less than 3 weeks. Similarly, the duration of catheterisation prior to the initiation of conservative treatment was deemed to have been unsuccessful varied considerably, making true estimates of the effectiveness of this approach impossible; generally this varied between 10 days and 3 months.[132] Reported success rates varied between 0% and 100% (although 5 series had a sample size of 1!), although in several series it was difficult to determine how many women had attempted conservative management.[132] In large series of obstetric fistulae where a consistent approach to conservative management has been applied, spontaneous healing has been reported in up to 28% of cases.[133-135] In one series of urogenital fistulae of varying aetiologies, spontaneous closure was seen in 19/238 or 8.0% of surgical cases, 4/38 or 10.5% of obstetric cases, 1/36 or 2.8% of miscellaneous (largely traumatic cases) and 0/34 or 0.0% of radiotherapy related cases.[17] It is likely that in this, and many other reported series, data are an underestimate of the value of this approach to management,[17] nevertheless, combining available data (see **Table 4**) gives an overall spontaneous closure rate from 348 surgical fistulae treated by initial catheterisation of 13% ± 23%.[8, 17, 21, 136-145]. Patients with ongoing, continuous vaginal leakage despite a functioning indwelling catheter are unlikely to have resolution of the VVF without additional measures such as surgery. Such patients should be spared prolonged catheter drainage and proceed with more definitive repair as soon as medically appropriate.Small epithelialized fistulas may benefit from minimally invasive cystoscopic electrocoagulation of the fistula tract, followed by prolonged catheter drainage. In patients with fistulae less than 3.5mm in diameter, 11/15 had successful fistula tract ablation with cauterization and catheter drainage in a study by Stovsky et al.[146] In general, conservative measures are successful in small fistulas only, usually less than 2-3mm in diameter.

b) Pharmacotherapies to assist fistula closure

Several case reports describe successful fistula closure following the induction of amenorrhoea by oestrogen, oestrogen/progesterone combinations, or luteinising hormone releasing hormone analogues,[147] in the management of vesicovaginal,[148] and more frequently, uretero- or vesicouterine fistula following caesarean section.[149-153] The overall closure rate in these studies is 88%±16%. Spontaneous closure of vesico-uterine fistula has also been reported on a number of occasions,[150, 154] with a rate of 41/786 or 5% calculated in one review.[150] Whilst comparison across studies is obviously highly problematic (especially where many are single case reports, with success rates of 0% or 100%), it seems highly likely that the rate of closure following hormone treatment [14/16] is significantly higher than that of spontaneous closure [41/786] ($p<0.0005$ – Fisher's exact test).

In quasi-randomised controlled study (alternate allocation) in patients with continuing urinary leakage following ureteric or pelvi-calyceal surgery, the use of intranasal desmopressin was shown to significantly reduce the duration of leakage compared to 'watchful waiting'.[126] The use of such treatment should be avoided in patients with complicating factors such as infection.

It should be recognised that some fistulae may be associated with minimal symptoms, and even if persistent these may not require surgical treatment. Small distal urethro-vaginal fistulae, utero-vesical fistulae with menouria, colo-vesical fistulae associated with diverticular disease, and some low recto-vaginal fistulae may fall into this category.

c) Palliation and skin care

During the waiting period between diagnosis and repair, incontinence pads should be provided in generous quantities so that patients can continue to function socially to some extent as well as avoid skin complications related to chronic urinary leakage. Urinary fistula patients usually leak considerably larger quantities of urine than those with urethral incontinence from whatever cause, and this needs to be recognised in their provision of supplies.

The vulvar skin may be at considerable risk from urinary or faecal dermatitis,[155, 156] particularly if there is additional radiation change in the skin;[157, 158] liberal use of silicone barrier cream should be encouraged. Steroid therapy has been advocated in the past as a means of reducing tissue oedema and fibrosis, although these benefits are refuted and there may be a risk of compromise to subsequent healing. Some authors have recommended local oestrogen, and whilst empirically one might expect benefit in post-menopausal women,[159, 160] or those obstetric fistula patients with prolonged amenorrhoea,[161, 162] the evidence for this is limited.

d) Nutrition

To maximise the prospects for postoperative healing it is essential, that the general health of the patient should be optimised. This is most relevant to obstetric fistula patients, where social ostracism and the effects of prolonged sepsis, may commonly result in malnutrition and anaemia.[163-168] Where there is severe inflammatory bowel disease the question of an elemental diet or even total parenteral nutrition may need to be considered.[96, 99, 169-172] Nutritional support may also be important in patients with malignant or radiotherapy induced fistulae,[173] or in those with complications following diversion surgery.[172, 174, 175]

e) Physiotherapy

Obstetric fistulae are commonly associated with lower limb weakness, foot drop and limb contracture. In a group of 479 patients studied prospectively 27% had signs of peroneal nerve weakness at presentation and a further 38%, whilst having no current signs, gave a history of relevant symptoms.[176] Early involvement of the physiotherapist in preoperative management and rehabilitation of such patients is essential.[177] Although nerve injury is rarely seen in association with fistulae of other (non-obstetric) aetiologies, the value of physiotherapist support in the preoperative management and rehabilitation of patients with complex fistulae or with intercurrent pathologies should not be under-emphasised.[172]

f) Antimicrobial therapy

Active infection in the genital or urinary tracts should be treated prior to attempted surgical repair. In tropical countries the treatment of systemic infections such as malaria, typhoid, tuberculosis and parasitic infections are not uncommon and should be rigorously pursued and treatment undertaken before elective surgery. One randomised trial reported no difference in outcome between single dose IV gentamycin and continued postoperative use of amoxicillin, chloramphenicol or cotrimoxazolein obstetric fistula patients (although re-analysis suggests that a difference favouring peri-operative gentamycin may be present).[122] A further placebo controlled trial of ampicillin found no evidence of benefit from prophylactic antibiotics in terms of fistula closure or residual incontinence following repair, although the use of postoperative antibiotics was reduced.[178] A recent review of obstetric fistula practices has called for further trials in this aspect of fistula management.[179] Opinions differ on the desirability of prophylactic antibiotic coverage for surgery in the developed world, some avoiding their use other than in the treatment of specific infection, and some advocating broad-spectrum treatment in all cases. A systematic review found only weak evidence that antibiotic prophylaxis (compared to giving antibiotics when clinically indicated) reduced the rate of bacteriuria, pyuria and symptomatic urinary tract infection in female patients undergoing abdominal surgery who had a urethral catheter for at least 24 hours; this limited evidence related to women receiving antibiotics during the first three postoperative days or from postoperative day two until catheter removal.[180]

g) Bowel preparation

Although many surgeons continue to employ mechanical or stimulant laxative bowel preparation prior to recto-vaginal fistula repair,[181] and may even suggest alternative approaches to surgery where this has not been possible,[94] a recent systematic review that included 18 trials (5805 participants), found no evidence that patients benefit from mechanical bowel preparation, nor the use of rectal enemas, and concluded that bowel cleansing can be safely omitted prior to colonic surgery, without increasing the risk of perioperative complications.[117]

h) Counselling

Surgical (non-obstetric) fistula patients are usually previously healthy individuals, who entered hospital

for what was expected to be a routine procedure, and they end up with symptoms infinitely worse than their initial complaint. In contrast, obstetric fistula patients in the developing world are often social outcasts. In both situations therefore these women are invariably devastated by their situation; significant impact on their mental health has been objectively confirmed.[182, 183] It is vital that they understand the nature of the problem, why it has arisen, and the plan for management at all stages. In the setting of an iatrogenic fistula, there may be considerable medico-legal consequences. Confident but realistic counselling by the surgeon is essential and the involvement of nursing staff or counsellors with experience of fistula patients is also highly desirable. The support given by previously treated sufferers can also be of immense value in maintaining patient morale, especially where a delay prior to definitive treatment is required.[184]

2. SURGICAL MANAGEMENT

Whilst most commonly occurring after hysterectomy, virtually any operation undertaken in the pelvis may be complicated by the development of urogenital fistula.[17] In the series from UK recently published by Hilton, 238/348 or 68% were of surgical aetiology, 172 (72% of surgical cases and 49% of the series) followed excision of uterus and/or cervix.[17] It should be borne in mind also that so-called 'minimally invasive' procedures may result in fistula formation, including mid-urethral tape procedures,[119] and peri-urethral injections.[185]Minimally invasive procedures are not without risk as ureterovaginal fistula has been reported following a robotically-assisted procedure.[186]

a) Timing of surgery

The most appropriate timing for repair of vesicovaginal fistulae remains one of the more contentious issues in this area. The debate continues between the advocates of early intervention, in order to minimise the distress to the patient from continuing urinary leakage, vs. those in favour of delaying intervention until local inflammatory change has resolved, necrotic tissues have sloughed, and the patient's recovery from the causative event completed, so as to optimise results.

There is no consensus in the literature as to the definition of 'early' in this context, with different studies either failing to specify at all, or giving a broad range of definition. Although some studies have used the terms 'immediate',[187] 'less than two weeks',[188] or 'less than 30 days',[145] most reports have considered either less than 6 weeks,[189-191] or less than 3 months,[130, 188, 192, 193] as their definition of early intervention. Although relatively few studies have reported their outcomes for both early and late approaches to management, overall the results do not appear to be significantly different (see **Table 5**). The overall results for early management are estimated at 91%±6% and for later management (where provided) 90%±27% (p=1.00; Fisher's Exact test).

b) Outcomes from treatment and follow-up

Comparing the outcomes of treatment between different reports and different methods is made difficult by the inconsistent and relatively inefficient outcome measures used. These have ranged from the apparent achievement of a water-tight repair based on dye-testing in the operating theatre, to patient reported symptoms at the time of discharge from hospital. Follow-up in obstetric fistula patients is inevitably difficult in many developing world centres, but even amongst surgical or radiotherapy cases in the developed world, relatively few reports describe examination findings or symptoms at later postoperative review. Long-term outcomes and quality of life measures haveonly rarely been reported.[194, 195]

Table 5. Data from studies examining outcome from vesicovaginal fistula repair using an 'early' approach to management; where comparative data from alternative timings are available these are included.

Authors	Date	Definition of 'early'	early			late		
			n	cure	%	*n*	cure	%
Collins et al	1960	< 8 weeks	24	16	67%			
Persky et al	1979	< 10 weeks	7	6	86%			
Fourie	1983	unspecified	6	5	83%			
Badenoch et al	1987	<6 weeks	19	19	100%			100%
Cruikshank	1988	5 weeks	11	11	100%			
Wang & Hadley	1990	<3 months	7	7	100%	9	8	89%
Blandy et al (see also Badenc	1991	<6 weeks	25	25	100%			100%
Moriel et al	1993	<3 months	16	16	100%			
Blaivas et al	1995	<12 weeks	13	13	100%	10	10	100%
Soong & Lim	1997	< 1 month	2	2	100%	1	0	0%
Kostakopoulos et al	1998	unspecified	20	18	90%			
Kam et al	2003	<6 weeks	6	4	67%	14	13	93%
Shelbaiia & Hashish	2007	<2 months	12	12	100%			
Lee et al	2010	immediate	5	5	100%			
Radoja et al	2010	< 3months	14	12	86%	7	6	86%
			187	171	91%	41	37	90%
			Confidence interval		6%			27%

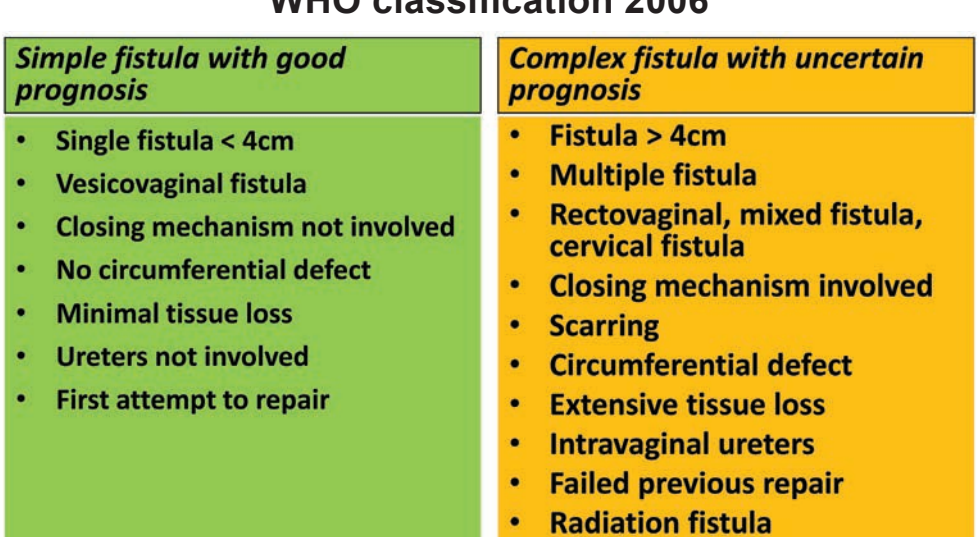


Figure 3. Adapted WHO classification of fistula. Although this classification was developed for obstetric fistula initially, it could be relevant for iatrogenic fistula as well. (400)

c) Surgical approaches

Despite the fact that there is no universally agreed upon classification of iatrogenic fistula, it is probable that there is a relationship between the complexity of the fistula and the outcome of the fistula repair.

The WHO published a classification on obstetric fistula in 2006 that divided fistula in simple or complex fistula. We adapted that classification by adding the radiation fistula to the complex fistula group. (**Figure 3**)

1. Vaginal Procedures

There are two main types of closure technique applied to the repair of urinary fistulae, the classical saucerization technique described by Sims,[196] and subsequently modified as a partial colpocleisis by Latzko,[142] and the more commonly used dissection and repair in layers or 'flap-splitting' technique (variously attributed to Hayward, Collis & Lawson Tait).[197] Individual surgeons inevitably employ these techniques somewhat variably, and in different situations, and there are no data comparing their outcomes.

The conventional dissection and repair in layers is entirely appropriate for the majority of post-surgical fistulae, although modifications may be necessary in specific circumstances. In juxta-cervical fistulae in the anterior fornix, vaginal repair may be feasible if the cervix can be drawn down to provide access. Dissection should include mobilisation of the bladder from the cervix, and the repair should usually be undertaken in such a manner (usually transversely) to reconstruct the underlying trigone and prevent distortion of the ureteric orifices.

Vault fistulae, particularly those following hysterectomy, can again usually be managed vaginally. The vault is incised transversely and mobilisation of the fistula is often aided by deliberate opening of the Pouch of Douglas.[198] The peritoneal opening does not require to be closed separately, but is incorporated into the vaginal closure.

Where there is substantial urethral loss, reconstruction may be undertaken using the method described by ChassarMoir[199] or Hamlin & Nicholson.[200] A strip of anterior vaginal wall is constructed into a tube over a catheter. Plication behind the bladder neck is probably important if any prospect for continence is to be achieved. The interposition of a labial fat or muscle graft not only fills up the potential dead space, but may also provide additional bladder neck support and improve continence by reducing scarring between bladder neck and vagina. These are indeed technically demanding procedures and outcomes of such complex repairs using robust measures as regards continence or sexual function are lacking.

With very large fistulae extending from bladder neck to vault, the extensive dissection required may produce considerable bleeding. The main surgical difficulty is to avoid injuring the ureters. They are usually situated close to the supero-lateral angles of the fistula, and if they can be identified endoscopically, they should be catheterised. Straight ureteric catheters passed transurethrally, or double pigtail catheters may both be useful in directing the intramural portion of the ureters internally; nevertheless great care must be taken during dissection. In such cases where the ureters cannot be visualized cystoscopically, interventional radiological techniques may be utilized to place antegrade ureteral stents from a percutaneous nephrostomy access tract.

2. Abdominal procedures

Repair by the abdominal route is indicated when high fistulae are fixed in the vault and are inaccessible through the vagina; most typically this might be following hysterectomy in nulliparous women, in endometriosis, or in those who have not delivered vaginally. Other indications for transabdominal repair are the need for simultaneous augmentation cystoplasty, or in the setting of a ureteric injury requiring reimplantation or simultaneous VVF and ureterovaginal fistula.

A transvesical repair has the advantage of being entirely extraperitoneal. It is often helpful to elevate the fistula site by a vaginal pack. The ureters should be catheterised under direct vision either endoscopically prior to skin incision, or following opening of the bladder. The technique of closure is similar to that of the transvaginal flap-splitting repair except that for purposes of haemostasis the bladder mucosa is usually closed with a continuous suture.

A simple transperitoneal repair is relatively uncommonly employed (although this technique does seem to be favoured by some using the laparoscopic approach – see below), although a combined transperitoneal and transvesical procedure is favoured by many urologists and is particularly useful for fistula repair following Caesarean section. A midline incision is made in the vault of the bladder; this is extended downwards in a racquet shape around the fistula. The fistulous track is excised and the vaginal or cervical defect closed in a single layer. The bladder is then closed in two layers.

There are no randomised studies comparing abdominal and vaginal approaches; given that those surgeons undertaking both routes for repair would usually see specific indications for the two such a comparison is most unlikely ever to be seen as feasible, ethical or appropriate. Nine non-randomised cohort studies reporting results from both abdominal and vaginal procedures were identified in the current review.[9, 17, 128, 191, 201-205] In all, these series included 388 vaginal repairs and 345 abdominal repairs with overall closure rates at first operation of 89% and 87% respectively (p=0.367; Fisher's exact test). The same reports included 255 transvesical repairs with a 93% cure rate, and 399 transperitoneal repairs with an 89% success rate (p=0.130; Fisher's exact test) (see **Table 6**).

With respect to attempted repair of a previously failed VVF surgery, the law of diminishing returns appears to be as evident in these types of procedures as in many other forms of surgery. Although repeat operations are certainly justified, the success rate decreases progressively with increasing numbers of previously unsuccessful procedures. In a series of 2484 largely obstetric fistulae, the success rate fell from 81% for first procedures to 65% for those requiring 2 or more procedures.[206] Series of surgical cases are rarely large enough for this effect to be evident, although the recent series published by Hilton found successful fistula closure was significantly more likely in the women who had not had attempts at closure before referral (98.2%) than in those who had one or more previous unsuccessful procedures (88.2%) (p=0.003; Fisher's exact test).[17]

There is only a single randomised trial comparing aspects of surgical technique; Shaker et al. report an RCT comparing trimming of the fistula edge with no trimming.[125] Although there was no statistical difference in success rates between the two groups, in those cases where repair was unsuccessful and trimming had been undertaken, the fistula tended to become larger, whereas those where there was no trimming were more likely to be smaller upon recurrence(see **Figure 4**).[125]

3. Laparoscopic

Laparoscopic repair of a VVF was first reported by Nezat et al., in 1994.[207] Fifteen series were identified in the current review,[187, 207-220] (plus an additional series in which 2 laparoscopic procedures were undertaken amongst a small series of vaginal and open abdominal operations).[205] All reported series are quite small (1-25 cases, median 6 cases), and in total only 119 patients were included, with an overall cure rate of 92% (confidence interval 4%) (See **Table 7**). It is not clear from these series whether they include all fistula repairs undertaken in the reporting centres, or whether they were selected in some way; if the latter, it is not clear what selection criteria were used. It is possible that there may be both selection and reporting biases that make it difficult to fully evaluate laparoscopic procedures against alternative surgical approaches.

4. Robotic

The first report of a robotically-assisted repair of vesico-vaginal fistula was from Melamud et al. in 2005.[221] Since that time four additional reports have been identified,[222-225] including a total of 17 cases (see **Table 7**). The reported cure rate is 100% in all series, although the same comments as above, in relation to possible selection and reporting biases, apply equally here. At this stage, whilst one could state that fistula repair with robotic-assistance appears to be feasible, it is not possible to indicate what its place or potential advantagesare over alternative approaches.

5. Fibrin glue

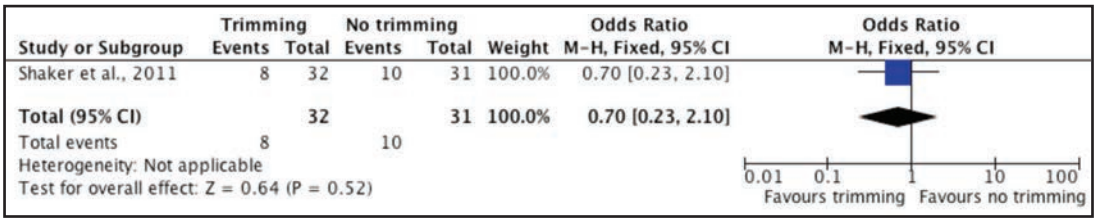
The use of fibrin glue in urological indications was reviewed by Shekarriz and Stoller;[226] they identified nine reports (eight in human subjects) of the use of fibrin glue in fistula repair, including a total of 16 patients.[227-234] A further six more recent reports were identified in the current review, where fibrin glue was used either by endoscopic injection or direct application, making a total of now 53 patients with fistu-

Table 6. Results from series reporting vaginal and abdominal (transvesical or transperitoneal) repairs in exclusively or largely surgical fistulae.

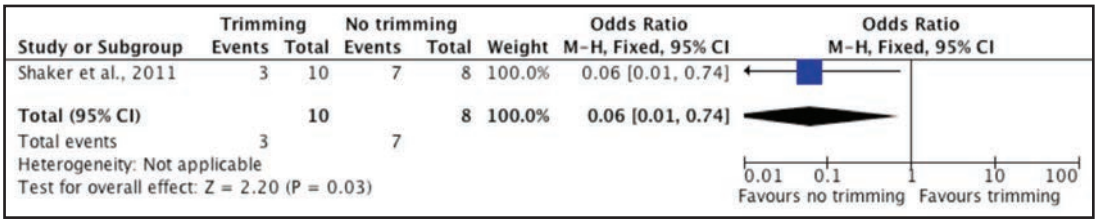
n.b.those studies highlghted in orange give results for vaginal procedures only, those in blue from abdominal (transvesical or transperitoneal), and those in green provide non-randomised data on both surgical approaches.

Authors	Date	Total series	Vaginal			Abdominal			Transvesical			Transperitoneal		
		N	*n*	cures	% cures at 1st repair	*n*	cures	% cures at 1st repair	*n*	cures	% cures at 1st repair	*n*	cures	% cures at 1st repair
Wang & Hadley	1990	16	16	15	94%									
Iselin et al	1998	20	20	20	100%									
Milicic et al	2001	21	21	20	95%									
Eilber et al	2003	207	207	200	97%									
Flynn et al	2004	40	40	40	100%									
Lentz	2005	6	6	6	100%									
Xu et al	2005	9	9	9	100%									
Ansquer et al	2006	11	11	11	100%									
Pushkar et al	2006	71	71	64	90%									
Doraiajan et al	2008	10	10	10	100%									
Pushkar et al	2008	21	21	19	90%									
Radopoulos et al	2008	8	8	8	100%									
Fu et al	2009	11	11	11	100%									
Mehmood	2009	86	86	86	100%									
Robles et al	2009	2	2	2	100%									
Eshani et al	2010	6	6	5	83%									
Radoja et al	2010	22	22	18	82%									
Shoukry et al	2010	20	20	20	100%									
Langkilde et al	1999	30	7	5	71%	23	22	96%				23	22	96%
Ou et al	2004	16	6	5	83%	6	6	100%				8	8	100%
Ayed et al	2006	73	54	30	56%	35	21	60%				35	21	60%
Okrim et al	2009	44	20	19	95%	24	18	75%				24	18	75%
Cantanzaro et al	2005	34	28	27	96%	4	4	100%				4	4	100%
Kam et al	2003	20	4	3	75%	15	13	87%	7	6	86%	8	7	88%
Hadzi-Djokic et al	2009	220	59	55	93%	161	150	93%	129	120	93%	32	30	94%
Hilton	2011	348	201	193	96%	60	50	83%	16	14	88%	44	36	82%
Denirel et al	1993	32	9	8	89%	17	15	88%	17	15	88%			
Badenoch et al	1987	19				19	19	100%	19	19	100%			
El-Lateef Moharram	2004	26				26	26	100%	26	26	100%			
Shelbaia & Hashish	2009	12				12	12	100%	12	12	100%			
Udeh	1985	29				29	25	86%	29	25	86%			
Dalela et al	2006	26				26	26	100%				26	26	100%
Islam & Ahmed	2010	32				32	30	94%				32	30	94%
Jovanovic et al	2010	49				49	48	98%				49	48	98%
Mondet et al	2001	28				28	24	86%				28	24	86%
Nesrallah et al	1999	29				29	29	100%				29	29	100%
Orford & Theron	1985	59				59	55	93%				59	55	93%
		1713	975	909	93%	654	593	91%	255	237	93%	401	358	89%
		Confidence interval			4%	Confidence interval		5%	Confidence interval		5%	Confidence interva		6%

(i) Forest plot of comparison: 1 Trimming vs. no trimming of fistula edge, outcome: 1.1 Failure of fistula closure



(ii) Forest plot of comparison: 1 Trimming vs. no trimming of fistula edge, outcome: 1.2 Recurrence smaller than original



(iii) Forest plot of comparison: 1 Trimming vs. no trimming of fistula edge, outcome: 1.3 Recurrence larger than original

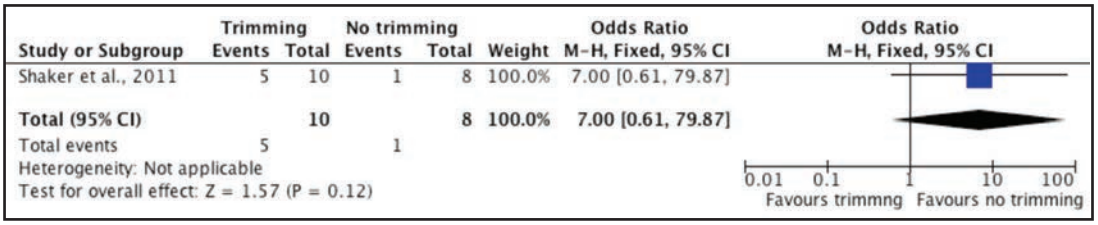


Figure 4. Forest plots relating trimming of edges at fistula surgery

Table 7. Results from series reporting conventional and robotically-assisted laparoscopic fistula repairs. n.b. those studies highlighted in orange give results for vaginal procedures only, those in blue from abdominal (transvesical or transperitoneal), and those in green provide nonrandomised data on both surgical approaches.

Authors	Date	Total series	Laparoscopic			Robotic		
		N	*n*	cures	% cures at 1st repair	*n*	cures	% cures at 1st repair
Nehzat et al	1994	1	1	1	100%			
Phipps	1996	6	6	6	100%			
Miklos et al	1999	1	1	1	100%			
Chibber et al	2005	8	8	8	100%			
Sotelo et al	2005	15	15	14	93%			
Wong et al	2006	2	2	2	100%			
Das Mahapatra et al	2007	12	12	11	92%			
Otsuka et al	2008	7	7	6	86%			
Gozen et al	2009	3	3	3	100%			
Porpiglia et al	2009	4	4	4	100%			
Shah	2009	25	25	18	72%			
Lee et al	2010	5	5	5	100%			
Rizvi et al	2010	8	8	8	100%			
Abdel-Karim et al	2011	15	15	15	100%			
Abdel-Karim et al	2011	5	5	5	100%			
Melamud et al.	2005	1				1	1	100%
Sundaram et al	2006	5				5	5	100%
Schimpf et al	2007	1				1	1	100%
Hemal et al	2008	7				7	7	100%
Kurz et al	2012	3				3	3	100%
			117	107	91%	17	17	100%
			Confidence interval		4%	Confidence interval		0%

lae of various aetiologies.[124, 229, 235-239] Several of these publications were individual case reports, although there was also one randomised trial comparing fibrin glue (20 patients) with a Martius graft (20 patients) in obstetric fistula patients.[124] All of the case reports described successful repair (1/1=100% cure); the RCT reported 13/20=65% cure; the overall success rate therefore for the 53 reported patients was 77.4% (confidence interval 7.3%) (See **Table 8**). In one case successful closure of a radiation induced fistula was reported from the combined use of bovine collagen and fibrin glue.[229] Overall, the indications for, and optimal patient selection for this approach are not defined.

6. Endoscopic repair

Mackay described a technique for transurethral endoscopic suture repair of vesico-vaginal fistula in 1997.[240]; there have been three further papers using a similar technique on between one and four patients (total 10 cases).[202, 240-242] Although in three of these series the reported cure rate was 100%, overall, fistula closure was found in 80% (confidence interval 24%).

c) Adjuvant Techniques in the Repair of VVF: Tissue Interposition

Tissue flaps are often added as an additional layer of repair during VVF surgery.[243-247]Most commonly, such flaps are utilized in the setting of recurrence after a prior attempt at repair, for VVF related to previous radiotherapy (described later), ischemic or obstetrical fistula, large fistula, and finally those associated with a difficult or tenuous closure due to poor tissue quality. However, there is no high level evidence for the use of such flaps in any of these situations. Furthermore, there is no high level evidence that the use of such flaps improves outcomes in the setting of an uncomplicated VVF.

For those VVF repaired transvaginally, a labial fat pad (Martius flap) or a peritoneal flap can easily be mobilized. From a transabdominal approach, greater omentum can be used as an interposition flap.

A variety of other flaps including gracilis muscle flaps, labial myocutaneous flaps, seromuscularintestinal flaps, and rectus abdominis flapsas well as free grafts of bladder mucosa have been utilized as adjunctive measures in the repair of complex VVF.[248-255]

3. POST-OPERATIVE MANAGEMENT.

a) Catheter type

No studies were identified comparing different catheter types or duration of drainage following fistula repair. Most reports do not describe their catheterisation practices in any detail; in those that do, the majority have employed urethral catheterisation, with a small number preferring suprapubic drainage or a combination of both. The reason for catheterisation is to ensure free urine drainage until such time as the repair is soundly healed; for this reason some have advocated both suprapubic and urethral drainage, arguing that whilst one catheter might easily become blocked, two are unlikely to do so simultaneously.[17]

b) Duration

There appears to be no obvious consensus over the duration of catheterisation recommended following fistula repair of various types and aetiologies. In a retrospective study of obstetric fistula patients in Ethiopia, approximately equal numbers of patients were catheterised for 10, 12 or 14 days. Patients were not randomised, and there were differences between the groups in terms of the extent of urethral involvement, fistula size, and degree of vaginal scarring, with the more extensively damaged patients being catheterised for longer. Despite this, there was no significant difference in outcome in terms of the rate of repair breakdown, and the authors therefore suggested that postoperative catheterisation for 10 days may be sufficient in the management of less complicated obstetric vesico-vaginal fistulae.[256]

Table 8: Studies using fibrin glue in the management of urogenital fistula.

Author	Date	Fistula	*n*	cures	%
Gumbt et al	1984	Vesico-perineal	1	1	100.0%
Rossi et al	1991	VVF (surgery)	3	3	100.0%
Schneider et al	1992	VVF (endoscopic)	6	4	66.7%
Tostain	1992	VVF	2	2	100.0%
Welp et al	1996	VVF	3	3	100.0%
Yashi et al	1998	Colo-vesical	1	1	100.0%
Morita et al	1998	Neovesico-cutaneous	1	1	100.0%
Morita & Tokue	1999	VVF (radiation)	1	1	100.0%
Evans	2003	VVF	5	4	80.0%
Sharma et al	2005	Various	7	5	71.4%
Daley et al	2006	VVF	1	1	100.0%
Lazarou	2006	VVF (surgery)	1	1	100.0%
Sarfan et al	2009	VVF (obstetric)	20	13	65.0%
D'arcy et al	2010	VVF (surgery)	1	1	100.0%
			53	41	77.4%
			Confidence interval		7.3%

In a recent review of practices amongst obstetric fistula surgeons, Arrowsmith reported a considerable range of practice. For 'simple' fistulae, the average duration of bladder drainage used was 12 days (range 5-21 days); for 'large' fistula the average was 17 days (range 0-30 days); and for 'difficult' fistulae, the average was 21 days (range 14-42 days).[179]

Studies of non-obstetric fistula management are no more consistent in their description of duration of catheterisation. Most report periods of between seven and 21 days drainage; most typically 10-14 days for surgical fistulae and 14-21 days for radiotherapy-associated fistulae. There is no more than level 3/4 evidence to support any particular practice in these aspects of fistula management.

The summary of the surgical management of VVF can be found in **Figure 5-7**.

Conclusions & recommendations

Spontaneous closure of surgical fistulae does occur, although it is not possible to establish the rate with any certainty; if a vesicovaginal fistula is diagnosed within six weeks of surgery, indwelling catheterisation can be considered for a period of up to 9 weeks (i.e. up to 12 weeks after the causative event)	C
Attention should be given as appropriate to skin care, nutrition, rehabilitation, counselling and support prior to and following fistula repair	D
Perioperative antibiotic prophylaxis should follow local policies	D
There is no benefit from mechanical or laxative bowel preparation prior to colonic surgery; it is reasonable that this recommendation be extrapolated to apply to fistula surgery	B
There is no proven benefit to delayed repair of vesicovaginal fistula; the timing of repair should be tailored to the individual patient and surgeon requirements, but can be undertaken as soon as any oedema, inflammation, tissue necrosis, infection are resolved	B
There are no high quality data to indicate greater cure rates for any one technique as compared to others; level 3 evidence indicates similar success rates for vaginal and abdominal, and for transvesical and transperitoneal approaches	C
Surgeons involved in fistula surgery should have appropriate training, skills, and experience to select an appropriate procedure for each patient	D
The majority of vesico-vaginal and all urethro-vaginal fistulae can be repaired vaginally, regardless of aetiology	C
Where concurrent ureteric re-implantation or augmentation cystoplasty are required, the abdominal approach is necessary	D
A variety of interpositional grafts can be used in either abdominal or vaginal procedures, although there is little evidence to support their use in any specific setting	C

Surgical fistulae

Immediate management
- If a vesico-vaginal fistula is diagnosed within (*three to*) six weeks of surgery, indwelling catheterisation should be considered for a period of up to (*six to*) 9 weeks (*i.e.* up to 12 weeks after the causative event
- Retrograde, ureteroscopically-assisted or antegrade ureteric stenting should be considered for immediate management for all uretero-vaginal fistulae

Timing of surgery
The timing of VVF repair should be tailored to the individual patient requirements, and can be undertaken as soon as any local oedema, inflammation, necrosis & infection resolved

Bowel preparation
No benefit from mechanical or laxative bowel preparation prior to colonic surgery; this can be extrapolated to include fistula surgery

Antibiotic prophylaxis
Perioperative antibiotic prophylaxis should follow local policies

Counselling & support
- Realistic counselling by the surgeon, nursing staff and/ or counsellors with experience of fistula patients is highly desirable
- Support from previously treated patients is appreciated and very valuable

Surgical approach
- Surgeons involved in fistula surgery should have appropriate training, skills, experience and versatility to select an appropriate procedure for any patient
- Both vaginal and abdominal approaches have an established role in fistula repair
- The majority of VVFs and all urethro-vaginal fistulae can be repaired vaginally, regardless of aetiology
- Where concurrent ureteric re-implantation or augmentation cystoplasty are required, and abdominal approach is essential
- A variety of interposition grafts are described for use in either abdominal or vaginal procedures, although there is no high level evidence to support their use
- Conventional and robotically-assisted laparoscopic approaches have both been shown to be feasible in selected cases; the place of these techniques is not yet clear

Postoperative drainage
A period of continuous bladder drainage is crucial to successful fistula repair
- 10-14 days for simple and/or surgical
- 14-21 days for complex and/or radiation

Figure 5. Treatment recommendations for vesicovaginal fistula

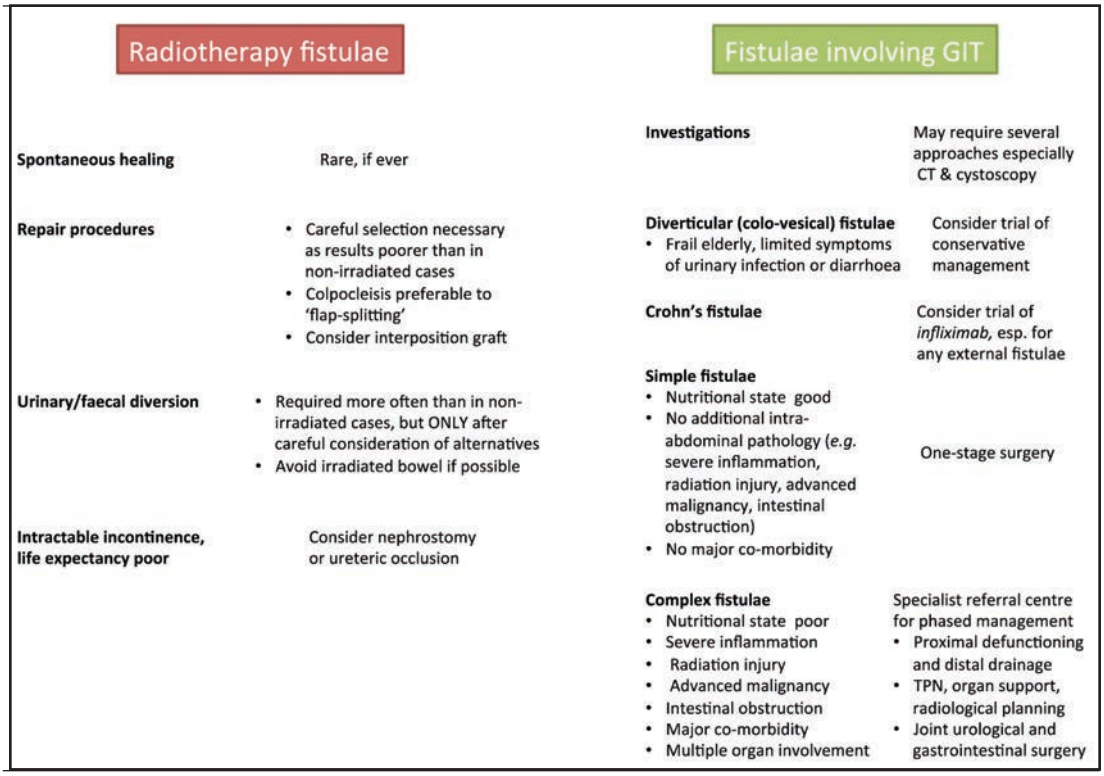


Fig 6. Treatment recommendations for radiation fistula and fistula involving the gastro-intestinal tract.

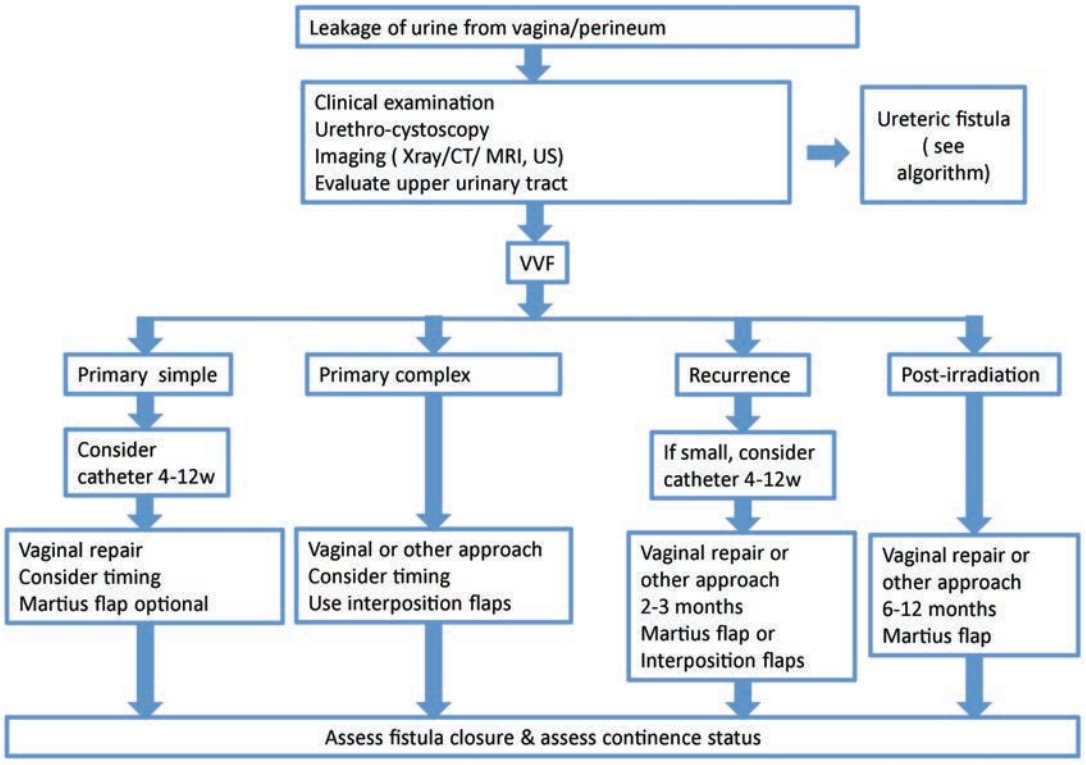


Figure 7. Algorithm for iatrogenic vesicovaginal fistula

4. MANAGEMENT OF RADIATION FISTULA

The literature relating to the management of radiotherapy-associated fistula is again limited in quantity and quality. Forty-nine papers of possible relevance were identified, of which only 35 contained any relevant material. Seven systematic reviews were identified, although none contained information of direct relevance. No randomised trials and only four non-randomised cohort studies of relevance were identified. All other identified material comprised case series or individual case reports or procedure descriptions, and represent level 3or 4- evidence.

Injury to the gastrointestinal or urinary tracts may arise following therapeutic radiation, with the incidence of complications increasing when the dose exceeds 50 Gy. The obliterative endarteritis associated with ionizing radiation in therapeutic dosages may proceed over many years and may result in fistula formation long after the primary malignancy has been treated. [17, 58] The associated devascularisation in the adjacent tissues means that conventional surgical repair has a high likelihood of failure, and may also result in re-presentation with several fistulae over a period of many years. In those cases where abdominal repair surgery or urinary diversions are undertaken, a high risk of GI anastomotic leak and progressive sepsis has been reported perhaps related either to inadequate resection of irradiated bowel or to damage to other organs at operation.[59] All these factors often make the management of post-radiation fistulae more challenging than that of post-surgical or even obstetric fistulae. Modified surgical techniques are often required, and indeed, where the same techniques have been applied to both surgical and post-radiation fistulae, the results from the latter have been consistently poorer.[203, 257, 258] Spontaneous healing seems rarely if ever to occur,[17, 40] and only one case report was identified, of a radiation fistula presenting 22 years after initial treatment, in which healing occurred following cauterisation (for biopsy) and prolonged catheter drainage.[259]

a) Diversion procedures

Because of the wide field abnormality surrounding many radiotherapy-associated fistulae, several authors have suggested that urinary and/or faecal diversion should be seen as the treatment of choice in such cases.[39, 62, 63, 203] Others have employed a routine policy of preliminary urinary and faecal diversion, with later undiversion in selected cases.[260] In a non-randomised cohort of recto-urethral fistula repairs, Vanni et al. reported 100% closure at first operation in 35 non-irradiated cases, compared to 84% in 39 irradiated cases.[260] Additionally, 97% of the non-irradiated cases subsequently underwent 'undiversion', whereas 31% of the irradiated cases required permanent faecal diversion due to a non-compliant rectum or severe sphincter dysfunction.[260]

Some authors have emphasised the place of repair in carefully selected cases of radiotherapy-associated fistulae.[17] Of 36 radiation/malignant fistulae in the series reported by Hilton, although 11 declined surgery or died before treatment, and 6 underwent primary diversion, of the 19 (53%) who underwent repair, 18 (95%) were closed at first operation.[17] Finally, some seem to take the view that diversion has little or no place in the management of radiation-induced vesicovaginal fistula in particular.[57] Of 216 radiation-induced fistula managed over a 47 year period by Pushkar et al., 210 underwent a vaginal and 6 an abdominal repair procedure (although it should be noted that this is a retrospective case series, and whilst not stated in the paper, it is possible that other patients not included in this review actually underwent diversion).[57] It should be noted, however, that with this almost exclusive use of the vaginal repair procedure, whilst a cumulative closure rate of 80% was eventually achieved after 4 or more operations, only 48% were closed after first repair, 40% were closed following a second operation, 52% following a third operation, and 35% following a fourth operation.

In view of the anastomotic problems associated with radiation-induced fistula, the transverse colon has often been favoured over ileum as a conduit in this context, to avoid the risk of employing irradiated bowel and distal ureter.[261-263] Whilst these benefits seem clear, it should be noted that high perioperative morbidity (37%) and re-operation rates (20%) have been reported from this procedure.[262]

As an alternative to the latter operation, where both urinary and faecal diversion are proposed, Hampson et al. described the technique of left colic urinary diversion with distal transverse end colostomy.[264] This technique allows a shorter operation time, and avoids the necessity for an intestinal anastomosis. In patients wishing to remain sexually active following such procedures, the residual bladder or rectal wall may be used to augment the vagina.[265] Where vesicovaginal fistula co-exists with significant bladder contracture following surgery or radiation, an abdominal (transperitoneal) repair might be considered, along with simultaneous ileocystoplasty,[266, 267] or colocystoplasty. [268] Fistula repair concurrently with vaginal reconstruction using sigmoidovaginoplasty has also been described by Verbaeys et al.[269] Whilst one might anticipate a very high operative and postoperative morbidity from such complex multiple procedures, the outcome in the very small numbers reported appears to have been good.

b) Repair techniques

Several different techniques for the vaginal repair of fistulae have been reported, although the methods of 'flap-splitting' or dissection and repair in layers (variously attributed to Hayward, Collis & Lawson Tait),[197] and partial colpocleisis,[142] have been the most widely advocated in radiation-associated fistulae. Where patients do not wish to maintain sexual function, complete colpocleisis may be used to good effect.[270] In a non-randomised cohort study, Hilton reported anatomical closure by colpocleisis in 94.7% of radiation-associated cases, compared to 96.1%

from a range of repair procedures in fistulae of surgical aetiology.[17]

The technique of sigmoid exclusion or isolation has been described for the management of radiation-associated colo- or entero-vesical and colo- or entero-vaginal fistulas.[271, 272] Although the results have generally been good, with the avoidance of a permanent urinary or faecal stoma, Levenback et al. reported poorer results than following resection of the affected bowel, largely related to bleeding from the isolated segment, and bacterial infection.[272]

c) Interposition grafts

Several techniques have been described to reinforce fistula repair in different sites depending on the type of repair undertaken. These include the Martius bulbocavernosus muscle and labial fat graft, a gracilis muscle or myocutaneous graft, omental pedicle grafts, and peritoneal flaps. Whilst there is no high level evidence to support the use of these techniques, the interposed tissue has been presumed to help by creating an additional layer in the repair, to fill in 'dead space' and reduce the risk of haematoma formation beneath the repair, to bring in a new blood supply into the area, and to reduce scarring. For each of these hypotheses, interposition grafts might be considered to have their greatest benefit in the repair of radiation-associated fistulae.

At abdominal repair of vesicovaginal or recto-vaginal fistulae, the use of a pedicled omental graft has been widely advocated.[245, 273] The omentum is dissected from the greater curve of the stomach and rotated down into the pelvis on either the right or left gastro-epiploic arteries; this may be used at any transperitoneal procedure, but has its greatest potential advantage in radiation-associated fistulae.

The role of interposition flaps in trans-abdominal repair procedures was reviewed by Evans et al.[247] They reported 37 patients with fistulae of largely surgical aetiology, of whom 12 of 12 treated employing an omental or peritoneal interposition flap were cured, compared to 16 of 25 managed without interposition (64%); this finding was consistent for fistulae of both benign and malignant aetiology. Although their cases were not randomised, and the authors acknowledge that their overall cure rate (75%) was rather lower than many series, nevertheless, they concluded that an interposition flap should be recommended, when a trans-abdominal repair is undertaken, particularly when the repair is performed by a less experienced surgeon.

Although widely employed in the context of obstetric fistula repair in the past, there is no high level evidence to support the use of the Martius graft in this context and there seems to be a general move away from it amongst obstetric fistula surgeons. One small non-randomised cohort study reported benefit in patients with multiple or recurrent fistulae, based on a univariate analysis,[243] another reported no advantage to the experienced obstetric fistula surgeon.[127] In the series of fistulae of all aetiologies from UK reported by Hilton, the fistula closure rate was not significantly different between those procedures where an interposition graft (omental or labial) was (92.0%) or was not (96.1%) used in the repair ($p=0.264$; Fisher ' s Exact test).[17]

In the situation of vaginal repair of radiation-associated fistula Pushkar et al. strongly advocate the use of the labial fat graft interposed at fistula repair;[57] Hilton advocates its use to fill 'dead space' in the lower vagina at complete colpocleisis.[17, 270] (**figure 8**)With the former technique closure at first operation was 48%,[57] with the latter 95% closure at first operation is described.[17]

Labial skin grafts have also been employed in the repair of radiation-associated fistulae, either as an interposition, or replacement for sloughed or indurated vaginal skin. Labia minora flaps, with the outer surface de-epithelialized,[274] and labia majora flaps,[275, 276] have both been described in this context.

Muscle and myocutaneous grafts have also been employed as interposition in fistula repair. These tend to be very bulky grafts, and are perhaps best used therefore in circumstances of extreme tissue loss. The technique of rectus abdominis flap interposition was described in one series of 10 patients, although none of their cases were radiotherapy related.[277]Viennas et al. reported one case of a radiation-induced vesicovaginal fistula repair by this technique.[252] Gracilis muscle along with selective use of a buccal mucosal overlay graft has been used in recto-urethral fistulae, with 84% cure in radiation-associated cases.[260]

d) Other management approaches

In patients with intractable urinary incontinence from radiation-associated fistula, percutaneous nephrostomy or ureterostomy might be considered.[63] This may in some cases extend life perhaps inappropriately, and where life expectancy is deemed to be very short, ureteric occlusion might be more appropriate. Several methods have been described, including the insertion of coils,[278] coils with gelatin sponge,[279, 280]clips,[281] nylon plugs with injection of polidocanol,[282] Isobutyl-2-cyanoacrylate,[283] and balloons.[283-286] These were reviewed by Avritscher et al. with success rates ranging from 50% to 100% for the different methods, and with an overall success of 77% in 150 cases from nine papers reviewed.[287]

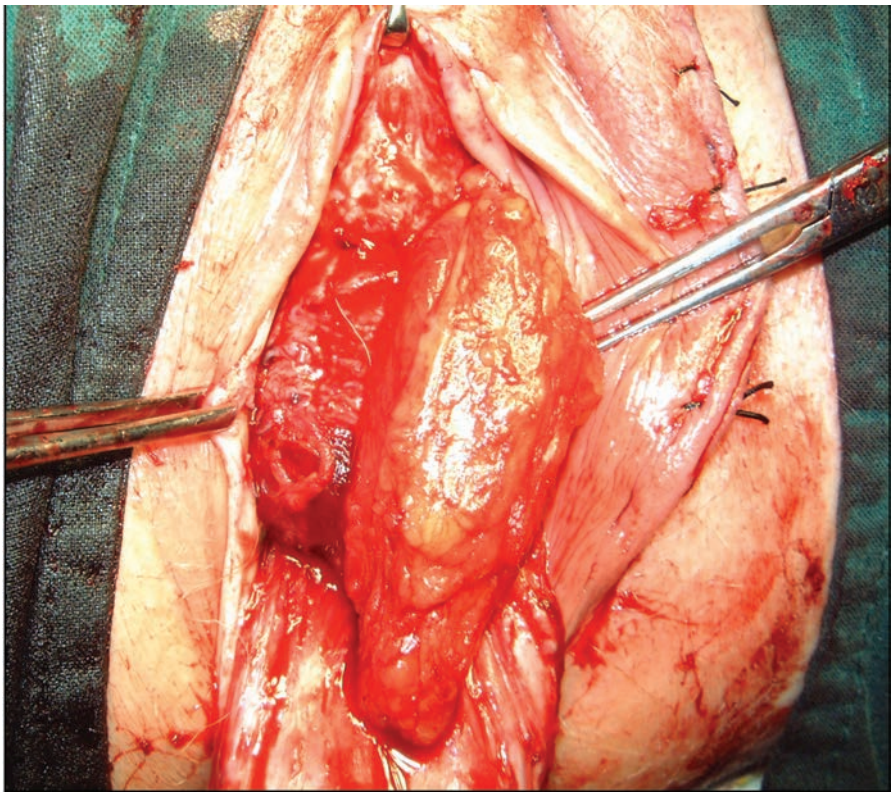


Figure 8. Martius labial fat graft passed subcutaneously to overlie fistula repair (combined with complete colpocleisis)

Recommendations Radiation Fistula

Whilst diversion is used more widely in radiation-associated fistulae of all types as compared to non-radiated fistulae, there is low level evidence that repair procedures can achieve successful fistula closure and continence in appropriately selected cases	C
Where urinary and/or faecal diversions are required, attempts should be made to avoid using irradiated tissues wherever possible, and to minimise the potential for anastomotic complications	C
There is low level evidence to support the use of interposition grafts when repair of radiation-associated fistula is undertaken	C
In patients with intractable urinary incontinence from radiation-associated fistula, where life expectancy is very short, ureteric occlusion might be considered; there is insufficient evidence to recommend any particular technique	D

VII. MANAGEMENT OF GI FISTULA

1. LITERATURE REVIEW

The literature relating to the management of urinary fistula involving the gastro-intestinal tract is limited in quantity and quality. Forty-six papers of possible relevance were identified, of which 39 contained any relevant material. One systematic review was identified, albeit of only indirect relevance, and with no mention of fistula.[117] A single non-systematic review of the management of internal fistulae in Crohn's disease was identified;[288] this included only a single randomised trial,[289] although this did not include patients with urinary fistulae. No further randomised trials or cohort studies of relevance were identified, either from within the review, or independently. One decision analysis model,[290] 26 case series and 10 individual case reports or procedure descriptions were found, including a total of 852 patients.

2. NON-SURGICAL MANAGEMENT

In the context of colo-vesical fistulae associated with diverticular disease, a surgical approach is most commonly advocated. One non-randomised cohort of 30 patients included six who did not undergo surgery, four of whom remained well for periods of up to 14 years; of the 24 who underwent surgical treatment, five (21%) died in the postoperative period.[291]

Ileo-vesical fistula in Crohn's disease may be managed with antibiotics, nutritional support, often including total parenteral nutrition, and various combinations of immunomodulatory agents; in a non-systematic review of the management of internal fistulae in Crohn's disease, Levy &Tremaine describe the drugs that have been reported to close internal fistulas partially or completely including azathioprine, 6-mercaptopurine, mycophenolatemofetil, cyclosporine A, tacrolimus, and infliximab.[288]

One case series of 500 patients with Crohn's disease included 17 with entero-vesical fistulas; all received sulfasalazine, and most were treated with corticosteroids and antibiotics intermittently, and eight in addition received 6-mercaptopurine. Although it is not clear that their fistulae closed completely, six continued on medical treatment alone for several years.[84]

Present et al. reported a placebo controlled randomised trial of the tumour necrosis factor α (TNFα) neutralising agent infliximab, a murine/human chimeric monoclonal antibody that binds both the soluble subunit and the membrane-bound precursor of TNFα, in patients with externally draining fistulae associated with Crohn's disease.[289] Adverse events were very common, but complete resolution of all fistulae was achieved in 55%, and 50% reduction in fistulous drainage was achieved in 68% of patients on 5mg infliximab. This latter study did not include intestino-vesical fistulae, although a case of successful use of infliximab in an ileo-vesical fistula has been reported.[169]

3. SURGICAL MANAGEMENT

The most frequently advocated surgical approach to colo-vesical fistula in diverticular disease has been sigmoid resection with primary colorectal anastomosis, and closure of the bladder. Dissection of the fistula track followed by closure of the bladder and bowel, with interposition of omentum, but without resection was described in three patients by Lewis & Abercrombie.[292]This approach should perhaps be reserved for cases with minimal diverticular disease in otherwise healthy bowel, where, were it not for the presence of the fistula, there would be no indication for colonic surgery.

One series of 74 patients described a technique in which only visible or palpable full-thickness defects in the bladder were repaired; otherwise the bladder was not repaired, but simply drained by indwelling catheter for one week following sigmoid colectomy (in diverticular disease) or small bowel resection (in Crohn's disease).[91] At median 6 month follow-up there was a single recurrence of a colo-cutaneous/vesico-cutaneous fistula, but no recurrence of the colovesical fistulae. Other authors have similarly advocated leaving the bladder unrepaired in patients with Crohn's ileo-vesical fistulae, to heal by secondary intention with catheter drainage alone.[87, 293]

The main contention in the management of intestino-vesical fistulae has been over the feasibility and role of a one-stage management with resection of the affected bowel segment, primary anastomosis, and closure of the bladder, as compared to a two- or three-stage approach.

The authors of many case series have advocated a one-stage approach in the majority of cases, but have indicated that this should be limited to those patients whose nutritional state is good, and where there is no evidence of severe inflammation, radiation injury, advanced malignancy, intestinal obstruction, major medical problem, or advanced age.[90, 93, 94, 96, 294, 295] More recent series have tended to imply a greater advocacy of the one-stage approach; Garcea et al. in a series of 90 patients with colo-vesical fistula reported primary anastomosis in 61/65=94% of cases where left colon resection was undertaken.[92] Balaguera et al. argue against diverting colostomy or Hartmann's procedure as being unnecessary, and possibly bringing additional morbidity.[296] Several reports have described a laparoscopic approach to one-stage treatment of colo-vesical fistulae, including a total of 30 patients.[95, 171, 297, 298] The overall conversion rate was seen to be higher for fistulae involving the duodenum, vagina and sigmoid colon, than those involving the bladder (10%), although a low threshold for conversion to open surgery was advocated in one series.[95]

In addition to the above criteria, it is intuitive that the more complex a fistula track, the more relevant a phased approach to treatment becomes. Shackley et al. described a series of 10 patients with highly complex fistulae involving between 3 and 6 separate organs/surfaces.[172] They advocate a three-stage multidisciplinary management package, involving: [1] an acute stage involving proximal defunctioning and distal drainage of both the gastrointestinal and urinary tracts to isolate the fistula, together with the eradication of sepsis; [2] a recovery stage consisting of total parenteral nutrition, organ support, radiological planning of surgical reconstruction and intensive nursing; [3] joint urological and gastrointestinal reconstructive surgery, when the patient was stable, nutritionally replenished, and sepsis was controlled. Whilst the mean time to reconstruction was 5 [1-20] months, the fistulae were treated successfully in all patients, with functional restoration in four, and/or diversion of the gastrointestinal and urological tracts in six.[172]

4. RECOMMENDATIONS

There is limited evidence to support a non-surgical or conservative surgical approach in colo-vesical fistulae where there are minimal symptoms or evidence of limited bowel involvement	C
There is only limited low level evidence to support a non-surgical approach in colo-vesical fistula associated with diverticular disease; nevertheless, in the frail elderly, or in patients who have limited symptoms of urinary infection or urinary diarrhoea it is reasonable to consider a trial of conservative management	D
There is evidence that infliximab is efficacious in the treatment of external fistulae, but only very limited low level evidence of efficacy in urinary fistulae in association with Crohn's disease	B/D
A one-stage approach to surgery for intestino-vesical fistulae is appropriate in many cases, but should be limited to those patients whose nutritional state is good, and where there is no evidence of additional intra-abdominal pathology (e.g. severe inflammation, radiation injury, advanced malignancy, intestinal obstruction) or major co-morbidity	B
A laparoscopic approach to one-stage management has been shown to be feasible, although there is no high level evidence to allow comparison of outcomes with open surgery	D

VIII. MANAGEMENT OF URETERIC FISTULA

1. GENERAL PRINCIPLES

The relevant clinical principles are related to prevention, diagnosis, management, and after care. [299] Patients at higher risk of ureteric injury such as those undergoing complicated childbirth, radical or repeated pelvic surgery, or surgery following pelvic radiotherapy require experienced surgeons who can identify and protect the ureter and its blood supply to prevent injury and also recognise injury promptly when it occurs. Immediate repair of any intraoperative injury should be performed observing the principles of debridement, adequate blood supply and tension free anastomosis with internal drainage using stents.[300] Delayed presentation of upper tract injury should be suspected in patients whose recovery after relevant abdominal or pelvic surgery is slower than expected, if there is any fluid leak, and if there is any unexpected dilatation of the pelvi-calyceal system. Fluid should be sent for creatinine determination to differentiate serous from urinary leak. Repair of such cases should be undertaken by an experienced team and may consist of conservative management with internal or external drainage, endoluminal management using nephrostomy and stenting where available, and early (< 3 months) or delayed (> 6 months) surgical repair when required.[301] Surgery should again adhere to the standard principles of tissue repair and safe anastomosis. Functional and anatomical imaging should be used to follow up patients after repair to guard against late deterioration in function of the affected renal unit. These general aspects of care of patients with trauma to the upper tract and subsequent fistula formation are covered in standard textbooks of urology and guideline documents. [300, 301] This review will concentrate on developments in the past six years.

2. EVIDENCE QUALITY

A total of 127 abstracts were screened which were categorised as being not relevant [26], cases reports without useful information [63] and for possible inclusion [38]. After review of full text, 27 were selected for the review and 11 rejected due to duplicate information (n=7) and no relevance (n=4). Four further possible papers were identified from the reference lists of included articles of which two were included in the review. The selected papers [29] included one poor quality randomised trial [302], one poor quality quasi-randomised trial [303], one high-quality population case control study[3], one registry study[76], one systematic review[304], one cost analysis[305], 14 cases series, 8 case reports, and one unstructured review.

3. EVIDENCE SUMMARY

a) Management of Specific Fistula

1. Urinary leak after renal preservation surgery

A large case series identified urinary fistula, defined as urinary drainage from a drain site more than 14 days post-operatively, in 4% [45/1118] of patients undergoing partial nephrectomy.[306] This was associated with larger tumours, higher blood loss, and longer ischemia time, but not the mode of surgery (laparoscopic versus open). The majority resolved without intervention but 30% required ureteric stent insertion or percutaneous drainage. A poor quality quasi-randomised study involving 16 patients with persistent leakage after pelvi-calyceal surgery despite stenting found that use of intranasal desmopressin 40 µg daily resulted in a shorter time to resolution of leak compared to control.[303]

2. Urinary leak after renal transplantation

A case series from Brazil observed a fistula rate of 2.9% [31/1046]presenting at a mean of 28 [1-131] days following transplantation predominantly due to distal ureteric necrosis and with most cases requiring open repair.[307] Fistula occurred more commonly in patients with diabetes and was associated with lower graft survival and two deaths from sepsis. A case se-

ries from China observed fistula development in 3.5% [43/1223] of patients presenting at a mean (range) of 6 [3-20] days following transplantation again primarily due to necrosis of the distal transplanted ureter. [308] Open intervention with re-implantation of the ureter into the bladder or native ureter was required in 34 patients, with one other patient requiring transplant nephrectomy. The occurrence of a fistula did not appear to prejudice graft or patient survival. Initial implantation of the transplant ureter into the native ureter appeared to result in a lower rate of fistula. A further case series form Serbia found a fistula rate following renal transplantation of 2.2% [5/224] and all required open repair.[309]

3. Uro-enteral fistula following percutaneous renal surgery

Case reports of ureterocolic fistulae occurring after renal cryotherapy, and gunshot trauma all resolved with insertion of ureteric stent.[310, 311] This is in line with previous accounts of this complication following percutaneous nephrolithotomy.[312]

4. Uretero-arterial fistula

A systematic literature review found reports of 139 cases of uretero-arterial fistula published between 1899 and 2008.[304] All patients presented with haematuria with 25% also having other urinary symptoms or back pain. Virtually all cases had a relevant past surgical history particularly pelvic cancer surgery (54%) and arterial surgery with graft insertion (31%), and 61% had a ureteric stent in situ. The great majority affected the iliac segment and pre-operative imaging was not always diagnostic. A total of 18 (13%) patients died as a result of the fistula. Many vascular and urologic interventions were used either alone or in combination. Later cases suggested that endovascular repair of the arterial defect gave the best results with lower mortality. Another, more recent case series of 20 patients also showed a high mortality of 10 – 20% but did not find any difference in outcome between open or endovascular graft insertion techniques.[313]

5. Ureterovaginal fistula

Ureterovaginal fistula occurring in the early postoperative phase predominantly after hysterectomy is the most frequent presentation to urologists of upper urinary tract fistula. A randomised study involving 3,141 women undergoing open or laparoscopic gynaecological surgery lasting > 30 min found that the incidence of ureteric injury after prophylactic insertion of ureteric stents (1.2 % [19/1583]) was similar to control (1.1% (17/1558]).[302] A previous cost analysis from the United States perspective suggested stenting was only worthwhile if the risk of injury was > 3.2%.[305] If injury does occur, many cases, even those with bilateral injury, can be managed by endoscopic techniques. [314](**Figure 9)**

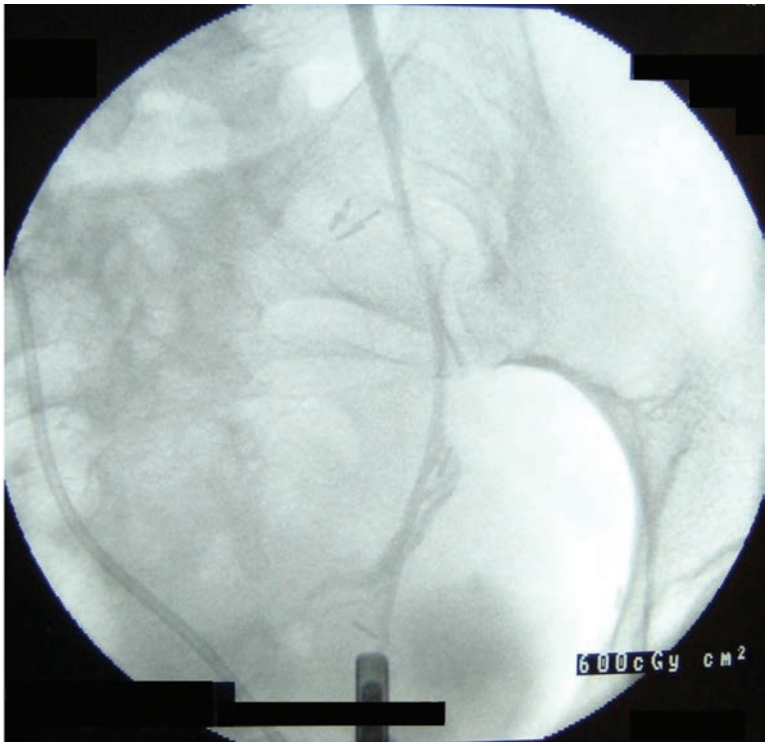


Figure 9. Conservative management of bilateral lower ureteric injury. Retrograde ureterogram showing successful cannulation of left ureter by guide wire and successful placement of right ureteric stent.

The use of ureteric stenting in patients with ureterovaginal fistulae was reported in 11 studies, including 126 patients in total;[315-325] this resulted in closure in 63 cases altogether. Success rates were between 6% and 100%, although the overall closure rate across all series is calculated at 50% ± 18% (see **Table 9**).

Where retrograde stenting proves impossible, percutaneous nephrostomy and antegrade stenting might be considered if there is some degree of pelvicalyceal dilatation. Ureteroscopy may also be helpful,[320, 324] and a technique for combined antegrade and retrograde ureteroscopic cannulation has been reported.[317] In one report all cases of uretero-vaginal fistula were managed by temporary diversion using a percutaneous nephrostomy followed by delayed repair 4-6 weeks later,[156] and a similar approach was taken in the management of one uretero-uterine fistula.[326]

If endoluminal techniques fail or result in secondary stricture, the abdominal approach to repair is standard and may require end-to-end anastomosis, re-implantation into the bladder using psoas hitch or Boari flap, or replacement with bowel segments with or without reconfiguration. Recent case series suggest that this standard surgery can be performed safely and with reasonable operative times using laparoscopic or robotic techniques if the relevant skills and facilities are available.[327-329] A recent case report has suggested that open repair through the vagina is possible if abdominal access is problematic.[330]

6. Ureteric fistula associated the terminal phase of pelvic malignancy

Urinary leakage is very distressing for people dying of advanced pelvic malignancy but palliation by open diversion may be associated with a high rate of complications. Recent case series have described the technique of occlusion of the distal ureter with coils or other devices using an antegrade approach combined with chronic urinary diversion using nephrostomy tubes.[331-333]Natarajan et al reported successful management of five patients with two requiring repeat embolization but all achieving good palliation until death without adverse effects.[331]Shindel et al reported on 29 patients with bothersome urinary fistula despite chronic nephrostomy drainage, and poor performance status.[332] In all cases palliation of the urinary leakage was achieved. The majority of patients [23/29] died of their underlying cancer at a mean of 8 months after the procedure. Three patients with benign disease subsequently underwent definitive surgical diversion with the remaining 2 lost to follow up. Coil migration was seen in one patient without serious consequence and there were no other complications specific to the embolization. Kim et al used the technique to temporally palliate five women with ureterovaginal fistula prior to delayed definitive repair.[333]

Table 9: Data from studies including rates of closure of uretero-vaginal fistulae with ureteric stenting.

Authors	Date	*N*	Spontaneous closure	%
Andrioli et al	1984	10	5	50%
Lang	1984	10	9	90%
Lingeman et al	1985	4	4	100%
Dowling et al	1986	23	11	48%
Mandal et al	1990	31	2	6%
Barton et al	1992	5	4	80%
Koonings et al	1992	1	1	100%
Campbell et al	1993	14	6	43%
Baeghler et al	1997	1	1	100%
Narang et al	2007	3	2	67%
Ustinoz et al	2008	24	18	75%
		126	63	50%
		Confidence interval		18%

The algorithm for uretero-vaginal fistula can be found in **Figure 10**

Evidence table

Prophylactic ureteric stent insertion does not reduce risk of ureteric injury during gynaecological surgery	2
The use of desmopressin may hasten resolution of urinary leak after pelvi-calyceal surgery	3
Uretero-arterial fistula is associated with a high mortality rate	3
Antegrade endoluminal distal ureteric occlusion combined with nephrostomy tube diversion often palliates urinary leakage due to malignant fistula in the terminal phase	4

4. RECOMMENDATIONS

Surgeons undertaking complex pelvic surgery should be competent at identifying, preserving and repairing the ureter	D
Ureteric stents are not required as prophylaxis against injury during routine gynaecological surgery, while their role in more extensive surgery remains to be established	B
Ureteric injury or fistula may be suspected in patients following pelvic surgery if a fluid leak or pelvi-calyceal dilatation occurs postoperatively	D
Uretero-arterial fistula may be suspected in patients presenting with haematuria with a history of relevant pelvic surgery and indwelling ureteric stent	D
Elevated levels of creatinine in drainage fluid following pelvic surgery are suggestive of a urinary tract injury	D
Most upper urinary tract fistula should be initially managed by conservative or endoluminal techniques where such expertise and facilities exist	B
Persistent ureterovaginal fistula should be repaired by an abdominal approach using open, laparoscopic or robotic techniques according to availability and competence	D
For patients with ureteric fistula associated with advanced pelvic cancer and poor performance status, palliation by nephrostomy tudediversion and endoluminal distal ureteric occlusion is an option	C

IX. MANAGEMENT OF URETHRO-VAGINAL FISTULA

1. INTRODUCTION

Urethrovaginal fistulas are a rather rare complication of some surgical and medical conditions or treatments. Most of the literature consists of small retrospective series or case reports. There are no randomized prospective trials.

2. AETIOLOGY

Excluding obstetric aetiologies,In the developing world, urethrovaginal fistula may occur as a result of obstructed labor with or without associated VVF. In industrialized countries urethrovaginal fistula in adults mostly have an iatrogenic aetiology. (See **Table 10**)

In feminizing genital reconstructions in children with ambiguous genitalia and surgical repairs of cloacal malformations, urethrovaginal fistula can occur as early or late complications. [334][335, 336][337, 338] Also in transsexual adults undergoing female to male reconstruction, urethrovaginal fistulae have been reported. [339]

In the surgical treatment of stress incontinence in women with bulking agents [340, 341] or synthetic slings several cases of urethrovaginal fistula have been reported.[342-345] [119] (see **Figure 11**) Even conservative treatment of prolapse with pessaries can lead to the formation of fistula, if these pessaries are neglected for an extended period of time, although fistula formation after only 2 weeks of pessary use has been described.[18, 346](see **Figure 12**).

Trauma – including inappropriate catheterisation- and foreign bodies are obvious causes of fistula. [347-353]

Urethral diverticula and their surgical repair may also lead to urethrovaginal fistula.[354-356]

Urethrovaginal fistula have also been described in some Behçet patients with vasculitis and local necrosis of the urethrovaginal septum. [357, 358]

Irradiation complications can also result in the formation of urethrovaginal fistula.[359]

3. DIAGNOSIS

Clinical vaginal examination is often sufficient to diagnose the presence of an urethrovaginal fistula. Urethroscopy and cystoscopy can be performed to assess the extent and location of the fistula. In cases of difficult diagnosis, voiding cystourethrography (VCUG) or ultrasound can be useful. [360] Double balloon urethrography is the classic examination to show urethral diverticulum and urethrovaginal fistula, but 3D MRI or CT scan is becoming utilized more widely.. [361-363]

4. SURGICAL REPAIR

Several techniques for urethrovaginal fistula closure have been described. A vaginal approach is mostly used. Surgical correction intends to create a continent urethra that permits volitional, painless, and unobstructed passage of urine. Depending on the size, localisation and aetiology of the fistula and the amount of tissue loss urethral reconstruction techniques may be necessary to restore the urethra and to achieve post-operative continence. [347]

a) Vaginal approach

Goodwin described in his series that a vaginal approach yielded a success rate of 70% at first attempt and 92% at second attempt, but that an abdominal

Table 10: Etiology of urethrovaginal fistula

Traumatic	Iatrogenic	Medical
Direct trauma	Bulking agents	Beçhet's disease
Foreign body	Sling surgery	
	Urethral diverticula repair	
	Catheterisation	
	Irradiation	

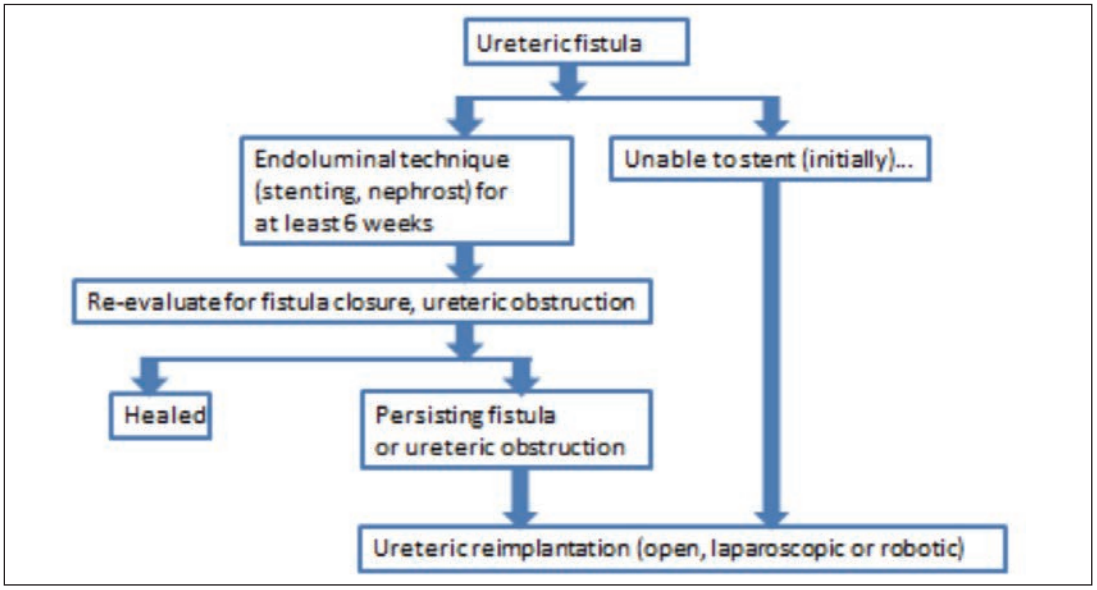


Figure 10. Algorithm for uretero-vaginal fistula

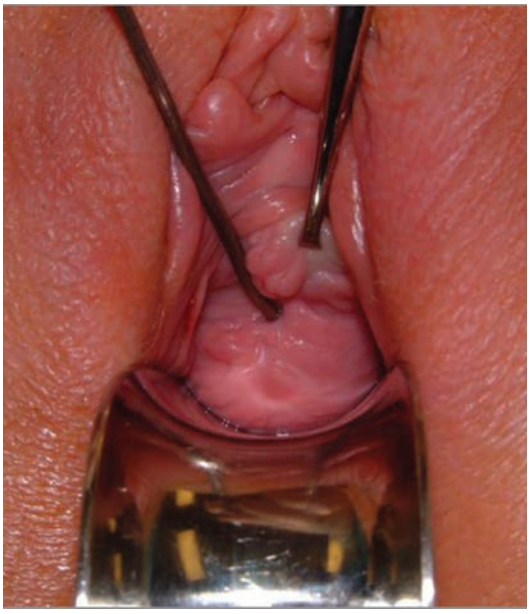


Figure 11. Urethro-vaginal fistula following mid-urethral tape procedure for SUI.

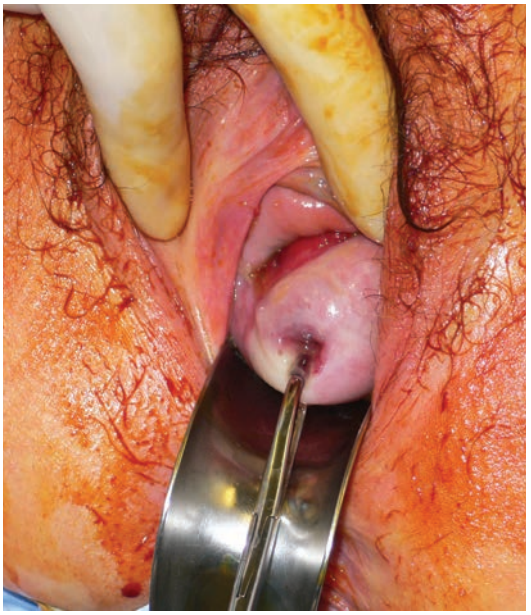


Figure 12. Fistula in anterior vaginal fornix following use of shelf pessary for utero-vaginal prolapse.

approach only leads to a successful closure in 58% of cases. A vaginal approach required less operating time, had less blood loss and a shorter hospitalisation time.[364]

Most authors describe surgical principles that are identical to those of vesicovaginal fistula repair: identifying the fistula, creation of a dissection plane between vaginal wall and urethra, watertight closure of urethral wall, eventual interposition of tissue, and closure of the vaginal wall. Primary closure rates of 53%-95.4% have been described (see **Table 11**). Pushkar et al. described a series of 71 women, treated for urethrovaginal fistula. 90.1% of fistula were closed at the first vaginal intervention. Additionally 7.4% were closed during a second vaginal intervention. Despite successful closure, stress incontinence developed in 52%. The stress incontinent patients were treated with synthetic or autologous slings and nearly 60% became dry and an additional 32% improved. Urethral obstruction occurred in 5.6% and was managed by urethral dilation ororurethrotomy.[365]

Advancement flaps of vaginal wall can be used to cover the urethral suture line. In some cases more advanced methods are used to close or to protect the urethral closure.

In cases of difficult dissection and visualisation, urethral sectioning has been advocated. [366] This technique is also being used in the repair of complex urethral diverticula.[367] Fistulae that are located in the distal third of the urethra may also be marsupialized without compromising the continence mechanism.[368] Distal urethrovaginal fistula may be entirely without symptoms, and in such cases, repair is not mandated.

Blaivas advocates that vaginal flaps are usually the best option in dealing with urethral reconstruction, next to the possibility of offering anterior or posterior bladder flaps. Options for vaginal repair of fistula include primary closure, peninsula flaps, bilateral labial pedicle flaps, and labial island flaps. Outcomes are optimised by using exacting surgical principles during repair and careful postoperative management by an experienced reconstructive surgeon. [347]

1. Labial and vaginal flaps and neourethra

The simplest flap is a vaginal advancement flap. [369]

Labial tissue can be harvested as a pedicled skin flap. This labial skin can be used as a patch to cover the urethral defect, but can also be used to create a tubular neo-urethra. [370, 371] The construction of a neo-urethra has mostly been described in traumatic aetiologies. In some cases a transpubic approach has been used. [372] The numbers of patients reported are small and there are no data on the long-term outcome of fistula closure and continence rates. The underlying bulbocavernosus tissue can be incorporated in the pedicled flap and probably offers a better vascularisation and more bulking to the repair. This could allow a safer placement of a sling afterwards, in those cases where bothersome stress incontinence would occur postoperatively. [373, 374]

2. Martius flap

While in obstetrical fistula repair, it was not found to have any benefit in a large retrospective study in 440 women, the labial bulbocavernosus muscle / fat flap by Martius is still considered by some to be an important adjunctive measure in the treatment of genitourinary fistula where additional bulking with well vascularised tissue is needed. [375] Rangnekar et al. report on 12 patients with urethrovaginal fistula, of whom 8 were treated with a Martius flap and 4 with a conventional repair. Only one out of the 8 had a fistula recurrence, while 3out of 4 of the conventional repairs broke down; it should be noted however that these cases were not randomised between surgical techniques.[376] Punekar et al. described 15 patients with complex and recurrent fistula, using the skin island flap modification with excellent results.[377]Radopoulus published a small series of 5 recurrent and complex urethrovaginal fistulas that all healed using a Martius flap.[378]The series of non-obstetrical aetiology are small and all of them are retrospective. There are no prospective data, nor randomized studies.[379, 380] The indications for Martius flap in the repair of all types of fistula remain unclear.

Table 11: Closure rates of urethrovaginal fistula

Author	N patients	Success at first surgery	Success at second surgery	
Blaivas[347]	24	79%		
Goodwin[364]	24	70%	92%	
Lee [12]	50	92%	100%	
Keetel[401]	24	87.5%		
Pushkar[365]	71	90.1%	98.6%	52% incontinent
Benchekroun[402]	186	53%		Mostly obstetrical
Henriksson[403]	6	67%	100%	
Kumar[79]	43	95.4%	100%	

3. Rectus muscle flap

Rectus abdominis muscle flaps have been described by some authors. [381, 382]Transvaginal urethrovaginalfistula closure was performed followed by a pedicled rectus abdominis muscle flap interposed between the fistula closure and vaginal suture line. The muscle flap was based on the inferior epigastric vessels, and provided additional support to the urethra, bladder neck and bladder base. Urethrovaginalfistula repair with the rectus abdominis muscle flap was successful in all cases without recurrence.. Of the patients 5 (83%) were continent and able to void to completion at a mean follow-up of 23 months (range 2 to 66).

4. Other interposition material

A range of non-traditional interposition flaps and grafts have been reported by several authors. All of the publications only report on small patient numbers without long term outcomes or continence data.

Golomb et al. reported the use of a fascial patch, while adding a rectus fascia sling to a urethrovaginal fistula repair.[383] Omentum is extensively used in abdominal approaches to VVF, but Janez et al. used it during a vaginal approach in 3 patients with good results.[384]

The gracilis muscle can be used as well, although the experience is limited. The graciloplasty was described by Ingelman-Sundberg in 1947 and has been adapted by other surgeons in the treatment of fistula. The number of patients reported is low as is the quality of the evidence. [385-387]

Non-autologous material has been used as well. Lowman et al. described the use of porcine dermis interposition and a synthetic sling in an irradiated patient. Other biodegradable materials have been used, although the quality of available data is lowand is insufficient to advocate their use. [388] [389] Non-vascularized tissue grafts should be used with caution in such cases as the aetiology of the initial tissue damage resulting in fistula is often ischemic.

b) Posterior approach

In cases of high fistula with difficult vaginal access, a perineal pararectal approach has been described. Some variations exist in the incisions and dissection planes. The anterior sagittal transrectal approach (ASTRA technique) and the posterior sagittal pararectal approach only have been reported in small observational series. [390, 391][392-394]

c) Abdominal approach

Female urethral injuries may cause serious morbidity with loss of the entire urethra in some cases. Ahmed et al. reported the results of construction of a neourethra by the flipped anterior bladder-tube technique in five girls aged 3-18 years (mean 8 years). All had pelvic fractures. Three patients came with a suprapubic cystostomy, one was totally incontinent, and another had an urethrovaginal fistula. Three had an associated vaginal injury. All five patients underwent construction of a neourethra using a flipped anterior bladder-wall tube (FABWT) and have been followed for 18-80 months (mean 44 months). All patients were continent in the daytime and three were voiding spontaneously without the need for catheterization. Two were managed by clean intermittent catheterization (CIC), one per urethram and other via a continent abdominal stoma (Mitrofanoff). [395]

A retropubicretrourethral technique has been described by Koriatim[396] This approach allows a urethrovesical flap tube to be fashioned to form a continent neourethra. Urodynamic studies showed that the proximal vesical and distal urethral components of the neourethra contribute to sphincteric function. For larger fistula an enwrapping technique has been described as well.[397]

5. COMPLICATIONS

Little information can be found on complications after urethrovaginal fistula repair. A short report on 4 cases by Tehan et al. describes a disappointing experience in the transvaginal repair of these fistulas. These authors advocate a suprapubic bladder flap or bladder tube technique to achieve a functioning urethra. Complications following surgical repair have been fistula recurrence, urethral shortening and retraction, persistent reflux, bladder calculi, and bladder cancer [398].

6. FOLLOW UP

In most series of urogenital fistula repair, follow-up is of very short duration. Dolan et al. investigated urinary and sexual symptoms and quality of life in a group of 31 women 50 months (median) after successful repair of urogenital fistula using the Bristol Female Lower Urinary Tract Symptom questionnaire. [399] All women had undergone urodynamic investigation prior to their repair surgery, and only36% had normal findings. Almost all women reported one or more symptoms, and for 65%, these caused at least ‘a bit of a problem’, although 87% said that their urinary symptoms had little or no impact on their quality of life. Symptoms were similar in urethrovaginal and vesicovaginal fistulae and were not significantly associated with prior functional abnormality.

7. RECOMMENDATIONS

Urethrovaginal fistula are preferably treated by a vaginal approach	C
A variety of autologous tissue interposition techniques have been described, but their value remains uncertain	C
Urethrovaginal fistula repair may be complicated by stress incontinence, urethral stricture and urethral shortening necessitating long-term follow-up	C

REFERENCES

1. De Ridder D, Badlani GH, Browing A, Sing P, Sombie I, Wall LL. Fistula in the developing world. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. 4th Edition ed. Paris: Healt Publications Ltd.; 2009. p. 1419-58.
2. Wall LL, Arrowsmith S, Briggs ND, Browning A, Lassey A. The obstetric vesicovaginal fistula in the developing world. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. Paris: Health Publications; 2005. p. 1403-54.
3. Forsgren C LC, Johansson AL, Cnattingius S, Altman D. Hysterectomy for benign indications and risk of pelvic organ fistula disease. Obstetrics & Gynecology. 2009;114:594-9.
4. Abrams P, Khoury S. International Consultation on Urological Diseases: Evidence-based medicine overview of the main steps for developing and grading guideline recommendations. Neurourology and urodynamics. 2010;29(1):116-8. Epub 2009/12/22.
5. De Ridder D. An update on surgery for vesicovaginal and urethrovaginal fistulae. Curr Opin Urol. 2011;21(4):297-300. Epub 2011/05/04.
6. Fischer W. [Long-term analysis of causes, sites and results of treatment of urogenital fistulas at the Charite Gynecologic Clinic]. Zentralbl Gynakol. 1990;112(12):747-55. Epub 1990/01/01. Langzeitanalyse uber Ursachen, Lokalisation und Behandlungsergebnisse von Urogenitalfisteln an der Charite--Frauenklinik.
7. Raashid Y, Tmajeed T, Majeed N, Shahzad N. Iatrogenic vesicovaginal fistula. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2010;20(7):436-8. Epub 2010/07/21.
8. Tancer ML. Observations on prevention and management of vesicovaginal fistula after total hysterectomy. Surg Gynecol Obstet. 1992;175(6):501-6. Epub 1992/12/01.
9. Hadzi-Djokic J, Pejcic TP, Acimovic M. Vesico-vaginal fistula: report of 220 cases. International Urology & Nephrology. 2009;41(2):299-302. Epub 2008/09/24.
10. Ozdemir E, Ozturk U, Celen S, Sucak A, Gunel M, Guney G, et al. Urinary complications of gynecologic surgery: iatrogenic urinary tract system injuries in obstetrics and gynecology operations. Clinical and experimental obstetrics & gynecology. 2011;38(3):217-20. Epub 2011/10/15.
11. Forsgren C, Altman D. Risk of pelvic organ fistula in patients undergoing hysterectomy. Current opinion in obstetrics & gynecology. 2010;22(5):404-7. Epub 2010/08/27.
12. Lee RA, Symmonds RE, Williams TJ. Current status of genitourinary fistula. Obstet Gynecol. 1988;72(3 Pt 1):313-9. Epub 1988/09/01.
13. Song T, Kim TJ, Kang H, Lee YY, Choi CH, Lee JW, et al. A review of the technique and complications from 2,012 cases of laparoscopically assisted vaginal hysterectomy at a single institution. Aust N Z J Obstet Gynaecol. 2011;51(3):239-43. Epub 2011/06/03.
14. Forsgren C, Lundholm C, Johansson AL, Cnattingius S, Altman D. Hysterectomy for benign indications and risk of pelvic organ fistula disease. Obstetrics & Gynecology. 2009;114(3):594-9. Epub 2009/08/25.
15. Harkki-Siren P, Sjoberg J, Tiitinen A. Urinary tract injuries after hysterectomy. Obstet Gynecol. 1998;92(1):113-8.
16. Hospital Episode Statistics [database on the Internet]. Department of Health. 2010 [cited 28/12/10]. Available from: http://www.hesonline.nhs.uk.
17. Hilton P. Urogenital fistula in the UK - a personal case series managed over 25 years. 2011; (early view)]. Available from: http://dx.doi.org/10.1111/j.1464-410X.2011.10630.x.
18. Hilton P, Cromwell D. The risk of urogenital fistula after hysterectomy performed under the National Health Service in England - patterns of care between 2000 and 2008. 2012:(submitted).
19. Roberto Martinez P, SE RC, Escobar del Barco L, Ramirez Isarraraz C. Vesicovaginal fistula. Experience at the Instituto Nacional de Perinatologia. Ginecol Obstet Mex. 2007;75(1):31-4.
20. Duong TH, Gellasch TL, Adam RA. Risk factors for the development of vesicovaginal fistula after incidental cystotomy at the time of a benign hysterectomy. Am J Obstet Gynecol. 2009;201(5):512.e1-.e4.
21. Mathevet P, Valencia P, Cousin C, Mellier G, Dargent D. Operative injuries during vaginal hysterectomy. European Journal of Obstetrics, Gynecology & Reproductive Biology. 2001;97(1):71-5. Epub 2001/07/04.
22. Mondet F, Chartier-Kastler EJ, Conort P, Bitker MO, Chatelain C, Richard F. Anatomic and functional results of transperitoneal-transvesical vesicovaginal fistula repair. Urology. 2001;58(6):882-6. Epub 2001/12/18.
23. Chesson RR. Cystoscopy should be a routine procedure in the performance of hysterectomy. J Reprod Med. 2011;56(9-10):371-2. Epub 2011/10/21.
24. Benchekroun A, Lachkar A, Soumana A, Farih MH, Belahnech Z, Marzouk M, et al. [Ureter injuries. Apropos of 42 cases]. Ann Urol (Paris). 1997;31(5):267-72. Epub 1997/01/01. Les traumatismes de l'uretere. A propos de 42 cas.
25. Modarress M, Maghami FQ, Golnavaz M, Behtash N, Mousavi A, Khalili GR. Comparative study of chemoradiation and neoadjuvant chemotherapy effects before radical hysterectomy in stage IB-IIB bulky cervical cancer and with tumor diameter greater than 4 cm. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2005;15(3):483-8. Epub 2005/05/11.
26. Narayanan P, Nobbenhuis M, Reynolds KM, Sahdev A, Reznek RH, Rockall AG. Fistulas in malignant gynecologic disease: etiology, imaging, and management. Radiographics. 2009;29(4):1073-83. Epub 2009/07/17.
27. Baalbergen A, Veenstra Y, Stalpers LL, Ansink AC. Primary surgery versus primary radiation therapy with or without chemotherapy for early adenocarcinoma of the uterine cervix [Systematic Review]. Cochrane Database of Systematic Reviews. 2010;5:5.
28. Denton AS, Clarke N, Maher J. Non-surgical interventions for late radiation cystitis in patients who have received radical radiotherapy to the pelvis [Systematic Review]. Cochrane Database of Systematic Reviews. 2002(Issue 3):Art. No.: CD001773.
29. Marchiole P, Benchaib M, Buenerd A, Lazlo E, Dargent D, Mathevet P. Oncological safety of laparoscopic-assisted vaginal radical trachelectomy (LARVT or Dargent's operation): a comparative study with laparoscopic-assisted vaginal radical hysterectomy (LARVH). Gynecologic oncology. 2007;106(1):132-41. Epub 2007/05/12.
30. Likic IS, Kadija S, Ladjevic NG, Stefanovic A, Jeremic K, Petkovic S, et al. Analysis of urologic complications after radical hysterectomy. American Journal of Obstetrics & Gynecology. 2008;199(6):644 e1-3. Epub 2008/08/30.
31. Baltzer J, Kaufmann C, Ober KG, Zander J. [Complications in 1,092 radical abdominal hysterectomies with pelvic lymphadenectomies (author's transl)]. Geburtshilfe Frauenheilkd. 1980;40(1):1-5. Epub 1980/01/01. Komplikationen bei 1092 erweiterten abdominalen Krebsoperationen mit obligatorischer Lymphonodektomie. Ergebnisse einer kooperativen Studie an vier Universitats-Frauenkliniken.
32. Bostofte E, Serup J. Urological complications of Okabayashi's operation for cervical cancer. Acta Obstet Gynecol Scand. 1981;60(1):39-42. Epub 1981/01/01.
33. Draca P. Wertheim hysterectomy: a ten year experience. Int Surg. 1979;64(5):59-63. Epub 1979/08/01.

34. Genta RM, Ramchandani MK, Gyorkey F, Buzanis CT, Lahart CJ. Enterovesical fistula due to non-Hodgkin lymphoma in AIDS. Journal of Clinical Gastroenterology. 1993;16(4):333-5.

35. Murdoch M, Hilton P. Classical Hodgkin's lymphoma presenting as vesicovaginal fistula. 2012:(submitted).

36. Averette HE, Nguyen HN, Donato DM, Penalver MA, Sevin BU, Estape R, et al. Radical hysterectomy for invasive cervical cancer. A 25-year prospective experience with the Miami technique. Cancer. 1993;71(4 Suppl):1422-37. Epub 1993/02/15.

37. Hallum IAV, Hatch KD, Nour M, Saucedo M. Comparison of radical abdominal hysterectomy with laparoscopic-assisted radical vaginal hysterectomy for treatment of early cervical cancer. Journal of Gynecologic Techniques. 2000;6(1):3-6.

38. Hatch KD, Parham G, Shingleton HM, Orr JW, Jr., Austin JM, Jr. Ureteral strictures and fistulae following radical hysterectomy. Gynecologic oncology. 1984;19(1):17-23. Epub 1984/09/01.

39. Jones CR, Woodhouse CR, Hendry WF. Urological problems following treatment of carcinoma of the cervix. Br J Urol. 1984;56(6):609-13. Epub 1984/12/01.

40. Ralph G, Tamussino K, Lichtenegger W. Urological complications after radical hysterectomy with or without radiotherapy for cervical cancer. Archives of Gynecology & Obstetrics. 1990;248(2):61-5. Epub 1990/01/01.

41. Riss P, Koelbl H, Neunteufel W, Janisch H. Wertheim radical hysterectomy 1921-1986: changes in urologic complications. Archives of Gynecology & Obstetrics. 1988;241(4):249-53. Epub 1988/01/01.

42. Yan X, Li G, Shang H, Wang G, Chen L, Han Y. Complications of laparoscopic radical hysterectomy and pelvic lymphadenectomy--experience of 117 patients. Int J Gynecol Cancer. 2009;19(5):963-7. Epub 2009/07/04.

43. Chen Y, Xu H, Li Y, Wang D, Li J, Yuan J, et al. The outcome of laparoscopic radical hysterectomy and lymphadenectomy for cervical cancer: A prospective analysis of 295 patients. Annals of Surgical Oncology. 2008;15(10):2847-55.

44. Monk BJ, Montz FJ. Invasive cervical cancer complicating intrauterine pregnancy: treatment with radical hysterectomy. Obstetrics & Gynecology. 1992;80(2):199-203. Epub 1992/08/01.

45. Blythe JG, Hodel KA, Wahl TP. A comparison between peritoneal sheathing of the ureters (Ohkawa technique) and retroperitoneal pelvic suction drainage in the prevention of ureteral damage during radical abdominal hysterectomy. Gynecologic oncology. 1988;30(2):222-7.

46. Hopkins MP, Morley GW. Pelvic exenteration for the treatment of vulvar cancer. Cancer. 1992;70(12):2835-8. Epub 1992/12/15.

47. Berek JS, Howe C, Lagasse LD, Hacker NF. Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA. Gynecologic oncology. 2005;99(1):153-9. Epub 2005/08/02.

48. Ungar L, Palfalvi L, Novak Z. Primary pelvic exenteration in cervical cancer patients. Gynecologic oncology. 2008;111(2 Suppl):S9-12. Epub 2008/09/09.

49. Langebrekke A, Istre O, Hallqvist AC, Hartgill TW, Onsrud M. Comparison of laparoscopy and laparotomy in patients with endometrial cancer. J Am Assoc Gynecol Laparosc. 2002;9(2):152-7. Epub 2002/04/18.

50. Xu H, Chen Y, Li Y, Zhang Q, Wang D, Liang Z. Complications of laparoscopic radical hysterectomy and lymphadenectomy for invasive cervical cancer: Experience based on 317 procedures. Surgical endoscopy. 2007;21(6):960-4.

51. Kadar N, Reich H. Laparoscopically assisted radical Schauta hysterectomy and bilateral laparoscopic pelvic lymphadenectomy for the treatment of bulky stage IB carcinoma of the cervix. Gynaecological Endoscopy. 1993;2(3):135-42.

52. Colombel M, Pedron P, Missirlu A, Abbou C, Chopin D. Vesicovaginal fistula after laser vaporization of vaginal condyloma. Journal of Urology. 1995;154(5):1860.

53. Nwabineli NJ, Davis JA. Fistula injury to the bladder at repeat cone biopsy by laser. Eur J Obstet Gynecol Reprod Biol. 1992;43(3):245-6. Epub 1992/02/28.

54. Ahuja A, Safaya R, Prakash G, Kumar L, Shukla NK. Primary mixed mullerian tumor of the vagina--a case report with review of the literature. Pathology, research and practice. 2011;207(4):253-5. Epub 2011/03/08.

55. Kucera H, Skodler W, Weghaupt K. [Complications of postoperative radiotherapy in uterine cancer]. Geburtshilfe Frauenheilkd. 1984;44(8):498-502. Epub 1984/08/01. Komplikationen der postoperativen Strahlentherapie beim Korpuskarzinom.

56. Biewenga P, Mutsaerts MA, Stalpers LJ, Buist MR, Schilthuis MS, van der Velden J. Can we predict vesicovaginal or rectovaginal fistula formation in patients with stage IVA cervical cancer? Int J Gynecol Cancer. 2010;20(3):471-5. Epub 2010/04/09.

57. Pushkar DY, Dyakov VV, Kasyan GR. Management of radiation-induced vesicovaginal fistula. Eur Urol. 2009;55(1):131-7. Epub 2008/05/20.

58. Zoubek J, McGuire EJ, Noll F, DeLancey JO. The late occurrence of urinary tract damage in patients successfully treated by radiotherapy for cervical carcinoma. Journal of Urology. 1989;141(6):1347-9. Epub 1989/06/01.

59. Cochrane JP, Yarnold JR, Slack WW. The surgical treatment of radiation injuries after radiotherapy for uterine carcinoma. The British journal of surgery. 1981;68(1):25-8. Epub 1981/01/01.

60. de Crevoisier R, Sanfilippo N, Gerbaulet A, Morice P, Pomel C, Castaigne D, et al. Exclusive radiotherapy for primary squamous cell carcinoma of the vagina. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2007;85(3):362-70. Epub 2007/10/30.

61. Demanes DJ, Schutz KL, Quackenbush JJ, Ewing T, Rodriguez RR. Low dose rate brachytherapy in vaginal carcinoma: Long-term outcome and morbidity. Journal of Brachytherapy International. 2000;16(1):11-24.

62. Emmert C, Kohler U. Management of genital fistulas in patients with cervical cancer. Archives of Gynecology & Obstetrics. 1996;259(1):19-24. Epub 1996/01/01.

63. Krause S, Hald T, Steven K. Surgery for urologic complications following radiotherapy for gynecologic cancer. Scandinavian Journal of Urology & Nephrology. 1987;21(2):115-8. Epub 1987/01/01.

64. Maier U, Ehrenbock PM, Hofbauer J. Late urological complications and malignancies after curative radiotherapy for gynecological carcinomas: a retrospective analysis of 10,709 patients. Journal of Urology. 1997;158(3 Pt 1):814-7. Epub 1997/09/01.

65. Monk BJ, Walker JL, Tewari K, Ramsinghani NS, Nisar Syed AM, DiSaia PJ. Open interstitial brachytherapy for the treatment of local-regional recurrences of uterine corpus and cervix cancer after primary surgery. Gynecologic oncology. 1994;52(2):222-8. Epub 1994/02/01.

66. Angioli R, Penalver M, Muzii L, Mendez L, Mirhashemi R, Bellati F, et al. Guidelines of how to manage vesicovaginal fistula. Critical Reviews in Oncology/Hematology. 2003;48(3):295-304.

67. Chassagne D, Sismondi P, Horiot JC, Sinistrero G, Bey P, Zola P, et al. A glossary for reporting complications of treatment in gynecological cancers. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 1993;26(3):195-202. Epub 1993/03/01.

68. Caputo RM, Copeland LJ. Gynecologic effects of tamox-

ifen: case reports and review of the literature. Int Urogynecol J. 1996;7(4):179-84.

69. Behtash N, Ghaemmaghami F, Ayatollahi H, Khaledi H, Hanjani P. A case-control study to evaluate urinary tract complications in radical hysterectomy. 2005 [updated 16 Feb; cited 3 12]; Available from: http://dx.doi.org/10.1186/1477-7819-3-12.

70. Monk BJ, Solh S, Johnson MT, Montz FJ. Radical hysterectomy after pelvic irradiation in patients with high risk cervical cancer or uterine sarcoma: morbidity and outcome. European journal of gynaecological oncology. 1993;14(6):506-11. Epub 1993/01/01.

71. Mitsuhashi N, Takahashi M, Yamakawa M, Nozaki M, Takahashi T, Sakurai H, et al. Results of postoperative radiation therapy for patients with carcinoma of the uterine cervix: evaluation of intravaginal cone boost with an electron beam. Gynecologic oncology. 1995;57(3):321-6. Epub 1995/06/01.

72. Koumantakis E, Haralambakis Z, Koukourakis M, Mazonakis M, Haldeopoulos D, Papageorgiou N, et al. A pilot study on concurrent platinum chemotherapy and intracavitary brachytherapy for locally advanced cancer of the uterine cervix. British Journal of Radiology. 1998;71(MAY):552-7.

73. Matsumura M, Takeshima N, Ota T, Omatsu K, Sakamoto K, Kawamata Y, et al. Neoadjuvant chemotherapy followed by radical hysterectomy plus postoperative chemotherapy but no radiotherapy for Stage IB2-IIB cervical cancer--irinotecan and platinum chemotherapy. Gynecologic oncology. 2010;119(2):212-6. Epub 2010/08/17.

74. Brummer TH JJ, Fraser J, Heikkinen AM, Kauko M, Mäkinen J, Seppälä T, Sjöberg J, Tomás E, Härkki P. FINHYST, a prospective study of 5279 hysterectomies: Complications and their risk factors. Hum Reprod. 2011;26:1741-51.

75. Likic IS KS, Ladjevic NG, Stefanovic A, Jeremic K, Petkovic S, Dzamic Z. . . . Analysis of urologic complications after radical hysterectomy. American Journal of Obstetrics & Gynecology. 2008;199:644.e1-3.

76. Frankman EA WL, Bunker CH, Lowder JL. Lower urinary tract injury in women in the united states, 1979–2006. Am J Obstet Gynecol. 2010;202:495.e1-5.

77. El-Tabey NA A-E-DB, Shaaban AA, El-Kappany HA, Mokhtar AA, El-Azab M, Kheir AA. Urological trauma after gynecological and obstetric surgeries. Scandinavian Journal of Urology & Nephrology 2011;185:945-50.

78. Sachdev P.S. HN, Abbasi R.M., Das C.M. Genito-urinary fistula: a major morbidity in developing countries. Journal of Ayub Medical College, Abbottabad (JAMC). 2009;21:8-11.

79. Kumar A, Goyal NK, Das SK, Trivedi S, Dwivedi US, Singh PB. Our experience with genitourinary fistulae. Urol Int. 2009;82(4):404-10. Epub 2009/06/10.

80. Nawaz H. KM, Tareen F.M., Khan S. Retrospective study of 213 cases of female urogenital fistulae at the Department of Urology & Transplantation Civil Hospital Quetta, Pakistan. Journal of the Pakistan Medical Association. 2010;60:28-32.

81. Chadha R, Agarwal K, Choudhury SR, Debnath PR. The colovesical fistula in congenital pouch colon: a histologic study. J Pediatr Surg. 2008;43(11):2048-52. Epub 2008/10/31.

82. Ben-Ami H, Ginesin Y, Behar DM, Fischer D, Edoute Y, Lavy A. Diagnosis and treatment of urinary tract complications in Crohn's disease: an experience over 15 years. Canadian journal of gastroenterology = Journal canadien de gastroenterologie. 2002;16(4):225-9. Epub 2002/05/01.

83. Greenstein AJ, Sachar DB, Tzakis A, Sher L, Heimann T, Aufses AH, Jr. Course of enterovesical fistulas in Crohn's disease. Am J Surg. 1984;147(6):788-92.

84. Margolin ML, Korelitz BI. Management of bladder fistulas in Crohn's disease. Journal of Clinical Gastroenterology. 1989;11(4):399-402.

85. Woods RJ, Lavery IC, Fazio VW, Jagelman DG, Weakley FL. Internal fistulas in diverticular disease. Diseases of the Colon & Rectum. 1988;31(8):591-6.

86. Glass RE, Ritchie JK, Lennard-Jones JE, Hawley PR, Todd IP. Internal fistulas in Crohn's disease. Diseases of the Colon & Rectum. 1985;28(8):557-61.

87. Kyle J. Urinary complications of Crohn's disease. World J Surg. 1980;4(2):153-60. Epub 1980/01/01.

88. Najjar SF, Jamal MK, Savas JF, Miller TA. The spectrum of colovesical fistula and diagnostic paradigm. Am J Surg. 2004;188(5):617-21.

89. Schofield PF. Colovesical fistulas. Br J Hosp Med (Lond). 1988;39(6):483-7.

90. Pollard SG, Macfarlane R, Greatorex R, Everett WG, Hartfall WG. Colovesical fistula. Annals of the Royal College of Surgeons of England. 1987;69(4):163-5. Epub 1987/07/01.

91. Ferguson GG, Lee EW, Hunt SR, Ridley CH, Brandes SB. Management of the Bladder During Surgical Treatment of Enterovesical Fistulas from Benign Bowel Disease. J Am Coll Surg. 2008;207(4):569-72. Epub 2008/10/18.

92. Garcea G, Majid I, Sutton CD, Pattenden CJ, Thomas WM. Diagnosis and management of colovesical fistulae; six-year experience of 90 consecutive cases. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2006;8(4):347-52. Epub 2006/04/25.

93. McBeath RB, Schiff M, Jr., Allen V, Bottaccini MR, Miller JI, Ehreth JT. A 12-year experience with enterovesical fistulas. Urology. 1994;44(5):661-5. Epub 1994/11/01.

94. Mileski WJ, Joehl RJ, Rege RV, Nahrwold DL. One-stage resection and anastomosis in the management of colovesical fistula. Am J Surg. 1987;153(1):75-9. Epub 1987/01/01.

95. Pokala N, Delaney CP, Brady KM, Senagore AJ. Elective laparoscopic surgery for benign internal enteric fistulas: a review of 43 cases. Surgical endoscopy. 2005;19(2):222-5. Epub 2004/12/30.

96. Hsieh JH, Chen WS, Jiang JK, Lin TC, Lin JK, Hsu H. Enterovesical fistula: 10 years experience. Zhonghua yi xue za zhi = Chinese medical journal; Free China ed. 1997;59(5):283-8. Epub 1997/05/01.

97. Liu CH, Chuang CK, Chu SH, Chen HW, Chen CS, Chiang YJ, et al. Enterovesical fistula: experiences with 41 cases in 12 years. Chang Gung Medical Journal (Changgeng Yi Xue Za Zhi). 1999;22(4):598-603.

98. Ouyang Q, Xue LY. Inflammatory bowel disease since the 21st Century in China–Turning challenges into opportunities. Journal of Digestive Diseases. 2012:accepted article (online). Available from: http://dx.doi.org/10.1111/j.751-2980.012.00579.x.

99. Bahadursingh AM, Longo WE. Colovaginal fistulas. Etiology and management. Journal of Reproductive Medicine. 2003;48(7):489-95. Epub 2003/09/05.

100. Altman D, Forsgren C, Hjern F, Lundholm C, Cnattingius S, Johansson AL. Influence of hysterectomy on fistula formation in women with diverticulitis. The British journal of surgery. 2010;97(2):251-7. Epub 2009/12/26.

101. Ostrzenski A, Ostrzenska KM. Bladder injury during laparoscopic surgery. Obstetrical & gynecological survey. 1998;53(3):175-80. Epub 1998/03/26.

102. Kochakarn W, Pummangura W. A new dimension in vesicovaginal fistula management: an 8-year experience at Ramathibodi hospital. Asian J Surg. 2007;30(4):267-71. Epub 2007/10/27.

103. Kursh ED, Morse RM, Resnick MI, Persky L. Prevention of the development of a vesicovaginal fistula. Surg Gynecol Obstet. 1988;166(5):409-12. Epub 1988/05/01.

104. Ho AM, Roth P, Cowan WD. Gaseous distention of the urinary bag indicating bladder perforation during laparoscopic pelvic procedures. Int J Gynaecol Obstet. 1996;55(3):297-8. Epub 1996/12/01.

105. O'Brien WM, Lynch JH. Simplification of double-dye test

to diagnose various types of vaginal fistulas. Urology. 1990;36(5):456. Epub 1990/11/01.

106. Indraratna PL, Walsh CA, Moore KH. Intra-operative cystoscopy in gynaecological surgery: A brief overview. Australian and New Zealand Journal of Obstetrics & Gynaecology. 2011;51(3):272-5. Epub 2011/06/03.

107. Gilmour DT, Dwyer PL, Carey MP. Lower urinary tract injury during gynecologic surgery and its detection by intraoperative cystoscopy. Obstetrics & Gynecology. 1999;94(5 pt.2):883-9. Epub 1999/11/05.

108. Sohail S, Siddiqui KJ. Trans-vaginal sonographic evaluation of vesicovaginal fistula. JPMA The Journal of the Pakistan Medical Association. 2005;55(7):292-4. Epub 2005/08/20.

109. Volkmer BG, Kuefer R, Nesslauer T, Loeffler M, Gottfried HW. Colour Doppler ultrasound in vesicovaginal fistulas. Ultrasound in medicine & biology. 2000;26(5):771-5. Epub 2000/08/16.

110. Kruger PS, Whiteside RS. Pseudo-renal failure following the delayed diagnosis of bladder perforation after diagnostic laparoscopy. Anaesthesia and intensive care. 2003;31(2):211-3. Epub 2003/04/26.

111. Narayanan P NM, Reynolds KM, Sahdev A, Reznek RH, Rockall AG. Fistulas in malignant gynaecologic disease: Etiology, imaging, and management. Radiographics 2009;29:1073-83.

112. Amendola MA, Agha FP, Dent TL, Amendola BE, Shirazi KK. Detection of occult colovesical fistula by the Bourne test. American Journal of Roentgenology. 1984;142(4):715-8.

113. Bernstine H, Steinmetz AP, Hardoff R. Urinary diarrhea detected by Tc-99m DTPA scintigraphy in a 3-year-old girl. Clinical nuclear medicine. 2002;27(4):287-9. Epub 2002/03/27.

114. Jarrett TW, Vaughan ED, Jr. Accuracy of computerized tomography in the diagnosis of colovesical fistula secondary to diverticular disease. Journal of Urology. 1995;153(1):44-6. Epub 1995/01/01.

115. Kavanagh D, Neary P, Dodd JD, Sheahan KM, O'Donoghue D, Hyland JM. Diagnosis and treatment of enterovesical fistulae. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2005;7(3):286-91. Epub 2005/04/30.

116. Kuhlman JE, Fishman EK. CT evaluation of enterovaginal and vesicovaginal fistulas. Journal of computer assisted tomography. 1990;14(3):390-4. Epub 1990/05/01.

117. Guenaga KF, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database of Systematic Reviews. 2011;9:CD001544. Epub 2011/09/09.

118. Lapitan CM, Rienhardt G. Surgical management of vesicovaginal and/or urethrovaginal fistulae [Protocol]. Cochrane Database of Systematic Reviews. 2010;6:6.

119. Morton HC, Hilton P. Urethral injury associated with minimally invasive mid-urethral sling procedures for the treatment of stress urinary incontinence: A case series and systematic literature search. BJOG: An International Journal of Obstetrics and Gynaecology. 2009;116(8):1120-6.

120. Meeks GR, Sams JOt, Field KW, Fulp KS, Margolis MT. Formation of vesicovaginal fistula: the role of suture placement into the bladder during closure of the vaginal cuff after transabdominal hysterectomy. American Journal of Obstetrics & Gynecology. 1997;177(6):1298-304. Epub 1998/01/10.

121. Horng SG, Huang KG, Lo TS, Soong YK. Bladder Injury after LAVH: A Prospective, Randomized Comparison of Vaginal and Laparoscopic Approaches to Colpotomy during LAVH. The Journal of the American Association of Gynecologic Laparoscopists. 2004;11(1):42-6. Epub 2004/04/24.

122. Muleta M, Tafesse B, Aytenfisu HG. Antibiotic use in obs stetric fistula repair: single blinded randomized clinical trial. Ethiopian medical journal. 2010;48(3):211-7. Epub 2010/11/16.

123. Tomlinson AJ, Thornton JG. A randomised controlled trial of antibiotic prophylaxis for vesico-vaginal fistula repair. British Journal of Obstetrics & Gynaecology. 1998;105(4):397-9.

124. Safan A, Shaker H, Abdelaal A, Mourad MS, Albaz M. Fibrin glue versus martius flap interpositioning in the repair of complicated obstetric vesicovaginal fistula. A prospective multi-institution randomized trial. Neurourology and urodynamics. 2009;28(5):438-41. Epub 2009/05/29.

125. Shaker H, Saafan A, Yassin M, Idrissa A, Mourad MS. Obstetric vesico-vaginal fistula repair: should we trim the fistula edges? A randomized prospective study. Neurourology and urodynamics. 2011;30(3):302-5. Epub 2011/02/11.

126. Razzaghi MR, Rezaei A, Javanmard B, Lotfi B. Desmopressin as an alternative solution for urinary leakage after ureterocaliceal surgeries. Urology Journal. 2009;6(2):120-2. Epub 2009/05/28.

127. Browning A. Lack of value of the Martius fibrofatty graft in obstetric fistula repair. International Journal of Gynecology & Obstetrics. 2006;93(1):33-7. Epub 2006/03/15.

128. Demirel A, Polat O, Bayraktar Y, Gul O, Okyar G. Transvesical and transvaginal reparation in urinary vaginal fistulas. International Urology & Nephrology. 1993;25(5):439-44. Epub 1993/01/01.

129. Eilber KS, Kavaler E, Rodriguez LV, Rosenblum N, Raz S. Ten-year experience with transvaginal vesicovaginal fistula repair using tissue interposition. Journal of Urology. 2003;169(3):1033-6.

130. Wang Y, Hadley HR. Nondelayed transvaginal repair of high lying vesicovaginal fistula. Journal of Urology. 1990;144(1):34-6. Epub 1990/07/01.

131. Visco AG, Taber KH, Weidner AC, Barber MD, Myers ER. Cost-effectiveness of universal cystoscopy to identify ureteral injury at hysterectomy. Obstetrics & Gynecology. 2001;97(5 Pt 1):685-92. Epub 2001/05/08.

132. Bazi T. Spontaneous closure of vesicovaginal fistulas after bladder drainage alone: Review of the evidence. International Urogynecology Journal & Pelvic Floor Dysfunction. 2007;18(3):329-33.

133. Waaldijk K. The immediate surgical management of fresh obstetric fistulas with catheter and/or early closure. International Journal of Gynaecology & Obstetrics. 1994;45(1):11-6. Epub 1994/04/01.

134. Waaldijk K. Immediate indwelling bladder catheterisation at postpartum urine leakage - personal experience of 1200 patients. Tropical Doctor. 1997;27:227-8.

135. Waaldijk K. The immediate management of fresh obstetric fistulas. American Journal of Obstetrics & Gynecology. 2004;191(3):795-9. Epub 2004/10/07.

136. Chittacharoen A, Theppisai U. Urological injury during gynecologic surgical procedures. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 1993;76 Suppl 1:87-91. Epub 1993/01/01.

137. Davits RJ, Miranda SI. Conservative treatment of vesicovaginal fistulas by bladder drainage alone. Br J Urol. 1991;68(2):155-6. Epub 1991/08/01.

138. Dogra PN, Nabi G. Laser welding of vesicovaginal fistula. International Urogynecology Journal & Pelvic Floor Dysfunction. 2001;12(1):69-70. Epub 2001/04/11.

139. Falk HC, Orkin LA. Nonsurgical closure of vesicovaginal fistulas. Obstetrics & Gynecology. 1957;9(5):538-41. Epub 1957/05/01.

140. Frang D, Jilling A. Techniques for surgical repair of vesicovaginal fistulae. International Urology & Nephrology. 1983;15(2):161-9. Epub 1983/01/01.

141. Gorrea AM, Zuazu FJ, Sanchis MJA, Cruz JJF. Spontaneous healing of uretero-vesico-vaginal fistulas. Eur Urol. 1985;11(5):341-3. Epub 1985/01/01.

142. Latzko W. Postoperative vesicovaginal fistulas: genesis and therapy. Am J Surg. 1942;58:211-8.

143. Lentz SS. Transvaginal repair of the posthysterectomy vesicovaginal fistula using a peritoneal flap: the gold standard. Journal of Reproductive Medicine. 2005;50(1):41-4. Epub 2005/02/26.

144. Milicic D, Sprem M, Bagovic D. A method for the repair of vesicovaginal fistulas. International Journal of Gynaecology & Obstetrics. 2001;73(1):35-9. Epub 2001/05/05.

145. Soong Y, Lim PH. Urological injuries in gynaecological practice--when is the optimal time for repair? Singapore medical journal. 1997;38(11):475-8. Epub 1998/04/29.

146. Stovsky MD, Ignatoff JM, Blum MD, Nanninga JB, O'Conor VJ, Kursh ED. Use of electrocoagulation in the treatment of vesicovaginal fistulas. J Urol. 1994;152(5 Pt 1):1443-4. Epub 1994/11/01.

147. Yokoyama M, Arisawa C, Ando M. Successful management of vesicouterine fistula by luteinizing hormone-releasing hormone analog. International Journal of Urology. 2006;13(4):457-9. Epub 2006/06/01.

148. Goh JT, Howat P, de Costa C. Oestrogen therapy in the management of vesicovaginal fistula. The Australian & New Zealand journal of obstetrics & gynaecology. 2001;41(3):333-4. Epub 2001/10/11.

149. Hemal AK, Wadhwa SN, Kriplani A, Hemal U. Youssef's syndrome: An appraisal of hormonal treatment. Urol Int. 1994;52(1):55-7. Epub 1994/01/01.

150. Jozwik M, Jozwik M. Spontaneous closure of vesicouterine fistula. Account for effective hormonal treatment. Urol Int. 1999;62(3):183-7. Epub 1999/10/26.

151. Kumar A, Vaidyanathan S, Sharma SK, Sharma AK, Goswami AK. Management of vesico-uterine fistulae: a report of six cases. International Journal of Gynaecology & Obstetrics. 1988;26(3):453-7. Epub 1988/06/01.

152. Rubino SM. Vesico-uterine fistula treated by amenorrhoea induced with contraceptive steroids. Two case reports. Bjog. 1980;87(4):343-4. Epub 1980/04/01.

153. Tarhan F, Erbay E, Penbegul N, Kuyumcuoglu U. Minimal invasive treatment of vesicouterine fistula: A case report. International Urology & Nephrology. 2007;39(3):791-3. Epub 2006/09/29.

154. Novi JM, Rose M, Shaunik A, Ramchandani P, Morgan MA. Conservative management of vesicouterine fistula after uterine rupture. International Urogynecology Journal & Pelvic Floor Dysfunction. 2004;15(6):434-5. Epub 2004/11/19.

155. Garrido-Ruiz MC, Rosales B, Luis Rodriguez-Peralto J. Vulvar pseudoverrucous papules and nodules secondary to a urethral--vaginal fistula. American Journal of Dermatopathology. 2011;33(4):410-2. Epub 2011/02/03.

156. Onuora VC, al-Mohalhal S, Youssef AM, Patil M. Iatrogenic urogenital fistulae. Br J Urol. 1993;71(2):176-8.

157. Gruen A, Musik T, Kohler C, Fuller J, Wendt T, Stromberger C, et al. Adjuvant chemoradiation after laparoscopically assisted radical vaginal hysterectomy (LARVH) in patients with cervical cancer: Oncologic outcome and morbidity. Strahlentherapie und Onkologie. 2011;187(6):344-9.

158. Nashiro T, Yagi C, Hirakawa M, Inamine M, Nagai Y, Sakumoto K, et al. Concurrent chemoradiation for locally advanced squamous cell carcinoma of the vagina: Case series and literature review. International Journal of Clinical Oncology. 2008;13(4):335-9.

159. Arias BE, Ridgeway B, Barber MD. Complications of neglected vaginal pessaries: case presentation and literature review. International Urogynecology Journal & Pelvic Floor Dysfunction. 2008;19(8):1173-738. Epub 2008/02/28.

160. Carr LK, Webster GD. Abdominal repair of vesicovaginal fistula. Urology. 1996;48(1):10-1. Epub 1996/07/01.

161. Aimakhu VE. Reproductive functions after the repair of obstetric vesicovaginal fistulae. Fertility & Sterility. 1974;25(7):586-91. Epub 1974/07/01.

162. Hilton P, Ward A. Epidemiological and surgical aspects of urogenital fistulae: a review of 25 years' experience in southeast Nigeria. Int Urogynecol J. 1998;9(4):189-94.

163. Hilton P. Vesico-vaginal fistulae - new perspectives. Current Opinion in Obstetrics and Gynecology - Clinical Urogynaecology. London: Balliere-Tindall; 2002. p. 513-20.

164. Hilton P. Vesico-vaginal fistulas in developing countries. International Journal of Gynaecology & Obstetrics. 2003;82(3):285-95.

165. Miller S, Lester F, Webster M, Cowan B. Obstetric fistula: a preventable tragedy. Journal of Midwifery & Women's Health. 2005;50(4):286-94. Epub 2005/06/24.

166. Onolemhemhen DO, Ekwempu CC. An investigation of sociomedical risk factors associated with vaginal fistula in northern Nigeria. 0363-0242. 1999;28(3):103-16.

167. Tahzib F. Epidemiological determinants of vesicovaginal fistulas. British Journal of Obstetrics and Gynaecology. 1983;90:387-91.

168. Tahzib F. Vesicovaginal fistula in Nigerian children. Lancet. 1985;2:1291-3.

169. Game X, Malavaud B, Alric L, Mouzin M, Sarramon JP, Rischmann P. Infliximab treatment of Crohn disease ileovesical fistula. Scandinavian journal of gastroenterology. 2003;38(10):1097-8. Epub 2003/11/19.

170. Sato S, Sasaki I, Naito H, Funayama Y, Fukushima K, Shibata C, et al. Management of urinary complications in Crohn's disease. Surgery today. 1999;29(8):713-7. Epub 1999/09/14.

171. Serizawa H, Hibi T, Ohishi T, Watanabe N, Hamada Y, Watanabe M, et al. Laparoscopically assisted ileocecal res section for Crohn's disease associated with intestinal stenosis and ileovesical fistula. Journal of gastroenterology. 1996;31(3):425-30. Epub 1996/06/01.

172. Shackley DC, Brew CJ, Bryden AA, Anderson ID, Carlson GL, Scott NA, et al. The staged management of complex entero-urinary fistulae. BJU International. 2000;86(6):624-9. Epub 2000/11/09.

173. Tsai MS, Liang JT. Surgery is justified in patients with bowel obstruction due to radiation therapy. Journal of Gastrointestinal Surgery. 2006;10(4):575-82.

174. Eyre RC, Rosenthal JT, Libertino JA, Zinman LM. Management of urinary and bowel complications after ileal conduit diversion. Journal of Urology. 1982;128(6):1177-80. Epub 1982/12/01.

175. Penalver MA, Angioli R, Mirhashemi R, Malik R. Management of early and late complications of ileocolonic continent urinary reservoir (Miami pouch). Gynecologic oncology. 1998;69(3):185-91.

176. Waaldijk K, Elkins T. The obstetric fistula and peroneal nerve injury: an analysis of 947 consecutive patients. International Urogynecological Journal. 1994;5:12-4.

177. Hilton P. Vesico-vaginal fistulas in developing countries. International Journal of Gynecology & Obstetrics. 2003;82(3):285-95.

178. Tomlinson AJ, Thornton JG. A randomised controlled trial of antibiotic prophylaxis for vesico- vaginal fistula repair. British Journal of Obstetrics and Gynaecology. 1998;105:397-9.

179. Arrowsmith SD, Ruminjo J, Landry EG. Current practices in treatment of female genital fistula: a cross sectional study. BMC pregnancy and childbirth. 2010;10(73):73. Epub 2010/11/12.

180. Niel-Weise BS, van den Broek PJ. Antibiotic policies for short-term catheter bladder drainage in adults. Cochrane Database of Systematic Reviews. 2005;2005(3):CD005428. Epub 2005/07/22.

181. Ojengbede OA, Morhason-Bello IO, Shittu O. One-stage repair for combined fistulas: myth or reality? International Journal of Gynaecology & Obstetrics. 2007;99(1).

182. Browning A, Fentahun W, Goh JT. The impact of surgical treatment on the mental health of women with obstetric fistula. BJOG: an International Journal of Obstetrics & Gynaecology. 2007;114(11):1439-41. Epub 2007/10/02.

183. Goh JT, Sloane KM, Krause HG, Browning A, Akhter S. Mental health screening in women with genital tract fistulae. BJOG: an International Journal of Obstetrics & Gynaecology. 2005;112(9):1328-30.

184. Hilton P. Debate: 'Post-operative urinary fistulae should be managed by gynaecologists in specialist centres'. Brit J Urol. 1997;80, suppl 1:35-42. Epub 1997/07/01.

185. Hilton P. Urethrovaginal fistula associated with 'sterile abscess' formation following periurethral injection of dextranomer/hyaluronic acid co-polymer (Zuidex (TM)) for the treatment of stress urinary incontinence-a case report. BJOG. 2009;116(11):1527-30.

186. Gortchev G, Tomov S, Tantchev L, Velkova A, Radionova Z. Da Vinci S robotic surgery in the treatment of benign and malignant gynecologic tumors. Gynecological Surgery. 2009;7(2):153-7.

187. Lee JH, Choi JS, Lee KW, Han JS, Choi PC, Hoh JK. Immediate laparoscopic nontransvesical repair without omental interposition for vesicovaginal fistula developing after total abdominal hysterectomy. JSLS : Journal of the Society of Laparoendoscopic Surgeons / Society of Laparoendoscopic Surgeons. 2010;14(2):187-91. Epub 2010/10/12.

188. Shelbaia AM, Hashish NM. Limited Experience in Early Management of Genitourinary Tract Fistulas. Urology. 2007;69(3):572-4. Epub 2007/03/27.

189. Badenoch DF, Tiptaft RC, Thakar DR, Fowler CG, Blandy JP. Early repair of accidental injury to the ureter or bladder following gynaecological surgery. Br J Urol. 1987;59(6):516-8. Epub 1987/06/01.

190. Blandy JP, Badenoch DF, Fowler CG, Jenkins BJ, Thomas NW. Early repair of iatrogenic injury to the ureter or bladder after gynecological surgery. Journal of Urology. 1991;146(3):761-5. Epub 1991/09/01.

191. Kam MH, Tan YH, Wong MY. A 12-year experience in the surgical management of vesicovaginal fistulae. Singapore medical journal. 2003;44(4):181-4. Epub 2003/09/04.

192. Moriel EZ, Meirow D, Zilberman M, Farkas A. Experience with the immediate treatment of iatrogenic bladder injuries and the repair of complex vesico-vaginal fistulae by the transvesical approach. Archives of Gynecology & Obstetrics. 1993;253(3):127-30. Epub 1993/01/01.

193. Radoja I, Sudarevic B, Perkovic J, Rakin I, Cosic I, Pavlovic O, et al. Our experience with vesicovaginal fistula repair surgery. European Urology, Supplements. 2010;9 (6):637.

194. Dolan LM, Dixon WE, Hilton P. Urinary symptoms and quality of life following urogenital fistula repair: a long-term follow-up study. BJOG. 2008;115(12):1570-4.

195. Browning A, Menber B. Women with obstetric fistula in Ethiopia: a 6-month follow up after surgical treatment. BJOG: an International Journal of Obstetrics & Gynaecology. 2008;115(12):1564-9. Epub 2008/11/28.

196. Sims J. On the treatment of vesico-vaginal fistula. American Journal of the Medical Sciences. 1852;XXIII:59-82.

197. Wall LL. Dr. George Hayward (1791-1863): a forgotten pioneer of reconstructive pelvic surgery. Int Urogynecol J Pelvic Floor Dysfunct. 2005;16(5):330-3. Epub 2005/06/25.

198. Lawson J. Vesical fistulae into the vaginal vault. Br J Urol. 1972;44:623-31.

199. Moir JC. The vesico-vaginal fistula and its treatment. J R Coll Surg Edinb. 1962;7:268-74. Epub 1962/07/01.

200. Hamlin R, Nicholson E. Reconstruction of urethra totally destroyed in labour. Br Med J. 1969;2:147-50.

201. Ayed M, El Atat R, Hassine LB, Sfaxi M, Chebil M, Zmerli S. Prognostic factors of recurrence after vesicovaginal fistula repair. International Journal of Urology. 2006;13(4):345-9. Epub 2006/06/01.

202. Catanzaro F, Pizzoccaro M, Cappellano F, Catanzaro M, Ciotti G, Giollo A. Vaginal repair of vesico-vaginal fistulas: our experience. Archivio italiano di Urologia, Andrologia. 2005;77(4):224-5. Epub 2006/02/01.

203. Langkilde NC, Pless TK, Lundbeck F, Nerstrom B. Surgical repair of vesicovaginal fistulae--a ten-year retrospective study. Scandinavian Journal of Urology & Nephrology. 1999;33(2):100-3. Epub 1999/06/09.

204. Ockrim JL, Greenwell TJ, Foley CL, Wood DN, Shah PJR. A tertiary experience of vesico-vaginal and urethro-vaginal fistula repair: factors predicting success. BJU International. 2009;103(8):1122-6. Epub 2009/01/22.

205. Ou CS, Huang UC, Tsuang M, Rowbotham R. Laparoscopic Repair of Vesicovaginal Fistula. Journal of Laparoendoscopic and Advanced Surgical Techniques. 2004;14(1):17-21. Epub 2004/03/24.

206. Hilton P, Ward A. Epidemiological and surgical aspects of urogenital fistulae: a review of 25 years experience in south-east Nigeria. International Urogynecology Journal & Pelvic Floor Dysfunction. 1998;9:189-94.

207. Nezhat CH, Nezhat F, Nezhat C, Rottenberg H. Laparoscopic repair of a vesicovaginal fistula: A case report. Obstet Gynecol. 1994;83(5 II):899-901.

208. Abdel-Karim AM, Mousa A, Hasouna M, Elsalmy S. Laparoscopic transperitoneal extravesical repair of vesicovaginal fistula. International Urogynecology Journal & Pelvic Floor Dysfunction. 2011;22(6):693-7. Epub 2010/11/26.

209. Abdel-Karim AM, Moussa A, Elsalmy S. Laparoendoscopic single-site surgery extravesical repair of vesicovaginal fistula: early experience. Urology. 2011;78(3):567-71. Epub 2011/07/26.

210. Chibber PJ, Shah HN, Jain P. Laparoscopic O'Conor's repair for vesico-vaginal and vesico-uterine fistulae. BJU International. 2005;96(1):183-6. Epub 2005/06/21.

211. Das Mahapatra P, Bhattacharyya P. Laparoscopic intraperitoneal repair of high-up urinary bladder fistula: a review of 12 cases. International Urogynecology Journal & Pelvic Floor Dysfunction. 2007;18(6):635-9. Epub 2006/10/13.

212. Gozen AS, Teber D, Canda AE, Rassweiler J. Transperitoneal laparoscopic repair of iatrogenic vesicovaginal fistulas: Heilbronn experience and review of the literature. Journal of Endourology. 2009;23(3):475-9. Epub 2009/02/17.

213. Miklos JR, Sobolewski C, Lucente V. Laparoscopic management of recurrent vesicovaginal fistula. International Urogynecology Journal & Pelvic Floor Dysfunction. 1999;10(2):116-7. Epub 1999/06/29.

214. Otsuka RAP, Amaro JL, Tanaka MT, Epacagnan E, Mendes Jr JB, Kawano PR, et al. Laparoscopic repair of vesicovaginal fistula. Journal of Endourology. 2008;22(3):525-7. Epub 2008/03/22.

215. Phipps J. Laparoscopic repair of posthysterectomy vesicovaginal fistula: Two case reports. Gynaecological Endoscopy. 1996;5(2):123-4.

216. Porpiglia F, Fiori C, Morra I, Ragni F, Vaccino D, Scarpa RM. Laparoscopic vesico-vaginal fistula repair: our experience and review of the literature. [Review] [25 refs]. Surgical laparoscopy, endoscopy & percutaneous techniques. 2009;19(5):410-4. Epub 2009/10/24.

217. Rizvi SJ, Gupta R, Patel S, Trivedi A, Trivedi P, Modi P. Modified laparoscopic abdominal vesico-vaginal fistula repair-'Mini- o'Conor' vesicotomy. Journal of Laparoendoscopic and Advanced Surgical Techniques. 2010;20(1):13-5. Epub 2010/01/12.

218. Shah SJ. Laparoscopic transabdominal transvesical vesicovaginal fistula repair. Journal of Endourology. 2009;23(7):1135-7. Epub 2009/07/09.

219. Sotelo R, Mariano MB, Garcia-Segui A, Dubois R, Spaliviero M, Keklikian W, et al. Laparoscopic repair of vesicovaginal fistula. Journal of Urology. 2005;173(5):1615-8. Epub 2005/04/12.

220. Wong C, Lam PN, Lucente VR. Laparoscopic transabdominal transvesical vesicovaginal fistula repair. Journal of Endourology. 2006;20(4):240-3. Epub 2006/05/02.

221. Melamud O, Eichel L, Turbow B, Shanberg A. Laparoscopic vesicovaginal fistula repair with robotic reconstruction. Urology. 2005;65(1):163-6. Epub 2005/01/26.

222. Hemal AK, Kolla SB, Wadhwa P. Robotic Reconstruction for Recurrent Supratrigonal Vesicovaginal Fistulas. Journal of Urology. 2008;180(3):981-5.

223. Kurz M, Horstmann M, John H. Robot-assisted laparoscopic repair of high vesicovaginal fistulae with peritoneal flap inlay. Eur Urol. 2012;61(1):229-30. Epub 2011/10/11.

224. Schimpf MO, Morgenstern JH, Tulikangas PK, Wagner JR. Vesicovaginal fistula repair without intentional cystotomy using the laparoscopic robotic approach: a case report. JSLS : Journal of the Society of Laparoendoscopic Surgeons / Society of Laparoendoscopic Surgeons. 2007;11(3):378-80. Epub 2007/10/13.

225. Sundaram BM, Kalidasan G, Hemal AK. Robotic repair of vesicovaginal fistula: Case series of five patients. Urology. 2006;67(5):970-3.

226. Shekarriz B, Stoller ML. The use of fibrin sealant in urology. Journal of Urology. 2002;167(3):1218-25. Epub 2002/02/08.

227. Grumbt H, Kurz W, Knoth HJ. [Closure of a vesico-perineal fistula with fibrin glue]. Zentralblatt fur Chirurgie. 1984;109(5):364-5. Epub 1984/01/01. Verschluss einer Blasen-Damm-Fistel durch Fibrinkleber.

228. Morita T, Tachikawa N, Tokue A. Successful closure of neovesicocutaneous fistula with fibrin glue. Urol Int. 1998;61(2):130-1. Epub 1999/01/05 21:58.

229. Morita T, Tokue A. Successful endoscopic closure of radiation induced vesicovaginal fistula with fibrin glue and bovine collagen. Journal of Urology. 1999;162(5):1689. Epub 1999/10/19.

230. Rossi D, Bladou F, Berthet B, Coulange C, Serment G. [A simple alternative for the treatment of urinary fistulas: fibrin glue]. Progres en Urologie. 1991;1(3):445-8. Epub 1991/06/01. Une alternative simple dans le traitement des fistules urinaires: la colle de fibrine.

231. Schneider JA, Patel VJ, Hertel E. [Closure of vesicovaginal fistulas from the urologic viewpoint with reference to endoscopic fibrin glue technique]. Zentralbl Gynakol. 1992;114(2):70-3. Epub 1992/01/01. Der Verschluss von Blasenscheidenfisteln aus urologischer Sicht unter Berucksichtigung der endoskopischen Fibrinklebung.

232. Tostain J. [Conservative treatment of urogenital fistula following gynecological surgery: the value of fibrin glue]. Acta Urol Belg. 1992;60(3):27-33. Epub 1992/01/01. Traitement conservateur des fistules urogenitales apres chirurgie gynecologique: interet de la colle de fibrine.

233. Welp T, Bauer O, Diedrich K. [Use of fibrin glue in vesicovaginal fistulas after gynecologic treatment]. Zentralbl Gynakol. 1996;118(7):430-2. Epub 1996/01/01. Fibrinkleber im Einsatz bei Blasen-Scheiden-Fisteln nach gynakologischer Behandlung.

234. Yashi M, Muraishi O, Yuzawa M, Tokue A. [A case of colovesico-vaginal fistula caused by sigmoid colon diverticulitis]. Hinyokika Kiyo. 1998;44(7):513-5. Epub 1998/09/30.

235. D'Arcy FT, Jaffry S. The treatment of vesicovaginal fistula by endoscopic injection of fibrin glue. The surgeon : journal of the Royal Colleges of Surgeons of Edinburgh and Ireland. 2010;8(3):174-6. Epub 2010/04/20.

236. Daley SM, Lallas CD, Swanson SK, Novicki DE, Itano NB. Fibrin Sealant Closure of a Persistent Vesicovaginal Fistula After Failed Transabdominal Closure. Journal of Pelvic Medicine & Surgery. 2006;12(4):229-30.

237. Evans LA, Ferguson KH, Foley JP, Rozanski TA, Morey AF. Fibrin sealant for the management of genitourinary injuries, fistulas and surgical complications. Journal of Urology. 2003;169(4):1360-2. Epub 2003/03/12.

238. Lazarou G, Grigorescu B, Powers K, Mikhail MS. Transvaginal injection of fibrin sealant for closure of vesicovaginal fistula. Journal of Pelvic Medicine & Surgery. 2006;12(6):335-7.

239. Sharma SK, Perry KT, Turk TMT. Endoscopic injection of fibrin glue for the treatment of urinary-tract pathology. Journal of Endourology. 2005;19(3):419-23. Epub 2005/05/04.

240. McKay HA. Vesicovaginal and vesicocutaneous fistulas: transurethral suture cystorrhaphy as a new closure technique. Journal of Urology. 1997;158(4):1513-6. Epub 1997/09/25.

241. McKay HA. Transurethral suture cystorrhaphy for repair of vesicovaginal fistulas: Evolution of a technique. International Urogynecology Journal & Pelvic Floor Dysfunction. 2001;12(4):282-7. Epub 2001/09/25.

242. Okamura K, Kanai S, Kurokawa T, Kondo A. Endoscopic transvesico-transurethral approach for repair of vesicovaginal fistula: Initial case report. Journal of Endourology. 1997;11(3):203-5. Epub 1997/06/01.

243. Rangnekar NP, Imdad Ali N, Kaul SA, Pathak HR. Role of the martius procedure in the management of urinary-vaginal fistulas. J Am Coll Surg. 2000;191(3):259-63. Epub 2000/09/16.

244. Zimmern P, Schmidbauer CP, Leach GE, Staskin DR, Hadley HR, Raz S. Vesicovaginal and urethrovaginal fistulae. Semin Urol. 1986;4(1):24-9. Epub 1986/02/01.

245. Turner-Warwick R. The use of the omental pedicle graft in urinary tract reconstruction. Journal of Urology. 1976;116:341-7.

246. Wein AJ, Malloy TR, Carpiniello VL, Greenberg SH, Murphy JJ. Repair of vesicovaginal fistula by a suprapubic transvesical approach. Surg Gynecol Obstet. 1980;150(1):57-60. Epub 1980/01/01.

247. Evans DH, Madjar S, Politano VA, Bejany DE, Lynne CM, Gousse AE. Interposition flaps in transabdominal vesicovaginal fistula repairs: are they really necessary? Urology. 2001;57(4):670-4. Epub 2001/04/18.

248. Izes J, Smith J, Zinman L. The gracilis muscle iin repair of complex lower urinary tract fistulae (15 year experience). . J Urol. 1992;147 (suppl):281A.

249. Symmonds RE, Hill LM. Loss of the urethra: a report on 50 patients. Am J Obstet Gynecol. 1978;130(2):130-8. Epub 1978/01/15.

250. Mraz JP, Sutory M. An alternative in surgical treatment of post-irradiation vesicovaginal and rectovaginal fistulas: the seromuscular intestinal graft (patch). J Urol. 1994;151(2):357-9. Epub 1994/02/01.

251. Menchaca A, Akhyat M, Gleicher N, Gottlieb L, Bernstein J. The rectus abdominis muscle flap in a combined abdominovaginal repair of difficult vesicovaginal fistulae. A report of three cases. J Reprod Med. 1990;35(5):565-8. Epub 1990/05/01.

252. Viennas LK, Alonso AM, Salama V. Repair of radiation-induced vesicovaginal fistula with a rectus abdominis myocutaneous flap. Plastic & Reconstructive Surgery. 1995;96(6):1435-7.

253. Brandt FT, Lorenzato FR, Albuquerque CD. Treatment of vesicovaginal fistula by bladder mucosa autograft technique. J Am Coll Surg. 1998;186(6):645-8. Epub 1998/06/19.

254. Ostad M, Uzzo RG, Coleman J, Young GP. Use of a free bladder mucosal graft for simple repair of vesicovaginal fistulae. Urology. 1998;52(1):123-6. Epub 1998/07/22.

255. Sharifi-Aghdas F, Ghaderian N, Payvand A. Free bladder mucosal autograft in the treatment of complicated vesicovaginal fistula. BJU Int. 2002;89 Suppl 1:54-6. Epub 2002/03/06.

256. Nardos R, Browning A, Member B. Duration of bladder catheterization after surgery for obstetric fistula. International Journal of Gynaecology & Obstetrics. 2008;103(1):30-2.

257. Hedlund H, Lindstedt E. Urovaginal fistulas: 20 years of experience with 45 cases. Journal of Urology. 1987;137(5):926-8. Epub 1987/05/01.

258. Jovanovic MD, Milovic N, Aleksic P, Bancevic V, Kosevic B, Campara Z, et al. Efficiency of urinary fistulas surgical treatment. European Urology, Supplements. 2010;9 (6):572.

259. Madjar S, Gousse A. Postirradiation vesicovaginal fistula completely resolved with conservative treatment. International Urogynecology Journal & Pelvic Floor Dysfunction. 2001;12(6):405-6. Epub 2002/01/25.

260. Vanni AJ, Buckley JC, Zinman LN. Management of surgical and radiation induced rectourethral fistulas with an interposition muscle flap and selective buccal mucosal onlay graft. Journal of Urology. 2010;184(6):2400-4. Epub 2010/10/19.

261. Kisner CD, Kesner KM. Use of the transverse colon conduit for vesicovaginal fistula in late-stage carcinoma of the cervix. Br J Urol. 1987;59(3):234-8.

262. Ravi R, Dewan AK, Pandey KK. Transverse colon conduit urinary diversion in patients treated with very high dose pelvic irradiation. Br J Urol. 1994;73(1):51-4. Epub 1994/01/01.

263. Schmidt JD, Hawtrey CE, Buchsbaum HJ. Transverse colon conduit: a preferred method of urinary diversion for radiation-treated pelvic malignancies. Journal of Urology. 1975;113(3):308-13. Epub 1975/03/01.

264. Hampson SJ, Morris SB, Gordon EM, Shearer RJ. Management of inoperable pelvic carcinomas with complex fistulas: a new approach. Annals of the Royal College of Surgeons of England. 1994;76(3):188-9. Epub 1994/05/01.

265. Leissner J, Black P, Filipas D, Fisch M, Hohenfellner R. Vaginal reconstruction using the bladder and/or rectal walls in patients with radiation-induced fistulas. Gynecologic oncology. 2000;78(3 Pt 1):356-60. Epub 2000/09/14.

266. Hsu TH, Rackley RR, Abdelmalak JB, Madjar S, Vasavada SP. Novel technique for combined repair of postirradiation vesicovaginal fistula and augmentation ileocystoplasty. Urology. 2002;59(4):597-9. Epub 2002/04/03.

267. Tabakov ID, Slavchev BN. Large post-hysterectomy and post-radiation vesicovaginal fistulas: repair by ileocystoplasty. Journal of Urology. 2004;171(1):272-4. Epub 2003/12/11.

268. Kulkarni JN, Gulla RI. 1-Stage repair of radiation induced colovesical fistula by resection and colocystoplasty. Journal of Urology. 1998;160(6 Pt 1):2149-50. Epub 1998/11/17.

269. Verbaeys C, Hoebeke P, Oosterlinck W. Complicated postirradiation vesicovaginal fistula in young women: keep off or try reconstruction? Eur Urol. 2007;51(1):243-6; discussion 6. Epub 2006/07/11.

270. Hilton P. Fistula repair. In: Smith R, del Priore G, Curtin J, Monaghan J, editors. An Atlas of Gynaecological Oncology. 3rd ed. London: Taylor & Francis Medical Books; 2011. p. 236-50.

271. Aitken RJ, Elliot MS. Sigmoid exclusion: a new technique in the management of radiation-induced fistula. The British journal of surgery. 1985;72(9):731-2. Epub 1985/09/01.

272. Levenback C, Gershenson DM, McGehee R, Eifel PJ, Morris M, Burke TW. Enterovesical fistula following radiotherapy for gynecologic cancer. Gynecologic oncology. 1994;52(3):296-300. Epub 1994/03/01.

273. Kiricuta I, Goldstein AM. The repair of extensive vesicovaginal fistulas with pedicled omentum: a review of 27 cases. Journal of Urology. 1972;108(5):724-7. Epub 1972/11/01.

274. Bizic M, Kojovic V, Majstorovic M, Djordjevic M. A versatile labia minora skin flap in severe vesicovaginal fistula repair. European Urology, Supplements. 2010;9 (6):572.

275. Lai YL, Chang CJ. Vulvovaginal reconstruction following radical tumor resection: report of 12 cases. Chang Gung Medical Journal. 1999;22(2):253-8.

276. Stanojevic D, Djordjevic M, Martins F, Rudic J, Stanojevic M, Bizic M, et al. [Repair of vesicovaginal fistula caused by radiation therapy with labia maiora skin flap]. Srp Arh Celok Lek. 2010;138(5-6):356-61. Epub 2010/07/09.

277. Tran KT, Kuijpers HC, van Nieuwenhoven EJ, van Goor H, Spauwen PH. Transposition of the rectus abdominis muscle for complicated pouch and rectal fistulas. Diseases of the Colon & Rectum. 1999;42(4):486-9. Epub 1999/04/24.

278. Amsellem-Ouazana D, Cornud F, Conquy S, Beuzeboc P, Massault PP, Vieillefond A, et al. Management of a malignant urinary fistula by ureteral embolization with coils. Urology. 2006;68(2):427.e1-.e3.

279. Gaylord GM, Johnsrude IS. Transrenal ureteral occlusion with Gianturco coils and gelatin sponge. Radiology. 1047;172(3 Pt 2):1047-8.

280. Farrell TA, Wallace M, Hicks ME. Long-term results of transrenal ureteral occlusion with use of Gianturco coils and gelatin sponge pledgets. Journal of Vascular & Interventional Radiology. 1997;8(3):449-52.

281. Farrell T, Yamaguchi T, Barnhart W, Lang E. Percutaneous ureteral clipping: long-term results and complications. Journal of Vascular & Interventional Radiology. 1997;8(3):453-6.

282. Kinn AC, Ohlsen H, Brehmer-Andersson E, Brundin J. Therapeutic ureteral occlusion in advanced pelvic malignant tumors. Journal of Urology. 1986;135(1):29-32. Epub 1986/01/01.

283. Schild HH, Gunther R, Thelen M. Transrenal ureteral occlusion: results and problems. Journal of Vascular & Interventional Radiology. 1994;5(2):321-5.

284. Papanicolaou N, Pfister RC, Yoder IC. Percutaneous occlusion of ureteral leaks and fistulae using nondetachable balloons. Urol Radiol. 1985;7(1):28-31.

285. Sanchez R, Quinn SF, Morrisseau PM, Roberts W, Kavanagh J, Clark RA. Urinary diversion by using a percutaneous ureteral occlusion device. American Journal of Roentgenology. 1988;150(5):1069-70. Epub 1988/05/01.

286. Horenblas S, Kroger R, Van Boven E, Meinhardt W, Newling DWW. Use of balloon catheters for ureteral occlusion in urinary leakage. Eur Urol. 2000;38(5):613-7.

287. Avritscher R, Madoff DC, Ramirez PT, Wallace MJ, Ahrar K, Morello FA, Jr., et al. Fistulas of the lower urinary tract: percutaneous approaches for the management of a difficult clinical entity. Radiographics. 2004;24(suppl 1):S217-S36. Epub 2004/10/16.

288. Levy C, Tremaine WJ. Management of internal fistulas in Crohn's disease. Inflammatory bowel diseases. 2002;8(2):106-11. Epub 2002/02/21.

289. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. New England Journal of Medicine. 1999;340(18):1398-405. Epub 1999/05/06.

290. Sonnenberg A, Gavin MW. Timing of surgery for enterovesical fistula in Crohn's disease: decision analysis using a time-dependent compartment model. Inflammatory bowel diseases. 2000;6(4):280-5. Epub 2001/01/10.

291. Amin M, Nallinger R, Polk HC, Jr. Conservative treatment of selected patients with colovesical fistula due to diverticulitis. Surg Gynecol Obstet. 1984;159(5):442-4. Epub 1984/11/01.

292. Lewis SL, Abercrombie GF. Conservative surgery for vesicocolic fistula. Journal of the Royal Society of Medicine. 1984;77(2):102-4. Epub 1984/02/01.

293. McNamara MJ, Fazio VW, Lavery IC, Weakley FL, Farmer RG. Surgical treatment of enterovesical fistulas in Crohn's disease. Diseases of the Colon & Rectum. 1990;33(4):271-6. Epub 1990/04/01.

294. Pontari MA, McMillen MA, Garvey RH, Ballantyne GH. Diagnosis and treatment of enterovesical fistulae. The American surgeon. 1992;58(4):258-63. Epub 1992/04/01.

295. McConnell DB, Sasaki TM, Vetto RM. Experience with colovesical fistula. Am J Surg. 1980;140(1):80-4. Epub 1980/07/01.

296. Balaguera CJ, Camunas Segovia J, Pena Gamarra L, Oliart Delgado de Torres S, Martin Garcia-Almenta M, Viso Ciudad S, et al. Colovesical fistula complicating diverticular disease: one-stage resection. Int Surg. 2006;91(1):17-23.

297. Menenakos E, Hahnloser D, Nassiopoulos K, Chanson C, Sinclair V, Petropoulos P. Laparoscopic surgery for fistulas that complicate diverticular disease. Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie. 2003;388(3):189-93. Epub 2003/07/02.

298. Tsivian A, Kyzer S, Shtricker A, Benjamin S, Sidi AA. Laparoscopic treatment of colovesical fistulas: technique and review of the literature. International Journal of Urology. 2006;13(5):664-7. Epub 2006/06/15.

299. Dobrowolski Z KJ, Drewniak T, Habrat W, Lipczynski W, Jakubik P, Weglarz W. Renal and ureteric trauma: Diagnosis and management in Poland. BJU international 2002;89:748-51.

300. Djakovic N PE, Martínez-Piñeiro L, Lynch T, Mor Y, Santucci RA, Serafetinidis E, Turkeri LN, Hohenfellner M. European Association of Urology Guidelines on Urological Trauma 2009. http://wwwuroweborg/gls/pdf/20_Urological_Trauma%202009pdf. 2009.

301. Brandes S CM, Armenakas N, McAninch J. Diagnosis and management of ureteric injury: An evidence-based analysis. BJU International 2004;95:277-89.

302. Chou MT WC, Lien RC. Prophylactic ureteral catheterization in gynecologic surgery: a 12-year randomized trial in a community hospital. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20:689-93.

303. Razzaghi MR RA, Javanmard B, Lotfi B. Desmopressin as an alternative solution for urinary leakage after ureterocaliceal surgeries. Urology Journal 2009;6:120-2.

304. Van den Bergh RN MF, De Vries JP, Lock TM. Arteriioureteral fistulas: Unusual suspects-systematic review of 139 cases. Urology. 2009;74:251-5.

305. Schimpf M GE, Wagner J. Universal ureteral stent placement at hysterectomy to identify ureteral injury: a decision analysis. Bjog. 2008;115:1151-8.

306. Kundu SD TR, Kallingal GJ, Cambareri G, Russo P. Urinary fistulae after partial nephrectomy. BJU International. 2010;106:1042-4.

307. Mazzucchi E SG, Hisano M, Antonopoulos IM, Piovesan AC, Nahas WC, Lucon AM, Srougi M. Primary reconstruction is a good option in the treatment of urinary fistula after kidney transplantation. International Braz J Urol 2006;32:398-403.

308. Nie ZL ZK, Li QS, Jin FS, Zhu FQ, Huo WQ. Treatment of urinary fistula after kidney transplantation. Transplantation Proceedings. 2009;41:1624-6.

309. Basic D DJ, Milutinovic D, Dzamic Z, Topuzovic C, Pejcic T. Ureteral fistulae after kidney transplantation: Experience with 224 cases. Acta Chir Iugosl. 2011;58:89-94.

310. Vanderbrink BA RA, Caplin D, Ost MC, Lobko I, Lee BR. Successful conservative management of colorenal fistula after percutaneous cryoablation of renal-cell carcinoma. Journal of Endourology. 2007;21:26-9.

311. Ould Ismail T HF, Janane A, Dekkak Y, Sossa J, Chafiki J, Lahrech Y, Qarro A, Jira H, Ghadouane M, Ameur A, Abbar M. Renocolic fistula following abdominal trauma: a case study. Progres en Urologie 2010;20:230-2.

312. El-Nahas AR SA, El-Assmy AM, Shoma AM, Eraky I, El-Kenawy MR, El-Kappany HA. Colonic perforation during percutaneous nephrolithotomy. Urology. 2006;67:937–41.

313. Fox JA KA, McPhail AF, Lightner D. Ureteroarterial fistula treatment with open surgery versus Endovascular Management: Long-Term Outcomes. Journal of Urology. 2009;185:945-50.

314. Shaw MB TM, Rix DA, Dorkin TJ, Murthy LN, Pickard RS The management of bilateral ureteric injury following radical hysterectomy. Adv Urol. 2008;524919.

315. Andriole GL, Bettmann MA, Garnick MB, Richie JP. Indwelling double-J ureteral stents for temporary and permanent urinary drainage: experience with 87 patients. Journal of Urology. 1984;131(2):239-41. Epub 1984/02/01.

316. Barton DP, Morse SS, Fiorica JV, Hoffman MS, Roberts WS, Cavanagh D. Percutaneous nephrostomy and ureteral stenting in gynecologic malignancies. Obstetrics & Gynecology. 1992;80(5):805-11. Epub 1992/11/01.

317. Beaghler MA, Taylor FC, McLaughlin KP. A combined antegrade and retrograde technique for reestablishing ureteral continuity. Tech Urol. 1997;3(1):44-8. Epub 1997/04/01.

318. Campbell SC, Streem SB, Zelch M, Hodge E, Novick AC. Percutaneous management of transplant ureteral fistulas: patient selection and long-term results. Journal of Urology. 1993;150(4):1115-7. Epub 1993/10/01.

319. Dowling RA, Corriere JN, Jr., Sandler CM. Iatrogenic ureteral injury. Journal of Urology. 1986;135(5):912-5. Epub 1986/05/01.

320. Koonings PP, Huffman JL, Schlaerth JB. Ureteroscopy: A new asset in the management of postoperative ureterovaginal fistulas. Obstetrics & Gynecology. 1992;80(3 Pt 2):548-9. Epub 1992/09/01.

321. Lang EK. Antegrade ureteral stenting for dehiscence, strictures, and fistulae. American Journal of Roentgenology. 1984;143(4):795-801. Epub 1984/10/01.

322. Lingeman JE, Wong MYC, Newmark JR. Endoscopic management of total ureteral occlusion and ureterovaginal fistula. Journal of Endourology. 1995;9(5):391-6. Epub 1995/10/01.

323. Mandal AK, Sharma SK, Vaidyanathan S, Goswami AK. Ureterovaginal fistula: Summary of 18 years' experience. Br J Urol. 1990;65(5):453-6. Epub 1990/05/01.

324. Narang V, Sinha T, Karan SC, Sandhu AS, Sethi GS, Srivastava A, et al. Ureteroscopy: savior to the gynecologist? Ureteroscopic management of post laparoscopic-assisted vaginal hysterectomy ureterovaginal fistulas. Journal of Minimally Invasive Gynecology. 2007;14(3):345-7. Epub 2007/05/05.

325. Ustunsoz B, Ugurel S, Duru NK, Ozgok Y, Ustunsoz A. Percutaneous management of ureteral injuries that are diagnosed late after cesarean section. Korean journal of radiology : official journal of the Korean Radiological Society. 2008;9(4):348-53. Epub 2008/08/07.

326. Wang AC, Hung CF. Endourologic diagnosis and treatment of ureterouterine fistula. International Urogynecology Journal & Pelvic Floor Dysfunction. 1997;8(3):164-7. Epub 1997/01/01.

327. Puntambekar S PR, Gurjar AM, Sathe RM, Talaulikar AG, Agarwal GA, Kashyap M. Laparoscopic ureteroneocystostomy with psoas hitch. Journal of Minimally Invasive Gynecology. 2006;13:302-5.

328. Modi P GR, Rizvi SJ. Laparoscopic ureteroneocystostomy and psoas hitch for post-hysterectomy ureterovaginal fistula. Journal of Urology. 2008;180:615-7.

329. Laungani R PN, Krane LS, Hemal AK, Raja S, Bhandari M, Menon M. Robotic-assisted ureterovaginal fistula repair: Report of efficacy and feasibility. Journal of Laparoendoscopic and Advanced Surgical Techniques. 2008;18: 731-4.

330. Chen SS YS-H, Yang J-M, Huang W-C. Transvaginal repair of ureterovaginal fistula by Latzko technique. Int Urogynecol Journal 2007;18:1381-3.

331. Natarajan V BN, Meiring P, Spencer P, Parys BT, Oakley NE. Ureteric embolization: An alternative treatment strategy for urinary fistulae complicating advanced pelvic malignancy. BJU International. 2007;99:147-9.

332. Shindel AW ZH, Hovsepian DM, Brandes SB. Ureteric embolization with stainless-steel coils for managing refractory lower urinary tract fistula: a 12-year experience. BJU International. 2007;99:364-8.

333. Kim SK LY, Kyung MS, Choi JS. Transrenal ureteral occlusion with the use of microcoils in five patients with ureterovaginal fistulas. Abdom Imaging 2008;33:615–20.

334. Park S, Ha SH, Kim KS. Long-term follow-up after feminizing genital reconstruction in patients with ambiguous genitalia and high vaginal confluence. J Korean Med Sci. 2011;26(3):399-403. Epub 2011/03/12.

335. Dhabalia JV, Nelivigi GG, Satia MN, Kakkattil S, Kumar V. Congenital urethrovaginal fistula with imperforate hymen: a first case report. J Obstet Gynaecol Can. 2009;31(7):652-3. Epub 2009/09/19.

336. Oguzkurt P, Ince E, Ezer SS, Temiz A, Demir S, Hicsonmez A. Primary vaginal calculus secondary to urethrovaginal fistula with imperforate hymen in a 6-year-old girl. J Pediatr Surg. 2009;44(7):e11-3. Epub 2009/07/04.

337. Levitt MA, Bischoff A, Pena A. Pitfalls and challenges of cloaca repair: how to reduce the need for reoperations. J Pediatr Surg. 2011;46(6):1250-5. Epub 2011/06/21.

338. Levitt MA, Pena A. Cloacal malformations: lessons learned from 490 cases. Semin Pediatr Surg. 2010;19(2):128-38. Epub 2010/03/24.

339. Hage JJ, Bouman FG, Bloem JJ. Construction of the fixed part of the neourethra in female-to-male transsexuals: experience in 53 patients. Plast Reconstr Surg. 1993;91(5):904-10; discussion 11-3. Epub 1993/04/01.

340. Hilton P. Urethrovaginal fistula associated with 'sterile abscess' formation following periurethral injection of dextranomer/hyaluronic acid co-polymer (Zuidex) for the treatment of stress urinary incontinence--a case report. Bjog. 2009;116(11):1527-30. Epub 2009/08/18.

341. Carlin BI, Klutke CG. Development of urethrovaginal fistula following periurethral collagen injection. J Urol. 2000;164(1):124. Epub 2000/06/07.

342. Estevez JP, Colin P, Lucot JP, Collinet P, Cosson M, Boukerrou M. [Urethrovaginal fistulae resulting from sub-urethral slings for stress urinary incontinence treatment. A report of two cases and review of the literature]. J Gynecol Obstet Biol Reprod (Paris). 2010;39(2):151-5. Epub 2010/01/23. Fistules uretrovaginales apres cure d'incontinence urinaire d'effort par bandelettes sous-uretrales. A propos de deux cas et revue de la litterature.

343. Estevez JP, Cosson M, Boukerrou M. An uncommon case of urethrovaginal fistula resulting from tension-free vaginal tape. Int Urogynecol J. 2010;21(7):889-91. Epub 2010/01/07.

344. Reisenauer C, Wallwiener D, Stenzl A, Solomayer FE, Sievert KD. Urethrovaginal fistula--a rare complication after the placement of a suburethral sling (IVS). Int Urogynecol J Pelvic Floor Dysfunct. 2007;18(3):343-6. Epub 2006/05/05.

345. Glavind K, Larsen EH. Results and complications of tension-free vaginal tape (TVT) for surgical treatment of female stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12(6):370-2. Epub 2002/01/25.

346. Walker KF, Dasgupta J, Cust MP. A neglected shelf pessary resulting in a urethrovaginal fistula. Int Urogynecol J. 2011;22(10):1333-4. Epub 2011/04/07.

347. Blaivas JG, Purohit RS. Post-traumatic female urethral reconstruction. Curr Urol Rep. 2008;9(5):397-404. Epub 2008/08/16.

348. Liu GC, Xia HM, Wen YQ, Zhang LY, Li ZM. Considerations before repair of acquired rectourethral and urethrovaginal fistulas in children. World J Pediatr. 2008;4(1):53-7. Epub 2008/04/12.

349. Holland AJ, Cohen RC, McKertich KM, Cass DT. Urethral trauma in children. Pediatr Surg Int. 2001;17(1):58-61. Epub 2001/04/11.

350. Parkhurst JD, Coker JE, Halverstadt DB. Traumatic avulsion of the lower urinary tract in the female child. J Urol. 1981;126(2):265-7. Epub 1981/08/01.

351. Kobayashi K, Otoshi T, Madono K, Momohara C, Imamura R, Takada S, et al. [A case of urethrovaginal fistula caused by a foreign body in the vagina]. Hinyokika Kiyo. 2010;56(7):389-91. Epub 2010/08/21.

352. Thrumurthy SG, Hill SR, Islam S. Iatrogenic urethrovaginal fistula from catheterization in labour. Br J Hosp Med (Lond). 2010;71(7):414. Epub 2010/07/16.

353. Cameron AP, Atiemo HO. Unusual presentation of an obstetrical urethrovaginal fistula secondary to improper catheter placement. Can Urol Assoc J. 2009;3(4):E21-E2. Epub 2009/08/13.

354. Ben Amna M, Hajri M, Moualli SB, Mehrez R, Chebil M, Ayed M. [The female urethral diverticula: apropos of 21 cases]. Ann Urol (Paris). 2002;36(4):272-6. Epub 2002/08/07. Le diverticule de l'uretre feminin, a propos de 21 observations.

355. Porpiglia F, Destefanis P, Fiori C, Fontana D. Preoperative risk factors for surgery female urethral diverticula. Our experience. Urol Int. 2002;69(1):7-11. Epub 2002/07/18.

356. Ganabathi K, Leach GE, Zimmern PE, Dmochowski R. Experience with the management of urethral diverticulum in 63 women. J Urol. 1994;152(5 Pt 1):1445-52. Epub 1994/11/01.

357. Chung HJ, Goo BC, Lee JH, Bang D, Lee KH, Lee ES, et al. Behcet's disease combined with various types of fistula. Yonsei Med J. 2005;46(5):625-8. Epub 2005/11/01.

358. Waidelich RM, Brunschweiger SM, Schmeller NT. [Urethrovaginal fistula in Behcet disease]. Urologe A. 1994;33(2):163-6. Epub 1994/03/01. Urethrovaginale Fistel bei Morbus Behcet.

359. Flottorp J, Inversen S. [Vesicovaginal and urethrovaginal fistulas treated at the Norwegian Radium Hospital 1940-1952 and in the gynecological department of the Rikshospitalet 1953-1959]. Tidsskr Nor Laegeforen. 1960;80:597-9. Epub 1960/06/15.

360. Ying T, Li Q, Shao C, Zhu Z, Feng L, Hu B. Value of transrectal ultrasonography in female traumatic urethral injuries. Urology. 2010;76(2):319-22. Epub 2010/02/17.

361. Abet L, Richter J, Lenk S, Kotalla H, Hegenscheid F. [Double-balloon urethrography in the female]. Z Urol Nephrol. 1983;76(1):19-28. Epub 1983/01/01. Die Doppelballonurethrographie der Frau.

362. Quiroz LH, Shobeiri SA, Nihira MA. Three-dimensional ultrasound imaging for diagnosis of urethrovaginal fistula. Int Urogynecol J. 2010;21(8):1031-3. Epub 2010/01/14.

363. Schoellnast H, Lindbichler F, Riccabona M. Sonographic diagnosis of urethral anomalies in infants: value of perineal sonography. J Ultrasound Med. 2004;23(6):769-76. Epub 2004/07/13.

364. Goodwin WE, Scardino PT. Vesicovaginal and ureterovaginal fistulas: a summary of 25 years of experience. J Urol. 1980;123(3):370-4. Epub 1980/03/01.

365. Pushkar DY, Dyakov VV, Kosko JW, Kasyan GR. Management of urethrovaginal fistulas. Eur Urol. 2006;50(5):1000-5. Epub 2006/09/02.

366. Parks J. Section of the urethral wall for correction of urethrovaginal fistulae and urethral diverticula. Am J Obstet Gynecol. 1965;93(5):683-92. Epub 1965/11/01.

367. Rovner ES, Wein AJ. Diagnosis and reconstruction of the dorsal or circumferential urethral diverticulum. J Urol. 2003;170(1):82-6; discussion 6. Epub 2003/06/11.

368. Lamensdorf H, Compere DE, Begley GF. Simple surgical correction of urethrovaginal fistula. Urology. 1977;10(2):152-3. Epub 1977/08/01.

369. Fall M. Vaginal wall bipedicled flap and other techniques in complicated urethral diverticulum and urethrovaginal fistula. J Am Coll Surg. 1995;180(2):150-6. Epub 1995/02/01.

370. Xu YM, Sa YL, Fu Q, Zhang J, Xie H, Jin SB. Transpubic access using pedicle tubularized labial urethroplasty for the treatment of female urethral strictures associated with urethrovaginal fistulas secondary to pelvic fracture. Eur Urol. 2009;56(1):193-200. Epub 2008/05/13.

371. Pushkar D. Editorial comment on: Transpubic access using pedicle tubularized labial urethroplasty for the treatment of female urethral strictures associated with urethrovaginal fistulas secondary to pelvic fracture. Eur Urol. 2009;56(1):200. Epub 2008/05/13.

372. Huang CR, Sun N, Wei p, Xie HW, Hwang AH, Hardy BE. The management of old urethral injury in young girls: analysis of 44 cases. J Pediatr Surg. 2003;38(9):1329-32. Epub 2003/10/03.

373. Candiani P, Austoni E, Campiglio GL, Ceresoli A, Zanetti G, Colombo F. Repair of a recurrent urethrovaginal fistula with an island bulbocavernous musculocutaneous flap. Plast Reconstr Surg. 1993;92(7):1393-6. Epub 1993/12/01.

374. McKinney DE. Use of full thickness patch graft in urethrovaginal fistula. J Urol. 1979;122(3):416. Epub 1979/09/01.

375. Browning A. Lack of value of the Martius fibrofatty graft in obstetric fistula repair. Int J Gynaecol Obstet. 2006;93(1):33-7. Epub 2006/03/15.

376. Rangnekar NP, Imdad Ali N, Kaul SA, Pathak HR. Role of the Martius procedure in the management of urinary-vaginal fistulas. J Am Coll Surg. 2000;191(3):259-63.

377. Punekar SV, Buch DN, Soni AB, Swami G, Rao SR, Kinne JS, et al. Martius' labial fat pad interposition and its modification in complex lower urinary fistulae. J Postgrad Med. 1999;45(3):69-73. Epub 2000/03/29.

378. Radopoulos DK, Dimitriadis GP, Vakalopoulos IK, Ioannidis SS, Tzakas KA, Vasilakakis IE. Our experience with salvage genitourinary fistulae repair: technique and outcomes. Int Urol Nephrol. 2008;40(1):57-63. Epub 2007/07/05.

379. Baskin D, Tatlidede S, Karsidag SH. Martius repair in urethrovaginal defects. J Pediatr Surg. 2005;40(9):1489-91. Epub 2005/09/10.

380. Birkhoff JD, Wechsler M, Romas NA. Urinary fistulas: vaginal repair using a labial fat pad. J Urol. 1977;117(5):595-7. Epub 1977/05/01.

381. Atan A, Tuncel A, Aslan Y. Treatment of refractory urethrovaginal fistula using rectus abdominis muscle flap in a six-year-old girl. Urology. 2007;69(2):384 e11-3. Epub 2007/02/27.

382. Bruce RG, El-Galley RE, Galloway NT. Use of rectus abdominis muscle flap for the treatment of complex and refractory urethrovaginal fistulas. J Urol. 2000;163(4):1212-5. Epub 2000/03/29.

383. Golomb J, Leibovitch I, Mor Y, Nadu A, Ramon J. Fascial patch technique for repair of complicated urethrovaginal fistula. Urology. 2006;68(5):1115-8. Epub 2006/11/11.

384. Janez J. [Use of the great epiploon in the treatment of complex vesico- and urethro-vaginal fistulae]. Ann Urol (Paris). 1985;19(4):267-8. Epub 1985/01/01. Utilisation du grand epiploon dans le traitement des fistules vesico- et uretro-vaginales complexes.

385. Ingelman-Sundberg A. An extravaginal technic in the operation for urethro-vaginal and vesico-vaginal fistulas. Gynaecologia. 1947;123(6):380-5. Epub 1947/06/01.

386. Patil U, Waterhouse K, Laungani G. Management of 18 difficult vesicovaginal and urethrovaginal fistulas with modified Ingelman-Sundberg and Martius operations. J Urol. 1980;123(5):653-6. Epub 1980/05/01.

387. Hamlin RH, Nicholson EC. Reconstruction of urethra totally destroyed in labour. Br Med J. 1969;2(5650):147-50. Epub 1969/04/19.

388. Lowman J, Moore RD, Miklos JR. Tension-free vaginal tape sling with a porcine interposition graft in an irradiated patient with a past history of a urethrovaginal fistula and urethral mesh erosion: a case report. J Reprod Med. 2007;52(6):560-2. Epub 2007/08/19.

389. Scott R, Gorham SD, Aitcheson M, Bramwell SP, Speakman MJ, Meddings RN. First clinical report of a new biodegradable membrane for use in urological surgery. Br J Urol. 1991;68(4):421-4. Epub 1991/10/01.

390. Mauermann J, Gonzalez R, Franc-Guimond J, Filipas D. The anterior sagittal transrectal approach for traumatic urethrovaginal fistula closure. J Urol. 2004;171(4):1650-1. Epub 2004/03/17.

391. Rossi F, De Castro R, Ceccarelli PL, Domini R. Anterior sagittal transanorectal approach to the posterior urethra in the pediatric age group. J Urol. 1998;160(3 Pt 2):1173-7. Epub 1998/08/27.

392. Domini M, Aquino A, Rossi F, Lima M, Ruggeri G, Domini R. Recurrent posttraumatic urethrovaginal fistula: a new application for ASTRA. J Pediatr Surg. 2000;35(3):522-5. Epub 2000/03/22.

393. Nikolaev VV, Bizhanova DA. High posttraumatic vaginal stricture combined with urethrovaginal fistula and urethral stricture in girls: reconstruction using a posterior sagittal pararectal approach. J Urol. 1998;160(6 Pt 1):2194-6. Epub 1998/11/17.

394. Pena A. The surgical management of persistent cloaca: results in 54 patients treated with a posterior sagittal approach. J Pediatr Surg. 1989;24(6):590-8. Epub 1989/06/01.

395. Ahmed S, Kardar AH. Construction of a neourethra in girls: follow-up results. Pediatr Surg Int. 2000;16(8):584-5. Epub 2001/01/10.

396. Koraitim M. A new retropubic retrourethral approach for large vesico-urethrovaginal fistulas. J Urol. 1985;134(6):1122-3. Epub 1985/12/01.

397. Massoudnia N. [G. Doderlein's «enwrapping plasty» for the surgical treatment of large bladder- and urethrovaginal fistulas]. Zentralbl Gynakol. 1974;96(20):624-9. Epub 1974/05/17. Ein Beitrag zur «Einrollplastik» nach G. Doderlein zur operativen Behandlung grosser Blasen- und Harnrohren-Scheidenfisteln.

398. Tehan TJ, Nardi JA, Baker R. Complications associated with surgical repair of urethrovaginal fistula. Urology. 1980;15(1):31-5. Epub 1980/01/01.

399. Dolan LM, Dixon WE, Hilton P. Urinary symptoms and quality of life in women following urogenital fistula repair: a long-term follow-up study. Bjog. 2008;115(12):1570-4. Epub 2008/11/28.

400. de Bernis L. Obstetric fistula: guiding principles for clinical management and programme development, a new WHO guideline. Int J Gynaecol Obstet. 2007;99 Suppl 1:S117-21.

401. Keettel WC, Sehring FG, deProsse CA, Scott JR. Surgical management of urethrovaginal and vesicovaginal fistulas. Am J Obstet Gynecol. 1978;131(4):425-31. Epub 1978/06/15.

402. Benchekroun A, Lakrissa A, Essakalli HN, Faik M, Abakka T, Hachimi M, et al. [Vesicovaginal fistula. Apropos of 600 cases]. J Urol (Paris). 1987;93(3):151-8. Epub 1987/01/01. Les fistules vesico-vaginales. A propos de 600 cas.

403. Henriksson C, Kihl B, Pettersson S. Urethrovaginal and vesicovaginal fistula. A review of 29 patients. Acta Obstet Gynecol Scand. 1982;61(2):143-8. Epub 1982/01/01.

Committee 19

Bladder Pain Syndrome

Chair

P. Hanno (USA)

Members

P. Dinis (Portugal)

A. Lin (Taiwan)

C. Nickel (Canada)

J. Nordling (Denmark)

A. van Ophoven (Germany)

T. Ueda (Japan)

CONTENTS

I. INTRODUCTION

1. EVIDENCE ACQUISITION
2. DEFINITION

II. HISTORY/ NOMENCLATURE/ TAXONOMY

1. HISTORICAL NOTES
2. NOMENCLATURE AND TAXONOMY

III. EPIDEMIOLOGY

1. EARLY EPIDEMIOLOGICAL STUDIES:
2. PATIENT SELF REPORT SURVEYS:
3. PHYSICIAN DIAGNOSES STUDIES
4. SYMPTOM BASED SURVEYS
5. INCIDENCE:
6. OTHER CONSIDERATIONS

IV. ETIOLOGY

1. MAST CELL ACTIVATION
2. INCREASED PERMEABILITY OF THE UROTHELIUM DUE TO UROTHELIAL DYSFUNCTION/GAG-LAYER DEFECTS
3. INHIBITION OF UROTHELIAL BLADDER CELL PROLIFERATION
4. AUTOIMMUNE MECHANISMS
5. INFECTION
6. NEUROBIOLOGY/PELVIC CROSS-TALK
7. TOXIC AGENTS
8. HYPOXIA
9. THE ROLE OF GENETICS IN BPS
10 . CONCLUSIONS:

V. PATHOLOGY

VI. DIAGNOSIS

1. HISTORY
2. PHYSICAL EXAMINATION
3. PAIN MAPPING
4. LABORATORY TESTING
5. URODYNAMICS
6. POTASSIUM TESTING
7. CYSTOSCOPY AND HYDRODISTENSION
8. MORPHOLOGY
9. BIOMARKERS
10 . CONFUSABLE DISEASES

VII. CLASSIFICATION

VIII. CONSERVATIVE TREATMENT (TABLE 4)

1. BEHAVIORAL MODIFICATION
2. PHYSICAL THERAPY
3. STRESS REDUCTION
4.DIETARY MANIPULATION

IX. ORAL THERAPY (TABLE 5)

1. ANALGESICS
2. ANTIDEPRESSANTS
3. ANTIHISTAMINES
4. IMMUNOSUPPRESSANT
5. SODIUM PENTOSANPOLYSULFATE
6. OTHER ORAL MEDICATIONS THAT HAVE BEEN USED FOR BPS

X. INTRAVESICAL / INTRAMURAL THERAPY (TABLE 5)

1.DMSO (DIMETHYL SULFOXIDE)
2. HEPARIN
3. HYALURONIC ACID
4. CHONDROITIN SULFATE
5. PENTOSAN POLYSUFATE
6. VANILLOIDS (CAPSAICIN, RESINIFERATOXIN)
7. BACILLUS CALMETTE-GUERIN (BCG)
8. OXYBUTYNIN
9. LIDOCAINE
10. BOTULINUM TOXIN (INTRAMURAL)

XI. NEUROMODULATION

XII. PAIN EVALUATION AND TREATMENT

1. EVALUATION OF PAIN:
2. PHARMACOLOGIC MANAGEMENT OF CHRONIC PELVIC PAIN

XIII. SURGICAL THERAPY

1. HYDRODISTENTION
2. TRANSURETHRAL RESECTION
3. CYSTOLYSIS – PERIPHERAL DENERVATION
4. SYMPATHETIC DENERVATION
5. PARASYMPATHETIC DENERVATION
6. BOWEL SURGERY
7. URINARY DIVERSION WITH OR WITHOUT TOTAL CYSTECTOMY AND URETHRECTOMY

XIV. CLINICAL SYMPTOM SCALES

XV. OUTCOME ASSESSMENT

1. THE PROBLEM
2. THE PLACEBO ISSUE
3. OUTCOME INTERPRETATION
4. IMMPACT RECOMMENDATIONS

XVI. PRINCIPLES OF MANAGEMENT

1. HARMONIZATION

XVII. RECOMMENDATIONS OF INTERNATIONAL CONSULTATION ON INCONTINENCE:

1.HISTORY / INITIAL ASSESSMENT
2.INITIAL TREATMENT
3.SECONDARY ASSESSMENT
4.REFRACTORY BPS

XVIII. FUTURE DIRECTIONS IN RESEARCH

XIX. SUMMARY

1. DEFINITION
2. BLADDER PAIN SYNDROME (BPS)

REFERENCES

Bladder Pain Syndrome

P. Hanno

P. Dinis, A. Lin, C. Nickel, J. Nordling, A. van Ophoven, T. Ueda

I. INTRODUCTION

1. EVIDENCE ACQUISITION

The unrestricted, fully exploded Medical Subject Heading (MeSH) “interstitial cystitis” (including all related terms as “painful bladder syndrome”, bladder pain syndrome”, or different terms such as “chronic interstitial cystitis”, etc.) were used to thoroughly search the PubMed database (http://www.ncbi.nim.nih.gov/pubmed) of the United States National Library of Medicine of the National Institutes of Health from the years 2009-2011. Three hundred forty-nine publications in English or with English abstracts were reviewed.

Abstracts if available and titles of the 349 hits were reviewed, focusing on (but not limited to) clinical trials, randomized controlled trials, meta-analyses, scientific guidelines, and core clinical journals. The literature update ths achieved was added to the pre-existing database, covering the time period before and during 2008 (generated for the 2008 International Consultation on Incontinence[1]) that was established according to the same protocol.

Rating of the level of evidence and grade of recommendation was performed according to the Oxford Scale. The committee believes that the Oxford system for categorizing levels of evidence is primarily relevant only for the sections on treatment which follow. While the committee’s opinions will be expressed, where applicable, regarding evidence and conclusions for other areas, including diagnosis, aetiology, and pathophysiology, use of the Oxford system in this context is more open to interpretation.

2. DEFINITION

Bladder Pain Syndrome (BPS) is a clinical diagnosis that relies on symptoms of pain in the bladder and or pelvis and other urinary symptoms like urgency and frequency. Based on the evolving consensus that BPS probably is strongly related to other pain syndromes like Irritable Bowel Syndrome, Fibromyalgia and Chronic Fatigue Syndrome, the European Society for the Study of Bladder Pain Syndrome (ESSIC) published a comprehensive paper on definition and diagnosis of BPS.[2]

BPS was defined as chronic (>6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies. (see **Table 2** in section I.1) The presence of other organ symptoms as well as cognitive, behavioural, emotional, and sexual symptoms should be addressed.

This definition has been broadly accepted although actual wording differs somewhat[3]. Because omitting the name “Interstitial Cystitis” might cause serious problems in different health systems by affecting reimbursement and disability determinations, the name Bladder Pain Syndrome/ Interstitial Cystitis (BPS/IC) could be used in parallel with BPS for the time being. **In this chapter, as in the 2008 Consultation, the term Bladder Pain Syndrome largely replaces the older Interstitial Cystitis term, but the two are essentially interchangeable as there is no accepted definition that clearly delineates the interstitial cystitis syndrome from bladder pain syndrome. The Consultation believes the latter term more appropriately describes the disorder.**

Historically, definitions of IC have moved from a severe inflammatory bladder disease to a condition described primarily by symptoms (**Table 1**) [3].

The International Continence Society [13] (ICS) used the term Painful Bladder Syndrome (PBS) defined as “ the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology”. ICS reserved the diagnosis Interstitial Cystitis (IC) to patients with “typical cystoscopic and histological features”, without further specifying these. It has however been shown,

Table 1: Historical definitions of interstitial cystitis.

1887 Skene [4]: An inflammation that has destroyed the mucous membrane partly or wholly and extended to the muscular parietes.

1915 Hunner [5]: A peculiar form of bladder ulceration whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment in patients with frequency and bladder symptoms (spasms).

1951 Bourque [6] : Patients who suffer chronically from their bladder; and we mean the ones who are distressed, not only periodically but constantly, having to urinate at all moments of the dav and of the night suffering pains every time they void.

1978 Messing and Stamey [7]: Nonspecific and highly subjective symptoms of around-the-clock frequency, urgency, and pain somewhat relieved by voiding when associated with glomerulations upon bladder distention under anesthesia.

1990 Revised NIDDK Criteria: Pain associated with the bladder or urinary urgency, and, glomerulations or Hunner's ulcer on cystoscopy under anesthesia in patients with 9 months or more of symptoms, at least 8 voids per day, 1 void per night, and cystometric bladder capacity less than 350cc [8].

1997 NIDDK Interstitial Cystitis Database Entry Criteria [9]: Unexplained urgency or frequency (7 or more voids per day), OR pelvic pain of at least 6 months duration in the absence of other definable etiologies.

2008 European Society for the Study of Bladder Pain Syndrome (ESSIC)[10]: Chronic (>6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded.

2009 East Asian Guideline [11]: A disease of the urinary bladder diagnosed by 3 conditions: lower urinary tract symptoms, bladder pathology, and exclusion of confusable diseases. The characteristic symptom complex (hypersensitive bladder syndrome) includes bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain.

2011 American Urological Association [12]: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes.

that only a fraction of patients believed by experts to have BPS fulfil this definition [14].

In the remainder of this chapter the condition will be referred to as bladder pain syndrome (BPS). Some of the older literature may be discussed using the original terminology in the interests of clarity. Logically "interstitial cystitis" should include some form of demonstrable inflammation in the bladder wall, while "bladder pain syndrome" should include pain in the region of the bladder. The diagnosis of BPS is based on exclusion of other diseases in the bladder, urethra, and other pelvic organs including the musculoskeletal system. As with other diseases without clear objective diagnostic criteria or pathophysiological explanation, countless theories have been put forward without adding much to the delineation or understanding of the disease.

In practice, patients with symptoms of BPS are screened to exclude other relevant diagnoses or confusable diseases[2], and a focused evaluation is performed at the discretion of the physician or centre. This evaluation might include cystoscopy under local or general anaesthesia, bladder distension with registration of bladder capacity and/or the presence of glomerulations and Hunner's lesion. Bladder wall biopsies might be obtained and evaluated for inflammation, ulcer, fibrosis, mast cells etc. The evaluation might also include urodynamics with registration of bladder capacity, compliance and bladder stability[15]. One view of the relationship of BPS with OAB is graphically depicted in **Figure 1** [16]. The 14% incidence of urodynamic detrusor overactivity in the BPS [17] patients is probably close to what one might expect in the general population if studied urodynamically [18].

In the end, these investigations might prove to be normal and the patients are identified as having BPS as a diagnosis of exclusion. The relevance of urodynamic, cystoscopic and histological findings is limited by a lack of consistency in technique, and it is therefore recommended to use the standardisations described by ESSIC [2].

II. HISTORY/NOMENCLATURE/ TAXONOMY

1. HISTORICAL NOTES

Recent historical reviews confirm that interstitial cystitis was recognized as a pathologic entity during the 19th century.[19,20] In his textbook Practical Observations on Strangulated Hernia and Some Diseases of the Urinary Organs, Joseph Parrish, a Philadelphia surgeon, described 3 problematic cases of recurrent, severe lower urinary tract symptoms in which he made repeated attempts to locate a bladder stone, which was the most common source for these symptoms in early 19th century America. [21] As Teichman et al have convincingly argued,

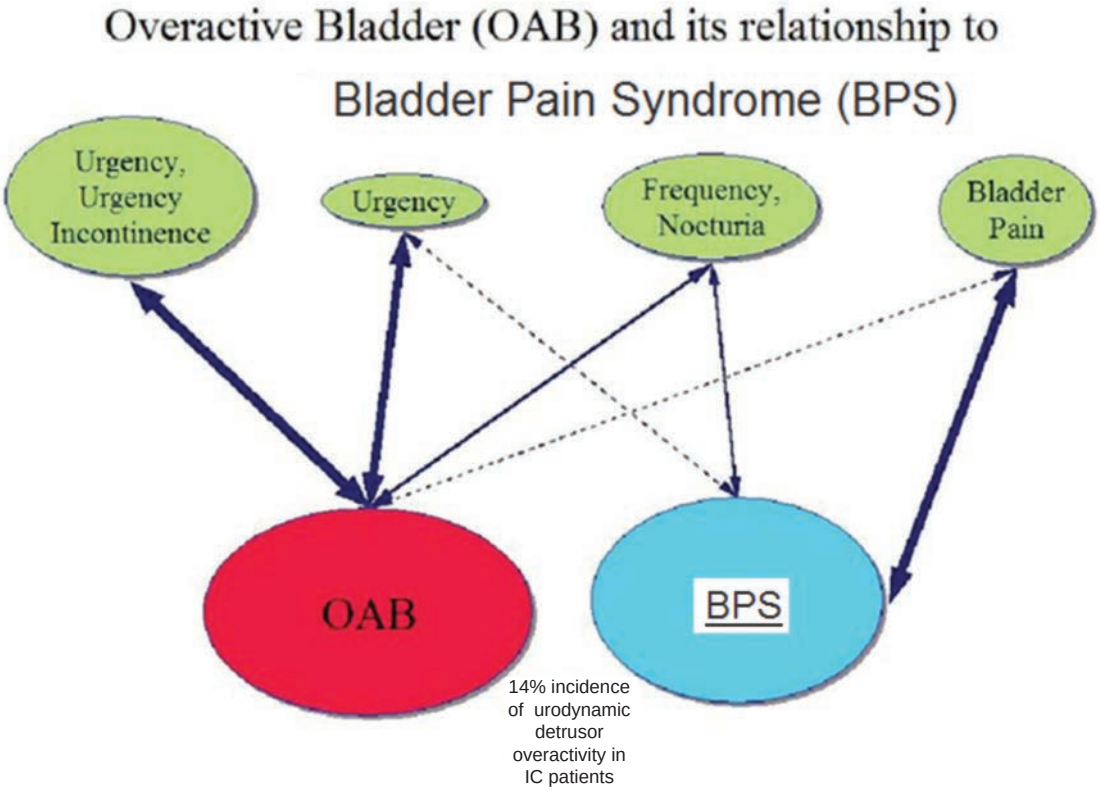


Figure 1: Overactive Bladder (OAB) and its relationship to Bladder Pain Syndrome (BPS). Abrams, P., Hanno, P., and Wein, A.: Neurourol Urodyn, 24: 149, 2005.

these patients displayed all of the clinical hallmarks of IC including chronic frequency, urgency, dysuria and pelvic pain in the absence of demonstrable pathology.[22] Although he used the term repeatedly in his manuscript, Parrish did not elaborate upon the clinical definition of "tic douloureux," likely because contemporaneous physicians would have been familiar with the concept. However, Parrish attributed the term Tic doloreux to his mentor, Dr. Phillip Syng Physick, who had applied it to patients with severe lower urinary tract symptoms with no discernible etiology, with the most common etiology during the 19th century being bladder stones.

A review of archival material from the Philadelphia College of Physicians indicates that by 1808 Physick had developed a concept of bladder inflammation, a "bladder ulcer," that produced lower urinary tract symptoms in the absence of bladder stone.[19] Tic douloureux at its time represented a neurological irritation, most often associated with the trigeminal nerve but applicable to other sensory distributions as well, which produced pain and discomfort in the absence of injury or other specific physical findings. In applying the concept of tic douloureux to bladder sensation Parrish was ascribing the paroxysmal lower urinary tract symptoms occurring in patients to an idiopathic process affecting the nerves of the bladder. This sophisticated concept continues to be a prominent component of modern theories of BPS pathogenesis. Furthermore, Tic douloureux allowed him to formulate a diagnosis for those patients who chronically manifested the symptoms caused by a stone (severe frequency, urgency, dysuria and pelvic pain) but had no stone that could be detected. That is, he considered a neuropathic etiology in the absence of any other tangible causes of bladder pain. Clearly, this experience strongly resonates with the contemporary diagnosis of BPS.

50 years after Parrish's first publication on the condition, Skene used the term interstitial cystitis to describe an inflammation that has "destroyed the mucous membrane partly or wholly and extended to the muscular parietes".[4] Early in the 20th century, at a New England Section meeting of the American Urological Association, Guy Hunner reported on 8 women with a history of suprapubic pain, frequency, nocturia, and urgency lasting an average of 17 years.[5,23] He drew attention to the disease, and the red, bleeding areas he described on the bladder wall came to have the pseudonym "Hunner's ulcer". As Walsh observed, this has proven to be unfortunate.[24] In the early part of the 20th century,

the very best cystoscopes available gave a poorly defined and ill-lit view of the fundus of the bladder. It is not surprising that when Hunner saw red and bleeding areas high on the bladder wall, he thought they were ulcers. For the next 60 years, urologists would look for ulcers and fail to make the diagnosis in their absence. The disease was thought to be a focal, rather than a pancystitis.

Hand authored the first comprehensive review about the disease, reporting 223 cases.[25] Many of his epidemiologic findings have held up to this day. His description of the clinical findings bears repeating. “I have frequently observed that what appeared to be a normal mucosa before and during the first bladder distention showed typical interstitial cystitis on subsequent distension”. He notes, “small, discrete, submucosal hemorrhages, showing variations in form…dot-like bleeding points…little or no restriction to bladder capacity.” He portrays three grades of disease, with grade 3 matching the small-capacity, scarred bladder described by Hunner. Sixty-nine percent of patients were grade 1 and only 13% were grade 3. Walsh later coined the term “glomerulations” to describe the petechial haemorrhages that Hand had described.[24] But it was not until Messing and Stamey discussed the “early diagnosis” of IC that attention turned from looking for an ulcer to make the diagnosis to the concepts that 1) symptoms and glomerulations at the time of bladder distention under anesthesia were the disease hallmarks, and 2) the diagnosis was primarily one of exclusion.[7,24] However, this description was not suitable for defining this disease in a manner that would help physicians make the diagnosis and set up research protocols.

The National Institute of Diabetes, Digestive, and Kidney Disorders (NIDDK) held a major meeting in 1987 with researchers and clinicians from around the world[26]. This ultimately resulted in the **1990 Revised NIDDK Criteria**: Pain associated with the bladder or urinary urgency, **and**, glomerulations or Hunner’s ulcer on cystoscopy under anesthesia in patients with 9 months or more of symptoms, at least 8 voids per day, 1 void per night, and cystometric bladder capacity less than 350cc.[8]

In order to validate the criteria, which were designed not for clinical diagnosis, but rather to ensure that patients enrolled in research trials could be agreed upon to have the disease, a database with broad entry criteria was created. The **1997 NIDDK Interstitial Cystitis Database Entry Criteria**: Unexplained urgency or frequency (7 or more voids per day), **OR** pelvic pain of at least 6 months duration in the absence of other definable etiologies[27] Urgency was not defined in the protocol. Participants were given a 10 point scale, and those who scored 2 or higher on self report satisfied the urgency criteria. The protocol was written in 1992, a time when the definition of “urgency” was not a particularly controversial topic. When a comparison of the NIDDK revised criteria with the database entry criteria was performed, it was apparent that up to 60% of patients clinically believed to have interstitial cystitis by experienced clinicians were being missed when the NIDDK research criteria were used as a definition of the disease. [28] With the demise of the NIDDK criteria as an appropriate clinical definition of the disorder, the last decade became an active one from an international standpoint in terms of wrestling with the issues of nomenclature, taxonomy and diagnosis.[3,29,30]

2. NOMENCLATURE AND TAXONOMY

The literature over the last 170 years has seen numerous changes in description and nomenclature of the disease. The syndrome has variously been referred to as tic doloureux of the bladder, interstitial cystitis, cystitis parenchymatosa, Hunner’s ulcer, panmural ulcerative cystitis, urethral syndrome, and painful bladder syndrome.[4,6,20,22,23,31,32] The term ‘‘interstitial cystitis,’’ which Skene is credited with coining and Hunner for bringing it in to common usage, is a misnomer; in many cases not only is there no interstitial inflammation, but also, histopathologically, there may be no inflammation at all.[33-36] By literally focusing exclusively on the urinary bladder, the term interstitial cystitis furthermore does not do justice to the condition from both the physician’s and the patient’s perspective. The textual exclusiveness ignores the high co-morbidity with various pelvic, extra-pelvic and non-urological symptoms[37] that frequently precede the onset of the bladder condition.[38]

With the formal definition of the term ‘‘painful bladder syndrome’’ by the ICS in 2002, the terminology discussion became an intense international focal point.[13]

- In Kyoto at the ICICJ in March 2003, it was agreed that the term ‘‘interstitial cystitis’’ should be expanded to ‘‘interstitial cystitis/chronic pelvic pain syndrome’’ when pelvic pain is at least of 3 months duration and associated with no obvious treatable condition/pathology[39].

- The European Society for the Study of Interstitial Cystitis (ESSIC) held its first meeting in Copenhagen soon after Kyoto. Nomenclature was discussed, but no decision was reached, as the meeting concentrated on how to evaluate patients for diagnosis[15].

- At the 2003 meeting of the NIDDK titled, ‘‘Research Insights into Interstitial Cystitis,’’ it was concluded that ‘‘interstitial cystitis’’ will inexorably be replaced as a sole name for this syndrome. It will be a gradual process over several years. At the meeting it was referred to as ‘‘interstitial cystitis/painful bladder syndrome’’ in keeping with International Continence Society nomenclature.[40]

- At the 2004 inaugural meeting of the Multinational Interstitial Cystitis Association in Rome, it was

concluded that the syndrome should be referred to as ''painful bladder syndrome/interstitial cystitis'' or ''PBS/IC'' to indicate an intellectual and taxonomical hierarchy within the acronym.[40]

- The International Consultation on Incontinence in 2004, cosponsored by the ICS and Societe Internationale d'Urologie in association with the World Health Organization, included the syndrome as a part of its consultation. The chapter in the report was titled, ''painful bladder syndrome (including interstitial cystitis),'' suggesting that the IC formed an identifiable subset within the broader syndrome. Because such a distinction is difficult to define, within the body of the chapter, co-authored by nine committee members and five consultants from four continents, it was referred to as PBS/ IC (one inclusive entity).[41]

- In June 2006 Abrams and colleagues published an editorial focusing on the nomenclature problem.[42] They noted that: "It is an advantage if the medical term has clear diagnostic features that translate to a known pathophysiologic process so that effective treatment may be given. Unfortunately, the latter is not the case for many of the pain syndromes suffered by patients seen at most pain, gynecological, and urological clinics. For the most part these ''diagnoses'' describe syndromes that do not have recognized standard definitions, yet imply knowledge of a pathophysiologic cause for the symptoms. Unfortunately the terminology used to describe the condition may promote erroneous thinking about treatment on the part of physicians, surgeons and patients. These organ based diagnoses are mysterious, misleading and unhelpful, and can lead to therapies that are misguided or even dangerous." The editorial went on to note that a single pathologic descriptive term (interstitial cystitis) for a spectrum of symptom combinations ill serves patients. The umbrella term ''painful bladder syndrome'' was proposed, with a goal to define and investigate subsets of patients who could be clearly identified within the spectrum of PBS. It would fall within the rubric of chronic pelvic pain syndrome. Sufferers would be identified according to the primary organ that appears to be affected on clinical grounds. Pain not associated with an individual organ would be described in terms of the symptoms.

One can see in this the beginnings of a new paradigm that might be expected to change the emphasis of both clinical and basic science research, and that removes the automatic presumption that the end-organ in the name of the disease should necessarily be the sole or primary target of such research.

•At the major biannual IC research conference in the fall of 2006, held by the National Institute of Diabetes, Digestive, and Kidney Disorders (Frontiers in Painful Bladder Syndrome/Interstitial Cystitis), the ESSIC group was given a block of time in which to present their thoughts and conclusions. Because PBS did not fit into the taxonomy of other pelvic pain syndromes such as urethral or vulvar pain syndromes, and because IC is open to different interpretations, ESSIC suggested that Painful Bladder Syndrome be redesignated as Bladder Pain Syndrome (BPS), followed by a type designation. BPS is indicated by two symbols, the first of which corresponds to cystoscopy with hydrodistention findings (1, 2, or 3, indicating increasing grade of severity) and the second to biopsy (A, B, and C, indicating increasing grade of severity of biopsy findings) (**Table 2**). Although neither cystoscopy with hydrodistention nor bladder biopsy was prescribed as an

Table 2: Cystoscopy with hydrodistension.

		cystoscopy with hydrodistension			
		not done	normal	glomerulations[1]	Hunner's lesion[2]
biopsy	not done	XX	1X	2X	3X
	normal	XA	1A	2A	3A
	inconclusive	XB	1B	2B	3B

[1]cytoscopy. glomerulations grade II-III
[2]with or without glomerulations
[3]histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis

van de Merwe, J. P., Nordling, J., Bouchelouche, P., Bouchelouche, K., Cervigni, M., Daha, L. K. et al.: Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol, 53: 60, 2008

essential part of the evaluation, by categorizing patients as to whether either procedure was done, and if so, the results, it is possible to follow patients with similar findings and study each identified cohort to compare natural history, prognosis, and response to therapy [2].

- As Baranowski et.al. conceived it in early 2008[43], BPS is thus defined as a pain syndrome with a collection of symptoms, the most important of which is pain perceived to be in the bladder. IC is distinguished as an end-organ, visceral-neural pain syndrome, whereas BPS can be considered a pain syndrome that involves the end-organ (bladder) and neuro-visceral (myopathic) mechanisms. In IC, one expects end-organ primary pathology. This is not necessarily the case in the broader BPS.

A didactically very demonstrative way to conceptualize the dawning shift in conception of the condition is with the drawing of a target (**Figure 2**). There may be many causes of chronic pelvic pain. When an aetiology cannot be determined, it is characterized as pelvic pain syndrome. To the extent that it can be distinguished as urologic, gynecologic, dermatologic, and the like, it is further categorized by organ system. A urologic pain syndrome can sometimes be further differentiated on the site of perceived pain. Bladder, prostate, testicular, and epididymal pain syndromes follow. Finally, types of BPS can be further defined as IC, or simply categorized by ESSIC criteria. Patient groups have expressed their concerns with regard to any nomenclature change that potentially drops the term ''interstitial cystitis'' because the U.S. Social Security Administration and private insurances recognize IC but not the term BPS, and benefits potentially could be adversely affected. Whether the term "interstitial cystitis", as difficult as it is to define and as potentially misleading as it is with regard to aetiology and end-organ involvement, should be maintained, is a subject of ongoing controversy.

Taxonomy and nomenclature in Japan, Korea, and Taiwan use the umbrella term of "frequency/urgency syndrome" characterized by frequency (frequent voiding) and urgency (strong desire to void). It is an inclusive term incorporating overactive bladder syndrome (OAB), hypersensitive bladder syndrome (HSB), and other conditions that are associated with frequency and urgency. Urgency in OAB is characterized by sudden onset and/or fear of leakage, while urgency in HSB is of a persistent nature and is associated with the fear of pain. OAB-wet is a subgroup of OAB. Painful bladder syndrome (PBS) is a subgroup of HSB with pain. Interstitial cystitis is one of the diseases manifest by frequency/urgency and overlaps with HSB and PBS.[11,44,45] (**Figure 3**).

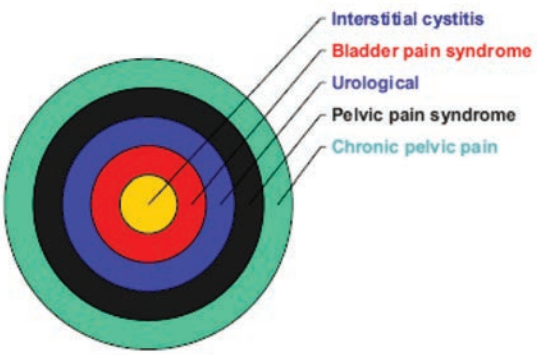


Figure 2: Conceptual Diagram of Pelvic Pain.

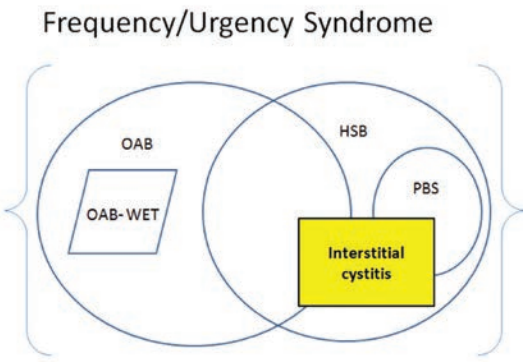


Figure 3: East Asian View of Taxonomy adapted from Homma[44] (see text for explanation).

The American Urological Association refers to the syndrome under consideration as "interstitial cystitis/bladder pain syndrome" (IC/BPS) and considers the terms synonymous [12].

The International Association for the Study of Pain (IASP) has dropped the terms interstitial cystitis, painful bladder syndrome, and PBS/IC or BPS/IC and now recognizes the term "bladder pain syndrome" as the occurrence of persistent or recurrent pain perceived in the urinary bladder region accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. www.iasp-pain.org The reader is referred to the IASP website for an in depth discussion of pain taxonomy. This work was spearheaded by Dr. Andrew Baranowski and the Pain of Urogenital Origin (PUGO) group that is associated with IASP and contributed to advancement of nomenclature and taxonomy over the last 5 years [42].

The Consultation will continue to refer to the symptom complex as "bladder pain syndrome".

III. EPIDEMIOLOGY

Since the clinical diagnosis of BPS remains controversial, epidemiology studies of BPS have been

problematic [46]. The lack of an accepted definition, the absence of a validated diagnostic marker, and questions regarding etiology and pathophysiology make much of the literature difficult to interpret. Overlapping patterns of bladder pain, lower urinary tract symptoms and pelvic pain are common and present challenges for clinical practice and research [47]. The other major difficulty in evaluating various prevalence trials is that some are based on unverified self report, others by physician diagnoses (with or without some type of verification) or by identification of BPS symptoms (with or without exclusion of other confusable conditions). This confusion becomes apparent when one looks at the variation in prevalence reports in the United States and around the world. These range from 4.5 per 100,000 females in Japan [48], to a questionnaire based study that suggests a figure in 20,000 per 100,000 in US women [49]. Studies, however, have consistently shown that bladder pain symptoms are more common than suggested by coded physician diagnoses [50]. Therefore it is important to realize when examining epidemiological data in BPS, that the prevalence of this enigmatic condition can be estimated from patient self-reports, physician diagnoses and/or symptom based surveys, all of which will give a different figure. A Conceptual diagram of the various manifestations of pelvic pain illustrates the problems in determining prevalence data. (**Figure 2**)

1. EARLY EPIDEMIOLOGICAL STUDIES:

One of the first population-based studies [51] included "almost all the patients with interstitial cystitis in the city of Helsinki". This superb, brief report from Finland surveyed all diagnosed cases in a population approaching 1 million. The prevalence of the disease in women was 18.1 per 100,000. The joint prevalence in both sexes was 10.6 cases per 100,000. Ten per cent of cases were in men.

Another early population study, this in the United States, first demonstrated the potential extent of what had been considered a very rare disease [52]. The following population groups were surveyed: 1) random survey of 127 board-certified urologists 2) 64 IC patients selected by the surveyed urologists and divided among the last patient with IC seen, and the last patient with IC diagnosed 3) 904 female patients belonging to the Interstitial Cystitis Association and 4) random phone survey of 119 persons from the US population. This 1987 study reached the following conclusions (interestingly, most of these conclusions have stood the test of time and many further epidemiological studies described later in this section)::

1. 43,500 to 90,000 diagnosed cases of IC in the USA (twice the Finnish prevalence)
2. Up to a five-fold increase in IC prevalence if all patients with painful bladder and sterile urine had been given the diagnosis, yielding up to half million possible cases in the USA
3. Median age of onset 40 years
4. Late deterioration in symptoms unusual
5. 50% temporary spontaneous remission rate, mean duration 8 months
6. 10 times higher incidence of childhood bladder problems in IC patients vs controls
7. 2 times the incidence of a history of urinary tract infection vs. controls
8. Lower quality of life than dialysis patients
9. Costs including lost economic production in 1987 of $427 million.

2. PATIENT SELF REPORT SURVEYS:

As mentioned earlier, the prevalence of BPS can be estimated from patient self-reports, physician diagnoses and/or symptom based surveys. Jones and Nyberg [53] obtained their data from unverified self-report of a previous diagnosis of IC in the 1989 National Household Interview Survey. The survey estimated an overall prevalence of 500 per 100,00 populations (0.5% of the population), or >1,000,000 people in the United States with a self-reported diagnosis of IC. For women this prevalence figure was 865 per 100,000. As part of the third National Health and Nutrition Examination Survey (NHANES III), patients were answered yes to two questions (pain in the bladder/frequent urination and a diagnosis of IC or PBS) and the figures were remarkably similar with an estimated prevalence of 470 per 100,000 (850 per 100,000 women) [54]. These numbers must be viewed with caution because of inaccurate patient recall or confusion with other pain or bladder related conditions. However these patient-reported diagnoses figures certainly suggest that BPS is a common occurrence.

3. PHYSICIAN DIAGNOSES STUDIES

Estimations of prevalence based on physicians' diagnoses may be thought to produce more accurate estimates, and while they do provide different figures, these are in part based on the local or geographic diagnostic criteria employed. Bade et al [55] used a physician questionnaire-based survey in the Netherlands yielding an overall prevalence of 8-16 per 100,000 females, with diagnosis heavily dependent on pathology and presence of mast cells. The Nurses Health Study I and II [56] showed a prevalence of IC between 52 and 67 per 100,000 in the USA. This report was based on self-reports with validation using data from medical records. The prevalence of a physician based diagnosis of BPS in men and women in a managed care population in the US Northwest[57] was 197 per 100,00 women and 41 per 100,000 men. However these rates decreased to 99 per 100,000 women and 19 per 100,000 men

if the definition of the condition was limited to individuals who had undergone cystoscopy. Nickel, et al [58] performed a prospective practice audit in outpatient urology practice populations of 65 urologists and noted that the prevalence of IC and IC diagnosis in urology outpatient practice, confirmed by both investigation and symptom scoring, was determined to be 2.8%. This of course does not represent in any way the burden of this condition in the general population, but rather reflects the national referral and practice traditions. There are other limitations using physician diagnoses to determine prevalence. Studies that utilize physician diagnoses to define the presence of BPS will likely underestimate the true prevalence, primarily because they do not identify patients with undiagnosed disease or they may not assign a diagnosis when the symptoms are present (reluctance to label a patient with the condition or alternatively are not familiar with diagnosing it).

4. SYMPTOM BASED SURVEYS

Another and possibly more sensitive method to examine prevalence and incidence of BPS is to assess the presence of symptoms that suggest BPS. A follow-up study utilizing the Nurses' Health Study (NHS) cohort) [59] used a mailed questionnaire followed by a detailed supplementary questionnaire if the participant responded "yes" to a bladder or pelvic pain question. They observed that the prevalence of PBS symptoms was 1.7% in women younger than 65 years and increased progressively to 4.0% in women aged 80 years or older. This study suggested that the prevalence of BPS increases with age. Warren, et al [60] combined a mail-in survey with randomly selected telephone surveys to determine the prevalence of BPS amongst first degree relatives in comparison to that of the general population. They concluded that adult female first degree relatives of patients with BPS may have a prevalence of BPS 17 times that found in the general population. This suggests but does not prove a genetic susceptibility to BPS. The Boston Area Community Health (BACH) 0Survey [61], a population based cross-sectional survey of individuals in the Boston area which included an in person interview, determined the prevalence of painful bladder symptoms to be 0.83% to 2.71% in women and 0.25% to 1.22% in men depending of the definition used.

The O'Leary Sant (OLS) and the Pelvic Pain and Urgency/Frequency (PUF) questionnaires were compared by Rosenberg and Hazard [62] in the same general practice population of 1218 patients. The prevalence of BPS with the OLS was determined to be 0.57%, with the PUF the prevalence was determined to be 12.6%. Leppilahti and colleagues [63,64] estimated the prevalence of BPS in the general Population of Finland using a rather robust definition based on the OLS to be 0.68%. However, when a sample of those women was examined by one of the urologists, the more accurate prevalence was 0.3%.

Clemens et al employed [65] 3 different definitions of BPS related symptoms. The first included only self reported pelvic pain with voiding symptoms. The second included increasing pain with bladder filling and relief with urination. The third included a score of 12 or more on the OLS, including 2 episodes of nocturia and a pain score of 2 or greater. The prevalence estimates based on these definitions were 11,200 per 100,00 women and 6,200 per 100,000 men for definition 1; 3,300 per 100,00 women and 1,400 per 100,00 men for definition 2; and 6,200 per 100,000 women and 2,300 per 100,00 men for definition 3. Using a similar methodology, [66] concluded that the prevalence of BPS-like symptoms in South Korean women appear to be lower than in Europe [67] and the United States, similar to Japan and higher than in China [68]. It is conceivable that the acknowledgement by individual patients of these specific IC/BPS symptoms may be influence by cultural differences.

The most comprehensive and probably most accurate estimation of the prevalence of BPS symptoms involved population based symptom prevalence estimate using 2 validated case definitions to identify bladder pain syndrome/interstitial cystitis in 131,691 adult females [69]. Based on a high sensitivity definition, 6.5% (6,500 per 100,000) of women met the symptoms criteria, while 2.7% (2,700 per 100,000) of women met the criteria for a high specificity definition. These percentages translated into 3.3 to 7.9 million US women over 18 years of age with symptoms of bladder pain and/or interstitial cystitis. But only 9.7% of these identified women reported being assigned a bladder pain syndrome or interstitial cystitis diagnosis. A further study compared 3,397 women identified in this RAND Interstitial Cystitis Epidemiology (RICE) survey [46]with urinary symptoms consistent with a diagnosis of IC/BPS to 277 women with an actual BPS diagnosis recruited from specialist practices in the USA [70]. The two cohorts showed remarkably similar demographics, symptoms and quality of life measures, confirming that BPS is a very prevalent condition that is very likely under diagnosed and undertreated in the USA.

Conclusion:

Based on these studies, it is impossible to determine an accurate estimation of the prevalence of BPS, but a review of studies done in the US shows that this is a very prevalent medical condition (**Figure 4**). It is clear that the most inaccurate prevalence figures are derived from patients self-reported recollection, while the prevalence of BPS symptom complexes are more common than those based on physician diagnoses. It is apparent that there has been no standardized method of determining the prevalence of BPS, with wide variation of estimates in the same study employing different definitions or criteria for identifying the condition. Many factors including bias, cultural differences, methodology,

geographic variations in diagnostic criteria and/or possibly real differences in different populations lead to further variations between countries.

Recommendation:

A reasonable prevalence estimation for patients diagnosed with BPS would be about 100-200 per 100,000 women with a male prevalence of 10% to 20% of the female estimate. The prevalence of women and men with symptoms suggestive of BPS could be as much as 10 to even a 100 times more. (**Figure 4**) Level of **Evidence: 1 Grade of Recommendation: A**

5. INCIDENCE:

Only a few estimates of Incidence have been reported. The annual incidence of new female cases in Oravisto et al, 1975 study[51] was 1.2 per 100,000. The overall age- and sex-adjusted incidence rate of physician assigned diagnoses of BPS in Olmstead county [73] was 1.1 per 100,00 per year (1.6 per 100,00 per year for women and 0.6 per 100,000 for men. Another review of physicians' diagnoses identified a much higher yearly incidence of 21 per 100,000 women and 4 per 100,000 men [57]. A physician-coded diagnosis supplemented with chart review of the Kaiser Permanente database [74] suggested a BPS incidence rate of 15 per 100,000 women per year. The mean average age of patients was 51 years. With such a wide variation between two similar studies in the same country, it is evident that we really do not have an accurate estimation of BPS incidence.

Recommendation:

The available data suggests that the incidence of BPS diagnoses is somewhere between 1 and 15 per 100,000 per year. This does not include the women who have developed symptoms but have not been diagnosed with the condition.

Level of Evidence: 1 Grade of Recommendation: A

6. OTHER CONSIDERATIONS

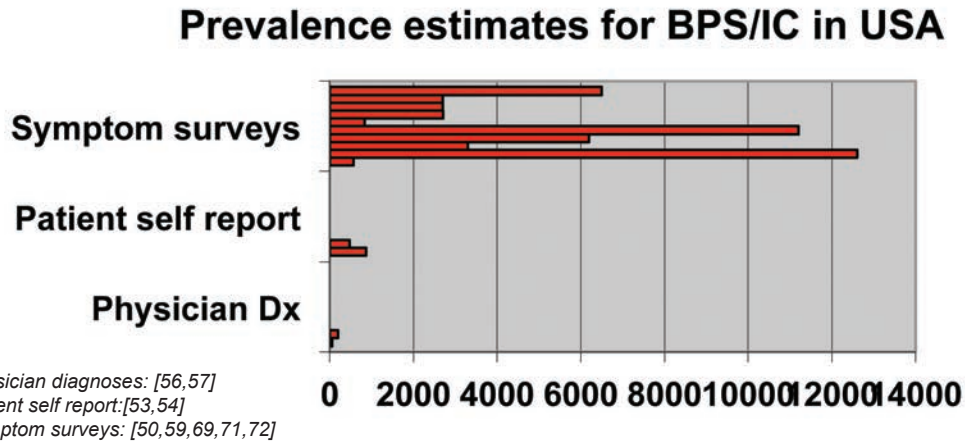
a) Children

Geist and Antolak [75] reviewed and added to reports of disease occurring in childhood. A childhood presentation of BPS is extremely rare and must be differentiated from the much more common and benign-behaving condition variously called the urinary frequency syndrome of childhood or dysfunctional elimination syndrome, a self-limited condition of unknown etiology. Nevertheless, there is a small cohort of children with chronic symptoms of bladder pain, urinary frequency, and sensory urgency in the absence of infection who have been evaluated with urodynamics, cystoscopy, and bladder distention and have findings consistent with the diagnosis of BPS. In Close and colleagues' review [76] of 20 such children, the median age of onset was younger than 5 years, and the vast majority of patients had long-term remissions with bladder distention. Rakow et al [77] assessed 28 women aged 13 to 25 with chronic pelvic pain syndrome and confirmed that 39% had a diagnosis of IC while a further 25% had both IC and endometriosis. The relationship between dysfunctional voiding and bowel symptoms in early life was suggested in a mail based questionnaire study in 215 BPS patients and 823 controls [78]. Another study examining early childhood events [79] showed that early childhood trauma, in particular sexual trauma was more common in IC/BPS patients than asymptomatic control subjects. While not proven in these studies, it may be possible to link early childhood events to the eventual development of BPS symptoms.

Recommendation:

C/BPS should be evaluated in young women with complaining of chronic pelvic pain.

Level of Evidence: 1 Grade of Recommendation: A



Physician diagnoses: [56,57]
Patient self report:[53,54]
Symptom surveys: [50,59,69,71,72]

Figure 4: Prevelence estimates for BPS/IC in USA

b) Men

Most studies show a female to male preponderance of 5:1 or greater [41,57,80]. In the absence of a validated marker, it is often difficult to distinguish BPS from the chronic pelvic pain syndrome (nonbacterial prostatitis, prostatodynia) that affects males [81,82], and the percentage of men with BPS may actually be higher [83,84]. Men tend to be diagnosed at an older age and have a higher percentage of Hunner's lesion in the case series reported.

Recommendation:

The Male to Female ratio of BPS cases is 1:5-10

Level of Evidence: 1 Grade of Recommendation: A

c) Overlapping Non bladder syndromes

Observations have shown that BPS patients are more likely than controls to have syndromes manifesting symptoms beyond the bladder and even the pelvis. In 1997, Clauw, et al [37] reported on the symptom overlap between two cohorts of patients, one with fibromyalgia and one with BPS. In the same year an analysis of a survey by Alagiri, et al [85] of over 6,700 persons who had a physician diagnosis of Interstitial Cystitis reported that individuals with IC were 100 times more likely to have inflammatory bowel disease, and that allergies, irritable bowel syndrome, sensitive skin, and fibromyalgia also have an increased association with IC. The presence of non-bladder syndromes (NBSs) and BPS has further complicated the interpretation of epidemiological studies. Investigators have subsequently compared BPS patients to controls on multiple NBSs. Wu et al. [86] compared 749 cases with BPS them to 1498 randomly selected and matched controls. Significantly more cases had FM, IBS, chronic pelvic pain (CPP), endometriosis, depression, anxiety and vulvodynia. Clemens et al.[87] compared 239 women with ICD-coded BPS to 717 matched controls and showed that cases significantly exceeded controls in myalgias, gastrointestinal symptoms, gynecologic pain, headache, back disorders, depression, and anxiety. Warren et al. [88] demonstrated that significantly more BPS cases than matched controls had 11 antecedent syndromes: FM, CFS, IBS, sicca syndrome, Chronic pelvic pain, migraine, allergies, asthma, depression, panic disorder, and vulvodynia. Nickel et al. [89] found significantly higher prevalence of self-reported FM, CFS, IBS, migraine and tension headaches, vulvodynia, temporomandibular disorder and low back pain in 207 female BPS cases than in 117 controls as well as significantly more with depression and anxiety [90] in a study in several urology practices in 3 continents. A recent review confirmed that fibromyalgia (FM), chronic fatigue syndrome (CFS), and and irritable bowel syndrome (IBS) were associated with IC/BPS [91]. The etiological and epidemiological questions that remain unanswered is how are these NBSs associated with BPS, do these NBSs precede or follow IC/BPS and do multiple NBSs increase the risk of BPS. Warren and colleagues [92] have introduced a number of hypotheses, however the studies to validate these have not yet been done.

One other NBS that is sometime neglected or forgotten in these epidemiological associations is the association of BPS with sexual dysfunction. Multiple studies have shown that women with BPS diagnoses or symptoms experience very high levels of sexual dysfunction [93-96].

Recommendation:

Overlapping Non-bladder syndromes are common in patients with a diagnosis of BPS.

Level of Evidence: 1 Grade of Recommendation: A

d) Progression:

The disease onset is generally described as subacute rather than insidious, and full development of the classic symptom complex occurs over a relatively short time. It appears that BPS does progress continuously, but usually reaches its final stage rapidly (within 5 years) [97] and then continues without significant change in symptomatology. Subsequent major deterioration is unusual[51]. The duration of symptoms before diagnosis was 3-5 years in the Finnish study [51] while a very early American study quoted 7-12 years [25]. The Interstitial Cystitis Database Cohort (ICDB) of patients has been carefully studied, and the findings seem to bear out those of other epidemiologic surveys [98]. Patterns of change in symptoms with time suggest regression to the mean and an intervention effect associated with the increased follow-up and care of cohort participants. Although all symptoms fluctuated, there was no evidence of significant long-term change in overall disease severity. The data suggest that BPS is a chronic disease and no current treatments have a significant impact on symptoms over time in the majority of patients. There is some data [89] to suggest that some patients undergo a phenotypic progression over time from a purely organ specific (eg. bladder) condition to a regional pain syndrome (eg. IBS, vulvodynia) to a more generalized pain syndrome (eg. FM, CFS). Long term longitudinal studies examining progression issues in BPS are lacking.

Recommendation:

Epidemiological data required to describe progression patterns of BPS is lacking.

Level of Evidence: 1 Grade of Recommendation: A

IV. ETIOLOGY

The etiology of BPS is still an enigma. Quite often hypotheses abound with sparse evidence to support

them and some quickly are found to be untrue. For example disturbed nitric oxide metabolism has been proposed to contribute to BPS, but later controlled studies using L-arginine therapy did not show therapeutic effect and failed to support the hypothesis. It is highly possible that BPS is induced by a variety of causes. Symptoms of urinary frequency and bladder pain are likely the final common presentation of bladder injury resulting from single or a combination of etiologies.

1. MAST CELL ACTIVATION

Mast cells are thought to have a role in the etiology and/or pathogenesis of BPS. They are multifunctional immune cells that contain highly potent inflammatory mediators such as histamine, leukotrienes, serotonins, and cytokines.[99] These cells are the repositories of many potent inflammatory factors. Many of the symptoms and findings in ulcerative BPS such as pain, frequency, oedema, fibrosis, and the production of new vessels in the lamina propria, could possibly be ascribed to the release of mast cell-derived factors. Hence, the mast cell-IgE system and its interaction with other inflammatory cells and the nervous system[100] seems to be of importance when it comes to pathogenesis. There is a ten-fold increase in mast cell count in bladder tissue from patients with ulcerative BPS as compared to controls. In non-ulcer BPS, however, the mast cell count is normal or only slightly increased. [99,101,102]

Other mechanisms have also been put forward. Bouchelouche[103] compared the urinary excretion of leukotrienes E4 and eosinophil protein X in patients in BPS and noted detrusor mastocytosis and both increased urinary leukotrienes E4 and eosinophil protein X.

Level of Evidence: 1 - Grade of Recommendation: A

2. INCREASED PERMEABILITY OF THE UROTHELIUM DUE TO UROTHELIAL DYSFUNCTION/GAG-LAYER DEFECTS

The bladder urothelium plays a key barrier to keep low and high molecular weight solutes in the urine from leaking into bladder interstitium. The barrier includes a dense layer of glycosaminoglycans on the luminal surface and intercellular junctions. Intracellular junctions consist of tight junction, adherence junction, demosome and gap junction in the order of location from the luminal layer to the basal layer. Studies have shown impaired function of intercellular junctions of bladder urothelium of BPS patients. Zhang et al demonstrated significantly increased paracellular permeability, decreased expression of the tight junction proteins ZO-1 and occludin, and increased expression of the adhesion protein E-cadherin from patients with BPS.[104] Shie et al further showed that in the urothelium of the BPS bladder a reduced E-cadherin expression was associated with a higher level of apoptosis.[105] A defect in the glycosaminoglycan (GAG) layer has been proposed by Parsons and co-workers.[106] With such a defect the sub-mucosal nerve filaments might become accessible to noxious substances in the urine and this might explain bladder pain and urinary frequency. In ulcerative BPS there is granulation tissue indicating a reparative process following repeated disruption of the mucosa.[107] Widened tight junctions and increased permeability have been demonstrated by scanning electron microscopy and other techniques.[108,109]

A study by Parsons et al[110] has shown that Tamm-Horsfall protein is quantitatively different in BPS patients as compared to controls. Tamm-Horsfall protein is synthesized in the kidney and excreted into the urine. It has been suggested to have a role in immune defense and in preventing damage to the urothelial cells by injurious urinary constituents.

Level of Evidence: 2 - Grade of Recommendation: B

3. INHIBITION OF UROTHELIAL BLADDER CELL PROLIFERATION

One explanation of the bladder epithelial dysfunction might be the fact that the cells produce an inhibitor of heparin-binding epidermal growth factor-like growth factor in BPS.[111] It was shown that explanted urothelial cells from BPS patients differ from controls not only as to production of epithelial growth factors but also in the rate of proliferation and the production of an antiproliferative factor (APF). Keay and co-workers[112] studied gene expression patterns in normal bladder urothelial cells treated with APF and with mock APF as compared to patterns expressed by BPS urothelial cells. The results indicate that the mechanism of APF inhibition of urothelial cells may involve both down-regulation of genes that stimulate cell proliferation along with up-regulation of genes that inhibit cell growth. The same group of researchers has indicated that APF seems to be specifically elevated in the urine of patients with BPS but not in normals or patients with confusable diseases. These findings might open up new avenues for identification and development of urine markers for BPS.[113] There has not yet been confirmation of the importance of antiproliferative factor by other laboratories.

Level of Evidence:2 - Grade of Recommendation: B

4. AUTOIMMUNE MECHANISMS

There are numerous reports on autoantibodies in patients with BPS.[114-117] The precise identity of these of autoantibodies has yet to be determined. Some of the common clinical and histopathological characteristics present in BPS patients show certain similarities with other known autoimmune disturbances. Studies on autoantibodies in BPS have shown that these mainly consist of antinuclear antibodies[116] and these findings are in turn similar to the autoantibody profiles in some systemic diseases like Sjögren syndrome, which is known to be of

autoimmune origin.[118-120] Only a portion of BPS patients have auto-antibodies. It has been proposed that the presence of auto-antibodies in these patients could be a reflection of disease severity.[121]

Vascular immunopathology with immune deposits in the bladder wall was found by Mattila.[122] Further studies also suggest activation of complement.[123] By means of immunophenotyping and flow cytometric analyses of the bladder mucosa and peripheral blood, differences between ulcerative and non-ulcer BPS patients have been demonstrated. In the former group intense T-cell infiltrates and B-cell nodules were seen, compared to far less T-cell infiltrates in non-ulcer BPS.[124] Involvement of the immune system is one feature found in some individuals with BPS, but findings are conflicting and have not been helpful in explaining the etiology. The lack of thorough descriptions of patients in many published studies has made classification and comparison between series impossible.

Level of Evidence: 2 - Grade of Recommendation: C

5. INFECTION

No microorganism has ever been revealed as the cause of BPS. Lynnes and coworkers did not find any evidence of recent or remote Gram negative or Gram positive infections in patients with BPS, nor did they find increased urinary IgA and IgG elevation.[125] This makes infection by an untested organism unlikely. Warren et al[126] in a case control study of women with recent onset of BPS symptoms, reported that documented evidence of UTI at symptom onset was found in only a minority of patients. Polymerase chain reaction techniques to amplify bacterial 16S rRNA genes that would be present if there were bacteria in bladder tissue or urine in BPS patients despite negative cultures have been without success.[127] Contrary to what was demonstrated for chronic gastritis, there is no evidence for helicobacter in BPS patients.[128] However, Zhang et al showed that a high prevalence (11 in 27 patients) of nanobacteria (NB) was observed in female BPS patients, and anti-NB treatment effectively improved the symptoms, suggesting that some BPS might be caused by nanobacteria.[129] Nevertheless, the possibility of a microbial contribution to the etiology of BPS remains an open question.

Level of Evidence: 1 - Grade of Recommendation: C

6. NEUROBIOLOGY/PELVIC CROSS-TALK

Several authors have described autonomic nerve changes[130-132], but the findings are far from uniform. An increase of sympathetic innervation and activation of purinergic neurotransmission has been reported. The S-100 family of proteins appear in Schwann cells of the peripheral nervous system.[133,134] Decreased levels of S-100 protein in the non-ulcer group as compared to controls has been found[135], which is consistent with a decreased nerve content in patients with non-ulcer BPS, a finding conflicting with the results of Hohenfellner [131] who used polyclonal antihuman protein gene product 9.5 antibody and found the overall nerve content increased in BPS patients as compared to controls. However, their study did not include subtyping of the disease into ulcerative and non-ulcer type. A distinctive utrastructural appearance of specimens from patients with non-ulcer BPS prompted Elbadawi and Light to propose neurogenic inflammation as a trigger to a cascade of events taking place in this disease.[136] In this context it should be noted that afferent nerves release transmitters like substance P which could activate immune cells, or vasoactive intestinal polypeptide. These events may constitute a link to the immune cell system and promote a decrease of lymphocyte proliferation.

A prominent increase of tyrosine hydroxylase immunoreactivity in bladder tissue of BPS patients, as compared to controls, has been described.[137] This can presumably be interpreted as a sign of generally increased sympathetic outflow. This lends support to the notion of a neurogenic aetiology and or pathogenesis.

Malykhina and others[138-142] have demonstrated in innovative animal studies that there is a bidirectional neural cross-sensitization of the colon and lower urinary tract. Acute colitis sensitized lumbosacral spinal neurons receiving input from the urinary bladder result in spinal neuronal hyperexcitabiity that may be involved in central cross-organ sensitization of visceral nociception between the colon and urinary bladder. This provides information which not only supports a neurogenic etiology but also may account for the substantial overlap of BPS with other chronic pelvic pain disorders, especially the inflammatory bowel disorders.[85] Rudick and Colleagues have shown in a murine model organ cross talk in pelvic pain and modulation of pain responses by visceral inputs distinct from the inflamed site.[143]

Level of Evidence: 2 - Grade of Recommendation: B

7. TOXIC AGENTS

There are a few publications which have suggested that toxic substances in the urine may cause injury to the bladder resulting in symptoms consistent with BPS. One published hypothesis is that heat labile, cationic urine components of low molecular weight may exert a cytotoxic effect.[144] Another group of investigators has suggested that defective constituent cytokine production may decrease mucosal defense to toxic agents.[145]

Level of Evidence: 3 - Grade of Recommendation: D

8. HYPOXIA

Decreased microvascular density has been reported to be a feature of bladders from some individuals with BPS.[146] One group of investigators

has reported that bladder perfusion decreased with bladder distension in some BPS patients compared to the opposite effect in control subjects.[147] The hypoxic hypothesis is further supported a report by Lee et al, who found an increased expression of hypoxia-inducible factor-1(HIF-1) alpha in bladder tissue obtained from BPS patients.[148] However, it is still unknown why the BPS bladders would become hypoxic.

Level of Evidence: 4 - Grade of Recommendation: D

9. THE ROLE OF GENETICS IN BPS

Warren et al[149] report findings from a small cohort of twins which demonstrated a greater concordance of BPS among monozygotic that among dizygotic twins. A later study by the same research group[60] suggested that adult female first-degree relatives of patients with BPS may have a prevalence of IC 17 times that found in the general population. This coupled with the previously reported twin data suggests, but does not prove, a genetic component adds to the susceptibility for BPS. Another study on more than 25,000 twins, Altman et al found that in female twins genetic factors contributed less than one-third of the total variation in susceptibility to BPS, suggesting that there could be a genetic susceptibility to BPS, although environmental factors might also be substantial in the development of BPS. [150]

The report by Weissman et al[151] of the increased frequency of BPS in patients and their first degree relatives with panic disorder and other seemingly disparate disorders, has suggested that there is a familial syndrome consisting of BPS and other disorders of possible autonomic or neuromuscular dysfunction. More recent studies by the same group[152] from a case control study, suggested that this syndrome might include other anxiety disorders as well, and that families with and without this collection of symptoms were genetically distinguishable on chromosome 13.

Level of Evidence: 1 - Grade of Recommendation: B

10 . CONCLUSIONS:

There have been no significant conclusive advances made in understanding either the etiology or pathogenesis of BPS. It is now believed that the etiology of BPS is more complex than has been previously envisioned.[37,85,87,153-155] The consideration of BPS as a part of a generalized somatic disorder should open new pathways to the study of BPS. Investigators should continue to explore central neurological mechanisms of pathogenesis, as well as genetic/familial, immunological and infectious etiologies of this puzzling, complex disorder.

An algorithm that attempts to illustrate an etiologic schema is presented (**Figure 5**).

V. PATHOLOGY

One can have pathology consistent with the diagnosis of BPS, but there is no histology pathognomonic of this syndrome. The role of histopathology in the diagnosis of BPS is primarily one of excluding other possible diagnoses. One must rule out carcinoma and carcinoma-in-situ, eosinophilic cystitis, tuberculous cystitis, as well as any other entities with a specific tissue diagnosis[107,156,157].

Level of Evidence: 1 Grade of Recommendation: A

While earlier reports described a chronic, edematous pancystitis with mast cell infiltration, submucosal ulcerations and involvement of the bladder wall and chronic lymphocytic infiltrate[158,159], these were cases culled from patients with severe disease and not representative of the majority of cases currently diagnosed. The pathologic findings in BPS are not consistent. There has been a great variation in the reported histologic appearance of biopsies from BPS patients, and even variation among biopsies taken from the same patients over time[26].

Lepinard and colleagues[160] reported a pancystitis affecting the 3 layers of bladder wall. In nonulcerative disease the vesical wall was never normal, epithelium being thinned and muscle being affected. Johansson and Fall[107] looked at 64 patients with ulcerative disease and 44 with nonulcerative IC. The former group had mucosal ulceration and hemorrhage, granulation tissue, intense inflammatory infiltrate, elevated mast cell counts and perineural infiltrates. The nonulcer group, despite the same severe symptoms, had a relatively unaltered mucosa with a sparse inflammatory response, the main feature being multiple, small, mucosal ruptures and suburothelial hemorrhages that were noted in a high proportion of patients. As these specimens were almost all taken immediately after hydrodistention, how much of the admittedly minimal findings in the nonulcer group were purely iatrogenic is a matter of speculation.

One can see completely normal biopsies in the nonulcerative BPS group[161]. Transition from nonulcerative to ulcerative BPS is a rare event[101], and pathologically the two types of IC may be completely separate entities. While mast cells are more commonly seen in the detrusor in ulcerative BPS[162], they are also common in patients with idiopathic bladder instability[163]. Mastocytosis in BPS is best documented by tryptase immunocytochemical staining[164]. Larsen and colleagues recommend taking biopsies from the detrusor of patients with suspected BPS and examining them with tryptase-stained 3 micron thick sections, with every seventh section used for quantification. They consider 27 mast cells/mm2 indicative of mastocytosis.[165] Despite attempts to develop a diagnostic algorithm based on the detrusor to mucosa mast cell ratio and

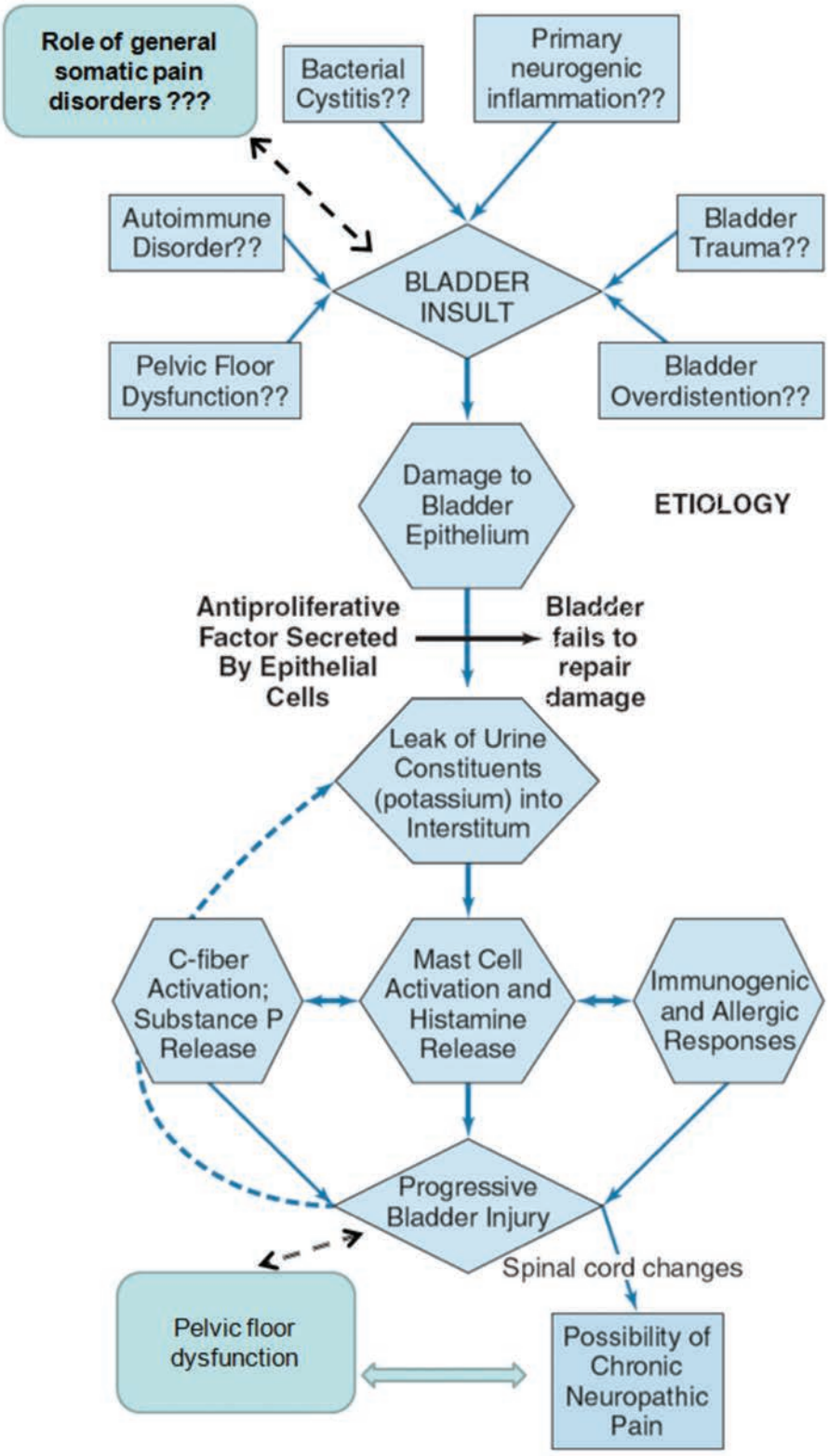


Figure 5: Theories of Etiology.

nerve fiber proliferation[100], mast cell counts per se have no place in the differential diagnosis of this clinical syndrome.

Mast cells could be valuable in clinical phenotyping, but as yet that is unproven. Mast cells trigger inflammation that is associated with local pain, but the mechanisms mediating pain are unclear. In a murine model of neurogenic cystitis, Rudick and colleagues[166] demonstrated that mast cells promote cystitis pain and bladder pathophysiology through the separable actions of histamine and tumor necrosis factor respectively. Therefore, pain is independent of pathology and inflammation, and histamine receptors may represent direct therapeutic targets for the pain of BPS and other chronic pain conditions.

Lynes and coworkers[35] concluded that biopsy specimens are often not helpful in confirming the diagnosis. Although BPS patients in his study had a higher incidence and degree of denuded epithelium, ulceration, and submucosal inflammation, none of these findings was pathognomonic. In addition, these "typical" findings occurred only in BPS patients with pyuria or small bladder capacity. Epithelial and basement membrane thickness, submucosal edema, vascular ectasia, fibrosis, and detrusor muscle inflammation and fibrosis were not significantly different in the BPS and control patients.

Attempts to definitively diagnose BPS by electron microscopy have also been unsuccessful. Collan's group[167], in the first such study, wrote that the similarity of the ultrastructure of epithelial cells in controls and IC patients makes it improbable that the disease process originates in the epithelium. Other investigators found no differences in the morphologic appearances of the glycocalyx and of urothelial cells in patients with IC when compared with controls[168]. Anderstrom and colleagues[109] saw no surface characteristics specific for IC, but believed that the mucin layer covering the urothelial cells seemed reduced in IC compared with controls, a fact disputed by Nickel in a very elegant paper[169]. Elbadawi and Light[136] observed ultrastructural changes sufficiently distinctive to be diagnostic in specimens submitted for pathologic confirmation of nonulcerative interstitial cystitis. Marked edema of various tissue elements and cells appeared to be a common denominator of many observed changes. The wide-ranging discussion of the etiology of IC in his paper is fascinating, but the pathological findings are potentially marred by the methodology, in that specimens were obtained after diagnostic hydrodistention[170].

So what is the place of pathologic examination of tissue in BPS? Attempts to classify the painful bladder by the pathoanatomical criteria described by Holm-Bentzen[171] are of questionable value. There is a group of patients with what she describes as "nonobstructive detrusor myopathy"[172]. In her series, these patients with degenerative changes in the detrusor muscle often had residual urine, a history of urinary retention, and an absence of sensory urgency on cystometry with bladder capacities over 400cc. Most would not be clinically confused with BPS. A similar English series[173], however, included patients who met NIDDK research criteria and associated detrusor myopathy with diminished detrusor compliance and ultimate bladder contracture.

The Interstitial Cystitis Database (ICDB) study worked backwards from symptoms to pathology, and concluded that certain symptoms are predictive of specific pathologic findings[33,174]. Denson et. al.[36] analyzed forceps biopsies from 65 females and 4 males with BPS. Ten per cent of specimens showed vasodilatation or submucosal edema. Inflammation was absent in 30% of patients, and mild in another 41%. Cystoscopic changes did not correlate with degree of inflammation. Hanus and colleagues[175] studied 84 biopsies from 112 BPS patients and reported a linear relationship between the mean bladder capacity under anesthesia and severity of glomerulations. They did not find a correlation between severity of symptoms and histopathological changes observed by light or electron microscopy.

Richter and the Danish group showed studied 349 consecutive BPS patients and concluded that nocturia, detrusor mastocytosis, and detrusor intrafasicular fibrosis are associated with multiple treatments and presumed failure of standard urological therapy while bladder capacity and glomerulations are not.[176] In a Belgian study, cystoscopic parameters (glomerulations, bleeding, mucosal tears, bladder capacity) showed no correlations with the histological features of bladder biopsies. No correlations were found between inflammatory infiltrate and detrusor mastocytosis. In fact, detrusor mastocytosis was more elevated in biopsies with normal urinary epithelium than in those with damaged epithelium. The study concludes that the clinical significance of pathological findings awaits future research findings. [177]

Rosamilia reviewed the pathology literature pertaining to BPS in 2 recent publications and presented her own data[34,41]. She compared forceps biopsies from 35 control and 34 PBS/IC patients, 6 with bladder capacities less than 400cc under anesthesia. Epithelial denudation, submucosal edema, congestion and ectasia and inflammatory infiltrate were increased in the BPS group. Submucosal hemorrhage did not differentiate the groups, but denuded epithelium was unique to the BPS group and more common in those with severe disease. The most remarkable finding in her study was that histological parameters were normal and indistinguishable from control subjects in 55% of BPS subjects. Method of biopsy can be important in interpreting findings, as transurethral resection biopsies tend to show mucosal ruptures, submucosal hemorrhage and mild inflammation[107], while

histology is normal approximately half the time with cold-cup forceps biopsies [34,35,178].

Histopathology plays a supportive diagnostic role at best[179]. Major reconstructive procedures appear to have better outcomes in patients with pathology consistent with Hunner's lesions.[180] Inflammatory features can be seen in 24% to 76% of patients without a visible Hunner's lesion.[181] While recent studies suggest that a severely abnormal pathology may be associated with poor prognosis[182,183], this is not necessarily the case [184].

At this point in time, excluding other diseases that are pathologically identifiable is the primary utility of bladder biopsy in this group of patients.[185,186]

VI. DIAGNOSIS

Much work has been put into the attempt to define objective diagnostic criteria based on, among other factors, cystoscopy under local or general anesthesia, bladder distention with registration of bladder capacity and/or possible presence of glomerulations and Hunner's lesion, bladder wall biopsies evaluated for inflammation, ulcer, fibrosis, mast cells, etc. and urodynamics with registration of bladder capacity, compliance and bladder stability. Results have, however, been frustrating. It is more fruitful to establish a broad clinical diagnosis, mainly on the basis of symptoms and exclusion of other diseases, and then stratify patients by urodynamic, cystoscopic, histological, and other tests on the basis of the significance of these findings for results of treatment and prognosis of disease. Current efforts to phenotype the disorder by the presence or absence of associated syndromes and diseases may also prove useful in the same way.

What follows is based solely on expert opinion.

Level of Evidence: 4 Grade of Recommendation: C

It is hoped that future Consultations will have the data to base such suggestions on a firmer foundation.

1. HISTORY

A general thorough medical history should be taken.

Special emphasis should be given to:

- Previous pelvic operations
- Previous UTI
- Bladder history/urological diseases
- Location of pelvic pain (referred pain) and relation to bladder filling/emptying.
- Characteristics of pain: onset, correlation with other events, description of pain
- Previous pelvic radiation treatment
- Autoimmune diseases

2. PHYSICAL EXAMINATION

A common physical examination should be performed including palpation of the lower abdomen for bladder fullness and tenderness:

- Standing: kyphosis, scars, hernia
- Supine: abduction/adduction of the hips, hyperaesthetic areas

In **females** physical examination should include a vaginal examination with pain mapping of the vulvar region and vaginal palpation for tenderness of the bladder, urethra, levator and adductor muscles of the pelvic floor. Tenderness might be graded as mild, moderate or severe.

3. PAIN MAPPING

Inspection:

- Vulva
  - exclusion of vulvar/vestibular diseases (vulvitis, dermatosis etc.)
  - evaluation of introital area (endometriosis)
  - tenderness of vestibular glands or vulvar skin (Touch Test: use wet cotton stick or finger tip)
- Vagina
  - tenderness during insertion and opening of speculum
  - cervical pathology
  - vaginal fornices (endometriosis)
- Bimanual physical examination
  - tenderness of urethra, trigone and bladder
  - superficial/deep vaginal tenderness
  - tenderness of pelvic floor muscles (levator, adductor)
  - tenderness in adnexal areas

In **males** digital rectal examination (DRE) should be performed with pain mapping of the scrotal–anal region and palpation of tenderness of the bladder, prostate, levator and adductor muscles of the pelvic floor and the scrotal content.

4. LABORATORY TESTING

- Urine dipstick (ABS, pH, leucocytes, nitrate), urine culture in all. If sterile pyuria culture for tuberculosis.
- Urine cytology in risk groups.
- Investigations for vaginal Ureaplasma and Chlamydia in females and prostatitis in men are optional.

5. SYMPTOM EVALUATION

- Voiding diary with volume intake and output for 3 days at initial evaluation. Patient sensation at voiding might be recorded (see chapter outcome assessment, Hanno).
- At follow-up only number of voidings during day and night time is necessary. Morning volume might be recorded as a help to monitor highest functional capacity.
- The O'Leary–Sant Symptom Score supplemented should be used as basic symptom score supplemented with the Quality of Life Score from the International Prostate Symptom Score (see chapter symptom scales, Hanno3).

Pain should be recorded using a Visual Analogue Scale (VAS) for pain during the last 24 hours (to fit with the voiding diary). Separate scores for the average, mildest and worst pain should be obtained (see symptom scales)

6. URODYNAMICS

Level of Evidence:4 Grade of Recommendation:C

The NIDDK criteria excluded patients with detrusor overactivity at filling cystometry in order not to confuse the picture in clinical trials.[8] This does not however mean that detrusor overactivity can not coexist with bladder pain syndrome. In the interstitial cystitis database approximately 14% of BPS patients had overactive bladders[17]. Whether these patients respond better to antimuscarinics than BPS patients with stable bladders has never been systematically investigated. If so, a rationale for routinely employing urodynamics as a part of the evaluation would follow. In males, infravesical obstruction might be a differential diagnosis[187], and it is recommended to do flowmetry in all males and pressure-flow studies in men with a peak flow rate below 20ml/seconds.

There are no data to support the following recommendations:

In females, flowmetry, post void residual urine volume and pressure- flow study are optional. In males, a flowmetry should be done in all, and if maximum flow rate <20 ml/s a pressure-flow study and measure of residual urine volume should be done. It is recommended to perform filling cystometry with a filling rate of 50 ml/s (to comply with the revised Potassium Test - see below) to look for overactivity, volume at first desire to void and cystometric capacity.

7. POTASSIUM TESTING

Level of Evidence:1 Grade of Recommendation: -A (not recommended)

Parsons has championed an intravesical potassium chloride challenge, comparing the sensory nerve provocative ability of sodium versus potassium using a 0.4 M potassium chloride solution. The test has proved controversial [188]. Pain and provocation of symptoms constitutes a positive test. Whether the results indicate abnormal epithelial permeability in the subgroup of positive patients, or hypersensitivity of the sensory nerves is unclear. Normal bladder epithelium can never be absolutely tight, and there is always some leak, however small[189]. The concentration of potassium used is 400meq per liter, far exceeding the physiologic urinary concentrations of 20-80meq/liter depending upon dietary intake[190]. Healthy controls can distinguish KCl from sodium chloride, though they don't experience severe pain[191]. The hope is that this test may stratify patients into those who will respond to certain treatments (perhaps those designed to fortify the glycosaminoglycan layer) [192].

Used as a diagnostic test for bladder pain syndrome, the potassium chloride test is not valid[193]. The gold standard in defining BPS for research purposes has been the NIDDK criteria. These criteria are recognized to constitute a set of patients that virtually all researchers can agree have BPS, though they are far too restrictive to be used in clinical practice[28]. Thus, this group of patients should virtually all be positive if the KCl test is to have the sensitivity needed to aid in diagnosis. Up to 25% of patients meeting the NIDDK criteria will have a negative KCl test[194]. In the group it should perform the best in, it is lacking in sensitivity. When we look at the specificity side of the equation, in the universe of asymptomatic persons, it performs relatively well and is rarely positive, although a recent study reported a 36% false positive rate in asymptomatic men[195]. It is in the patient population with confounding conditions for which we would want help in sorting out BPS from other disorders. Sixty percent of patients with overactive bladder test positive[196] and virtually all patients with irritative symptoms from radiation cystitis and urinary tract infection test positive[194,197]. The results with chronic prostatitis / chronic pelvic pain syndrome in men are variable, but 50-84% of men have been reported to test positive[195,198,199]. In women with pelvic pain results are similar[200], and based on these findings, Parsons has expressed the view that BPS may affect over 20% of the female population of the United States[201]! Others have reported prevalence in unselected female textile workers in Turkey using similar methods at 32.8%[202]. Another way to interpret the findings would be that the KCl test is very nonspecific, missing a significant number of BPS patients and over-diagnosing much of the population.

Prospective and retrospective studies looking at the KCl test for diagnosis in patients presenting with symptoms of BPS have found no benefit of the test in comparison with standard techniques of diagnosis[193,203,204]. A later modification of the test

using 0.3 molar potassium chloride for potential differentiation between patients with IC and detrusor overactivity (DO) showed that the 0.3 M KCl reduces maximum cystometric capacity in BPS and DO, the effect being more pronounced in DO. Urothelial hyperpermeability was not specific to IC. Comparative cystometry using NS and 0.3 M KCl does not help to differentiate BPS from DO [205,206].

The development of a painless modification of the potassium chloride test[207] using cystometric capacity and a 0.2M solution may improve acceptability among patients. The so-called revised or Comparative Potassium Test has shown prognostic value in bladder irrigation studies[208] but is considered optional by ESSIC. If performed it should be performed according to Daha et al.[207]: A Foley balloon catheter (14F) is inserted and the bladder drained. Instill into the bladder 500 ml saline (0.9%) at a rate of 50 ml/min via an infusion set until the maximum capacity is reached. Drain the bladder and measure the saline filling volume. Repeat the instillation and measurement with 500 ml 0.2 M potassium chloride at a rate of 50 ml/min (taking care that filling lines are emptied of all saline before KCl instillation), and calculate the filling volume difference. A difference in bladder capacity > 30% is considered positive. Besides reduction of bladder capacity with 0.2 M KCl there is a stronger feeling of urgency in IC patients compared to the saline filling, which is also clinically relevant.

8. CYSTOSCOPY AND HYDRODISTENSION

Level of Evidence:2 Grade of Recommendation:B

The classic cystoscopic picture of BPS as an "elusive" bladder ulcer with a corresponding cystoscopic appearance of patches of red mucosa exhibiting small vessels radiating to a central pale scar was described by Hunner in 1915 [5]. (**Figures 6, 7 & 8**) courtesy of Jorgen Nordling)

After 1978, glomerulations, described as punctuate petechial hemorrhages and observed after hydrodistention, became the primary cystoscopic feature of BPS[7]. (**Figures 9 and 10**, courtesy of Tomohiro Ueda)

But not all patients with symptoms of BPS have glomerulations[9,28,36,176], and not all patients with glomerulations have symptoms of BPS [196,209-212]. Neither presence nor severity of glomerulations correlate with any of the primary symptoms of BPS [33], although the presence of a Hunner's lesion is significantly associated with bodily pain and urinary urgency [211]. The finding of a Hunner's lesion or glomerulations has been somewhat subjective. Some researchers find a Hunner's lesion in 50% of their BPS patients [213], while others rarely see one [214].

No study comparing individual perceptions and variations in reporting or classifying glomerulations has ever been reported. Bladder capacity during hydrodistention has not drawn much attention, although it is strongly associated with increased urgency [215].

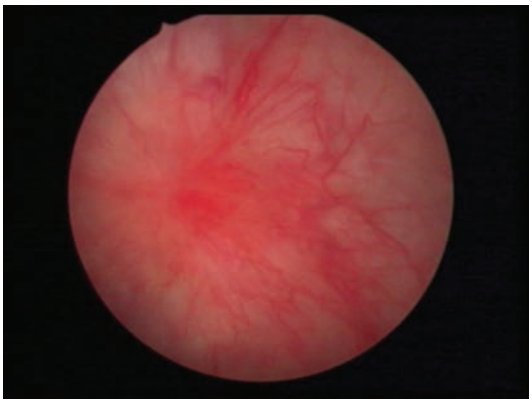


Figure 6: Hunner's lesion prior to bladder distention.

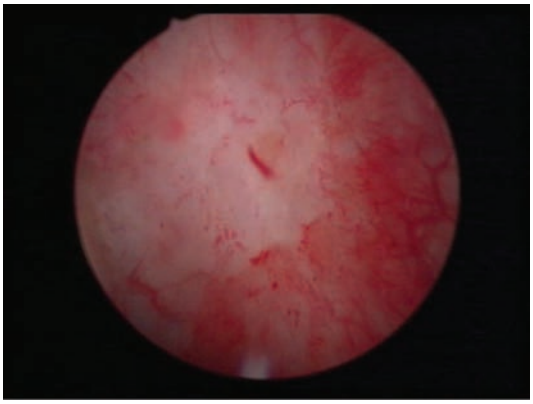


Figure 7: Hunner's lesion at bladder distention to 80cm pressure.

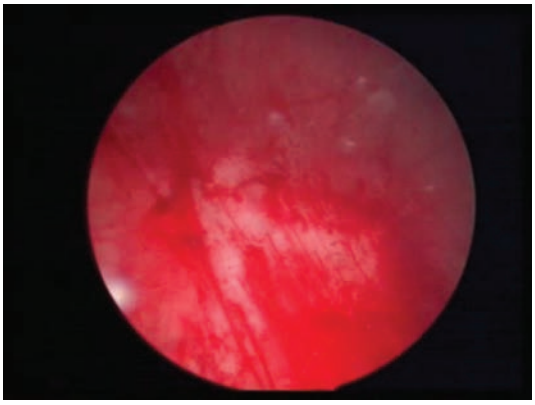


Figure 8: Hunners lesion after distention and release of fluid.

Because considerable variation in the duration of distension, repetition of distension, the pressure used for distension, and the measurement of bladder capacity have been described [216]}, the ESSIC

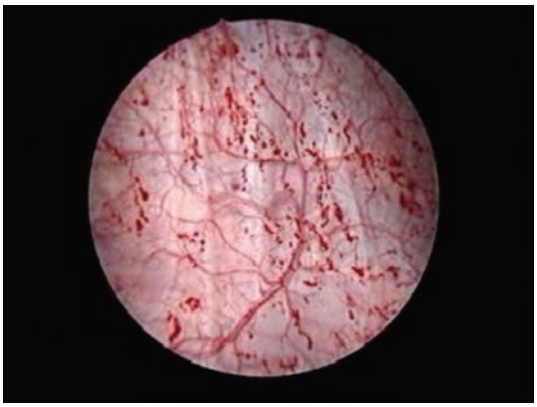


Figure 9: Glomerulations at 80cm water pressure.

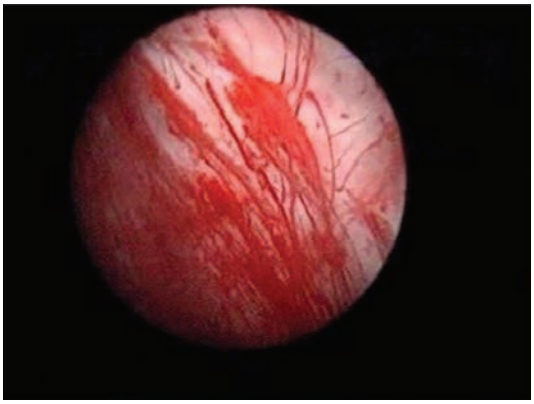


Figure 10: Typical waterfall after release of bladder pressure.

has suggested a standardized procedure for cystoscopy and **hydrodistension** [15]:

A rigid cystoscope is preferred to facilitate taking of adequate biopsies. Glycine or corresponding filling fluid should be used to allow for coagulation after biopsies. Infusion height should be approximately 80 cm above the Symphysis Pubis. **(note: some would recommend a pressure of only 60cm to minimize risk of bladder perforation and in the absence of data that a higher pressure is beneficial)**. A dripping chamber is used and the bladder is filled until fluid dribbling stops. If necessary, a digital block is applied around the urethra to prevent leakage. Pre-distension inspection includes observation for radiating vessels, coagulum or fibrine deposits, white spots, hyperaemia, oedema, cracks, scars or any other mucosal changes. Continuous inspection while filling the bladder is advised. When maximum capacity is reached, the distension is maintained for 3 minutes. The bladder is emptied and the colour of the fluid checked for the degree of bleeding. The total volume drained is the measured maximum bladder capacity. During a second filling, the bladder is filled to approximately 1/3rd to 2/3rd of the bladder capacity to achieve optimal vision for inspection and biopsies. The bladder should not be filled to maximum capacity or distended again to avoid further provocation of changes with doubtful reproducibility.

a) Inspection

Describe lesions in anterior wall, posterior wall, lateral quadrants and fundus. At the fundus one should be alert for possible artefacts if there is blind introduction of the scope. Bladder mapping by drawing is mandatory. Photographs are recommended but optional.

b) Classification

Grade 0 = normal mucosa

Grade I = petechiae in at least two quadrants

Grade II = large submucosal bleeding (ecchymosis)

Grade III = diffuse global mucosal bleeding

Grade IV = mucosal disruption, with or without bleeding/oedema

The importance of the finding of the finding of glomerulations after hydrodistension is however as mentioned been questioned since 45% of asymptomatic females, 20% of males with LUTS suggestive of BOO and 85% of females with OAB and no bladder pain demonstrates typical glomerulations after hydrodistension[196,210,212] and 10-34% of patients with BPS do not [9,176]

c) How useful is hydrodistention?

Hydrodistension results fail to identify any statistically significant differences in post-distention objective findings (anesthetic capacity, glomerulations) or therapeutic benefits when patients are categorized according to presenting symptoms[217]. Cystoscopy with hydrodistention may provide little useful information above and beyond the history and physical examination findings. In one study, 56% of 84 patients reported symptom improvement, but the duration was short lived with a mean of 2 months[218]. It is necessary to distinguish between short term hydrodistension (2-10 min.) for classification of BPS and long term hydrodistension (20-30 min.) for treatment[219]. Many reports on the therapeutiv effect of hydrodistension are from Asia and from patient material with IC based on the Asian definition[45], where up to 2/3 of the patients have frequency-urgency and no pain.

Lamale and colleagues examined the relationships between symptoms and cystoscopic findings in 12 women newly diagnosed with BPS who had not previously received treatment. Pain symptoms had consistent positive correlations with the cystoscopic findings. An increase in pain with bladder filling was associated with inflammation ($P = 0.011$), ulceration, and smaller bladder capacity. Pain relief after voiding correlated with smaller bladder capacity ($P = 0.019$), hematuria, and total cystoscopic score. Pain

intensity in the urethra was related to ulceration and hematuria, and pain in the lower abdomen was related to a smaller bladder capacity (P = 0.047), glomerulations, and a larger total cystoscopic score. Daytime frequency correlated negatively with most cystoscopic findings, and nocturnal frequency had a positive relationship with most cystoscopic findings and was significantly associated with a smaller bladder capacity (P = 0.010). Urgency showed no strong associations with any cystoscopic findings. The results of this study contradict those of previous studies that found no relationship between symptom reports and cystoscopic findings suggesting possible effects of treatment on pain perception and therapeutic influence on cystoscopic findings[220] .

It is important to keep in mind that the cystoscopic appearance of the bladder wall after hydrodistention may not be constant over time, and the absence of initial findings of glomerulations or terminal hematuria does not preclude further development of these findings of the disease on subsequent evaluation [221]. Rare cases of hydrodistension induced bladder necrosis have been described [222].

9. MORPHOLOGY

Pathological changes in light microscopic and electron microscopic features in patients with BPS have been described including infiltration with inflammatory cells in all or specific parts of the bladder wall. Although these findings are important in our attempt to understand the disease and perhaps as an aid to stratification of patients, there are at this time no pathognomonic findings on biopsy in terms of diagnosis[33]. Expert opinion as per the ESSIC suggests the following procedures when biopsy is planned for BPS evaluation[15]:

a) Biopsies

During cystoscopy the bladder is distended to full capacity. After draining the bladder, bladder biopsies are taken at roughly half full bladder capacity: Biopsy procedures should be performed by using large forceps and include detrusor muscle; alternatively double punch biopsies or resections of lesions can be used.

b) Number of biopsies

At least 3 biopsies from the two lateral walls and bladder dome should be taken in addition to biopsies from visually abnormal areas. The biopsies are to be immediately fixed in neutral buffered 4% formalin.

c) Biopsy handling

Biopsies are treated conventionally. Six adjacent 3 mm sections are cut and placed with 3 specimens on each of two specimen slides. The first slide is stained with H&E, the next with a connective tissue stain suitable for the individual institute. Twenty-four 10 mm sections are then cut and every third section is mounted on a specimen slide for mast cell counting. The specimens are stained by Lederstain (naphtolesterase) according to routine procedures. Finally, a 3mm section is obtained to ensure the presence of detrusor muscle in the specimens.

d) Mast cell counting

The use of a measuring grid (e.g. Leitz periplan 6F 10_N ocular containing a standardized grid) is necessary. Only mast cells containing nucleus are included. When counting the cells those covering or touching the bottom should be excluded whereas those covering the upper and left line are included. At least 3 biopsies must be the subject of mast cell counting and if possible one including a lesional area. Biopsies for mast cell counting should contain detrusor muscle.

e) The pathology report

- Epithelium
  - Not present
  - Present
  - Dysplasia with grading
  - Abnormal but no dysplasia: description is mandatory.
- Propria
  - Normal
  - Inflammation: description with a grading
  - Other findings are described
- Detrusor muscle. Abnormal muscle cells: describe
- Intrafascicular fibrosis
  - Not present
  - Present
- Mast cell count: At least three biopsies should be included in the counting. Only the biopsy with the highest number of mast cells per mm2 should be reported

The enzymatic (naphtolesterase) staining is, for the time being, recommended since standardized values are available:

- less than20mast cells/mm2:no detrusor mastocytosis;
- between 20 and 28 grey zone!
- more than 28 mast cells/mm2: detrusor mastocytosis.

Larsen recommends examining the detrusor biopsies with tryptase-stained 3 micron thick sections, with every seventh section used for quantification; 27 mast cells/mm2 is considered indicative of mastocytosis[165].

These guidelines have been reported to be easy to follow. A statistically significant correlation was found between the cystoscopic aspect and inflammatory infiltration, mast cell count in the detrusor muscle and stromal edema. Maximum bladder capacity was negatively correlated with inflammation, detrusor mast cell count, hemorrhages and the overall cystoscopic aspect[223]. Correlations have also been demonstrated between urothelial damage and inflammatory infiltrates and between normal epithelium and detrusor mastocytosis suggesting either 2 different types of BPS or different stadiums in the pathophysiological process of BPS [177]. Also in a large retrospective study of 349 patients with BPS, it was found that treatment intensity ranging from hydrodistension only to major surgery correlated positively to detrusor mast cell count, detrusor fibrosis and nocturia, but not to maximum bladder capacity or glomerulations after hydrodistension [224].

10. BIOMARKERS

The lack of universally accepted clinical diagnostic criteria for BPS affects all aspects of making progress in understanding this disease. Insights into risk factors, pathogenesis, trials for effective therapy, prognosis, and outcome criteria for treatment are all affected by this lack of diagnostic criteria. A major factor affecting the controversy over accepted clinical diagnostic criteria is that the current criteria are predominantly symptom specific. An objective biomarker would advance the establishment of reproducible diagnostic criteria for BPS and also aid in monitoring effects of treatment.

A biomarker for any disease needs to demonstrate high sensitivity and high specificity. In addition, the marker assay needs to be reproducible in many laboratories and should be suitable for use in a clinical diagnostic laboratory.

Many of the published studies on biomarkers for BPS have been on biomarkers isolated from urine. Erickson et.al has published excellent reviews of urine markers for BPS [225,226]. The most thoroughly investigated marker is antiproliferative factor (APF). This factor has been identified and characterized by Dr. Susan Keay and her colleagues at the University of Maryland [227,228]. Control subjects for this study included asymptomatic individuals, patients with bacterial cystitis, and patients with vulvovaginitis. APF is found in urine from the bladder and not from the renal pelvis [229-231]. Treatment of symptomatic BPS by either hydrodistention or neurostimulation normalized the APF levels concurrent with symptom relief [232]. It is not known if other forms of treatment will affect APF levels. Preliminary studies in 58 women with documented BPS demonstrated a sensitivity value of 91.4% and a specificity of 90.6%[233]. A later study with 219 symptomatic BPS patients and 325 controls with and without other urological disorders documented the sensitivity as 94% and the specificity at 95%[234]. APF has been isolated from urine and found to be a frizzled 8 protein-related sialoglycopeptide which interacts with the epithelial cell receptor CKAP4/p63[235,236]. Keay et al have suggested that APF might inhibit cell proliferation by the downregulation of genes that stimulate cell proliferation along with the upregulation of genes that inhibit cell growth[112]. Cell growth inhibition of human urothelial cells appears to be mediated by p53[237]. APF treatment caused significant increases in the paracellular permeability of normal bladder epithelial cell monolayers and the attenuation of tight junctions compared to mock APF, similar to changes seen in IC cells. APF treatment also decreased expression of the tight junction proteins zonula occludens-1 and occluding [236].

APF seems an ideal candidate for a biomarker for symptomatic BPS. There need to be additional studies to determine if it can serve as a BPS marker for patients in remission or for those who have not yet become symptomatic. As of 2008, the findings on symptomatic patients have yet to be replicated by laboratories around the world, and the biologic assay has not proven suitable for commercial development as it currently exists. The ultimate fate of APF as an important biomarker and etiologic factor remains to be determined.

GP-51 is a glycoprotein present in both the transitional epithelium and urine of humans and other mammals. Moskowitz et. al have shown that bladder biopsies of BPS patients had decreased staining for GP-51[238] The same laboratory also demonstrated that although GP-51 demonstrates a high specificity for BPS, it is not as sensitive as APF[239].

There have also been many published studies on heparin-binding epidermal growth factor-like growth factor (HB-EGF)[112,230,231,240,241]. HB-EGF is a growth factor found in normal urine. It has been shown that APF inhibits the production of HB-EGF. There have been no large population studies focusing solely on HB-EGF as a biomarker for BPS.

11. CONFUSABLE DISEASES

Criteria for a diagnosis are needed only if the target disease may be confused with other diseases (confusable diseases) because of overlapping features[242]. For a diagnosis, the target disease has to be recognized in a pool of confusable diseases in one of two ways: by recognition of the specific combination of features of the target disease or by exclusion of confusable diseases. For the diagnosis of BPS both methods might be used because:

- Confusable diseases are more common than BPS, so recognition is mandatory because many can be treated.
- Failure to diagnose a confusable disease would automatically incorrectly yield a diagnosis of BPS.
- Patients may have a confusable disease plus BPS.

The diagnosis of BPS can thus made on the basis of exclusion of confusable diseases and confirmation by the recognition of the presence of the specific combination of symptoms and signs of BPS. If the main urinary symptoms are not explained by a single diagnosis (confusable disease or BPS), the presence of a second diagnosis is possible. Symptoms and signs for use in diagnostic criteria do not need to be specific for the target disease. On the contrary, if a specific symptom or sign existed for the target disease, a diagnosis would only require the presence of the specific feature and diagnostic criteria would not be necessary.

In evidence-based medicine, diagnoses are based on medical history, physical examination, and appropriate clinical investigations to eliminate diseases from a list of differential diagnoses (confusable diseases) and to confirm the final diagnosis. BPS may occur together with confusable diseases such as chronic or remitting urinary infections or endometriosis. Cystoscopy with hydrodistention and biopsies might in this situation document positive signs of BPS thereby making a double diagnosis more probable. For therapeutic studies it makes sense to exclude patients who also have a confusable disease because symptoms and signs may be caused by BPS, the confusable disease, or by both. For prevalence studies of BPS, on the other hand, all cases with BPS should be included, also those with a confusable disease. This approach eliminates the need for separate diagnostic criteria for clinical practice and scientific studies. **Table 3** summarizes confusable diseases related to BPS and their mode of exclusion based upon the aforementioned diagnostic proposals and procedures [15,243].

VII. CLASSIFICATION

Interstitial cystitis was originally described as bladder disease with severe inflammation of the bladder wall described by Hunner as an ulcer[5]. The lesion is however not an ulcer but an inflammatory infiltrate that can crack upon distention, and the name of the bladder lesion has consequently been changed to "Hunner's lesion[243]". The finding of a Hunner's lesion could therefore originally be regarded as a diagnostic criterion for IC. Messing and Stamey introduced glomerulations as another typical finding for IC and this was included in the NIDDK criteria[8]. Magnus Fall proposed, that patients with Hunner's lesion (classic IC) and patients with glomerulations (non-ulcer type) represented two different subtypes [101] with different clinical pictures, different outcomes, and different responses to treatment [213] meaning that patients fulfilling the NIDDK criteria represents at least two different patient populations. Moreover up to 60% of patients clinically believed to have BPS by experienced clinicians do not fulfil the NIDDK criteria [28] and whether or not these patients are comparable to the patients fulfilling the NIDDK criteria is unknown. Finally Japanese urologists con-

Table 3: Differential Diagnosis of Bladder Pain Syndrome.

Carcinoma and carcinoma in situ	Cystoscopy and biopsy
Infection with	
Common intestinal bacteria	Routine bacterial culture
Chlamydia trachomatis, Ureaplasma urealyticum	Special cultures
Mycoplasma hominis, Mycoplasma genitalium	
Corynebacterium urealyticum, Candida species	
Mycobacterium tuberculosis	Dipstick; if "sterile" pyuria culture for *M. tuberculosis*
Herpes simplex and human papilloma virus	Physical examination
Radiation	Medical history
Chemotherapy, including immunotherapy with cyclophosphamide	Medical history
Anti-inflammatory therapy with tiaprofenic acid	Medical history
Bladder-neck obstruction and neurogenic outlet obstruction	Uroflowmetry and ultrasound
Bladder stone	Imaging or cystoscopy
Lower ureteric stone	Medical history and/or hematuria: upper urinary tract imaging such CT or IVP
Urethral diverticulum	Medical history and physical examination
Urogenital prolapse	Medical history and physical examination
Endometriosis	Medical history and physical examination
Vaginal candidiasis	Medical history and physical examination
Cervical, uterine, and ovarian cancer	Physical examination
Incomplete bladder emptying (retention)	Postvoid residual urine volume measured by ultrasound scanning
Overactive bladder	Medical history and urodynamics
Prostate cancer	Physical examination and PSA
Benign prostatic obstruction	Uroflowmetry and pressure-flow studies
Chronic bacterial prostatitis	Medical history, physical examination, culture
Chronic non-bacterial prostatitis	Medical history, physical examination, culture
Pudendal nerve entrapment	Medical history, physical examination, nerve block may prove diagnosis
Pelvic floor muscle-related pain	Medical history, physical examination

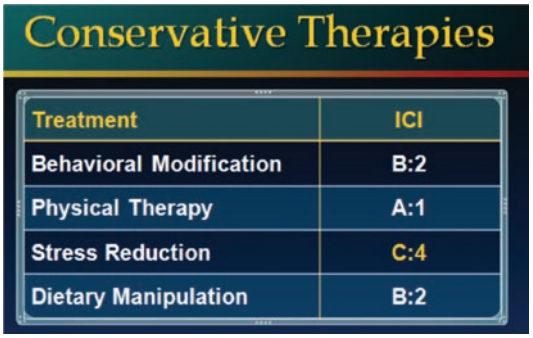
Van de Merwe J, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK et al. Diagnostic criteria, classification, and nomenclature for Painful Bladder Syndrome/Interstitial Cystitis: An ESSIC proposal. Eur. Urol. 2008;53:60.

sider that “interstitial cystitis” should be preserved as a disease name for patients with urinary symptoms and cystoscopic findings of glomerulations or Hunner’s lesion as outlined in the NIDDK criteria [45].

In an attempt to unite these different philosophies into a coherent schema, ESSIC proposed a classification of BPS based on findings during cystoscopy with hydrodistension and morphological findings in bladder biopsies[243] (**Table 2**) . The classification includes groups not having had cystoscopy with hydrodistension (group X) as well as groups not having had morphological investigation of bladder biopsies (group XX). By using this classification future research will be able to identify if findings of glomerulations and/or Hunner’s lesion as well as morphological changes in bladder biopsies does have significant importance for disease prognosis and/or treatment outcome.

VIII. CONSERVATIVE TREATMENT (TABLE 4)

Table 4: conservative therapies graded by Oxford Criteria



1. BEHAVIORAL MODIFICATION

Behavioral therapy for BPS includes education, timed voiding (scheduled voiding time and interval), controlled fluid intake, pelvic floor muscle training and bladder training (gradually extending voiding interval).

Chaiken et al [244] reported that when they conducted behavioral therapy consisting of frequency-volume chart, timed voiding, controlled fluid intake and pelvic floor muscle training for the treatment of 24 female patients, 50% of the patients showed improvement in the number of urinations and bladder capacity. At the same time, they considered that as the data was collected from 12 weeks’ intensive therapy conducted by skilled therapists for selected patients whose main symptom was urinary frequency, it should not be generalized. Parsons and Koprowski [245] reported that when 21 patients with the main symptom of urinary frequency underwent bladder training using a frequency-volume chart, 15 patients showed improvement. In 15 patients, the mean voided volume after one month increased by 65cc, whereas a persistent sensation of bladder fullness remained unchanged.

Participants in both arms of a large NIH funded randomized placebo controlled trial evaluating amitriptyline in BPS [246] received a standardized education and behavioral modification program (EBMP) .Adherence to the EBMP at 6 weeks was assessed in 4 categories of 1) symptom management, 2) fluid management, 3) diet modification and 4) bladder training. For each of these EBMP categories adherence was defined as the overall percentage of participants who reported adhering to each component of the EBMP at each telephone contact or clinic visit. For the 241 subjects evaluable for EBMP adherence, the rate at 6 weeks was 75% (181 of 241) for symptom management, 83% (201 of 241) for fluid management, 82% (196 of 240) for diet modification and 71% (172 of 241) for bladder training. The overall GRA response rate was approximately 57% for adherers in any of the 4 EBMP categories, whereas it was lower for nonadherers. This rate neared statistical significance for diet modification, which demonstrated only a 41% response rate among nonadherers (p = 0.051).

Recommendation:

Behavioral therapy should be a cornerstone of treatment for patients with BPS.

Level of evidence: 2 Grade of recommendation: B

2. PHYSICAL THERAPY

Women with BPS may have associated pelvic floor dysfunction [247]. Physical therapy for the pelvic floor is said to be effective for genitourinary and anorectal disorders[248]. Biofeedback and soft tissue massage may stimulate the relaxation of the pelvic floor muscles [249,250]. Lukban et al [251] conducted a direct myofascial release treatment on 16 BPS patients with high-tone pelvic floor dysfunction and sacroiliac dysfunction. The treatment was effective for urinary frequency and suprapubic pain. Fifteen patients (94%) showed improvement in the O’Leary & Sant symptom score. Coital pain relief was observed in 15 of 16 patients, with 9 patients becoming able to resume sexual intercourse [252]. Transvaginal Theile massage was also reported to be effective for 9 of 10 patients of the same group [253]. Mendelowitz et al [250] showed a 69% success rate when treating 16 patients using electromyographic biofeedback. However, it was suggested that a placebo effect may have occurred because the effect did not correlate with the improvement in patient’s awareness of the pelvic floor muscle movement and position before and after the therapy. Weiss [254] reported that 70% of 10 patients with IC showed symptomatic improvement, rating from “effective” to “remarkably effective”.

An NIH study[255] to determine the feasibility of conducting a randomized clinical trial was undertaken to compare 2 methods of manual therapy (myofascial physical therapy and global therapeutic massage) in patients with urological chronic pelvic pain syndromes. The global response assessment response rate was 57% in the myofascial physical therapy group compared

to 21% in the global therapeutic massage treatment group. This statistically significant difference (P=0.03) was primarily driven by the response seen in women (24 women) compared to the men (24 men) enrolled in this small pilot study. A follow-up randomized trial comparing similar treatments [256] but only in women with BPS and demonstrable pelvic floor pathology showed a clear benefit of directed myofascial physical therapy.

Recommendation:

Physical therapy of selected and motivated patients with BPS, particularly those with demonstrable pelvic floor dysfunction, is indicated.

Level of evidence: 1 Grade of recommendation: A

3. STRESS REDUCTION

It is long been observed that mental stress is one of the factors which aggravate the symptoms of BPS. Koziol et al [97] reported, in a survey of 374 patients, that more than half of the patients experienced intensified pain due to stress. Rothrock et al [257] reported that when comparing patients with BPS and healthy people, increased pain and urgency caused by stress were observed only in patients with BPS. Case-cohort studies have confirmed that patients diagnosed with IC/BPS experience considerably more stress than patients without the condition [90]. Stress was shown to correlate with both the severity of symptoms and quality of life. In another study of patients with BPS identified in urology tertiary care clinic populations [258], mental health disorders were identified in 23 % of IC/BPS female cases compared to 3% of female control subjects. Medications for anxiety, depression or stress were taken by 37% of patients with IC/BPS compared to 13% of female controls.

It is believed that exercise and bathing favorably influence the quality of life by reducing stress [259] however, the effect of such nonspecific therapies are difficult to assess and have not been proven in clinical trials. It would seem reasonable to suggest, when possible, to shorten working hours, choose a job with less stress or create a less stressful home environment. Involvement in patient education programs and patient support groups are considered by most practitioners to be beneficial [259,260]. Worldwide patient support groups, including the Interstitial Cystitis Association (ICA) [261], http://www.ichelp.org/ , the International Painful Bladder Foundation, http://www.painful-bladder.org/, are important sources of information for patients with BPS. Patients with BPS frequently suffer depression, which may negatively impact upon the quality of life [90] and perhaps symptoms. Effective self-care strategies taught by psychiatric nurses are considered to be useful [262,263].

Recommendation:

Stress and depression are related to poorer quality of life and increase in severity of symptoms. **Level of evidence: 1 Grade of recommendation: A.** Reduction of stress and depression may contribute to an overall improvement in quality of life and perhaps even symptoms. **Level of evidence: 4 Grade of recommendation: C.**

4. DIETARY MANIPULATION

Acidic beverages, coffee, spicy food, and alcohol may aggravate the symptoms of most patients with BPS [97,259,264,265]. The symptoms of the majority of BPS patients are generally believed to be improved by dietary manipulation [259,264,266,267]. However this has proven difficult to document and Nguan et al [268] reported that there was no statistically significant difference in pain and other symptoms, when they evaluated the influence of the changes in urinary pH on the symptoms of 26 patients with BPS by instilling pH5.0 and pH7.5 saline solutions into the bladder. One of the best studies designed to determine the effect of particular foods, beverages and/or supplements (comestibles) on IC/BPS symptoms was undertaken by Shorter et al [269]. One hundred and four patients with IC/BPS were asked to indicate on a validated questionnaire whether each of 175 individual items worsened, improved or had no effect on symptoms. Of the patients surveyed, 90% indicated that the consumption of certain foods or beverages caused symptom exacerbation. The comestible items that had the most effect were caffeinated, carbonated and alcoholic beverages, certain fruits, artificial sweeteners and spicy foods.

Dietary manipulation was ranked in the top five frequently used treatments in a cohort study of the Interstitial Cystitis Data Base (ICDB).[270]. As the influence of diet is variable with regard to food, beverage, and patient, there is no reason for patients to be uniformly on a strict diet. It is advised that each patient experiment to find out the foods that tend to aggravate their symptoms and avoid them. The ICA home page, (http://www.ichelp.org/) introduces the foods often avoided by patients with BPS.

Recommendation:

Personalized dietary manipulation should be part of the therapeutic strategy for patients with IC/BPS.

Level of evidence:2 Grade of recommendation :B

IX. ORAL THERAPY (TABLE 5)

Several categories of medication have been used in the management of patients with bladder pain syndrome including analgesics, antidepressants, antihistamines, Immunosuppressants, and glycosaminoglycans. Many

Table 5: Grade and Level of Evidence according to Oxford System for oral and intravesical therapies: ICI (International Consultation On Incontinence 2012); EAU: European Association of Urology[342]; Giannantoni Systematic Review[343].

Note wide disparity in evidence interpretation.

Oral Therapies

Treatment	ICI	EAU	Giannantoni
Amitriptyline	B: 2	A: 1	A: 1
Analgesics	C: 4	C: 2	
Hydroxyzine	D: 1	A: 1	
PPS	D: 1	A: 1	C: 1
Cyclosporine	C: 3	A: 1	A: 1
L-arginine	-A: 1		A: 1
Antibiotics Regimens	D: 4		
Azathioprine	D: 4		

Oral Therapies

Treatment	ICI
Benzydamine	D: 3
Chloroquine Derivatives	D: 4
Cimetidine	C: 3
Doxycycline	D: 4
Duloxetine	-C: 4
Gabapentin	C: 4
Methotrexate	D: 4

Oral Therapies

Treatment	ICI
Misoprostol	D: 4
Montellukast	D: 4
Nalmefene	-A: 1
Nifedipine	D: 4
Quercetin	D: 4
Tanezumab	D: 1
Suplatast tosilate	D: 3
Vitamin E	D: 4

Intravesical Therapies

Treatment	ICI	EAU	Giannantoni
Lidocaine	C: 2		
DMSO	B: 2	A: 1	
Heparin	C: 3		
Hyaluronic Acid	D: 1	B: 2	
Chondroitin Sulfate	D: 4	B: 2	A: 1
PPS	D: 4	A: 1	
Capsaicin/RTX	-A: 1		
BCG	-A: 1		A: 1
Oxybutinin	D: 4		
BTX (intramural)	A:1		A:1

of these drugs are used empirically. Only a few of them have been studied in randomized controlled trials and none have a grade A recommendation.

1. ANALGESICS

Grade of Recommendation: C - Level of Evidence: 4

The long-term, appropriate use of pain medications is indispensible in the treatment of bladder pain syndrome. Many nonopioid analgesics including acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDs) and even antispasmodic agents [271] have a place in pain therapy. Patients with more severe symptoms can often be helped with medical pain management using medications commonly used for chronic neuropathic pain syndromes including antidepressants, anticonvulsants, and opioids.

Gabapentin, introduced as an anticonvulsant, has found efficacy in neuropathic pain disorders including diabetic neuropathy [272] and postherpetic neuralgia [273]. It demonstrates synergism with morphine in neuropathic pain[274]. Two patients with IC showed improved functional capacity and received adequate pain control when gabapentin was added to their regimen [275]. Sasaki et al reported that 10 of 21 male and female patients with refractory genitourinary pain had subjective improvement of their pain following treatment with gabapentin[276]. Recently gabapentin was one compound of a triple mix including amitriptyline and etodolac, a NSAID. The interpretation of the observed efficacy in 74 patients is hampered by an uncontrolled open lable study protocol that additionally allowed uptitration of gabapentin and amitriptyline. The impact and contribution of amitriptyline, whose exclusive efficacy for BPS has been proven better than for any other oral drug, on the reported amelioration was not discussed[277].

Pregabalin has similar structure as gabapentin and also has been shown to reduce the pain of diabetic neuropathy [278]. Pregabalin was proved effective for treating pain associated with fibromyalgia [279]. Pregabalin might be worthwhile to try for bladder pain syndrome, particularly for those with concurrent fibromyalgia, though studies are lacking.

Opioids are seldom the first choice of analgesics in chronic pain states, but they should not be withheld if less powerful analgesics have failed [280]. Chronic opioid therapy can be considered as a last resort in selected patients, who have disabling pain and often receive inadequate doses of short-acting pain medications, which put them on cycles of short-term relief, anxiety, and pain.

The major impediment to the proper use of opioids when they are prescribed for long-term nonmalignant pain is the fear of addiction. Some studies suggest the risk is low [281], but not zero. [282] Using opiates is a difficult decision that requires much thought and discussion between patient and urologist, and a pain specialist. They are best administered in a pain clinic setting, requiring frequent reassessment by both patient and physician [283].

In addition to narcotics, concurrent usage of nonsteroidal anti-inflammatory drugs, cyclooxygenase inhibitors, acetaminophen, and tricyclic antidepressants may provide better pain control [284]. The common side effects of opioids include sedation, nausea, mild confusion, and pruritis. These are generally transient and easily managed. Respiratory depression is extremely rare if they are used as prescribed. Constipation is common and a mild laxative is generally necessary. The long-acting narcotic formulations that result in steady levels of drug over many hours are preferable.

2. ANTIDEPRESSANTS

a) Amitriptyline

Grade of Recommendation: B - Level of Evidence: 2

Amitriptyline is a tricyclic antidepressant with the property of blocking H1-histaminergic receptors [285]. It stabilizes mast cells and inhibits mediator stimulated vascular leakage. It inhibits synaptic reuptake of serotonin and norepinephrine, thus inhibiting painful nociception from the bladder at the level of the central nervous system. Its nighttime sedation can be therapeutic in the BPS population and its purported beta-adrenergic receptor sti¬mulation in the bladder may facilitate urine storage [286].

Using a dose titration of up to 75mg taken before bed, Hanno and Wein reported success in about half of 20 patients who could tolerate the medication. Twenty percent of the initial 25 patients dropped out because of fatigue, weight-gain, or dry mouth. In a follow-up report [287], 18 of 28 patients who could tolerate the drug had major relief of symptoms within 3 to 6 weeks of onset of therapy with a mean follow-up of 14.4 months. However, about one-third of patients initially placed on the drug could not continue on it because of side effects. Kirkemo et. al [288] treated 30 patients and 90% had subjective improvement in 8 weeks. Pranikoff and Constantino [289] reported improvement in 16 of 22 patients with urinary frequency and pain who did not have a diagnosis of interstitial cystitis, noting that 5 of the 22 could not tolerate the drug.

van Ophoven et al performed the first prospective, double-blind, placebo-control¬led study of amitriptyline. Fifty patients were randomized to placebo or a titrated dose of ami¬triptyline up to 100mg daily. Forty-two per¬cent of amitriptyline patients had greater than 30% decrease in O'Leary/Sant symptom and problem scores at 4 months compared to 13% in the placebo group[290]. They subsequently reported a long-term follow-up of amitriptyline for patients who can tolerate the side effects and continued the medication. With a mean follow-up of 19 months, 64% of 94 patients had response [291].

Foster and Hanno reported a second multicenter, randomized, double-blind, placebo controlled clinical trial of amitriptyline in subjects with interstitial cystitis/painful bladder syndrome who were naïve to therapy. Study participants in both treatment arms received a standardized education and behavioral modification program. Only of the subgroup of 207 subjects who achieved a drug dose of at least 50 mg, a significantly higher response rate was observed in the amitriptyline group (66%) compared to placebo (47%) ($p = 0.01$). When all randomized subjects were considered, amitriptyline plus an education and behavioral modification program did not significantly improve symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. However, amitriptyline may be beneficial in persons who can achieve a daily dose of 50 mg or greater[246].

b) Doxepin, desipramine, duloxetine

Other tricyclic antidepressants that have been used for bladder pain syndrome are doxepin and desiprami¬ne. Wammack et al used the combination of doxepin and piroxicam, a cox-2 inhibitor. Twenty-six of 32 patients (81%) experienced remission of symptoms [292]. One study reported satisfactory outcome with desiprami¬ne. [293] Duloxetine, a serotonin-norepinephrine reuptake inhibitor has also been tried but without therapeutic effects [294]

3. ANTIHISTAMINES

Grade of Recommendation: D - Level of Evidence: 1

Simmons first proposed use of antihista¬mines in 1955 [295]. His findings of mast cells in the wall of a normal bladder and the edema and increased vascularity seen in the IC bladder suggested that histamine may be responsible for the development of interstitial cystitis. He reported on 6 patients who had some improvement with pyribenzamine for limited periods [296].

a) Hydroxyzine

Hydroxyzine is the most widely used antihistamine for bladder pain syndrome. Its ability as an H-1 receptor antago¬nist, to inhibit bladder mast cell activation, along with its anticholinergic and anxiolytic

properties and good safety profile, have made it a reasonable candida¬te for use as a therapeutic agent for bladder pain syndrome.[297]In 1933, Theoharides first reported significant benefits of hydroxyzine in reducing pain and urinary symptoms. [298] His two subsequent reports of totally uncontrolled series further suggested the therapeutic effects of hydroxyzine. [299] [300] However, in an NIDDK randomized controlled trial, the global response rate for hydroxyzine was only 31% compared to a 20% response to those not treated with hydroxyzine. When looked at by itself the response was 23% vs. 13% on placebo. None of the results in this under-powered trial reached statistical significance [301].

b) Cimetidine

Grade of Recommendation: C - Level of Evidence: 3

Cimetidine, a H2 histamine receptor antagonist, has been explored for treatment of bladder pain syndrome. In a pilot study [302], 9 patients were treated with a dose of 300mg orally twice daily for one month. At follo¬wup 26 to 42 months later, 4 patients had complete relief of urinary symptoms and suprapubic pain. Lewi [303] reported 31 patients given 200mg three times daily with mean follow up of 6.6 months. Seventy-one per cent experienced varying degrees of symptomatic relief, 45% were pain free, and 26% went into remission of all symptoms. In a later report [304] of 69 patients treated over a 4 year period, 67% of patients had complete relief of all symptoms.

A small, prospective, placebo-controlled RCT studied 36 patients who either received oral cimetidine or placebo [305]. Median supra¬pubic pain and frequency scores improved signifi¬cantly, but the publication does not state exactly how many patients in each group improved.

4. IMMUNOSUPPRESSANTS

a) Cyclosporine

Grade of Recommendation: C - Level of Evidence: 3

Cyclosporine, a widely used immunosuppressive drug in organ transplantation, was the subject of a novel bladder pain syndrome trial. [306] Eleven patients recei¬ved cyclosporine for 3-6 months at an initial dose of 2.5-5 mg/kg daily and a maintenance dose of 1.5 to 3mg/kg daily. Micturition frequency decreased, and mean and maximum voided volumes increased significantly. Bladder pain decreased or disappeared in 10 patients. After cessation of treatment, symp¬toms recurred in the majority of patients.

In a lon¬ger-term follow-up study, 20 of 23 refractory IC patients on cyclosporine therapy followed for a mean of 60.8 months became free of bladder pain. Bladder capacity more than doubled. Eleven patients subsequently stopped the¬rapy, and in 9, symptoms recurred within months, but responded to reinitiating cyclosporine [307]. Sairanen et al further found that cyclosporine A was far superior to sodium pentosanpolysulfate in all clinical outcome parameters measured at 6 months. [308] Patients who responded to cyclosporine A had a significant reduction of urinary levels of epidermal growth factor (EGF) [309].

b) Suplatast Tosilate

Grade of Recommendation: D - Level of Evidence: 3

Suplatast Tosilate (IPD-1151T) is an immunoregulator that selectively suppresses IgE production and eosinophilia via suppression of helper T cells that produce IL-4 and 5. It is used in Japan to treat allergic disorders including asthma, atopic dermati¬tis, and rhinitis. Ueda et al reported a small study in 14 women with interstitial cystitis. [310] Treatment for one year resulted in a significantly increased bladder capacity and decreased urinary urgency, fre¬quency, and lower abdominal pain in 10 women. Concomitant changes occurred in blood and urine markers suggesting an immune system response. Larger, multicenter, randomized controlled trials in the United States and Japan have been completed and results are unpublished. Further studies with this drug for bladder pain syndrome are not planned and approval for this indication is not expected.

c) Azathioprine and Chloroquine derivatives

Grade of Recommendation: D - Level of Evidence: 4

In a single report in 1976, Oravisto et al used azathioprine or chloroquine derivatives for BPS patients not responding to other treatments.[311] About 50% patients responded.

d) Corticosteroids

Reports on outcome with corticosteroid therapy have been both promising (131) and discouraging (132). Soucy et al. (133) have suggested a trial of prednisone (25 mg daily for 1–2 months, afterwards reduced to the minimum required for symptom relief) in patients with severe ulcerative IC, which is otherwise unresponsive to conventional treatment. The side effects of steroids can be very serious, making it difficult to justify their use[312-314].

5. SODIUM PENTOSANPOLYSULFATE

Grade of Recommendation: D - Level of Evidence: 1

Sodium pentosan¬polysulfate (PPS), a synthetic sulfated polysaccharide, is available in an oral formulation, 3-6% of which is excreted into the urine and theoretically may replenished the damaged glycosaminoglycan (GAG) layer overlying transitional epithelium of the urinary bladder of BPS patients. An intact urothelial GAG layer has been proposed to be essential to keep the urothelium impermeable to urinary components. A defective bladder GAG layer is hypothesized to be one important cause for BPS. [315]

PPS's mechanism of action has been attributed not only to correction of a putative defect in the GAG layer, but also its ability to inhibit histamine release from mast cells, [316] and a pos¬sible effect mediated by nonspecific binding of the molecule with the inflammatory stimulants of uro-thelial activation, an action that would occur in the urine rather than at the mucosal membrane [317].

PPS is the most intensively studied treatment ever proposed for BPS. It is the only medication approved by the Food and Drug Administration for the pain of interstitial cystitis. Parsons initially administered the drug at a dosage of 50mg 4 times daily or 150mg twice daily in an open trial involving 24 patients. [318] Twenty-two of 24 patients experienced a good or excellent response within 8 weeks. In a subsequent randomi¬zed, placebo-controlled trial using a dose of 100mg three times daily in 62 patients, pain and urgency improved in 44% vs. a placebo response of 15%. Urgency improved by 38% vs. 18% on placebo. The average number of daily voids was unchanged [319].

Five randomized controlled trials for pentosan polysulfate have yieled conflicting results of efficacy. Holm-bentzen et. al[320] reported the first multicenter double-blind placebo controlled trial in 1987 looking at 115 patients with bladder pain syndrome. Patients were randomized to a dose of 200mg twice daily vs. placebo for 4 months. The results showed no difference between pre and post trial values with regard to symptoms, urodynamic parameters, cystoscopic appearance, or mast cell counts in the two groups. The study concluded that the drug had no clinically significant effect.

The first of two pivotal studies for the FDA was per¬formed in the United States in 1990.[321] A total of 110 patients in 5 medical centers were studied for 3 months on a dosage of 100mg three times daily. Twenty-eight per cent of patients on PPS reported "more than slight improve¬ment" versus 13% of those on placebo. Pain and pressure to urinate were the main parameters to show benefit with PPS.

The FDA asked for a second study which was reported 3 years later. [322] In a multi¬center, placebo-controlled RCT 148 patients were randomized to 100mg three times daily of pentosan-polysulfate vs. placebo. In the primary endpoint of patient self-evaluation of global improvement, 32% of those on PPS reported 50% or more overall impro¬vement vs. 16% on placebo at 3 months. Pain, urgen¬cy, and pressure showed significant improvement with drug. Frequency, nocturia, and volume voided showed no significant changes between study groups.

The NIDDK performed their own 2 X 2 factorial study to evaluate PPS and hydroxyzine. [301] Each drug was used alone and in combination and compa¬red to a placebo group. Patients were treated for 6 months. There were 121 participants in 7 centers. No statistically significant response to these medi¬cations was documented. A non-significant trend was seen in the PPS treatment groups (34%) compa¬red to non-PPS groups (18%). Of the 29 patients on PPS alone, 28% had global response (primary end¬point) of moderately or markedly improved vs. 13% on placebo, very similar in this 6-month study to improvement rates in the 3-month pivotal studies, though not reaching statistical significance in the longer study.

In summary

Of 5 RCTs 2 had unfavorable and 3 had favorable results for PPS. Most recent non randomized studies showed a complex heterogenity in efficacy as well[323-326]. Such conflicting results might suggest that a minority of patients do respond to PPS, but currently there is no reliable method to identify such patients.

Long-term, open-label studies with PPS have been reported. Populations of patients receiving extended treatment for up to 90 months or more in the com¬passionate use program showed no further improve¬ment in symptoms after 1-2 years, though there seemed to be little tachyphylaxis [301,327]. A total of 2809 patients had begun treatment with a 3 month supply of PPS and 21% continued with treatment beyond this point and reordered medication. This seems to cor¬relate with the 28-32% improvement rate previously reported. The dropout rate in the first 6 months was extraordinarily high with only 178 active patients out of 1742 who initially ordered the drug. There was an overall improvement in symptoms in 62% of the patients who did remain in treatment for 6-35 months.

PPS appears to be a very well-tolerated medi¬cation [327] with no common central nervous sys-tem side effects, and appears to be beneficial with regard to improving the pain associated with inter-stitial cystitis in up to one-third of patients, a stan¬dard often expected with a placebo. A 3-6 month course is required to see an effect in most patients. Claims suggesting greater efficacy and claims urging its use in patients who do not meet the standard defi¬nition of bladder pain syndrome should be regarded with caution.

6. OTHER ORAL MEDICATIONS THAT HAVE BEEN USED FOR BPS

a) L-arginine

Grade of Recommendation: -A - Level of Evidence: 1

Foster and Weiss were the original proponents of L-arginine in the therapy of interstitial cystitis [328]. Eight patients with IC were given 500mg of L-arginine 3 times daily. After one month, urinary nitric oxide synthase activity increased 8-fold and 7 of the 8 patients noticed improvement in IC symptoms. An open-label study of 11 patients showed improvement in all 10 of the patients who remained on L-arginine for 6 months [329].

An open-label study of 9 women in Sweden failed to find any change in symptom scores or in nitric oxide production in the bladder [330]. A placebo-control¬led randomized controlled trial of 53 IC patients could find no difference on an intention to treat analysis between drug and pla¬cebo-treated patients [331]. A smaller randomized placebo-controlled crossover trial of 16 IC patients found no clinically significant improvement with L-arginine and concluded that it could not be recom¬mended for IC treatment [332].

Data does not support the use of L-arginine for the relief of symptoms of interstitial cystitis.

b) Quercetin

Grade of Recommendation: D - Level of Evidence: 4

Quercetin, a bioflavenoid available in many over-¬the-counter products, may have the anti-inflammato¬ry effects of other members of this class of com¬pounds found in fruits, vegetables, and some spices. Katske et. al [333] administered 500mg twice daily to 22 BPS patients for 4 weeks. All but one patient had some improvement in the O'Leary/Sant symptom and problem scores as well as in a global assessment score. Further studies are necessary to determine efficacy.

c) Antibiotics

Grade of Recommendation: D - Level of Evidence: 4

Warren et. al [334] randomized 50 patients to recei¬ve 18 weeks of placebo or antibiotics in-cluding rifampin plus a sequence of doxycycline, erythromy¬cin, metronidazole, clindamycin, amoxi-cillin and ciprofloxacin for 3 weeks each. Intent to treat ana¬lysis demonstrated that 12 of 25 patients in the anti¬biotic and 6 of 25 patients in the placebo group reported overall improvement while 10 and 5 respec¬tively noticed improvement in pain and urgency. The study was complicated by the fact that 16 of the patients in the antibiotic group un-derwent new BPS therapy during the study as did 13 of the placebo patients. There was no statistical signi¬ficance reached. What was statistically sig-nificant were adverse events in 80% of participants who received antibiotic compared to 40% in the pla-cebo group. Nausea and/or vomiting and diarrhea were the predominant side effects. Most patients on antibio¬tics correctly guessed what treatment arm they were in, and those that guessed correctly were significant¬ly more likely to note improvement after the study. No duration in improvement after comple-tion of the trial of antibiotics was reported.

Burkhard et.al [335] reported a 71% success in 103 women presenting with a history of urinary urgen-cy and frequency and chronic urethral and/or pel-vic pain often associated with dyspareunia and/or a his¬tory of recurrent urinary tract infection. This was a large, inclusive group and one that is prob-ably broa¬der than the bladder pain syndrome we are focu¬sing on. Nevertheless, he recommended empiric doxycycline in this group. The overwhelm-ing majo¬rity of BPS patients have been treated with empiric antibiotics prior to diagnosis. The role of tetracyclines to eradicate nanobacteria in urine of BPS patients has recently been addressed in small Chinese open label study, leaving the significance of nanobacterias as a reasonable pathogen or trig-ger of the condition open [129,324-326].

At this time there is no evidence to suggest that an-tibiotics have a place in the therapy of BPS in the absence of a culture-documented infection [336].

d) Methotrexate

Grade of Recommendation: D - Level of Evidence: 4

Low dose oral methotrexate significantly improved bladder pain in 4 of 9 women with BPS, but did not change urinary frequency, maximum voided vol-ume, or mean voided volume [337]. No placebo-controlled, RCT has been done with this agent.

e) Montelukast

Grade of Recommendation: D - Level of Evidence: 4

Mast cell triggering releases 2 types of proinflamma¬tory mediators, including granule stored pre-formed types such as heparin and hista-mine, and newly syn¬thesized prostaglandins, and leukotriene B4 and C4. Classic antagonists, such as montelukast, zafirlukast and pranlukast, block cys-teinyl leukotriene 1 recep¬tors. In a pilot study,[338] 10 women with IC and detrusor mastocytosis re-ceived 10mg of montelukast daily for 3 months. Fre-quency, nocturia, and pain improved dramatically in 8 of the patients. Further study would seem to be warranted, especially in patients with detrusor mas-tocytosis, defined as >28 per mm2.

f) Nifedipine

Grade of Recommendation: D - Level of Evidence: 4

The calcium channel antagonist nifedipine inhib-its smooth muscle contraction and cell-mediated immu¬nity. In a pilot study, [339] 30mg of an ex-tended release preparation was administered to 10 female patients and titrated to 60mg daily in 4 of the patients who did not get symptom relief. Within 4 months five patients showed at least a 50% de-crease in symptom scores, and 3 of the 5 were as-ymptomatic. No further studies have been reported.

g) Misoprostol

Grade of Recommendation: D - Level of Evidence: 4

The oral prostaglandin analogue misoprostol was studied in 25 patients at a dose of 600 micro-grams daily [340]. At 3 months 14 patients were signifi¬cantly improved, and at 6 months 12 patients still had a response. A cytoprotective action in the urina¬ry bladder was postulated.

h) Tanezumab

Grade of Recommendation: D - Level of Evidence: 1

A recent randomized, double-blind, placebo controlled phase two 64 patient study investigated tanezumab, a humanized monoclonal antibody that specifically inhibits nerve growth factor as a treatment for BPS pain[341]. At week 6 tanezumab produced a significant reduction from baseline in average daily pain score vs placebo . A significantly higher proportion of patients on tanezumab responded as improved in the global response assessment and tanezumab also significantly reduced urgency episode frequency vs placebo. Studies with this drug have been suspended by the Food and Drug Administration because of the occurrence of osteonecrosis in nonurologic trials.

X. INTRAVESICAL / INTRAMURAL THERAPY (TABLE 5)

Intravesical therapies form one of the staples of BPS therapy, though regulatory approvals and availability throughout the world differ from nation to nation. What follows are treatments that have been reported in the recent literature, some of which are commonly used. Older therapies that are rarely used now include silver nitrate[80,344-347] and chlorpactin WCS90.[7,348-352] These have not been included in this current edition of the Consultation, but have level 3 evidence to support a grade C recommendation based on original reports.

1.DMSO (DIMETHYL SULFOXIDE)

Grade of Recommendation: B - Level of evidence 2

A small number of significant side effects. Not approved in Japan.

DMSO is believed to reduce inflammation, relax muscles, eliminate pain, dissolve collagen, and degranulate mast cells. It has long been used as a therapeutic agent for BPS. Its mechanism of action, however, has not been clarified. Ten articles on DMSO for the treatment of IC were retrieved. Peeker et al[353] reported that in a randomized study, frequency and pain were improved in ulcer-type IC patients, although no improvement was observed in maximum bladder capacity. Perez-Marrero et al[354] reported that in a non-randomized controlled study, 53% of the patients showed remarkable improvement in subjective evaluation (placebo 18%), and 93% in objective evaluation (placebo 35%). Around an 80% improvement rate has been reported in case series and retrospective studies.[355-362]

With regard to side effects after instillation of DMSO, most patients recognize a garlic-like odor, which disappears within a day, and about 10% of patients report bladder irritative symptoms which resolve with or without symptomatic treatment.[363] It is hypothesized that these transient exacerbations occur as the result of mast cell degranulation. The number of significant side effects is considered to be small[362]. Cataracts have been reported in animal studies,[364,365] though not in humans. Negative effects on bladder compliance have been noted in rat detrusor.[366] DMSO may accelerate the absorption of other drugs instilled simultaneously, which could be a source of side effects.

The instillation method has not been standardized. Generally, 50cc of a solution of medical grade 50% DMSO is instilled into the bladder. If pain occurs immediately following instillation, local anesthesia (e.g. 20ml of 2% lidocaine solution) may be instilled. Average retention time is considered to be 10 to 20 minutes.[363] The instillation is performed weekly for 6-8 weeks. After an initial course, treatment is suspended until symptoms recur. If a good result was obtained, another 6 week course (often followed by monthly maintenance) can be initiated. The long-term effect is unknown, although there is no upper limit for the duration of the treatment. DMSO is medically approved in the US, while it has not been approved yet in Japan.

2. HEPARIN

Grade of Recommendation: C - Level of Evidence: 3

Side effects primarily related to effects intravesical catheterization and slight chance of bladder hemorrhage.

The glycosaminoglycan (GAG) layer on the bladder urothelium is a kind of muco-polysaccharide, working as a non-specific defense mechanism. It is believed that a deficiency or abnormality of GAG secondarily causes inflammation of the bladder by increasing the permeability of the bladder mucosa, leading to the pathologic cascade of BPS. Heparin has similarities to the GAG layer of the bladder. When instilled into the bladder, theoretically it might replace the damaged GAG layer. Kuo[367] reported that the International Prostate Symptom Score, as well as bladder capacity at initial desire to void and maximum bladder capacity, improved significantly. According to the report by Parsons et al[368] symptoms were reduced in 56% of patients treated 3 times weekly for 12 weeks. These reports suggest the efficacy of heparin, however, there is no randomized comparative study to give conclusive evidence. One study indicated that intravesical heparin instillations may prolong the response to dimethyl sulfoxide treatment.[369]

No significant side effects have been reported, as it does not affect systemic coagulation parameters. In the case of patients with hematuria, however, it may exacerbate local hemorrhage.

The instillation method has not been standardized. Generally, 10,000-40,000 units of heparin are instilled. It is unusual to have pain or irritation as a

result of instillation, and retention times can be 30 minutes or more. Instillation frequency can be up to every other day and is often administered at home by the patient. Parsons et al[370] recently reported that when 40,000 units of heparin combined with 1 to 2% lidocaine was instilled 3 times a week for 2 weeks, about 80% efficacy was obtained. There is no upper limit for the duration of the treatment, but a long-term effect is unknown. A bleeding tendency may occur. Heparin for intravesical use is not approved by drug regulatory authorities.

3. HYALURONIC ACID

Grade of Recommendation : D - Level of Evidence: 1

No significant side effects.

Hyaluronic acid, like heparin, is a muco-polysaccharide, that could theoretically repair a damaged GAG layer of the bladder mucosa. Seven reports have indicated efficacy.[371-376] In the summer of 2003 Bioniche Life Science Inc http://www.medicalnews-today.com/articles/112053.php and in the spring of 2004 Seikagaku Corporation reported double-blind, placebo-controlled, multicenter clinical studies of their hyaluronic acid preparations (40mg or 200mg per cc respectively) and neither showed significant efficacy of sodium hyaluronate compared to placebo. These negative studies have not been published in peer reviewed literature. Neither preparation has been approved for use for BPS in the United States. At the same time, no significant side effects were observed.

A non-placebo-controlled study has demonstrated a favorable effect of hyaluronic acid on pain reduction [192]. Forty-eight patients with typical symptoms and a positive potassium (0.4 M) sensitivity test were treated with weekly instillations of 40 mg hyaluronic acid for 10 weeks. Visual analogue scale scores showed symptom relief due to hyaluronic acid therapy, irrespective of bladder capacity. The improvement was particularly evident in patients with a reduction in Cmax < 30% compared to patients with a reduction of < 30% with 0.2 M KCl solution (P = 0.003). Long-term effects were investigated in a study of 70 patients previously treated with hyaluronan [377]. Of the initial 70, 48 improved. Of these, 50% reported complete remission with no further therapy. Another 41.7% of patients with symptom recurrence improved after retreatment

A recent interventional study from China suggested a prolonged effect of bladder distension when combined with instillation of hyaluronic acid [378]

4. CHONDROITIN SULFATE

Grade of Recommendation: D - Level of Evidence: 4

No significant side effects.

Chondroitin sulfate is another mucopolysaccharide. Its efficacy was suggested for the first time 2002 when used alone [379]and in another trial when used in combination with hyaluronic acid (364). Intravesical chondroitin sulphate demonstrated beneficial effects in patients with a positive potassium stimulation test in two non-randomised, uncontrolled, open-label pilot studies. Steinhoff (363) treated 18 patients with 40 mL instilled intravesically once weekly for 4 weeks and then once monthly for 12 months. Thirteen of 18 patients were followed for the entire 13-month study. Twelve of these patients responded to treatment within 3–12 weeks. A total of 6/13 (46.2%) showed a good response, 2/13 (15.4%) had a fair response, 4/13 (30.8%) had a partial response, and 1/13 (7.7%) showed no response. In a second trial [380] 24 refractory patients with BPS/IC were treated with high-dose (2.0%) chondroitin sulphate instillations twice weekly for 2 weeks, then weekly with 0.2% solution for 4 weeks, and monthly thereafter for 1 year. The average symptom improvement reported in 20 patients completing the trial was 73.1% (range: 50–95%). The time to optimum response was 4–6 months. A more concentrated 2.0% solution was needed in eight patients to maintain results. Chondroitin sulphate instillation was effective and well tolerated in the therapy of various chronic forms of cystitis associated with a possible GAG layer deficit including BPS in a large multicenter but open srudy [381].

Sixty-five patients with IC/BPS were treated in a prospective, randomized, double-blind, inactive vehicle-controlled, 12-week study (6 weeks treatment, followed by 6 weeks follow-up) . At the primary endpoint analysis (week 7), 22.6% of the vehicle control group were responders compared with 39.4% of the active therapy group, however, the difference was not significant [382]. A follow up randomized placebo-controlled trial with 98 female patients showed only minor improvements in IC/BPS symptoms and pain and failed to demonstrate a statistically significant drug effect vs. placebo [383] . The authors concluded that the study did not support the use of intravesical chondroitin sulfate as a monotherapy for this condition.

5. PENTOSAN POLYSUFATE

Grade of Recommendation: D - Level of evidence: 4

No significant side effects are considered to be present.

Pentosan polysufate (PPS) is a mucopolysaccharide similar to heparin, with a similar postulated mode of action when used locally. Like other muco-polysaccharides, it has not been well-studied clinically. Bade et al in a randomized controlled trial found benefit in 4 patients out of 10 on PPS versus 2 of 10 on placebo.[384] A more recent placebo-controlled study of 41 patients found the addition of a 6 week course of intravesical PPS to a regimen of oral PPS significantly improved results.[385]

6. VANILLOIDS (CAPSAICIN, RESINIFERATOXIN)

Grade of Recommendation: -A (ineffective) - Level of Evidence: 1

Significant side effects: local irritation possible

It would seem reasonable that capsaicin, a C-fiber afferent neurotoxin, could alleviate the pain of BPS by desensitizing bladder afferents. Resiniferatoxin (RTX) is considered to have a stronger action than capsaicin, by desensitizing C-fibers more quickly, and causing less initial irritation. Efficacy was indicated in five relatively small clinical trials.[386-390] No severe side effects were reported. A randomized multicenter placebo-controlled clinical trial of RTX failed to demonstrate benefit over placebo.[391]

7. BACILLUS CALMETTE-GUERIN (BCG)

Grade of Recommendation: -A (ineffective) - Level of Evidence: 1

Potential serious complications

Seven articles reported on a BCG instillation therapy. Zeidman et al first reported that 5 patients who did not respond to other therapies showed symptomatic improvement.[392] Peters et al conducted a randomized double blind study showing a 60% improvement compared to 27%[393] placebo response with good long-term results at 27 months.[394] Sixty-five percent of the patients experienced burning sensation, 41% irritation of the bladder, and 35% pelvic pain. One patient was reported to have dropped out due to joint pain.

Peeker et al conducted a randomized double blind study comparing intravesical BCG and DMSO and failed to find any efficacy with BCG.[353] A very large, multicenter randomized placebo controlled trial conducted by the National Institute of Diabetes, Digestive, and Kidney Disorders failed to identify benefit from BCG, although the side-effect profile was surprisingly similar to that of placebo.[395]

8. OXYBUTYNIN

Grade of Recommendation D - Level of Evidence: 4

Side effect profile is unknown

Barbalias et al observed significant improvement when combining intravesical instillation of oxybutynin with bladder training.[396] Randomized trials are lacking.

9. LIDOCAINE

Grade of Recommendation: C - Level of Evidence: 2

No significant side effects.

Lidocaine is a local anesthetic that relieves pain by blocking sensory nerves in the bladder. Four articles[397-400] reported on the electromotive drug administration (EDMA) of lidocaine. Using EMDA, ionized lidocaine is actively introduced into the bladder using an electrical current. Three articles reported that lidocaine and dexamethasone were instilled following hydrodistention. According to the report by Rosamilia et al[400], 85% of the patients had a good result, with the effect persisting for 6 months in 25%. There are two other case reports.[401,402] A report on a pharmacokinetic effect, demonstrated safe levels of lidocaine absorption into the bladder.[403] 102 adult patients (99 women) with a clinical diagnosis of BPS were randomised from 19 centres in the USA and Canada to receive a daily intravesical instillation of alkalinised lidocaine or placebo (double-blind), for 5 consecutive days. Treated patients had significant sustained symptom relief for up to 1 month [404]. However, further randomized, placebo-controlled trials are needed to ascertain efficacy, optimal treatment parameters, and length of response to intravesical lidocaine preparations.[405] Advantages seem to be immediate response, low-cost of generic medication, and ability of patients to self-administer at home.

10. BOTULINUM TOXIN (INTRAMURAL)

Grade of Recommendation: A - Level of Evidence: 1

• Side effects include dysuria, incomplete emptying

Botulinum toxin type A (BTX-A) acts by binding to the nerve endings within muscles, blocking the release of acetylcholine, and probably other neurotransmitters, to modulate muscle contraction and reduce the sensitization of sensory nerve endings. There is increasing evidence for an additional, direct effect on the sensory bladder pathways and subsequent modulation of the efferent overactivity or hyperexcitability involved in the pathophysiology of the detrusor and other muscle dysfunction.[406]

Thirteen BPS patients were injected with 100–200 IU of BTX-A (abobotulinumtoxin A or onabotulinumtoxin A) into 20–30 sites submucosally in the trigone and floor of the bladder. Overall, nine (69%) patients noted subjective improvement, and ICSI scores improved by 70% ($P < 0.05$). There were significant decreases in daytime frequency, nocturia and pain, and a significant increase in first desire to void and maximal cystometric capacity. However .dysuria occurred in a majority of patients and persisted in a minority for several months after initial injection. Three patients required clean intermittent catheterization for 2-3 months following therapy.[407]

To ascertain effect of repeat injections a total of 13 patients were followed up for 2 years, while 58 injections were administered with a mean of 4.8 ± 0.8 injections per patient. The mean interval between two consecutive injections was 5.25 ± 0.75 months. At 1 and 4 months follow-up, 10 patients reported a subjective improvement. Mean VAS scores, mean daytime and night-time urinary frequency decreased significantly. The three non-responders to

the first intravesical treatment session underwent further treatment 3 months later with satisfactory results. At 1 and 2 years follow-up, the beneficial effects persisted in all patients [408]

These results are in contrast with those in another study from Kuo of BTX-A (onabotulinumtoxin A) in 10 patients with BPS. One hundred units were injected suburothelially into 20 sites in five patients, while 100 U were injected into the trigone in the remaining five. None of the patients became symptom-free; two showed only limited improvement in bladder capacity and pain score.[409]

However in an RCT, Kuo and Chancellor analysed the difference between hydrodistension and hydrodistension plus intravesical, sub mucosal BTX-A (onabotulinumtoxin A).[410] Of the 67 patients, 44 were divided in two groups: one received 200 U and the other 100 U, and cystoscopic hydrodistension was performed after 2 weeks. The remaining 23 patients received hydrodistension only. There was symptomatic improvement in all groups. However, in the hydrodistension group, 70% had returned to their previous symptoms after the first month, while in the BTX-A-treated groups, there was improvement of VAS, functional bladder capacity and cystometric bladder capacity at 3 months. At 12 and 24 months, the results in the active group were 55 and 30% versus 26 and 17% in the hydrodistension group

Trigonal-only injection seems effective and long-lasting since 87% of patients (n = 23) reported improvement after a 3-month follow-up period in a study by Pinto et al.[411] Over 50% referred continuity of the beneficial effect 9 months after the first treatment. When retreatment was needed, similar results were obtained. No cases of urinary retention were reported. The authors concluded that this treatment is safe, effective and can be repeated.

Further studies will be needed to obtain conclusive evidence for its efficacy, duration of effect, and side-effect profile.

XI. NEUROMODULATION

Grade of Recommendation: B - Level of Evidence: 1

Sacral nerve stimulation (SNS) involves implanting permanent electrode(s) to stimulate S3 or S4 roots. As early as 1989, Tanago et al showed that stimulation of S3 may modulate detrusor and urethral sphincter function [412]. FDA approved the usage of sacral neuromodulation for treating refractory detrusor overactivity in 1997 and for urinary urgency and frequency in 1999. Although the effectiveness of SNS for detrusor overactivity is largely confirmed by a goodnumber of papers, only a few papers report the effect of SNS in treating BPS.

Zerman et. al reported significant improvement in a 60-year-old woman treated for severe BPS pain using sacral nerve stimulation implant. Pain and accompanying bladder dysfunction were improved by temporary and permanent sacral nerve stimulation for up to six months [413]. Maher et al [414] showed that temporary stimulation was effective in 73% of 15 women with refractory BPS. Mean voided volume during treatment increased and mean daytime frequency, nocturia and pain decreased significantly. As indicated by the Short Urinary Distress Inventory and SF-36 Health Survey, the quality of life parameters of social functioning, bodily pain and general health significantly improved during the stimulation period.

Chai et. al[230] found that percutaneous S3 nerve root stimulation improves symptoms and normalizes urinary HB-EGF levels and antiproliferative activity in patients with BPS. In their report in 2003, Comiter et al[415] prospectively investigated the effect of SNS on a series of 17 patients with refractory BPS. At an average of 14 months follow-up mean daytime frequency, nocturia and mean voided volume improved significantly. The average pain decreased from 5.8 to 1.6 points on a scale of 0 to 10 and Interstitial Cystitis Symptom and Problem Index scores (ICSI and ICPI) decreased from16.5 to 6.8 and 14.5 to 5.4, respectively. Of the 17 patients 16 (94%) with a permanent stimulator demonstrated sustained improvement in all parameters at the last postoperative visit. Whitmore el al [416] applied percutaneous sacral nerve root stimulation on 33 patients with refractory interstitial cystitis. Statistically significant improvements were seen in pain and urinary symptoms. Significant improvements were also seen in ICSI and ICPI scores.

Peters et al [417] reported a reduction of narcotic usage in 18 BPS patients following SNS for a mean of 15.4 months, although the dose reduction was modest (36%) and only 4 of 18 discontinued the narcotics. However, Elhilali and colleagues [418] found that both of two patients with interstitial cystitis reported no improvement following sacral neuromodulation. Zabihi et al [419] more extensively stimulate S2-S4 by implanting electrodes into epidural space through sacral hiatus. 23 of 30 (77%) patients had successful trial stimulation and were permanently implanted. Among these patients, the symptom score was improved by 35% (p=0.005). The pain score improved by 40% (p=0.04). Patients reported an average of 42% improvement in their symptoms.

In the first prospective, single-blind, crossover trial of sacral nerve stimulation (SNS) versus pudendal nerve stimulation (PNS) for patients with BPS (n = 22), PNS gave an overall 59% improvement in symptoms, whereas SNS gave an overall 44% improvement (P = 0.05). Most patients who tested both a sacral and pudendal electrode chose PNS as the better site. Follow-up showed marked improvements in voiding variables

and validated BPS symptom questionnaires. Over 90% of patients treated with neuromodulation stated that they would undergo implantation again [420].

Long-term results were verified in a retrospective study of 78 patients treated from 1994 to 2008. Permanent sacral neuromodulation implantation was performed in patients who showed at least 50% improvement in their symptoms with a temporary peripheral nerve evaluation test. Median follow-up was 61.5 ± 27.7 months. Good long-term success of sacral neuromodulation was seen in 72% of the patients. The explantation rate was 28%. The most frequent reason for explantation was poor outcome (54% of the failed patients). The revision rate was 50% [421] In another observational, retrospective, case-controlled review (January 2002–March 2004), 34 female patients underwent permanent device implants . Mean pre-/postoperative pelvic pain and urgency/frequency scores were 21.61 ± 8.6/9.22 ± 6.6 ($P < 0.01$), and mean pre-/postoperative visual analogue pain scale (VAPS) scores were 6.5 ± 2.9/2.4 ± 1.1 ($P < 0.01$). Mean follow-up was 86 ± 9.8 months. Sacral neuromodulation showed adequate improvement for the symptoms of refractory BPS. Reoperation rate was 25%.[422]

Sacral nerve modulation is still considered an investigational procedure for BPS by the Consultation. Pudendal nerve stimulation has shown better results. Therapeutic benefits of both appear to be significant in selected cases. Strict patient selection and detailed discussion with patients prior to surgery is mandatory. Long-term results should be collected and reported, and trial results discussed with patients before employing this treatment modality.

XII. PAIN EVALUATION AND TREATMENT

1. EVALUATION OF PAIN:

The first premise that all physicians treating patients diagnosed with BPS is that they deserve to have their chronic pain assessed and treated. It is now recognized that successful management of BPS is only possible using a multidisciplinary and multimodal treatment approach which must include management of the associated chronic pain. This includes evaluation of the whole patient, not just the urology related symptoms. As described in previous sections, this will involve assessment of clinical symptoms, physical signs and history to best define the underlying diagnosis and overlapping conditions, while not ignoring the problems of mood, sleep and sexual problems. The patient's self report should be the primary source of assessment. Clinicians should assess pain with easily administered rating scales and should document the efficacy of pain relief at regular intervals after starting or changing treatment. Systematic evaluation of the pain involves the following:

- Evaluation of severity
- Detailed history of the pain including assessment of pain intensity and character
- Evaluation of the psychological state of the patient, including assessment of mood and coping responses
- Physical examination emphasizing the neurologic examination
- Diagnostic workup to determine the cause of the pain
- Re-evaluation of therapeutic strategy and response.

The initial evaluation of pain should include a description of the pain, **PQRST** has been described for this purpose:

P: Palliative or Provocative factors, 'what makes it less intense?'

Q: Quality, 'what is it like?'

R: Radiation, 'does it spread anywhere else?'

S: Severity, 'how severe is it?'

T: Temporal factors, 'is it there all the time, or does it come and go?'

Pain measurement

A number of different rating scales have been devised to attempt to methodically measure pain and to allow patient follow-up. These have been used in research, audit and in clinical practice. They all rely on a subjective assessment of the pain and therefore make inter-individual comparisons difficult. Additionally, pain is a multidimensional complex phenomenon and is not adequately described by one-dimensional scales, however there is value in making some sort of an assessment to aid clinical practice.

- Categorical scales e.g., verbal rating scales: mild, moderate, severe pain
- Visual analogue, Likert or Numerical Rating scale (VAS)
- Complex pain assessment compendiums e.g., Brief Pain Inventory (BPI), McGill Pain Questionnaire [423-425]

The BPI consists of several visual analogue scales grouped together assessing pain at rest, on movement, and other aspects of the pain including interference with function and effect on work. The McGill Pain Questionnaire measures pain quality by asking patients to rate the intensity of 15 verbal descriptors of pain on a 0 to 3 rating scale. The pain rating index is composed of 2 scores, including a sensory pain score and an affective pain score. Some versions also use a standard pain intensity VAS.

2. PHARMACOLOGIC MANAGEMENT OF CHRONIC PELVIC PAIN

Physicians using pharmacologic measures to control BPS pain must be committed to the following principles [426]:

1. drugs are prescribed and monitored with knowledge of the patient's history and risks,

2. patients understand potential benefits and harms and participate in reducing harms

3. clinicians assess outcomes for both effectiveness and harms.

a) Non-acidic antipyretic analgesics

Acetaminophen (paracetamol) is the main representative of this group. It has antipyretic activity and is a simple analgesic. There is very little evidence about its role in chronic pelvic pain [427,428]. Acetaminophen should be considered for only mild pain. Acetaminophen is a common cause of hepatotoxicity [429,430] and risk increases with alcohol use [431].

b) Acidic antipyretic analgesics

The classical non-steroidal anti-inflammatory drugs (NSAIDs) fall into this group and include salicylic acid. They are known to act on the cyclooxygenase (COX) enzyme. The early NSAIDs tended to have little selectivity for COX2 over COX1, and are therefore said to be associated with more side effects than the newer COX2 selective inhibitors [432]. The COX1 enzyme is mainly involved in normal 'housekeeping' functions, such as mediating gastric mucosal integrity, and renal and platelet function. Blocking the COX1 enzyme is the cause of the platelet, gastric and renal complications that can occur with NSAIDs. It has been suggested that the COX2 enzyme is inducible as a result of tissue damage, and that it is the main enzyme involved in inflammation and peripheral sensitization of nociceptors [433]. As a result, the analgesic efficacy of COX2 selective drugs should be as good as that of the nonselective drugs, however the benefit is primarily seen in acute inflammatory type pain The selective COX2 agents should not be prescribed in patients with increased risk of cardiovascular disease including congestive cardiac failure [434]. There is very little evidence for a role of NSAIDs in the management of chronic pelvic pain and even less evidence for a role for the COX2 selective drugs. Most of the analgesic studies have investigated dysmenorrhoea in which NSAIDs have been found to be superior to placebo and possibly paracetamol [428,435]

For practical purposes the NSAIDs may be divided into:

1. Non-selective, low potency (e.g. salicylic acid, ibuprofen).

2. Non-selective, high potency (e.g. ketoprofen, diclofenac, ketorolac).

3. COX2 selective drugs (e.g. celecoxib).

Non-selective, low potency NSAIDs can be used as first-line analgesics [436]. They are most likely to be of help if there is an inflammatory component to the pain. More potent NSAIDs should be reserved for those conditions in which the low potency drugs have been tried and failed to produce significant benefit. COX2 selective drugs should be used with caution as an alternative to the non-selective drugs where there is an increased risk of gastric complications. They should be avoided in patients with known cardiovascular disease. NSAIDs should be taken with food and consideration must be given to the use of gastric protective agents. The benefits of the NSAIDs must be demonstrated to outweigh the risks. All NSAIDs are contraindicated in active gastrointestinal ulceration/bleeding and renal disease. They may seriously exacerbate asthma and produce fluid retention. Even if stronger analgesics such as opioids are added, the NSAIDs can be continued as they are likely to have a synergistic action improving pain control above and beyond that obtained with opioids alone [437]

c) Neuropathic analgesics

1. Tricyclic Antidepressants

Tricyclics have a definite analgesic effect on neuropathic pain compared with placebo [438]: 30% of patients should obtain more than 50% pain relief; 30% will have minor adverse effects; and 4% will have to stop treatment because of side effects. Tricyclics are said to work in doses that are too low to affect mood. They may work by increasing levels of norepinephrine and/or serotonin. They also have actions at sodium channels. They are extensively used for pelvic pain and good evidence exists to justify their usage [290,439]. A recent randomized placebo controlled study sponsored by the US National Institutes of Health [246] evaluated increasing doses of amitriptyline with or without standardized education and behavioural modification in treatment naïve patients with IC/PBS. While this study did not confirm the overall benefit of amitriptyline plus education and behavior modification was superior to only the education and behavioral changes, they did show that amitriptyline may be beneficial in persons who can achieve a daily dose of 50 mg or greater.

2. Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors appear to be less effective for the management of pelvic pain [440]. Fluoxetine can increase plasma levels of amitriptyline and induce toxicity, and therefore care must be exercised if the drugs are combined.

Anticonvulsants have been used in the management of pain for many years.

3. Anticonvulsants

Gabapentin and pregabalin have recently been introduced for pain management. There is evidence to show that both compounds are effective in chronic neuropathic pain [441,442]. Whereas

there is little evidence to support the use of anticonvulsants in the management of genitourinary pain, they should be considered if there is a suggestion of neuropathic pain or central sensitization [275,443-445].

N-methyl-D-aspartate (NMDA) antagonists. Ketamine is thought to act primarily at the NMDA receptor, though it may also have actions at sodium channels, as well as opioid (kappa and mu) receptors [446]. Ketamine has been shown in both human [447] and animal models [448] of neuropathic pain to reduce central sensitization and wind-up. Ketamine has been found to be useful in a number of chronic pain states including: peripheral neuropathies with allodynia, stump and phantom pain, central pain, as well as fibromyalgia [449-453] However it has become evident that ketamine should only be used with caution (or not at all) by an experienced practitioner trained in its use. Ketamine is a street drug of addiction and has recently been associated with disastrous bladder consequences, the so-called ketamine bladder. [454]

4. Opioids

There is now a general acceptance that opioids have a role in the management of chronic non-malignant pain [455]. While the use of opioids in urogenital pain is poorly defined, they should be considered for patients with BPS in whom all other treatments to reduce pain have failed. Opioid use does present very real risks and potential harms [284] and include overdose, addiction, and opioid diversion and prescribers have an obligation to assess risks and minimize harms. Unfortunately, not enough is known about the long-term benefits, risks, and side effects of opioid therapy, not only in IC/PS, but other chronic non-cancer pain conditions. More research is needed in this area. The following guidelines for the use of opioids in chronic/non-acute urogenital pain are suggested by the European Association of Urology [436].

1. All other reasonable treatments must have been tried and failed.
2. The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (preferably the patient's family doctor).
3. Where there is a history or suspicion of drug abuse, a psychiatrist or psychologist with an interest in pain management and drug addiction should be involved.
4. The patient should undergo a trial of opioids.
5. The dose required needs to be calculated by careful titration.
6. The patient should be made aware (and possibly give written consent):

I. that opioids are strong drugs and associated with addiction and dependency

II. the opioids will normally only be prescribed from one source

III. the drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period

IV. the patient will be subjected to spot urine and possibly blood checks to ensure that the drug is being taken as prescribed and that non-prescribed drugs are not being taken

V. inappropriate aggressive behaviour associated with demanding the drug will not be accepted

VI. hospital specialist review will normally occur at least once a year

VII. the patient may be requested to attend a psychiatric/psychology review

VIII. failure to comply with the above may result in the patient being referred to a drug dependency agency and the use of therapeutic, analgesic opioids being stopped.

- *Morphine*. There is no compelling evidence that one opiate is better than another. Morphine has, however, become the traditional gold standard. Morphine is the first-line drug, unless there are contraindications to morphine or special indications for another drug. The drug should be prescribed in a slow release/modified release form. Short-acting preparations are undesirable and should be avoided where possible. Parenteral dosing is undesirable and should be avoided where possible. In an acute situation, the daily morphine requirement may be calculated by titration of the drug with progressively increasing doses of 4-hourly rapid-release morphine. However, in most cases, starting with a low dose of slow-release morphine and confining the increments to occur at intervals of no less than 3 days to 1 week is adequate. Chronic non-cancer pain can be managed effectively in most patients with dosages at or below 200 mg/day of morphine or equivalent.
- A *fentanyl patch* can be used when oral absorption is restricted or when the patient suffers from nausea and vomiting. Patches are generally changed every 72 hours. The problem with the currently available patches is that the dosing increments between patches are large. Care needs to be exercised when increments in dose are undertaken. Fentanyl has contributed to numerous overdose deaths [456,457].
- *Methadone* is a strong analgesic which has a long track record [458]. While it may have a useful role in the management of urogenital pain, there is very little science to support this. Methadone has the

tendency to accumulate with repeated dosing and cause delayed respiratory arrest. Therefore, whereas it may be a very useful drug, it should only be prescribed by a practitioner familiar with its use as an analgesic. Methadone as an analgesic is usually prescribed 6 hourly as its analgesic action is relatively short-lived compared with the longer benefits seen from using the drug in drug addiction.

- *Meperidine* (Demerol) 300 mg intramuscular (i.m.) is about as effective as morphine 30 mg i.m.(conversion factor 0.1). Its oral bioavailability is, however, poor. Meperidine has a short duration of action, can accumulate with multiple dosing and is therefore not recommended for use in chronic, non-acute pain [459].

- *Oxycodone*, *hydromorphone* and *hydrocodone* are available as slow/modified-release preparations. They may be useful for opiate rotation if side effects or tolerance is a problem. They are powerful opioids and should be used with the same caution as morphine. 20 mg of oxycodone and 6 mg hydromorphnone is equivalent to 30 mg of Morphine (1.5 and 5 X conversion factor). Oxycodone, hydromorphone and hydrocodone may have a higher abuse liability than morphine [460].

- *Codeine* is a less potent opioid than morphine and the other opioids discussed and could be useful in mild to moderate pain. 20 mg of Codeine is equivalent to 30 mg of morphine (conversion factor 0.15). Tramadol produces analgesia by two mechanisms: an opioid effect; and an enhancement of serotoninergic and adrenergic pathways [461,462]. It has fewer of the typical opioid side effects (notably, less respiratory depression, less constipation and less addiction potential) [463]. Morphine dose equivalences with tramadol has not been reliably established. Codeine and tramadol may have a lower abuse risk than more potent opioids [460,464].

Opioid Recommendation:

A stepped approach to opioid selection should be based on a patient's clinical profile and individual characteristics and should proceed in a stepwise fashion. First line therapy for mild to moderate pain would include codeine or tramadol while second line therapy for mild to moderate pain could include morphine, oxycodone or hydromorphone. First line therapy for severe pain would include these same agents, morphine, oxycodone or hydromorphone while second and third line therapy for severe pain could include fentanyl and methodone respectively. It is important to determine the optimal dose, i.e., a dose that will improve function or reduce pain intensity by at least 30% without causing major adverse effects or complications. It is recommended to start the opioid trial with a low dose and increase the dose in small quantities over several days or weeks carefully monitoring for effectiveness (or plateauing of response) and adverse effects or complications. Opioids produce a graded analgesic response: the patient experiences the greatest benefits at lower doses and a plateauing of analgesic response and adverse effects at higher doses.

Recommendation Pain Treatment

BPS patients deserve to have their chronic pain treated. There are few well controlled long term pain therapy studies in this area, therefore most of our recommendations must come from studies in other non-cancer pain conditions. As discussed in the previous sections, management of symptoms of BPS, including the chronic pain must start with conservative therapies along with BPS condition-specific treatments. For those whose chronic pain is refractory to these therapies including standard analgesics, therapy for the chronic pain should normally start with a tricyclic and/or gabapentinoid (gabapentin or pregabalin), followed by addition of an opioid such as codeine, tramadol, morphine or oxycodone as a last resort. **Level of Evidence: 4 Recommendation: C**

XIII. SURGICAL THERAPY

Bladder Pain Syndrome (BPS) is a chronic and debilitating disease. Major surgical options should be considered only when all conservative treatment has failed (**Table 6**) The patient should be informed of all aspects of surgery and understand consequences and potential side effects of surgical intervention. An experienced surgeon familiar with the particular surgical technique should perform the procedure.

Table 6: surgical therapies rated according to the Oxford System

Surgical Therapies: ICI

Neurostimulation	B:1
Cysto Hydrodistention	C:3
Hunner's Directed Rx	C:3
Cystolysis	-A:3
Sympathetic Deinervation	-A: 4
Parasympathetic Deinervation	-A: 4
Augmentation Cystoplasty +/- partial cystectomy	C: 3
Diversion +/- cystectomy	C:3

1. HYDRODISTENTION

Bladder distension has been used for many years [465] not only as a diagnostic/ classification tool but also for treatment of BPS. In 1957 Franksson reported on a retrospective series of 33 patients, with symptom improvement in all, and lasting up to 1 year in 7 patients[466]. Reports from the seventies were contradictory. Using the Helmstein method [467] Dunn reported complete absence of symptoms in 16 of 25 patients[468], while Badenoch found no improvement in 44 of 56 patients[312]. More recent literature reports poor results with only a minority of patients reporting a small improvement in symptoms for a relatively short period of time[217,218,232,469]. Most studies are retrospective and uncontrolled.

Level of evidence 3; recommendation C

2. TRANSURETHRAL RESECTION

In his first papers Hunner described open resection of the bladder ulcer in the treatment of patients with IC[5]. He later abandoned this treatment due to operative morbidity and recurrence of symptoms. Results of transurethral resection were originally reported by Greenberg et al.[470] and Fall[471]. The retrospective results of this treatment in 116 patients with Hunner's lesion from Fall's Swedish clinic was later reported by Peeker et al.[472]. Hunner's lesion was first recognized by bladder distension under general anesthesia. All lesions were then resected including at least half of the underlying muscular coat. Large areas of the bladder might be treated to resect all diseased tissue. Ninety-two of the 116 patients experienced amelioration of their symptoms. Average duration of symptom alleviation was 23 months ranging from 0-180 months. Up to 16 reresections were performed if symptoms recurred. This is the only center having reported a large clinical series of patients with BPS treated in this manner. Shanberg and Malloy reported in 1987 on laser fulgeration of 39 patients with BPS[473]. Nineteen of 39 had Hunner's lesion. Of the 19 patients with Hunner's lesion 17 reported good pain relief lasting between 6 and 18 months. In the 20 patients without Hunner's lesion, reddened areas in the bladder were photocoagulated with the Neodynium:Yag laser. Thirteen felt marked improvement of symptoms but time to symptom recurrence was not reported. Small bowel perforation in 2 patients was the most important complication in this series. This series was extended to 76 patients [474] where 21 of 27 patients with Hunner's lesion (BPS ESSIC type 3X) experienced symptom improvement; 12 had relapse within 18 months. Of patients with BPS ESSIC type 1 or 2, 20 of 49 improved but 10 required further therapy within 1 year. Rofeim et al. [475] reported on Nd:YAG laser ablation of Hunner's lesion in 24 patients with BPS type 3X. All had symptom improvement within days without complications. Pain, urgency, nocturia, and frequency were improved after 23 months, but relapse in 11 patients required up to four additional treatments.

Payne et al. reported on 14 patients with Hunners lesion treated by cystoscopic ablation. Eight became symptom free and 4 improved symptomatically more than 50%. Four had symptomatic recurrence with improvement after repeat ablation[476]. Intravesical, submucosal injection of triamcinolone has in uncontrolled studies been reported to have as good symptomatic effect as resection/fulgeration[477].

Transurethral resection, coagulation, or laser ablation of Hunner's lesions is a recommended treatment for patients with BPS type 3X.

Level of Evidence: 3 Grade of Recommendation: C

3. CYSTOLYSIS – PERIPHERAL DENERVATION

Hunner [5] simply dissected bladder from surrounding tissue. Initial results were encouraging, however after 3 years of follow-up, symptoms reoccurred. Worth and Turner-Warwick [478] attempted to do more formal cystolysis and were more successful with regard to symptoms. Worth [479] followed patients up to 7 years and found bladder areflexia to be a significant complication of this procedure. Patients had to use Credé technique or even be on intermittent self-catheterisation. Albers & Geyer [480] reported symptom recurrence after 4 years in most of the patients.

- **Cystolysis – peripheral denervation is not indicated for BPS; Level of Evidence: 3 Grade of Recommendation: -A (not recommended)**

4. SYMPATHETIC DENERVATION

Visceral pain is transmitted in most cases by the sympathetic nervous system. Gino Pieri [481] applied this principle to the bladder pathology and suggested resection of the superior hypogastric plexus (presacral nerves), paravertebral sympathetic chain, and gray rami from S1-3 ganglia (Level 4). This was repeated by Douglass [482] a few years later . Immediate results were very good; however Nesbit [483] showed that the long term results were short lived.

- **Sympathetic denervation is not indicated for BPS**

Level of Evidence: 4 Grade of Recommendation: -A (not recommended)

5. PARASYMPATHETIC DENERVATION

Based on the contribution of S2-S4 segments to bladder innervation, Moulder and Meirowsky [484] used S3 neurectomy in 3 patients with good long term follow-up. Larger series were reported by Milner [485] and Mason[486] but results after five years were not encouraging. To improve results selective dorsal sacral root neurectomy, unilateral or bilateral, was introduced by Bohm and Franksson[487]. The outcomes of this procedure were unclear.

• Parasympathetic denervation is not indicated for BPS;

Level of Evidence: 4 Grade of Recommendation: -A (not recommended)

6. BOWEL SURGERY

a) Bladder augmentation-cystoplasty has been commonly used for refractory BPS for 50 years. First reports of ileocystoplasty from 1958 were very promising[488]. Later publications were less sanguine with good results varying from up to 100% [489,490] to 25%[312,491]. Cystoplasty is usually done with or without bladder resection.

Cystoplasty alone was reported as early as 1967 by Turner-Warwick and Ashken[492], advocating augmentation with removal of the diseased tissue. Several subsequent studies indicated that cystoplasty with subtrigonal cystectomy offers better results than without subtrigonal cystectomy[490,493-495]. These were all retrospective studies and conclusions should be taken with reservation. Cystoplasty with partial or total removal of the bladder requires bowel tissue substitution. Different bowel segments are used to enlarge the bladder. It is the general consensus that the intestine segment used for bladder augmentation should be detubularized[496]. Experiences with different bowel segments have been reported in numerous articles with level 4 evidence:

- Ileum [312,489,490,495,497-501]
- ileocecum [344,490,491,493,502,503]
- cecum [489,504]
- right colon [312,490,505]
- sigmoid colon [493,495,499,502]
- gastric segments [506,507]

There is no significant different between different bowel segments with regard to outcome except for gastric tissue substitution which is associated with dysuria and persistent pain due to production of acids.

b) Cystoplasty with Supratrigonal Resection (i.e. trigone-sparing) has been reported in various studies. Von Garrelts[489] described excellent results in eight of 13 patients with a follow-up of 12-72 months. Bruce et. al [495] reported satisfactory relief of BPS symptoms by ileocystoplasty and colocystoplasty in eight patients. Dounis and Gow [508] reported improvement in pain and frequency in seven BPS patients after supratrigonal cystectomy with ileocecal augmentation. Kontturi et. al [493] used segments of colon and sigmoid colon in 12 cases with 100% symptom-free outcome in five patients augmented with sigmoid colon over 4.7 years of follow-up. Two of seven cases augmented with colon required ileal conduit and cystectomy. Linn et. al [509] followed six BPS patients for 30 months, and reported that all were symptom-free and voided spontaneously. The report by Nielsen et. al [491] was less favorable. Six out of eight patients had good results. Van Ophoven et. al [510] reported the long-term (mean 5 years) results of orthotopic substitution enteroplasty in 18 women with BPS, using ileocecal (n = 10) or ileal (n = 8) segments with only two failures. In the group [511] augmented with ileum, three patients required self-catheterization and one a suprapubic catheter. Peeker et. al [512] found that patients with end-stage ulcerative BPS had excellent results following ileocystoplasty but not so the patients with non-ulcer disease. A follow up on this paper was recently published [180] with the same conclusion for the patients with end stage BPS ESSIC type 3C, while both continent diversion and iliocystoplasty were unrewarding in patients with type 2X BPS. Patients with low cystoscopic capacity (<200 ml) under general anaesthetic have achieved better results [7,25,513,514].

There is some weak evidence that cystoplasty with supratrigonal resection may benefit some selected patients with end stage ESSIC type 3C BPS.

Level of Evidence: Level 3; Grade of Recommendation: C

c) Cystoplasty with Subtrigonal Cystectomy — orthotopic continent bladder augmentation (i.e. with trigone removal but preservation of the bladder neck) in the management of BPS has been reported less often[511,515-517]. Because of the need of ureteral reimplantation, it is associated with some risks of urine leakage, urethral stricture and reflux[516]. Linn et. al [509] had three failures in 17 patients and half of the patients with good symptomatic response required self catheterization. Nielsen et. al [491] had better results following orthotopic substitution with low bladder capacity (200 mL versus 525 mL, respectively). Orthotopic continent bladder augmentation, particularly when removing the trigone, may cause incomplete voiding requiring intermittent self-catheterization. Therefore patients considering such procedures should be advised accordingly and must be considered capable of performing, accepting and tolerating self catheterization. Nurse suggested that the decision on whether to due a subtrigonal or supratrigonal cystectomy be based on the results of trigonal biopsy, with the former procedure indicated in the patient with trigonal inflammation[518].

There is no compelling evidence that subtrigonal cystectomy with cystoplasty has any outcome advantage over supratrigonal cystectomy but it tends to be associated with more complications and poorer functional bladder rehabilitation. Level of evidence: 3; Grade of Recommendation: C

7. URINARY DIVERSION WITH OR WITHOUT TOTAL CYSTECTOMY AND URETHRECTOMY

This is the ultimate, final and most invasive option. It should be used as a last therapeutic resort in selected

patients. Techniques include simple or continent urinary diversion. Continent diversion may be preferable for cosmetic reasons in younger patients.

Simple urinary diversion with formation of an ileal conduit is the most common surgical treatment for BPS [519]. Initially, diversion can be done without cystectomy and only when bladder pain is persistent, cystectomy may be considered. Bladder defunctionalization alone produced symptom-relief in several reports. [7,25,312,520,521]

Often diversion is performed as a next step after unsuccessful bladder augmentation. To avoid further bowel resection, a bowel segment used for cystoplasty can often be converted to a conduit[522] In some patients chronic inflammatory changes have been seen in the cystoplasty pouch resembling interstitial cystitis[7,312,523,524], preventing one from using this technique. Similar bowel changes however have been described when cystoplasty is performed for pathology other than interstitial cystitis, suggesting that these pathologic findings are not a direct result of the exposure of bowel to BPB urine [525]. Relatively good responses to diversion without cystectomy have been reported in small series. [491,526]

Urinary diversion with and without cystectomy may be the ultimate option for refractory patients. Continent diversion may have better cosmetic and life style outcome but recurrence of pain in the pouch is a real possibility. Level of Evidence: 3; Grade of Recommendation: C

XIV. CLINICAL SYMPTOM SCALES

Symptom scales have enabled patients to be categorized by symptom severity and have also served to follow results of treatment in patients with bladder pain syndrome. Their future development may enable a presumptive diagnosis of the syndrome but at this time that is not possible. A brief survey that reliably segregates BPS from other urologic disorders would make the ability to diagnose the syndrome reliable, inexpensive, and available to all healthcare providers. It would aid in epidemiologic studies as well. Currently such work sponsored by NIDDK is ongoing. www.mappnetwork.org

A process for development of a case definition for BPS has been developed by adapting the RAND/University of California, Los Angeles Appropriateness Method.[46] This involves a panel consisting of nine experts with experience in BPS and related diseases, literature review of case definitions of BPS, initial ratings of symptoms as indicators of the BPS diagnosis, and discussion and a second set of ratings to establish criteria for diagnosis through patient reports. Symptom questionnaire development, based on the results of the case definition exercise, and validation have been successful in establishing a population-based estimate for disease prevalence using both high specificity and high sensitivity models.[69] If this could be adapted for use in screening by primary care physicians, the potential benefits in early diagnosis of BPS are evident.

Questionnaires and symptom scales are currently utilized to measure treatment outcome and are especially valuable in clinical research studies as well as for guiding therapy for individual patients.

There are 3 published BPS symptom questionnaires: the University of Wisconsin IC Scale (**Figure 11**), the O'Leary-Sant IC Symptom Index (ICSI) and IC Problem Index (ICPI) (**Figure 12**), and the Pelvic Pain and Urgency/Frequency (PUF) Scale (**Figure 13**).

The University of Wisconsin IC Scale includes 7 BPS symptom items and has not been validated for identification or diagnosis of BPS. It captures severity of symptom expression [527,528]. Unlike the other two instruments, it addresses some quality-of-life issues, and this is an advantage when such issues are subject of investigation. Its most attractive aspects are its clinically apparent face validity and its ease of implementation.

The O'Leary-Sant indexes are validated questionnaires that were originally developed by focus groups, subjected to test-retest reliability analysis, and validated by administration to BPS patients and asymptomatic controls[529,530]. The questionnaires center on 3 questions related to urgency/frequency and one on bladder-associated pain. It does not address generalized pelvic pain or symptomatology associated with sexual activity. This is not because these questions were not considered in the formulation of the questionnaire. Of 73 questions in the preliminary instrument covering domains of urinary symptoms, pain, sexual function, menstrual variability, and general health, only the four questions now in the instrument were needed to reliably and validly describe the illness experience of those with IC and distinguish these patients from those without the disorder[531].

The Pelvic Pain, Urgency, Frequency (PUF) questionnaire[201] was specifically designed to include questions that directly reflect a wide variety of the symptoms experienced by patients who are affected by this disorder. One-third of the questions address pelvic pain, including pain anywhere in the pelvis: the vagina, labia, lower abdomen, urethra, perineum, testes, penis, or scrotum.

The PUF is marred by the fact that patients were not included in its development. If used to monitor outcomes, question 4 regarding sexual activity may worsen the score as the outcome improves. These and other problems make its use highly dubious.[532]

A large study utilizing the PUF questionnaire has concluded that up to 23% of American females have BPS[201]. This makes one wary as to the utility and

KELLER UNIVERSITY OF WISCONSIN SYMPTOM INSTRUMENT

Please circle the one number answer that comes closest to the way you feel, whether or not you have the following symptoms.

APPENDIX 1:.

Symptom	Not At All	(Circle one number on each line)				A Lot
1. Bladder Discomfort	0	1	2	3	4	5
2. Bladder Pain	0	1	2	3	4	5
3. Other Pelvic Discomfort	0	1	2	3	4	5
4. Headache	0	1	2	3	4	5
5. Backache	0	1	2	3	4	5
6. Dizziness	0	1	2	3	4	5
7. Feelings of Suffocation	0	1	2	3	4	5
8. Chest Pain	0	1	2	3	4	5
9. Ringing in Ears	0	1	2	3	4	5
10. Getting Up at Night to Go to the Bathroom	0	1	2	3	4	5
11. Aches in Joints	0	1	2	3	4	5
12. Swollen Ankles	0	1	2	3	4	5
13. Nasal Congestion	0	1	2	3	4	5
14. Flu	0	1	2	3	4	5
15. Abdominal Cramps	0	1	2	3	4	5
16. Numbness or Tingling in Fingers or Toes	0	1	2	3	4	5
17. Nausea	0	1	2	3	4	5
18. Going to the Bathroom frequently during the day	0	1	2	3	4	5
19. Blind Spots or Blurred Vision	0	1	2	3	4	5
20. Heart Pounding	0	1	2	3	4	5
21. Difficulty Sleeping because of Bladder Symptoms	0	1	2	3	4	5
22. Sore Throat	0	1	2	3	4	5
23. Urgency to Urinate	0	1	2	3	4	5
24. Coughing	0	1	2	3	4	5
25. Burning Sensation in Bladder	0	1	2	3	4	5

Figure 11: University of Wisconsin Symptom Instrument.

face-validity of the PUF[533]. A total score of 10-14 =74% likelihood of positive potassium test (PST); 15-19=76%; 20+=91%. To the extent that the PST is suspect, the reliability of PUF data comes into question.

Neither the PUF nor O'Leary Sant questionnaires have been shown to be of value in diagnosis of the individual patient[534]. In an interesting epidemiologic study in Finland, Leppilahti and colleagues randomly selected 2000 participants from the Finnish population registry and administered the O'Leary Sant IC symptom and problem index[64]. Women with symptom scores 7 or higher with no history of urinary tract infection in the preceding month were invited to undergo clinical examination. Of these 32 women, 21 underwent examination of whom 3 had probable interstitial cystitis and 4 had possible interstitial cystitis. Based on this specificity, a population prevalence in Finnish women of 230/100,000 probable interstitial cystitis and 530/100,000 possible interstitial cystitis was calculated. Thus, one can get some idea as to O'Leary Sant specificity. For probable BPS it would be about 14% using a parameter of 7 or greater on the symptom index.

The O'Leary-Sant and University of Wisconsin instrument correlate strongly in a large population of patients with BPS.[535] Clemons and co-workers administered the ICSI to 45 patients scheduled to undergo laparoscopy for pelvic pain. Seventeen were diagnosed with BPS based on the finding of glomerulations on bladder distention associated with urgency, frequency, or nocturia. A score of 5 on the ICSI had a 94% sensitivity and a 93% negative predictive value in this enriched population of patients with pelvic pain[536]. However, Clemens and colleagues have found a high degree of overlap in International Prostate Symptom Scores, the O'Leary Sant Symptom Index, and the Chronic Prostatitis Symptom Index in a random sample of over 1400 men and women with urologic symptoms, underscoring that we should be cautious in using these questionnaires as a basis for diagnosis in epidemiologic studies[537].

Rosenberg and Hazzard[62] surveyed 1218 consecutive patients presenting to their primary care office and found 7 (0.6%) who had a 7 ICSI score. Likely BPS was noted in 12.6% of patients on the PUF scale, a **Figure 21** times higher, suggesting that either the PUF drastically overestimates BPS, or the ICSI lacks sensitivity. Based on the correlation of the potassium sensitivity test and the PUF questionnaire, Parsons[49] stated that 30.6% of 3'rd year female medical students at his California institution had probable BPS. Sahinkanat and co-workers[202] in Turkey administered the PUF questionnaire to all 442 female textile workers in two local factories. Eighty-six per cent of those with a PUF score 7 or greater had an 86% positive rate of PST testing verses 9% positive in the group with PUF less than 7. They extrapolated that bladder epithelial permeability dysfunction was present in 32.8% of these unselected women. The ICSI estimate seems much more in line with current epidemiologic data.

While perhaps not ideally suited for epidemiologic studies, these questionnaires can reveal important

Interstitial Cystitis Symptoms Index During the past month:

How often have you felt the strong need to urinate with little or no warning:
0. __ Not at all
1. __ Less than 1 time in 5
2. __ Less than half the time
3. __ About half the time
4. __ More than half the time
5. __ Almost always

Have you had to urinate less than 2 hours after you finished urinating?
0. __ Not at all
1. __ Less than 1 time in 5
2. __ Less than half the time
3. __ About half the time
4. __ More than half the time
5. __ Almost always

Interstitial Cystitis Symptoms Index During the past month:

How often did you most typically get up at night to urinate?
0. __ Not at all
1. __ Once per night
2. __ 2 times per night
3. __ 3 times per night
4. __ 4 times per night
5. __ 5 or more times per night

Have you experienced pain or burning in your bladder?
0. __ Not at all
1. __ A few times
2. __ Fairly often
3. __ Usually
4. __ Almost always

Add the numerical values of the checked entries:
Total score

Interstitial Cystitis Problem Index During the past month how much has each of the following been a problem for you.
Frequent urination during the day?
0. __ No problem
1. __ Very small problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem

Getting up at night to urinate?

0. __ No problem
1. __ Very small problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem Need to urinate with little warning?

Interstitial Cystitis Problem Index During the past month how much has each of the following been a problem for you.
Need to urinate with little warning?
0. __ No problem
1. __ Very small problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem

Burning, pain, discomfort, or pressure in your bladder?
0. __ No problem
1. __ Very small problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem

Add the numerical values of the checked entries:
Total score

Figure 12: O'Leary Sant Symptom and Problem Indexes

	0	1	2	3	4	Symptom score	Bother score
1. How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
b. If you get up at night to go to the bathroom, does it bother you?	Never	Occasionally	Usually	Always			
3. Are you currently sexually active? YES ____ NO ____							
4a. IF YOU ARE SEXUALLY ACTIVE, do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Occasionally	Usually	Always			
b. If you have pain, does it make you avoid sexual intercourse?	Never	Occasionally	Usually	Always			
5. Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, testes, or scrotum)?	Never	Occasionally	Usually	Always			
6. Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always			
7a. If you have pain is it usually		Mild	Moderate	Severe			
b. Does your pain bother you?	Never	Occasionally	Usually	Always			
8a. If you have urgency, is it usually		Mild	Moderate	Severe			
b. Does your urgency bother you?	Never	Occasionally	Usually	Always			

Figure 13: Pelvic Pain, Urgency, Frequency Scale

epidemiologic data. Porru and colleagues[538] compared University of Wisconsin scores including both urinary and non-urinary symptoms, for 30 BPS female patients and 30 female controls. While the IC group had significantly higher scores for the urinary symptoms, they did not appear to indiscriminately report higher scores than controls for different somatic and general complaints, as might be expected if this disease is a manifestation of a more generalized disorder. Diggs and colleagues[539] used the ICSI to investigate how interstitial cystitis patients interpret urgency. The ICSI question regarding: "the strong need to urinate with little or no warning" consistently underestimated the response to the International Continence Society definition of urgency: "the compelling urge to urinate that is difficult to postpone.

Treatment outcome studies have also used the Global Response Assessment (**Figure 14**); a balanced patient self-report on overall response to therapy, developed for NIDDK sponsored multicenter therapeutic trials[301]. The O'Leary Sant and University of Wisconsin questionnaires are responsive to change over time in patients with BPS and have been recommended as secondary endpoints in future clinical trials of the disorder. Propert and colleagues in the Interstitial Cystitis Clinical Trials Group determined that a 1.2 point change in the O'Leary Sant indexes and a 3.1 point change in Wisconsin IC inventory corresponded to a one-category change in the GRA. Individual symptoms were also responsive [540].

A self-report measure that reliably identifies moderate to severe bladder pain syndrome patients for inclusion into clinical trials was recently reported by Pfizer Inc. [532]. Whether it will have value in diagnosis of the syndrome or following patients' clinical course remains to be seen. A quality of life scale for women with BPS has also been developed for use in clinical trials and reportedly can be used to examine the effects of psychosocial and treatment interventions on quality of life.[541]

Conclusions

The three commonly employed clinical symptom scales include the O'Leary Sant, the University of Wisconsin, and the Pelvic Pain, Urgency, Frequency scales. None of the questionnaires have the sensitivity or specificity to be used in the clinical diagnosis of patients. The O'Leary Sant and University of Wisconsin indexes have been validated as reliable instruments for following the course of the disease and results of treatment interventions. All have shown some value in assessing the severity of disease. The Global Response Assessment has become one of several primary endpoints used in judging the response to specific therapies.

XV. OUTCOME ASSESSMENT

1. THE PROBLEM

BPS/IC has been a difficult condition for which to assess therapeutic impact. There is a 50% inci-

-3:	Markedly worse
-2:	Moderately worse
-1:	Slightly worse
0:	No change
+1:	Slightly improved
+2:	Moderately improved
+3:	Markedly improved

Figure 14: Global Response Assessment (GRA)

dence of temporary remission unrelated to therapy, with a mean duration of 8 months [52]. A somewhat surprising finding from the Interstitial Cystitis Database was that although there was initial improvement in symptoms partially due to regression to the mean[542] and the intervention effect, there was no evidence of a long-term change in average symptom severity over the four year course of follow-up[98]. In a chronic, devastating condition with primarily subjective symptomatology, no known cause, and no cure, patients are desperate and often seem to respond to any new therapy. A skeptical view of outcomes is essential (**Figure 15**), as patients can be victims of unorthodox health care providers using unproven forms of therapy, some medical, some homeopathic, and some even surgical.

2. THE PLACEBO ISSUE

Where possible, the results of randomized controlled studies should be used for decision making. Placebo, double-blind studies are optimal in this disorder for which there is no generally effective standard therapy.

Placebo effects influence patient outcomes after any treatment which the clinician and patients believe is effective, including surgery. Placebo effects plus disease natural history and regression to the mean can result in high rates of good outcomes, which may be misattributed to specific treatment effects.[98,543-545] Unfortunately, few BPS treatments have been subjected to a placebo-controlled trial. This is not to say that what seems effective is not, but rather that a high index of skepticism is healthy, even in treatments tested in controlled trials.[546]

While in many diseases an argument can be made against using a true placebo control as opposed to an orthodox treatment of approved or accepted value[547], a good case for true placebo comparison can readily be made for BPS. The vagaries of the natural history, the general lack of progression of symptom severity over time, and the fact that it is not life threatening, mean that there is little to lose and much to gain by subjecting new treatments to the vigorous scrutiny of placebo control. Many patients who volunteer for such trials have already run the gamut of accepted (though generally unproved) therapies. It has long been recognized in protocols that use subjective criteria for assessment that “improvement” may be expected in up to 35% of placebo-treated patients[548]. As the spontaneous remission rate (though temporary) for BPS is 11%[311] to 50%[52], combined with the placebo improvement it can be difficult to prove efficacy.

Even in placebo controlled trials, it is reasonable to surmise that some degree of unblinding may occur as a result of somatic or psychological side effects of the active arm, impairing the validity of the trial results and giving the active arm a slight edge over placebo.[549,550] Failure to recognize unblinding can easily bias results of a study and has not been routinely measured in clinical trials.[551] When occurring late in a study after one would expect onset of a therapeutic effect, unblinding could be the result of side effect profile or drug efficacy. Early in the trial it reflects poor placebo or study design. The degree of blinding needs to be ascertained throughout the trial. This is of specific concern in BPS and any disorder where primary outcomes may be subject to patient-specific psychological and physiological factors.

The ethics and necessity of placebo-controlled trials have been questioned, especially in situations in which an effective treatment exists and also where delay in treatment has been shown to result in disease progression[552-554]. However, there are methodological concerns with equivalence and non-inferiority active agent comparison trials[555]. These include an inability to determine if the treatments are equally good or equally bad, and the possibility that successive non-inferiority trials can lead to a gradual decrease in treatment efficacy. Although the use of placebo-controlled trials raises ethical concerns when proven effective treatment exists for the condition under investigation, they are ethically justified, provided that stringent criteria for protecting research subjects are satisfied [556].

The value of placebo-controlled trials is aptly illustrated by the recent decisions by pharmaceutical manufacturers not to pursue FDA approval in the United States for seemingly promising intravesical therapies for BPS[557,558] after placebo-controlled trials failed to establish efficacy. These include low concentration hyaluronic acid (Bioniche, Canada), high concentration hyaluronic acid (SKK, Tokyo), and resiniferatoxin (ICOS, Bothell, Washington, USA). Nalmefene, an initially promising oral therapy in the 1990’s,[559] also failed phase 3 trials (IVAX, Miami). Placebo trials are impractical in surgery and it can be difficult to evaluate surgical reports. The many older medications currently used off-label might not meet success if tested in the stringent manner in which new molecular entities are tested. The expense of testing therapies currently used off-label often requires dependence on the largesse of government agencies like the National Institute of Health [301,395,560].

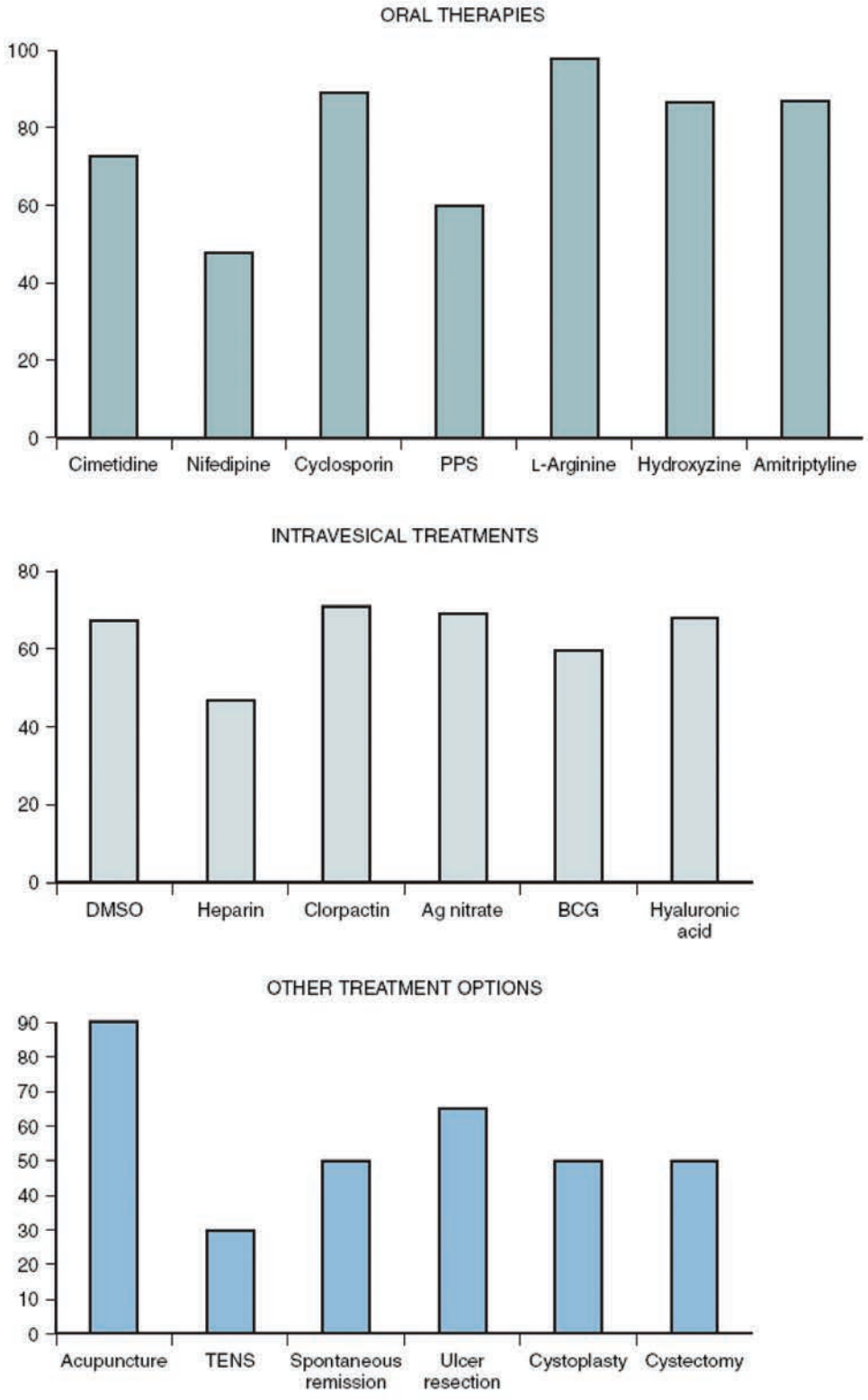


Figure 15: Selected reported treatment outcomes in uncontrolled studies in IC literature: Percentage of patients initially improved.

3. OUTCOME INTERPRETATION

As has been discussed with regard to rheumatologic disorders[561], the interpretation of measurements of physical functioning in clinical trials should consider the composition of the study sample, with attention to the stage of disease and the heterogeneity in disease duration. Patients with long-standing disease or compromised bladder capacity or central sensitization can be expected to be less responsive to treatments directed toward the bladder itself. Finally, when considering objective changes, the concept of statistical versus clinical significance is paramount. Investigators should, but rarely do, point out differences between statistical improvement and what they consider to be clinically significant improvement[562]. As Gertrude Stein reportedly stated, "A difference, to be a difference, must make a difference". An increase in bladder capacity of 30cc may be statistically significant but clinically irrelevant. Number needed to treat and number needed to harm data[563] may be particularly important in BPS and have not typically been included in efficacy analysis.

4. IMMPACT RECOMMENDATIONS

The core outcome domains for chronic pain clinical trials have been published.[423,564] The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations indicate that core outcome domains should be considered in all clinical trials of the efficacy and effectiveness of treatments for chronic pain. These domains include:

1. Pain
2. Physical functioning
3. Emotional functioning
4. Participant ratings of improvement and satisfaction with treatment
5. Symptoms and adverse effects, participant disposition

CONCLUSIONS:

Currently for BPS/IC there are no accepted biologic disease markers that can be used for the assessment of response to therapy. The O'Leary Sant, University of Wisconsin, and Global Response Assessment are well-validated questionnaires to follow disease progression and response to therapy. The IMMPACT recommendations suggest that, as well as symptoms scores, any future study on a pain syndrome must involve more general assessments of psycho-physical functioning. There is limited experience in BPS/IC for the use of well-validated measures available for the study of chronic pain. Future NIDDK research initiatives may help to rectify this. http://www.mappnetwork.org

International recognition of an agreed upon definition and inclusion and exclusion criteria of BPS/IC will help future studies to fulfill the highest standards available, and placebo-controlled, double blind, randomized controlled trials, where possible, will provide the highest level of evidence to move the field forward.

LEVEL 2 GRADE C RECOMMENDATIONS

XVI. PRINCIPLES OF MANAGEMENT

The information currently available in the literature does not lend itself to easily formulating a diagnostic or treatment guideline. Different groups of "experts" would undoubtedly create different "best practices".[565] The compromise approach devised by an experienced cross-section of urologists and gynecologists from around the world at the International Consultation on Continence 2004 meeting in Monaco[41] and subsequently modified at the 2008 meeting in Paris[1] has been reviewed and updated by the committee and allows for significant latitude to reflect varying individual practice patterns and to account for patient preference.

An underlying principle is that, where possible, decisions on the treatment of bladder pain syndrome should be evidence based[566]. Unfortunately, high level evidence of efficacy is lacking for many common treatments, either because such studies have not been done, or were done and failed to demonstrate efficacy.[343,567,568]

Another principle is that we should be guided by patient perceived and driven outcomes for bladder pain syndrome, which is, after all, diagnosed on the basis of symptoms after exclusion of confusable diseases. Many patients prefer noninvasive therapies[569], and it would seem reasonable to start with physical therapy and/or oral therapies if conservative non-medical interventions (i.e. education, diet, behavioral modification, stress reduction) fail to result in significant symptom amelioration. Use of surgical therapies should be approached with some caution. It has been reported that women with BPS have had significantly more pelvic surgeries than controls, and the majority were performed prior to diagnosis of BPS, possibly for pain related to undiagnosed BPS.[570,571]

1. HARMONIZATION

With representatives from Asia, Europe, and North America, the Consultation has attempted to create a document that is harmonious with guidelines developed around the world in the last several years, many since the last meeting of the Consultation. The Canadian Urological Association[572], the International Society for the Study of Bladder Pain Syndrome (ESSIC)[2,15], the European Association of Urology[342], the Japanese Urological Association[45], East Asian countries[11], and the American Urological Association[12] all have published

consensus guidelines, many of which have been reviewed in a recent publication[565].

In the Japanese and Asian view, urinary frequency/urgency is the primary symptom, with overactive bladder (OAB) and hypersensitive bladder (HSB) listed as subgroups (with painful bladder syndrome (PBS) as its extreme form)[44]. (**Figure 3**)

In the European view as reflected in European Association of Urology and ESSIC guidelines, pain is the key symptom, with frequency being secondary to pain, while urgency basically represents a different pathology. American and Canadian guidelines are concordant with the European view. They emphasize pain, pressure, and discomfort perceived by the patient to be related to the bladder and associated with urinary frequency or urgency.

Pathologic afferent activity is a feature in overactive bladder as well as BPS, making the philosophy of the Asian guidelines conceptually attractive. But the knowledge gaps on lower urinary tract sensory functions are tremendous and from a neurophysiologic point of view it may be premature to link the conditions.

As a disorder based on symptoms, it is remarkable that we do not know if sensations described by the patient as pain, urge, or pressure are physiologically different or identical, if they represent various grades of the same pathology, or if this set of terms merely represents linguistically different ways of presenting the same problem. Do cultural differences play a part? Are Asian patients more reluctant to use the word pain to describe the same symptoms?

Cystoscopic and pathologic findings have a more important role in Asia and Europe than in North America, but nowhere do guidelines now recommend invasive procedures like endoscopy with or without biopsy as essential to make a diagnosis of BPS.

The latest algorithms from the European Association of Urology, American Urological Association, and East Asian nations are presented below and illustrate different approaches to a difficult problem. (**Figures 16, 17, 18)** Opportunities for future harmonization are apparent.

XVII. RECOMMENDATIONS OF INTERNATIONAL CONSULTATION ON INCONTINENCE:

1.HISTORY / INITIAL ASSESSMENT

Men or women with ***an* unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes** should be evaluated for bladder pain syndrome[12] The initial assessment consists of a frequency/volume chart, focused physical exam, urinalysis, and urine culture. Cytology and cystoscopy are recommended if clinically indicated.

Patients with infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and/or hematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms are they diagnosed with BPS.

2.INITIAL TREATMENT

Patient education and support, dietary manipulation, stress reduction, nonprescription analgesics, and pelvic floor relaxation techniques comprise the initial management of BPS. **It is important at every stage to address the patient's pain, and understand that at some point in the progression of treatment, referral to a pain specialty clinic may be desirable.** When the conservative approach fails, or symptoms are severe and conservative management unlikely to succeed, oral medication, physical therapy, and/or intravesical treatment can be prescribed.

3.SECONDARY ASSESSMENT

If oral or intravesical therapy fails, **or before beginning such therapy at the discretion of the clinician**, it is reasonable to consider further evaluation which can include urodynamics, pelvic imaging, and cystoscopy with bladder distention and possible bladder biopsy under anesthesia. Laparoscopy may be indicated if there is a suspicion of gynecologic disease. Findings of bladder overactivity suggest a trial of antimuscarinic therapy. Findings of a Hunner's lesion suggest therapy with transurethral fulguration or resection of the ulcer. Distention itself can have therapeutic benefit in up to one-third of patients, though benefits rarely persist for longer than a few months.

4.REFRACTORY BPS

Those patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive modalities. These might include neuromodulation, intradetrusor botulinum toxin, or cyclosporine. At any stage of the treatment algorithm, experimental pharmacologic protocols of promising new treatments are reasonable to consider if symptoms warrant and the risk-benefit ratio is acceptable.

The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urine stream. Augmentation (substitution) cystoplasty and urinary diversion with or without cystectomy have been used with good results in very well selected patients.

A treatment algorithm by the Consultation is presented in **Figure 19**.

Assessment	Treatment	
Urine culture	Grade A recommended	Standard: Hydroxyzine, Amitriptyline, Pentosanpolysulphate
Uroflowmetry		Limited data: antibiotics, cyclosporin A,
Cystoscopy with hydrodistension		Intravesical: PPS, DMSO,
Bladder biopsy	Grade B recommended	Oral: Cimetidine
Micturition diary		Intravesical: hyaluronic acid, chondroitin sulphate,
Pelvic floor muscle testing		Electromotive drug administration for intravesical drugs
Phenotyping		Sacral nerve stimulation, bladder training, physical therapy ,
ICSI score list		Psychological therapy
	Not recommended	Bacillus Calmette Guerin
		Intravesical Chlorpactin
	Other comments	Data on surgical treatment are largely variable.
		Coagulation and laser only for Hunner's lesions

Figure 16: European Association of Urology guidelines 2012/2013.

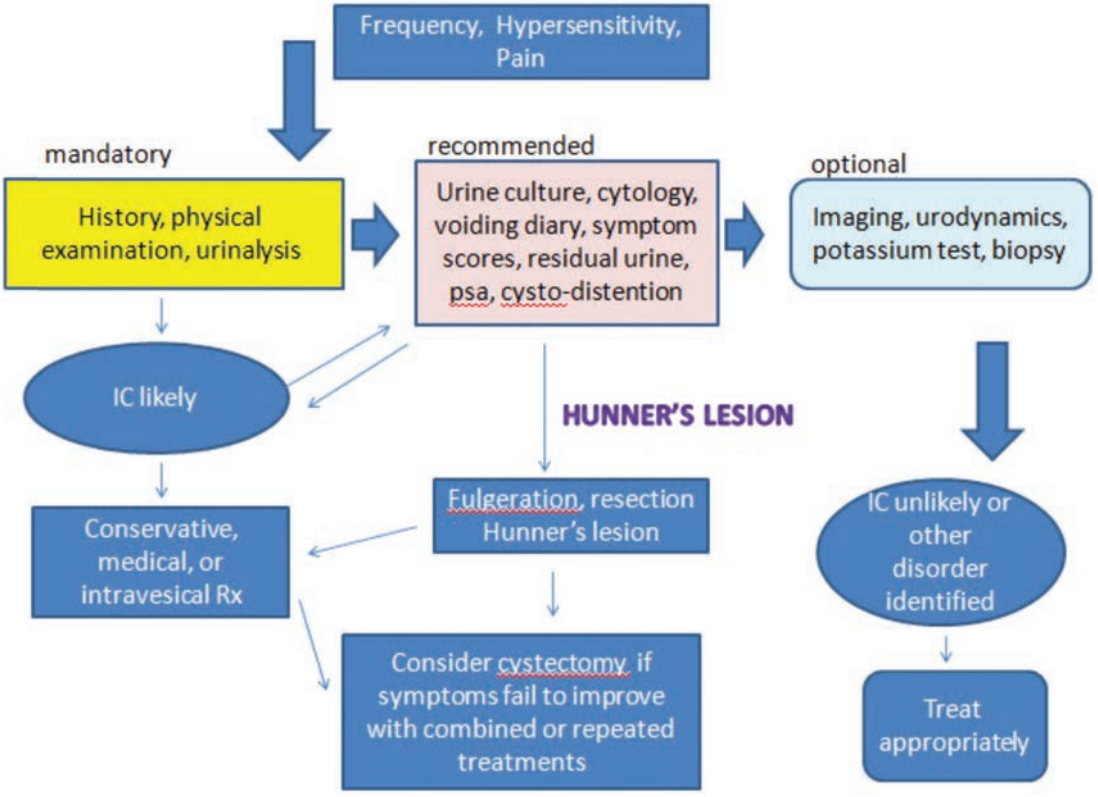


Figure 17: Management proposed by Japanese Urological Association and urologists in Taiwan and Korea, modified from Homma[573].

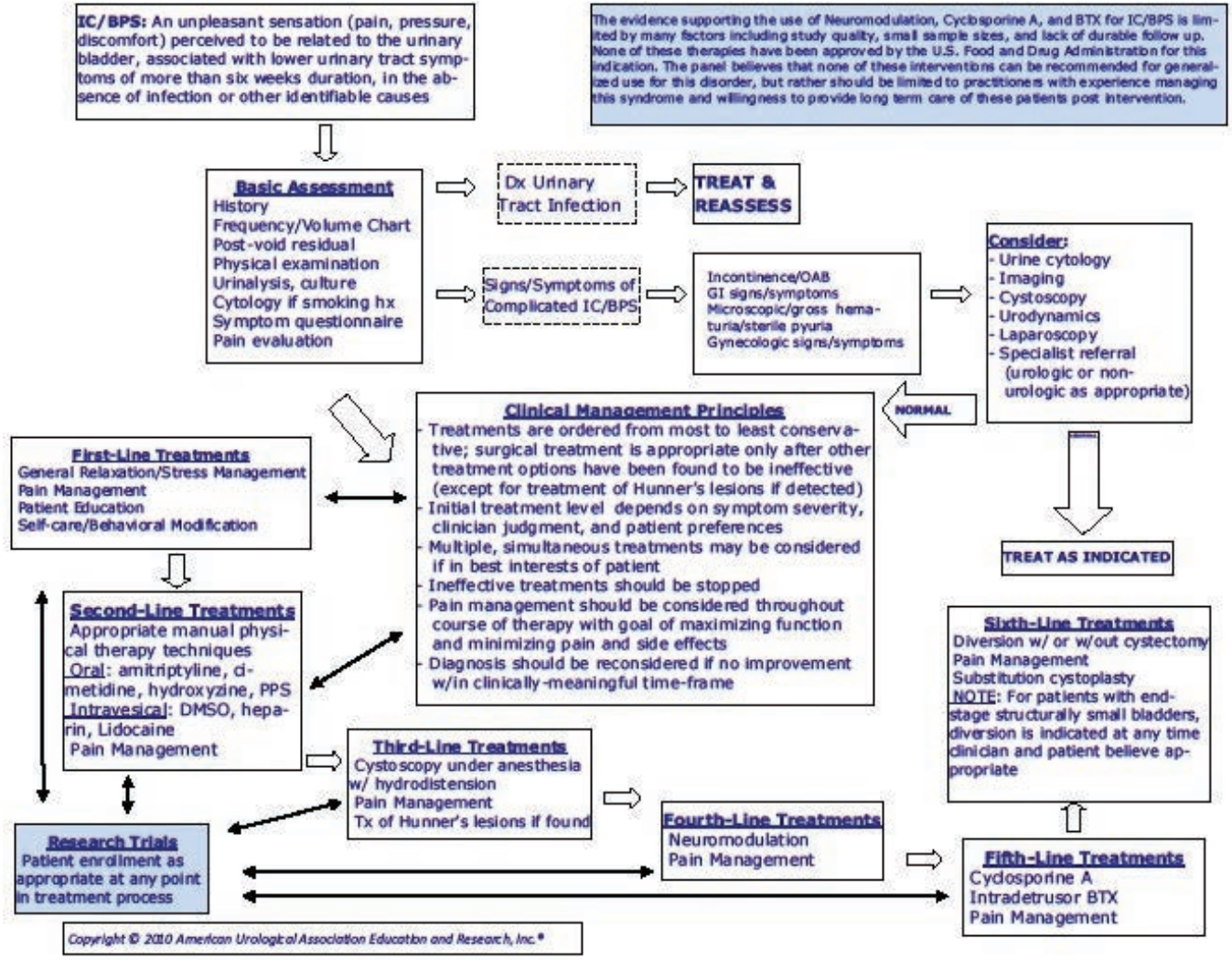


Figure 18: Management Guideline of American Urological Association[12].

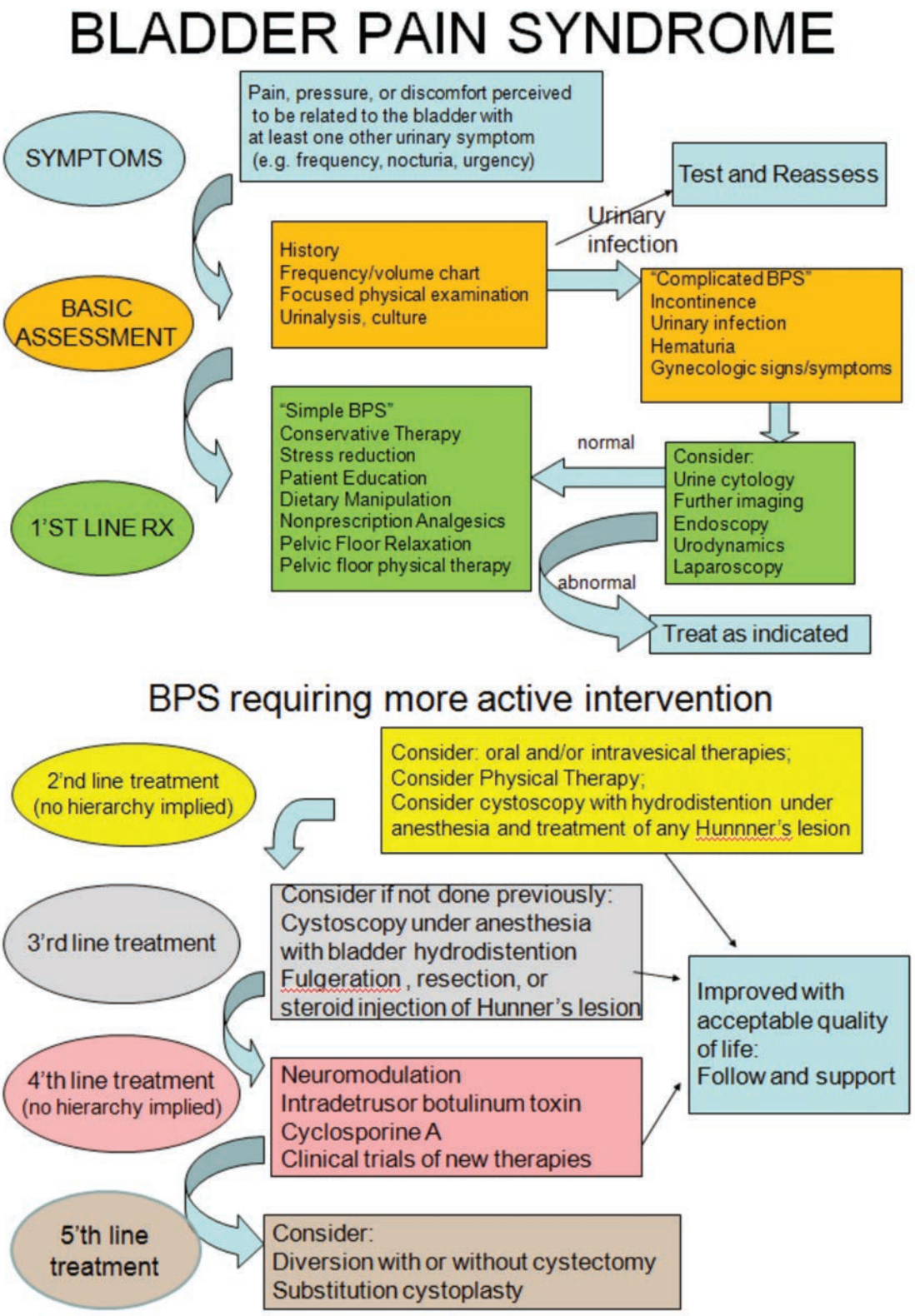


Figure 19: Algorithm for Diagnosis and Treatment: 2012 International Consultation on Incontinence.

It is the opinion of the committee that, because of the natural history of the disorder, it is best to cautiously progress through a variety of treatments. Whereas the shotgun approach, starting newly diagnosed patients on a variety of simultaneous medications, seems to have many adherents, employing one treatment at a time makes the natural history of the disease itself an ally in the treatment process. If a treatment has no efficacy, it should be stopped. It a treatment results in modest improvement, it should be continued and another treatment option employed in an attempt to further improve symptoms. The goal is to maximize quality of life and dispense with ineffective treatments in a somewhat controlled fashion. The patient and clinician must remember that "perfect is the enemy of good" and expectations should be realistic. One should encourage patients to maximize their activity and live as normal a life as possible, not becoming a prisoner of the condition. Although some activities or foods may aggravate symptoms, nothing has been shown to negatively affect the disease process itself. Therefore, patients should feel free to experiment and judge for themselves how to modify their lifestyle without the guilt that comes from feeling they have harmed themselves if symptoms flare. Dogmatic restriction and diet are to be avoided unless they are shown to improve symptoms in a particular patient.

Level 4 Grade C

XVIII. FUTURE DIRECTIONS IN RESEARCH

The committee believes that further research is needed in the following broad areas:

1. The recent American Urological Association guideline[12] points out numerous areas for which there was not enough information to allow an evidence basis for recommendations, and these areas require further study.
2. Pathology of BPS
3. Biomarker development
4. Immunology of BPS
5. Neurological aspects with particular attention to the relationship of BPS to overactive bladder
6. The relationship of bladder pain syndrome to chronic pelvic pain syndrome (nonbacterial prostatitis)

The majority of current treatments options are still targeting the bladder. However, as said in the AUA guideline, IC/BPS, which was originally considered to be a bladder disease, has now been recognized as a part of chronic pain syndromes. There is a growing body of literature demonstrating that different visceral pain syndromes, as well as pain syndromes in other body regions, and other systemic diseases often occur together in the same patient. Thus, the efforts to understand the pathophysiology and to design therapeutic modalities have recently shifted from an organ-based approach to a more global approach. Therefore, "phenotyping" of the disease conditions would be important to identify "bladder-related" and "non-bladder" (=outside the bladder) components that contribute to the symptoms for improving the treatment efficacy.

For this purpose, following issues require major research initiatives:

1. To improve symptom-based classification to identify the degree of bladder and non-bladder symptoms, for example, based on the responses to local treatment such as lidocaine intravesical application.
2. To identify bladder-specific pathology (urothelial changes, ulcer, hypervasculization, and the potential role of narrow band imaging[574], Neurometer[575] etc.
3. To identify bladder-specific biomarker (NGF or other neurotrophic factors, angiogenic growth factors, urothelial markers such as antiproliferative factor, cytokines/chemokines profile, uroplakin [antibody, splice variant]) .
4. To identify bladder-specific or systemic immunological process (cytokines/chemokines profile) Identification of these factors could also identify the difference in the disease process between IC/BPS and OAB (=LUTS with and without pain, respectively)

Finally, if we can identify the "bladder-related" and "non-bladder" (=outside the bladder) components that contribute to the symptoms, we should be able to develop the agent(s) to control bladder pain based on its pathology.

Major recommendations of the last Consultation for future directions in research on BPS still have pertinence today. They include:

A) Epidemiological study

i. Develop a reliable screening tool with adequate sensitivity and specificity to conduct epidemiologic research in the general population to study the incidence, prevalence and identify risk factors for the development of BPS.

ii. Establish patient data bases in different regions and conduct longitudinal follow up to understand the natural history of the disease and to examine the differences in disease natural history among regions.

B) Sub-grouping/phenotyping patients.

Patients who have or develop additional pain syndromes, such as vulvodynia, temporomandibular disorder, irritable bowel syndrome, fibromyalgia and

chronic fatigue syndrome, or autoimmune diseases such as lupus erythematosus and Sjögren's syndrome might have different pathophysiology, natural history and treatment response from those patients without co-morbidities. Sub-grouping patients not only allows us to develop better treatment strategy but also may answer the question: Is BPS an end-organ disease of the bladder or a systemic condition? [37,576] [87] However, to properly phenotype patients, it is necessary to develop an easy-to-use tool for non-specialists to identify those with co-morbidities. It is also important to validate the concept that categorizes all types of pelvic pain into one "chronic urological pelvic pain syndrome", as some patients' symptoms involve multiple pelvic organs, concurrently or sequentially along with other body systems.

C) Developing a simple, non-invasive diagnostic test for BPS.

This will most likely involve urinary markers. Urinary markers may help to sub-classify various types of BPS. This test will determine the diagnosis of BPS in the female population, as well as determine the subset of men currently diagnosed with non-bacterial chronic prostatitis/chronic pelvic pain syndrome who may actually have BPS.

D) Develop a practical multi-disciplinary care model.

In addition to physical morbidities (urinary frequency, pain), many BPS patients have associated psychological co-morbidities. [577] These can often be managed by psychological intervention. BPS patients also need help from dietitians and physiotherapists. A practical multi-disciplinary care model, which includes physicians, dietitians, physiotherapists, pain specialists, psychologists, psychiatrists and patient support groups, should be developed and tested in various settings.

XIX. SUMMARY

1. DEFINITION

Bladder Pain Syndrome (in the absence of a universally agreed definition, the European Society for the Study of Interstitial Cystitis –ESSIC definition is given along with the definition of the American Urological Association

ESSIC: *Chronic pelvic pain, pressure or discomfort of greater than 6 months duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.*

American Urological Association Guideline Definition: *An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes.*

2. BLADDER PAIN SYNDROME (BPS)

a) Nomenclature

The scientific committee of the International Consultation voted to use the term "bladder pain syndrome" for the disorder that has been commonly referred to as interstitial cystitis (IC). The term painful bladder syndrome was dropped from the lexicon. The term IC implies an inflammation within the wall of the urinary bladder, involving gaps or spaces in the bladder tissue. This does not accurately describe the majority of patients with this syndrome. Painful Bladder Syndrome, as defined by the International Continence Society, is too restrictive for the clinical syndrome.

Properly defined, the term Bladder Pain Syndrome appears to fit in well with the taxonomy of the International Association for the Study of Pain (IASP) (see below), and focuses on the actual symptom complex rather than what appears to be long-held misconception of the underlying pathology.

Bladder Pain Syndrome (XXIII-2) (per IASP)

Bladder pain syndrome is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. There is no proven infection or other obvious local pathology. Bladder pain syndrome is often associated with negative cognitive, behavioral, sexual, or emotional consequences as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.

b) History / Initial Assessment

Males or females whose symptoms meet the requirements of the definition of bladder pain syndrome should be evaluated. The presence of commonly associated disorders including irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia in the presence of the cardinal symptoms of bladder pain syndrome also suggests the diagnosis. Abnormal gynecologic findings in women and well-characterized confusable diseases that may explain the symptoms must be ruled out.

The initial assessment consists of a frequency/volume chart, focused physical examination, urinalysis, and urine culture. Urine cytology, cystoscopy, and urodynamic evaluation are recommended if clinically indicated and/or the diagnosis is in doubt. Patients with urinary infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and microscopic or gross hematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms, are they diagnosed with BPS. **Grade of recommendation: C**

c) Initial Treatment

- Patient education,
- dietary manipulation,

- nonprescription analgesics,
- stress reduction,
- pelvic floor relaxation techniques comprise the initial treatment of BPS. In the patient with findings suggesting pelvic floor dysfunction, pelvic floor physical therapy with myofascial trigger point release and intravaginal Thiele massage is often an effective therapeutic intervention. The treatment of pain needs to be addressed directly, and in some instances referral to an anesthesia/pain center can be an appropriate early step in conjunction with ongoing treatment of the syndrome.

When conservative therapy fails or symptoms are severe and conservative management is unlikely to succeed,

- oral medication or
- intravesical treatment can be prescribed. It is recommended to initiate a single form of therapy and observe results, adding other modalities or substituting other modalities as indicated by degree of response or lack of response to treatment. Grade of recommendation: C

d) Secondary Assessment

If initial oral or intravesical therapy fails, *or before beginning such therapy based on clinician judgment*, it is reasonable to consider **further evaluation** which can include Urodynamics, pelvic imaging, and cystoscopy with bladder distention and possible bladder biopsy under anesthesia.

- Findings of bladder overactivity suggest a trial of antimuscarinic therapy.
- The presence of a Hunner's lesion suggests therapy with transurethral resection, fulguration of the lesion, or direct steroid injection into the lesion.
- Distention itself can have therapeutic benefit in 30-50% of patients, though benefits rarely persist for longer than a few months. **Grade of recommendation: C**

e) Refractory BPS

Those patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive modalities. Many of these are best administered within the context of a clinical trial if possible. These may include

- neuromodulation,
- intradetrusor botulinum toxin,
- oral cyclosporine A, or
- clinical trials of newly described pharmacologic management techniques. At this point, most patients will benefit from the expertise of an anesthesia pain clinic.

The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urinary stream.

- Urinary diversion with or without cystectomy has been used as a last resort with good results in selected patients.
- Augmentation or substitution cystoplasty seems less effective and more prone to recurrence of chronic pain in small reported series.

Grade of recommendation: C

- Pain management is a primary consideration at every step of algorithm
- Patient enrollment in appropriate research trial is reasonable option at any point
- Evidence supporting neuromodulation, cyclosporine A, and botulinum toxin for BPS indication is limited. These interventions are appropriate only for practitioners with experience treating BPS and willing to provide long-term care post-intervention.

REFERENCES

1. Hanno P, Lin AT, Nordling J, Nyberg L, van Ophoven A, Ueda T. Bladder Pain Syndrome. In Abrams P, Cardozo L, Khoury S, Wein A, eds, Incontinence. Paris, France: Health Publication Ltd, 2009: 1459-1518.
2. van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 2008: 53(1):60-67.
3. Hanno P, Nordling J, van Ophoven A. What is new in bladder pain syndrome/interstitial cystitis? Curr Opin Urol 2008: 18(4):353-358.
4. Skene AJC. Diseases of the Bladder and Urethra in Women. New York: William Wood, 1887.
5. Hunner GL. A rare type of bladder ulcer in women; report of cases. Boston Med Surg Journal 1915: 172:660-664.
6. Bourque JP. Surgical management of the painful bladder. Journal of Urology 1951: 65:25-34.
7. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. Urology 1978: 12(4):381-392.
8. Wein A, Hanno PM, Gillenwater JY. Interstitial Cystitis: an introduction to the problem. In Hanno PM, Staskin DR, Krane RJ, Wein AJ, eds, Interstitial Cystitis. London: Springer-Verlag, 1990: 3-15.
9. Simon LJ, Landis JR, Erickson DR, Nyberg LM. The Interstitial Cystitis Data Base Study: concepts and preliminary baseline descriptive statistics. Urology 1997: 49(5A Suppl):64-75.
10. van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 2008: 53(1):60-67.
11. Homma Y, Ueda T, Tomoe H, Lin AT, Kuo HC, Lee MH et al. Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. Int J Urol 2009: 16(7):597-615.
12. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, FitzGerald MP et al. AUA Guideline for the Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome. J Urol 2011: 185(6):2162-2170.
13. Abrams PH, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society. Neurourology and Urodynamics 2002: 21:167-178.
14. Warren JW, Meyer WA, Greenberg P, Horne L, Diggs C, Tracy JK. Using the International Continence Society's definition of painful bladder syndrome. Urology 2006: 67(6):1138-1142.
15. Nordling J, Anjum FH, Bade JJ, Bouchelouche K, Bouchelouche P, Cervigni M et al. Primary evaluation of patients suspected of having interstitial cystitis (IC). Eur Urol 2004: 45(5):662-669.
16. Abrams P, Hanno P, Wein A. Overactive bladder and painful bladder syndrome: there need not be confusion. Neurourol Urodyn 2005: 24(2):149-150.
17. Nigro DA, Wein AJ, Foy M, Parsons CL, Williams M, Nyberg LM, Jr. et al. Associations among cystoscopic and urodynamic findings for women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. Urology 1997: 49(5A Suppl):86-92.
18. Salavatore S, Khullar V, Cardozo L, Anders K, Zocchi G, Soligo M. Evaluating ambulatory urodynamics: a prospective study in asymptomatic women. British Journal of Obstetrics and Gynaecology 2003: 110(1):83-84.
19. Parsons JK, Parsons CL. The historical origins of interstitial cystitis. J Urol 2004: 171(1):20-22.
20. Christmas TJ. Historical aspects of interstitial cystitis. In Sant GR, ed, Interstitial Cystitis. Philadelphia: Lippincott-Raven, 1997: 1-8.
21. Parrish J. Tic doloureux of the urinary bladder. Practical observations on strangulated hernia and some of the diseases of the urinary organs. Philadelphia: Key and Biddle, 1836: 309-313.
22. Teichman JM, Thompson IM, Taichman NS. Joseph Parrish, tic doloureux of the bladder and interstitial cystitis. J Urol 2000: 164(5):1473-1475.
23. Hunner GL. A rare type of bladder ulcer. Further notes, with a report of eighteen cases. JAMA 70[4], 203-212. 1-26-1918. Ref Type: Journal (Full)
24. Walsh A. Interstitial cystitis. In Harrison JH, Gittes RF, Perlmutter AD, al. e, eds, Campbell's Urology, 4th edn. Philadelphia: W. B. Saunders Company, 1978: 693-707.
25. Hand JR. Interstitial cystitis: report of 223 cases (204 women and 19 men). Journal of Urology 1949: 61:291-310.
26. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol 1988: 140(1):203-206.
27. Simon LJ, Landis JR, Tomaszewski JE, Nyberg LM. The interstitial cystitis database (ICDB) study. In Sant GR, ed, Interstitial Cystitis. Philadelphia: Lippincott-Raven, 1997: 17-24.
28. Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L, Jr. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol 1999: 161(2):553-557.
29. Hanno PM. Re-imagining Interstitial Cystitis. Urol Clin North Am 2008: 35(1):91-99.
30. Hanno P. Interstitial cystitis/painful bladder syndrome/bladder pain syndrome: the evolution of a new paradigm. International Consultation Interstitial Cystitis Japan 2008:(2):2-9.
31. Dell JR, Parsons CL. Multimodal therapy for interstitial cystitis. J Reprod Med 2004: 49(3 Suppl):243-252.
32. Powell NB, Powell EB. The female urethra: A clinico-pathological study. Journal of Urology 1949: 61:557-570.
33. Tomaszewski JE, Landis JR, Russack V, Williams TM, Wang LP, Hardy C et al. Biopsy features are associated with primary symptoms in interstitial cystitis: results from the interstitial cystitis database study. Urology 2001: 57(6 Suppl 1):67-81.
34. Rosamilia A, Igawa Y, Higashi S. Pathology of interstitial cystitis. Int J Urol 2003: 10 Suppl:S11-S15.
35. Lynes WL, Flynn SD, Shortliffe LD, Stamey TA. The histology of interstitial cystitis. Am J Surg Pathol 1990: 14(10):969-976.
36. Denson MA, Griebling TL, Cohen MB, Kreder KJ. Comparison of cystoscopic and histological findings in patients with suspected interstitial cystitis. J Urol 2000: 164(6):1908-1911.
37. Clauw DJ, Schmidt M, Radulovic D, Singer A, Katz P, Bresette J. The relationship between fibromyalgia and interstitial cystitis. J Psychiatr Res 1997: 31(1):125-131.
38. Wu EQ, Birnbaum H, Kang YJ, Parece A, Mallett D, Taitel H et al. A retrospective claims database analysis to assess patterns of interstitial cystitis diagnosis. Curr Med Res Opin 2006: 22(3):495-500.
39. Ueda T, Sant GR, Hanno PM, Yoshimura N. Interstitial cystitis and frequency-urgency syndrome (OAB syndrome). Int J Urol 2003: 10 Suppl:S39-S48.
40. Hanno P, Keay S, Moldwin R, vanOphoven A. International Consultation on IC - Rome, September 2004/Forging an International Consensus: progress in painful bladder syndrome/interstitial cystitis. Report and abstracts. Int Urogynecol J Pelvic Floor Dysfunct 2005: 16 Suppl 1:S2-S34.
41. Hanno P, Baranowski A, Fall M, Gajewski JB, Nordling J, Nyberg L et al. Painful bladder syndrome (including interstitial cystitis). In Abrams PH, Wein AJ, Cardozo L, eds, Incontinence, 3 edn, Vol. 2. Chapt 23. Paris: Health Publications Limited, 2005: 1456-1520.

42. Abrams P, Baranowski A, Berger R, Fall M, Hanno P, Wesselmann U. A new classification is needed for pelvic pain syndromes -- are existing terminologies of spurious diagnostic authority bad for patients? J Urol 2006: 175:1989-1990.

43. Baranowski AP, Abrams P, Berger RE, Buffington CA, de CWA, Hanno P et al. Urogenital pain--time to accept a new approach to phenotyping and, as a consequence, management. Eur Urol 2008: 53(1):33-36.

44. Homma Y. Lower urinary tract symptomatology: Its definition and confusion. International Journal of Urology 2008: 15(1):35-43.

45. Homma Y, Ueda T, Ito T, Takei M, Tomoe H. Japanese guideline for diagnosis and treatment of interstitial cystitis. Int J Urol 2009: 16(1):4-16.

46. Berry SH, Bogart LM, Pham C, Liu K, Nyberg L, Stoto M et al. Development, validation and testing of an epidemiological case definition of interstitial cystitis/painful bladder syndrome. J Urol 2010: 183(5):1848-1852.

47. Barry MJ, Link CL, McNaughton-Collins MF, McKinlay JB. Overlap of different urological symptom complexes in a racially and ethnically diverse, community-based population of men and women. BJU Int 2008: 101(1):45-51.

48. Ito T, Miki M, Yamada T. Interstitial cystitis in Japan. BJU Int 2000: 86(6):634-637.

49. Parsons CL, Tatsis V. Prevalence of interstitial cystitis in young women. Urology 2004: 64(5):866-870.

50. Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LM, Jr., McKinlay JB. Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urol 2007: 177(4):1390-1394.

51. Oravisto KJ. Epidemiology of interstitial cystitis. Ann Chir Gynaecol Fenn 1975: 64(2):75-77.

52. Held PJ, Hanno PM, Wein AJ. Epidemiology of interstitial cystitis: 2. In Hanno PM, Staskin DR, Krane RJ, Wein AJ, eds, Interstitial Cystitis. London: Springer-Verlag, 1990: 29-48.

53. Jones CA, Nyberg L. Epidemiology of interstitial cystitis. Urology 1997: 49(5A Suppl):2-9.

54. Clemens J, Payne C, Pace J. Prevalence of self-reported interstitial cystitis in a nationally representative United States Survey. J.Urol 173. 2005.

55. Bade JJ, Rijcken B, Mensink HJ. Interstitial cystitis in The Netherlands: prevalence, diagnostic criteria and therapeutic preferences. J Urol 1995: 154(6):2035-2037.

56. Curhan GC, Speizer FE, Hunter DJ, Curhan SG, Stampfer MJ. Epidemiology of interstitial cystitis: a population based study. J Urol 1999: 161(2):549-552.

57. Clemens JQ, Meenan RT, O'Keeffe Rosetti MC, Brown SO, Gao SY, Calhoun EA. Prevalence of interstitial cystitis symptoms in a managed care population. J Urol 2005: 174(2):576-580.

58. Nickel JC, Teichman JM, Gregoire M, Clark J, Downey J. Prevalence, diagnosis, characterization, and treatment of prostatitis, interstitial cystitis, and epididymitis in outpatient urological practice: the Canadian PIE Study. Urology 2005: 66(5):935-940.

59. Lifford KL, Curhan GC. Prevalence of painful bladder syndrome in older women. Urology 2009: 73(3):494-498.

60. Warren JW, Jackson TL, Langenberg P, Meyers DJ, Xu J. Prevalence of interstitial cystitis in first-degree relatives of patients with interstitial cystitis. Urology 2004: 63(1):17-21.

61. Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LM, Jr., McKinlay JB. Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urol 2007: 177(4):1390-1394.

62. Rosenberg MT, Hazzard M. Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. J Urol 2005: 174(6):2231-2234.

63. Leppilahti M, Tammela TL, Huhtala H, Auvinen A. Prevalence of symptoms related to interstitial cystitis in women: a population based study in Finland. J Urol 2002: 168(1):139-143.

64. Leppilahti M, Sairanen J, Tammela TL, Aaltomaa S, Lehtoranta K, Auvinen A. Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finland. J Urol 2005: 174(2):581-583.

65. Clemens J, Meenan R, Rosetti M, Calhoun E. Prevalence and incidence of interstitial cystitis in a managed care population. J Urol 2005: 173:98-102.

66. Choe JH, Son H, Song YS, Kim JC, Lee JZ, Lee KS. Prevalence of painful bladder syndrome/interstitial cystitis-like symptoms in women: a population-based study in Korea. World J Urol 2011: 29(1):103-108.

67. Temml C, Wehrberger C, Riedl C, Ponholzer A, Marszalek M, Madersbacher S. Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. Eur Urol 2007: 51(3):803-808.

68. Song Y, Zhang W, Xu B, Hao L, Song J. Prevalence and correlates of painful bladder syndrome symptoms in Fuzhou Chinese women. Neurourol Urodyn 2009: 28(1):22-25.

69. Berry SH, Elliott MN, Suttorp M, Bogart LM, Stoto MA, Eggers P et al. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. J Urol 2011: 186(2):540-544.

70. Konkle KS, Berry SH, Elliott MN, Hilton L, Suttorp MJ, Clauw DJ et al. Comparison of an Interstitial Cystitis/Bladder Pain Syndrome Clinical Cohort With Symptomatic Community Women From the RAND Interstitial Cystitis Epidemiology Study. J Urol 2012: 187(2):508-512.

71. Clemens J, Markossian T, Meenan R, Rosetti M, Calhoun EA. Overlap of voiding symptoms, storage symptoms and pain in men and women. J Urol 2007: 178:1354-1358.

72. Rosenberg MT, Page S, Hazzard MA. Prevalence of interstitial cystitis in a primary care setting. Urology 2007: 69(4 Suppl):48-52.

73. Roberts RO, Bergstralh EJ, Bass SE, Lightner DJ, Lieber MM, Jacobsen SJ. Incidence of physician-diagnosed interstitial cystitis in Olmsted County: a community-based study. BJU Int 2003: 91(3):181-185.

74. Patel R, Calhoun EA, Meenan RT, O'Keeffe Rosetti MC, Kimes T, Clemens JQ. Incidence and clinical characteristics of interstitial cystitis in the community. Int Urogynecol J Pelvic Floor Dysfunct 2008: 19(8):1093-1096.

75. Geist RW, Antolak SJ, Jr. Interstitial cystitis in children. J Urol 1970: 104(6):922-925.

76. Close CE, Carr MC, Burns MW, Miller JL, Bavendam TG, Mayo ME et al. Interstitial cystitis in children. J Urol 1996: 156(2 Pt 2):860-862.

77. Rackow BW, Novi JM, Arya LA, Pfeifer SM. Interstitial cystitis is an etiology of chronic pelvic pain in young women. J Pediatr Adolesc Gynecol 2009: 22(3):181-185.

78. Peters KM, Killinger KA, Ibrahim IA. Childhood symptoms and events in women with interstitial cystitis/painful bladder syndrome. Urology 2009: 73(2):258-262.

79. Nickel J, Tripp DA, Pontari M, Moldwin R, Mayer R, Lesley L et al. Childhood sexual trauma in women with interstitial cystitis / bladder pain syndrome: A case control study. Can Urol Assoc J 2011: 5(6):410-415.

80. Hanash KA, Pool TL. Interstitial cystitis in men. J Urol 1969: 102(4):427-428.

81. Forrest JB, Schmidt S. Interstitial cystitis, chronic nonbacterial prostatitis and chronic pelvic pain syndrome in men: a common and frequently identical clinical entity. J Urol 2004: 172(6 Pt 2):2561-2562.

82. Forrest JB, Nickel JC, Moldwin RM. Chronic prostatitis/chronic pelvic pain syndrome and male interstitial cystitis: enigmas and opportunities. Urology 2007: 69(4 Suppl):60-63.

83. Miller JL, Rothman I, Bavendam TG, Berger RE. Prostatodynia and interstitial cystitis: one and the same? Urology 1995: 45(4):587-590.

84. Novicki DE, Larson TR, Swanson SK. Interstitial cystitis in men. Urology 1998: 52(4):621-624.

85. Alagiri M, Chottiner S, Ratner V, Slade D, Hanno PM. Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. Urology 1997: 49(5A Suppl):52-57.

86. Wu EQ, Birnbaum H, Kang YJ, Parece A, Mallett D, Taitel H et al. A retrospective claims database analysis to assess patterns of interstitial cystitis diagnosis. Curr Med Res Opin 2006: 22(3):495-500.

87. Clemens JQ, Meenan RT, O'Keeffe Rosetti MC, Kimes TA, Calhoun EA. Case-control study of medical comorbidities in women with interstitial cystitis. J Urol 2008: 179(6):2222-2225.

88. Warren JW, Howard FM, Cross RK, Good JL, Weissman MM, Wesselmann U et al. Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. Urology 2009: 73(1):52-57.

89. Nickel JC, Tripp DA, Pontari M, Moldwin R, Mayer R, Carr LK et al. Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. J Urol 2010: 184(4):1358-1363.

90. Nickel JC, Tripp DA, Pontari M, Moldwin R, Mayer R, Carr LK et al. Psychosocial phenotyping in women with interstitial cystitis/painful bladder syndrome: a case control study. J Urol 2010: 183(1):167-172.

91. Rodriguez MA, Afari N, Buchwald DS. Evidence for overlap between urological and nonurological unexplained clinical conditions. J Urol 2009: 182(5):2123-2131.

92. Warren JW, van de Merwe JP, Nickel JC. Interstitial cystitis/bladder pain syndrome and nonbladder syndromes: facts and hypotheses. Urology 2011: 78(4):727-732.

93. Bogart LM, Suttorp MJ, Elliott MN, Clemens JQ, Berry SH. Prevalence and correlates of sexual dysfunction among women with bladder pain syndrome/interstitial cystitis. Urology 2011: 77(3):576-580.

94. Gardella B, Porru D, Nappi RE, Dacco MD, Chiesa A, Spinillo A. Interstitial cystitis is associated with vulvodynia and sexual dysfunction--a case-control study. J Sex Med 2011: 8(6):1726-1734.

95. Tripp DA, Nickel JC, FitzGerald MP, Mayer R, Stechyson N, Hsieh A. Sexual functioning, catastrophizing, depression, and pain, as predictors of quality of life in women with interstitial cystitis/painful bladder syndrome. Urology 2009: 73(5):987-992.

96. Zaslau S, Riggs DR, Perlmutter AE, Jackson BJ, Osborne J, Kandzari SJ. Sexual dysfunction in patients with painful bladder syndrome is age related and progressive. Can J Urol 2008: 15(4):4158-4162.

97. Koziol JA, Clark DC, Gittes RF, Tan EM. The natural history of interstitial cystitis: a survey of 374 patients. J Urol 1993: 149(3):465-469.

98. Propert KJ, Schaeffer AJ, Brensinger CM, Kusek JW, Nyberg LM, Landis JR. A prospective study of interstitial cystitis: results of longitudinal followup of the interstitial cystitis data base cohort. The Interstitial Cystitis Data Base Study Group. J Urol 2000: 163(5):1434-1439.

99. Peeker R, Enerback L, Fall M, Aldenborg F. Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. J Urol 2000: 163(3):1009-1015.

100. Hofmeister MA, He F, Ratliff TL, Mahoney T, Becich MJ. Mast cells and nerve fibers in interstitial cystitis (IC): an algorithm for histologic diagnosis via quantitative image analysis and morphometry (QIAM). Urology 1997: 49(5A Suppl):41-47.

101. Fall M, Johansson SL, Aldenborg F. Chronic interstitial cystitis: a heterogeneous syndrome. J Urol 1987: 137(1):35-38.

102. Dundore PA, Schwartz AM, Semerjian H. Mast cell counts are not useful in the diagnosis of nonulcerative interstitial cystitis. J Urol 1996: 155(3):885-887.

103. Bouchelouche K, Kristensen B, Nordling J, Horn T, Bouchelouche P. Increased urinary leukotriene E4 and eosinophil protein X excretion in patients with interstitial cystitis. J Urol 2001: 166(6):2121-2125.

104. Zhang CO, Wang JY, Koch KR, Keay S. Regulation of tight junction proteins and bladder epithelial paracellular permeability by an antiproliferative factor from patients with interstitial cystitis. J Urol 2005: 174(6):2382-2387.

105. Shie JH, Kuo HC. Higher levels of cell apoptosis and abnormal E-cadherin expression in the urothelium are associated with inflammation in patients with interstitial cystitis/painful bladder syndrome. BJU Int 2011: 108(2 Pt 2):E136-E141.

106. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol 1991: 145(4):732-735.

107. Johansson SL, Fall M. Clinical features and spectrum of light microscopic changes in interstitial cystitis. J Urol 1990: 143(6):1118-1124.

108. Fellows G. The permeability of human bladder epithelium to water and sodium. Invest Urol 1972: 9:339.

109. Anderstrom CR, Fall M, Johansson SL. Scanning electron microscopic findings in interstitial cystitis. Br J Urol 1989: 63(3):270-275.

110. Parsons CL, Stein P, Zupkas P, Chenoweth M, Argade SP, Proctor JG et al. Defective Tamm-Horsfall protein in patients with interstitial cystitis. J Urol 2007: 178(6):2665-2670.

111. Keay S, Kleinberg M, Zhang CO, Hise MK, Warren JW. Bladder epithelial cells from patients with interstitial cystitis produce an inhibitor of heparin-binding epidermal growth factor-like growth factor production. J Urol 2000: 164(6):2112-2118.

112. Keay S, Seillier-Moiseiwitsch F, Zhang CO, Chai TC, Zhang J. Changes in human bladder epithelial cell gene expression associated with interstitial cystitis or antiproliferative factor treatment. Physiol Genomics 2003: 14(2):107-115.

113. Keay S, Reeder JE, Koch K, Zhang CO, Grkovic D, Peters K et al. Prospective evaluation of candidate urine and cell markers in patients with interstitial cystitis enrolled in a randomized clinical trial of Bacillus Calmette Guerin (BCG). World J Urol 2007: 25(5):499-504.

114. Silk MR. Bladder antibodies in interstitial cystitis. J Urol 1970: 103(3):307-309.

115. Oravisto KJ. Interstitial cystitis as an autoimmune disease. A review. Eur Urol 1980: 6(1):10-13.

116. Jokinen EJ, Alfthan OS, Oravisto KJ. Antitissue antibodies in interstitial cystitis. Clin Exp Immunol 1972: 11(3):333-339.

117. Anderson JB, Parivar F, Lee G, Wallington TB, MacIver AG, Bradbrook RA et al. The enigma of interstitial cystitis--an autoimmune disease? Br J Urol 1989: 63(1):58-63.

118. Tan EM. Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. Adv Immunol 1989: 44:93.

119. Peeker R, Atanasiu L, Logadottir Y. Intercurrent autoimmune conditions in classic and non-ulcer interstitial cystitis. Scand J Urol Nephrol 2003: 37(1):60-63.

120. Leppilahti M, Tammela TL, Huhtala H, Kiilholma P, Leppilahti K, Auvinen A. Interstitial cystitis-like urinary symptoms among patients with Sjogren's syndrome: a population-based study in Finland. Am J Med 2003: 115(1):62-65.

121. Ochs RL. Autoantibodies and interstitial cystitis. Clin Lab Med 1997: 17(3):571-579.

122. Mattila J, Harmoinen A, Hallstrom O. Serum immunoglobulin and complement alterations in interstitial cystitis. Eur Urol 1983: 9(6):350-352.

123. Mattila J, Linder E. Immunoglobulin deposits in bladder epithelium and vessels in interstitial cystitis: possible relation-

ship to circulating anti-intermediate filament autoantibodies. Clin Immunol Immunopathol 1984: 32(1):81-89.

124. Harrington DS, Fall M, Johansson SL. Interstitial cystitis: bladder mucosa lymphocyte immunophenotyping and peripheral blood flow cytometry analysis. J Urol 1990: 144(4):868-871.

125. Lynes WL, Sellers RG, Dairiki Shortliffe LM. The evidence for occult bacterial infections as a cause for interstitial cystitis. J Urol 141, 268. 1989.

126. Warren JW, Brown V, Jacobs S, Horne L, Langenberg P, Greenberg P. Urinary tract infection and inflammation at onset of interstitial cystitis/painful bladder syndrome. Urology 2008: 71(6):1085-1090.

127. Duncan JL, Schaeffer AJ. Do infectious agents cause interstitial cystitis? Urology 1997: 49(5A Suppl):48-51.

128. English SF, Liebert M, Cross CA, McGuire EJ. The incidence of Helicobacter pylori in patients with interstitial cystitis. J Urol 1998: 159(3):772-773.

129. Zhang QH, Shen XC, Zhou ZS, Chen ZW, Lu GS, Song B. Decreased nanobacteria levels and symptoms of nanobacteria-associated interstitial cystitis/painful bladder syndrome after tetracycline treatment. Int Urogynecol J 2010: 21(1):103-109.

130. Palea S, Artibani W, Ostardo E, Trist DG, Pietra C. Evidence for purinergic neurotransmission in human urinary bladder affected by interstitial cystitis. J Urol 1993: 150(6):2007-2012.

131. Hohenfellner M, Nunes L, Schmidt RA, Lampel A, Thuroff JW, Tanagho EA. Interstitial cystitis: increased sympathetic innervation and related neuropeptide synthesis. J Urol 1992: 147(3):587-591.

132. Christmas TJ, Rode J, Chapple CR, Milroy EJ, Turner-Warwick RT. Nerve fibre proliferation in interstitial cystitis. Virchows Arch A Pathol Anat Histopathol 1990: 416(5):447-451.

133. Sugimura K, Haimoto H, Nagura H. Immunohistochemical differential distribution of S-100 alpha and S-100 beta in the peripheral nervous system of the rat. Muscle Nerve 1989: 12:929.

134. Stefansson K, Wollmann RL, Moore BW. Distribution of S-100 protein outside the central nervous system. Brain Res 1982: 234:309.

135. Peeker R, Aldenborg F, Haglid K, Johansson SL, Rosengren L, Fall M. Decreased levels of S-100 protein in non-ulcer interstitial cystitis. Scand J Urol Nephrol 1998: 32(6):395-398.

136. Elbadawi AE, Light JK. Distinctive ultrastructural pathology of nonulcerative interstitial cystitis: new observations and their potential significance in pathogenesis. Urol Int 1996: 56(3):137-162.

137. Peeker R, Aldenborg F, Dahlstrom A, Johansson SL, Li JY, Fall M. Increased tyrosine hydroxylase immunoreactivity in bladder tissue from patients with classic and nonulcer interstitial cystitis. J Urol 2000: 163(4):1112-1115.

138. Malykhina AP, Qin C, Greenwood-Van MB, Foreman RD, Lupu F, Akbarali HI. Hyperexcitability of convergent colon and bladder dorsal root ganglion neurons after colonic inflammation: mechanism for pelvic organ cross-talk. Neurogastroenterol Motil 2006: 18(10):936-948.

139. Malykhina AP. Neural mechanisms of pelvic organ cross-sensitization. Neuroscience 2007: 149(3):660-672.

140. Noronha R, Akbarali H, Malykhina A, Foreman RD, Greenwood-Van MB. Changes in urinary bladder smooth muscle function in response to colonic inflammation. Am J Physiol Renal Physiol 2007: 293(5):F1461-F1467.

141. Pezzone MA, Liang R, Fraser MO. A model of neural cross-talk and irritation in the pelvis: implications for the overlap of chronic pelvic pain disorders. Gastroenterology 2005: 128(7):1953-1964.

142. Qin C, Malykhina AP, Akbarali HI, Greenwood-Van MB, Foreman RD. Acute colitis enhances responsiveness of lumbosacral spinal neurons to colorectal distension in rats. Dig Dis Sci 2008: 53(1):141-148.

143. Rudick CN, Chen MC, Mongiu AK, Klumpp DJ. Organ cross talk modulates pelvic pain. Am J Physiol Regul Integr Comp Physiol 2007: 293(3):R1191-R1198.

144. Parsons CL, Bautista SL, Stein PC, Zupkas P. Cyto-injury factors in urine: a possible mechanism for the development of interstitial cystitis. J Urol 2000: 164(4):1381-1384.

145. Hang L, Wullt B, Shen Z, Karpman D, Svanborg C. Cytokine repertoire of epithelial cells lining the human urinary tract. J Urol 1998: 159(6):2185-2192.

146. Rosamilia A, Cann L, Scurry J, Rogers P, Dwyer P. Bladder microvasculature and the effects of hydrodistention in interstitial cystitis. Urology 2001: 57(6 Suppl 1):132.

147. Pontari MA, Hanno PM, Ruggieri MR. Comparison of bladder blood flow in patients with and without interstitial cystitis. J Urol 1999: 162(2):330-334.

148. Lee JD, Lee MH. Increased expression of hypoxia-inducible factor-1alpha and vascular endothelial growth factor associated with glomerulation formation in patients with interstitial cystitis. Urology 2011: 78(4):971-975.

149. Warren JW, Keay SK, Meyers D, Xu J. Concordance of interstitial cystitis in monozygotic and dizygotic twin pairs. Urology 2001: 57(6 Suppl 1):22-25.

150. Altman D, Lundholm C, Milsom I, Peeker R, Fall M, Iliadou AN et al. The genetic and environmental contribution to the occurrence of bladder pain syndrome: an empirical approach in a nationwide population sample. Eur Urol 2011: 59(2):280-285.

151. Weissman MM, Gross R, Fyer A, Heiman GA, Gameroff MJ, Hodge SE et al. Interstitial cystitis and panic disorder: a potential genetic syndrome. Arch Gen Psychiatry 2004: 61(3):273-279.

152. Talati A, Ponniah K, Strug LJ, Hodge SE, Fyer AJ, Weissman MM. Panic disorder, social anxiety disorder, and a possible medical syndrome previously linked to chromosome 13. Biol Psychiatry 2008: 63(6):594-601.

153. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med 2001: 134(9 Pt 2):868-881.

154. Clauw DJ. The pathogenesis of chronic pain and fatigue syndromes, with special reference to fibromyalgia. Med Hypotheses 1995: 44(5):369-378.

155. Sand PK. Proposed pathogenesis of painful bladder syndrome/interstitial cystitis. J Reprod Med 2006: 51(3 Suppl):234-240.

156. Hellstrom HR, Davis BK, Shonnard JW. Eosinophilic cystitis. A study of 16 cases. Am J Clin Pathol 1979: 72(5):777-784.

157. Tsiriopoulos I, Lee G, O' RA, Smith R, Pancharatnam M. Primary splenic marginal zone lymphoma with bladder metastases mimicking interstitial cystitis. Int Urol Nephrol 2006: 38(3-4):475-476.

158. Jacobo E, Stamler FW, Culp DA. Interstitial cystitis followed by total cystectomy. Urology 1974: 3(4):481-485.

159. Smith BH, Dehner LP. Chronic ulcerating interstitial cystitis (Hunner's ulcer). A study of 28 cases. Arch Pathol 1972: 93(1):76-81.

160. Lepinard V, Saint-Andre JP, Rognon LM. [Interstitial cystitis. Current aspects]. J Urol (Paris) 1984: 90(7):455-465.

161. Johansson SL, Fall M. Pathology of interstitial cystitis. Urol Clin North Am 1994: 21(1):55-62.

162. Holm-Bentzen M, Jacobsen F, Nerstrom B, Lose G, Kristensen JK, Pedersen RH et al. Painful bladder disease: clinical and pathoanatomical differences in 115 patients. J Urol 1987: 138(3):500-502.

163. Moore KH, Nickson P, Richmond DH, Sutherst JR, Manasse PR, Helliwell TR. Detrusor mast cells in refractory idiopathic instability. Br J Urol 1992: 70(1):17-21.

164. Theoharides TC, Kempuraj D, Sant GR. Mast cell involvement in interstitial cystitis: a review of human and experimental evidence. Urology 2001: 57(6 Suppl 1):47-55.

165. Larsen MS, Mortensen S, Nordling J, Horn T. Quantifying mast cells in bladder pain syndrome by immunohistochemical analysis. BJU Int 2008.

166. Rudick CN, Bryce PJ, Guichelaar LA, Berry RE, Klumpp DJ. Mast cell-derived histamine mediates cystitis pain. PLoS ONE 2008: 3(5):e2096.

167. Collan Y, Alfthan O, Kivilaakso E, Oravisto KJ. Electron microscopic and histological findings on urinary bladder epithelium in interstitial cystitis. Eur Urol 1976: 2(5):242-247.

168. Dixon JS, Holm-Bentzen M, Gilpin CJ, Gosling JA, Bostofte E, Hald T et al. Electron microscopic investigation of the bladder urothelium and glycocalyx in patients with interstitial cystitis. J Urol 1986: 135(3):621-625.

169. Nickel JC, Emerson L, Cornish J. The bladder mucus (glycosaminoglycan) layer in interstitial cystitis. J Urol 1993: 149(4):716-718.

170. Elbadawi A. Interstitial cystitis: a critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. Urology 1997: 49(5A Suppl):14-40.

171. Holm-Bentzen M. Pathology and pathophysiology of painful bladder diseases. Urol Int 1989: 44(6):327-331.

172. Holm-Bentzen M, Larsen S, Hainau B, et.al. Nonobstructive detrusor myopathy in a group of patients with chronic abacterial cystitis. Scand J Urol Nephrol 1985: 19:21-26.

173. Christmas TJ, Smith GL, Rode J. Detrusor myopathy: an accurate predictor of bladder hypocompliance and contracture in interstitial cystitis. Br J Urol 1996: 78(6):862-865.

174. Tomaszewski JE, Landis JR, Brensinger C, Hardy C, et.al. Baseline associations among pathologic features and patient symptoms in the national interstitial cystitis data base. Journal of Urology 1999: 161 S:28.

175. Hanus T, Zamecnik L, Jansky M, Jarolim L, Povysil C, Benett R. The comparison of clinical and histopathologic features of interstitial cystitis. Urology 2001: 57(6 Suppl 1):131.

176. Richter B, Hesse U, Hansen AB, Horn T, Mortensen SO, Nordling J. Bladder pain syndrome/interstitial cystitis in a Danish population: a study using the 2008 criteria of the European Society for the Study of Interstitial Cystitis. BJU Int 2010: 105(5):660-667.

177. Geurts N, Van DJ, Wyndaele JJ. Bladder pain syndrome: do the different morphological and cystoscopic features correlate? Scand J Urol Nephrol 2011: 45(1):20-23.

178. Mattila J. Vascular immunopathology in interstitial cystitis. Clin Immunol Immunopathol 1982: 23(3):648-655.

179. Johansson SL, Ogawa K, Fall M. The pathology of interstitial cystitis. In Sant GR, ed, Interstitial Cystitis. Philadelphia: Lippincott-Raven, 1997: 143-152.

180. Rossberger J, Fall M, Jonsson O, Peeker R. Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: subtyping is imperative. Urology 2007: 70(4):638-642.

181. Erickson DR, Tomaszewski JE, Kunselman AR, Stetter CM, Peters KM, Rovner ES et al. Urine markers do not predict biopsy findings or presence of bladder ulcers in interstitial cystitis/painful bladder syndrome. J Urol 2008: 179(5):1850-1856.

182. Mcdougald M LC. The diagnosis of interstitial cystitis: Is histology helpful ? Int.Urogynecol.J.Pelvic.Floor.Dysfunct. 14[Suppl 1], S40-S41. 2003.

183. Nordling J, Anderson JB, Mortensen S, Bouchelouche K, Horn T, Hald T et al. Clinical outcome in patients with interstitial cystitis, relative to detrusor myopathy. Poster 42 Research Insights into Interstitial cystitis, NIDDK Washington Oct 30-Nov 1, 2003 . 11-1-2003.

184. MacDermott JP, Charpied GC, Tesluk H, Stone AR. Can histological assessment predict the outcome in interstitial cystitis? Br J Urol 1991: 67(1):44-47.

185. Flores-Carreras O, Martinez-Espinoza CJ, Gonzalez-Ruiz MI, Montes-Casillas YE. [Contribution of bladder biopsy to the study of urogynaecological patient]. Ginecol Obstet Mex 2010: 78(3):187-190.

186. Zamecnik L, Hanus T, Pavlik I, Dundr P, Povysil C. Statistical analysis of symptoms, endoscopy and urothelial morphology in 58 female bladder pain syndrome/interstitial cystitis patients. Urol Int 2009: 83(2):193-199.

187. Kaplan SA, Ikeguchi EF, Santarosa RP, D'Alisera PM, Hendricks J, Te AE et al. Etiology of voiding dysfunction in men less than 50 years of age. Urology 1996: 47:836-839.

188. Hanno P. Is the potassium sensitivity test a valid and useful test for the diagnosis of interstitial cystitis? Int Urogynecol J Pelvic Floor Dysfunct 2005: 16(6):428-429.

189. Hohlbrugger G. Disintegrity of the vesical blood-urine barrier in interstitial cystitis: a vicious circle. In Sant GR, ed, Interstitial Cystitis. Philadelphia: Lippincott-Raven, 1997: 87-92.

190. Vander AJ. Renal Physiology. New York: McGraw Hill Health Professions Division, 1995.

191. Roberto PJ, Reich JD, Hirshberg S, Knight L, Hanno PM, Ruggieri M. Assessment of bladder permiability and sensation in interstitial cystitis patients. Journal of Urology 1997: 157(S):317.

192. Daha LK, Riedl CR, Lazar D, Hohlbrugger G, Pfluger H. Do cystometric findings predict the results of intravesical hyaluronic acid in women with interstitial cystitis? Eur Urol 2005: 47(3):393-397.

193. Chambers GK, Fenster HN, Cripps S, Jens M, Taylor D. An assessment of the use of intravesical potassium in the diagnosis of interstitial cystitis. J Urol 1999: 162(3 Pt 1):699-701.

194. Parsons CL, Greenberger M, Gabal L, Bidair M, Barme G. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. J Urol 1998: 159(6):1862-1866.

195. Yilmaz U, Liu YW, Rothman I, Lee JC, Yang CC, Berger RE. Intravesical potassium chloride sensitivity test in men with chronic pelvic pain syndrome. J Urol 2004: 172(2):548-550.

196. Chung MK, Butrick CW, Chung CW. The overlap of interstitial cystitis/painful bladder syndrome and overactive bladder. JSLS 2010: 14(1):83-90.

197. Parsons CL, Stein PC, Bidair M, Lebow D. Abnormal sensitivity to intravesical potassium in interstitial cystitis and radiation cystitis. Neurourol Urodyn 1994: 13(5):515-520.

198. Parsons CL, Albo M. Intravesical potassium sensitivity in patients with prostatitis. J Urol 2002: 168(3):1054-1057.

199. Parsons CL, Rosenberg MT, Sassani P, Ebrahimi K, Koziol JA, Zupkas P. Quantifying symptoms in men with interstitial cystitis/prostatitis, and its correlation with potassium-sensitivity testing. BJU Int 2005: 95(1):86-90.

200. Parsons CL, Dell J, Stanford EJ, Bullen M, Kahn BS, Willems JJ. The prevalence of interstitial cystitis in gynecologic patients with pelvic pain, as detected by intravesical potassium sensitivity. Am J Obstet Gynecol 2002: 187(5):1395-1400.

201. Parsons CL, Dell J, Stanford EJ, Bullen M, Kahn BS, Waxell T et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. Urology 2002: 60(4):573-578.

202. Sahinkanat T, Guven A, Ekerbicer H, Aral M. Prevalence of positive potassium sensitivity test which is an indicator of bladder epithelial permeability dysfunction in a fixed group of Turkish women. Urol Int 2008: 80(1):52-56.

203. Gregoire M, Liandier F, Naud A, Lacombe L, Fradet Y. Does the potassium stimulation test predict cystometric, cystoscopic outcome in interstitial cystitis? J Urol 2002: 168(2):556-557.

204. Kuo HC. Urodynamic study and potassium sensitivity test for women with frequency-urgency syndrome and interstitial cystitis. Urol Int 2003: 71(1):61-65.

205. Philip J, Willmott S, Irwin P. Interstitial cystitis versus detrusor overactivity: a comparative, randomized, controlled study of cystometry using saline and 0.3 M potassium chloride. J Urol 2006: 175(2):566-570.

206. Philip J, Willmott S, Owen D, Samsudin C, Irwin PP. A double-blind, randomized controlled trial of cystometry using saline versus 0.3 M potassium chloride infusion in women with overactive bladder syndrome. Neurourol Urodyn 2007: 26(1):110-114.

207. Daha LK, Riedl CR, Hohlbrugger G, Knoll M, Engelhardt PF, Pfluger H. Comparative assessment of maximal bladder capacity, 0.9% NaCl versus 0.2 M Kcl, for the diagnosis of interstitial cystitis: a prospective controlled study. J Urol 2003: 170(3):807-809.

208. Riedl CR, Engelhardt PF, Daha KL, Morakis N, Pfluger H. Hyaluronan treatment of interstitial cystitis/painful bladder syndrome. Int Urogynecol J Pelvic Floor Dysfunct 2008: 19(5):717-721.

209. Erickson DR. Glomerulations in women with urethral sphincter deficiency: report of 2 cases [corrected]. J Urol 1995: 153(3 Pt 1):728-729.

210. Furuya R, Masumori N, Furuya S, Oda T, Takahashi S, Takeuchi M. Glomerulation observed during transurethral resection of the prostate for patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia is a common finding but no predictor of clinical outcome. Urology 2007: 70(5):922-926.

211. Messing E, Pauk D, Schaeffer A, Nieweglowski M, Nyberg LM, Jr., Landis JR et al. Associations among cystoscopic findings and symptoms and physical examination findings in women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. Urology 1997: 49(5A Suppl):81-85.

212. Waxman JA, Sulak PJ, Kuehl TJ. Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. J Urol 1998: 160(5):1663-1667.

213. Peeker R, Fall M. Toward a precise definition of interstitial cystitis: further evidence of differences in classic and nonulcer disease. J Urol 2002: 167(6):2470-2472.

214. Bade J, Ishizuka O, Yoshida M. Future research needs for the definition/diagnosis of interstitial cystitis. Int J Urol 2003: 10 Suppl:S31-S34.

215. Messing EM. Interstitial cystitis--a light at the end of the tunnel? J Urol 1999: 161(6):1797.

216. Turner KJ, Stewart LH. How do you stretch a bladder? A survey of UK practice, a literature review, and a recommendation of a standard approach. Neurourol Urodyn 2004.

217. Cole EE, Scarpero HM, Dmochowski RR. Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? Neurourol Urodyn 2005: 24(7):638-642.

218. Ottem DP, Teichman JM. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 2005: 66(3):494-499.

219. Rigaud J, Delavierre D, Sibert L, Labat JJ. [Diagnostic approach to chronic bladder pain]. Prog Urol 2010: 20(12):930-939.

220. Lamale LM, Lutgendorf SK, Hoffman AN, Kreder KJ. Symptoms and cystoscopic findings in patients with untreated interstitial cystitis. Urology 2006: 67(2):242-245.

221. Shear S, Mayer R. Development of glomerulations in younger women with interstitial cystitis. Urology 2006: 68(2):253-256.

222. Zabihi N, Allee T, Maher MG, Mourtzinos A, Raz S, Payne CK et al. Bladder necrosis following hydrodistention in patients with interstitial cystitis. J Urol 2007: 177(1):149-152.

223. Wyndaele JJ, Van DJ, Toussaint N. Cystoscopy and bladder biopsies in patients with bladder pain syndrome carried out following ESSIC guidelines. Scand J Urol Nephrol 2009: 43(6):471-475.

224. Richter B, Roslind A, Hesse U, Nordling J, Johansen JS, Horn T et al. YKL-40 and mast cells are associated with detrusor fibrosis in patients diagnosed with bladder pain syndrome/interstitial cystitis according to the 2008 criteria of the European Society for the Study of Interstitial Cystitis. Histopathology 2010: 57(3):371-383.

225. Erickson DR, Xie SX, Bhavanandan VP, Wheeler Ma, Hurst RE, Demers LM et al. A comparison of multiple urine markers for interstitial cystitis. J Urol 2002: 167(6):2461-2469.

226. Erickson DR. Urinary markers of interstitial cystitis. In Sant GR, ed, Interstitial Cystitis. Philadelphia: Lippincott-Raven, 1997: 123-128.

227. Keay S, Zhang CO, Trifillis AL, Hise MK, Hebel JR, Jacobs SC et al. Decreased 3H-thymidine incorporation by human bladder epithelial cells following exposure to urine from interstitial cystitis patients. J Urol 1996: 156(6):2073-2078.

228. Keay SK, Szekely Z, Conrads TP, Veenstra TD, Barchi JJ, Jr., Zhang CO et al. An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. Proc Natl Acad Sci U S A 2004: 101(32):11803-11808.

229. Keay S, Warren JW, Zhang CO, Tu LM, Gordon DA, Whitmore KE. Antiproliferative activity is present in bladder but not renal pelvic urine from interstitial cystitis patients. J Urol 1999: 162(4):1487-1489.

230. Chai TC, Zhang C, Warren JW, Keay S. Percutaneous sacral third nerve root neurostimulation improves symptoms and normalizes urinary HB-EGF levels and antiproliferative activity in patients with interstitial cystitis. Urology 2000: 55(5):643-646.

231. Chai TC, Zhang CO, Shoenfelt JL, Johnson HW, Jr., Warren JW, Keay S. Bladder stretch alters urinary heparin-binding epidermal growth factor and antiproliferative factor in patients with interstitial cystitis. J Urol 2000: 163(5):1440-1444.

232. Erickson DR, Kunselman AR, Bentley CM, Peters KM, Rovner ES, Demers LM et al. Changes in urine markers and symptoms after bladder distention for interstitial cystitis. J Urol 2007: 177(2):556-560.

233. Keay S, Zhang CO, Hise MK, Hebel JR, Jacobs SC, Gordon D et al. A diagnostic in vitro urine assay for interstitial cystitis. Urology 1998: 52(6):974-978.

234. Keay S, Zhang CO, Marvel R, Chai T. Antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor: sensitive and specific urine markers for interstitial cystitis. Urology 2001: 57(6 Suppl 1):104.

235. Keay S, Zhang CO, Chai T, Warren J, Koch K, Grkovic D et al. Antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor in men with interstitial cystitis versus chronic pelvic pain syndrome. Urology 2004: 63(1):22-26.

236. Conrads TP, Tocci GM, Hood BL, Zhang CO, Guo L, Koch KR et al. CKAP4/p63 is a receptor for the frizzled-8 protein-related antiproliferative factor from interstitial cystitis patients. J Biol Chem 2006: 281(49):37836-37843.

237. Kim J, Keay SK, Dimitrakov JD, Freeman MR. p53 mediates interstitial cystitis antiproliferative factor (APF)-induced growth inhibition of human urothelial cells. FEBS Lett 2007: 581(20):3795-3799.

238. Moskowitz MO, Byrne DS, Callahan HJ, Parsons CL, Valderrama E, Moldwin RM. Decreased expression of a glycoprotein component of bladder surface mucin (GP1) in interstitial cystitis. J Urol 1994: 151(2):343-345.

239. Byrne DS, Sedor JF, Estojak J, Fitzpatrick KJ, Chiura AN, Mulholland SG. The urinary glycoprotein GP51 as a clinical marker for interstitial cystitis. J Urol 1999: 161(6):1786-1790.

240. Keay SK, Zhang CO, Shoenfelt J, Erickson DR, Whitmore K, Warren JW et al. Sensitivity and specificity of antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor as urine markers for interstitial cystitis. Urology 2001: 57(6 Suppl 1):9-14.

241. Keay S, Zhang CO, Kagen DI, Hise MK, Jacobs SC, Hebel JR et al. Concentrations of specific epithelial growth

factors in the urine of interstitial cystitis patients and controls. J Urol 1997: 158(5):1983-1988.

242. Fries J, Hochberg M, Medsger T, Hunder G. Criteria for rheumatic disease. Different types and different functions. Arthritis Rheum 1994: 37(4):454-462.

243. Van De Merwe J, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an essic proposal. European Urology 2008: 53:60-67.

244. Chaiken DC, Blaivas JG, Blaivas ST. Behavioral therapy for the treatment of refractory interstitial cystitis. J Urol 1993: 149(6):1445-1448.

245. Parsons CL, Koprowski PF. Interstitial cystitis: successful management by increasing urinary voiding intervals. Urology 1991: 37(3):207-212.

246. Foster HE, Jr., Hanno PM, Nickel JC, Payne CK, Mayer RD, Burks DA et al. Effect of amitriptyline on symptoms in treatment naive patients with interstitial cystitis/painful bladder syndrome. J Urol 2010: 183(5):1853-1858.

247. Peters KM, Carrico DJ, Kalinowski SE, Ibrahim IA, Diokno AC. Prevalence of pelvic floor dysfunction in patients with interstitial cystitis. Urology 2007: 70(1):16-18.

248. Markwell SJ. Physical therapy managment of pelvi/perineal and perianal syndromes. World J Urol 2001: 19:194-199.

249. Meadows E. Treatments for patients with pelvic pain. Urologic Nursing 1999: 19:33-35.

250. Mendelowitz F, Moldwin R. Complementary approaches in the management of interstitial cystitis. In Sant GR, ed, Interstitial Cystitis. Philadelphia: Lippincott-Raven, 1997: 235-240.

251. Lukban J, Whitmore K, Kellogg-Spadt S, Bologna R, Lesher A, Fletcher E. The effect of manual physical therapy in patients diagnosed with interstitial cystitis, high-tone pelvic floor dysfunction, and sacroiliac dysfunction. Urology 2001: 57(6 Suppl 1):121-122.

252. Lukban JC, Whitmore K. Pelvic floor muscle reeducation treatment of the overactive bladder and painful bladder syndrome. Clinical Obstetrics and Gynecology 2002: 45:273-285.

253. Holzberg A, Kellog-Spadt S, Lukban J, Whitmore K. Evaluation of transvaginal theile massage as a therapeutic intervention for women with interstitial cystitis. Urology 2001: 57(6 Suppl 1):120.

254. Weiss JM. Pelvic floor myofascial trigger points: manual therapy for interstitial cystitis and the urgency-frequency syndrome. J Urol 2001: 166(6):2226-2231.

255. FitzGerald MP, Anderson RU, Potts J, Payne CK, Peters KM, Clemens JQ et al. Randomized Multicenter Feasibility Trial of Myofascial Physical Therapy for the Treatment of Urological Chronic Pelvic Pain Syndromes. J Urol 2009.

256. Payne C, Fitzgerald M, Burks D, Nickel J, Lukacz ES, Kreder K et al. Randomized multicenter clinical trial shows efficacy of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome (IC/PBS). J Urol 183[4], e402. 2010.

257. Rothrock NE, Lutgendorf SK, Kreder KJ, Ratliff T, Zimmerman B. Stress and symptoms in patients with interstitial cystitis: a life stress model. Urology 2001: 57(3):422-427.

258. Clemens JQ, Brown SO, Calhoun EA. Mental health diagnoses in patients with interstitial cystitis/painful bladder syndrome and chronic prostatitis/chronic pelvic pain syndrome: a case/control study. J Urol 2008: 180(4):1378-1382.

259. Whitmore KE. Self-care regimens for patients with interstitial cystitis. Urol Clin North Am 1994: 21(1):121-130.

260. McCormick NB. Psychological aspects of interstitial cystitis. In Sant GR, ed, Interstitial Cystitis. Philadelphia: Lippincott-Raven, 1997: 193-204.

261. Ratner V, Slade D. The Interstitial Cystitis Association: patients working for a cure. Semin Urol 1991: 9(2):72.

262. Webster DC, Brennan T. Use and effectiveness of psychological self-care strategies for interstitial cystitis. Health Care Women Int 1995: 16(5):463-475.

263. Webster DC, Brennan T. Self-care effectiveness and health outcomes in women with interstitial cystitis: implications for mental health clinicians. Issues Ment Health Nurs 1998: 19(5):495-519.

264. Gillespie L. Metabolic appraisal of the effects of dietary modification on hypersensitive bladder symptoms. Br J Urol 1993: 72(3):293-297.

265. Li GZ, Zhang N, Du P, Yang Y, Wu SL, Xiao YX et al. Risk factors for interstitial cystitis/painful bladder syndrome in patients with lower urinary tract symptoms: a Chinese multi-center study. Chin Med J (Engl) 2010: 123(20):2842-2846.

266. Moldwin RM, Sant GR. Interstitial cystitis: a pathophysiology and treatment update. Clin Obstet Gynecol 2002: 45(1):259-272.

267. Nickel JC. Interstitial cystitis. Etiology, diagnosis, and treatment. Can Fam Physician 2000: 46(12):2430-2440.

268. Nguan C, Franciosi LG, Butterfield NN, Macleod BA, Jens M, Fenster HN. A prospective, double-blind, randomized cross-over study evaluating changes in urinary pH for relieving the symptoms of interstitial cystitis. BJU Int 2005: 95(1):91-94.

269. Shorter B, Lesser M, Moldwin RM, Kushner L. Effect of comestibles on symptoms of interstitial cystitis. J Urol 2007: 178(1):145-152.

270. Rovner E, Propert KJ, Brensinger C, Wein AJ, Foy M, Kirkemo A et al. Treatments used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Data Base Study Group. Urology 2000: 56(6):940-945.

271. Rummans TA. Nonopioid agents for treatment of acute and subacute pain. Mayo Clin Proc 1994: 69:481-490.

272. Backonja M, Beydoun A, Edwards KR, Schwartz SL, et.al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. JAMA 1998: 280:1831-1836.

273. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998: 280(21):1837-1842.

274. Gilron I, Bailey J, Tu D, Holden R, Weaver D, Houlden R. Morphine, gabapentin, or their combination for neuropathic pain. NEJM 2005: 352(13):1324-1334.

275. Hansen HC. Interstitial cystitis and the potential role of gabapentin. South Med J 2000: 93(2):238-242.

276. Sasaki K, Smith CP, Chuang YC, Lee JY, Kim JC, Chancellor MB. Oral gabapentin (neurontin) treatment of refractory genitourinary tract pain. Tech Urol 2001: 7(1):47-49.

277. Lee JW, Han DY, Jeong HJ. Bladder pain syndrome treated with triple therapy with gabapentin, amitriptyline, and a nonsteroidal anti-inflammatory drug. Int Neurourol J 2010: 14(4):256-260.

278. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005: 115(3):254-263.

279. Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP, Jr., Sharma U et al. A 14-week, Randomized, Double-Blinded, Placebo-Controlled Monotherapy Trial of Pregabalin in Patients With Fibromyalgia. J Pain 2008.

280. Portenoy RK, Dole V, Joseph H, Lowinson J, et.al. Pain management and chemical dependency. JAMA 1997: 278:592-593.

281. Gourlay GK. Long-term use of opiods in chronic pain patients with nonterminal disease states. Pain Rev 1994: 1:62-76.

282. Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med 2002: 17(3):173-179.

283. Portenoy RKaFKM. Chronic use of opioid analgesics in nonmalignant pain: Report of 38 cases. Pain 1986: 171.

284. Nickel JC. Opioids for chronic prostatitis and interstitial cystitis: lessons learned from the 11th World Congress on Pain. Urology 2006: 68(4):697-701.

285. Richelson E. Tricyclic antidepressants and histamine H1 receptors. Mayo Clin Proc 1979: 54(10):669-674.

286. Hanno PM. Amitriptyline in the treatment of interstitial cystitis. Urol Clin North Am 1994: 21(1):89-91.

287. Hanno PMaWAJ. Conservative therapy of interstitial cystitis. Semin Urol 1991: 9:143.

288. Kirkemo AK, Miles BJ, Peters JM. Use of amitriptyline in the treatment of interstitial cystitis. Journal of Urology 1990: 143:279A.

289. Pranikoff K, Constantino G. The use of amitriptyline in patients with urinary frequency and pain. Urology 1998: 51(5A Suppl):179-181.

290. van Ophoven A, Pokupic S, Heinecke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol 2004: 172(2):533-536.

291. van Ophoven A, Hertle L. Long term results of amitriptyline treatment for interstitial cystitis. J Urol 2005: 173(4):86.

292. Wammack R, Remzi M, Seitz C, Djavan B, Marberger M. Efficacy of oral doxepin and piroxicam treatment for interstitial cystitis. Eur Urol 2002: 41(6):596-600.

293. Renshaw DC. Desipramine for interstitial cystitis. JAMA 1988: 260(3):341.

294. van OA, Hertle L. The dual serotonin and noradrenaline reuptake inhibitor duloxetine for the treatment of interstitial cystitis: results of an observational study. J Urol 2007: 177(2):552-555.

295. Simmons JL, Bunce PL. On the use of an antihistamine in the treatment of interstitial cystitis. Am Surg 1958: 24(9):664-667.

296. Indent1440Lim0Lim1 Simmons JL. Interstitial cystitis: An explanation for the beneficial effect of an antihistamine. Journal of Urology 1961: 85:149.

297. Minogiannis P, El Mansoury M, Betances JA, Sant GR, Theoharides TC. Hydroxyzine inhibits neurogenic bladder mast cell activation. Int J Immunopharmacol 1998: 20(10):553-563.

298. Theoharides TC. Hydroxyzine for interstitial cystitis. J Allergy Clin Immunol 1993: 91(2):686-687.

299. Theoharides TC. Hydroxyzine in the treatment of interstitial cystitis. Urol Clin North Am 1994: 21(1):113-119.

300. Theoharides TC, Sant GR. Hydroxyzine therapy for interstitial cystitis. Urology 1997: 49(5A Suppl):108-110.

301. Sant GR, Propert KJ, Hanno PM, Burks D, Culkin D, Diokno AC et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol 2003: 170(3):810-815.

302. Seshadri P, Emerson L, Morales A. Cimetidine in the treatment of interstitial cystitis. Urology 1994: 44(4):614-616.

303. Lewi HJ. Cimetidine in the treatment of interstitial cystitis. British Journal of Urology 1996: 77(suppliment 1):28.

304. Lewi H. Medical therapy in interstitial cystitis: the essex experience. Urology 2001: 57(6 Suppl 1):120.

305. Thilagarajah R, Witherow RO, Walker MM. Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. BJU Int 2001: 87:207-212.

306. Forsell T, Ruutu M, Isoniemi H, Ahonen J, Alfthan O. Cyclosporine in severe interstitial cystitis. J Urol 1996: 155(5):1591-1593.

307. Sairanen J, Forsell T, Ruutu M. Long-term outcome of patients with interstitial cystitis treated with low dose cyclosporine A. J Urol 2004: 171(6 Pt 1):2138-2141.

308. Sairanen J, Tammela TL, Leppilahti M, Multanen M, Paananen I, Lehtoranta K et al. Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. J Urol 2005: 174(6):2235-2238.

309. Sairanen J, Hotakainen K, Tammela TL, Stenman UH, Ruutu M. Urinary epidermal growth factor and interleukin-6 levels in patients with painful bladder syndrome/interstitial cystitis treated with cyclosporine or pentosan polysulfate sodium. Urology 2008: 71(4):630-633.

310. Ueda T, Tamaki M, Ogawa O, Yamauchi T, Yoshimura N. Improvement of interstitial cystitis symptoms and problems that developed during treatment with oral IPD-1151T. J Urol 2000: 164(6):1917-1920.

311. Oravisto KJ, Alfthan OS. Treatment of interstitial cystitis with immunosuppression and chloroquine derivatives. Eur Urol 1976: 2(2):82-84.

312. Badenoch AW. Chronic interstitial cystitis. Br J Urol 1971: 43(6):718-721.

313. Pool TL. Interstitial cystitis: clinical considerations and treatment. Clin Obstet Gynecol 1967: 10(1):185-191.

314. Soucy F, Gregoire M. Efficacy of prednisone for severe refractory ulcerative interstitial cystitis. J Urol 2005: 173(3):841-843.

315. Parsons CL. Bladder surface glycosaminoglycan: efficient mechanism of environmental adaptation. Urology 1986: 27(2 Suppl):9-14.

316. Chiang G, Patra P, Letourneau R, Jeudy S, Boucher W, Green M et al. Pentosanpolysulfate inhibits mast cell histamine secretion and intracellular calcium ion levels: an alternative explanation of its beneficial effect in interstitial cystitis. J Urol 2000: 164(6):2119-2125.

317. Sadhukhan PC, Tchetgen MB, Rackley RR, Vasavada SP, Liou L, Bandyopadhyay SK. Sodium pentosan polysulfate reduces urothelial responses to inflammatory stimuli via an indirect mechanism. J Urol 2002: 168(1):289-292.

318. Parsons CL, Schmidt JD, Pollen JJ. Successful treatment of interstitial cystitis with sodium pentosanpolysulfate. J Urol 1983: 130(1):51-53.

319. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol 1987: 138(3):513-516.

320. Holm-Bentzen M, Jacobsen F, Nerstrom B, Lose G, Kristensen JK, Pedersen RH et al. A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease. J Urol 1987: 138(3):503-507.

321. Mulholland SG, Hanno P, Parsons CL, Sant GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. Urology 1990: 35(6):552-558.

322. Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR, Webster G. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. J Urol 1993: 150(3):845-848.

323. Al-Zahrani AA, Gajewski JB. Long-term efficacy and tolerability of pentosan polysulphate sodium in the treatment of bladder pain syndrome. Can Urol Assoc J 2011: 5(2):113-118.

324. Chuang YC, Lee WC, Lee WC, Chiang PH. Intravesical liposome versus oral pentosan polysulfate for interstitial cystitis/painful bladder syndrome. J Urol 2009: 182(4):1393-1400.

325. Nickel JC, Kaufman DM, Zhang HF, Wan GJ, Sand PK. Time to initiation of pentosan polysulfate sodium treatment after interstitial cystitis diagnosis: effect on symptom improvement. Urology 2008: 71(1):57-61.

326. Sand PK, Kaufman DM, Evans RJ, Zhang HF, Alan Fisher

DL, Nickel JC. Association between response to pentosan polysulfate sodium therapy for interstitial cystitis and patient questionnaire-based treatment satisfaction. Curr Med Res Opin 2008: 24(8):2259-2264.

327. Hanno PM. Analysis of long-term Elmiron therapy for interstitial cystitis. Urology 1997: 49(5A Suppl):93-99.

328. Foster HESSWM. Nitric oxide and interstitial cystitis. Advances in Urology 1997: 10:1.

329. Smith SD, Wheeler Ma, Foster HE, Jr., Weiss RM. Improvement in interstitial cystitis symptom scores during treatment with oral L-arginine. J Urol 1997: 158(3 Pt 1):703-708.

330. Ehren I, Lundberg JO, Adolfsson J, Wiklund NP. Effects of L-arginine treatment on symptoms and bladder nitric oxide levels in patients with interstitial cystitis. Urology 1998: 52(6):1026-1029.

331. Korting GE, Smith SD, Wheeler Ma, Weiss RM, Foster HE, Jr. A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. J Urol 1999: 161(2):558-565.

332. Cartledge JJ, Davies AM, Eardley I. A randomized double-blind placebo-controlled crossover trial of the efficacy of L-arginine in the treatment of interstitial cystitis. BJU Int 2000: 85(4):421-426.

333. Katske F, Shoskes DA, Sender M, Poliakin R, Gagliano K, Rajfer J. Treatment of interstitial cystitis with a quercetin supplement. Tech Urol 2001: 7(1):44-46.

334. Warren JW, Horne LM, Hebel JR, Marvel RP, Keay SK, Chai TC. Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. J Urol 2000: 163(6):1685-1688.

335. Burkhard FC, Blick N, Hochreiter WW, Studer UE. Urinary urgency and frequency, and chronic urethral and/or pelvic pain in females. Can doxycycline help? J Urol 2004: 172(1):232-235.

336. Maskell R. Broadening the concept of urinary tract infection. British Journal of Urology 1995: 76:2-8.

337. Moran PA, Dwyer PL, Carey MP, Maher CF, Radford NJ. Oral methotrexate in the management of refractory interstitial cystitis. Aust N Z J Obstet Gynaecol 1999: 39(4):468-471.

338. Bouchelouche K, Nordling J, Hald T, Bouchelouche P. Treatment of interstitial cystitis with montelukast, a leukotriene D(4) receptor antagonist. Urology 2001: 57(6 Suppl 1):118.

339. Fleischmann J. Calcium channel antagonists in the treatment of interstitial cystitis. Urol Clin North Am 1994: 21(1):107-111.

340. Kelly JD, Young MR, Johnston SR, Keane PF. Clinical response to an oral prostaglandin analogue in patients with interstitial cystitis. Eur Urol 1998: 34(1):53-56.

341. Evans RJ, Moldwin RM, Cossons N, Darekar A, Mills IW, Scholfield D. Proof of concept trial of tanezumab for the treatment of symptoms associated with interstitial cystitis. J Urol 2011: 185(5):1716-1721.

342. Fall M, Baranowski AP, Elneil S, Engeler D, Hughes J, Messelink EJ et al. EAU guidelines on chronic pelvic pain. Eur Urol 2010: 57(1):35-48.

343. Giannantoni A, Bini V, Dmochowski R, Hanno P, Nickel JC, Proietti S et al. Contemporary Management of the Painful Bladder: A Systematic Review. Eur Urol 2011.

344. DeJuana CP, Everett JC, Jr. Interstitial cystitis: experience and review of recent literature. Urology 1977: 10(4):325-329.

345. Ingelman-Sundberg A. Urge incontinence in women. Acta Obstet Gynecol Scand 1975: 54(2):153-156.

346. Kerr WS, Jr. Interstitial cystitis: treatment by transurethral resection. J Urol 1971: 105(5):664-666.

347. Pool TL, Rives HF. Interstitial cystitis: Treatment with silver nitrate. Journal of Urology 1944: 51:520-525.

348. MERTZ JH, Nourse MH, WISHARD WN, Jr. Use of clorpactin WCS 90 for relief of symptoms due to interstitial cystitis. Trans Am Assoc Genitourin Surg 1956: 48:86-89.

349. Messing EM, Freiha FS. Complication of Clorpactin WCS90 therapy for interstitial cystitis. Urology 1979: 13(4):389-392.

350. O'Connor VJ. Clorpactin WCS-90 in the treatment of interstitial cystitis. Q Bull Northwest Univ Med Sch 1955: 29(4):392-395.

351. SOKOL JK. Treatment of interstitial cystitis with clorpactin. Postgrad Semin Am Urol Assoc North Cent 1957: 36:104-106.

352. Wishard WN, Jr., Nourse MH, Mertz JH. Use of clorpactin WCS 90 for relief of symptoms due to interstitial cystitis. J Urol 1957: 77(3):420-423.

353. Peeker R, Haghsheno MA, Holmang S, Fall M. Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized double-blind study. J Urol 2000: 164(6):1912-1915.

354. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol 1988: 140(1):36-39.

355. Fowler JE, Jr. Prospective study of intravesical dimethyl sulfoxide in treatment of suspected early interstitial cystitis. Urology 1981: 18(1):21-26.

356. Ghoniem GM, McBride D, Sood OP, Lewis V. Clinical experience with multiagent intravesical therapy in interstitial cystitis patients unresponsive to single-agent therapy. World J Urol 1993: 11(3):178-182.

357. Nishimura M, Takano Y, Toshitani S. Systemic contact dermatitis medicamentosa occurring after intravesical dimethyl sulfoxide treatment for interstitial cystitis. Arch Dermatol 1988: 124(2):182-183.

358. Okamura K, Mizunaga M, Arima S, Tokunaka S, Inada F, Takamura T et al. [The use of dimethyl sulfoxide in the treatment of intractable urinary frequency]. Hinyokika Kiyo 1985: 31(4):627-631.

359. Ruiz JL, Alonso M, Moreno B, Server G, Osca JM, Jimenez JF. [Dimethyl sulfoxide in the treatment of interstitial cystitis]. Actas Urol Esp 1991: 15(4):357-360.

360. Shirley SW, Stewart BH, Mirelman S. Dimethyl sulfoxide in treatment of inflammatory genitourinary disorders. Urology 1978: 11(3):215-220.

361. Sotolongo JR, Jr., Swerdlow F, Schiff HI, Schapira HE. Successful treatment of lupus erythematosus cystitis with DMSO. Urology 1984: 23(2):125-127.

362. Rossberger J, Fall M, Peeker R. Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side-effects and treatment outcome. Scand J Urol Nephrol 2005: 39(1):73-77.

363. Sant GR. Intravesical 50% dimethyl sulfoxide (Rimso-50) in treatment of interstitial cystitis. Urology 1987: 29(4 Suppl):17-21.

364. Rubin L, Mattis P. Dimethyl sulfoxide: lens changes in dogs during oral administration. Science 1966: 153(731):83-84.

365. Wood D, Wirth N. Changes in rabbit lenses following DMSO therapy. Ophthalmologica 1969: 158S:488-493.

366. Melchior D, Packer CS, Johnson TC, Kaefer M. Dimethyl sulfoxide: does it change the functional properties of the bladder wall? J Urol 2003: 170(1):253-258.

367. Kuo HC. Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome and interstitial cystitis. J Formos Med Assoc 2001: 100(5):309-314.

368. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. Br J Urol 1994: 73(5):504-507.

369. Perez-Marrero R, Emerson LE, Maharajh DO, et.al. Prolongation of response to DMSO by heparin maintenance. Urology 1993: 41 (suppl):64-66.

370. Parsons CL. Successful downregulation of bladder

sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. Urology 2005: 65(1):45-48.

371. Iavazzo C, Athanasiou S, Pitsouni E, Falagas ME. Hyaluronic Acid: An Effective Alternative Treatment of Interstitial Cystitis, Recurrent Urinary Tract Infections, and Hemorrhagic Cystitis? Eur Urol 2007.

372. Kallestrup EB, Jorgensen SS, Nordling J, Hald T. Treatment of interstitial cystitis with Cystistat: a hyaluronic acid product. Scand J Urol Nephrol 2005: 39(2):143-147.

373. Leppilahti M, Hellstrom P, Tammela TL. Effect of diagnostic hydrodistension and four intravesical hyaluronic acid instillations on bladder ICAM-1 intensity and association of ICAM-1 intensity with clinical response in patients with interstitial cystitis. Urology 2002: 60(1):46-51.

374. Morales A, Emerson L, Nickel JCea. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol 1996: 156:45-48.

375. Morales A, Emerson L, Nickel JC. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. Urology 1997: 49(5A Suppl):111-113.

376. Porru D, Campus G, Tudino D, Valdes E, Vespa A, Scarpa RM et al. Results of treatment of refractory interstitial cystitis with intravesical hyaluronic acid. Urol Int 1997: 59(1):26-29.

377. Engelhardt PF, Morakis N, Daha LK, Esterbauer B, Riedl CR. Long-term results of intravesical hyaluronan therapy in bladder pain syndrome/interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 2010.

378. Shao Y, Shen ZJ, Rui WB, Zhou WL. Intravesical Instillation of Hyaluronic Acid Prolonged the Effect of Bladder Hydrodistention in Patients With Severe Interstitial Cystitis. Urology 2009.

379. Steinhoff G, Ittah B, Rowan S. The efficacy of chondroitin sulfate 0.2% in treating interstitial cystitis. Can J Urol 2002: 9(1):1454-1458.

380. Sorensen R. Chondroitin sulphate in the treatment of interstitial cystitis and chronic inflammatory disease of the urinary bladder. Eur Urol 2003: suppliment 2:14-16.

381. Nordling J, van OA. Intravesical glycosaminoglycan replenishment with chondroitin sulphate in chronic forms of cystitis. A multi-national, multi-centre, prospective observational clinical trial. Arzneimittelforschung 2008: 58(7):328-335.

382. Nickel JC, Egerdie RB, Steinhoff G, Palmer B, Hanno P. A multicenter, randomized, double-blind, parallel group pilot evaluation of the efficacy and safety of intravesical sodium chondroitin sulfate versus vehicle control in patients with interstitial cystitis/painful bladder syndrome. Urology 2010: 76(4):804-809.

383. Nickel J, Hanno P, Kumar K, Thomas H. A Second Multi-Center, Randomized, Double- Blind, Parallel Group Evaluation of the Effectiveness and Safety of Intravesical Sodium Chondroitin Sulfate Compared to Inactive Vehicle Control in Subjects with Interstitial Cystitis/ Bladder Pain Syndrome. Urology 2012.

384. Bade JJ, Laseur M, Nieuwenburg A, van der Weele LT, Mensink HJ. A placebo-controlled study of intravesical pentosanpolysulphate for the treatment of interstitial cystitis. Br J Urol 1997: 79(2):168-171.

385. Davis EL, El K, Sr., Talbott EO, Davis J, Regan LJ. Safety and efficacy of the use of intravesical and oral pentosan polysulfate sodium for interstitial cystitis: a randomized double-blind clinical trial. J Urol 2008: 179(1):177-185.

386. Apostolidis A, Gonzales GE, Fowler CJ. Effect of intravesical Resiniferatoxin (RTX) on lower urinary tract symptoms, urodynamic parameters, and quality of life of patients with urodynamic increased bladder sensation. Eur Urol 2006: 50(6):1299-1305.

387. Chen TY, Corcos J, Camel M, Ponsot Y, Tu IM. Prospective, randomized, double-blind study of safety and tolerability of intravesical resiniferatoxin (RTX) in interstitial cystitis (IC). Int Urogynecol J Pelvic Floor Dysfunct 2005: 16(4):293-297.

388. Lazzeri M, Spinelli M, Beneforti P, Malaguti S, Giardiello G, Turini D. Intravesical infusion of resiniferatoxin by a temporary in situ drug delivery system to treat interstitial cystitis: a pilot study. Eur Urol 2004: 45(1):98-102.

389. Peng CH, Kuo HC. Multiple intravesical instillations of low-dose resiniferatoxin in the treatment of refractory interstitial cystitis. Urol Int 2007: 78(1):78-81.

390. Fagerli J, Fraser MO, deGroat WC, Chancellor MB, Flood HD, Smith D et al. Intravesical capsaicin for the treatment of interstitial cystitis: a pilot study. Can J Urol 1999: 6(2):737-744.

391. Payne CK, Mosbaugh PG, Forrest JB, Evans RJ, Whitmore KE, Antoci JP et al. Intravesical resiniferatoxin for the treatment of interstitial cystitis: a randomized, double-blind, placebo controlled trial. J Urol 2005: 173(5):1590-1594.

392. Zeidman EJ, Helfrick B, Pollard C, Thompson IM. Bacillus Calmette-Guerin immunotherapy for refractory interstitial cystitis. Urology 1994: 43(1):121-124.

393. Peters K, Diokno A, Steinert B, Yuhico M, Mitchell B, Krohta S et al. The efficacy of intravesical Tice strain bacillus Calmette-Guerin in the treatment of interstitial cystitis: a double-blind, prospective, placebo controlled trial. J Urol 1997: 157(6):2090-2094.

394. Peters KM, Diokno AC, Steinert BW, Gonzalez JA. The efficacy of intravesical bacillus Calmette-Guerin in the treatment of interstitial cystitis: long-term followup. J Urol 1998: 159(5):1483-1486.

395. Mayer R, Propert KJ, Peters KM, Payne CK, Zhang Y, Burks D et al. A randomized controlled trial of intravesical bacillus calmette-guerin for treatment refractory interstitial cystitis. J Urol 2005: 173(4):1186-1191.

396. Barbalias GA, Liatsikos EN, Athanasopoulos A, Nikiforidis G. Interstitial cystitis: bladder training with intravesical oxybutynin. J Urol 2000: 163(6):1818-1822.

397. Gurpinar T, Wong HY, Griffith DP. Electromotive administration of intravesical lidocaine in patients with interstitial cystitis. J Endourol 1996: 10(5):443-447.

398. Riedl CR, Knoll M, Plas E, Pfluger H. Electromotive drug administration and hydrodistention for the treatment of interstitial cystitis. J Endourol 1998: 12(3):269-272.

399. Riedl CR, Knoll M, Plas E, Stephen RL, Pfluger H. Intravesical electromotive drug administration for the treatment of non-infectious chronic cystitis. Int Urogynecol J Pelvic Floor Dysfunct 1997: 8(3):134-137.

400. Rosamilia A, Dwyer PL, Gibson J. Electromotive drug administration of lidocaine and dexamethasone followed by cystodistension in women with interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 1997: 8(3):142-145.

401. Asklin B, Cassuto J. Intravesical lidocaine in severe interstitial cystitis. Case report. Scand J Urol Nephrol 1989: 23(4):311-312.

402. Giannakopoulos X, Champilomatos P. Chronic interstitial cystitis. Successful treatment with intravesical idocaine. Arch Ital Urol Nefrol Androl 1992: 64(4):337-339.

403. Henry R, Patterson L, Avery N, Tanzola R, Tod D, Hunter D et al. Absorption of alkalized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. J Urol 2001: 165(6 Pt 1):1900-1903.

404. Nickel JC, Moldwin R, Lee S, Davis EL, Henry RA, Wyllie MG. Intravesical alkalinized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. BJU Int 2009: 103(7):910-918.

405. Welk BK, Teichman JM. Dyspareunia response in patients with interstitial cystitis treated with intravesical lidocaine, bicarbonate, and heparin. Urology 2008: 71(1):67-70.

406. Chancellor MB, Fowler CJ, Apostolidis A, de Groat WC, Smith CP, Somogyi GT et al. Drug Insight: biological effects of botulinum toxin A in the lower urinary tract. Nat Clin Pract Urol 2008: 5(6):319-328.

407. Smith CP, Radziszewski P, Borkowski A, Somogyi GT, Boone TB, Chancellor MB. Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. Urology 2004: 64(5):871-875.

408. Giannantoni A, Cagini R, Del ZM, Proietti S, Quartesan R, Porena M et al. Botulinum A toxin intravesical injections for painful bladder syndrome: impact upon pain, psychological functioning and Quality of Life. Curr Drug Deliv 2010: 7(5):442-446.

409. Kuo HC. Preliminary results of suburothelial injection of botulinum a toxin in the treatment of chronic interstitial cystitis. Urol Int 2005: 75(2):170-174.

410. Kuo HC, Chancellor MB. Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int 2009: 104(5):657-661.

411. Pinto R, Lopes T, Frias B, Silva A, Silva JA, Silva CM et al. Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/interstitial cystitis. Eur Urol 2010: 58(3):360-365.

412. Tanagho EA, Schmidt RA, Orvis BR. Neural stimulation for control of voiding dysfunction: a preliminary report in 22 patients with serious neuropathic voiding disorders. J Urol 1989: 142(2 Pt 1):340-345.

413. Zermann DH, Weirich T, Wunderlich H, Reichelt O, Schubert J. Sacral nerve stimulation for pain relief in interstitial cystitis. Urol Int 2000: 65(2):120-121.

414. Maher CF, Carey MP, Dwyer PL, Schluter PL. Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. J Urol 2001: 165(3):884-886.

415. Comiter CV. Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: a prospective study. J Urol 2003: 169(4):1369-1373.

416. Whitmore KE, Payne CK, Diokno AC, Lukban JC. Sacral neuromodulation in patients with interstitial cystitis: a multicenter clinical trial. Int Urogynecol J Pelvic Floor Dysfunct 2003: 14(5):305-308.

417. Peters KM, Konstandt D. Sacral neuromodulation decreases narcotic requirements in refractory interstitial cystitis. BJU Int 2004: 93(6):777-779.

418. Elhilali MM, Khaled SM, Kashiwabara T, Elzayat E, Corcos J. Sacral neuromodulation: long-term experience of one center. Urology 2005: 65(6):1114-1117.

419. Zabihi N, Mourtzinos A, Maher MG, Raz S, Rodriguez LV. Short-term results of bilateral S2-S4 sacral neuromodulation for the treatment of refractory interstitial cystitis, painful baldder syndrome, and chronic pelvic pain. Int Urogynecol J Pelvic Floor Dysfunct 2008: 19(4):553-557.

420. Peters KM, Feber KM, Bennett RC. A prospective, single-blind, randomized crossover trial of sacral vs pudendal nerve stimulation for interstitial cystitis. BJU Int 2007: 100(4):835-839.

421. Gajewski JB, Al-Zahrani AA. The long-term efficacy of sacral neuromodulation in the management of intractable cases of bladder pain syndrome: 14 years of experience in one centre. BJU Int 2011: 107(8):1258-1264.

422. Marinkovic SP, Gillen LM, Marinkovic CM. Minimum 6-year outcomes for interstitial cystitis treated with sacral neuromodulation. Int Urogynecol J 2011: 22(4):407-412.

423. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008: 9(2):105-121.

424. Melzack R. The short-form McGill pain questionnaire. Pain 1987: 30:191-197.

425. Melzack R. The McGill pain questionnaire: Major properties and scoring methods. Pain 1975: 1:277-299.

426. Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain — Part B: Recommendations for Practice. 4-30-2010.

427. Milsom I, Andersch B. Effect of ibuprofen, naproxen sodium and paracetamol on intrauterine pressure and menstrual pain in dysmenorrhoea. Br J Obstet Gynaecol 1984: 91(11):1129-1135.

428. Zhang W, Li P. Efficacy of minor analgesics in primary dysmenorrhoea: a systemic review. Br J Obstet Gynaecol 1998: 105(7):780-789.

429. Amar PJ, Schiff ER. Acetaminophen safety and hepatotoxicity--where do we go from here? Expert Opin Drug Saf 2007: 6(4):341-355.

430. Krenzelok EP. The FDA Acetaminophen Advisory Committee Meeting - what is the future of acetaminophen in the United States? The perspective of a committee member. Clin Toxicol (Phila) 2009: 47(8):784-789.

431. Schmidt LE, Dalhoff K, Poulsen HE. Acute versus chronic alcohol consumption in acetaminophen-induced hepatotoxicity. Hepatology 2002: 35(4):876-882.

432. Gilroy D, Tomlinson A, Willoughby D. Differential effects of inhibitors of cyclooxygenase (cyclooxygenase 1 and cyclooxygenase 2) in acute inflammation. Eur J Clin Pharmacol 1998: 355(2-3):211-217.

433. Gilroy D, Colville-Nash P, Willis D, Chivers J, Paul-Clark M, Willoughby D. Inducible cyclooxygenase may have anti-inflammatory properties. Nat Med 1999: 5(6):698-701.

434. Jones S, Power I. Postoperative NSAIDs and Cox-2 inhibitors: cardiovascular risks and benefits. Br J Anaesth 2005: 95(3):281-284.

435. Furniss L. Nonsteroidal anti-inflammatory agents in the treatment of primary dysmenorrhea. Clin Pharmacol Ther 1982: 1(4):327-333.

436. Fall M, Baranowski A, Fowler CJ, Lepinard JG, Malone-Lee JG, Messelink EJ et al. EAU guidelines on chronic pelvic pain. Eur Urol 2004: 46:681-689.

437. Christie M, Vaughan C, Ingram S. NSAIDs and 5-lipoxygenase inhibitors act synergistically in brain via arachidonic acid metabolism. Inflamm res 1999: 48(1):1-4.

438. McQuay H. A systematic review of antidepressants in neuropathic pain. Pain 1996: 68(2-3):217-227.

439. van Ophoven A, Hertle L. Long-term results of amitriptyline treatment for interstitial cystitis. J Urol 2005: 174(5):1837-1840.

440. Engel C, Walker E, Engel A, Bullis J, Armstrong A. A randomized, double-blind crossover trial of sertraline in women with chronic pelvic pain. J Psychosom Res 1998: 44(2):203-207.

441. Dworkin RH, OConnor A, Backonja M, Farrar JT, Finnerup N, Jensen T. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007: 132(3):237-251.

442. Wiffen P, McQuay H, Edwards J, Moore R. Gabapentin for acute and chronic pain. Cochrane Database Syst Rev 2005: 3(CD005452).

443. Nickel J, Crossland A, Davis E, Haab F, Mills I, Rovner E et al. Investigation of a Ca2+ Channel á2ä Ligand for the Treatment of Interstitial Cystitis: Results of a Randomized, Double-blind, Placebo-Controlled Phase II Trial. J.Urol . 2012.

444. Pontari M, Krieger JN, Litwin MS, White P, Anderson RU, McNaughton-Collins M et al. Pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome: a randomized controlled trial. Archives of Internal Medicine 2010: 170:1586-1593.

445. Sasaki K, Smith C, Chuang Y, Lee J, Kim J, Chancellor M. Oral gabapentin (neurontin) treatment of refractory genitorurinary tract pain. Tech Urol 2001: 7(1):47-49.

446. Mikkelsen S, Ilkjaer S, Brennum J, Borgbjerg F, Dahl J. The effect of naloxone on ketamine-induced effects on hyperalgesia and ketamine-induced side effects in humans. Anaesthesiology 1999: 90(6):1539-1545.

447. Guirimand F, Dupont X, Brasseur L, Chauvin M, Bouhassira D. The effects of ketamine on the temporal summation

(wind-up) of the R(III) nociceptive flexion reflex and pain in humans. Anesth Analg 2000: 90(2):408-414.

448. Laurido C, Pelissier T, Perez H, Flores F, Hernandez A. Effect of ketamine on spinal cord nociceptive transmission in normal and monoarthritic rats. Neuroreport 2001: 12(8):1551-1554.

449. Backonja M, Arndt G, Gombar K, Check B, Zimmermann M. Response of chronic neuropathic pain syndromes to ketamine: a preliminary study. Pain 1994: 56(1):51-57.

450. Eide P, Jorum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain 1994: 58(3):347-354.

451. Graven-Nielsen T, Aspegren K, Henriksson K, Bengtsson M, Sorensen J, Johnson A. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain 2000: 85(3):483-491.

452. Eide P, Stubhaug A, Stenehjem A. Central dysesthesia pain after traumatic spinal cord injury is dependent on N-methyl-D-aspartate receptor activation. Neurosurgery 1995: 37(6):1080-1087.

453. Sorensen J, Bengtsson A, Backman E, Henriksson K, Bengtsson M. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. Scand J Rheumatol 1995: 24(6):360-365.

454. Middela S, Pearce I. Ketamine-induced vesicopathy: a literature review. Int J Clin Pract 2011: 65(1):27-30.

455. McQuay H. Opioids in pain management. Lancet 1999: 353(9171):2229-2232.

456. Zacny J, Lichtor J, Zaragoza J, de Wit H. Subjective and behavioral responses to intravenous fentanyl in healthy volunteers. Psychopharmacology (Berl) 1992: 107(2-3):319-326.

457. Schneider U, Bevalaqua C, Jacobs R, Karst M, Dietrich D, Becker H. Effects of fentanyl and low doses of alcohol on neuropsychological performance in healthy subjects. Neuropsychobiology 2012: 39(1):38-43.

458. Hewitt D. The use of NMDA-receptor antagonists in the treatment of chronic pain. Clin J Pain 2000: 16(2 suppl):S73-79.

459. Seifert C, Kennedy S. Meperidine is alive and well in the new millennium: evaluation of meperidine usage patterns and frequency of adverse drug reactions. Pharmacotherapy 2004: 24(6):776-783.

460. Cicero T, Dart R, Inciardi J, Woody G, Schnoll S, Munoz A. The development of a comprehensive risk-management program for prescription opioid analgesics: Researched abuse, diversion and addiction-related surveillance (RADARS). Pain Med 2007: 8:157-170.

461. Desmeules J, Piguet V, Collart L, Dayer P. Contribution of monoaminergic modulation to the analgesic effect of tramadol. Br J Clin Pharmacol 1996: 41(1):7-12.

462. Sagata K, Minami K, Yanagihara N, Shiraishi M, Toyohira Y, Ueno S. Tramadol inhibits norepinephrine transporter function at desipramine-binding sites in cultured bovine adrenal medullary cells. Anesth Analg 2002: 94(4):901-906.

463. Radbruch L, Grond S, Lehmann K. A risk-benefit assessment of tramadol in the management of pain. Drug Safety 1996: 15(1):8-29.

464. Preston K, Jasinski D, Testa M. Abuse potential and pharmacological comparison of tramadol and morphine. Drug Alcohol Dependence 1991: 27(1):7-17.

465. Bumpus HC. Interstitial cystitis: its treatment by overdistention of the bladder. Med Cl N A 1930: 13:1495-1498.

466. FRANKSSON C. Interstitial cystitis: a clinical study of fifty-nine cases. Acta Chir Scand 1957: 113(1):51-62.

467. Helmstein K. Treatment of bladder carcinoma by a hydrostatic pressure technique. Report on 43 cases. British Journal of Urology 1972: 44(4):434-450.

468. Dunn M, Ramsden PD, Roberts JB, Smith JC, Smith PJ. Interstitial cystitis, treated by prolonged bladder distension. Br J Urol 1977: 49(7):641-645.

469. McCahy PJ, Styles RA. Prolonged bladder distension: experience in the treatment of detrusor overactivity and interstitial cystitis. Eur Urol 1995: 28(4):325-327.

470. Greenberg E, Barnes R, Stewart S, Furnish T. Transurethral resection of Hunner's ulcer. J Urol 1974: 111(6):764-766.

471. Fall M. Conservative management of chronic interstitial cystitis: transcutaneous electrical nerve stimulation and transurethral resection. J Urol 1985: 133(5):774-778.

472. Peeker R, Aldenborg F, Fall M. Complete transurethral resection of ulcers in classic interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 2000: 11(5):290-295.

473. Shanberg AM, Malloy T. Treatment of interstitial cystitis with neodymium:YAG laser. Urology 1987: 29(4 Suppl):31-33.

474. Malloy TR, Shanberg AM. Laser therapy for interstitial cystitis. Urol Clin North Am 1994: 21(1):141-144.

475. Rofeim O, Hom D, Freid RM, Moldwin RM. Use of the neodymium: YAG laser for interstitial cystitis: a prospective study. J Urol 2001: 166(1):134-136.

476. Payne RA, O'Connor RC, Kressin M, Guralnick ML. Endoscopic ablation of Hunner's lesions in interstitial cystitis patients. Can Urol Assoc J 2009: 3(6):473-477.

477. Cox M, Klutke JJ, Klutke CG. Assessment of patient outcomes following submucosal injection of triamcinolone for treatment of Hunner's ulcer subtype interstitial cystitis. Can J Urol 2009: 16(2):4536-4540.

478. Worth PH, Turner-Warwick R. The treatment of interstitial cystitis by cystolysis with observations on cystoplasty. Br J Urol 1973: 45(1):65-71.

479. Worth PH. The treatment of interstitial cystitis by cystolysis with observations on cystoplasty. A review after 7 years. Br J Urol 1980: 52(3):232.

480. Albers DD, Geyer JR. Long-term results of cystolysis (supratrigonal denervation) of the bladder for intractable interstitial cystitis. J Urol 1988: 139(6):1205-1206.

481. Pieri G. Enervation ou ramisection? Lookup 1926: 34:1141-1142.

482. Douglass H. Excision of the superior hypogastric plexus in the treatment of intractable interstitial cystitis. Am J Surg 1934: 25:249-257.

483. Nesbit RM. Anterolateral chordotomy for refractory interstitial cystitis with intractable pain. J Urology 1947: 57:741-745.

484. Moulder MK, Meirowsky AM. The management of Hunner's ulcer by differential sacral neurotomy: preliminary report. J Urology 1956: 75:261-262.

485. MILNER WA, GARLICK WB. Selective sacral neurectomy in interstitial cystitis. J Urol 1957: 78(5):600-604.

486. Mason TH, Haines GL, Laversee BW. Selective sacral neurotomy for Hunner's ulcer. J Neurosurg 1960: 17:22-6.

487. BOHM E, FRANKSSON C. Interstitial cystitis and sacral rhizotomy. Acta Chir Scand 1957: 113(1):63-67.

488. Goodwin WE, Turner RD, Winter CC. Results of ileocystoplasty. J Urol 1958: 80:461-6.

489. von Garrelts B. Interstitial cystitis: thirteen patients treated operatively with intestinal bladder substitutes. Acta Chir Scand 1966: 132(4):436-443.

490. Webster GD, Maggio MI. The management of chronic interstitial cystitis by substitution cystoplasty. J Urol 1989: 141(2):287-291.

491. Nielsen KK, Kromann-Andersen B, Steven K, Hald T. Failure of combined supratrigonal cystectomy and Mainz ileocecocystoplasty in intractable interstitial cystitis: is

histology and mast cell count a reliable predictor for the outcome of surgery? J Urol 1990: 144(2 Pt 1):255-258.

492. Turner-Warwick R, Ashken HM. The functional results of partial, subtotal, and total cystoplasty with special reference to ureterocystoplasty, selective sphincterotomy, and cystocystoplasty. Br J Urol 1967: 39:3-12.

493. Kontturi MJ, Hellstrom PA, Tammela TL, Lukkarinen OA. Colocystoplasty for the treatment of severe interstitial cystitis. Urol Int 1991: 46(1):50-54.

494. Hanley H. Ileocystoplasty. A clinical review. J Urol 1959: 82:317.

495. Bruce PT, Buckham GJ, Carden AB, Salvaris M. The surgical treatment of chronic interstitial cystitis. Med J Aust 1977: 1(16):581-582.

496. Hinman FJ. Selection of intestinal segments for bladder substitution: physical and physiological characteristics. J Urol 1988: 139:519-523.

497. Awad SA, Al Zahrani HM, Gajewski JB, Bourque-Kehoe AA. Long-term results and complications of augmentation ileocystoplasty for idiopathic urge incontinence in women. Br J Urol 1998: 81(4):569-573.

498. Christmas TJ, Holmes SA, Hendry WF. Bladder replacement by ileocystoplasty: the final treatment for interstitial cystitis. Br J Urol 1996: 78(1):69-73.

499. Guillonneau B, Toussaint B, Bouchot O, Buzelin JM. [Treatment of interstitial cystitis with sub-trigonal cystectomy and enterocystoplasty]. Prog Urol 1993: 3(1):27-31.

500. Koskela E, Kontturi M. Function of the intestinal substituted bladder. Scand J Urol Nephrol 1982: 16:129-33.

501. Shirley SW, Mirelman S. Experiences with colocystoplasties, cecocystoplasties and ileocystoplasties in urologic surgery: 40 patients. J Urol 1978: 120(2):165-168.

502. Hradec H. Bladder substitution: Indications and results in 114 operations. J Urol 1965: 94:406-417.

503. Whitmore WF, Gittes RF. Reconstruction of the urinary tract by cecal and ileocecal cystoplasty: review of a 15-year experience. J Urol 1983: 129:494-498.

504. Holm-Bentzen M, Klarskov P, Opsomer R, Hald T. Cecocystoplasty: an evaluation of operative results. Urol Int 1986: 41:21-5.

505. Seddon JM, Best L, Bruce AW. Intestinocystoplasty in treatment of interstitial cystitis. Urology 1977: 10(5):431-435.

506. Singla A, Galloway N. Early experience with the use of gastric segment in lower urinary tract reconstruction in adult patient population. Urology 1997: 50:630-5.

507. Leong CH. Use of stomach for bladder replacement and urinary diversion. Ann R Coll Surg Engl 1978:(60):282-289.

508. Dounis A, Gow JG. Bladder augmentation--a long-term review. Br J Urol 1979: 51(4):264-268.

509. Linn JF, Hohenfellner M, Roth S, Dahms SE, Stein R, Hertle L et al. Treatment of interstitial cystitis: comparison of subtrigonal and supratrigonal cystectomy combined with orthotopic bladder substitution. J Urol 1998: 159(3):774-778.

510. van Ophoven A, Oberpenning F, Hertle L. Long-term results of trigone-preserving orthotopic substitution enterocystoplasty for interstitial cystitis. J Urol 2002: 167(2 Pt 1):603-607.

511. Lotenfoe RR, Christie J, Parsons A, Burkett P, Helal M, Lockhart JL. Absence of neuropathic pelvic pain and favorable psychological profile in the surgical selection of patients with disabling interstitial cystitis. J Urol 1995: 154(6):2039-2042.

512. Peeker R, Aldenborg F, Fall M. The treatment of interstitial cystitis with supratrigonal cystectomy and ileocystoplasty: difference in outcome between classic and nonulcer disease. J Urol 1998: 159(5):1479-1482.

513. Counseller VS. Bilateral transplantation of the ureters of the female. Am J Obstet Gynecol 1937: 33:234-248.

514. Hohenfellner M, Black P, Linn JF, Dahms SE, Thuroff JW. Surgical treatment of interstitial cystitis in women. Int Urogynecol J Pelvic Floor Dysfunct 2000: 11(2):113-119.

515. Bejany DE, Politano VA. Ileocolic neobladder in the woman with interstitial cystitis and a small contracted bladder. J Urol 1995: 153(1):42-43.

516. Nurse DE, McCrae P, Stephenson TP, Mundy AR. The problems of substitution cystoplasty. Br J Urol 1988: 61(5):423-426.

517. Hughes OD, Kynaston HG, Jenkins BJ, Stephenson TP, Vaughton KC. Substitution cystoplasty for intractable interstitial cystitis. Br J Urol 1995: 76(2):172-174.

518. Nurse DE, Parry JR, Mundy AR. Problems in the surgical treatment of interstitial cystitis. Br J Urol 1991: 68(2):153-154.

519. Gershbaum D, Moldwin R. Practice trends for the management of interstitial cystitis. Urology 2001: 57(6 Suppl 1):119.

520. Freiha FS, Faysal MH, Stamey TA. The surgical treatment of intractable interstitial cystitis. J Urol 1980: 123(5):632-634.

521. Tait L. On the cure of the chronic perforating ulcer of the bladder by the formation of an artificial vesico-vaginal fistula. Lancet 1870: 54:738.

522. Ahmed E, Bissada NK, Herchorn S, Aboul-Enein H, Ghoneim M, Bissada MA et al. Urinary conduit formation using a retubularized bowel from continent urinary diversion or intestinal augmentations: ii. does it have a role in patients with interstitial cystitis? J Urol 2004: 171:1559-62.

523. Kisman OK, Nijeholt AA, van Krieken JH. Mast cell infiltration in intestine used for bladder augmentation in interstitial cystitis. J Urol 1991: 146(4):1113-1114.

524. McGuire EJ, Lytton B, Cornog JL, Jr. Interstitial cystitis following colocystoplasty. Urology 1973: 2(1):28-29.

525. MacDermott JP, Charpied GL, Tesluk H, Stone AR. Recurrent interstitial cystitis following cystoplasty: fact or fiction? J Urol 1990: 144(1):37-40.

526. Webster GD, Galloway N. Surgical treatment of interstitial cystitis. Indications, techniques, and results. Urology 1987: 29(4 Suppl):34-39.

527. Goin JE, Olaleye D, Peters KM, Steinert B, Habicht K, Wynant G. Psychometric analysis of the University of Wisconsin Interstitial Cystitis Scale: implications for use in randomized clinical trials. J Urol 1998: 159(3):1085-1090.

528. Keller ML, McCarthy DO, Neider RS. Measurement of symptoms of interstitial cystitis. A pilot study. Urol Clin North Am 1994: 21(1):67-71.

529. Lubeck DP, Whitmore K, Sant GR, Alvarez-Horine S, Lai C. Psychometric validation of the O'leary-Sant interstitial cystitis symptom index in a clinical trial of pentosan polysulfate sodium. Urology 2001: 57(6 Suppl 1):62-66.

530. O'leary MP, Sant GR, Fowler FJ, Jr., Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. Urology 1997: 49(5A Suppl):58-63.

531. O'leary MP, Sant G. The interstitial cystitis symptom and problem indices: rationale, development, and application. In Sant G, ed, Interstitial Cystitis. Chapt 34. Philadelphia: Lippincott-Raven, 1997: 271-276.

532. Humphrey L, Arbuckle R, Moldwin R, Nordling J, van de Merwe JP, Meunier J et al. The Bladder Pain/Interstitial Cystitis Symptom Score: Development, Validation, and Identification of a Cut Score. Eur Urol 2012: 61(12):280-281.

533. Ito T, Tomoe H, Ueda T, Yoshimura N, Sant G, Hanno P. Clinical symptoms scale for interstitial cystitis for diagnosis and for following the course of the disease. Int J Urol 2003: 10 Suppl:S24-S26.

534. Kushner L, Moldwin RM. Efficiency of questionnaires used to screen for interstitial cystitis. J Urol 2006: 176(2):587-592.

535. Sirinian E, Azevedo K, Payne CK. Correlation between 2

interstitial cystitis symptom instruments. J Urol 2005: 173(3):835-840.

536. Clemons JL, Arya LA, Myers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. Obstet Gynecol 2002: 100(2):337-341.

537. Clemens JQ, Markossian TW, Meenan RT, O'Keeffe Rosetti MC, Calhoun EA. Overlap of voiding symptoms, storage symptoms and pain in men and women. J Urol 2007: 178(4 Pt 1):1354-1358.

538. Porru D, Tinelli C, Gerardini M, Giliberto GL, Stancati S, Rovereto B. Evaluation of urinary and general symptoms and correlation with other clinical parameters in interstitial cystitis patients. Neurourol Urodyn 2005: 24(1):69-73.

539. Diggs C, Meyer WA, Langenberg P, Greenberg P, Horne L, Warren JW. Assessing urgency in interstitial cystitis/painful bladder syndrome. Urology 2007: 69(2):210-214.

540. Propert KJ, Mayer RD, Wang Y, Sant GR, Hanno PM, Peters KM et al. Responsiveness of symptom scales for interstitial cystitis. Urology 2006: 67(1):55-59.

541. Bogart LM, Suttorp MJ, Elliott MN, Clemens JQ, Berry SH. Validation of a quality-of-life scale for women with bladder pain syndrome/interstitial cystitis. Qual Life Res 2011.

542. Sech SM, Montoya JD, Bernier PA, Barnboym E, et.al. The so-called "placebo effect" in benign prostatic hyperplasia treatment trials represents partially a conditional regression to the mean induced by censoring. Urology 1998: 51:242-250.

543. Gillespie L, Bray R, Levin N, Delamarter R. Lumbar nerve root compression and interstitial cystitis--response to decompressive surgery. Br J Urol 1991: 68(4):361-364.

544. Gillespie L. Destruction of the vesicoureteric plexus for the treatment of hypersensitive bladder disorders. Br J Urol 1994: 74(1):40-43.

545. Turner JA, Deyo RA, Loeser JD, et.al. The importance of placebo effects in pain treatment and research. JAMA 1994: 271:1609-1614.

546. Schulz KF, Chalmers I, Hayes RJ, et.al. Empirical evidence of bias; dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995: 273:408-412.

547. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. N Engl J Med 1994:394-398.

548. Benson H, Epstein MD. The placebo effect. JAMA 1976: 232:1225-1226.

549. DuBeau C, Khullar V, Versi E. "Unblinding" in randomized controlled drug trials for urinary incontinence: implications for assessing outcomes when adverse effects are evident. Neurourol Urodyn 2005: 24(13-20).

550. Rees J, Wade T, Levy D, Colford J, Hilton J. Changes in beliefs identify unblinding in randomized controlled trials: a method to meet CONSORT guidelines. Contemporary Clinical Trials 2005: 26:25-37.

551. Desbiens NA. In randomized controlled trials, should subjects in both placebo and drug groups be expected to guess that they are taking drug 50% of the time? Med Hypotheses 2002: 59(3):227-232.

552. Polman CH, Reingold SC, Barkhof F, Calabresi PA, Clanet M, Cohen JA et al. Ethics of placebo-controlled clinical trials in multiple sclerosis: a reassessment. Neurology 2008: 70(13 Pt 2):1134-1140.

553. Anderson JA. The ethics and science of placebo-controlled trials: assay sensitivity and the Duhem-Quine thesis. J Med Philos 2006: 31(1):65-81.

554. Streiner DL. Placebo-controlled trials: when are they needed? Schizophr Res 1999: 35(3):201-210.

555. Streiner DL. Alternatives to placebo-controlled trials. Can J Neurol Sci 2007: 34 Suppl 1:S37-S41.

556. Miller FG, Emanuel EJ, Rosenstein DL, Straus SE. Ethical issues concerning research in complementary and alternative medicine. JAMA 2004: 291(5):599-604.

557. Chancellor MB, de Groat WC. Intravesical capsaicin and resiniferatoxin therapy: spicing up the ways to treat the overactive bladder. Journal of Urology 1999: 162:3-11.

558. Morales A, Emerson L, Nickel JC, Lundie M. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol 1996: 156(1):45-48.

559. Stone NN. Nalmefene in the treatment of interstitial cystitis. Urol Clin North Am 1994: 21(1):101-106.

560. Propert KJ, Payne C, Kusek JW, Nyberg LM. Pitfalls in the design of clinical trials for interstitial cystitis. Urology 2002: 60(5):742-748.

561. Ward MM. Interpreting measurements of physical function in clinical trials. Ann Rheum Dis 2007: 66 Suppl 3:iii32-iii34.

562. Wein AJ, Broderick GA. Interstitial cystitis. Current and future approaches to diagnosis and treatment. Urol Clin North Am 1994: 21(1):153-161.

563. McQuay H. Numbers need to care. Pain 2003: 106(3):213-214.

564. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005: 113(1-2):9-19.

565. Fall M, Hanno P, Nordling J. Bladder pain syndrome, interstitial cystitis, painful bladder syndrome, and hypersensitive bladder syndrome: new nomenclature/new guidelines. Current Bladder Dysfunction Reports 2011:(DOI 10.1007/s11884-011 -0098-3).

566. Fall M, Oberpenning F, Peeker R. Treatment of bladder pain syndrome/interstitial cystitis 2008: can we make evidence-based decisions? Eur Urol 2008: 54(1):65-75.

567. Dimitrakov J, Kroenke K, Steers WD, Berde C, Zurakowski D, Freeman MR et al. Pharmacologic management of painful bladder syndrome/interstitial cystitis: a systematic review. Arch Intern Med 2007: 167(18):1922-1929.

568. Fall M, Oberpenning F, Peeker R. Treatment of bladder pain syndrome/interstitial cystitis 2008: can we make evidence-based decisions? Eur Urol 2008: 54(1):65-75.

569. Hill JR, Isom-Batz G, Panagopoulos G, Zakariasen K, Kavaler E. Patient perceived outcomes of treatments used for interstitial cystitis. Urology 2008: 71(1):62-66.

570. Ingber MS, Peters KM, Killinger KA, Carrico DJ, Ibrahim IA, Diokno AC. Dilemmas in diagnosing pelvic pain: multiple pelvic surgeries common in women with interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 2008: 19(3):341-345.

571. Chung MK. Interstitial cystitis in persistent posthysterectomy chronic pelvic pain. JSLS 2004: 8(4):329-333.

572. Carr LK, Corcos J, Nickel JC, Teichman J. Diagnosis of interstitial cystitis June 2007. Can Urol Assoc J 2009: 3(1):81-86.

573. Homma Y, Ueda T, Tomoe H, Lin AT, Kuo HC, Lee MH et al. Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. Int J Urol 2009: 16(7):597-615.

574. Ueda T, Nakagawa M, Okamura M, Tanoue H, Yoshida H, Yoshimura N. New cystoscopic diagnosis for interstitial cystitis/painful bladder syndrome using narrow-band imaging system. Int J Urol 2008: 15(12):1039-1043.

575. Fujihara A, Ukimura O, Iwata T, Miki T. Neuroselective measure of the current perception threshold of A-delta and C-fiber afferents in the lower urinary tract. Int J Urol 2011: 18(5):341-349.

576. van de Merwe JP. Interstitial cystitis and systemic autoimmune diseases. Nat Clin Pract Urol 2007: 4(9):484-491.

577. Rothrock NE, Lutgendorf SK, Hoffman A, Kreder KJ. Depressive symptoms and quality of life in patients with interstitial cystitis. J Urol 2002: 167(4):1763-1767.

Committee 20

Management Using Continence Products

Chair

A. Cottenden (UK)

Members

D.Z. Bliss (USA),

B. Buckley (Ireland),

M. Fader (UK),

C. Gartley (USA),

D. Hayder (Germany),

J. Ostaszkiewicz (Australia),

M. Wilde (USA)

CONTENTS

I. INTRODUCTION

II. OVERALL GUIDELINES FOR SELECTING CONTINENCE PRODUCTS

1. PRODUCT CATEGORIES
2. IDENTIFYING THE NEEDS
3. PATIENT ASSESSMENT FACTORS
4. MAIN USER GROUPS
5. CHOOSING BETWEEN PRODUCT CATEGORIES
6. SUMMARY
7. RECOMMENDATIONS

III. PRODUCT EVALUATION METHODOLOGY

1. RESEARCH QUESTIONS
2. RESEARCH DESIGN
3. SUMMARY AND RECOMMENDATIONS
4. PRIORITIES FOR RESEARCH

IV. HANDHELD URINALS

1. FEMALE HANDHELD URINALS
2. MALE HANDHELD URINALS
3. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION
4. RECOMMENDATIONS
5. PRIORITIES FOR RESEARCH

V. COMMODES AND BEDPANS

1. RESULTS
2. SUMMARY
3. RECOMMENDATIONS
4. PRIORITIES FOR RESEARCH

VI. ABSORBENT PRODUCTS

1. INTRODUCTION
2. ABSORBENT PRODUCT CATEGORIES
3. ABSORBENT PRODUCT MATERIALS
4. ABSORBENT PRODUCT CAPACITY AND USER REQUIREMENTS
5. ABSORBENT PRODUCTS FOR WOMEN WITH LIGHT URINARY INCONTINENCE
6. ABSORBENT PRODUCTS FOR MEN WITH LIGHT URINARY INCONTINENCE
7. ABSORBENT PRODUCTS FOR MEN AND WOMEN WITH MODERATE-HEAVY URINARY INCONTINENCE
8. DISPOSABLE UNDERPADS
9. WASHABLE UNDERPADS
10. ABSORBENT PADS FOR CHILDREN WITH URINARY AND / OR FAECAL INCONTINENCE
11. PADS FOR FAECAL INCONTINENCE
12. GENERAL RECOMMENDATIONS ON PAD SELECTION
13. RECOMMENDATIONS RELATING TO WASHABLE PADS

VII. SHEATHS

1. PRODUCT CATEGORIES AND FEATURES
2. QUALITY OF DATA
3. RESULTS
4. SUMMARY
5. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION
6. RECOMMENDATIONS
7. PRIORITIES FOR RESEARCH

VIII. URINE DRAINAGE BAGS AND ACCESSORIES

1. PRODUCT CATEGORIES AND FEATURES
2. QUALITY OF DATA
3. RESULTS
4. SUMMARY
5. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION
6. RECOMMENDATIONS
7. PRIORITIES FOR RESEARCH

IX. BODYWORN URINALS

1. FEMALE BODYWORN URINALS
2. MALE BODYWORN URINALS AND DRIBBLE CONTAINERS
3. PRIORITIES FOR RESEARCH

X. MECHANICAL DEVICES FOR WOMEN WITH URINARY INCONTINENCE

1. DEVICES THAT OCCLUDE AT THE EXTERNAL MEATUS
2. INTRAURETHRAL DEVICES
3. INTRAVAGINAL DEVICES
4. OVERVIEW OF MECHANICAL DEVICES FOR WOMEN

XI. MECHANICAL DEVICES FOR MEN WITH URINARY INCONTINENCE

1. QUALITY OF DATA
2. RESULTS
3. SUMMARY
4. RECOMMENDATIONS
5. PRIORITIES FOR RESEARCH

XII. CATHETERS

1. INTERMITTENT CATHETERISATION
2. INDWELLING CATHETERISATION
3. CATHETER-RELATED QUALITY OF LIFE
4. OVERALL RECOMMENDATIONS RELATING TO CATHETERS
5. PRIORITIES FOR RESEARCH

XIII. PRODUCTS FOR PREVENTING OR CONTAINING FAECAL INCONTINENCE

1. PRODUCTS TO PREVENT OR CONTAIN LEAKED STOOL
2. QUALITY OF DATA
3. RESULTS: ANAL PLUGS
4. RESULTS: RECTAL TRUMPET
5. RESULTS: RECTAL CATHETER SYSTEMS
6. RESULTS: ANAL POUCH
7. SUMMARY
8. RECOMMENDATIONS
9. PRIORITIES FOR RESEARCH

XIV. SKIN HEALTH AND CONTINENCE PRODUCTS

1. BACKGROUND
2. CLINICAL STUDIES OF THE IMPACT OF PRODUCTS AND PRODUCT MATERIALS ON SKIN HEALTH
3. CLINICAL STUDIES OF SKIN-CARE PRODUCTS AND NURSING PRACTICES TO MAINTAIN OR IMPROVE SKIN HEALTH
4. SUMMARY
5. RECOMMENDATIONS
6. PRIORITIES FOR RESEARCH

XV. ODOUR CONTROL PRODUCTS

1. PRODUCTS FOR URINARY INCONTINENCE
2. PRODUCTS FOR FAECAL INCONTINENCE
3. RECOMMENDATIONS
4. PRIORITIES FOR RESEARCH

REFERENCES

Management Using Continence Products

A. Cottenden

D.Z. Bliss, B. Buckley, M. Fader, C.Gartley, D. Hayder, J. Ostaszkiewicz, M. Wilde

I. INTRODUCTION

Not all incontinence can be cured completely and even those who are ultimately successfully treated may have to live with incontinence for a time, for example, whilst they wait for surgery or for pelvic floor muscle training to yield its benefits. Still others – depending on their frailty, severity of incontinence and personal priorities – may not be candidates for treatment or may choose management over attempted cure. For all such people, the challenge is to discover how to deal with their incontinence so as to minimise its impact on their quality of life. This usually involves using some kind of continence product(s) to control or contain leakage of urine and / or faeces, and /or to manage urinary retention. In short, the possible role of continence products should be considered at each stage of patient assessment and treatment and, if treatment is not available, appropriate, acceptable or (fully) successful – subsequent management. Managing incontinence successfully with products is often referred to as contained incontinence, managed incontinence or social continence, in recognition of the substantial benefits it can bring to quality of life even though cure has not been achieved [1].

This chapter is aimed primarily at healthcare professionals seeking to make informed decisions as they choose – or help their patients to choose - between continence product categories and then select a specific product within their chosen category. We have also aimed to make this information accessible to the user, particularly in the summary and recommendation sections. The chapter includes a section for each of the major product categories, each section reviewing published data and – where possible - identifying evidence-based recommendations for product selection and use. Products designed to deal with skin and odour problems caused by incontinence are also addressed.

The sections on the major product categories are preceded by two others. The first provides overall guidelines for product selection, describing the key elements of patient assessment and suggesting a classification of people with incontinence into a number of broad groups based on gender, age (adult or child) and the nature and severity of their incontinence. A table is provided for each group summarising the user characteristics, priorities and contexts which commonly favour or discourage the use of each of the major product categories available to them. Following these overall guidelines and preceding the sections on the major product categories, a review is provided of the methodological challenges of conducting continence product evaluations and interpreting the results.

Much of the evidence base for product selection and effective use is patchy and so, where there is little published data to provide confident evidence-based advice on an issue commonly raised by patients and caregivers, an expert opinion is offered as the best advice available. The hope is that highlighting knowledge gaps in this way will help stimulate the research necessary to provide more robust evidence-based advice in the future.

To accompany this chapter, the International Consultation on Incontinence and the International Continence Society have collaborated to make the material more generally available via a new web site hosted by the International Continence Society at http://www.continenceproductadvisor.org/. The hope is that this will help people with incontinence and their caregivers to make informed choices in selecting appropriate products, and provide them with accessible, evidence-based advice on how to use them effectively.

The literature search strategy to identify material for this chapter additional to that reviewed for the third consultation [2] was conducted as follows. MEDLINE and CINAHL databases were searched from 2008 – 2011 for English language publications. Detailed search strategies were developed for each electronic database searched. Consideration was given to variations in terms used and spellings of terms in different countries so that studies were not missed. Relevant abstracts were examined and then pertinent articles were retrieved and reviewed, and the reference lists searched for further studies.

For product categories associated with little or no research literature, analysis relied on expert opinion from clinical practice papers.

The following main search terms were used: incontinence AND device*, toilet* AND facilities, female, male, urinal*, commode*, bedpan*, urin* AND sheath, condom AND catheter*, incontinence OR absorbent pad*, urinary AND catheter* (in title), urinary AND leg bag* OR legbag* OR drainage bag, faecal OR fecal AND incontinence AND plug OR pouch OR bag OR device, OR manage* system, incontinence OR perineal AND dermatitis OR inflammation OR skin damage.

II. OVERALL GUIDELINES FOR SELECTING CONTINENCE PRODUCTS

Selecting suitable continence products is critical for the well-being and quality of life of patients and carers. The ability to contain and conceal incontinence enables individuals to protect their public identity as a "continent person" and avoid the stigma associated with incontinence [3]. Failure to do so can result in limited social and professional opportunities, place relationships in jeopardy and detrimentally affect emotional and mental wellbeing [4]. The ability to contain and conceal incontinence enables carers to feel confident that the person(s) they care for will not be embarrassed publicly. It reduces the level of care required in relation to maintaining hygiene, skin care and laundry for the person who is dependent upon continence products [5].

Fortunately there is a diverse range of different products to choose from. However, without comprehensive and current information on the products available, this plethora of choice can be overwhelming and confusing [5]. Furthermore, the range of products actually accessible to users can vary enormously between and within countries, depending on the funding available, healthcare policy and the logistics of supply [5].

The choice of appropriate products for an individual with incontinence is influenced by the resources and care available and patient / carer preference, as well as assessment of specific client characteristics and needs [6] [7].

The stigma associated with incontinence means that another measure by which the success of products is judged is their ability to conceal the problem [8]. Such concealment may involve compromises: for example, in order to prevent leakage from a product, those with a larger capacity than strictly necessary may be preferred but this can in itself introduce issues to do with discretion when the product is worn. The intimate and stigmatised nature of incontinence means that issues relating to self-image can affect some patients' preferences. This may be especially marked in younger people for whom body-image may be particularly important and for whom disruption to normal social and interpersonal development may result in isolation or lack of access to normal experiences [9] [10].

1. PRODUCT CATEGORIES

The continence products considered in this chapter may be divided into those that are intended to assist with toileting and those to manage urinary retention and / or contain incontinence (urinary and / or faecal) (**Figure II-1**).

All toileting products can be useful for dealing with urine and / or faeces except for handheld urinals which are just for urine. Containment / control products are subdivided into three overlapping classes: those for urinary retention, urinary incontinence, and faecal incontinence. So, for example, someone with urinary retention is most likely to benefit from one of the products in the red ellipse, while someone with urinary incontinence will most likely benefit from one in the blue ellipse. A patient experiencing both problems will need two products (one from each ellipse) or one product from the intersection of the two ellipses.

2. IDENTIFYING THE NEEDS

The algorithms below (**Figures II-2 and II-3**) are designed to provide guidance for determining broadly which product(s) is likely to be of benefit to a particular patient. There are three main questions:

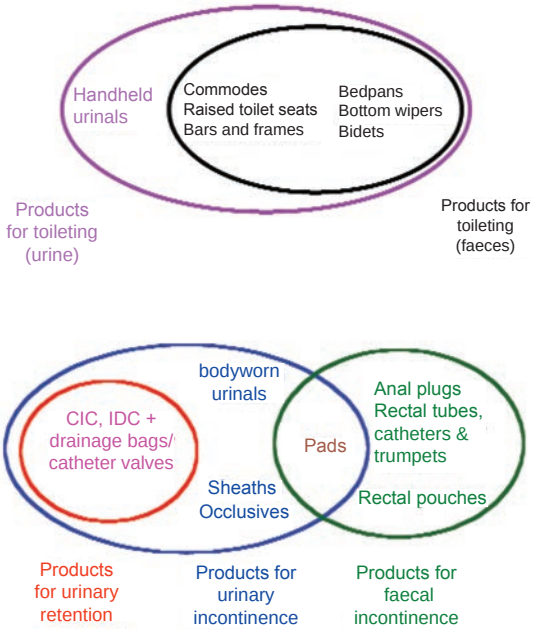


Figure II-1: Products for toileting (top) and for managing incontinence and / or urinary retention (bottom). CIC= Clean intermittent catheterisation; IDC= Indwelling catheter

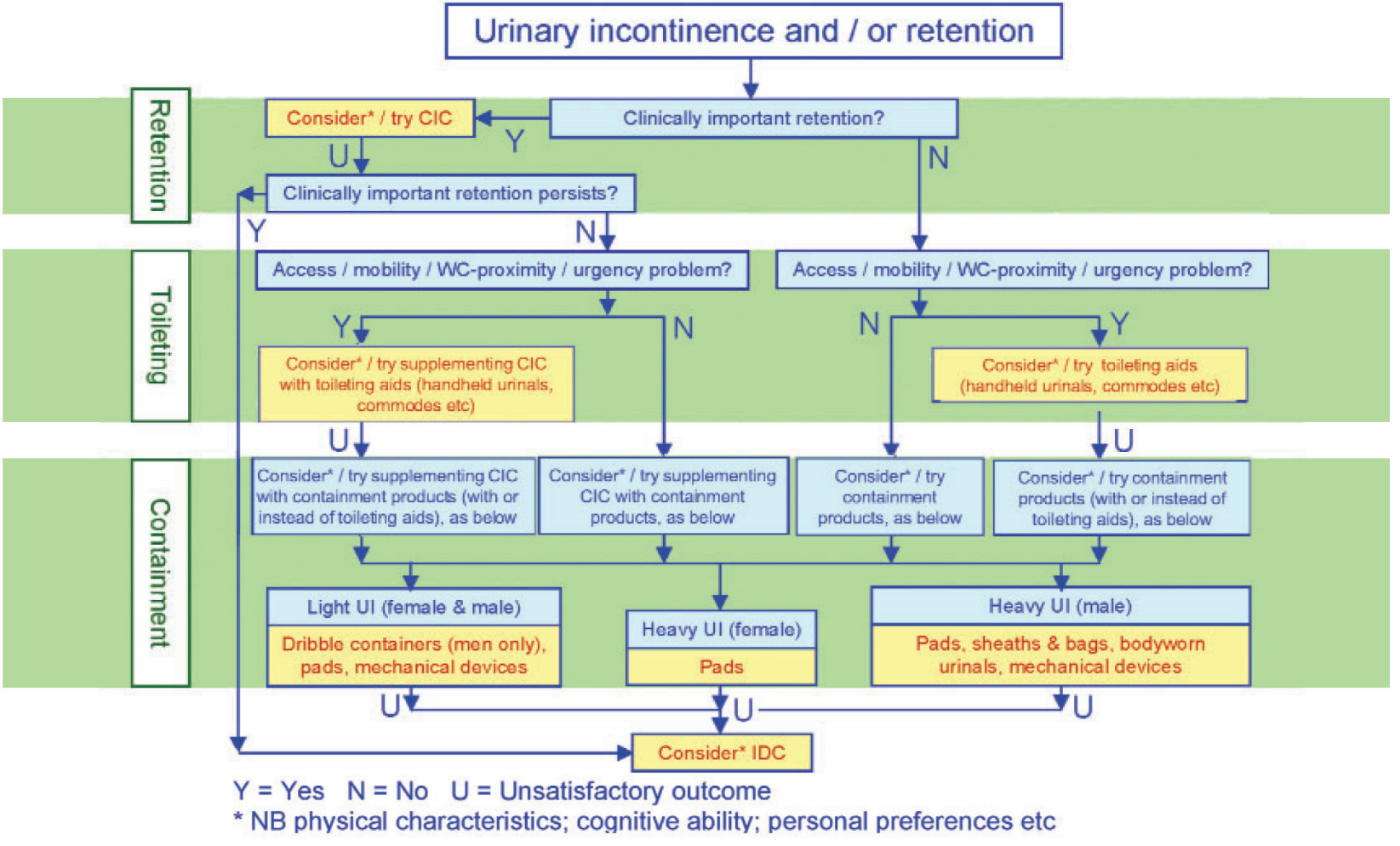


Figure II-2: Algorithm to help identify the category(s) of products most likely to help a patient with urinary incontinence and / or urinary retention. (Y = Yes; N = No; U = unsatisfactory ie considered and deemed unsuitable or tried and found not to work satisfactorily). * Consideration should be based on assessment of the patient's physical characteristics, cognitive ability and personal preferences, as well as the nature of their incontinence. (CIC = Clean intermittent catheterisation; IDC = Indwelling catheter).

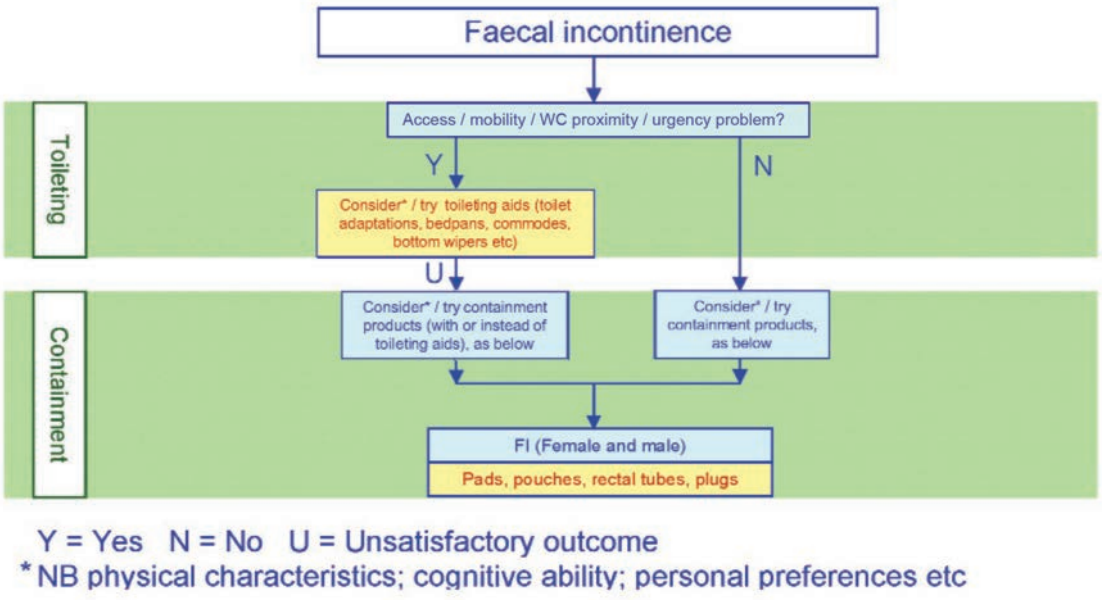


Figure II-3: Algorithm to help identify the category(s) of products most likely to help a patient with faecal incontinence. (Y = Yes; N = No; U = unsatisfactory ie considered and deemed inappropriate or tried and found not to work satisfactorily). * Consideration should be based on assessment of the patient's physical characteristics, cognitive ability and personal preferences, as well as the nature of their incontinence.

- Is there urinary retention (with or without incontinence)?
- Are there problems with toilet access (e.g. the proximity or design of the toilet; mobility or urgency problems for the patient)?
- Is there urinary incontinence or faecal incontinence or both?
- Answers to these questions will determine which one (or both) of the algorithms is most appropriate for an individual and help identify the category(s) of products most likely to help.

3. PATIENT ASSESSMENT FACTORS

A careful patient assessment is an important part of the process of product selection and **Table II-1** summarises the key elements to be considered.

The choice of appropriate products for an individual with incontinence is dependent upon the resources and care available. It must also be influenced by patient and carer preference as well as assessment of specific client characteristics and needs [6] [7].

Assessment of physical characteristics such as anthropometrics, level of independence, mobility and dexterity, mental acuity and the nature of the incontinence will determine which products may be appropriate. In addition to these factors, successful product choice and effective use involves other practical and psychosocial considerations. Product effectiveness depends upon the same factors as any assistive device intended to address a disability or impairment: patient participation in device selection [11] provision of adequate instructions for use [12] and the need for products to fulfil their function reliably and not be difficult to use [12] [9] [13].

While **Table II-1** provides general guidance on patient assessment relating to product selection, later sections in the chapter provide further discussion on assessment issues specifically related to the various product categories.

In addition to selection of appropriate and effective products following patient assessment, education and training of users or carers in the correct use of the devices is of importance if product use is to be optimal. This may be a simple matter of instruction in the effective fitting and changing of absorbent products, or may involve more in-depth training in the ongoing care of, for example, a suprapubic catheter.

Table II-1: Key elements of assessing a patient and his / her environment

Element	Rationale
Nature of the continence problem	The frequency, volume and flow rate of the incontinence influences product suitability.
Gender	Males may consider and prefer sheaths as a more masculine option to pads. Females may be attracted to products that are more feminine in design and presentation. Some 'unisex' products such as absorbent pads have different designs that work better for men (or women).
Physical characteristics	Anthropometrics (e.g. height and waist, thigh, penile circumference) will influence the comfort and effectiveness of a product.
Mental acuity	Mental impairment can affect the person's ability to manage the product. Products that resemble usual underwear (e.g. some absorbents) may be easiest to manage. Products which have health implications if used incorrectly (e.g. mechanical devices or catheter valves) should be avoided if mental impairment is likely to preclude correct and safe use.
Mobility	Impaired mobility may make some product choices impractical or require toilet or clothing modification to allow effective use of the product.
Dexterity	Problems with hand or finger movement can make it difficult to use some products (eg taps on leg bags, straps with buttons).
Eyesight	Impaired eyesight limits effective application and management of some products.
Leg abduction problems	Difficulty with abduction can make the use of some products impractical or ineffective.
Lifestyle and environments	Daily activities and environments can influence the choice of product and a mixture of products may provide optimum management. Different products may be most satisfactory for daytime and going out (when discreetness may be a priority) and night- time or staying in (when comfort may be a priority), for holidays (when laundry and / or large quantities of disposables may be a problem) or for use at work. The proximity and accessibility of a toilet in the various environments may be a key factor.
Independence / assistance	If a caregiver is required to apply or change the product then it may be important to involve them in the selection of the product and to establish their willingness and ability to use it.
Laundry facilities	Washable pads and bed linen may be very heavy when wet and take a long time to dry. It is important to check that the person doing the laundry has the ability and facilities to cope.
Disposal facilities	Ability to appropriately, safely and discreetly dispose of the selected products needs to be considered.
Storage facilities	Some products - notably, pads for heavy incontinence - can be bulky. Adequate space to store supplies between deliveries / purchases needs to be available.
Personal preferences	Different people like different products and where possible patients should be given a choice of products with which to experiment to determine the most satisfactory product.
Personal priorities	Everyone wants to avoid leakage but other factors such as discreetness may be more or less important to individuals.

Incontinence is often a long term condition and so monitoring and periodic reassessment is essential to maintain effective management with products.

4. MAIN USER GROUPS

Although needs, priorities and preferences vary between people with incontinence it is useful to divide patients into major user groups to help identify the category(s) of products most likely to benefit an individual. Seven primary groups are identified in this chapter:

- People with urinary retention.
- People who need help with toileting / toilet access.
- Females with light urinary incontinence.
- Males with light urinary incontinence.
- Females with moderate / heavy urinary incontinence.
- Males with moderate / heavy urinary incontinence.
- People with faecal incontinence.

An individual may belong to more than one group. Each group includes children and young people: the products available for them are broadly similar to those for adults.

5. CHOOSING BETWEEN PRODUCT CATEGORIES

- **Figures II-4 to II-9** summarise the user characteristics, priorities and contexts which favour or discourage the use of each of the categories of products available for six of the seven user groups identified in section II.4. Assistance with choosing appropriate products for the first group (people with urinary retention) is given in the section on catheters (**Table XII-1**) as all the product options for these people are in the same category (catheters).
- The recommendations given in these charts are based on the evidence presented in the sections of the chapter dedicated to different product categories and they are intended to help identify which product category (categories) are most likely to help an individual. However, it should be remembered that the same product will not suit all people, even if they have very similar assessment outcomes on the factors summarised in Table II-1. Different people prefer different products and where possible patients should be given access to a range with which to experiment to determine the most satisfactory product(s) for them. Similarly, the balance of priorities varies between users; for example, some pad users will opt for a bulky and, therefore, less discreet product to achieve an acceptably low risk of leakage while others will see the balance differently. It should also be noted that a mix of products from different categories may provide the best solution; for example, needs may vary between day / night and home / away. Once a product category of interest has been identified the corresponding chapter section should be consulted for further help.

6. SUMMARY

In conclusion, continence products can play an important role in enhancing the quality of life and reducing the stigma of incontinence of those who: are awaiting treatment; are waiting for treatment to take effect; elect not to pursue cure options; are unable to be fully cured and are living with an ongoing bladder / bowel problem.

7. RECOMMENDATIONS

- Incontinence should be actively managed with products to minimise the impact of incontinence on quality of life (**Grade of Recommendation C**).
- Patients should be carefully assessed (and reassessed periodically) to select the most appropriate products (**Grade of Recommendation C**).

III. PRODUCT EVALUATION METHODOLOGY

This section aims to assist those planning clinical trials of products. There have been relatively few large clinical trials of continence products (with the exception of urinary catheters) and for most product categories research evidence to guide the selection of individual products / designs / features is limited and in some cases absent.

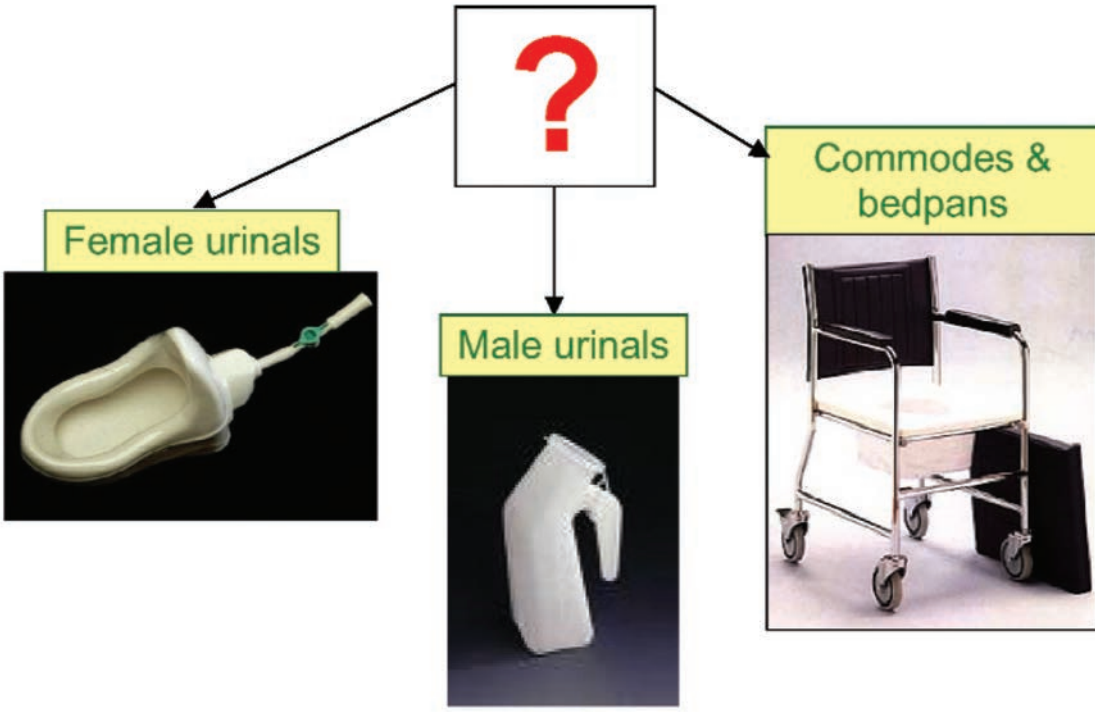
Measuring the performance of continence products is methodologically challenging. Manufacturers modify and change their products regularly - in terms of both materials and designs - and this limits the long-term validity of research results. There are also complex issues regarding research questions, study design, product representation, blinding and sample size [14] which are discussed below.

It is common for practitioners to be asked (by their employers or by companies) to do a small evaluation or trial – sometimes to 'test out' a new product and sometimes to help choose between competing brands for bulk-buying. Such trials should be approached with caution; they can be very demanding but their results may be of very limited value, even for local use. The methodological challenges identified below still apply but are compounded by small sample size and restricted product selection. These studies are likely to be helpful only for identifying gross product short-comings or benefits.

1. RESEARCH QUESTIONS

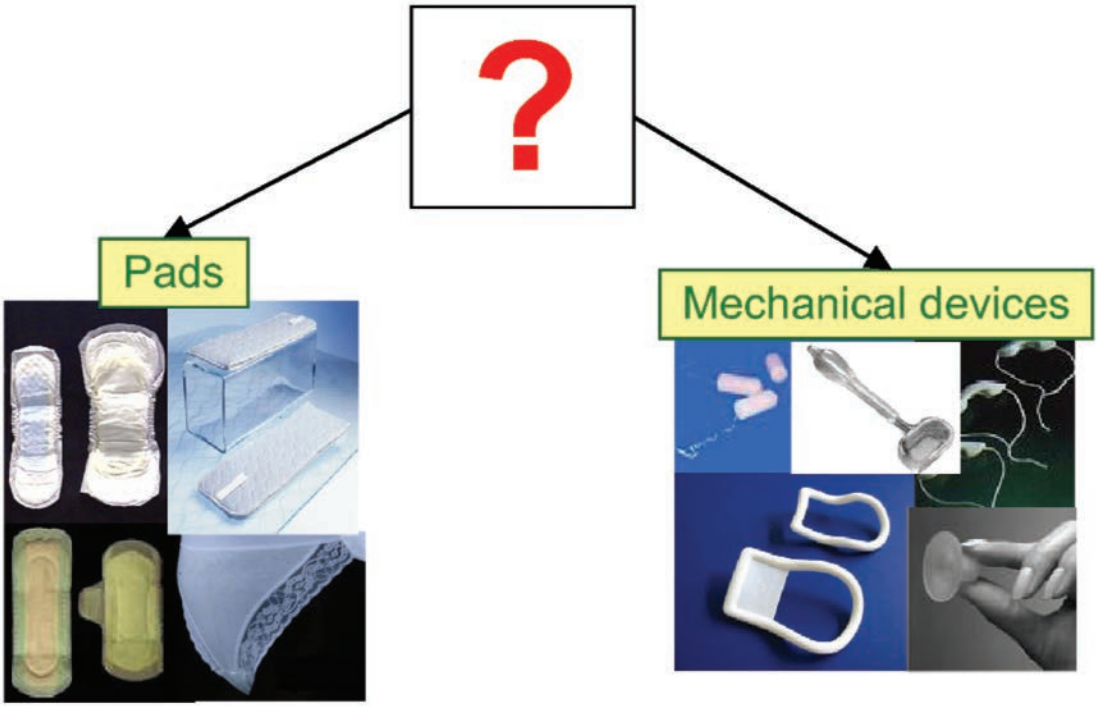
a) Comparisons

Part of the complexity of product evaluations stems from the sheer number and type of products available, meaning that many different comparisons could be made. **Table III-1** illustrates the problem



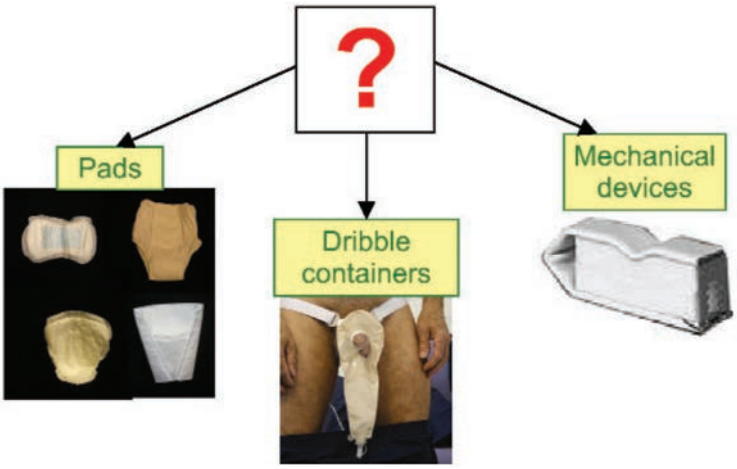
Product category	User characteristics / priorities / contexts which:		Notes
	FAVOUR use	DISCOURAGE use	
Female handheld urinals (Section IV.1)	• Any woman with mobility/urgency/access problems (C) • Able to stand or crouch (B/C) • Able to move to edge of chair (B/C)		• Many urinals: experiment using a library of urinals. • Urinals are less likely to succeed if woman needs to lie down or sit back in a chair.
Male handheld urinals (Section IV. 2)	• Any man with mobility/urgency/access problems (C) • Some manual dexterity (C) • Design concept acceptable (C)	• Inability to empty urinal independently (C) • Poor balance (C) • Impaired forward arm reach and wrist function (C) • Impaired cognition (C)	• Clothing adaptation may be needed. • NB Non-spill adaptors. • NB Flat-pack urinals for travel.
Commodes (Section V)	• Anyone with mobility/urgency/access problems (C)	• In rooms used by others (C) • Institutional settings (shower chairs preferred) (C) • Where there is a safety risk.	• Ensure privacy and dignity.
Bedpans (Section V)	• Unable to use toilet or commode / shower-chair (C)	• In general (C)	• Ensure privacy and dignity.

Figure II-4: Products for people who need assistance with toileting.(Grade of recommendation in brackets)



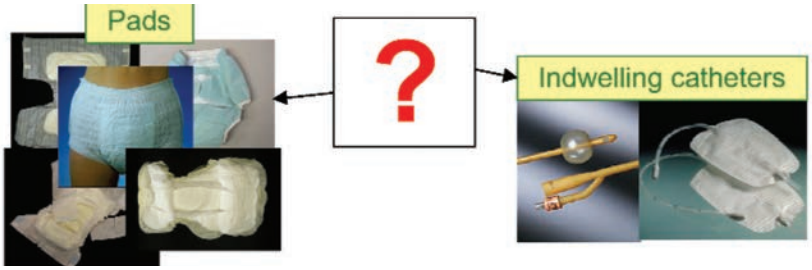
Product category	User characteristics / priorities / contexts which:		Notes
	FAVOUR use	DISCOURAGE use	
Pads (Section VI.5)	• In general (C)		• See Fig VI-16 for details.
Mechanical devices (Section X)	• Incontinence is predominantly stress (C) • Manual dexterity is good (C) • Sound cognition (C) • Device concept is acceptable / preferred (C) • Preventing leakage rather than containing it is attractive (C)	• Incontinence has a significant urgency component (C) • Concerns over risks of UTI are high (intra-urethral device) (C)	

Figure II-5: Products for females with light urinary incontinence (Grade of recommendation in brackets)



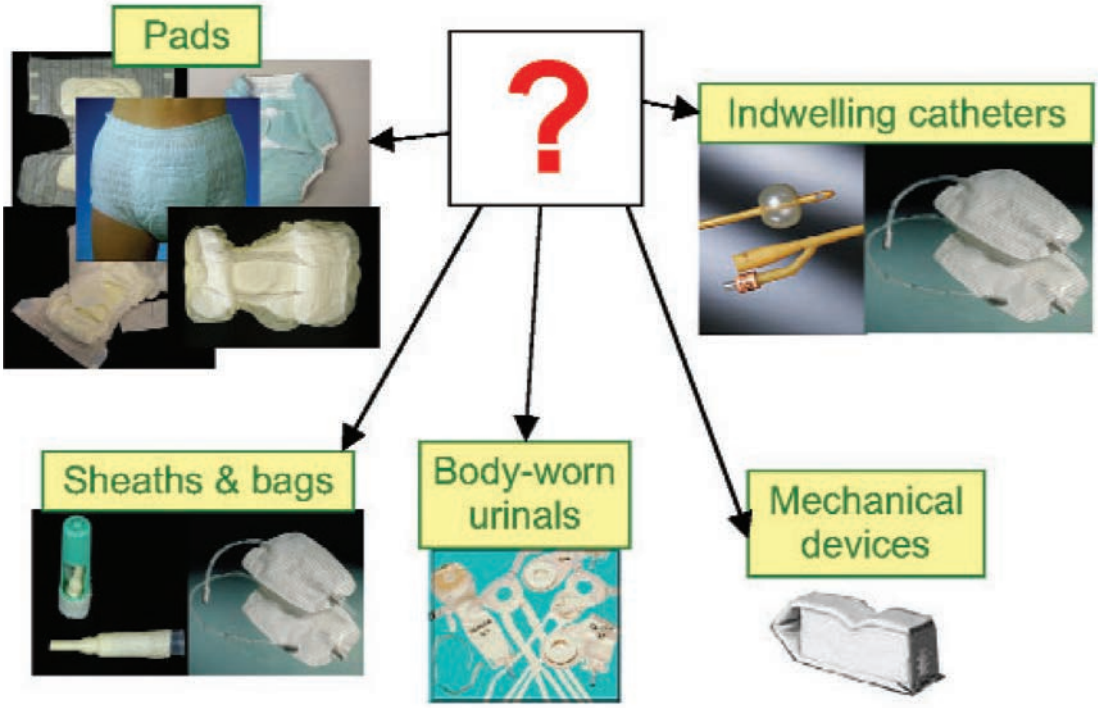
Product category	User characteristics / priorities / contexts which:		Notes
	FAVOUR use	DISCOURAGE use	
Pads (Section VI.6)	• In general		• See Fig VI-17 for details.
Dribble containers (Section IX.2)	• Device concept is acceptable / preferred (C)	• Unknown	
Mechanical devices (Section XI)	• Highly motivated (C) • Periodic / intermittent use (C) • Incontinence is predominantly stress (C) • Device concept is acceptable / preferred (C) • Preventing leakage rather than containing it is attractive (C)	• Incontinence has a significant urgency element (C) • Doubtful level of cognition (C) • Risk of skin / tissue damage (C) • Bladder sensation poor (C) • Poor dexterity (C)	• Skilled fitting by a professional is needed.

Figure II-6: Products for males with light urinary incontinence (Grade of recommendation in brackets)



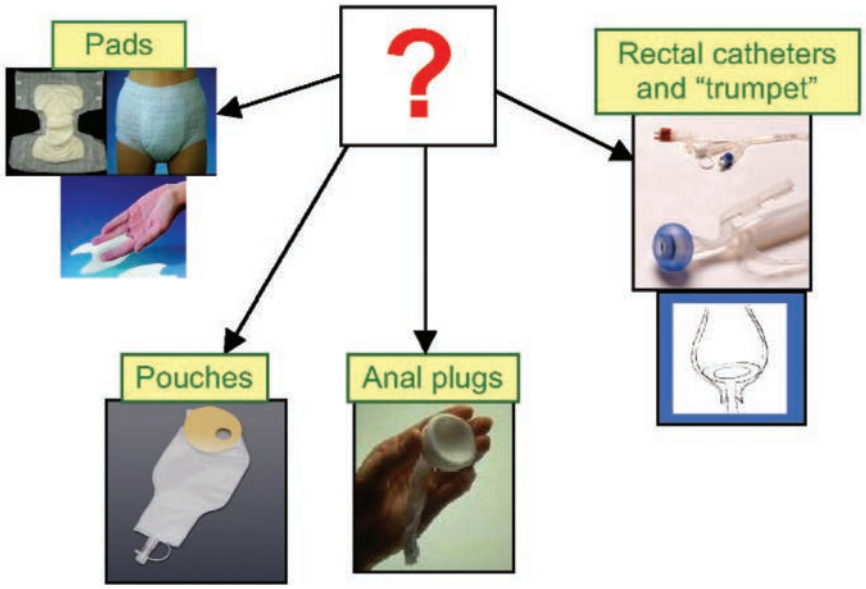
Product category	User characteristics / priorities / contexts which:		Notes
	FAVOUR use	DISCOURAGE use	
Pads (Section VI.7)	• In general (C)	• Skin is severely damaged (C)	• See Fig VI-18 for details.
Indwelling Catheters (Section XII.2)	• Retention / voiding problem (if no alternative) (C) • Skin is severely damaged (C) • Pads (or other products) unsuccessful / inappropriate (C) • Unable to perform CIC (C)	In general (A), but particularly if: • History of urethral trauma • Cognitive impairment (danger of interfering with catheter) • Avoidance of UTI is a priority	• See Table XII-1 for details.

Figure II-7: Products for females with moderate / heavy urinary incontinence. (Grade of recommendation in brackets)



Product category	User characteristics / priorities / contexts which:		Notes
	FAVOUR use	DISCOURAGE use	
Pads (Section VI.7)	• In general – particularly if active (C)	• Skin is severely damaged (C)	• See Fig VI-18 for details.
Sheaths & bags (Sections VII & VIII)	• Less risk of bacteruria, recurrent UTI's or death than indwelling catheters (C) • More comfortable than indwelling catheters (C) • Acceptable / preferred to pads (C) • Minimal physical intervention is a priority (C) • Good dexterity (C) • Sound cognition (C)	• Local skin breakdown (C) • Bacteruria, UTI (C) • Carer / user unable / reluctant to apply (C)	• Sheaths with integral adhesive are more popular than sheath with separate adhesive strip. • Sheath applicators are often ineffective and unpopular.
Body-worn urinals (Section IX.2)	• Desire to avoid pads (C) • Concept acceptable/preferred (C) • Mobile (not wheelchair user) (C)	• Latex / materials allergy (C)	
Mechanical devices (Section XI)	• Highly motivated (C) • Periodic / intermittent use (C) • Incontinence is predominantly stress (C) • Device concept is acceptable / preferred (C) • Preventing leakage rather than containing it is attractive (C)	• Incontinence has a significant urgency element (C) • Doubtful level of cognition (C) • Risk of skin / tissue damage (C) • Bladder sensation poor (C) • Poor dexterity (C)	• Skilled fitting by a professional is needed.
Indwelling catheters (Section XII.2)	• Retention / voiding problem (C) • Skin is severely damaged (C) • Pads (or other products) unsuccessful / inappropriate (C) • Unable to perform CIC (C)	In general (A), but particularly if: • History of urethral trauma • Cognitive impairment (danger of interfering with catheter) • Avoidance of UTI is a priority	• See Table XII-1 for details.

Figure II-8: Products for males with moderate / heavy urinary incontinence. (Grade of recommendation in brackets)



Product category	User characteristics / priorities / contexts which:		Notes
	FAVOUR use	DISCOURAGE use	
Pads (Section VI.11)	• In general (C)	• Skin problems (C)	• Few pads are specifically for faecal incontinence. • Dressing between buttocks favoured by some men for minor faecal incontinence
Pouches (Section XIII.6)	• Acute situations (C) • Liquid stool (C) • Post-surgical / enema drainage (C) • Immobile / in bed (C) • Risk of skin problems (C)	• Skin problems (C)	• Skin problems may depend on adhesive material.
Anal plugs (Section XIII.3)	• • Children tolerate better than adults (C) • After using enemas or rectal irrigation (C) • Spina bifida, anorectal malformation, rectal sphincter damage / tear (C) • Periodic use (eg sports or special occasions) (B/C)	• Possibly if there is bowel/rectal disease • Spinal cord patients with autonomic dysreflexia (C) • Device concept unacceptable (C) • Disruptive of successful established routines (B/C)	• Discomfort / pain influenced by plug design. • Discomfort and frequent expulsion are common cause of rejection. • Leakage around plug may occur.
Rectal trumpets (Section XIII.4)	• Acutely ill (C) • Liquid stool (B/C) • Post-surgical enema drainage (C) • Immobile / in bed (C) • Risk of skin problems (C)	• Skin problems (C)	
Rectal catheters (Section XIII.5)	• Acutely ill (C) • Liquid stool (B/C) • Immobile / in bed (C) • Skin problems or skin at high risk (B/C) • Wound contamination due to faecal incontinence (B/C)	• Possibly if there is bowel disease, large haemorrhoids, stricture / stenosis • Recent rectal surgery / injury (C) • Long term use	

Figure II-9: Products for people with faecal incontinence. (Grade of recommendation in brackets)

using a hierarchy of questions relating to absorbent products. So, in this example, once the decision is made to choose an absorbent product in response to question 1, successive further questions can be used to narrow down the choice to a specific product brand. Questions at any of these levels may form the basis for research projects.

Table III-1: Levels of questions

• Which product category (eg catheter, sheath, absorbent pad)?
• Which design of product design (eg pull-up or diaper design of pad)?
• Which material type (eg reusable or disposable)?
• Which features (eg with / without elastic gathers)?
• Which product brand?

In the field of absorbent products the practitioner and / or patient wishes to know whether to use an underpad or a bodyworn product, a reusable or a disposable, a diaper or an insert (if they select a bodyworn), a diaper with internal elastication (standing gathers) or without and, finally, which of the many diaper brands is likely to be most effective. Attempting to answer this final question is the most pertinent question for the practitioner (who may already have made decisions about questions 1-4, Table III-1) but is particularly problematic because of the high rate of product change. By the time the results of a clinical trial of product brands are known many of the test products will have been modified and the results will have limited value for product selection. However, these 'single design' studies do have value in demonstrating the range of performance within the group of product brands, and where objective measurements can be made (for example, of leakage performance) can allow for comparisons between groups of products. Single design studies are also helpful in promoting product improvement by revealing common problems experienced by patients and exposing particularly poor products or poor product features which are amenable to change by manufacturers.

Basic product designs, features and materials change much less frequently and attempting to answer questions 1-4 (Table III-1) is therefore likely to lead to more long-lasting results. Such studies have been attempted by many researchers, but these have frequently been confounded by problems with product representation.

b) Product representation

The single greatest (and most frequently overlooked) threat to the validity of clinical trials of products is the selection of the products entered into the study. Evaluations of a number of product variants of a similar design (eg different brands) have shown that patient 'overall opinion' scores can vary by as much as 70 percentage points between apparently similar products [15]. Accordingly, in an evaluation to compare different designs, the selection of one or more products to represent each design, is crucial. Studies that have purported to compare different designs or materials have often included a small number (most often just one) of arbitrarily selected product(s). Generalizing the results of such studies to whole product groups (e.g reusable underpads, or disposable bodyworns) is meaningless and misleading. It is perfectly possible to select (either by accident or design) a particularly 'good' product from one group and a particularly 'poor' product from another. A well-designed study will therefore be seriously flawed if there is no clear process or pilot study to determine and justify the choice of particular products. Even with a systematic process of product selection (or preferably a pilot study) it is unwise to select a single product to represent a whole group of products and selection of a small group of products (e.g. three) is preferable. This allows for any 'within group' differences to be detected and helps to demonstrate the 'representativeness' of the products selected.

The most controlled method of testing different designs, materials or features of products is to make up experimental batches which differ only in the aspect of interest (e.g. the material or the feature) and a small number of studies have attempted this [15] [16]. However, experimentally made products are not usually identical to those available on the market which impairs the validity of such studies.

2. RESEARCH DESIGN

A randomized controlled trial is not possible for clinical trials of products in most categories simply because a 'control' product does not usually exist. Nor is there a 'standard or reference' product to act as a control and comparisons with 'standard practice' (i.e. the product currently in use) are prone to bias.

Although it is methodologically simpler (and more robust) to compare only two different product groups, it is more clinically relevant to compare several competing groups, using a multiple cross-over design, where there are valid comparisons. For example, there are four main design groups of disposable bodyworn pads for moderate / heavy incontinence (inserts, diapers, pull-ups and T-shaped). Evaluation of all four groups together is much faster (and therefore gives more long-lasting results) and more cost-effective than several serial studies. Cross-over trials are vulnerable to order effects and randomization of the order of testing should be carried out using Latin squares [17] to ensure balance.

It is important that clinical trials of single designs of products (which aim to enable selection of particular product brands) are comprehensive (i.e. cover all the available products) because otherwise manufacturers

can justifiably claim that although their product may be similar to one of those tested even subtle distinctions may lead to clinically important differences.

A further problem with research design is the blinding of products. Different products have different appearances and it is impossible to blind subjects or staff to the product in use. Products can be repackaged to assist anonymising but this may have unwanted effects on the products and is expensive.

Previous product experience can also affect study results, particularly if a substantial proportion of subjects are currently using a product included in the study. It is therefore important to record which products are in current use in order to add this data to the model used in the analysis.

a) Sample size and study power

Studies that include more than two products (or two small groups of products) will need to be powered so that multiple comparisons can be made. As the number of products included in the study increases the number of possible comparisons of pairs of products rises. This requires a corresponding reduction in the significance level (e.g. by using the Bonferroni method) for each pair-wise comparison to retain the overall level of significance (usually $p<0.05$). Thus as the total number of pair-wise comparisons increases the likelihood of a type 2 error (accepting the null hypothesis when it is false) also increases.

Sample sizes therefore need to be calculated to allow for each pair-wise comparison. Sample size requirements rise rapidly if each subject does not test each product and the number of products entered into a study must therefore be limited by subject fatigue. As an example, a clinical trial of four product groups where the primary outcome variable will be binarised (e.g. satisfactory / unsatisfactory) will require a sample size of approximately 80 subjects with an alpha of < 0.05 and d (difference) of 20%.

b) Outcome variables

Studies of product performance have most frequently used self-report questionnaires at the end of the product test period to assess participant ratings of product performance. Diaries of product-related events such as leakage, laundry generation and product consumption are also commonly included. Subjects in some absorbent pad studies have been asked to identify and prioritise items of product performance [18] [19] [20] to inform questionnaires and **Table III-2** shows the most common items of high priority to women with light urinary incontinence identified by Getliffe and colleagues [19].

Outcome variables in studies designed to compare catheterisation strategies and / or catheter materials or other design features commonly encompass measures of urinary tract infection, tissue trauma and recurrent catheter encrustation leading to blockage (see Section XII-2).

Questionnaire items vary depending on the products being tested and for product groups where few studies have been carried out it is particularly important to tailor questionnaires to patient needs by asking study subjects to prioritise items and to assess final questionnaires for content and face validity. One study [21] has measured the test re-test reliability of a questionnaire to assess sheath performance and found moderately good Kappa scores (around 0.7) when assessing the same sheath twice with four weeks between assessment periods.

Skin health, urinary tract infection, pain or discomfort are the main physical health consequences of containment products and skin health (which can be rated by self-report or by skin inspection) has sometimes been used as the primary outcome variable (e.g. [22]). Urinary tract infection is an important outcome for invasive devices such as catheters.

Although leakage performance is most frequently

Table III-2. Most common items of high priority to women with light incontinence using absorbent products. Getliffe et al. [19]

Daytime:	% women (N =99)	Nightime:	% of women (N=81)
Hold urine without leaking	83.8	Hold urine without leaking	93.8
Contain smell	75.8	Stay in place	77.8
Stay in place	54.5	Contain smell	54.3
Discreetness	41.1	Comfortable when wet	54.3
Comfort when wet	40.4	To keep skin dry	48.1

rated as the top priority for users, good leakage performance is not adequate as a sole measure of patient satisfaction with performance. A single (or multiple) fatal flaw such as poor comfort, bulkiness, or poor fit may cause a product that performs well for leakage to be unacceptable to the patient. For this reason aggregate measures - which assumes that the overall performance of a product can be calculated using a weighted sum of the scores for specific aspects of performance (like comfort and freedom from leakage) - are ill-advised. Patient overall opinion or satisfaction with the product should therefore be used as the primary outcome variable [21].

There are no quality of life measurement tools specifically designed for clinical trials of products, but there is a need for such tools to measure the impact that good or bad product performance has on people's lives. Existing incontinence-specific quality of life tools are designed to measure change after interventions to improve incontinence and include urinary symptoms. These tools are therefore likely to be insensitive to changes in quality of life brought about by products which are designed to contain incontinence rather than reduce or prevent it. The first stage in the development of a quality of life tool for absorbent product users has been reported by Getliffe et al. [19] and a similar tool for catheter users is known to be under development.

3. SUMMARY AND RECOMMENDATIONS

There is little published evidence on which to base summary and recommendations regarding methodology and so the following summary points / recommendations are all **Level of Evidence 3 / Grade of Recommendation C.**

- Evaluation of continence products is methodologically complex and many attempts at providing robust evidence for product selection have been hampered by methodological weaknesses.
- Product representation is critical to providing robust and generalisable data. Selection of products for inclusion in a study needs to be transparent and systematic and several products should preferably be included to represent a product group. In particular, care should be taken not to select a particularly good or a particularly poor product to represent a whole class of products.
- Multiple crossover designs are likely to be more efficient than randomised controlled trials for many products (eg pads) and therefore sample sizes estimation needs to take into account the multiple comparisons that will be made.
- Outcome variables should include patient (or carer) questionnaire including items that have been established as important to patient users.
- Diary data should be included to determine leakage performance, skin health, laundry and product consumption.
- Incidence of urinary tract infection should be included when testing invasive devices such as catheters, but "significant" UTI/ bacteriuria needs to be carefully defined (see Section 12.2.8).
- The primary outcome variables should be patient overall opinion / satisfaction and patient preference.
- Health economics should be measured alongside product performance

4. RESEARCH PRIORITIES

- The development of Quality of Life tools for users of continence products.

IV. HANDHELD URINALS

Handheld urinals are portable devices designed to allow a person to empty their bladder when access to a toilet is not possible or convenient, often due to limited mobility, hip abduction or flexibility. They can be especially helpful for those suffering from frequency and / or urgency.

An effective hand held urinal must enable its user to empty his / her bladder in comfort and be confident of no spillage. It should not require excessive physical effort on their part and should be easy to empty without spillage.

General guidelines on patient assessment for product selection are discussed in Section 2. Aspects of patient assessment particularly important for handheld urinals are user postures (in bed, on side of bed, back in chair, on edge of chair, standing/ crouching/kneeling), leg abduction, approach of urinal (from front, side, behind, above), ability to initiate void, dexterity and strength to position and remove urinal, level and availability of assistance, user preference.

There has only been one clinical trial [23] of female urinals and there are no published trials of male urinals. However, much helpful guidance and expert opinion has been published [24] [25] [26] [27].

1. FEMALE HANDHELD URINALS

Female handheld urinals come in a variety of shapes and sizes (**Figure IV-1**). Most are moulded in plastic but they may be made from metal or (for single use items) cardboard. Some are designed for use in particular postures, like standing, sitting or lying down – (see below). Some have handles to facilitate grip and positioning. Some are intended to empty into a drainage bag during or after use.

Although female handheld urinals are often described and discussed in general nursing articles on continence products they have only been the subject of one published (cross-over) evaluation. Fader

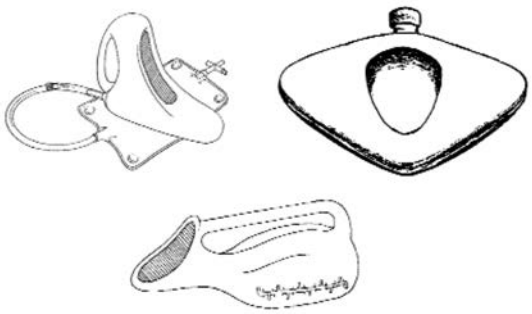


Figure IV-1: A variety of female handheld urinals.

et al. [23] carried out a multi-centre study in which each of 37 community-based women (age range 33-89y; mean age 61y) was invited to evaluate all 13 products on the UK market in 1997. No product suited everybody but each was successful for at least some subjects. The key requirements for success were that the user should be able to position the urinal easily and feel confident that it would catch urine without spilling (Level of Evidence 2). Many products were successful when used in the standing / crouching position or when sitting on the edge of a chair / bed / wheelchair. Fewer worked well for users sitting in a chair / wheelchair. Only one worked even reasonably well when users were lying / semi-lying (Subaseal), In general, subjects with higher levels of dependency found fewer urinals to be suitable for their needs.

Recently the development of a powered urinal designed to pump urine into a reservoir has been described [28]. The aim of the device was to provide active removal of urine without leakage and without the need for gravity-assisted drainage. The urinal was tested by 80 women from six countries. Although evaluated as 'good' or 'okay' by more than three-quarters of the women, nearly half the women found the device 'poor' for weight and size. Problems with reliability of the device were also common and the authors concluded that the current device needed further refinement but may have potential as an alternative to conventional urinals. Although this device is not currently on the market, at least one other powered device is available. However, there are no published reports on efficacy.

2. MALE HANDHELD URINALS

Most handheld urinals for men are somewhat similar, involving a narrowed neck opening into which the penis is placed. Some products come with a detachable or integral non-spill adaptor containing a flutter valve to impede back-flow of urine from the urinal. There are no published trials of such products.

A review paper by Vickerman [27] makes recommendations for selecting suitable urinals for men. A flat bottom urinal may be more stable (and less likely to spill) for those using a urinal in bed. Urinals made from soft plastic (jug-style or with a funnel) may be easier to grip for those with poor manual dexterity. Urinals designed to be attached to a drainage bag (for emptying the urinal) may also be helpful to men living at home with limited support.

Vickerman also suggests that home-made devices (such as empty wide-mouthed containers with a handle and lid (for example, those used for clothes-washing liquid or conditioner) may be a practical (and cheap) option for some men. For those with a retracted penis female urinals may be easier to use than male products.

3. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION

The literature [24] [25] [26] [27] suggests that successful use of urinals depends on many factors which are summarised below.

- Experimentation is often needed to find the optimum urinal for an individual. A 'library' of urinals (i.e. a collection of different types of urinals to be lent out to users for experimentation) has therefore been recommended [26] but rigorous cleaning methods are needed (see below).
- Clothing alterations can aid quick and easy use of a urinal. For men, extending the fly opening of trousers or replacing zips with Velcro can be helpful, as can boxer shorts. For women drop-front pants may be needed, particularly if mobility is limited.
- Disposable and reusable 'travel' hand-held urinals are available for both men and women. These urinals fold away to fit into a pocket and may therefore be more discreetly portable than conventional urinals.
- Some disposable urinals include superabsorbent polymer in their reservoirs which turns urine into a gel and help to prevent spillage. Sachets of superabsorbent polymer may also be added to reusable urinals.
- Use of a urinal is not always free from leakage and provision of absorbent chair or bedpads to protect bedding, clothes and furniture (particularly when testing out urinals) may be necessary.
- The limited range of urinal options in acute settings, where often only bedpans are available, has been criticised and the process of introducing hand-held urinals to hospital services has been described and recommended [29].
- When used by one individual in the home, urinals can be cleaned with soap and water between uses. But where urinals are shared (i.e. cleaned and used by others), or if a library of urinals is used then robust methods are necessary. Some urinals can be cleaned in a bedpan washer but cleaning methods vary with different designs and

materials and compliance with local infection control procedures will be needed.

4. RECOMMENDATIONS

- There is a wide range of female urinals and experimentation is likely to be necessary to identify the best one for an individual (dependent on their individual needs and abilities) (Grade of Recommendation C).
- A library of female urinals (used with robust cleaning methods) will help to facilitate experimentation (Grade of Recommendation C).
- Male urinals are less varied than female urinals, but may be supplemented by use of less conventional receptacles (e.g. jugs, home-made devices); experimentation will help to identify best options (Grade of Recommendation C).
- Section IV.3 addresses other more general recommendations regarding urinal use.

5. PRIORITIES FOR RESEARCH

- Further development of female urinals is encouraged, particularly for supine users and those unable to move to the edge of a chair.
- The range of male and travel urinals need to be evaluated to provide guidance for users and carers.

V. COMMODES AND BEDPANS

Toilets can be difficult to use by people with mobility problems and other disabilities. Toilet adaptations such as raised toilet seats, padded seats, and grab rails can be very helpful in enabling individuals to access the toilet easily and comfortably. Bottom wipers and bidets can also be useful. However, if access to the toilet is impossible, commodes and other toileting receptacles should be considered.

Commodes are devices that comprise a frame supporting a toilet seat with a pan (disposable or washable) beneath to receive urine and faeces. They are used independently of a toilet and may be static or mobile. Mostly, they are used by people with reduced mobility who find it difficult to access a conventional toilet. Bedpans are portable receptacles that may be used for passing urine or faeces while in bed or chair. Some female urinals (see section 4) may also be used to collect faeces.

General guidelines on patient assessment for product selection are discussed in Section II. Aspects of assessment that are particularly important regarding commodes and bedpans begin with appropriate indications for their use since Matsumoto and Inoue [30] reported that incontinent elderly persons or their caregivers misunderstand indications of commode use for incontinence. Other patient assessment elements include: a) physical characteristics of the person with incontinence (e.g. can an obese person fit on a commode and use its handrails?); b) mental acuity (e.g. will a person with dementia recognize a commode or bedpan as a device to be used for defecation?); c) need for supervision or foot supports whilst on the commode (what is the risk of falling?); d) mobility (e.g. does the person need a commode or bedpan?), ability to transfer and method of transfer to the commode (e.g. hoist, carer help, independent with transfer board), need for static or mobile commode (particularly when considering using commode over a toilet), postural stability and need for supportive commode, e) level of assistance needed and physical burden to caregiver involved; and f) personal preferences (e.g. comfort of bedpan type) including need for 'non-commode-like' appearance (e.g., particularly when used in own room, particularly the living room). Patient assessment findings need to be evaluated in terms of the safety and stability properties of a commode. The proximity of the area for waste disposal, storage facilities (i.e., the location / visibility of the commode in the household), the availability of privacy during defaecation, and length of time likely to remain on the commode (is there a need for a pressure-relieving commode cushion?), are additional factors to be considered.

Commodes (or better still toilets) are preferable to bedpans (which are relatively difficult to use and do not permit appropriate posture for passing urine/faeces). Bedpans are generally reserved for people who are confined to bed (e.g. post-operatively) and for whom safety (risk of falling) is an important assessment issue.

1. RESULTS

Fader [31] has reviewed the little work that has been done to evaluate existing commodes and bedpans and to identify the needs of users. An investigation of commode design by Nazarko [32] highlighted the problem of commodes providing poor trunk support for elderly and disabled people. Prolonged periods of sitting alone (for privacy) to enable defecation resulted in a risk of falls. Nazarko worked with a manufacturer to produce a design specification for a commode. Consultation with patients indicated that many would prefer to use a toilet. As a consequence, attention was focused in designing a shower chair which could also be used as a commode or could be wheeled over a toilet.

An evaluation of the four main types of commodes (standard; with adjustable height; with removable / drop-down arm; with adjustable height and removable / drop-down arm combination) was published by the UK Medical Devices Agency [33] [34]. One third of the 150 commodes on the UK market at the time were found to have backwards instability, and most of them scored poorly for aesthetics and comfort. A discussion of the results of this evaluation and its application to nursing was subsequently published by Ballinger et al. [35].

The maintenance of hospital commodes can be a problem and Gillan [36] complained about the poor condition of commodes in wards for elderly people. Commode cleaning has also been found to be poor [47] and a recent audit by Bucior and Cochrane [37] showed visible traces of faecal contamination on cleaned commodes. The authors concluded that it was necessary for ward staff to have clearly defined roles and responsibilities for commode cleaning. New commodes have been designed to overcome such problems by being easier to clean (e.g. design-bugs-out commode www.designcouncil.org.uk/our-work/challenges/Health/Design-Bugs-Out/Case-studies/Commode).

Naylor & Mulley [38] investigated the use of commodes in community-dwelling patients and the attitude of carers and users towards them (115 subjects and 105 carers). The main reasons for commode use were impaired mobility, difficulty climbing stairs and urinary incontinence. Main concerns were lack of privacy and embarrassment about using the commode, unpleasant smells and the poor physical appearance of the commode. Carers tended to view them negatively, particularly with regard to cleaning. Where commodes were used for defecation in a living area the authors highlighted the problem of odour that lingered even after a commode had been emptied, and recommended the use of a chemical toilet.

Thorough cleaning of commodes or bedpans after every use is necessary for hygienic purposes and to eliminate odours. Naylor & Mulley [38] report that typically a caregiver rather than the commode user empties and cleans a commode. No recommendations for cleaning a home commode or bedpan were found in the published literature. In institutional settings, large sinks with spray hoses or special sanitizing equipment are available. The size and shape of a bedpan or commode receptacle may be difficult to fit under a standard sink basin in the home. Whether certain commode cleaning products reduce any residual odour more than others is not known. Toilet bowl cleaning products are suitable for cleaning a commode or bedpan; many contain bleach or antibacterial ingredients but their effect on reducing odour of commodes or bedpans has not been studied. Gel formulations are advertised by manufacturers as being better able to cling to hard-to-reach surfaces than liquid agents. Use of a deodorizer can be considered (Level of evidence 4).

Nelson and colleagues [39] surveyed 147 spinal cord injured patients regarding their satisfaction and safety with the shower chairs (used for bowel care) used in the home. They found that around a half of patients were dissatisfied with their chairs and concerns expressed related to lack of hand access to the perianal area, difficulty in turning and rolling the chair and problems with keeping the chair clean. One third of patients experienced chair related falls and nearly a quarter reported pressure ulcers. Two-thirds of subjects felt that their safety was compromised.

The same group of researchers evaluated three shower chairs using video-taping, photography and questionnaires and produced performance criteria for the design of an optimal shower chair [40]. Pressure mapping devices were used to measure seat pressures on three subjects who tested all three bowel / shower chairs to inform seat design [41].

These researchers [42] then set about designing a more advanced commode-shower chair. It had lockable, swing-away armrests and lever activated brakes to facilitate transfers. To prevent pressure ulcers a chair frame and padding combination was designed to facilitate a seating position that distributed body weight and reduced pressure on pressure points. Cupped edgeless footrests were designed to reduce the risk of heel ulcers. An adapted version of this chair is now commercially available in the USA.

Matsumoto and Inoue [30] examined whether use of a commode in the home might prevent or delay nursing home admission of elderly people who were incontinent. A five-year follow-up of multiple predictors of institutionalization in elderly people in a rural town in Japan showed that 40% of incontinent men and only 17% of incontinent women used a commode. Use of a commode was not associated with institutionalization. The authors suggested several possible reasons: misunderstanding of appropriate indications for a commode based on the type of incontinence; physical burden in assisting a care recipient to use a commode that seemed no different than for cleansing after an incontinence episode; and inadequate muscle strength of the elderly for using either a Japanese-style or Western commode.

Bedpans and other portable receptacles are not well described in the literature. Wells and Brink [43] describe three general shapes of bedpans: concave, cutaway, and shovel. The concave pan has a rounded triangle shape that slopes back to front and a curved seat. The cutaway has a rounded triangle shape with a flatter seat and rolled edges that allow for handgripping. The shovel shape, commonly called a “fracture pan” is a wedge or rectangle shape that has a flattened end that goes under the individual and a handle at the distal end. Generally bedpans are considered to be unsuitable for defecation for safety and acceptability reasons. However, for individuals with specific needs (e.g. frequency and urgency of defecation) a portable receptacle may be beneficial. Although many portable urinals are now available for both men and women, very few are recommended for defecation [44] and they have yet to be formally evaluated.

Privacy and dignity need to be given high priority when patients need to use a bedpan or commode, in particular in institutional settings. Care needs to be taken when transporting patients on a shower

chair to maintain dignity and avoid revealing the patient's bottom.

Bottom wiping and cleaning can be difficult for people with disabilities, particularly manual dexterity problems, or caregivers. Simple moist wipes may be helpful and are widely available. Devices designed to assist with bottom wiping problems are on the market and portable bidets are also available, however there are no published trials of these products. Bedpans have other disadvantages including difficulty removing the bedpan from under an individual without spilling (particularly if the individual is obese), risk of spilling and odour when transporting the contents for disposal since none have lids, and lack of privacy during use.

2. SUMMARY

- There are major defects in most of the current designs of commodes, especially: poor aesthetics; poor trunk support; instability (i.e. a tendency to tip over easily); poor comfort; difficult to clean; poor pressure relief (**Level of Evidence 3**).
- If direct transfer to a toilet is impossible or unsafe a sani-chair / shower chair is usually preferable to a commode (**Level of Evidence 3**).
- The main concerns of users about commodes and bedpans are: lack of privacy; embarrassment over use; odour; poor aesthetics; poor perineal cleansing accessibility; and inadequate facilities for cleaning the devices in the home (**Level of Evidence 2**).
- Defecation on a bedpan or other portable receptacle presents problems of safety and unacceptability to users (**Level of Evidence 2**).

3. RECOMMENDATIONS

- If at all possible, access to a toilet should be made available for defecation (**Grade of Recommendation C**).
- If direct transfer to a toilet is impossible or unsafe, a sani-chair / shower chair should be offered in preference to a commode wherever possible (**Grade of Recommendation C**).
- If a commode is used, care should be taken to ensure good trunk support; that the chair is stable; and that methods of reducing noise and odour are offered (**Grade of Recommendation C**).
- With commodes and sani-chairs / shower chairs, the user's bottom should never be visible to others and transportation to the toilet and use of the toilet or commode should be carried out with due regard to privacy and dignity (**Grade of Recommendation C**).
- Bedpans and other portable receptacles should be avoided for defecation purposes (**Grade of Recommendation C**).
- Patients vulnerable to pressure ulcers should not sit on a commode / sani-chair / shower chair for prolonged periods (**Grade of Recommendation C**).
- The person should be given a direct method of calling for assistance when left on the toilet / commode / sani-chair / shower chair (**Grade of Recommendation C**).
- Cleaning of bedpans and commodes should be carried out after each use following local infection control policies (in institutional settings) (**Grade of Recommendation C**)
- There are no evidence-based published guidelines regarding frequency of cleaning or type of cleaning product. However, thorough cleaning after bowel evacuation (to avoid odour and maintain aesthetics) is important, together with rinsing after urine has been passed. Cleaning needs may vary according to personal hygiene standards and offensiveness of urine/faecal smells (**Grade of Recommendation C**).

4. PRIORITIES FOR RESEARCH

- Studies are needed to determine how to make toilets accessible to as many users as possible. These may lead to improved designs for toilets and associated equipment and / or strategies for toileting.
- Studies are needed to determine which commode / sani-chair / shower chair designs best meet performance and safety requirements.
- Development of better commodes designed to overcome the limitations identified

VI. ABSORBENT PRODUCTS

1. INTRODUCTION

Absorbent products (commonly known as pads) are available in a wide range of sizes and absorbencies encompassing light through to very heavy incontinence. Most pads are bodyworn but some are used on the bed or chair (underpads, see Section 6.2); in this section the term 'pad' refers to bodyworn absorbent products. Broadly speaking, absorbent products can be divided into two main sub-groups: those suitable for light incontinence (usually smaller products) and those suitable for moderate-heavy incontinence (usually larger products). Manufacturers generally indicate the severity of incontinence that each product is designed to accommodate, but see the discussion in Section VI.4. Although absorbent pads are most commonly used for urinary incontinence they are also used by individuals for both faecal and urinary / faecal incontinence; however, there have been no published studies which specifically address this issue.

Incidental findings from evaluations of products indicate that absorption capacity alone does not

determine whether a user will choose to use a product. Some users may have frequent, low flow-rate loss of small volumes of urine ("dribble"), whilst others may be dry for days but then have a higher volume, higher flow-rate incontinence incident ("gush" or "flooding". Both may prefer to use pads for light incontinence. Mobile and independent community-dwelling women of all levels of incontinence are reported to generally prefer small pads and are often willing to change them frequently rather than use larger products and change them less often [45]. Conversely, dependent, immobile individuals may prefer the security of larger products despite relatively low urine volumes due to their dependence on others for pad changing.

More recently studies have focused on the use of pads by men. Teunnissen and Lagro-Jansson [46] interviewed 56 men with UI of which only nine used absorbent pads. They concluded that men use pads less frequently than women, have little knowledge about purpose-built pads, are more likely to construct their own pads out of absorbent materials such as towels and are less satisfied with pads than women. Furthermore there are indications that men may prefer other devices such as urinary sheaths [47] (see Section VII Sheaths).

Studies that have collected and weighed used pads to measure urine volume have found overlap between the quantities contained by pads from different sub-groups of users; thus in a study of insert pads for moderate-heavy incontinence used by older people in residential care around 15% of insert pads for moderate-heavy incontinence contained less than 100g of urine [48] and in a study of older women with light incontinence living in the community about 10% of insert pads for light incontinence were found to contain more than 100g of urine [49].

It might be speculated that the number of pads used per day might be a good measure of degree of urinary incontinence, but this has not been found to be the case in nursing home residents in Norway [50]. Pads were collected and weighed from residents in six homes, but a poor correlation was found between the number of pads used and the mass of leaked urine measured over 48 hours. The authors concluded that this was due to pad changes being carried out at routine times by healthcare assistants.

It is possible that a proportion of patients are simply provided with inappropriate products that exceed or fall short of the absorption capacity they require. One study investigated this issue [51] and found that patients were more satisfied with their products once their urine loss had been determined by pad weighing and appropriately absorbent products were provided. But many of these patients were using inadequate products to start with (such as pads comprising tissue paper) and firm conclusions could not be drawn. In practice, it is probably hard to justify the need for pad weighing to determine which absorbents should be provided and if there is doubt about which group a patient falls into then the patient should be offered small pads for light incontinence in the first instance and the size of pad titrated upwards as necessary.

General guidelines on patient assessment for product selection are discussed in Section II. Aspects of assessment that are particularly important regarding absorbent pads are frequency / severity of leakage, day / night incontinence, gender (some products are designed for, or are better for, men / women than others), ability to change pad independently / need for carer, pad changing position (standing / lying), laundry / drying facilities, individual priorities (e.g. need for discreetness), personal preference for design / materials (washable / disposable), lifestyle (at home / travel / work etc).

Aspects of absorbent pad performance have been identified and prioritised (during interviews) by men and women taking part in a series of clinical trials of such products [19]. There was considerable consistency across patient groups (light / heavy, men / women) with the ability of a product to hold urine without leakage being the top priority, and the following aspects also being considered to be of high priority: discreetness, containment of smell, ability to stay in place, comfort when wet and ability to keep skin dry.

2. ABSORBENT PRODUCT CATEGORIES

Absorbent products may be classified into two broad categories - disposable (single-use) and washable (reusable) - with each category dividing into two sub-categories: bodyworn products (worn on the person) or underpads (placed under the person). Within each sub-category are different design groups such as diapers and pull-ups which are subdivided by size (to fit users of different sizes) and / or absorbency (to cater for different severities of incontinence). Some designs are further subdivided into those intended for men, women or children. This classification is shown in **Table VI-1**.

- ***Bodyworn*** absorbent products can be divided into four main design groups:

- ***Inserts*** (sometimes called liners or, in the case of small pads, shields) are held in place by close-fitting underwear or stretch mesh briefs (**Figure VI-1**). Some patients experience problems with keeping pads in place using the commonly supplied net pants. As a result, many use more robust stretch pants purchased privately (e.g. cotton / Lycra, etc). Many disposable inserts (**Figure VI-2 and Fig VI-3**) have an adhesive strip on the back to help secure them and may have an indicator that changes colour when the pad is wet to signal the need for a change. They may have longitudinal, elasticated standing gathers of hydrophobic material intended to impede lateral leakage of urine and faeces. They

Table VI-1. Classification of absorbent continence products

Categories:	Disposable (single use)		Washable (reusable)	
Sub-categories:	Bodyworns	Underpads	Bodyworns	Underpads
Design groups*	Inserts Diapers Pull-ups Pouches	Bedpads Chairpads	Inserts Diapers Pull-ups Pouches	Bedpads Chairpads
Sub-groups	Groups sub-divide according to the severity of incontinence (light or moderate / heavy) and the gender of the intended users (M, F or unisex).			
* The products within a given design group may vary considerably in their features and their constituent materials.				

are sometimes rectangular but are more usually shaped to fit the body more snugly. Elastication at the legs may also be used to enhance fit. Washable inserts (**Figure VI-4**) are usually more simply designed than disposable inserts, with no elastication and are either shaped or a simple rectangle. Inserts are made in a wide range of sizes suitable for light through to very heavy urinary incontinence. For light faecal incontinence, the liner may be a small cotton gauze dressing placed against the anus and held in place by the cheeks of the buttocks (**Figure VI-5**).

- ***Diapers*** (sometimes called all-in-ones or briefs) are adult-size versions of babies' diapers. Disposable diapers (**Figures VI-6**) usually have elasticated waist and legs and self-adhesive tabs (usually resealable), and often a wetness indicator and standing gathers. More recently modified diapers have been introduced that fasten round the waist before the front is pulled into position and secured, to enable users to apply the diaper whilst standing (**Figure VI-7**). Washable diapers are usually elasticated at the waist and legs and are fixed with Velcro or press-studs (**Figure VI-8**). Diapers are intended for moderate to very-heavy incontinence.

- ***Pull-ups*** are similar in construction to trainer pants for toddlers. The absorbent material is built into a pull-up pant and is either limited to the crotch area or distributed throughout the pants (**Figures VI-9 to VI-11**). Disposable pull-ups (**Figure VI-9**) are usually elasticated throughout the pants to give a close fit. Both disposable and washable pull-ups have versions for different levels of incontinence. Washable pull-ups for light incontinence are often known as pants with integral pad (**Figure VI-11**).

Some people use less conventional or home-made systems either instead of or as well as the designs described above. In particular terry-towelling squares may be used by those with heavy incontinence. These may be formed into briefs by folding into different configurations and fastening with pins and covered with plastic pants as a waterproof barrier. It is known that such pants may also be worn over more conventional designs in an attempt to reduce leakage and / or odour.

"Body" garments (like vests which have a crotch section which opens and closes with snap fasteners, much like those manufactured for babies) may be helpful to hold pads in place well and may reduce the rustling noise from plastic backing materials.

- Male ***pouches*** (sometimes called shields, guards or leaves) are for lightly incontinent men and are designed to fit around the penis and sometimes the scrotum too (**Figures VI-12 and VI-13**). All are worn with close-fitting underwear or stretch mesh briefs. An adhesive strip is often provided on the disposable versions to help hold them in place.

- ***Underpad*** absorbent products are usually simple rectangles of different sizes to be used on the bed or chair (**Figure VI-14**). Washable underpads (**Figure VI-15**) may have a high friction backing or have 'wings' for tucking beneath the mattress of single beds to help keep them in place. Underpads vary widely in absorbency with less absorbent products being used as 'back-up' with bodyworn absorbents and more absorbent products being used as sole protection on the bed at night.

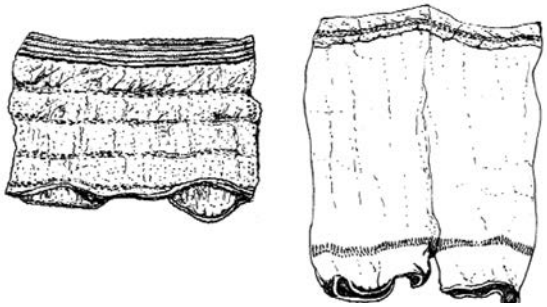


Table VI-1. Mesh pants with (right) and without (left) legs, for securing incontinence pads in position

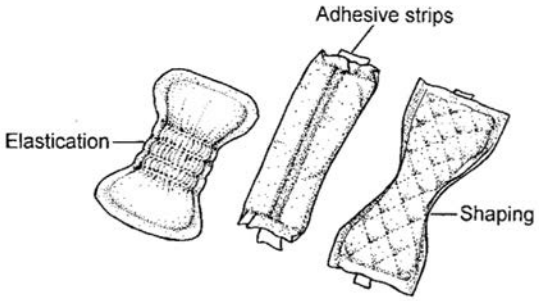


Table VI-2. Disposable inserts for light incontinence

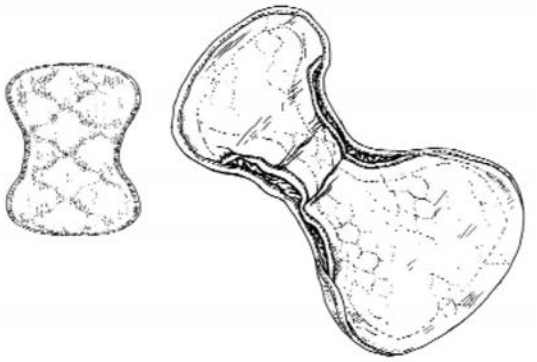


Figure VI-4: Reusable inserts for light (left) and moderate / heavy (right) incontinence.

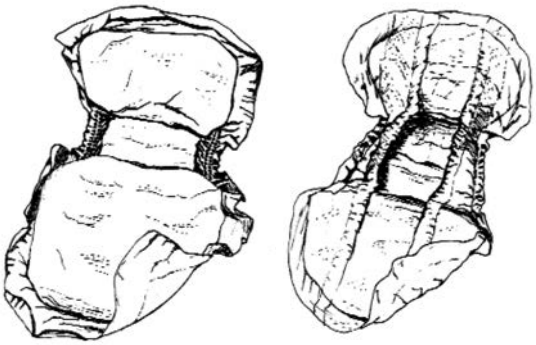


Figure VI-3: Disposable inserts with (right) and without (left) standing gathers, for moderate / heavy incontinence.

Figure VI-5: Liner for light faecal incontinence. It is positioned against the anus and held in place by the cheeks of the buttocks

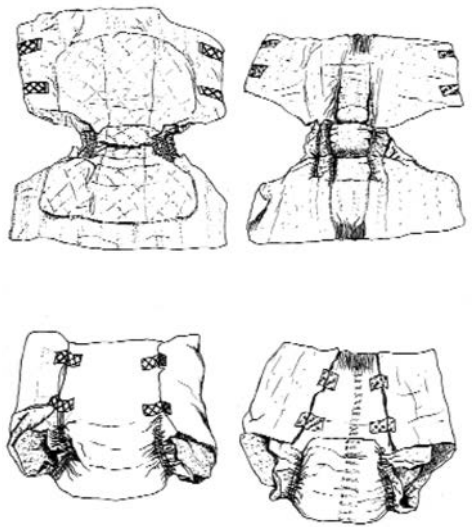


Figure VI-6: Disposable diapers with (right) and without (left) standing gathers, for moderate / heavy incontinence. Diapers are shown open (top) and with the tabs secured (bottom).

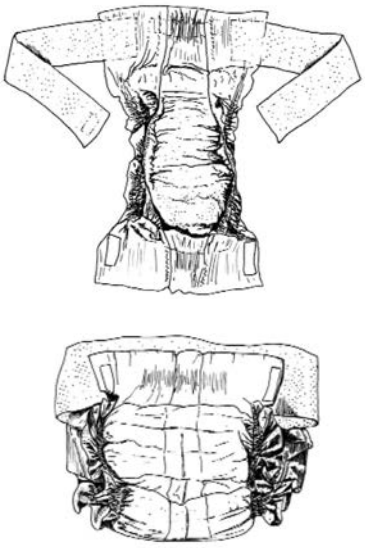


Figure VI-7: A modified (T-shaped) diaper. The waist band (left) is secured first and then the front pulled up and secured in position (right).

Figure VI-8: A reusable diaper

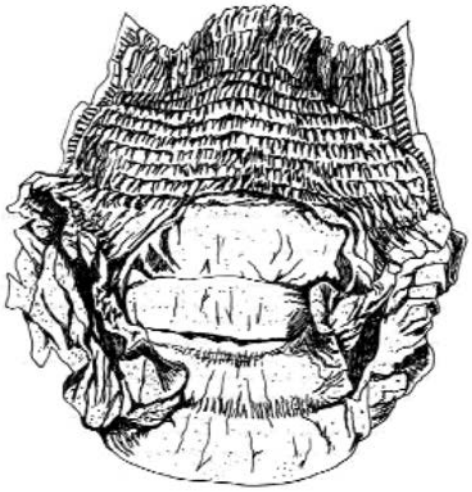


Figure VI-8: A disposable pull-up

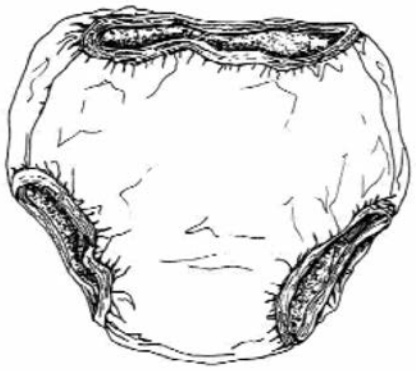


Figure VI-10: A reusable pull-up for heavy inconti- nence.

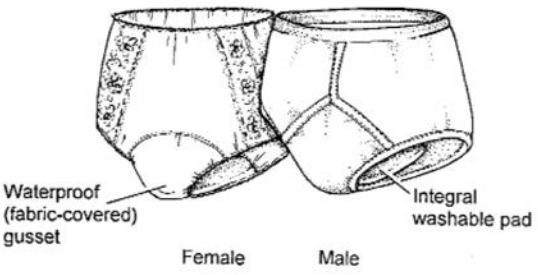


Figure VI-11: Reusable pull-up pant (also known as pants with integral pad) for lightly incontinent men (right) and women (left)

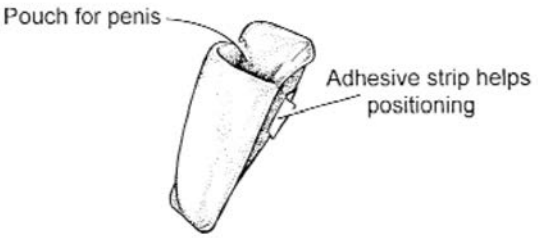


Figure VI-12: A disposable pouch for men

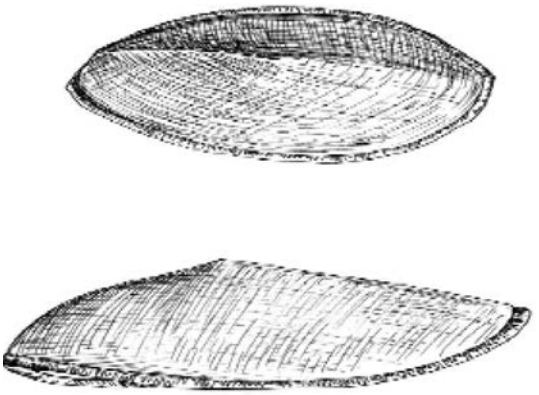


Figure VI-13: Reusable pouches for men: side view (left) and front view (right).

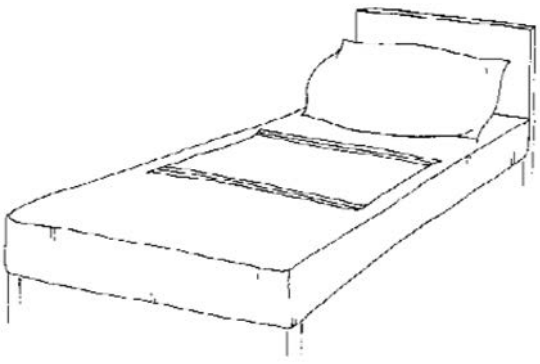


Figure VI-14: A disposable underpad.

3. ABSORBENT PRODUCT MATERIALS

Absorbent products – disposable or washable – usually comprise three main layers: an absorbent core sandwiched between a water-proof backing beneath and a water-permeable coverstock (or topsheet) next to the wearer's skin.

The main component in disposable absorbent cores is invariably some kind of fluffed wood pulp fibres, but most also contain some powdered superabsorber (sometimes referred to as SAP (superabsorbent polymer) or AGM (absorbent gelling material)), which is often concentrated in the crotch region. Superabsorbers hold much more urine – weight for weight – than fluff pulp and retain it far more tenaciously under pressure. They are usually based on cross-linked salts of polyacrylic acid whose chemistry can be varied according to the balance of properties such as absorption capacity and absorption speed desired. Some thermoplastic fibres are also sometimes included in absorbent cores to reduce core break up and the collapse of the structure when wet. It is increasingly common for absorbent cores to comprise two or more layers, each designed to perform a different function. For example, an upper layer might comprise low absorbency fibres engineered to receive and distribute urine efficiently and maintain a dry layer next to the skin, while lower layers provide absorption capacity. Some disposable products have 'breathable' plastic backings designed to reduce skin occlusion.

Washable absorbent cores are usually made from a needlefelt or knitted fabric comprising rayon and / or polyester fibres. A variety of polymers are used for the water-proofing. In general, the thicker, stiffer materials are more durable (the durability of the plastic backing often determines the lifetime of the product) but less comfortable. Topsheets are usually made from either cotton – which is hydrophilic and intended to have good dry comfort – or polyester – which is hydrophobic and intended to have good wet comfort.

Concern for the environment and also for controlling costs has led to an increase in the number of washable products available on the market. An important consideration in the comparison of washable and disposable designs is the relative environmental cost, particularly disposal (landfill) costs of disposable designs and energy costs associated with laundering the washables. A recent report on baby diapers concluded that there was no significant difference in environmental impact between three diaper systems (disposables, home and commercial laundered washables) although the types of impacts did vary [52].

4. ABSORBENT PRODUCT CAPACITY AND USER REQUIREMENTS

Pads come in a range of absorbencies to cater for users with different levels of urinary incontinence and, understandably, purchasers wish to know how much urine available pads will hold. But there is no simple answer: a pad does not have a volume of urine below which it is guaranteed not to leak; rather, the probability of success decreases as the volume of the urine increases. However, for higher absorbency pads the performance falls away more slowly with increasing urine volume than it does for lower absorbency products.

This is a complex concept to communicate in sales literature and product packaging and so companies commonly quote a simple absorption capacity figure. Some use the volume of fluid a pad will hold in a laboratory test - usually international standard ISO 11948-1[53] - but this figure can be very misleading. Although it has been show to correlate well with the leakage performance of pads for some groups of users (see Section VI.7.2), the volume of urine which a pad will hold when tested with ISO 11948-1 is enormous compared with how much it will hold in real use. For this reason, some companies prefer to quote a "working capacity", which might be calculated as some proportion (companies vary in the proportion they use) of the capacity in the laboratory. However, this is still misleading as it implies that the pad will not leak until the working capacity is exceeded. A simple, valid and widely accepted solution to this problem has yet to be devised.

It is equally difficult to determine the needs of users in terms of the volume of urine they need their pads to hold. Not only can different users leak widely differing volumes from each other but also a given user may leak widely differing volumes on different occasions. This means that, like pad performance, users' needs cannot be easily quantified. However, a number of studies have been published on work with pad users described as being lightly incontinent of urine in which the median and 90th percentile urine volumes in used pads have been of the order of 15ml and 100ml, respectively [54]. Similarly, a number of studies of pad users described as having moderate-heavy urinary incontinence have yielded corresponding figures of about 250ml and 600ml [54]. Accordingly, in this chapter the material is divided – somewhat simplistically – into that which relates to light incontinence and that which relates to moderate-heavy.

But the published work also makes it clear that some products work better for users whose inconti-

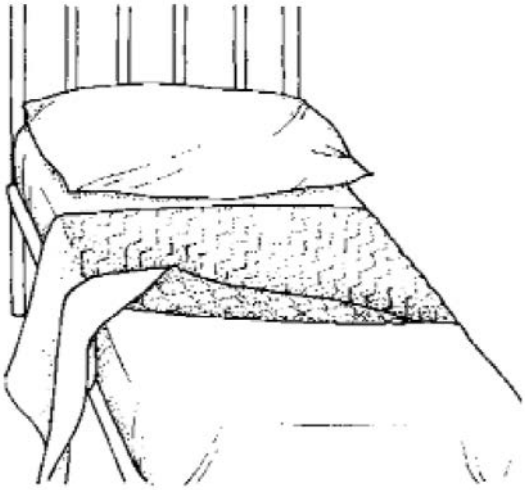


Figure VI-15: A reusable underpad.

nence is towards the lighter or the heavier end of the spectrum within each of these two groups and so, where necessary in the text and tables that follow, these distinctions are made by dividing light incontinence into "light LIGHT" and "heavy LIGHT"; and moderate-heavy incontinence into "light HEAVY" and heavy HEAVY".

5. ABSORBENT PRODUCTS FOR WOMEN WITH LIGHT URINARY INCONTINENCE

There are four main product designs for women with light incontinence (**Table VI-2**). In addition menstrual pads are known to be frequently used for light urinary incontinence. The disposable pull-up group are relatively expensive, single-use items and are seldom used for light incontinence except as 'emergency' items. Underpads are not commonly used for light incontinence.**(Figure VI-16)**

Aspects of assessment that are particularly important regarding pads for women with light incontinence include frequency / severity of leakage, day / night incontinence individual priorities (e.g. need for discreetness), personal preference for washables / disposables, lifestyle (home / travel / work).

a) Quality of data

A small number of robust comparative evaluations of absorbent pads for lightly incontinent women have been published and there has been a Cochrane review [55]. A recent study has compared the most common designs: disposable inserts, menstrual pads, washable inserts and washable pants with integral pad. One study has compared a range of disposable inserts and menstrual pads and there have been comprehensive single group studies of disposable inserts and washable pants with integral pads. A further study has compared specially made experimental products that have differed from one another in carefully controlled ways enabling more specific questions about product materials and design to be addressed.

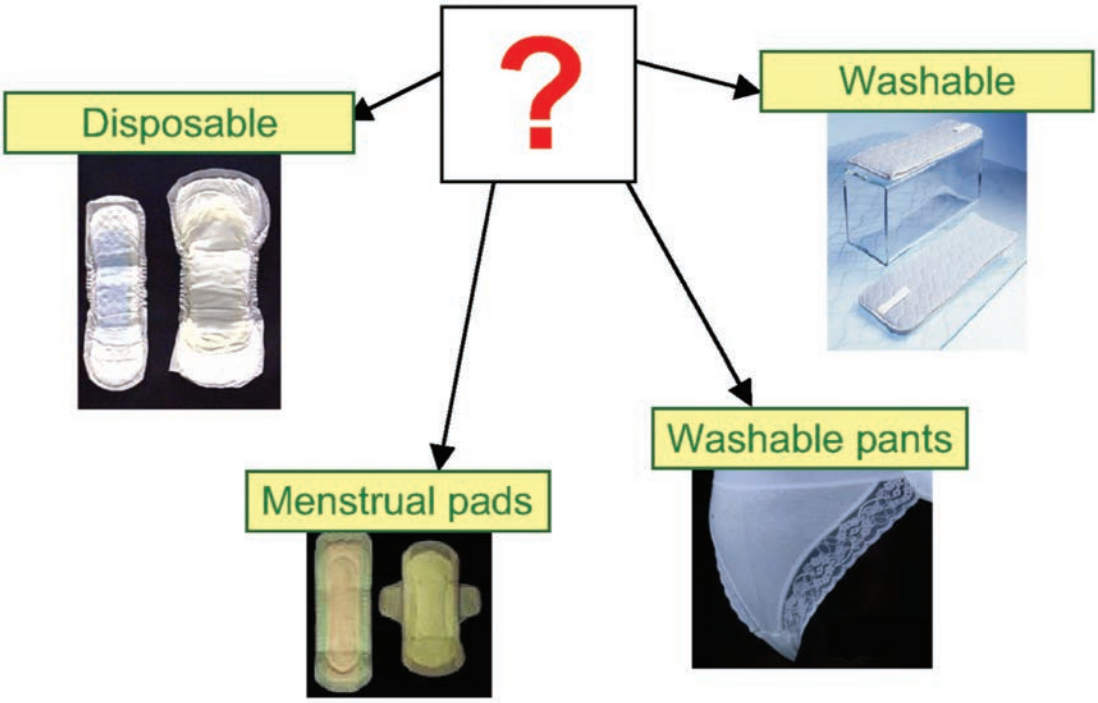
b) Results

Using a crossover design, Fader et al [54] compared disposable inserts, menstrual pads, washable pants with integral pad, and washable inserts. Three products were selected (based on previous study results) to represent each design and each product was tested for one week (three weeks for each design block, total 12 weeks). Order was randomised. Product performance was characterised using a validated questionnaire to evaluate pad performance (leakage, discreetness etc) with a five point scale (very good – very poor) at the end of each week of product testing. A pad change and leakage diary was used to record severity of leakage from pads (three-point scale: a lot, a little, or no leakage), and numbers of laundry items and pads used were recorded to estimate costs. Skin health changes were recorded weekly. At a final interview preferences were ranked (with and without costs), acceptability of the design recorded (highly acceptable – totally unacceptable) and overall opinion marked on a visual analogue scale (VAS) of 0-100 points (worst design – best design). This VAS score was used to estimate cost-effectiveness.

Eighty-five women (mean age 60) completed the study and 8691 used pads were weighed. The disposable insert was significantly better than the other designs on most variables except for discreetness. For leakage prevention, overall acceptability and preference, disposable inserts were found to be significantly better than menstrual pads, which were better than washable pants with integral pad, which were better than washable inserts. There was no clear benefit for skin health using either washable or disposable designs. Most women preferred the disposable insert pad but some preferred the other cheaper designs (6/85 preferred menstrual pads;

Table VI-2: Bodyworn absorbent products for women with light urinary incontinence

	Disposable	***Washable***
Design groups	Inserts (Fig VI-2)	Inserts (Fig VI-4)
	Pull-ups ie pants with integral pad (Fig VI-8)	Pull-ups ie pants with integral pad (Fig VI-10)
	Menstrual pads	



Product category	User characteristics / priorities / contexts which:		Notes
	FAVOUR use	DISCOURAGE use	
Disposable inserts	• Reliable leakage prevention is a priority (B)	• Low cost is a priority (B) • Discretion is a priority (B)	• Some users prefer a mix of products eg using different products at home / when out; or during the day / night.
Disposable menstrual / sanitary pads	• Low cost is a priority (B)	• Incontinence is heavy LIGHT (B)	
Washable pants	• Low cost is a priority (B) • The design concept is acceptable / preferred (B) • Incontinence is light LIGHT (B/C)	• Adequate laundry facilities are not available (C) • The design concept is unacceptable (C) • Carrying used pads when out is an issue (C) • Incontinence is heavy LIGHT (B/C)	
Washable inserts	• As for washable pants, but prefer separate pad (B/C)	• As for washable pants (B/C)	

Figure VI-16: Designs of pads for women with light urinary incontinence. For definitions of light LIGHT and heavy LIGHT, see Section VI.4. (Grade of recommendation in brackets)

13/85 preferred washable pants), both of which were >50% cheaper to use than disposable inserts. Washable inserts were significantly worse than the other designs (72/85 found them unacceptable). Overall there were generally more practical problems with washables, particularly when away from the home (**Level of Evidence 1**).

The authors concluded that allowing women to choose their preferred design of absorbent product (or combination of different designs for different circumstances) would be more cost-effective and provide better patient satisfaction than provision of disposable insert pads (the most expensive product) alone.

Clarke-O'Neill et al. [18] compared the range (12 products) of disposable inserts for lightly incontinent women available in the UK in 2000. Products were tested by 60 community-based women aged 50 years or older who currently used products similar to those to be evaluated. Products were evaluated using a pad performance questionnaire and a pad leakage diary. As a group, the products performed well in terms of their ability to hold urine without leakage. However, the 'overall opinion' scores of the testers showed large differences between products with 88% of subjects scoring the most successful insert as Good or OK compared with 51% for the least successful product ($p<0.001$) (**Level of Evidence 2**).

A similar study by the same research group [56] compared all 10 washable pants with integral pad for lightly incontinent women available in the UK in 1999. Seventy-two community-based women who usually used absorbent products for light incontinence tested each product for one week each. Leakage performance was found to be disappointing with 69% (CI: 59-78) of the best performing product not leaking at all with 10g of urine, compared to 40% (CI: 29-51) for the least successful product. Again subjects' 'overall opinion' scores showed wide differences between products with the best performing product scoring 85% Good or OK compared with 34% for the least successful product (**Level of Evidence 2**).

Baker and Norton [57] evaluated six small disposable inserts and two menstrual pads (available in the USA in 1991) with 65 community dwelling women. The products were rated using an evaluation questionnaire and daily diary of pad use. The two menstrual pads (which were the least expensive pads in the study) scored significantly higher than many of the incontinence products although neither was the most popular pad. The authors concluded that women should try a 'maxi' menstrual pad first and then move onto a higher capacity (incontinence) pad if this was inadequate. However, this study was carried out more than 10 years ago and products have changed considerably since then (**Level of Evidence 2**).

Thornburn et al. [16] studied 'wet comfort' using small disposable pads that had been experimentally made using different combinations of materials in an attempt to reduce 'wetback' (the tendency of pads to allow urine to escape back on to the wearer's skin). Twenty women tested the pads. Whenever differences in wet comfort, absorbency or overall performance were found they were in the expected order but differences were small and few reached statistical significance. The clinical value of including technically superior materials was not strongly supported. However, this was a small study and may have had insufficient power to detect significant differences (**Level of Evidence 2**).

More recently Erekson and colleagues [58] measured the wet-back performance of a range of 10 different branded products. This was a laboratory experiment involving two patients (of different BMIs) sitting on pre-wetted pads. Results showed that neither size nor price of the pads had any effect on the measured product performance. However it is difficult to determine how much such measurements reflect clinical performance.

c) Summary

There is robust evidence that disposable inserts are more effective in terms of leakage and more acceptable than menstrual pads, washable pants and washable inserts (**Level of Evidence 1**). Menstrual pads are cheaper and washable pants cheaper still (on a per-use basis) and are acceptable to many, particularly those with lighter incontinence and particularly when used at home. Washable inserts are not acceptable to most women. The user characteristics, priorities and contexts which favour or discourage the use of the different product designs are summarised in **Figure VI-16**.

d) Recommendations

- Disposable inserts are recommended as the most effective and preferred absorbent product for women with light incontinence (**Grade of Recommendation B**).
- Menstrual pads or washable pants may be sufficient for some patients with very light incontinence and are cheaper (**Grade of Recommendation B**).
- Washable inserts are not recommended (**Grade of Recommendation B**).
- Combinations of designs for different situations (e.g. disposable inserts for going out, washable pants with integral pad for staying at home) are likely to provide optimum management in terms of patient needs and cost-effectiveness, and product advice and provision (where purchased by institutions / services) should reflect this (**Grade of Recommendation B**).
- See also the general recommendations relating to pad selection in Section VI.11 and to washable pads in Section VI.12.

e) Research priorities

- Because the performance of washables is generally poor (particularly for leakage) compared to disposables, the development of better washable products is a priority.
- The use of combinations of designs for different situations needs to be evaluated.

6. ABSORBENT PRODUCTS FOR MEN WITH LIGHT URINARY INCONTINENCE

There are five main product designs for men with light urinary incontinence (**Table VI-4**). However, disposable and washable insert pads are often unappealing to men as they are frequently marketed specifically at women and bear a strong resemblance to menstrual pads. Anatomical differences are also likely to mean that they are less effective for men. Pouch, shield and leaf products (**Figures VI-11 and VI-12**) are designed to be more suitable for men by containing the penis or penis and scrotum.

Aspects of assessment that are particularly important regarding pads for men with light incontinence include frequency / severity of leakage, day / night incontinence, retraction of penis, individual priorities (e.g. need for discreetness), personal preference for washables / disposables, and lifestyle (home / travel / work).

Only one study has been published which has evaluated absorbent products for men with light urinary incontinence (59]. It compared the four main absorbent designs of products available in the UK in 2003: disposable insert pads, pouches and leafs and washable pants with integral pad. All six leaf products (five disposable and one washable) and all six pouches (all disposable) on the UK market in 2003 were evaluated, together with a selected disposable insert pad and a selected washable pant with integral pouch (chosen to represent their respective designs). Seventy men with light urinary incontinence completed the 14 week study and filled out product performance questionnaires at the end of testing each product for a week. Products were supplied in random order within their design group and the design group order was also randomised. Pad leakage diaries were used to record product performance and used pad weight. At the end of testing each design a design performance questionnaire was completed. 'Overall opinion' was used as the primary outcome variable. Results showed that the pouch design performed significantly worse than the leaf and the insert design. The most common problems with the pouch were staying in place and difficulties re-inserting the penis in the pouch once the pouch was wet. The leaf designs had the best leakage scores, but one product was significantly better than the other leafs (Tena). The disposable insert was also effective for leakage prevention and was substantially cheaper than the leaf designs. The washable leaf was the least successful of the leaf designs. The washable pants with integral pad received polarised overall opinion scores (loved or hated) and scored well for staying in place but poorly for leakage (Level of evidence 2). The user characteristics, priorities and contexts which favour or discourage the use of the different product designs are summarised in **Figure VI-17**.

a) Recommendations

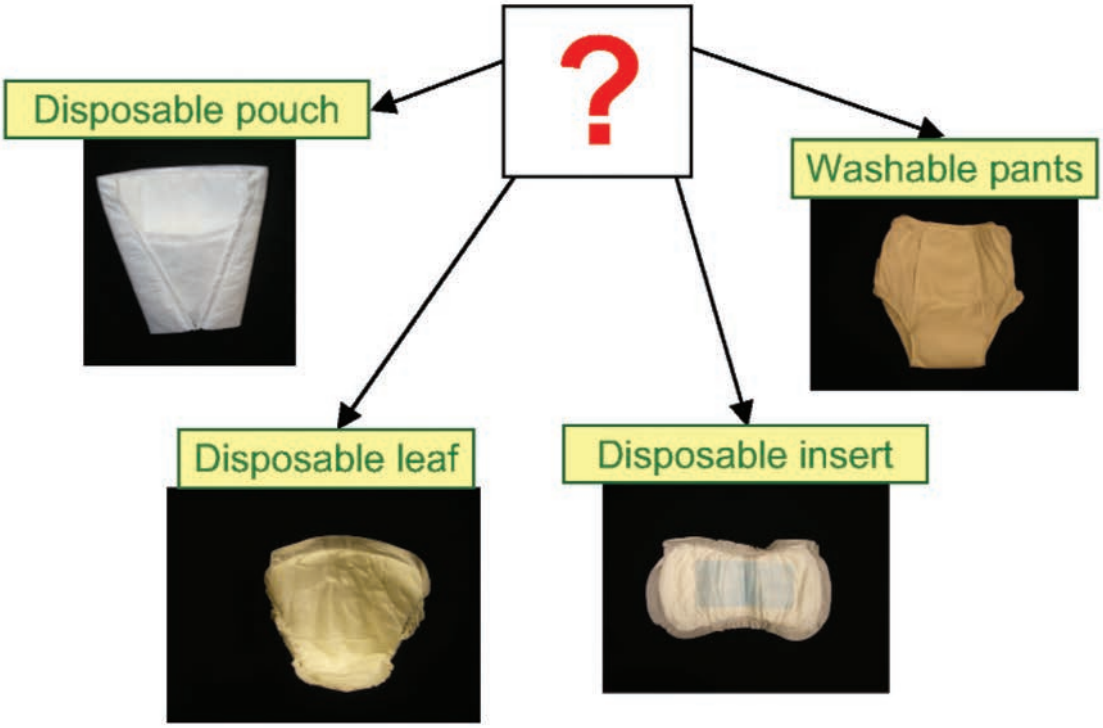
- Disposable leafs are recommended as the most acceptable and effective design for men with light incontinence, but some men prefer other designs which should be considered as alternatives (**Grade of Recommendation B**).
- Simple insert pads are cheaper and may be acceptable to some men (**Grade of Recommendation B**).
- Washable pants with integral pad are likely to be most suitable for men with very light incontinence who have difficulties keeping an insert or pouch in place (**Grade of Recommendation B**).
- See also the general recommendations relating to pad selection in Section VI.11 and to washable pads in Section VI.12.

b) Research priorities

Because the performance of washables was generally poor (particularly for leakage) compared to disposables, the development of better washable products is a priority.

7. ABSORBENT PRODUCTS FOR MEN AND WOMEN WITH MODERATE-HEAVY URINARY INCONTINENCE

There are at least 12 absorbent product designs for men and women with moderate-heavy urinary incontinence (**Table VI-5**). The most commonly used products are disposable bodyworn inserts and diapers (**Figures VI-3 and VI-6**). More recently, modified diapers (T-shaped diapers, **Figure VI-7**) have been introduced which can be applied by the wearer whilst standing. Pull-ups are also a relatively new innovation and comprise an absorbent pad integrated into a disposable elasticated pant (Figure VI-9). Washable counterparts to most disposable bodyworn designs are available but they have a much smaller market, where they are available. They are made from a variety of natural and synthetic materials. Disposable and washable bedpads are used on the bed at night with or without the support of a bodyworn product. Disposable and washable chairpads are used either without a bodyworn product (in which case the individual must sit directly on the pad with no underpants on) or in combination with bodyworn products to protect chairs from any leakage from the bodyworn. Both practices place an underpad on display and mark the individual as being incontinent and are therefore to be discouraged.



Product category	User characteristics / priorities / contexts which:		Notes
	FAVOUR use	DISCOURAGE use	
Disposable pouches	• Discretion is a priority (B/C) • Using a specifically male product is important (C)	• Penis is retracted (C) • Incontinence is heavy LIGHT (B/C)	
Disposable leafs	• In general (B/C)		• Appropriate whether or not penis is retracted
Disposable inserts	• Low cost is a priority (B/C) • Male specific product unimportant (C)		
Washables	• Incontinence is light LIGHT (B/C) • Low cost is a priority (B/C) • Design concept is acceptable / preferred (C) • User is mobile and active (B/C)	• Adequate laundry facilities are not available (B/C) • Design concept is unacceptable (B/C) • Carrying used pads when out is an issue (B/C) • Incontinence is heavy LIGHT (B/C)	

Figure VI-17: Designs of pads for men with light urinary incontinence. For definitions of light LIGHT and heavy LIGHT, see Section VI.4. (Grade of recommendation in brackets)

Table VI-4: Bodyworn absorbent products for lightly incontinent men

	Disposable	***Washable***
Design groups	Inserts (Fig VI-2)	Inserts (Fig VI-4)
	Pouch (Fig VI-11)	Pouch (Fig VI-12)
		Pull-ups ie pants with integral pad (Fig VI-10)

Aspects of assessment that are particularly important regarding absorbent pads for moderate / heavy UI are frequency / severity of leakage, day / night incontinence, gender (some products are better for men/women than others), ability to change pad independently / need for carer, pad changing position (standing / lying), laundry / drying facilities, individual priorities (e.g. need for discreetness), personal preference for design / materials (washable / disposable) and lifestyle (at home / travel / work etc).

a) Quality of data

There have been two recent clinical trials comparing the main designs of disposable bodyworn pads (one also included washable designs) which are included in a Cochrane review [55]. There have been no trials of underpads for the last 15 years. There have also been a large number of comparative studies of absorbent products for moderate-heavy incontinence but most are more than 10 years old and evaluated products that are no longer available. Furthermore, changes in materials and design features mean that it is impossible to generalise any particular findings to products of today. Brink [60] identified 30 studies of absorbent products published between 1965-1990. Some robust multi-centre international studies have examined the correlation between laboratory testing and the leakage performance of products clinically.

b) Results

1. Evaluations comparing different designs of disposable and / or washable bodyworn absorbent products for urinary incontinence

Fader et al. [54] carried out two clinical trials of absorbent products for moderate-heavy incontinence; one involving subjects in the community and the other subjects in nursing homes. In the community-based trial 85 moderate / heavily incontinent adults (urinary or urinary / faecal) living in their own homes [49 men and 36 women) were enrolled, and tested three (or two) products from each of five design categories (total of 14 test products): disposable inserts (with mesh pants); disposable diapers; disposable pull-ups; disposable T-shape diapers; and washable diapers. All products were provided in a daytime and a (mostly more absorbent) night-time variant. Products were selected based on having similar scores for absorbency across the designs (Rothwell scores, [53] see below) and performance data from pilot studies. In the nursing-home-based trial 100 moderate / heavily incontinent adults (urinary or urinary / faecal) living in a total of 10 nursing homes (27 men and 73 women) evaluated one product from each of the four disposable design categories above. Products were selected on the basis of product performance from the community-based trial and, again, day and night-time variants were provided.

Product performance was characterised using validated questionnaires which asked the participants (in the community-based trial) or carers (in the nursing home based trial) to evaluate various aspects of pad performance (leakage, ease of putting on, discreetness etc) using a five point scale (very good – very poor) at the end of the week (or two weeks for the nursing-home-based trial) of product testing. In addition, participants / carers were asked to save individual used pads in bags for weighing and to indicate the severity of any leakage from them on a three-point scale (none, a little, a lot). These data were used to determine differences in leakage performance. Numbers of laundry items and pads used were recorded to estimate costs, and skin health changes were recorded by the participant or by the researchers. At the end of testing participants were interviewed and ranked their preferences (with and without costs), stated the acceptability of the design (highly acceptable – totally unacceptable) and recorded their overall opinion on a visual analogues scale (VAS) of 0-100 points (worst design – best design). A pad changing experiment was conducted with 12 women from the nursing home based trial to determine any differences between product designs. Under idealised conditions the different designs were applied (by the same carers) in random order for each patient and the speed of pad changing was timed using a stop-watch.

Findings from the community-based and nursing home trials were broadly similar. The leakage performance for the disposable inserts was worse than the other designs for day and night and disposable pull-ups were preferred over inserts for the daytime. The new T-shape diaper was not better overall than the traditional disposable diaper. But there were important differences in performance and preference findings between men and women from both trials

Table VI-5: Absorbent products for moderate-heavy adult incontinence

	Disposable (single use)		Washable (reusable)	
Type	Bodyworns	Underpads	Bodyworns	Underpads
Design groups	Inserts Diapers T shaped diapers Pull-ups	Bedpads Chairpads	Inserts Diapers T shaped diapers Pull-ups	Bedpads Chairpads

and the men (in the community) had more severe urinary incontinence than the women - mean daytime urine mass in a pad 375 g for men and 215g for women (difference148g, CI: 80, 218).

Pull-ups (the most expensive design) were better overall than the other designs for women during the day and for community-dwelling women during the night too. Although disposable diapers were better for leakage than disposable inserts (the cheapest), women did not prefer them, but for men (in the nursing homes and the community) the diapers were better both overall and for leakage and were the most cost-effective design. No firm conclusions could be drawn about the performance of designs for faecal incontinence and there was no firm evidence that there were differences in skin health problems between designs (Level of Evidence 1).

In the nursing home trial the carers found pull-ups and inserts significantly easier to apply (in the standing position) and significantly quicker in the pad change experiment (mean time 35.2 and 37.9 seconds for inserts and pull-ups respectively and 53.2 and 62 seconds for diapers and T-shaped diapers respectively) and ability to stand was associated with preference for pull-ups or inserts. Despite being designed for ease of changing the T-shape diaper was not found to be easier or quicker to change than the diaper.

The washable products (used in the community-based trial) gave diverse results. Two of the products were made from cotton terry-towelling (one a simple square, folded and pinned in a diaper shape; the other a shaped diaper-like design, both worn with plastic pants) while the third product had a felt absorbent core, with an integral plastic backing and was fixed by poppers. This third product performed significantly worse for leakage than the other two washables and was therefore excluded from the final data analysis. The terry-towelling washables were better for leakage at night than the disposable designs, but were less popular overall for daytime use than the disposable designs. Three quarters of the women (27/36) found them unacceptable, but nearly two thirds of men (31/49) found them highly acceptable at night. Findings from the community-based trial showed that there were many practical problems dealing with washable products particularly when out of the house, but that they were more acceptable at home.

Macaulay et al, [20] carried out a pilot study of 19 washable products with 14 community dwelling subjects. The products included a mixture of washable insert and brief designs and two disposable bodyworn products. Product performances varied widely: the most popular was rated as good (for overall performance) by 78% of testers, while the least popular scored 22%. Although most of the washable products performed poorly for leakage, one washable product made of cotton towelling (used with plastic pants), scored better than both the other washable and disposable products (Level of Evidence 3).

Eight older trials have compared disposable with washable bodyworn products for moderate-heavy incontinence [61] [62] [63] [64] [65] [66] [67] [68]. The trials varied in size and design from a large controlled trial with 276 subjects [61] to a small trial of eleven subjects [64]. In addition some trials have compared disposable and washable bedpads and body-worns. Brown [22] [69] undertook a large trial of this kind. The fact that no systematic method of product selection was used for these studies limits the utility of the results since particularly good or poor products may have been selected to represent the disposable or washable groups.

Skin condition was used as an outcome measure in five of the above trials. However, only three used an experimental design and statistical methods of analysis. Beber [61] and Grant [62] both reported that they did not find statistically significant differences between their washable and disposable products in terms of an adverse change in skin condition. But Hu et al. [70] reported a statistically significant improvement in the skin condition of their disposable product users as compared to their users of washable products (See Section XIV).

Other parameters frequently investigated in these studies were staff preference, product leakage and laundry. Overall, the disposables in the studies were considered to have performed better than the washable products in terms of preventing leakage (often measured by quantity of laundry) and staff preference.

Four studies attempted to measure costs [63] [62] [71] and [69]. Of these, three used statistical methods of analysis. Hu et al. [71] and Brown [69] reported that although there were no statistically significantly differences in terms of per-day product costs of washable and disposable products, the laundry costs associated with the disposable product (ie for laundering soiled bed linen and clothes) were significantly lower than those associated with the washable product (ie for laundering the products as well as soiled bed linen and clothes). Brown [69] found no significant differences between daily costs of the washable and disposable products. However, statistically significant differences were found between the groups in terms of incontinence-related laundry, with the disposable group producing less laundry than the washable group. Grant [62] reported that the cost of washable products was significantly lower than that of disposables, but laundry costs were not taken into account.

2. Disposable absorbent products for urinary incontinence: studies of single designs, laboratory tests and studies of materials

Clancy and Malone-Lee [15] compared versions of the same pad experimentally engineered to have differ-

ent combinations of fluff pulp and topsheet materials. Forty-five heavily incontinent older adults participated. The main valuable finding from this study was that pads were more likely to leak if they were not held in place by pants ($p<0.0001$) and that, if there was any leakage from a pad, this tended to be less severe if the supplied mesh pants were worn than if normal pants were worn ($p<0.05$) (Level of Evidence 2). The mesh pants probably held pads more firmly to the body.

There have been two single design group studies of bodyworn products for moderate-heavy incontinence [72] [73], both carried out in nursing homes. A study of shaped insert pads involved 228 subjects from 33 nursing / residential homes who tested 20 ranges of insert pads [74 products in total). A similar study of diapers involved 192 subjects from 37 nursing / residential homes who tested a total of 36 products. These studies showed the wide range of product performance that can exist within single product groups. For example, the least successful diaper (based on 'overall opinion') was found to be unacceptable to 100% of the test subjects while the most successful was unacceptable to only 6% (Level of Evidence 2).

In addition, there have been a number of studies on the impact of wet pads on skin health and these are reviewed in Section XIV.

Because clinical evaluations are expensive and time-consuming, laboratory evaluation procedures are in widespread use. Few have been clinically validated but there is a clinically-validated International Standard (ISO 11948-1) relating to the leakage performance of disposable bodyworn pads for moderate-heavily incontinent adults in institutions [53]. It describes a simple method for measuring the absorption capacity of pads in the laboratory that was shown to correlate well with the leakage performance of 18 different products evaluated in an international multi-centre clinical study involving 112 heavily incontinent adults [74]. The strength of the correlation between technical and clinical data data depended on the exact parameters being compared, but typically $r = 0.9$ (Level of Evidence 2). This laboratory test (the Rothwell method) is now in common use in the UK, Sweden and other countries and provides a basis for selecting similar products with which to make direct comparisons (for cost purposes) or to select promising pads for inclusion in clinical trials.

The ability of ISO 11948-1 to predict the leakage performance of more recent bodyworn pads (138 diapers and inserts) for heavy incontinence was investigated by Cottenden et al. [75]. Correlations were poorer than in the original 1993 study ($r<0.87$ compared with $r<0.95$) but still strong enough to make the method useful. For a given Rothwell capacity, the leakage performance of diapers was far superior to inserts, but no evidence was found for any other design feature of the test products (inserts and diapers) having a significant impact on their leakage performance (Level of Evidence 2).

The repeatability and reproducibility of the ISO 11948-1 was investigated by Cottenden and co-workers [76] in three laboratories (UK, Spain and Sweden). Repeatability (precision between repeats in the same laboratory) was found to be very good with the co-efficient of variation for five repeats rarely exceeding 5%. However, the reproducibility (precision between laboratories) was poorer, revealing systematic differences: results from the Swedish and Spanish laboratories typically exceeded those from the English laboratory by 13% and 8%, respectively. Efforts to identify the source(s) of this poor reproducibility have so far been unsuccessful but it seems likely that minor variations in interpretation of the standard when constructing the apparatus and / or executing the test are to blame (Level of Evidence 2).

c) Summary

Results from these studies indicate that there is no single best design (i.e one design that is significantly better than all other designs for all users) (**Level of Evidence 1**).

There is evidence that different designs are better for men and women, and that men leak substantially higher volumes of urine than women (**Level of Evidence 1**).

Of the disposable designs, the more expensive pull-up and T-shaped diaper designs are not better overall than the cheaper diaper for men, indicating that the diaper is the most cost-effective design for men. For women pull-ups are better overall than the other designs (except for night-use in those living in nursing homes), but they are expensive (**Level of Evidence 1**).

Unlike men, women in the community do not favour diapers over insert pads and of these cheaper designs, inserts may be preferred for women. There is also evidence that the leakage performance of inserts is worse than other designs, but that they leak significantly less if they are held in place by mesh pants than by ordinary pants, and using no pants at all is associated with significantly more leakage than if either kind of pant is worn (**Level of Evidence 3**).

There is evidence that pads containing superabsorber leak less, are more comfortable, and keep the skin drier than those without (**Level of Evidence 2**).

The leakage performance of inserts and diapers for heavy incontinence can be predicted with reasonable precision using an international standard laboratory tests (**Level of evidence 2**).

This test has been shown to have very good repeatability and adequate reproducibility (**Level of Evidence 2**).

Washable products are very varied in design and materials, and also in performance. There is evidence that terry-towelling products (used with plastic pants) have good leakage performance, however they have limited acceptability - confined mainly to some men at night. There is no firm evidence regarding the perfor-

mance of different designs for faecal incontinence and no firm evidence that any particular design or type of material (washable or disposable) is better or worse for skin health.

The user characteristics, priorities and contexts which favour or discourage the use of the different product designs are summarised in **Figure VI-18**.

d) Recommendations

- Gender should be considered when products are prescribed / purchased for users. As men often have substantially higher incontinent urine volumes than women, men may require more products and / or more absorbent products than women (**Grade of Recommendation B**).
- Gender should also be considered when products are prescribed / purchased for users because men and women are likely to prefer different designs. Men generally prefer disposable diapers to inserts (**Grade of Recommendation B**).
- Women generally prefer disposable pull-ups to other designs, but these are expensive. Disposable inserts are a cost-effective alternative (**Grade of Recommendation B**).
- Caution is recommended if washable designs are being considered. Heavy bulk confines their use mainly to the night-time (where they may be particularly useful for users who lie on their side). They are unacceptable for most people during the daytime and for most women at any time and for this reason a blanket policy of health services providing washables alone is not recommended. If washables are being considered refer to points below (**Grade of Recommendation B**).
- Freedom from leakage: Where possible, international standard laboratory tests should be used to rank the likely leakage performance of different pads for heavy and light incontinence (Grade of Recommendation B). In general, diapers should be selected in preference to inserts to minimise leakage (**Grade of Recommendation B**).
- Carer application: When products are applied by a carer to a patient who can stand for pad changing, disposable inserts or pull-ups are easier and quicker to change than diapers or T-shaped diapers. If the patient is lying down (e.g. at night) pull-ups should be avoided (**Grade of Recommendation B**).
- Combinations of designs for different situations (e.g. disposable inserts for staying in, disposable pull-ups for going out, washable diapers at night) are likely to provide optimum management in terms of patient needs and cost-effectiveness (**Grade of Recommendation B**).
- See also the general recommendations relating to pad selection in Section VI.12 and recommendations specific to washable pads in Section VI.13.

e) Research priorities

- Comparison of absorbent products (disposable and washable) when used by carer-dependent users in the community.
- Development of more effective and aesthetically acceptable washable products, particularly for nighttime use and for women.
- Development of more effective and acceptable disposable designs specifically for men.

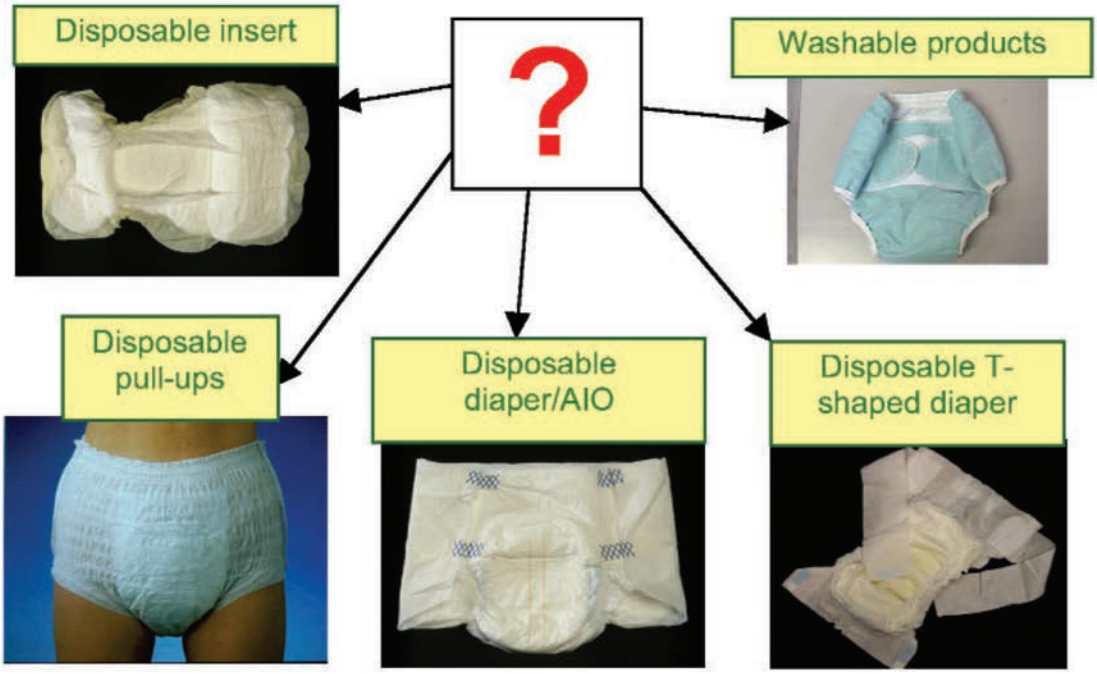
8. DISPOSABLE UNDERPADS

There have been no published studies examining the use of bedpads during the last 15 years. This probably reflects the recognition of their limited role in long-term management of incontinence. Disposable underpads on chairs declare their user to be incontinent and require clothes to be pulled up (or absent) which is unacceptable for dignity. In the bed disposable underpads easily become displaced, folded and creased under the patient which inhibits their performance and comfort, and may potentially be a threat to skin health. Large disposable underpads with wings to tuck into the bed may have a role as bed protection 'back-up' to bodyworn pads. The main role of disposable underpads should be confined to temporary bed or chair protection such as during clinical procedures (e.g. enemas) or when using a urinal.

Published trials comparing different disposable bedpads are few [77] [78] [22] and it is not possible to draw firm conclusions from them on the effectiveness of different product design features and materials. Some useful work has been done to highlight the risks of infection from disposable bedpads and to validate clinically some laboratory tests to assist with product selection by predicting pad leakage performance.

Bedpads are generally supplied as non-sterile items and Bradbury [79] has drawn attention to the risk of infection, particularly from products containing recycled paper. Leigh and Petch [80] and Sprott et al. [81] have conducted microbiological tests on a range of products. Both studies identified low levels of bacterial contamination but concluded that the risk to patients was minimal unless they were immunocompromised in some way. More recently, Stansfield and Caudle [82] reported an outbreak of wound colonization on a surgical orthopaedic hospital ward which they attributed to the use of disposable underpads containing virgin wood pulp.

Due to the paucity of published clinical data many technical tests have been devised to evaluate products in the laboratory. The only tests with published clinical validations are described by Cottenden et al. [74] who subjected six different bedpads to a variety of laboratory tests and to a multi-centre clinical evaluation in which 95 incontinent subjects tested each product in turn for a week, in random order.



Product category	User characteristics / priorities / contexts which:		Notes
	FAVOUR use	DISCOURAGE use	
Disposable inserts	• Carer is needed for pad change and user can stand (B/C) • Discretion is a priority (B/C) • Ease of putting on is a priority (B/C) • Female (B/C)	• Incontinence is heavy HEAVY (B/C) • Mobile and active (C)	
Disposable pull-ups	• Carer is needed for pad change and user can stand (B/C) • Reliable containment of leakage is a priority (B/C) • Ease of putting on is a priority (B/C) • Discretion is a priority (B/C) • Female (B/C)	• Removal of clothing for pad changing is an issue (B/C) • Low cost is a priority (B/C) • Night time use, with a carer (B/C)	
Disposable all-in-ones	• Incontinence is heavy HEAVY (B/C) • User can not stand for a pad change (B/C) • Male (B/C)	• Discretion is a priority (B/C)	
Disposable T-shaped pads	• Reliable containment of leakage is a priority (B/C) • Male (B/C)		
Washable bodyworns	• At night, if incontinence is heavy HEAVY (B/C) • Male (B/C)	• Adequate laundry facilities are not available (B/C) • The concept is unacceptable (B/C) • Discretion and appearance are a priority (B/C)	

Figure VI-18: Designs of pads for adults with moderate-heavy urinary incontinence. For definitions of light HEAVY and heavy HEAVY, see Section VI.4. (Grade of recommendation in brackets)

A combination of two laboratory tests (one to measure the absorption capacity and the other the absorption time of bedpads) gave a strong correlation with the percentage of subjects finding the leakage performance of a product acceptable when used as their sole protection (r = 0.94) and predicted the acceptability scores of all six products accurate to within ± eight percentage points. A different absorption capacity test produced a strong correlation for the leakage performance of bedpads used as back-up to bodyworn products (r = 0.96) and predicted the acceptability scores of all six products to within ± five percentage points.

a) Summary

No robust data are available on the effectiveness of current disposable bedpads or of their various design features or constituent materials. There is a risk of infection from bedpads made from recycled paper for immunocompromised users (**Level of evidence 2**). The leakage performance of bedpads (used alone or as back up to bodyworn pads) can be predicted with reasonable precision using clinically-validated laboratory tests (**Level of Evidence 2**).

b) Recommendations

- Disposable underpads should not be used for long-term management of incontinence, but have a useful role as temporary protection for chairs and beds during clinical procedures (**Grade of Recommendation C**).
- Immunocompromised people should not use bedpads made from recycled paper because of the risk of infection (**Grade of Recommendation B**).
- Where possible, clinically-validated laboratory tests should be used to rank the likely leakage performance of different products (**Grade of Recommendation B**).

c) Research priorities

Disposable underpads have a limited role in continence management but are known to be widely used. An exploration of patient views regarding their use may help demonstrate their limitations.

9. WASHABLE UNDERPADS

Aspects of assessment that are particularly important regarding washable underpads are patient acceptability and preference, particularly with regard to willingness to be naked below the waist (if sole use intended) and availability of laundry and drying facilities.

Cottenden [83] has reviewed comparative evaluations of different washable bedpads up to about 1990. Leiby and Shanahan[84] have since published a study. Some evaluations have found significant differences between products relating, for example, to leakage performance and impact on skin health but none of the products evaluated is still available in the variant tested. In addition, compared products always differed from one another in many respects making it impossible to draw reliable generic conclusions relating to the products now available. However, the choice of topsheet material and the presence or absence of features like tuck-in flaps and integral water-proofing appear to be, primarily, matters of personal preference.

In institutional settings washable bedpads are commonly used by multiple patients and questions are often asked about the risk of cross-infection. Cottenden et al. [85] assessed the risk by determining the microbial content of 145 bedpads of five different designs after a night's use by incontinent adults, followed by laundering using a standard foul wash procedure which included heat disinfection at 71^{o}C for three minutes. Laundering destroyed all known pathogenic organisms, although some commensal flora were isolated in small numbers. It was concluded that foul wash laundry had left bedpads safe for multiple patient reuse with no demonstrable risk of cross-infection.

a) Summary

The literature contains insufficient robust data on which to base guidelines for choosing between washable bedpads. Choice of topsheet material and the presence/absence of design features like tuck-in flaps and integral/separate water-proof backing appear to be, primarily, matters of personal preference (**Level of evidence 3**). Provided an approved foul wash procedure is used, the risk of cross-infection between different users of a bedpads is very low (**Level of Evidence 2**).

b) Recommendations

- If considering using washable underpads for sole use (ie without a bodyworn product) the patient will need to be naked below the waist. Patient consultation and approval will therefore be needed (**Grade of Recommendation C**).
- Personal preferences of users with regard to topsheet material, tuck-in flaps and integral waterproof backing should be considered in making product selections (**Grade of Recommendation C**).
- Provided an adequate foul laundry wash cycle is used, the risk of cross-infection between successive users of washable bedpads is low and not a contra-indication for their use (**Grade of Recommendation B**).

c) Research priorities

- Comparison of washable underpads with bodyworn products when used at night.

10. ABSORBENT PADS FOR CHILDREN WITH URINARY AND / OR FAECAL INCONTINENCE

Most children are expected to achieve daytime dryness by the age of three [86]. However, some children take longer to become dry and some (e.g.

children with learning and physical disabilities) may never reach this goal. These children usually require absorbent products to contain leakage.

Aspects of assessment that are particularly important regarding bodyworn products for children are presence of faecal incontinence, day / night incontinence, level of independence with toileting, and use of aids (e.g. callipers).

To date there has been only one study of absorbent products for children and this has compared the diaper design with the newer pull-up design [87]. Sixty-one children with physical and / or learning disabilities tested five diaper products and five pull-up products, each testing each product for one week. The children were randomised to receive either the pull-up or diaper group first and individual products were tested in random order within each design arm. Parents completed a product performance questionnaire and a pad leakage diary to record wet weights and severity of leakage. Parents were asked to state their preference for a design for day and night use.

Findings indicated that generally, the diaper products performed similarly to each other and so did the pull-up products, although there were some statistically significant differences between products within each of the two design groups. Overall diapers were preferred for night-time use by the majority of parents. By contrast, 40% of parents preferred pull-ups for daytime use and these were found to be particularly appropriate for older children and those who were attempting independent toileting, provided they did not have faecal incontinence and did not wear callipers or adapted footwear. Diapers were more suitable for children who were dependent on carers and / or had faecal incontinence, and wore callipers or adapted footwear. The authors recommended that both diapers and pull-ups should be supplied for children, with pull-ups (which are about 50% more expensive than diapers) being provided for selected children during the daytime.

a) Summary and recommendations

Diapers and pull-ups meet different needs of children and both should be made available to children with disabilities, dependent on assessment **(Level of Evidence 3 / Grade of Recommendation C)**.

b) Research priorities

Comparison of washable and disposable bodyworn products.

11. PADS FOR FAECAL INCONTINENCE

Most absorbent products are designed for urinary incontinence. No studies comparing available absorbent products for faecal incontinence were found. Bliss et al. [88] reported preliminary findings of a survey of the use and evaluation and suggested modifications of absorbent products for faecal incontinence by 188 community-living persons with the problem. Forty-five percent of persons used an absorbent product for FI. Ninety-eight percent of those with UI and FI used the same type of product for both. Suggested improvements in product designs included having better odour control, fit, and ability to stay in place; a clearer distinction between the front and back of a pantiliner or pad; adding wings for greater absorbency; and making them flushable, cooler feeling, wider and longer in the rear and more absorbent but less bulky. For mild faecal incontinence, especially when faeces remain between the buttocks without soiling underwear, persons have used a small disposable gauze surgical dressing placed between the buttocks. This product was more acceptable than a pantiliner or pad to some men [88] (**Level of Evidence 2**).

a) Recommendations

- A disposable gauze dressing that can be placed between the buttocks maybe acceptable for men with light faecal incontinence (Level of Recommendation C).

b) Research priorities

- Better designs of products are needed for light and moderate FI (with and without UI).

12. GENERAL RECOMMENDATIONS ON PAD SELECTION

- *Individuality*: No study has ever identified one product that worked best for all testers: needs and priorities vary. Accordingly, users are advised to try a variety of products when possible (**Grade of Recommendation B**).
- *Brand differences*: The individual product brands within a design group often exhibit a wide range of performance and acceptability for individuals, and it cannot therefore be assumed that pads of different brands but broadly similar design will be equally acceptable or effective (**Grade of Recommendation B**).
- *Combinations of designs*: Absorbent products vary greatly in price and performance and suitability for individual needs. Users may therefore find combinations of designs preferable and cost-effective. For example, women might use pull-ups (expensive, but discreet and good for leakage) for going out, and inserts (cheap, less good for leakage) for staying at home. Men might use disposable diapers for daytime, and washable terry-towelling products for night-time (**Grade of Recommendation B**).
- *Freedom from leakage*: In general, pads containing superabsorber should be selected in preference to those without (**Grade of Recommendation B**). Nobody wants their pad to leak but compromises have to be made: the pad needed to contain a person's most severe accident may be substantially more bulky and expensive than is needed most of the time. Some users choose to

tolerate a higher risk of pad leakage in exchange for being able to use cheaper, smaller (more discrete) pads. The balance of priorities for a given user should be investigated in making product selections (**Grade of Recommendation C**).

- *Comfort and skin health*: In general, pads containing superabsorber should be selected in preference to those without (Grade of Recommendation B). Shaped pads should usually be selected in preference to unshaped (**Grade of Recommendation C**).

- *Staying in place*: No product is effective if it slips from position. Inserts should be used with pants, preferably mesh pants (Grade of Recommendation B). Robust, stretch (e.g. cotton / lycra) pants may also help to provide a snug fit and minimise leakage. Shaped pads are preferable to rectangular (**Grade of Recommendation C**).

- *Ease of putting on and taking off*: The ease of putting pads on and taking them off should be considered, especially for caregivers and for incontinent users with reduced mobility or dexterity (**Grade of Recommendation C**).

- *Aesthetics and discretion*: A possible preference for small, more discrete pads (even if they are more likely to leak) should be considered, especially for those wishing to wear close fitting clothing (**Grade of Recommendation C**). The possibility of plastic backing materials rustling noisily should be considered (**Grade of Recommendation C**).

- *Independence and lifestyle*: The ability of a user to change his / her own pad should be considered (**Grade of Recommendation C**): those able to change their own pad can often manage with a smaller (less absorbent) one than those reliant on a caregiver. Users who travel should consider in their choice of product(s) the practicalities of carrying a supply of pads, disposing of used ones, and dealing with laundry (**Grade of Recommendation C**).

- *Costs*: Cost issues should be approached with caution (**Grade of Recommendation C**). Expensive pads do not necessarily work better than cheaper ones. Cheaper pads do not necessarily save money. If pads leak more they may have to be changed more frequently and / or lead to higher laundry costs. More pad changes will mean increased caregiver workload. However, more absorbent pads will not necessarily reduce pad consumption rates: pads are often changed according to ward or personal routine.

13. RECOMMENDATIONS RELATING TO WASHABLE PADS

- Laundry issues: Access to good, reliable washing and drying facilities should be checked before washable products are introduced (Grade of Recommendation B). Laundry – especially of bedpads – can be heavy work, beyond the capability of frail incontinent people or their caregivers. The number of washable products needed per user depends on laundry turn-around times. Drying times for washables can be long and expensive, especially for bodyworns for heavy incontinence and for bedpads.

- *Personal preferences*: Personal preferences (of both users and caregivers) with regard to choosing between washable and disposable products should be taken into account carefully (**Grade of Recommendation C**). Some users prefer the chore of laundering washables to anxiety over whether their next consignment of disposables will be delivered on time. Washables generally require less storage space than disposables. Discreet disposal of disposables can be a challenge. The possibility of using a mix of disposable and washable products should be considered (**Grade of Recommendation C**). Some users who choose disposables when at home prefer washables when travelling because of the space that disposables occupy in luggage and the possible inconvenience of disposal. Others use washables at home and disposables when away as they see the balance of disadvantages and advantages differently.

- *Personalisation of products*: In institutions, the chore of personalizing washable products and sorting them after each laundry cycle should be considered before they are introduced (**Grade of Recommendation C**). Washable bodyworns are often personalised to particular users. In institutions this means marking products with users' names and sorting them after laundry, an extra task for caregivers. Washable bedpads are not usually personalised.

- *Staining*: Washable products should not usually be used by those with faecal incontinence – beyond occasional light smearing – because of staining (**Grade of Recommendation C**). Skin sprays and ointments may stain washables too.

- *Costs*: Cost comparisons between washable and disposable products should be made with caution (**Grade of Recommendation C**). Key factors are: local arrangements (mostly laundry and transport costs); the durability of the products (which depends on how carefully they are used and the criteria for deciding when they should be replaced); the costs of ordering, transporting and disposing of disposables; and product purchase costs. Much of the cost of washables is encountered with the initial capital outlay for stock. This also represents a commitment to use the products for an extended period and so expensive mistakes can be made if it transpires that a better product was / has become available. It will usually be wise to experiment with samples of a variety of alternative products before committing to major purchases.

VII. SHEATHS

Close-fitting penile sheaths (sometimes called condom catheters, uridomes or external catheters) are commonly used male incontinence devices and they are used in combination with a urine drainage bag. They are suitable for males who are experiencing moderate to heavy urine loss, or have limited mobility and are experiencing frequency and urgency and may even be considered in combination with intermittent catheterisation (IC) for males who are leaking urine as a consequence of bladder emptying problems. Sheaths may not be suitable for males who are experiencing confusion, considered psychologically vulnerable or have decreased sensation through spinal cord injury [89], [90], [91]). There is strong opinion expressed in the literature that suggests assessment, selection and use of penile sheaths and the accompanying urine drainage systems needs to be undertaken with the guidance, education and monitoring of health professionals who have a knowledge of continence products. Failure to do so, according to this expert opinion [[90], [92], [91]], may result in serious penile trauma, impaired penile skin integrity and leakageof urine.

General guidelines on patient assessment for product selection are discussed in Section II. Aspects of assessment that are particularly important in relation to sheaths include: physical, mental, cultural, gender and socio-economic factors. This incorporates assessment of the cognitive and dexterous ability of the male or carer to apply the sheath and empty the drainage bag, the integrity of the penile skin, length and circumference of the penis and whether it is retracted, or retracts on sitting or bending down, history of latex or adhesive allergy and, most importantly, recognition that the assessment from the health professional needs to be ongoing. It is also important to assess factors known to encourage or discourage sheath usage. Expert opinion [[93], [90], [94]] suggests factors that encourage usage include: level of reimbursement, cultural expectation, resonance with masculine image, and ability to keep urine off the skin when the skin integrity is at risk because of incontinence. Factors which they suggest discourage usage include: ignorance of product efficacy by professionals and consumers and embarrassment between carer and client.

An effective sheath is one that stays securely in place for an acceptable period of time, is leak-free, comfortable to wear, easy to apply and remove, avoids skin damage and channels the urine effectively into a urine drainage bag.

1. PRODUCT CATEGORIES AND FEATURES

Sheaths come with a variety of features (**Figure VII-1**) of which the following are the most important to consider in making selections:

- Material: sheaths may be made from latex, silicone rubber or other synthetic polymers. Some men will be allergic to latex.
- Size: most sheaths are supplied in a range of lengths and sizes. Most companies supply them with diameters in the range of about 20 – 40 mm, in 5-10 mm increments.
- Adhesive: the adhesive may be integral to the sheath (one-piece systems) or come as a separate strip or spray (two-piece systems). Some men will be allergic to some adhesives.
- Applicator: some sheaths come with an applicator intended to help users and carers to put the sheath on.
- Anti-kinking / twisting features: some sheaths come with features intended to improve drainage by reducing kinking and twisting at the distal end, near the connection to the drainage bag tube.
- Anti-blow-off features: some sheaths come with features intended to reduce the likelihood of the sheath blowing off at high urine flow rates, for example, at the beginning of a void (eg the distal end of the sheath may be thickened and bulbous to stop the internal walls sticking to one another between voids).
- Connection to the drainage bag: some sheaths come with features intended to increase the ease and security of connection to the drainage tube (eg a push ring or ridge at the end of the outlet tubing)
- Retracted penis features: with or without specific features intended to accommodate a retracted penis (eg a shorter sheath or a wider adhesive seal).
- Durability: some sheaths are intended for use over a limited time period (eg 24 h) while other (generally, more robust) designs are intended for extended wear.
- Transparency: some sheaths are transparent allowing for observation of the condition of the skin along the shaft and glans of the penis.

2. QUALITY OF DATA

Some controlled comparative evaluations of different sheaths have been performed; one extensive market survey to identify the needs and priorities of sheath users; and two studies comparing sheaths with other product categories (versus indwelling urethral catheter, and versus absorbent pads). Other studies report on the problems encountered by various groups of sheath users.

3. RESULTS

Although many men use sheaths successfully, problems have been reported in the literature. In a study on an unspecified number of spinal cord injured men, Golji [95] found that 15% experienced side effects or complications when using sheaths. These were irritative, allergic or compressive in

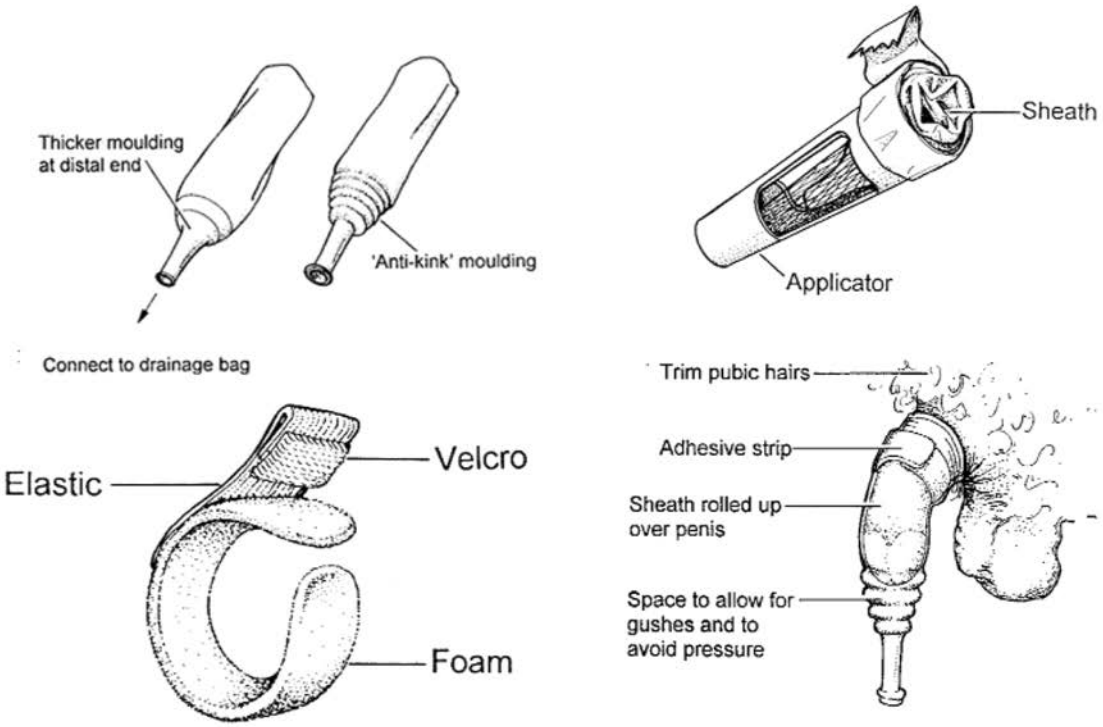


Figure VII-1: A variety of sheaths (top left and bottom right), a sheath applicator (top right) and an external fixation strip (bottom left).

nature. Jayachandran et al. [96] reported similar experiences with six incontinent men of widely varying aetiology and highlighted the importance of ensuring that the sheath does not become twisted near the distal end to avoid stagnation of urine and the risk of UTI. They also stressed the importance of good genital hygiene to avoid problems with infections. In a study of 94 men on medical / surgical wards, Hirsh et al. [97] found that none of the 79 who were judged as co-operative and able to manage their sheaths properly developed UTI (mean period of use, 21.2 days). By contrast, eight of 15 patients who tended to tug and kink the drainage tube attached to their sheath developed UTI within a mean of 9.6 days. In a retrospective study, Johnson et al. [98] compared the frequency of UTI in users (mean period of use, 35 months) and non-users of sheaths amongst 64 elderly men on an extended care unit. He found that 63% of users but only 14% of non-users developed UTI. No difference was found between men who did and did not tug and kink their tubing. Ouslander et al. [99] reported that 40% of 30 nursing home sheath users (mean period of use, 35.9 months) developed at least one UTI. The need for proper fitting of the sheath and regular monitoring of the skin integrity of the penile shaft, glans penis and prepuce of males who are regular sheath users has been highlighted in two articles that report a combined total of eight cases of fibropithelial polyps of the glans penis and prepuce of which six had a history of long term sheath use [92] [100].

A trial to compare sheaths and indwelling catheters in terms of infection, risk and patient satisfaction has been reported by Saint et al [101]. This was a prospective, randomised, unblinded, controlled trial which compared one type of sheath drainage with one type of indwelling urethral catheter using a small group of participants (N=75) across several locations in one hospital. There are important limitations of the study, including the low numbers drawn from a specific population, and the lack of comment on the changing / care routines associated with the sheaths and catheters. After making adjustments for age, mental score, history of UTI and history of catheterisation the conclusions of the study were that for males without dementia the use of sheaths has the potential to reduce infection compared to indwelling catheters and is more acceptable to patients in terms of comfort and pain. For males with dementia no significant difference in infection rates was found.

There has also been a cross-over trial [47] comparing sheaths with absorbent pads when used by men with moderate to severe UI (N=61). Products were used for two weeks each and the Kings Health

Questionnaire was used as the primary outcome measure. Scores for the sheath system were significantly better than for the pads on most domains and the number of men preferring sheaths was significantly higher than for pads.

Nichols and Balis [102] reported the results of a survey undertaken for marketing purposes of an international cohort of 216 men who had used sheaths for at least three years, and their carers. Their responses to 19 brands of sheath were gathered using a questionnaire in the form of a Likert scale. It was found that catheter security (presumed to mean staying in place and freedom from leakage) was the most important issue for both wearers and carers, followed by comfort and ease of application and removal.

There have been a number of comparative evaluations of different sheaths. Peifer and Hanover [103] reported on an evaluation in which 20 men compared a new branded sheath system that consisted of three ed parts: a tubular sheath impervious to urine with a drainage tube connection at one end and a ring at the other; an undergarment with a frontal opening through which the penis is extended; and a ring-like collar which is used to keep the sheath and penis in the correct position, with the variety of external sheaths they had previously been using. The participants were a convenience sample identified through pharmacy medication files. In all, 32 men were approached and 20 consented, all experienced users of urinary sheaths. A questionnaire was developed to test the participants pre and post intervention. The new sheath – which was used for a week - proved more popular with the participants: it was judged to provide superior security (13/20 experienced increased dryness by day; 10/20 by night), and considered easier to apply (19/20) and remove (20/20).

In a multi-centre study involving 35 men (age range 22-87y; mean age, 54y; 34 living in their own homes), the UK Medical Devices Agency [104] compared four latex sheaths: two with integral adhesive; and two in which the adhesive was supplied as a separate strip. They found the products with integral adhesive to be more successful in both overall performance and ease of application. Fader et al. [21] conducted a multi-centre study to compare all six sheaths with integral adhesive on the UK market in 1998. Five were made from latex, one from silicone rubber. Four were supplied with an applicator, two without. Fifty-eight men (age range 26-88y; mean age 53y) were given the opportunity to try each sheath in turn for one week. The silicone rubber sheath was found to be significantly better than four of the other sheaths in overall performance ($p<0.01$). The ease with which a sheath could be put on was found to be the best predictor of overall performance. Surprisingly, sheaths with an applicator were found to be unacceptable to a significantly higher proportion of subjects than sheaths without an applicator ($p<0.0001$). Subjects found that the silicone sheath fell off / blew off significantly less frequently than two of the other products ($p<0.01$).

Pemberton et al [94] report a randomised prospective open crossover design trial to test user preference for an established one-piece silicone rubber self-adhesive sheath with a new one-piece silicone rubber self-adhesive sheath in a study sponsored by the distributor of both products. To be included the males had to be currently using at least one, one-piece urinary sheath, per day. Fifty three males from seven centres participated in the trial and were each given 10 sheaths of each product. Data from the 44 participants who had evaluated at least three of each product were analysed. No reason was given for why nine males did not complete the trial. The data shows that there were some problems with both products, however, it is difficult to understand why the new product was preferred, as the report does not mention any differences in the features of the two products.

Watson & Kuhn [105] describe a crossover study with six male participants that found the choice of leg bags may influence the performance of penile sheaths. Goldyn, Buck and Chenelly [106] conducted an exploratory study on 10 patients in an extended care hospital to consider the efficacy of a brand name external sheath and a hospital constructed sheath. The brand name sheath was found to be more secure and the preferred nursing choice but it was recognised that the hospital-constructed sheath was useful for patients with fragile skin and limited mobility. A study by Saint et al. [107] provided further evidence (although low level) to support the importance of security and comfort to sheath users. Using questionnaires, they interviewed a convenience sample of 104 older men (response rate = 90%) and surveyed 99 nurses (response rate = 92%) about the relative merits and problems of sheaths and indwelling catheters. The study population was drawn from a university-affiliated Veterans Affairs Medical Centre in the USA. The patients using the sheaths were more likely to believe their product was comfortable ($p = 0.04$) and less likely to believe it was restrictive ($p = 0.002$) or painful ($p = 0.008$) than those using an indwelling catheter. This viewpoint was supported by the nurses surveyed, the majority of whom (no numbers given) believed that sheaths were more comfortable and less restrictive than indwelling urinary catheters for male users, but required more care time because they fell off or leaked.

4. SUMMARY

For incontinent males, sheath drainage can provide a good alternative to pads. However, the increased risk for complications such as local skin breakdown, bacteriuria and infection - especially in the frail confused elderly male – should be borne in mind (**Level of Evidence 2**). Also, there is the risk of urinary retention if the condom twists or the external band is

too tight, leading to poor drainage to the urine bag (**Level of Evidence 3**). Sheaths with integral adhesive are more popular with users and easier to apply than those with separate adhesive strip (**Level of evidence 2/3**). Secure fixation and the ease with which a sheath can be put on are the best indicators of its overall performance (**Level of Evidence 2**). Sheath applicators are often ineffective and unpopular (**Level of Evidence 2**). There can be considerable differences in performance between products with somewhat similar designs (**Level of Evidence 2**).

5. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION

- Prior to applying the sheath, ensure any remaining adhesive or barrier cream is removed from the penis and that it is thoroughly washed with soap and water and thoroughly dried.
- Trim long pubic hairs to prevent them being caught up in the adhesive.
- Protective skin wipes can be used to protect the skin, but make sure the skin has dried properly before applying the sheath.
- Leave a gap at the end of the sheath between the glans penis and the drainage tube to avoid trauma to the glans / prepuce. However, make sure the gap is not too large such as to cause kinking or twisting of the sheath [108].
- After the sheath has been applied, snip any reinforced ring or unrolled section of sheath sitting at the bottom of the shaft of the penis.
- Penile sheath removal should not be rushed and is made easier by gently rolling it off while bathing the penis in warm soapy water.

6. RECOMMENDATIONS

- Since there can be considerable differences in performance between products of similar design, men should be given the opportunity to experiment with different products before making a final selection (**Grade of Recommendation B**).
- The key performance characteristics which should be considered in selecting products are: security (ie ability to keep a leak-proof seal and channel urine to the drainage bag without leakage) and ease of putting the sheath on and taking it off (**Grade of Recommendation B**).
- In general, sheaths with integral adhesive (one-piece systems) should be selected rather than those in which the adhesive is supplied separately (two-piece systems) (**Grade of Recommendation C**).
- It should not be assumed that a sheath applicator will make sheath application easier: often it does not (**Grade of Recommendation B**).
- Potential sheath users should be asked if they have an allergy history and regular users should be routinely checked as their latex allergy status can change over time and with continued use. (Some health settings are moving to reduce or eliminate latex usage whenever possible and some manufacturers have moved to offer non-latex sheaths) (**Grade of Recommendation C**).
- Sheath users should be monitored for skin health, tissue damage and UTI (**Grade of Recommendation C**).
- When possible the external sheath rather than indwelling urethral catheter should be the urinary collection device of choice. (**Grade of recommendation B**).

7. PRIORITIES FOR RESEARCH

- Although products are continually being developed, changed, withdrawn and released, comparison studies that are controlled and use multiple sites to achieve larger numbers are recommended to further evaluate the effectiveness of the variety of sheaths available.
- More comparative studies of the risks of complications between the use of sheaths, pads and catheters are required.
- Since leg bag features may influence the performance of the sheath, further evaluation of design features claimed to reduce twisting and kinking at the drainage bag connection site and increase ease and security of connection to drainage bags is required.
- Well designed studies to generate and validate procedures to help identify the type of sheath most likely to suit an individual are needed.

VIII. URINE DRAINAGE BAGS AND ACCESSORIES

Urinary drainage bags are attached to an indwelling catheter or penile sheath to collect and store urine. Features of effective drainage bag systems include ease of operation of all components (connectors, taps, and support devices), comfort and discreetness.

General guidelines on patient assessment for product selection are discussed in Section II. Aspects of assessment that are particularly important regarding urine drainage bags are patient / carer dexterity [90] [109], and eyesight. Both are necessary to manage the urinary drainage bag system, including using the outlet tap to empty the drainage bag. It is also important to assess the patient's preferred and usual mode of dress [90] [109]; for example, a male whose preferred mode of dress is shorts will want a drainage system that is not visible and allows easy access for emptying,

1. PRODUCT CATEGORIES AND FEATURES

Urine drainage bags fall into two major categories:

leg / body worn bags for day-time usage; and large capacity body-free bags for night-time use (night drainage bag) which are suspended from a stand or bed hook.

Leg / body worn bags come with a variety of features of which the following are the most important to consider in making selections:

- Volume: most bags have a volume in the range of 350-750 ml, but some are bigger.
- Material: most bags are made from transparent PVC (polyvinyl chloride) but PVDF (polyvinylidene fluoride, less noise from rustling), polyethylene or rubber / latex may be used.
- Sterility: bags may or may not be supplied sterile.
- Wear position: bags may be designed for wearing over the knee, across or down the thigh, down the calf, or against the abdomen.
- Attachment / suspension system: most leg bags are attached to the leg with straps, which are usually made from latex or a (usually elasticated) fabric. A variety of hooks, loops, buttons / button holes and Velcro may be used to secure straps and to attach bags to straps. Some bags are designed to be suspended around the waist. Some straps and suspension devices can be bought separately from bags, but they are generally not suitable for use with all bags (**Figure VIII-1**).
- Connecting tube: bags come with a variety of connecting tube lengths (eg the length required for wearing a bag on the calf will be greater than that for the thigh). With some products the tube can be cut to the preferred length.
- Drainage tap: Drainable bags come with a variety of drainage tap designs (**Figure VIII-2**).
- Sampling port: bags may or may not have a sampling port in the drainage tubing for taking urine specimens.
- Comfort features: some bags come with features intended to increase comfort – most commonly, a fabric backing against the skin to reduce sweating.
- Discretion features: some bags come with features intended to increase discretion – most commonly, internal welds between the front and back faces to reduce bulging and / or sounds caused by a large volume of liquid moving about as the user mobilises.
- Anti-kinking / twisting features: some bags come with features intended to improve drainage by reducing kinking and twisting in the connecting tube.
- Infection reduction features: some bags come with features intended to reduce the risk of infection for the self-carer and cross-infection between bag users by care givers. Such features may include; a non-return flap valve, designed to help reduce reflux of urine up the tubing when the bag is moved by users or carers, a sampling port and / or a tap with an outlet sleeve which allows the overnight bag to be connected to the body worn bag. This linkage provides a mechanism to maintain a closed catheter drainage system designed to minimise the risk of cross-infection by reducing the handling of the catheter. Having connected the night bag to the leg bag sleeve, the leg bag tap is opened and urine flows freely from the sheath or catheter through the leg bag into the night drainage bag. Pre-sealed drainage systems to prevent breaking the closed system are also available, and these could be beneficial in reducing time to bacteriuria [110].

Night drainage bags are usually held on a suspension system away from the body. They may be connected directly to the catheter or sheath or they may be connected to the drainage tap of the leg / body worn bag to avoid the need for repeated connections and disconnections with the catheter or sheath (**Figure VIII-3**) ie a closed-link system. They usually have a capacity of 2000-4000 ml and come with a variety of design features many of which are similar to those for leg / body worn bags. Night drainage bags are available as non-drainable bags (NDB) i.e. without a tap for single use as well as with a variety of drainage tap designs for emptying and reuse. Glass bottles are also available for high volume or overnight urine drainage. It has been suggested that current standard drainage tubing / bag designs evacuate the bladder sub-optimally, leading to retention of residual urine. Outflow obstruction can be caused by the development of air-locks in the dependent curls of tubing. A new drainage tubing design which incorporates a coiled downward-spiral-shaped configuration has been reported to eliminate air-lock obstruction [111] in experimental and clinical studies. However the importance of this in relation to infection requires further study.

2. QUALITY OF DATA

Several controlled comparative evaluations of urine drainage bags and suspension systems have been performed, as well as a small number of studies addressing infection and cross-infection issues There are also two case-controlled studies which have investigated the purple urinary bag syndrome.

3. RESULTS

a) Evaluations of urine drainage bags

A randomized cross-over design compared use of a standard latex drainage bag with a cloth covered bag in 42 men with post prostatectomy incontinence [112]. Each bag was tested for about 4-5 days, and complete data were provided by 30 individuals. People with known latex allergy were excluded. Measures included adapted questionnaires for Leg Bag Evaluation and Skin Health. A statistically significant preference was found for the

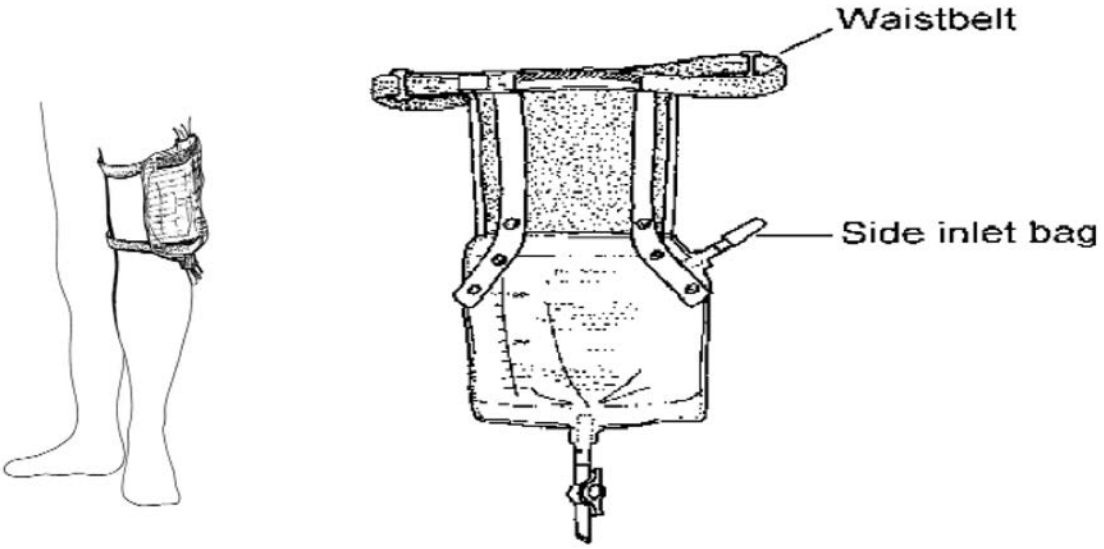


Figure VIII-1: Body worn urine drainage bags held in place using leg straps (left) and a waist band suspension system (right).

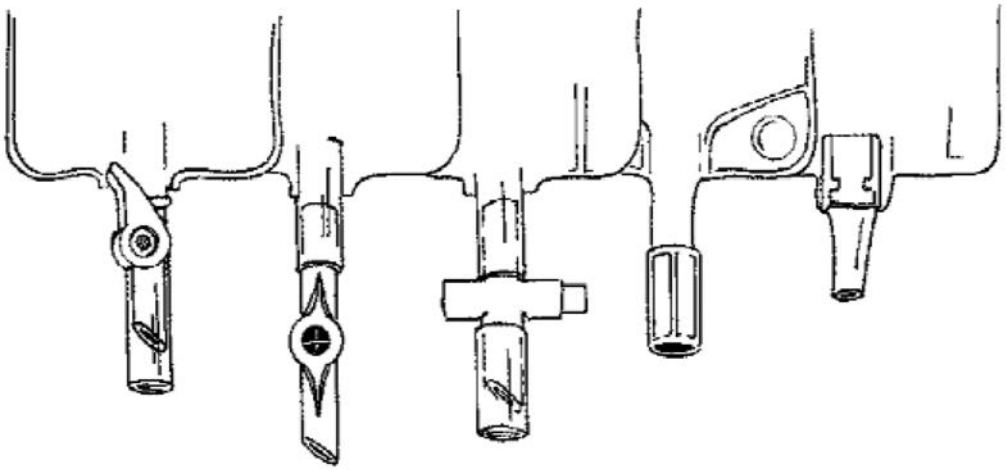


Figure VIII-2: A variety of urine drainage bag tap designs.

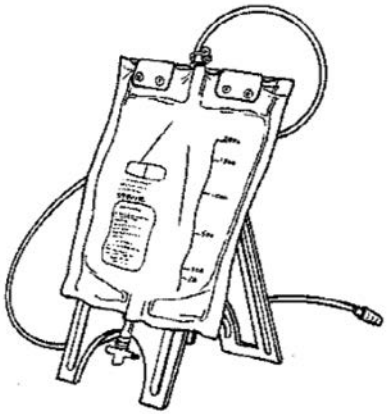


Figure VIII-3: A night urine drainage bag on a stand.

cloth covered bag with a main effect ($F= 36.614$, $df = 1.28$, $p<0.01$) as well as an effect related to the order provided ($F= 8.398$, $df = 1.28$, $p<0.01$). That is, those who used the cloth bag first had a stronger preference for it than those allocated to the latex bag first. The cloth backed bag seemed to have several positive features, including comfort under the bag and cloth straps, flexible adjustable tubing, and taps that did not cause urine spillage on fingers. But these bags had a tendency to slip down and pull on the catheter. Two persons using the latex bags had minor skin irritation, one a rash related to the straps pulling on hairs on the leg and the other minor redness and swelling which resolved within 24 hours.

Kennedy et al. [113] tested the performance of ten different drainage bags in a simulation study involving 40 subjects (mostly health-care staff) which focused particularly on taps. Significant differences ($p<0.05$) were found between many pairs of bags with regard to each of the performance aspects studied: ease of tap opening and closing, ability to empty the bag without urine wetting fingers; and how easy the tap mechanism was to understand. Taps comprising caps or bungs were found to be particularly fiddly and messy to use.

In a study which focused primarily on the cross-infection risks associated with leg bags, Wilson and Coates [114] evaluated four leg bags. Each of ten long-term catheterised patients was invited to try each bag for a week in turn. The authors concluded that no one bag suited every patient; rather, each was liked by some users. The popularity (or otherwise) of many features was a matter of personal preference. Adverse comments mostly related to the tap (difficult to operate, opened accidentally, causing leakage) and the straps.

The UK Medical Devices Agency [115] evaluated all 14 sterile 500 ml leg bags on the UK market in 1995 in a multi-centre study involving 83 test subjects (58 men, 25 women). About half (44) lived in their own homes and almost all the rest in nursing / residential homes. Subjects were divided into pairs matched for sex, mobility, manual dexterity and dependency and each pair was offered each of the 14 bags (seven each) to try for a week in turn. Preferences varied but the main concerns of users consistently focused on taps (many subjects found many taps difficult to operate), straps (discomfort was common) and the minimisation of leakage (through faults in bags and / or connectors; onto the fingers when emptying; or by the tap accidentally opening in use). The most popular bags tended to perform well in these three respects.

In a multi-centre study involving 34 men (age range 27-84y; mean age 55y; all sheath users) Fader et al. [116] evaluated all seven non-sterile 500-700 ml leg bags on the UK market in 1997. Twenty-five of the men lived in their own homes and the rest in residential/nursing homes or long stay wards. Conclusions were substantially similar to those for the earlier MDA study.

Some international standards have been developed which provide general advice on bag performance and test methods [53]. These standards can be useful to laboratories asked to advise on bulk buying choices.

b) Urine drainage bag suspension systems

Little research has been undertaken on urinary drainage bag suspensions apart from a study by Thelwell et al. [117]. Thelwell et al. conducted a cross-over study using 52 subjects (20 men, 32 women). This study compared four suspension systems for fastening leg bags with the leg straps they had used prior to the study. Each subject evaluated each product for a week in turn and recorded their findings on a weekly questionnaire. Again, difficulty of application, comfort, discreteness and cost were key issues. However, there is suggestion in the literature that urinary drainage bag suspensions have an important role to play not only in the comfort and security of the wearer but in the prevention of urinary tract infection regardless of whether the drainage system is connected to a sheath or an indwelling catheter.

Munnings and Cawood [118] report the findings of a pilot study designed to evaluate the use of a belly bag of 1,000ml capacity and worn 24 hours a day, thus eliminating the need to use two separate bags and reducing the number of times the closed system is broken, Twenty-nine patients from a variety of areas from within an acute care setting who were using continuous catheter drainage systems were invited to participate, with 27 of the participants completing the study. All agreed to wear and then compare the belly bag with their previous leg and night drainage bag system. Worn around the waist, the belly bag is not positioned below the bladder: the manufacturers claim that the pressure of the bladder muscles is sufficient to ensure that urine flows through the catheter from the bladder into the bag. The residual pressure of the bladder is reported to be around 10-25cm H_2O, while the manufacturer asserts that a pressure of only 6cm H_2O is necessary to ensure the urine drains into the bag. Following education of how to use the drainage bag, users were given a questionnaire designed to facilitate comparison between the previous drainage system used and the belly bag. This was followed up with a telephone call. All agreed the belly bag was an improvement over their previous system of leg and overnight drainage bags, and found it more convenient, comfortable and less likely to cause pain with movement.

It has been suggested that current standard drainage tubing / bag designs evacuate the bladder sub-optimally, leading to retention of residual urine. Outflow obstruction can be caused by the development of air-locks in the dependent curls of tubing. A new drainage tubing design which incorporates a coiled downward spiral shaped configuration has been reported to eliminate air-lock obstruction [119] in experimental and clinical studies. However the importance of this in relation to infection requires further study.

There is opinion in the literature that positioning standard drainage bags below the bladder in a

manner that averts kinking will prevent reflux of urine, and associated infection [120], [121], [122]. When doing so care must be taken not to increase traction or friction [109]. This can be achieved with the use of supports specially designed to divert accidental pulling on the catheter or sheath. When using these support systems allowance should be made for penile erection and tumescence [109].

The drainage system for indwelling catheters should be positioned off the floor to reduce the risk of cross infection [120], [121], [122]. Some sterile and unsterile leg bags come with a variety of tubing lengths or tubing that can be cut according to the needs of the individual, and leg straps that can be adjusted to allow positioning of the bag on the thigh or calf. Night bags - even if the tubing can be cut - rely on uniform stands or hangers to ensure that they are off the floor. Roe et al [123]) raised the issue of poorly designed support systems for night bags. Expert opinion suggests that this still remains an issue.

c) Infection and cross-infection issues for management of urine drainage systems for indwelling catheters.

Usage of urinary catheters and their drainage systems increases the risk of urinary tract infection and cross infection (See Section XII.2.h). There is evidence to suggest that catheter associated infections are reduced with the use of closed urinary drainage systems. A randomised controlled trial was reported by Platt et al [124]. This trial compared the incidence of infection (measured as 10^5 cfu/ml in catheter urine or drainage bag urine) between patients who were catheterised using sealed junction catheters (i.e. catheters pre-connected to a drainage bag using a sealed junction), and those catheterised using unsealed junction catheters (i.e. unconnected catheters and drainage bags), in a hospital setting with a median period of catheterisation of three days. For subjects not taking antibiotics, sealed junctions showed less infection than unsealed ($p=<0.01$). For subjects taking antibiotics there was no difference in infection rates between sealed junctions and unsealed junctions. The infection rate appeared to be consistently lower in the subjects taking antibiotics than the ones not taking antibiotic but no statistical significance tests of this effect were reported.

Maintaining a 'closed' system has since become an important tenet for avoidance of urine infection both particularly in acute care but also in long-term care. This has led to the introduction of products designed to maintain a 'closed' system. In the UK the 'link' system is advocated whereby legbags are designed with a connector to attach to a night drainage bag, thereby obviating the need to disconnect the legbag from the catheter in order to connect a night bag. Use of non-drainable (single-use) night bags is also recommended in the UK (RCN 2008) presumably to reduce the cost of using a new (and more expensive) drainable night bag every night and also to avoid the practice of cleaning and re-attaching drainable night-time bags. However it should be noted that this 'link' system is not completely 'closed' (because the night bags are still disconnected and reconnected every night – albeit at the legbag tap rather than at the catheter) and the legbag may still be disconnected at the catheter junction for other purposes such as bladder instillations.

If a 'link' system is not in use then whenever a legbag needs to be changed to a nightbag the bag will need to be disconnected at the catheter junction. The bag (leg or night) may then be replaced (or more commonly) will be cleaned and reused. As yet there have been no studies to compare the use of the 'link' system with a conventional disconnection system.

The number of days that a legbag may be safely (or acceptably) left in place before it is replaced is unknown. There is little research to support the common practice of changing drainage bags every five to seven days (or any other particular change regime). The practice appears to be based upon expert opinion, anecdotal evidence and manufacturers' recommendations. The five to seven day practice seems to be challenged by a study by Rogers et al. (1996) [125],of biofilm progression,which showed that it took only four days for colonization in the bladder model to extend all the way to the drainage bag (Royal College of Nursing, 2008).

A prospective study of catheter use in the US, of 43 long-term catheter users, indicated that drainage bags were changed less often than either commonly reported, or Rogers et al. suggest. In that study, drainage bags were replaced an average of every 23.5 (95% CI 21.1-25.9) days, during their six months' participation in the study [126].

Of interest is the study outlined by Keerasuntonpong et al. [127] which was a randomized controlled study that compared the incidence of catheter-related urinary tract infections in a group of 79 hospitalised patients whose catheter bag was changed every three days with that for a group of 74 patients who had their bag changed at the time of the catheter change or if the bag became faulty. A urine sample for culture was obtained for each participant every seven days, on the day the catheter was removed or on the day the participant was suspected of having an infection. The findings suggest that urinary drainage bags could be left for longer than three days but the authors were reluctant to define how long as the sample size was considered too small to rule out a false-negative result. They recommended additional study.

Single use drainage bags, including non-drainable urine bags (NDB), were recommended in England's Royal College of Nursing Catheter Guidelines (2008) for all sites of care (hospital based and community living patients). Only one study was found of this product. Hardyck and Perrinovich (1998) [128] described a retrospective home care trial of a NDB in 63 elderly patients, comparing with the same persons who had used a typical drainable bag (DB) in the previous months. The non-drainable bag was replaced when full, but no information was given about the capacity of the bags, the mean number of bags used per day or how often they were replaced. Fewer UTIs (and hospitalizations) were reported with the NDB, 71 (2) versus 1395 (27) in the DB. Unfortunately the methodology was flawed in several ways. Counts of UTIs were reported though the timeframes were vastly different, with a mean of 44.4 months for DB prior to the intervention period and a mean of 8.8 months for NDB. UTI diagnosis was determined by mailed questionnaires to 82 home care patients and information from nurses, physicians, and patients as well as chart information reviewed by the physicians. Comprehensiveness or completeness of the chart data extraction was not described. Additional analysis comparing matched timeframes of 16 months for a subsample of 15 (and 5 more within 2 months either direction) indicated that the mean number of UTI related hospitalizations in the NDB group was significantly higher: 12.1 (SD 8.87) as compared with 2.8 (SD 4.74) in the DB group (Wilcoxan rank test $p<0.005$). The matched pairs were selected based on whether the NBD was used for at least a month and chart data were available. Given questions on the methodology, it seems that a well designed randomized trial is needed, but no such study was found.

There is no evidence to support the practice of adding in situ antiseptic agents to drainage bags to reduce catheter-associated infection. A paper by Thompson et al. [129] which was primarily looking at the effectiveness of hydrogen peroxide instilled into closed drainage bags in reducing infection in drainage bags and in catheters also raises the question of whether catheters are infected primarily via drainage bags or vice versa. This prospective randomised study in a hospital setting involved daily sampling for bacteriuria (See Section XII.2.h for further discussion of outcome measures for catheter-associated infection) in catheters ($>=10^5$ cfu/ml) and drainage bags ($>= 10^3$ cfu/ml) and identifying the infecting bacteria species. In a sample size of 688, infection was found in 68 catheters and 78 bags. Although bag contamination was 8% in the H_2O_2 group and 16% in the control group ($p<0.001$) there was no significant difference in catheter bacteriuria (11% and 9%, respectively). One of the reasons given in the paper for questioning whether the drainage bag is the main source of catheter infection was that 77 % of the bags in this study were contaminated later than the catheters.

Best practice guidelines to prevent infections associated with short term indwelling urethral catheters are available. The most recent of these, the EPIC 2 guidelines, were revised in 2005 and reported by Pratt et al. [122]. Designed to prevent short term, indwelling urethral catheter associated infection in NHS Hospitals in England, the guidelines are based upon a series of systematic reviews that include the best available evidence (experimental and non-experimental research as well as expert opinion). These guidelines recommend a closed catheter system where drainage bags are changed according to the manufacturer's recommendations (5-7 days) or the patient's clinical need. The guidelines also recommend that antiseptic or antimicrobial solutions are not added to urinary drainage bags.

Recommendations for acute care settings were issued by the Society for Healthcare Epidemiology of America (SHEA) in 2008[130]addressing system wide infrastructure preventive activities. These include use of written guidelines, complete documentation, surveillance for catheter–associated UTI (CAUTI), education and training of personnel related to catheter insertion and management, and appropriate insertion technique. The authors noted that decreasing catheter use and duration are central to preventing bacteriuria and CAUTI. Suggestions were given for organization-wide strategies, such as reminder systems for review of catheter continuation, automatic stop order processes, ward rounds to enhance communication and review, catheter related protocols like post operative duration, and systems for data reporting. Guidelines from SHEA for preventing infection in long-term care facilities were updated also in 2008 [131].

d) Long-term management of urine drainage systems and reuse of components

The quandary for health professionals involved in the education and support of clients, who are self-managing and often financing their long term indwelling catheter drainage systems while living at home, is that they are aware that many of them are leaving the bags on for much longer than the manufacturers recommend and are often washing the bags out with a variety of solutions and reattaching the bags directly to the indwelling catheter. The reuse of drainage bags is often not a matter of choice but necessity in developing countries. In a survey of 28 continence nurses who were members of ICS, a majority (68%) said they advised their community dwelling patients to reuse drainage bags [132]. A number of reasons were given, such as cost of bags, evaluation of risk in the patient, policies, guidelines, and ability to do the procedure. While advice varied, most suggested a solution of water mixed with vinegar, household bleach, or dishwashing detergent.

There is a paucity of studies that have explored long-term self-management of urinary catheter drainage systems in a community setting. Moreover,

practices may vary considerably in parts of the world where catheter supplies are not routinely provided by prescription, as in the UK, or in developing nations where supplies are scarce. More research in this area is needed to provide guidance to clinicians. Implications involve cost, aesthetics, and environmental waste, particularly when single use non-drainable bags are used.

Madigan & Neff [133] undertook a literature review (50 studies) that explored the complications and long term management of long term indwelling catheters used for urinary retention and incontinence. Their recommendation in relation to management of drainage bags was that closed drainage systems were preferred best practice. However they also indicated that leg and bed bags may be used for up to four weeks if the system is broken daily to allow daily bag decontamination with a diluted (1:10) bleach solution This recommendation appears to be based on the following two trials, one of which involved 54 participants sampled from an acute care rehabilitation centre and one involving 14 community dwelling participants.

Dille et al [134] report a randomised group parallel study with a pre-test and multiple post-tests utilised to determine the safety of a four week re-use of vinyl leg and bed bags compared to the usual practice of one week when de-contaminated daily with a procedure that utilised dilute bleach (sodium hypochlorite, 1:10 bleach to water). This study was based on previous research in which daily decontamination of drainage bags was done as compared with replacing with new sterile bags each day [135]. Set in an acute rehabilitation unit, 54 participants (18 female and 36 males) completed the four week data collection period. Randomised by the flip of a coin, 28 participants were in the experimental group and 26 in the control group. All participants had an indwelling catheter and were using a leg bag during the day and a bed bag at night. Both groups received identical daily bag decontamination and weekly bag and urine cultures. A standard of 0 to 100 cfu/mL was used to measure bag decontamination effectiveness and the urine cultures were processed by the Associated Regional and University Pathologists Inc. No significant differences were found between groups and the authors concluded that it is safe and cost effective to reuse vinyl bags for four weeks as opposed to the previous practice of one week, if the protocol for daily decontamination described is used. This study does not compare the practice of washing out the drainage bags with the chlorine solution either weekly or for a period of four weeks with a closed urinary catheter system to determine if that would result in fewer UTI's.

Rooney [136] reported a study of 14 people with neurogenic bladders living at home. They changed from using daily sterile leg bags to non-sterile leg bags which were washed out after use each day with a dilute chlorine solution. Nine participants were on Foley catheter drainage and five were using sheaths. Bedside urine collection bags were used by all participants at night and there was no change made to the standard practice of rinsing the overnight bag with water each morning and recapping the drainage tubing. While the steps of the procedure were described, no information was given on who did the decontaminating, i.e., patients/caregivers or both. The study ran for three months including a preliminary baseline phase of one month. No comment was made on whether the non sterile bags were changed. There were no symptomatic UTI infections during the study and urine samples with bacteriuria (>105 cfu/ml) did not increase. However the sample was very small and no statistical tests were applied to the results.

e) Urinary drainage bag features intended to reduce the risk of cross infection

The cross-infection risks of leg bags (particularly via the tap or sampling port) have been studied by Glenister [137] and by Wilson and Coates [114]. In her study Glenister [137] concluded that designs in which the tap and outlet spouts were most widely separated were most effective at preventing contamination of the hands with urine. Wilson and Coates [114] studied sampling ports and contamination of leg bag spouts. They suggested that the night connector tubing attached to the taps on the four leg bags in their study made decontamination difficult.

A small comparative study of two sets of closed system bags with a double non-return valve and two set of bags with a single non-return valve - all inoculated with Escherichia Coli and using simulated laboratory conditions in two separate microbiological laboratories blinded to each other - found that the colonisation of a simulated bladder was significantly delayed when the double non return valve was used [138].

f) Purple urine bag syndrome

There are occasional reports in the literature of purple discolouration in urine drainage bags – termed, purple urine bag syndrome (PUBS) – and there is considerable debate and diversity of opinion over the cause and significance of the phenomenon. Two case controlled studies were found.Tsumura et al. (2008) [139] compared five persons with PUBS to10 without it.Urine sugar, serum amino acids, and leukocytes were similar, but the PUBS group differed in having a high alkaline urine in combination with bacteriuria. An earlier study had showed similar results with a high urinary pH. Mantani et al [140] conducted a case controlled study on 26 patients in three long-term wards. Fourteen (two men and 12 women) had exhibited PUBS while 12 (four men and eight women) had not. The clinical, microbiological and bacteriological backgrounds of the subjects in the two groups were compared to identify possible causes of PUBS. The findings of both studies suggest that urine that is alkaline and has a high

bacterial yield are most likely to exhibit PUBS. There is no evidence to suggest detrimental effects on patients' health or functioning of the drainage system. However, the smell can be very distressing.

Studies which have compared leg bags and catheter valves are reviewed in Section 12.

4. SUMMARY

Taken together, published studies agree that the main factors to consider in selecting leg bags are the ease of tap operation, the comfort of suspension systems and the minimisation of leakage (Level of Evidence 2). Bags in which the tap and outlet spout are widely separated are most likely to be effective at preventing contamination of the hands with urine and cross-infection (Level of Evidence 3). There is high level evidence from studies – predominantly in acute care settings - to support the use of closed urinary drainage systems (Level of Evidence 2).

5. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION

Provision of clearly presented information based on the best evidence available is needed for clinicians, carers and patients as many aspects of caring for a urinary drainage bag system are supported by scant or conflicting evidence or by custom.

There is agreement that the hands must be cleansed and clean non-sterile gloves put on prior to caring for the urinary drainage bag system and that, on completion of handling the system, the gloves must be discarded and the hands cleansed again [141], [122].

There is also mention of confusion arising for clinician, patient and carer because of the many different designs of urinary drainage bag taps, and the regularity with which such features are changed [142]. Manufacturers should ensure that the instructions and accompanying literature that they develop for their urinary drainage bag systems are clearly presented and easily understood [142] in a format which is convenient to retain and refer to.

6. RECOMMENDATIONS

In making urinary drainage bag selections particular attention should be focused on: the ability of the user to operate the tap; comfort (especially of the straps); freedom from leakage (especially from the welds and the tap); and discretion (especially visibility beneath clothing) (Grade of Recommendation B).

The patient's individual needs and personal preferences should determine the use of leg / suspension / attachments and position of where the bag is worn (Grade of Recommendation C)

Maintain closed urinary drainage system for indwelling urinary catheterisation where the system is only broken to change the sterile bag according to manufacturer's recommendation or in a shorter period of time if clinically indicated. (Grade of recommendation A).

7. PRIORITIES FOR RESEARCH

Jones, et al [141] identify many of the issues concerning the handling of urinary drainage bag systems that require further research, including the issue that has already been discussed above, of how long a closed urinary drainage system can be left unbroken before the urinary drainage bag is changed. Jones et al [141] also suggest research is needed into:

- How often and how drainage bags should be emptied?
- If a closed urinary drainage bag link system is used, does the night bag that is connected to the leg bag need to be sterile or can it be a reusable one?
- If a reusable night urinary drainage bag can be used, how should it be cared for when not in use?
- What is a reasonable method to dry reusable bags after they have been washed?
- Establishing whether the incidence of UTI is increased in hospital, community or residential aged care settings when urinary drainage bags in closed drainage systems are changed at different intervals (eg the time of catheter change rather than weekly).
- Determining in own home settings whether a closed catheter drainage system is more effective at preventing urinary tract infections than reusable non-sterile urinary drainage.
- Determining which method of cleaning non-sterile urinary drainage systems is most effective and acceptable to patients.

IX. BODYWORN URINALS

1. FEMALE BODYWORN URINALS

Pieper [143] has reviewed the many attempts to design bodyworn urine collection devices for women. The major challenge is in achieving a comfortable and aesthetically acceptable leak-proof seal with the body. Various designs have sought to achieve this by holding a collection device over the urethral meatus with the help of suction, straps, adhesive or close-fitting underwear. While none have found widespread success and usage, they are available commercially in some countries.

2. MALE BODYWORN URINALS AND DRIBBLE CONTAINERS

The urine collection devices most commonly used by men are sheaths (see Section VIII) but a variety of other products such as pubic pressure urinals are available. They comprise a ring-shaped opening or cone-shaped component which is worn around the

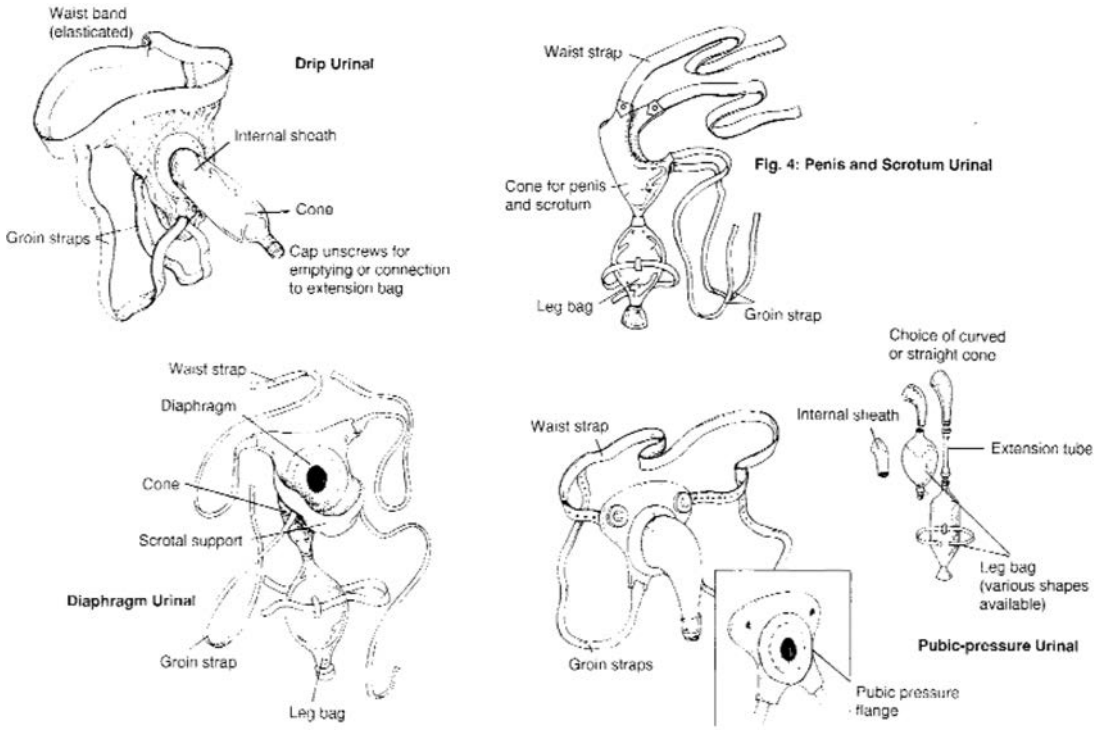


Figure IX-1: A variety of pubic pressure bodyworn urinals for men.

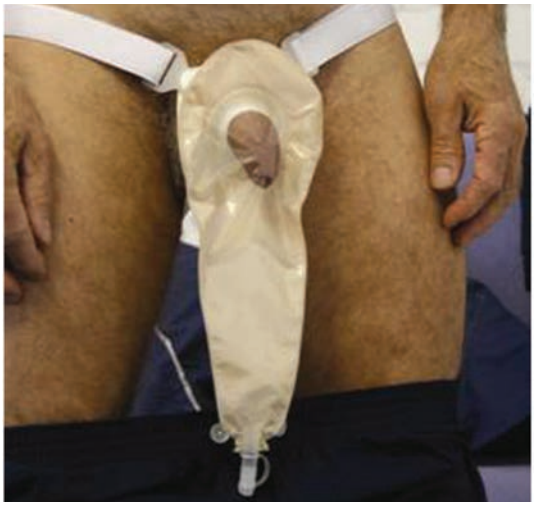


Figure IX-2: A dribble pouch

penis (and held firmly against the pubis by means of a belt and straps) and channels urine to an integral collection bag (**Figure IX-1**). Such devices are not widely used but they can be effective for individuals whose penis is too retracted for a sheath to be suitable. There are no published evaluations of these products.

They should be fitted by a specialist: a good fit is crucial for comfort and to avoid leakage. It is also important that the wearer / carer understands how to use the device and the importance of skin care, The wearer / carer will need good manual dexterity to manage the device. Several urinals will be needed to use in rotation, allowing each to be properly washed and dried between periods of use.

Dribble pouches are also available for light incontinence (**Figure IX-2**) but there are no published evaluations of these products.

3. PRIORITIES FOR RESEARCH

There is a need for leak-free, comfortable and aesthetically acceptable body-worn urine collection devices for women and improved (in these respects) products for men.

X. MECHANICAL DEVICES FOR WOMEN WITH URINARY INCONTINENCE

Female mechanical devices are designed to prevent urinary leakage in different ways and fall into three main categories: those that are applied over the urethra at the external meatus; those that are placed within the urethra (intraurethral devices) and those that are inserted into the vagina (intravaginal devices). Both designs of urethral device are intended to occlude the urethra and the intravaginal devices are intended to provide some support to the bladder neck and possibly some compression to the urethra. These devices are also known as occlusive devices and are primarily used by women with

stress incontinence. There is a recently updated Cochrane review of these devices [144].

General guidelines on patient assessment for product selection are discussed in Section II. Aspects of assessment that are particularly important regarding mechanical devices are high levels of motivation and acceptability of the concept of use, good cognition and good manual dexterity. They should probably be avoided by those with skin sensitivity or if avoidance of urinary tract infection is a priority.

1. DEVICES THAT OCCLUDE AT THE EXTERNAL MEATUS

Urethral occlusion devices have been developed to block urinary leakage at the external urethral meatus (**Figure X-1**). Several devices have utilized either adhesive or mild suction to achieve occlusion. In addition to the simple barrier effect, compression of the wall of the distal urethra has been hypothesized to contribute to continence.

Miniguard (Uromed Inc., but no longer available) is an angularly shaped foam device which utilizes an adhesive hydrogel to adhere to the peri-meatal area. The device is single use, removed prior to voiding, and disposable. FemAssist (InsightTM Medical Corp., but no longer available) is a hat-shaped silicone device, which adheres by applying an adhesive gel to the edge of the device, squeezing the central dome and creating a vacuum. The device is then placed over the urethral meatus and, upon release, the meatal mucosa is drawn up into the device and the urethral lumen is occluded. It may be worn for up to four hours or until voiding, after which the device is washed in hot soapy water and reapplied. The device was reusable for one week. CapSure (CR Bard Inc., no longer available) was applied and retained by suction. A petroleum based lubricant is applied prior to device use. The device is removed for voiding and re-utilized for up to two weeks.

a) Quality of data and results

Miniguard: Eckford et al. [145] studied the efficacy of a single application of this device during a one hour pad test and reported that 25% of patients were continent, 50% were improved, but 25% had worse incontinence. Brubaker et al. [146] enrolled 411 women to their study; 390 used the device, and 346 completed the study. Results showed significant improvement in symptoms. The incontinence impact scores significantly decreased from a mean of 41.0 (out of 300 – high scores worse) to a mean of 10.5 at 17 weeks. Twelve hour pad test showed mean urine loss decreased significantly from 15.8 to 6.9 ml and incontinence episodes from 14.2 episodes per week to 4.9 episodes at week 17. Symptoms of vulvar irritation or lower urinary tract discomfort occurred in a small percentage of subjects but it was generally transient, and only three women discontinued using the device for this reason. There were no statistically significant differences in the proportion of subjects reporting urinary tract infection during device use compared to beforehand. The authors concluded that the device was safe and effective (Level of Evidence 3).

Fem Assist: Versi et al. [147] studied 155 women with stress or mixed incontinence, of whom 133 attempted to use FemAssist and 96 enrolled in a four-week study. Their mean pad test loss fell from 27 g to 9.4 g ($p<0.001$) and 49% were dry. Symptomatic cure was more likely in those with mild incontinence. Of the nine women who had a positive pad test (>2 g) without the device, five were dry (<2 g) with the device ($p<0.05$). VAS scores showed a significant improvement for the symptom of stress incontinence ($p<0.05$). QoL scores improved significantly by 38% ($p<0.05$) for the IIQ and 29% ($p<0.01$) for UDI (Level of Evidence 3).

Moore et al. [148] reported on 57/100 recruited women who completed a one-month trial. Reduction of incontinence was statistically significant on pad testing, which revealed that 47% of the patients became continent and 33% had more than 50% benefit compared to baseline, while 9% had worse leakage. Those with severe baseline leakage were as likely to respond as those with mild or moderate pad test loss. Women with stress, urgency or mixed incontinence appeared to respond equally well. Dropouts included 13% who were unwilling to utilize the device (Level of Evidence 3).

Tincello et al. [149] in a 3-month prospective study involving 27 women with urodynamic stress incontinence found the median (range) loss with and without the device was 4.9 (0-65) ml and 21 (1-94) ml respectively ($p<0.01$); and 20 patients were

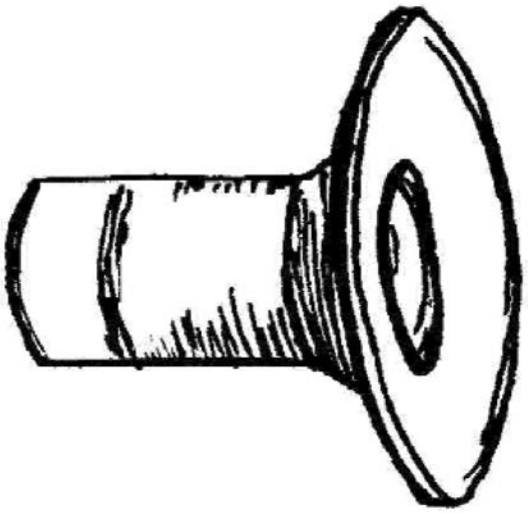


Figure X-1: A female occlusive device that occludes at the external meatus.

less wet when using the device. Discomfort was greater among the women with a greater loss. The acceptability correlated negatively with discomfort (r = -0.53) and negatively with embarrassment (r =-0.39); 15 patients (56%) reported that they would use the device in the long-term (Level of Evidence 3). Tincello et al. [150] later reported on 41 women recruited to use the device over a three month period, but 10 declined to participate, six withdrew before two weeks, 10 failed to attend two week follow-up and 11 did not attend three month follow-up. Only two completed the study. There was no difference in pad test or voiding diary grades. The authors concluded that the device had low acceptability and was ineffective, and could not be recommended for non-surgical management of stress incontinence (Level of Evidence 3).

CapSure: Bellin et al. [151] reported on 88/100 completers after 12 weeks, with 82% elimination of leakage on pad test, 91% continent on provocative stress test (single cough assessment of leakage), and 48% dry and 40% improved on urinary diaries. Pad test leakage decreased from 6.67 g (range 0.55-25.95 g) to 0.19 g (range, 0-2.5 g) by week 12. Five patients withdrew secondary to vaginal irritation and three due to poor device fit (Level of Evidence 3).

Shinopulos et al. [152] carried out a multi-centre study enrolling 100 women with stress incontinence who wore the device for 12 weeks. Eighty-four women completed the study. Mean pad weights reduced from 6.7g at baseline to 0.19 by week 12. Complications affected seven patients, including urethral / vaginal swelling and vulval abrasion, but none of the affected patients withdrew from the study. The IQOL tool showed significant mean improvement from 62.3 to 90.4.

b) Summary

External urethral occlusive devices were found to be of varying efficacy, with minimal morbidity. Efficacy of the combined studies reveals a continence rate of approximately 50% dry and two-thirds of patients improved, but this data is from open studies (typically pre-test / post-test with no control group) and there have been no randomised controlled trials. Devices achieve occlusion either by blocking at the meatus or compressing the distal urethral lumen and adherence to the peri-meatal area is essential to success. However, the method and degree of adherence is also the determining factor for the type and severity of local irritation. Patient selection based on motivation, appropriate anatomy, and manual dexterity, in combination with efficacy and morbidity will determine overall satisfaction. There is no data which compares one extra-urethral device to another, or to other categories of products. Cost comparisons for disposable versus short-term reusable devices are not available. Efficacy for different grades of incontinence has not been established. The objective degree of continence improvement in the clinical laboratory (pad and stress tests) is greater than in community use (diaries). The devices tested in these studies are no longer available and there are no external urethral devices currently on the market.

c) Recommendations

Although these devices have proved effective for some women (limited mainly to those with high motivation, manual dexterity and cognitive function), it appears that they have failed to find popularity with users and clinicians. They are no longer commercially available and so no recommendation on their use can be made.

d) Priorities for research

Further research on the development and role of devices which block urinary leakage at the external urinary meatus, with a focus on improving patient acceptability is recommended. One half of patients utilizing these devices in monitored studies were dry and two-thirds of the patients were improved with minimal morbidity. These devices may have a future role in the algorithm of conservative treatment based on patient acceptance, availability and cost, especially in those patients with mild or moderate stress incontinence, for occasional or intermittent use and/or for those who prefer to avoid pads or surgery.

2. INTRAURETHRAL DEVICES

Urethral inserts are silicone cylinders that are self-inserted or removed at the patient‘s discretion. They are intended for day-time use, especially during vigorous physical exercise. While some women manage exercise incontinence by limiting fluid intake before or during exercise, by choosing sports that allow frequent bathroom access, or wearing absorbent pads, 20% to 40% of women cope with leakage by ceasing exercise [153]. These devices have external retainers or flanges to prevent intravesical migration and proximal balloons to hold the device in place. They act by causing occlusion either in the urethra itself or at the external urethral meatus [154]. (**Figure X-2**)

The FemSoft (Rochester Medical Corporation) is the only urethral insert currently distributed. It has a soft, compressible, mineral oil-filled silicone layer with an insertion probe. Before insertion, the fluid distends the proximal end of the cylinder, as the user pushes the device (guided by the insertion probe) into the urethra, fluid transfers automatically to the distal end, allowing the device to pass through the urethra. Once in place, fluid flows back to the proximal end to hold the device in place. None of these devices are recommended for reuse after removal. The FemSoft Insert is currently packaged in a box of 28 inserts and each box is priced at $49.95. The Viva [155], Reliance and other intraurethral devices mentioned in this sub-section, are not currently marketed.

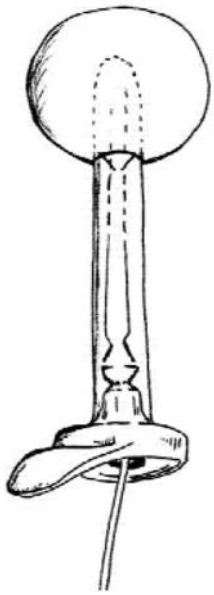


Figure X-2: A female intraurethral occlusive device.

a) Quality of data and results

The objective efficacy measurements utilized were the one-hour pad test, voiding diary and quality of life questionnaires. There have been no randomized control trials.

Nielsen et al. [155] [156] and Peschers [157] studied the Viva device. Peschers et al. screened 53 patients with USI and 21 patients accepted treatment with the two sphere device. During a four month study, the investigators analyzed subjective improvement and performed pad-weight and cough tests. The authors reported that 67% of patients had improvement in symptoms. Nielsen et al. [155] studied forty women who tested two variants of the device (with one or two spheres) each for two weeks in a cross-over study. They then continued with what they judged to be the better plug in period three (two months). Only 45% (18/40) completed this period but almost all (17/18) were reported to be subjectively and objectively continent or improved. Six women developed urinary tract infections and two of these had retained a plug in the bladder.

Staskin [158] reported on a four month study of 135 of 215 patients who utilized a disposable balloon tipped urethral insert made from thermoplastic elastomer, inflated with an applicator on insertion and deflated by pulling a string at the meatal plate for removal during voiding (Reliance, Uromed Corp., but no longer available). Eighty subjects discontinued the device prematurely, mostly because of discomfort and inability or unwillingness to use the device. Miller et al [159] and Sand et al [160] then reported on 63 of the 135 patients from the above cohort who utilized the device for one year.

The Reliance device provided 72% complete dryness with 17% improvement on diary, and 80% complete dryness and 15% improvement on pad weight testing in the study by Staskin et al. [158], and 79% complete dryness and 16% significant improvement on objective pad weight studies consistent with the improvement in subjective diaries ($p<0.0001$) for Miller et al. [159]. In the Miller study the patients reported improved comfort and ease of use over time. Sensation of device presence decreased from 35% at week one to 7% at 12 months. The volume of urine lost during exercise decreased from a median of 20g (range 4.9-80.2g) without the insert to 2.6g (1.3-6.8g) when the insert was worn ($p=0.03$). On a 5-point scale, in which 1 represented very comfortable and 5 very uncomfortable, subjects rated the mean comfort for the sessions performed with the insert in place as 2.1.

Treatment for positive urine cultures was undertaken in 20% of' symptomatic and 11% of asymptomatic patients, 39% of patients had positive cultures which were not treated and 30% had negative cultures at all monthly intervals for the four month study. The main reason for drop-out was discomfort [158]. One or more episodes of gross haematuria (24%), cystoscopic findings of mucosal irritation at four or at 12 months (9%) and asymptomatic bacteruria (30%) on monthly cultures were also documented [159].

Robinson et al [161] carried out a small randomised controlled trial comparing the NEAT device (intraurethral device with expandable tip) with the Reliance device. Twenty-four women (mean age 51 years) entered the study and there were eight withdrawals. Devices were randomly allocated and tested for four months. Improvement was reported for 6/8 women (NEAT) and 5/8 women (Reliance) when compared to baseline. There were no significant differences in the number of women improved, in mean reduction in urine loss, or in leakage scores between the two groups.

Boos et al. [162] reported in an abstract, a randomized prospective parallel group trial comparing the Reliance intra-urethral insert with the FemAssist external meatal occlusive device. Assessments at baseline, one month, and three months included subjective efficacy, seven day diary, and pad test (1 hour). Fifty-three females were randomized to the FemAssist and 49 to the Reliance device. There were some initial problems with sizing the Reliance. Once this was corrected, 40.8% (20) of women were subjectively dry and the remainder improved on completing the trial. Of women using the FemAssist, 28.3% [15] were dry, 60.4% [32] were improved, 9.4% [5] were no better and only one subject was made worse with device use. Problems experienced were few and minor with no serious adverse events. The conclusion was that both devices are efficacious, the FemAssist was more comfortable, but required a greater degree of user skill to achieve control of leakage (Level of Evidence 2).

Recent studies have investigated the efficacy of the FemSoft which is the only intra-urethral device which is currently available. Dunn et al. [153] measured pad weights during four standardized aerobics sessions during which six subjects were randomly assigned to exercise twice with the insert and twice without it. The medians of the averaged pad weights for the two different types of' sessions were compared. Median urine loss during standardized exercise sessions decreased from 20g (range, 4.9 to 80.2g) without the device to 2.6g (range, 1.3 to 6.8g) with the device (p=0.03). Five women used the device at home during unsupervised exercise; one subject had urinary tract infection. At the end of three months, satisfaction and comfort were rated high on a 5-point scale. The conclusion was that the FemSoft urethral device is an effective, safe, and comfortable treatment for exercise incontinence in women (Level of Evidence 3).

Results from a prospective three-year study, (FDA post-approval device safety data submitted by Rochester Medical Corporation, 2002 unpublished), for evaluation of the long term effect of the device involved 41 subjects. Of the group, nine women were 65 years or older (22%, 9/41); 80% were post-menopausal with 24 women (59%) being on hormone replacement. Thirty-eight, (93%) used absorbent products to contain urine leakage prior to enrolment. A total of 66 follow-up visits took place with an average participation period of 4.2 years. Seven patients withdrew in the third year, three due to non-study related health problems and one because of dissatisfaction due to urge symptoms. Two were lost to follow up. There was a significant difference in the rates of incontinence at the three-year follow-up between users and non-users of the device: 0.83 versus 2.64 episodes per day, according to voiding diaries. The difference in urine loss during pad weighing tests was also significant. There were 24 reported adverse events in the 41 subjects enrolled. None of these events required medical intervention except for antibiotic prescription in cases of urinary tract infection. The 24 events included: bacteriuria (11); symptomatic UTI (3); urinary symptoms (3); device performance problems (2); irritation (2); and migration (1).

In 33 women a total of 38 cystoscopies were performed at three years. Only one patient was reported to have an abnormal finding, but this was due to mucosal irritation produced by an indwelling Foley catheter during one hospitalization for a problem unrelated to the device. Patient satisfaction had not changed over the follow-up time interval. The Quality of Life questionnaire (I-QoL) scores at three years were compared to those at 12 months and there was improvement from the baseline of 60.6 to 74.0. No safety concerns concerning urethral integrity were identified after the three years of continuous use. The incidence of urinary tract infections, given the high number of insertions and removals, was considered low risk (Level of Evidence 3).

b) Summary

Intraurethral devices have demonstrated high efficacy, but have been associated with urinary tract infection, hematuria and discomfort. Bacteruria, without symptomatic infection, was similar to extraurethral device use, which approaches screening urinalysis data [146] or may be similar to the rates seen with self catheterization. Device migration into the bladder, which requires endoscopic removal is the most serious reported problem. Long-term results are limited. Patient and clinician acceptance of this form of therapy has also been limited and there is currently only one intraurethral device on the market. High cost is also a factor that probably precludes more widespread application but 'occasional' use, for example during exercise may be helpful and affordable for some patients. Good hand dexterity is necessary to use the device (**Level of Evidence 3**).

c) Recommendations

Intraurethral occlusive devices may be considered for women with stress incontinence but they are invasive devices with high cost and have had limited evaluation. They may be most appropriate for intermittent and occasional use (such as during vigorous exercise) (**Grade of Recommendation C**).

d) Priorities for research

It is important that new devices - particularly invasive ones - are evaluated by randomized trials and comparing to control approved devices. Long-term follow-up results are needed to demonstrate the effects of such devices on the urethra and / or bladder and will determine the real value and safety of devices that initially have been adopted enthusiastically.

Further development and study of the use of intraurethral devices for the treatment of urinary incontinence is recommended. In particular assessment of their cost-effectiveness and effects on quality of life, when used intermittently or for particular activities, is recommended.

3. INTRAVAGINAL DEVICES

Support of the bladder neck to correct urinary stress incontinence has been achieved, with varying success, utilizing traditional tampons, pessaries and contraceptive diaphragms, and intravaginal devices specifically designed to support the bladder neck.

a) Quality of data and results

1. Tampons / pessaries

Nygaard [163] performed a prospective, randomized, single blind, and laboratory based study testing 18 patients (age 33-73) with three 40 minute standardized aerobics sessions, utilizing a Hodge pessary, a super tampon, or no device. Urine loss was determined by a change in the weight of the pad worn while exercising. Statistical analysis of the log of urine loss revealed that women lost

significantly less urine when exercising with either the pessary or the tampon than when exercising with no device. Continence rates were 6/14 cured and 2/14 improved with tampons, 4/10 improved with a diaphragm (Level of Evidence 2).

2. Diaphragms / Pessaries

Realini et al, [164] analyzed the benefit for one week, in 10 selected patients of a coil-type diaphragm ring, which was softer than a pessary, utilizing diaries and a two hour pad test. They also gave an overall subjective evaluation of their experience. Urodynamic findings were essentially unchanged by wearing diaphragm rings. Four of the 10 women experienced clinically significant improvement in the amount of urine lost during pad tests, number of leaks per week, and overall assessment response (Level of Evidence 3).

Suarez et al. [165] included urodynamic testing in his evaluation of a contraceptive diaphragm in 12 patients. Complete resolution of SUI was achieved in eleven of twelve patients (91%) but two of them withdrew from the study because of associated discomfort from the diaphragm, therefore, complete resolution of SUI was achieved in 9/12 patients (75%) (Level of Evidence 3).

Bhatia et al. [166] reported on the urodynamic effects of the Hodge pessary on 30 women aged 29 to 71 with a history of UI. With the pessary, 24 of the 30 patients became continent when tested in supine position with a full bladder, three of the 24 patients lost urine with coughing in the standing position and demonstrated a positive cough profile despite the presence of the vaginal pessary. Uroflowmetry data show that the vaginal pessary did not produce any obstruction to the free flow of urine and suggested this is a modality to predict the outcome for bladder neck support surgery.

Richter et al (2010) [167] compared use of a pessary (ring or dish) with behavioural therapy (pelvic floor muscle training plus strategies for active use of muscles to prevent stress and urgency incontinence), compared with combined treatment in a randomized controlled trial of 446 women with stress incontinence. Outcomes were measured at 3, 6 and 12 months. There were small differences between groups at 3 months with slightly better results in terms of bothersome incontinence symptoms for the behavioural therapy group than the pessary group. Combined treatment was not significantly better than behavioural therapy alone and difference between groups were not sustained at 12 months.

The long-term discontinuation rates of ring pessaries (including the Introl device – see below) was investigated by Sarma et al (2009) [168]. A retrospective review of the notes of 273 women was carried out and found a surprisingly high rate of complications (93 (56%) of the 167 women who were successfully using a pessary at 4 weeks subsequently developed problems such as bleeding, extrusion, discharge and pain). The majority of women discontinued use of the pessary over time. It is therefore important that further studies of pessary use should include long-term follow-up results. Gorti et al (2009) [169] surveyed clinicians about use and follow-up of pessary placement and concluded that patients should be followed up at 6-12 monthly intervals.

3. Intra-vaginal devices designed specifically to support the bladder neck

Included in this category are:

1. Removable reusable intra-vaginal ring, composed of silastic, and constructed with two prongs which are placed behind the symphysis to support the bladder neck (Introl, no current distributor).

2. Single-use disposable devices: (i) A clam-type device composed of polyurethane foam, which is folded up upon its long axis and placed into the sagittal plane in the vagina, and when moistened, its dimensions expand by 30% and create a supportive cushion under the urethrovesical junction (originally called the Conveen Continence Guard, now known as Contrelle Activgard); (ii) A version of the expanding polyurethane design, with similarities to a tampon, (Conveen Continence Tampon, Coloplast, Denmark (no longer available) (**Figure X-3**); (iii) An expanding polyvinyl alcohol sponge (Ladycon, Home Care Engros, Norway); (iv) a simple surgical foam cylinder with drawstring e.g. Rocket stress incontinence device (Rocket Medical PLC)

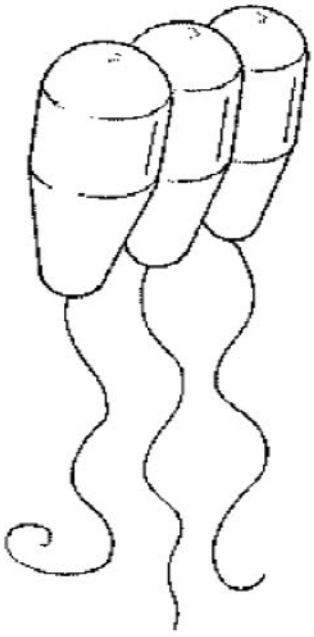


Figure X-3: A female intravaginal occlusive device.

4. Reusable intra-vaginal ring (Introl)

A pilot laboratory study was carried out by Biswas [170], the developer of the device, employed a straining cystogram. Eighty-six percent of the patients were continent with the device in place on cystogram. Following this study, the number of device sizes was increased from eight to 25. Evaluation studies followed examining efficacy, safety and satisfaction. Davila [171] initially demonstrated that 83% of patients were dry on pad weight test. Later [171] the researchers enrolled seventy women (53 completed) aged 24-76, 29 with stress, and 24 with mixed incontinence in a one month study. A statistically significant reduction in incontinence was noted on pad testing (stress mean 46.6-16.6g; mixed, mean 31.9-6.8 g) and in bladder diary (stress, mean 28.6-7.8 losses per week; mixed, mean 30.2-15 losses per week). QoL scores (I-QoL) improved in both groups. With the device in place, urodynamic testing indicated normalization of urethral function without evidence of outflow obstruction. Subjects found the device comfortable, easy to use and convenient. Side effects included five urinary tract infections and 23 cases of vaginal soreness or mild irritation (**Level of Evidence 3**).

Moore et al. [148] detailed problems with both sizing and efficacy. Of the 80 recruits, four could not be fitted, and 11 did not satisfy all entry criteria. Of the 65 participants, 39 (60%) withdrew; 20 for distorted vaginal anatomy which made fitting difficult, five for lack of efficacy, four for constipation, and ten for unrelated patient events. In the remaining 26 patients, pad test weights decreased from a baseline median of 19g to 2g ($p<0.001$), 62% were continent, and 15% were >50% improved, and wished no further therapy. Moore et al. commented that the device was difficult to fit in women who have had multiple vaginal surgeries or were oestrogen deficient. Long-term follow-up showed that 18 of 26 (from the original 65) continued to wear the device at six months (interim dropouts being due to concurrent illness in half, the remainder had declining efficacy). Of these, 78% continued to wear the device for a minimum follow-up of two years (**Level of Evidence 3**).

In a separate study of patients with mixed incontinence by Moore et al. [148], five of 21 recruits never wore the device home, leaving 16 participants. A further two did not reach week four, because of poor efficacy or inability to fit the device. In the 14 who reached week four, the median number of leaks/day declined from 4.3 to 1.0 ($p=0.002$). Median pad weight loss fell from 53g to 7g. ($p=0.012$). Cystometry showed an increase in maximum bladder capacity ($p<0.05$) and a modest reduction in severity of detrusor overactivity, with no evidence of outflow obstruction. Three women discontinued because of poor efficacy or a poorly fitting device, leaving 11 of 16 participants (69%) at week eight, when median pad weight decreased to 2 g (**Level of Evidence 3**).

Kondo,et al. [172] found no urinary flow obstruction with the device in place. Urine loss decreased from 20.6 to 4.8 g per hour ($p<0.001$) on the 60-minute pad weight test. Twenty two patients (29%), reported complete continence, and 39 (51 %) had decreased severity of incontinence by more than 50%. Minor adverse effects occurred in 26% of the patients. According to the global usefulness rating which was employed, 62 patients (81%) had some or maximum benefit (**Level of Evidence 3**).

5. Reusable intravaginal hollow tampon (Contiform)

The Contiform intravaginal device was first tested in 2003 and although significant benefit was shown only 20% of participants were completely dry on 24 hour pad test [173]. In 2007 Allen et al [174] enrolled 65 women to test the device and fitted 52 devices. 37 women completed the protocol (4 weeks testing). Urine loss on pad testing was significantly reduced from a median of 6.6g to 2.2g and there were significant improvements on the Incontinence Impact Questionnaire and Urinary Distress Inventory. Seven patients were unable to insert the device and two were shown to have residual urine over 100ml, but overall the authors concluded that the device was well tolerated.

6. Disposable intra-vaginal devices

Thyssen et al. [175] tested the Continence Guard in 26 women with stress incontinence before and after one month's use: four women discontinued the treatment because of discomfort or difficulties in using the device 9 (41%) were subjectively cured of incontinence, 10 (45%) improved while three (14%) claimed unchanged incontinence. With the device in place all had decreased leakage at the 24-hour pad weighing test and unchanged urodynamic tests. No vaginal or urinary infections were found (**Level of Evidence 3**).

Thyssen et al. [176] reported on 19/22 women with stress incontinence, subjectively and objectively cured or improved in a short-term study, and who then continued the treatment with the device for one year. All 19 completed the study, 13 (68%) were subjectively dry, (26%) were improved and one (5%) reported unchanged incontinence. All but one had decreased leakage at the 24h pad test, and 67% a greater than 50% decrease. Subjectively cure was 41%, and 36% were dry on 24 hour pad test. Overall reduced leakage was statistically significant ($p<0.0005$) No significant changes were found in the other urodynamic measurements, specifically, urinary flow rate.

Sander et al. [177] found subjective cure in 11/55 women (20%) and improvement in 27/55 (49%) was reported. Results of the 24-hour pad test and mean leakage and epi-sodes in the voiding diary significantly decreased. After three months, 58% of the 55 patients desired to continue device usage. There was a highly significant improvement in QoL scores using the IIQ, as well as two additional

incontinence-related quality of life questionnaires. Responses to the SF-36 general health questionnaire showed no significant changes

Hahnet al. [178] reported on 121 women, in a four week study. Patients dropped out because of vaginal irritation (25%), other product-related reasons (6%), lack of time (6%), or failure to complete a user questionnaire. Of the remaining 90 (mean age 47.5), 85 performed a 24 hour pad test, which showed that baseline leakage of 42 ml/24h decreased to 14 ml/24h ($p < 0.001$). Of these, 39 (46%) were continent. The device was considered unpleasant by 8%, and caused some local discomfort in 62% on direct questioning: 75% of these wished to continue using the device. The authors noted that older women (age 56-65) tolerated the device and appeared more motivated to continue. Coexistent atrophic vaginitis and the use of topical oestrogen was not discussed

Thyssen et al. [179] reported on 94 women recruited in a cross-over study, which compared two versions of the same device; the Conveen Continence Guard (CCG) and the Contrelle Continence Tampon CCT. 62 women (66%) completed the study with withdrawals mainly due to discomfort or for unknown reasons. Both devices reduced leakage significantly but the CCT was significantly better than the CCG. Few side-effects were reported. Thirty-two women continued the treatment for one year or more with 63% preferring the “tampon” type design for its ease of use.

The report on the polyvinyl sponge by Glavind [180] was an acute laboratory study of only six women utilizing a pad test measurement during 30 minutes of aerobic exercise Without the vaginal sponge the patients had a mean loss of 7g (range 2-18g) during exercise. With the vaginal sponge in situ there was no leakage.

Two papers have been published recently on the Tipi device (ConTIPI Ltd. Israel) [181] [182]. This device has a resin core with support ‘poles’ covered with a soft nylon mesh that stretches between the arms of the poles to act as a suburethral sling. Ziv et al. [183] recruited 60 women with severe stress incontinence to test the product. A seven day ‘control’ period was followed by a 28 day device usage period. There was no control arm or comparison product. Pre-weighed pads were used during the test period and the primary end point was the percentage of women achieving at least a 70% reduction in pad weight gain from the control period to the last 14 days of usage. Ten women withdrew from the study during the test period, four for device related reasons. Using intention to treat analysis 85% of women achieved at least 70% reduction in pad weight gain. The most common adverse events reported were mild and included genital tract discomfort, pain and spotting with blood; the only report of a moderate event was of candidiasis. The authors conclude that the device is easy to use, well-tolerated and effective.

Farage et al (2011) used a similar evaluation design with 57 women who had at least seven episodes of SUI per week. After a baseline period the women identified the best TIPI among a selection of three device sizes. The fitting period was followed by 14 days of device usage for up to 12 hours daily. The results of the 57 intention to treat population shows that 75% of the patients had at least a 60% reduction in SUI episodes, the subjective perspective of patients with regard to the severity of their incontinence improved and the results show also an improvement in the quality of life (statistically significant for: feeling frustrated, impact on social activities and impact on recreational activities). The authors stated that the device is safety in daily use and a nonsurgical alternative in the therapy for SUI.

b) Summary

Support of the bladder neck resulting in improved continence is possible with intravaginal devices without evidence that they cause significant lower urinary tract obstruction or morbidity, but the evidence is limited (Level of Evidence 3).

Studies performed in the acute setting, regardless of the device type, demonstrate better performance than diary based studies performed over time. Efficacy appears to be higher in patients with minimal to moderate urinary leakage.

Relatively high drop-out rates in monitored studies, during which patient support is provided, indicates the need for proper patient selection’ and patient and provider education, but may also indicate limitations in product efficacy, difficulties in application or other factors such as discomfort (Level of Evidence 3).

c) Recommendations

Intra-vaginal support devices may be considered as a treatment option when managing women with stress urinary incontinence, dependent upon the availability of product, patient ability to manage the product (particularly manual dexterity) patient acceptance, and cost (Grade of Recommendation C).

d) Priorities for research

Long-term results are not available and studies comparing these therapies to other forms of conservative therapy or surgery are needed

4. OVERVIEW OF MECHANICAL DEVICES FOR WOMEN

a) Overall summary

The recently updated Cochrane review of mechanical devices for urinary incontinence in women [144] review found seven trials that met their criteria and concluded that the role of such devices is questionable. The authors state that there are indications

that using mechanical devices might be better than no treatment but that the evidence was weak and that there was insufficient evidence to recommend any specific device or to show that mechanical devices are better than other forms of treatment.

In this section we have attempted to review all available evidence including many trials that did not meet Cochrane criteria. Most trials were open pre-test post-test trials with no comparators and the strength of this evidence is relatively weak. Although most trials showed positive effects on symptoms, this was often combined with relatively high drop-out rates and unwanted effects, such as discomfort, skin irritation or urinary tract infection.

Although many products have appeared on the commercial market, few have stood the test of time and are currently marketed – there are no external urethral devices available and there is only one intra-urethral device. There are at least two intra-vaginal devices available on the market and these may have potential to be more acceptable to women because of their similarities to familiar tampons. The relative lack of market success for these products may indicate low efficacy and unwanted effects, but may also reflect their relatively high cost compared to pads which are the main alternative.

b) Overall recommendations

It is possible that some of the mechanical devices currently marketed are effective and acceptable to a minority of women and, given that they are relatively non-invasive (with the exception of intra-urethral devices), they may be suggested to patients for consideration and testing, particularly for short-term or occasional use.

c) Overall priorities for research

The substantial withdrawal rate and the frequency of unwanted events indicates that that there is a need to establish efficacy of these devices (compared to no treatment) over longer time periods (more than a year), with careful identification of unwanted effects.

There is also a need to compare devices with simple, cheap devices. The Cochrane review recommends an intravaginal tampon as a suitable comparator.

There are indications that the devices may best be used occasionally or intermittently for specific activities and there is a need for this type of use to be tested, possibly compared to the most common alternative - an absorbent pad.

As these devices aim to prevent urine leakage there is also potential for testing their efficacy compared to other treatments such as pelvic-floor exercises or surgery.

XI. MECHANICAL DEVICES FOR MEN WITH URINARY INCONTINENCE

Male mechanical devices aim to prevent urine leakage by compressing the penis. A variety of designs are available but occlusion is usually achieved with either a clamp or a peri-penile strap (**Figure XI-1**). Such devices have the potential advantages of low cost and simplicity compared with a sheath and drainage bag. However there is potential for tissue damage and these devices should be used with caution.

Careful assessment is necessary for use of these devices because there is potential for damage to the penis from ischaemia (restriction of blood to the penis). Such devices should be fitted by a trained health professional and subject to regular review. Use should be limited to men who are assessed as being cognitively intact, are aware of bladder filling, have normal genital sensation and intact penile skin, have sufficient manual dexterity to open and close the device (Moore 2004) and are motivated and willing to use such a device.

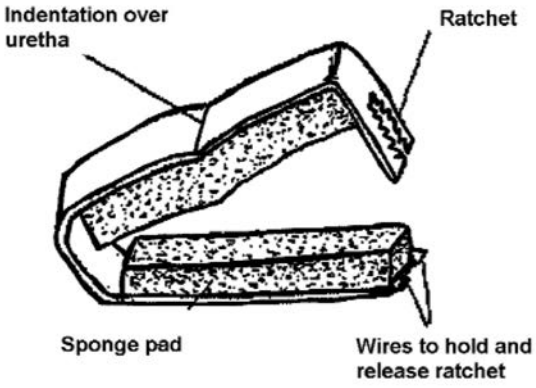


Figure XI-1: A penile clamp.

1. QUALITY OF DATA

The use of penile compression devices is described only rarely in the literature [184] [185] and is usually referred to as a last resort where other forms of management have failed or been judged inappropriate. There has only been one published evaluation [186].

2. RESULTS

Moore et al. [186] evaluated three different devices (Timms C3 penile compression device; Cunningham clamp; and U-Tex male adjustable tension band) in a cross-over study in which twelve men with stress urinary incontinence following radical prostatectomy tried each device in turn. Each of the devices significantly ($p<0.05$) reduced mean urine loss (measured using a 4h pad tests) compared with baseline measurements. There was some objective or subjective improvement in continence for

each of the 12 men with at least one of the devices, although none completely eliminated urine loss when applied at a comfortable pressure.

Ten of the 12 men rated the Cunningham clamp positively; two, the C3; and none, the U-Tex. However, the C3 and U-Tex allowed good cavernosal artery blood flow while the Cunningham clamp significantly reduced it. Overall Moore et al. concluded that, used correctly, the Cunningham clamp can be an effective method of controlling urinary incontinence (although it should be noted that complete control i.e. no leakage, was not achieved) in men with stress urinary incontinence who are cognitively intact and aware of bladder filling, and have normal genital sensation, intact penile skin and sufficient manual dexterity to open and close the device.

Expert opinion and anecdote suggest that penile clamps may be more successful when used for short periods, for example when undertaking activities such as swimming or jogging. Such activities may not only exacerbate incontinence but also preclude the use of bulky and / or absorbent products.

3. SUMMARY

Male mechanical devices can partially control urinary leakage (but not eliminate it at comfortable levels of use) but are likely to lead to reduced cavernosal artery blood flow and therefore care must be taken to ensure regular removal or release (Level of Evidence 2).

4. RECOMMENDATIONS

- Male mechanical devices may be considered for selected men with stress urinary incontinence who are cognitively intact and aware of bladder filling, and have normal genital sensation, intact penile skin and sufficient manual dexterity to open and close the device (B).
- The devices should be fitted by a trained health professional and reviewed regularly (Grade of Recommendation C).
- The devices may be considered for short-term use when undertaking sport or other activities, as an adjunct to management with other products (Grade of Recommendation C).

5. PRIORITIES FOR RESEARCH

- There is a need for mechanical devices for men which are discreet, easy to use and which prevent leakage without risk of tissue damage.

XII. CATHETERS

Urinary catheters can provide an effective way of draining the bladder in either the short-term or long-term, by intermittent or indwelling catheterisation, where alternative strategies are unsuitable or unsatisfactory. However, indwelling catheters are rarely completely trouble-free and the risk of catheter-related complications is high, with substantial detrimental impact on patients, carers and healthcare services. It is generally agreed that catheter use should be avoided wherever possible and only adopted for those for whom alternative strategies are unsuitable or unsatisfactory, after careful assessment of the patient and their particular problem [187].

This section examines the characteristics of urinary catheters, and provides a critical review of existing evidence to guide decision-making on choice of catheters, equipment and management strategies to minimise associated risks. Specific issues relating to short-term catheterisation are addressed, but the main focus of the section is on long-term management of bladder dysfunction, by intermittent catheterisation (least invasive) or indwelling catheterisation (most invasive). An overview of factors influencing choices of catheterisation strategy is provided in **Table XII-1**. Detailed discussion of key issues is provided under the following headings: user characteristics, catheter characteristics, associated risks / problems, catheter management.

The bulk of research evidence on catheter use relates to short-term catheterisation. In particular there are numerous trials which focus on catheter-associated urinary tract infection since this is well recognised as a major source of healthcare associated infection. The quality of data is very variable and many studies are limited by being underpowered and by other design issues, including poorly defined outcome criteria and highly selected study populations. Much less research has addressed intermittent or long-term indwelling catheter-related issues and guidance to healthcare practitioners remains largely based on expert opinion. Some of the difficulties in conducting research on use of continence products are discussed in Section III. Further discussion related specifically to catheters is provided within the following sections.

1. INTERMITTENT CATHETERISATION

Intermittent catheterisation (IC) is the act of passing a catheter into the bladder to drain urine via the urethra, or a catheterisable channel such as a Mitrofanoff diversion. The urine can be drained into a toilet, urinal, plastic bag, or other reservoir. The catheter is removed immediately after drainage. This technique avoids many of the problems associated with indwelling catheters. Intermittent catheterisation may be carried out using a sterile technique in some care settings, but clean intermittent catheterisation (CIC) or clean intermittent self-catheterisation CISC [188] is widely accepted as a safe technique for people who are self-caring in their own homes. Since some studies do not distinguish between CIC and CISC, the term CIC has been adopted to cover both throughout the following section. CIC provides much greater convenience than urethral catheterisation, without unacceptable

Table XII -1: Catheter choices. Catheters should only be considered where there is no satisfactory, non-invasive alternative to manage bladder drainage. ***(Grade of recommendation in brackets)***

Product category	User characteristics / priorities / contexts which:		Notes
	FAVOUR use	DISCOURAGE use	
Intermittent catheters (IC)	If more than 100ml retained in bladder (C) Concept of IC acceptable to user (or carer) User has sufficient dexterity and cognitive ability to manage regular drainage	In general (as with all catheters), where alternative, non-invasive management is satisfactory If user lacks motivation or unable to cope with regime	See Section 12.1 Greater independence for users No need for urine collection bags Reduced risk of catheter-associated complications Greater freedom for sexual activity.
Long-term indwelling catheters (LTC): general	Only for voiding problems which cannot be managed satisfactorily by other strategies (pads, other products or IC) (A) User or carer able to empty drainage bag regularly	In general (as with all catheters), where alternative, non-invasive management is satisfactory Avoidance of UTI is a priority (A) Cognitive impairment (danger of interfering with catheter) (C) High risk of recurrent catheter encrustation & blockage (B)	See Section 12-2 May be required: (i) to drain the bladder where there is urinary retention; (ii) to improve care of for those with severe incontinence who cannot manage otherwise, are terminally ill, or need secure urine drainage to heal skin lesions / wounds affected by the presence of urine
LTC: urethral insertion	Concept is acceptable	History of urethral trauma Haematuria of unknown origin High risk of catheter being expelled (bladder spasm)	
LTC: supra-pubic insertion	Concept is acceptable	Haematuria of unknown origin, Bladder tumour Small, contracted and fibrotic bladder User is obese	
Short-term indwelling catheter	Post-operative controlled drainage To monitor urine output To irrigate the bladder To instil medication To relieve retention of urine	In general (as with all catheters), where alternative, non-invasive management is satisfactory Avoidance of UTI is a priority (A)	

increases in infection rate, and has become a method of choice for management of bladder drainage for neurogenic and non-neurogenic bladder dysfunctions where urinary retention is a significant symptom and not easily remedied by other relatively simple means, eg TURP for prostatic obstruction. CIC can be taught to people of all ages, including the very elderly and children as young as four years old, with parental supervision [189] [190]. CIC can also be taught to carers, where this is an acceptable procedure to both patient and carer.

a) Quality of data

The majority of research evidence on intermittent catheterisation relates to catheter-associated urinary tract infection (CAUTI) and catheter materials and coatings. The most frequent complication of CIC is urinary tract infection (UTI) but it is unclear which catheter types, techniques or strategies, affect its incidence. There is wide variation in practice and important cost implications for using different catheters, techniques or strategies. Two relevant Cochrane reviews were identified; 'long-term bladder management by intermittent catheters in adults and children' [191]; and 'urinary catheter policies for long-term bladder drainage' [192]. The objective of the first review was to examine which intermittent catheter types, techniques or strategies, affect the incidence of UTI. Fourteen trials were included but sample sizes were small and attrition of participants was problematic. Definitions of outcome variables and follow-up periods differed, making it difficult to draw clinically useful conclusions. Several of the trials were more than 10 years old and were typically less rigorous in design and analysis. The authors concluded there is insufficient evidence to state that incidence of UTI is affected by use of sterile or clean technique, coated or uncoated catheters, single (sterile) or multiple use (clean) catheters, self-catheterisation or catheterisation by others, or by any other strategy. The objectives of the second review [193] were to determine if certain catheter policies are better than others in terms of effectiveness, complications, quality of life and economics. Comparisons included type of catheterisation (intermittent, indwelling urethral and indwelling supra-pubic) and antibiotic prophylaxis. Seven trials were included but all were small and confidence intervals were wide. There was limited evidence which indicated that prophylactic antibiotic therapy was associated with reduced episodes of bacteriuria (asymptomatic and symptomatic) in subjects using intermittent catheterisation. In both reviews, the trials which met the inclusion criteria were limited by small sample sizes and methodological weaknesses. A third review on 'catheter policies for management of long-term voiding problems in patients with neurogenic bladder' [194], which aimed to assess the effects of different types of urinary catheter (IC): in managing the neurogenic bladder, found there were no trials that met the inclusion criteria. Other research in this area is dominated by retrospective reviews of bladder management outcomes of patient cohorts. Long-term follow-up studies are almost exclusively of patient groups with neurogenic bladder disorders. Small scale, comparative studies of new products are common and are often industry-sponsored. Quality of life issues are vitally important for continence product users but studies are often limited by outcome measures predominantly based on user satisfaction, in the absence of clear criteria. Few studies have directly compared CIC with other methods of bladder drainage.

b) User characteristics:

CIC is a commonly recommended procedure for people with incomplete bladder emptying not satisfactorily managed by other methods. CIC can be appropriate for post-void residual urine volumes of 100ml or more in:

- Patients with neurological disorders that result in urinary retention problems, including failure to empty the bladder, incomplete emptying, detrusor sphincter dyssynergia.
- Patients with difficulty emptying the bladder after surgical procedures, if outflow obstruction occurs either in the short or long-term.
- Patients who accumulate a build up of residual urine caused by detrusor overactivity and inadequate bladder emptying.
- Acute urinary retention (most commonly in men).
- Management of urethral stricture.
- Emptying the bladder following continent urinary diversions such as a Mitrofanoff diversion.

CIC may be a practical option for patients who are:

- Sufficiently motivated to manage their bladder drainage by this technique.
- Sufficiently dexterous to perform the technique. An appropriate level of manual dexterity is essential but generally if people can write and feed themselves they have sufficient dexterity [195].
- Sufficiently cognitively aware to adhere to a regime and empty the bladder at appropriate time intervals to prevent bladder over-distension and preserve upper urinary tract function.
- Unable to perform the technique themselves but willing to accept the procedure from a caregiver.

Most men require some form of lubrication to aid catheterisation, which can be on the catheter surface or instilled into the urethra [196] (Level of Evidence 3). For those with preserved urethral sensation, a local anaesthetic gel may be needed. Many female patients also use a catheter lubricant / anaesthetic gel although some choose not to. In developing

countries, where resources are limited (or sometimes through patient choice), patients sometimes use plain water as lubricant [197] (Level of evidence 4). Some may benefit from adaptive equipment. An occupational therapist reported [198] on how a specially constructed penile trough (to hold the penis in a fixed position) allowed catheterisation with just one hand in a person with multiple brain injuries.

Regular bladder drainage is important to avoid potential damage to the upper urinary tract from urine reflux and raised intravesical pressure from build up of residual urine. Patients require individualised care plans to help identify appropriate catheterisation frequency, based on discussion of voiding dysfunction and impact on quality of life, frequency-volume charts, functional bladder capacity, and ultrasound bladder scans for residual urine. Some people need to catheterise several times per day, others less frequently. Catheterising frequently enough to avoid residual urine greater than 500ml is a general rule for adults but further guidance is also provided by urodynamic findings, detrusor pressures on filling, presence of reflux, and renal function. Disabilities such as blindness, lack of perineal sensation, tremor, mental disability and paraplegia do not necessarily preclude individuals from mastering the technique if they have sufficient manual dexterity [195]. Learning the technique may require more sessions for people with physical disability, such as MS, and cognitive impairment can contribute to less adherence over time [199]. Lack of motivation is the most common reason for failure, often linked to difficulty managing the technique or adhering to the required regime.

Children at school need a multi-professional assessment which may include a continence advisor, paediatric community nurse or school nurse, the child's consultant, the child and parents. With adequate training, suitable facilities and supportive teaching staff many children are able to carry out CIC themselves either on a toilet or from a wheelchair. CIC has been shown to be a viable therapeutic option for children with a large post-void residual urine volume in the absence of any neurological abnormality [200]. Intermittent catheterisation has also been shown to be an effective technique for elderly patients with post-void residuals more than 50% of the bladder capacity, resistant to other treatment [201]. In a group of 21 patients (mean age 76.5 years), 12 mastered the technique of CIC, with the remainder catheterised by their partners or nurses. Urinary continence was restored, urgency, frequency and nocturia decreased and UTI rate diminished, resulting in improved quality of life.

In a study in a 110-bed hospital, a bladder scanner was introduced to decrease unnecessary catheterizations using either a straight catheter (in-out) or an indwelling catheter [202]. Staff members were educated on the use of the new scanner in conjunction with an algorithm to guide decisions on treatment. Fourteen per cent (11) of the 79 scans resulted in catheterization, and there was an 80% decrease in catheterizations in 47 persons unable to void, based on clinical observation during a one month period. Most of those who required catheterization were surgical patients. There were three in-out catheterizations and eight indwelling catheters were inserted, more were female (73%), and over age 75 (p=0.035).

Advantages of intermittent over indwelling catheterisation include:

- Greater opportunity for individuals for self-care and independence.
- Reduced risk of common indwelling catheter-associated complications.
- Better protection of the upper urinary tract from reflux.
- Reduced need for equipment and appliances e.g. drainage bags.
- Greater freedom for expression of sexuality.
- Potential for improved continence between.

c) Catheter characteristics

Types and characteristics of catheters used in intermittent catheterisation vary considerably so evaluation and selection of products is complex [191]. Plain uncoated catheters, typically clear plastic polyvinyl chloride (PVC), are packed singly in sterile packaging. As per industry standards, all disposable catheters are intended for one time use, but PVC catheters are frequently cleaned and reused by individual users because of cost or concern about environmental issues. Recently, to address environmental concerns related to single use catheters, a new PVC-free catheter was created and evaluated by 173 persons in comparison to the standard PVC one [203]. Both catheters had a hydrophilic coating. No significant differences were found. Some health care professionals make a distinction between 'single-use' (i.e disposed of after insertion) and 'single patient use' (cleaned and re-used by the same patient for a limited period of time, such as one week). Where products are used in ways which differ from manufacturers' guidance, both patients and health care professionals should recognise their personal, professional / legal responsibilities. In some countries, including the US, there are very clear governmental directives that catheters identified as single-use devices should not be re-used in any setting. US patients should be provided with an adequate number of catheters to use a sterile catheter for each catheterisation, and patients and carers must be informed that catheters are identified for single use only. However, not everyone in the US using IC has the federal insurance program (Medicare), which began paying for single use catheters on April 1, 2008 at the rate of up to 200/month [204] [205]. In one US study of 34 IC users [206], many said they

did not have adequate insurance reimbursement for single use catheters, and 35% cleaned and reused catheters.

Most uncoated intermittent catheters are used with separate lubricant, although this is a matter of personal choice. Cleansing for re-use (where this occurs) varies from being washed with soap and water, boiled, soaked in disinfectants, or microwaved. Cleaned catheters are air dried and then stored in a convenient container (often plastic containers / Zip loc bags or paper bags). Metal catheters made from silver or stainless steel can be sterilized by heat or chemicals and may be used repeatedly for longer periods than other reusable materials.

Coated catheters are single use only (they are not currently suitable to be cleaned and reused) and are designed to improve catheter lubrication, ease of insertion and convenience. Coated catheters may reduce urethral trauma and CAUTI although good quality research evidence remains limited. The most common coatings are hydrophilic (which require the addition of water to the catheter to form a lubricious layer) or pre-lubricated (whereby the catheter is supplied pre-packed with a coating of water soluble gel). There are also several pre-lubricated products with an integrated collection bag (all-in-one) which gives flexibility for the user and are efficient for hospital use. Not all CIC users like this type of bag; thus trying several types of catheters for various activities, such as when home or when away, can help in decisions about what is best for the person [206].

Intermittent catheters range in size from 6-20 Ch, with most common sizes being 10-12 for females and 12-16 for males (**Figure XII -1**). Intermittent catheters are generally around 40cm long (male length) and are more rigid than indwelling catheters to aid insertion. A variety of aids to assist catheterisation are available (**Figure XII -2**).

Some women find a stiffer catheter easier to handle and some designs are slightly curved and made only in female length (around 18cm) to accommodate their requirements. A new compact catheter of 7cm was as effective in 23 of 24 women in removing residual urine as 20cm catheters [207]. Some manufacturers produce conveniently packaged 'catheter-sets' where the catheter is already attached to a urine containment pouch inside the pack and a non-touch, clean technique is facilitated by holding the catheter inside the bag and gradually advancing it from the bag during insertion. Catheter designs may include a protective tip to help reduce the transfer of bacteria from the distal region of the urethra further into the bladder. Patients should have the opportunity to try different catheters and choose which best suits their needs and lifestyle. Different catheters / packs may be appropriate at different times e.g. when added convenience for quick and efficient use and disposal is important, such as going to work or on holiday.

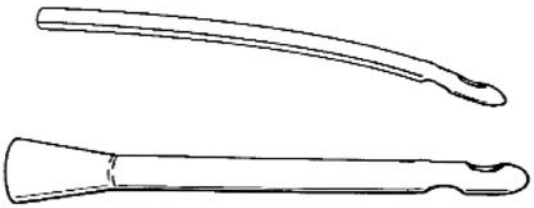


Figure XII-1: Examples of catheters for intermittent catheterisation: Scott (top) and Nelaton (bottom).

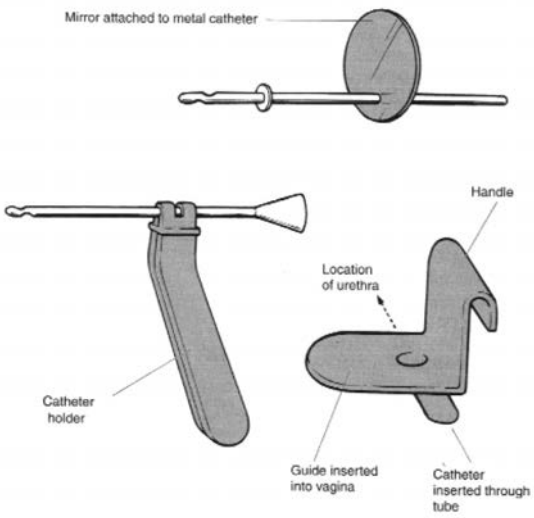


Figure XII-2: Examples of catheters for intermittent catheterisation: Scott (top) and Nelaton (bottom).

An effective intermittent catheter should have the following characteristics:

- Smooth for comfort, but sufficiently firm for easy insertion and maintenance of lumen patency.
- Minimal friction on insertion or removal.
- Smooth edges to catheter eyes to avoid tissue trauma on frequent catheterisation.
- Shaped for easy passage through urethral contours.
- Easy to hold and manipulate for those with limited dexterity.
- Easy to identify correct end for insertion and for drainage, for those with visual impairment.

Although there is an increasing range of intermittent catheter types on the market - including many pre-lubricated products with integrated collection bags - the quality of evidence for clinical benefit is poor. De Ridder et al [208] conducted a prospective, randomised, parallel, comparative trial of a hydrophilic coated catheter with an uncoated PVC catheter with

123 male spinal cord injured (SCI) patients. Only 57 completed the 12 month study but fewer patients with the coated catheter experienced one or more symptomatic UTIs (p=0.02). There was no difference in haematuria, leukocyturia and bacteriuria. However a recent Cochrane Review [191], concluded that overall current research evidence is weak, most studies are underpowered and conclusions are limited by serious design issues. A recent review indicated that hydrophilic catheters are beneficial for men with SCI, in relation to safety (preventing urethral damage and associated complications) and quality of life (comfort) [47].However research is limited in women, MS, and spina bifida. An earlier literature review [209] also indicated the wide variety of materials and techniques used for intermittent catheterisation. It concluded that there was no one best technique or material and that choice of both depend greatly on the patient's individual anatomic, social and economic status.

d) Associated risks / problems

Urinary tract infection is well-recognised as the most frequent complication of intermittent catheterisation [191]. The accumulation of urine in the bladder provides a reservoir for infection, but it has also been proposed that the increased intravesical pressure reduces the vascular supply to the bladder tissue rendering it more susceptible to bacterial invasion [210]. A post-void residual urine volume of 150ml has been demonstrated to be an independent risk factor for the development of UTI, in stroke patients [211] (Level of Evidence 2). In Wyndaele's review of complications of intermittent catheterisation (82 studies), prostatitis was identified as a risk in men but epididymitis and urethritis were relatively rare [209]. Trauma from catheterisation, measured by haematuria, was noted to occur regularly but lasting effects were more limited. The prevalence of urethral strictures and false passages increased with longer use of CIC but the review concluded that the most important preventative measures are good education of all involved in CIC, good patient compliance, use of an appropriate catheter material, good catheterisation technique and the avoidance of bladder over-filling. Similar findings were reported by Campbell [212] in a follow up of children with spina bifida who had used intermittent catheterisation with uncoated PVC catheters for at least five years. The incidence of urethritis, false passage, or epididymitis was very low whilst adherence to the protocol was excellent. However, Ku et al [213] found a higher incidence of epididymitis in their cohort review of 140 male, SCI patients followed over 16 years.

A study of medical and social complications of US data in 24,762 persons with SCI [214] who were evaluated every five years for 30 years, has been published (see section XII.1.g below for report on bladder management changes over time). Bladder management comparisons were done for indwelling (IC), CIC, condom, and spontaneous voiding. While there was some variation at different time points, medical complications were higher in persons with indwelling catheters, for pressure ulcers and days in the hospital, and kidney stones, though infrequent, were higher at times. Psychosocial outcomes also did not favour IC users, and each measure (satisfaction with life, perceived health status, and participation in society) was lower than the other groups, though not significantly so. The authors said that better understanding of psychosocial issues could be attained though prospective studies, as other factors than bladder management might affect quality of life.

1. Urinary tract infection

It is difficult to know the prevalence of UTI associated with intermittent catheterisation as reports vary widely and definitions of UTI are inconsistent, sometimes based on bacteriuria alone (asymptomatic) and sometimes on symptomatic UTI (with or without clearly defined criteria). In a study of 41 European centres serving children with spina bifida, although most centres had established protocols for diagnosis and treatment of UTI, no consensus was identified for common protocols [215]. Other variations found included methods of evaluation, catheterisation techniques, frequency of urinalysis / culture, administration or not of prophylactic antibiotics, and the patient group studied (including gender, functional ability, behavioural and personal hygiene factors).

In a prospective study of 128 SCI patients, where the incidence of UTI was calculated as the number of episodes per 100 person-days, the overall incidence of UTI was 0.68. The rate for males using CIC was 0.41, compared to 2.72 for those using an indwelling catheter [216]. Biering-Sorensen et al. [217] studied 77 SCI patients on CIC after five years and found that 81% had been treated for at least one UTI, 22% had two-three UTIs/year and 12% had four or more per year. The technique of intermittent catheterisation used does not seem to be a risk factor and despite different catheterisation techniques used, the number of episodes of clinically significant nosocomial urinary infections and the mean species turnover remains similar [218] (Level of Evidence 2).

In the Cochrane review cited above [191], the primary outcome measure was catheter-associated infection (definition of infection as used in the trial reports). Fourteen trials met the inclusion criteria but too little data could be entered into a metanalysis to produce meaningful data summaries. Based on the available data, the authors concluded that there appeared to be no clear difference between various methods of catheterisation (sterile catheterisation techniques, clean catheterisation with a single-use sterile catheter, or clean catheterisation with a clean reused catheter). Whilst the outcomes of this review raise questions over efficacy and cost-effectiveness of expensive coated catheters it is clear that further

robust research is needed. All sample sizes in the trials were small and only two included statistical power calculations, although they were unable to achieve their predicted sample sizes. Most studies suffered from high attrition rates and several reports were more than 10 years old. The challenges of obtaining sound data in this clinical area continue to hinder the accumulation of evidence to help guide healthcare practitioners. A common difficulty is in the establishment of robust outcome measures. UTI remains the most clinically important primary outcome variable but bacteriuria/ positive urine culture is not clinically relevant unless accompanied by symptoms. Symptoms themselves may present in vague and imprecise ways, especially in elderly and/or SCI patients where symptoms can be masked or unclear.

Since the Cochrane review two further studies have compared hydrophilic versus plastic IC catheters and examined the effect on UTI [219]. In a community study of patients with spinal cord injury (45 participants completed) Cardenas and Hoffman found no differences in the incidence of symptomatic UTI between the groups, although the number of antibiotic treated UTIs was significantly smaller in those using hydrophilic catheters. Regression analysis showed that women were more likely to have UTIs than men and it is noteworthy that there were twice the number of women in the control (plastic catheter) group compared to the hydrophilic group (N=11 versus N=5).

Cardenas and other co-workers also carried out a randomized trial of hydrophilic or plastic ICcatheters in SCI patients in hospital. This study demonstrated benefit from the hydrophilic catheter during initial early rehabilitation with a delay in the first symptomatic UTI [220]. Fifteen North American SCI centres took part, and 224 patients were randomized to the catheter type within 10 days of beginning IC, and were followed either in the hospital or rehabilitation then, when discharged to the community, for up to 3 months more, for a total of up to 6 months. This delay in first UTI resulted in a daily risk reduction of 33% and during the initial institutional time the UTI rate decreased by 21% ($p<0.05$) in the hydrophilic group. However, no differences were found between the two groups in the incidence of UTI over the whole study period.

A Cochrane review on urinary catheter policies for long-term bladder drainage [221] reported limited evidence that prophylactic antibiotic therapy was associated with reduced episodes of bacteriuria (asymptomatic and symptomatic) but all trials were small and confidence intervals were wide. The authors caution that possible benefits from prophylaxis must be balanced against possible adverse effects such as the development of antibiotic resistant bacteria.

In order to improve rigorous clinical evaluation of current and innovative products for CIC, more epidemiological data on user populations and characteristics of catheter use is needed. A recent Canadian national survey of intermittent catheterisation practices following SCI [222], reported on 912 responses to a 36-item self-report postal questionnaire. Fifty five per cent of respondents used intermittent catheterisation regularly, with users forming a significantly younger group than non-users ($p=0.001$). The majority of users (73%) used a clean technique. The remaining 27% reported using a sterile technique. Uncoated catheters were used most commonly; 74% only used uncoated catheters; 15% used hydrophilic coated catheters; and 11% reported using both types. These notable differences may be partially related to patient education, costs to patients and health insurance funding constraints. The majority of uncoated catheter users used their catheter only once (53%) but a further 30% used their catheter more than nine times. The mean frequency of self-reported CAUTIs in the past 12 months (symptomatic but not necessarily confirmed by laboratory evidence) was 2.6, with females experiences significantly more infections than males ($p=0.003$). Although the use of hydrophilic coated catheters was associated with a lower rate of CAUTI (2.46 versus 2.62 for those using uncoated catheters), this difference was not reported as statistically significant. However UTI rates are multi-factorial and are unlikely to be fully accounted for by the variables investigated. A significant relationship between number of catheterisations per day and CAUTI rates was identified, with those who catheterised only once a day having the highest rate of infections ($p=0.03$). This is consistent with previous suggestions that increasing the time that colonised urine is present in the bladder is associated with increased infection rates [208]. It is interesting to note that, while extra fluid intake was positively related to reduced rate of CAUTI ($p<0.001$), catheter re-use, catheter disinfection and antibiotic prophylaxis were not significantly associated with CAUTI rate. Clearly there are potential limitations in this study as with any which employs self-report methodology. These include self-selection of respondents, accuracy of recall and quality of information provided, but the large number of respondents and the degree of internal consistency reported by the researchers provide creditability to these results.

Several studies have sought to determine whether the antibacterial effects of cranberry extract will reduce or eliminate bacteriuria and pyuria in patients using intermittent catheterisation, particularly in SCI populations [223] [224]. In a randomised, double-blind, placebo-controlled study of 48 SCI patients living in the community and using intermittent catheterisation or external urine collection device, participants ingested 2g concentrated cranberry extract in capsule form or placebo daily for 6 months [224]. There were no differences between groups with respect to number of urine specimens with bacterial counts $>10^4$ cfu/ml, types and numbers of different bacterial species, numbers of urinary leukocytes, urinary pH, or episodes of symptomatic infection.

2. Tissue trauma, strictures and other complications

Long-term follow-up studies have examined other complications associated with intermittent catheterisation and found urethral trauma to be common [225] [226]. Urethral bleeding is frequent in new patients and has been noted to continue to occur in up to 30% on a long-term basis [226] [227], however risks of tissue trauma may be reduced with newer catheter products which are designed to reduce friction. Consequently the outcomes of older studies need to be considered with caution. The withdrawal frictional force was compared between two hydrophilic coated catheters and one uncoated catheter in a prospective, randomised, participant-blinded, crossover trial by Stensballe et al [228]. Forty participants completed the study and it was interesting to note that while one coated catheter (SpeediCath) exerted a lower mean withdrawal force than the other catheters, the second coated catheter (LoFric) exerted a significantly higher mean friction force than both the other catheters. Both hydrophilic coated catheters were associated with less microscopic haematuria than the uncoated catheter. Similarly, there was a lower incidence of microscopic haematuria reported in two of the coated catheter groups compared to uncoated catheters in trials included in the Cochrane review [191]; 0.31versus 0.65 [229]; 6/14 (43%) v 11/14 (78%) [230]. Trauma of the urethra, especially in men, can cause false passages. Treatment for false passages in SCI patients by six weeks indwelling catheter use and five days antibiotics, has been reported to be effective [231] (Level of Evidence 3). The false passages had disappeared on cystoscopy and CIC could be restarted.

It has been claimed that the long term risk of urethral stricture formation may be less when hydrophilic coated catheters are used [232]. The degree of urethral inflammation, measured by urethral cytology in two groups using CIC (one using ordinary PVC catheters with lubricant; the other using hydrophilic coated catheters), showed significantly less urethral inflammation in the hydrophilic coated catheter group. Although this data suggests some benefit in using hydrophilic coated catheters to minimise stricture formation in the long-term comparative studies are limited. One recent follow-up study of 31 females with spina bifida, using CIC for a median of 15 years, examined risk of urethral lesions. There were few problems reported (only on 20 occasions in a total of 459 patient-years), despite long-treatment periods and use of non-coated PVC catheters [233].

The relative importance and cost-effectiveness of hydrophilic catheter coatings has not been adequately addressed in large scale studies to date. Hedlund et al. [234] in their review of 28 CIC studies, called for a prospective, randomized, long-term, multi-centre study to address clinical benefit and cost effectiveness. Data on patient characteristics should include age; gender; diagnosis of bladder dysfunction; reason for CIC; physical and mental disability; manual dexterity; and previous treatments. Effect parameters should include number of catheterisations; urinary tract infection (symptomatic or asymptomatic); early and long-term urethral complications; patient satisfaction, preferences; and drop-out rates. Robust studies of this nature are still awaited.

3. Other complications

Formation of bladder stones has been found to be associated with long-term use of CIC in a number of studies [235] (Level of Evidence 2). Barroso et al. [236] reported an increased risk of developing bladder calculi in children performing CIC based on the records of 403 children. Stones were diagnosed in 28 patients. The incidence was slightly higher in those with a Mitrofanoff conduit but was not influenced by bladder augmentation (Level of Evidence 3). A retrospective study of 140 SCI patients, followed up from 1987 to 2003, identified 27.9% of patients diagnosed with epididymo-orchiditis. This problem was more common in patients using CIC compared to indwelling catheterisation (42.2% v 8.3%, P= 0.03). Multivariate analysis showed CIC to be an independent risk factor for epididymo-orchiditis, with SCI patients in this study subject to a 7-fold higher risk (OD 6.96; 95%CI, 1.26-38.53) [213]. While the risk of cancer in long-term indwelling catheter users is known, (see section 12.2.10 below) squamous cell cancer in persons with intermittent catheters has been reported also in at least eight cases. A number of factors may be involved including leukoplakia, bacteriuria, trauma from the catheter and squamous metaplasia, a premalignant change [237].

e) Catheter management

1. Education, support and quality of life (QoL)

Good education of all involved in CIC, good patient compliance, use of an appropriate catheter material, and good catheterisation technique have been identified as the most important measures to prevent adverse complications [209]. Factors affecting adherence to self-catheterisation procedures have been explored, addressing both initial mastery of technique and both short-term adherence and long-term adherence [238] [239]. Time taken to build confidence is variable and may range from days to years [239]. General determinants of adherence related to knowledge, complexity of the procedure, misconceptions, fears, shame, motivation, quality and continuity of professional care.

CIC may affect both sexuality and sexual activity [240] and sensitive support and teaching are needed. An emotionally negative response can occur, which requires individualized teaching in a relaxed, supportive environment [240]. Adequate information combined with thorough teaching and good

communication can help new CIC users gain initial acceptance and adherence to the procedure [239]. Some women are not able to locate the urinary meatus, and they may not be comfortable in learning and thus require additional coaching, encouragement, practice and support [241] [206] [240]. Other anatomical issues need to be considered as well, such as redundant prepuce in some males, false urethral passages, and bladder spasms [242]. In addition, lack of adequate bathroom accessibility, especially in public places, can be a major barrier to adherence [242] [206].

Integration of the CIC regime into everyday life was a recognised difficulty and for younger patients, in particular, availability of materials, physical impairments and resistance to 'sickness role' were factors which could also compromise adherence. Qualitative research studies using a grounded theory approach have identified similar factors influencing variations in quality of life (see also section XII.4). These include sex; lifestyle; frequency of duration of carrying out CIC; technical difficulties; type of catheter; comorbidities; and individual predispositions [241].

In the large scale Canadian survey above [222] 71% reported that CAUTIs had negatively impacted on their QoL score (a 10-point scale). Several significant variables associated with CAUTI and QoL were determined. Interestingly, time lost from social activities was more strongly associated with compromised QoL than actual number of infections or days lost from work. In another study in 41 persons with SCI, treatment success correlated positively with the Qualiveen QoL measure. Success criteria involved clinical symptoms of continence, lack of autonomic dysregulation (dysreflexia), and urodynamic testing for adequate bladder storage capacity (> 360 mL) and detrusor pressure (< 40cm water) [243].

Twenty two teenagers and young adults with myelomeningocele were interviewed about psychosocial factors related to CIC [244]. Deciding when to disclose CIC use was important in relation to peer support and friendships, and many wished they had done so at an earlier age, with the help of an adult. In fact everyone in a group needed to appreciate the need to avoid gossip. Those not in wheelchairs found it harder to convince others of their need to use CIC. In healthcare settings, many wanted to perform self-catheterisation instead of staff doing it. Information about sexual function was desired by many.

An Internet based qualitative study in the US aimed at discovering issues and problems in long-term CIC users [206] found key concerns related to use of bathrooms that were dirty and inaccessible and a lack of knowledge of options in supplies and/or insurance coverage. Other themes involved knowing the body, practising intermittent catheterization, hassles, and adjustment in making intermittent catheterization a part of life. Experienced CIC users explained how they made adjustments to include CIC in daily life by paying attention to their routines.

More education may be provided to catheter users through the Internet in the future. In a study using 18 articles written for persons with spinal cord injury (based on suggestions from patients and rehabilitation nurses), consumers were satisfied with the information and scored this approach as 8.02 on a 1-10 scale with 10 as being most satisfied [245]. Information was available in English and Spanish. Utilization during the 13 month study, scored as "hits" on the website, was far more frequent in the Spanish language materials (n=811, 70%) than "hits" for the English materials (n=351, 30%). Examples of article content in both languages included cranberry juice and UTIs, cleaning the drainage bag, types of urinary management and only in English, latex allergies and catheter use, autonomic dysreflexia, and sexuality.

2. Catheter cleaning for re-use

Where catheters are cleaned for re-use they may continue to be used many times, up to weeks or even months. However, health professionals and users need to recognise their personal responsibilities and liabilities in supporting this approach since manufacturers' guidance will normally relate to single use only (see also Section XII.1.c). Questions over how long the same catheter may be safely reused require further examination, and may be particularly important in developing countries, where access to new supplies may be limited [246]. Methods of cleaning or re-sterilising include soaking in a variety of antiseptic solutions or boiling water or microwave sterilisation. In a study which compared three home cleaning methods used by patients performing CIC, all of the following were found to be effective: 0.6% hydrogen peroxide; bleach in a 1:4 solution with tap water; and betadine in a 1:2 solution with tap water [247]. None of the cleaned catheters showed detectable bacterial growth for 48 hours after the cleaning procedure was performed (Level of evidence 4). Lavallee et al. [248] also compared the effectiveness of hydrogen peroxide, vinegar, dishwashing detergent, and tap water alone to clean catheters contaminated with Pseudomonas aeruginosa and Escherichia coli. They also examined the effect of immediate rinsing and drying before cleaning. Results indicated that rinsing and drying immediately after use was the most effective at reducing bacteria to near zero (Level of evidence 4). Microwave sterilization has been advocated by some, but has not been adequately evaluated. A study by Sherbondy, et al. [249] showed that even where standardized instructions (both verbal and written) were provided, microwave sterilization techniques by patients performing CIC varied considerably. Many patients surveyed did not follow the study instructions recommending sterilizing used catheters on a daily basis, cleaning with soap

Table XII-2 provides some guidance on patient education and troubleshooting for CIC.

Table XII-2: Intermittent catheterisation

Patient education & support:
• Discussion of individual bladder dysfunction and reasons for CIC. • Personal anatomy and identification of urethral orifice. • CIC technique – comfortable position, frequency, observation of patient's technique. • Hygiene. • Discussion of any psycho-sexual anxieties (body image, sexual function etc). • Single use versus reusable catheters (cleaning, storing, re-use, disposal). NB including awareness of personal / legal issues. • Difficulties and what to do. • Dietary advice and avoidance of constipation. • Obtaining supplies. • Follow-up visits and consultations.

Guidance for common problems:
• Catheter will not go in at first attempt – relax for a while and try again a bit later; lubricate catheter (eg dipping in water or gel); if necessary seek professional guidance. • Catheter inserted into vagina by mistake – withdraw, wash and re-insert. • Catheter will not come out – leave for a few minutes, relax and try to 'let go', cough gently and withdraw catheter. • UTI – report changes in urine (eg blood, sediment, smell). Know how to recognise signs of symptomatic infection and seek treatment and review of CIC technique.

and water and air drying before inserting into a microwave oven on a paper towel. Microwaving on a high setting for six minutes on a rotation table was recommended together with a heat sink – a cup of water in a microwave-safe container placed in the microwave to absorb extra heat. Catheter melting was reported by 63% and was significantly associated with the absence of a rotation table. If microwaving is to be accepted as an appropriate sterilization method then users must be provided with a standardised, evidence-based, protocol to follow. A recent study reported the development of titanium dioxide-coated catheters for CIC which were easily sterilized under certain light sources and were shown to be safe in experimental studies [250]. Preliminary clinical analysis with 18 volunteers was also promising.

f) Comparisons between intermittent and indwelling catheterisation

A systematic review of risk factors for UTI in adults with SCI reported evidence of fewer infections in patients using intermittent catheterisation compared to indwelling catheterisation [251]. Twenty two studies met the inclusion criteria for evaluation but the authors noted that many had important methodological deficiencies. Intermittent catheterisation has also been shown to be associated with fewer UTIs compared to indwelling catheterisation in elderly patients after surgical repair of hip fractures [252] and in a comparative study of patients at a hospital department of urology [253].

g) Catheter use over time in persons with SCI

Bladder management methods in 24,762 patients were tracked for over 30 years, using the US National Spinal Cord Injury Database, yielding the results summarsied in **Table XII-3** [168]. Surveys were completed every five years to evaluate catheter use at discharge from rehabilitation. In addition, continued use in the same individuals was evaluated 30 years later in follow up data with 12,984 to determine changes in use over time.

Table XII-3: From US data base of SCI, surveys of bladder management every five years for 30 years. (Cameron et al, 2010)[168). N=24,762.

Bladder management	Use (%) 1972	Use (%) 1991	Use (%) 2001	Continued use at 30 years (n= 12,984)
CIC	13	56	50	20
Indwelling catheter	33	17	23	71
Sheath	35	4.7	1.5	35

At discharge from rehabilitation, condom catheter use decreased gradually (35% in 1972 to 1.5% in 2001) while clean intermittent catheterization increased from 13% in 1972, peaked in 1991 at 56%, and fell slightly to 50% in 2001. Indwelling catheter use initially decreased during this time (33% in 1972 to 17% in 1991) but increased somewhat to 23% in 2001. In follow up data, the great majority of those originally using an indwelling catheter stayed with it, i.e., 71% after 30 years. However, most persons using CIC or condom drainage did not continue to use them, and only 20% and 35%, respectively, did so after 30 years. This indicates that despite CIC being the bladder drainage method of choice, individuals with SCI might use indwelling catheters if not able to manage CIC (Level of Evidence 3).

Patel et al. [254] examined the outcomes of different forms of urinary drainage for men with acute urinary retention. After a short period of indwelling urinary catheterisation patients were taught to use CIC (34 men). Patients who failed this were re-catheterised and taught to manage a valve or failing this a leg bag (16 men) and then discharged home. The CIC group had a higher rate of spontaneous voiding (56% v 25%) and a lower incidence of UTI (32% v 75%). At TURP 20% in the CIC group had a UTI compared to 69% in the indwelling catheter group. Patients using CIC preferred it and had fewer complications. The authors concluded that CIC was well accepted by those patients who were able to manage the technique, resulted in fewer UTIs and should be considered in patients presenting with acute retention.

In a recent 2-week prospective study of intermittent catheterisation versus indwelling urethral catheterisation in older female patients in a rehabilitation setting, 81 females >65 years with post-voiding residual volume persistently >300 ml were randomized to one of two groups [255]. Both groups demonstrated similar success in regaining bladder function and similar rates of bacteriuria. The authors concluded that intermittent catheterisation was justified in managing this patient group, particularly since indwelling catheters were deemed to hinder rehabilitation and adversely affected quality of life.

An RCT of 72 women post-urogyncological surgery (stress UI or pelvic organ prolapse) compared intermittent catheterization (CIC) with supra-pubic catheterization (SPC) [256]. The length of hospital stay was decreased significantly (Mann-Whitney p=0.003) with CIC (median 5 days, range 2-19) as compared with SPC (median 6 days, range 2-15). The days of catheterization also decreased significantly (Mann-Whitney p=0.01) with CIC (mean 4, SD 26, median 2) as compared with SPC (mean 5, SD 36, median 4), but the differences were viewed as limited clinically. Post-op UTIs were higher in the CIC group (13 versus nine in the SPC group), but not significantly (Fishers' exact p=0.44). Of note, the CIC group had the opportunity to void much sooner than the SPC group because the latter were on straight drainage for 48 hours post-operatively as hospital policy, and this may have had an impact on the results and clinical relevance.

In a prospective RCT of CIC versus supra-pubic catheterisation (SPC) for post-operative bladder care following hysterectomy in 40 women there was no significant difference in the length of bladder care between the two groups [257]. Bacteriuria was higher in the CIC group at days 3 and 5 (p=0.05 and 0.004, respectively) although it is unclear whether there was evidence of symptomatic infection. However, there was a higher incidence of symptoms / problems arising from the SPC site, of which 23% were shown to have a positive wound swab. The authors concluded that despite a higher rate of bacteriuria, the high incidence of site problems with SPC could be avoided by CIC. The technique of CIC was seen to be more acceptable to patients (p=0.009); allowing fewer disturbances at night (p=0.006); greater freedom to lead a normal life during the day (p=0.000); and less anxiety / embarrassment (p=0.005) compared to SPC. However, in a study of 43 persons with tetraplegia who were on artificial ventilation comparing IC and SPC, SPC users had significantly fewer urological complications and better quality of life, as measured by the ICIQ-SF (3 items), but not significantly better [258].

h) Summary

CIC is the preferred method of urinary drainage in patients with neurogenic bladder dysfunction and others with problems of bladder emptying who are

capable of performing the procedure and who find it acceptable. It can be taught to patients of all ages who have sufficient manual dexterity and motivation to manage the technique. Urinary tract infection is the most frequent complication and the most important preventative measures for all complications are good education of all involved in CIC management, good patient compliance and support, use of an appropriate catheter material and good catheterisation technique. Difficulties in carrying out the procedure such as physical and technical difficulties, embarrassment, time involved and lack of appropriate public facilities may deter users from adhering to the regime. Hydrophilic-coated catheters confer benefits in terms of comfort and minimised tissue trauma compared to non-coated catheters (Level of evidence 2/3) but evidence of benefit in relation to urinary tract infection is less clear.

The available data on intermittent catheterisation does not provide convincing evidence that any specific technique (sterile or clean), catheter type (coated or uncoated); method (single use or multiple use), person (self or other), or strategy is better than any other for all clinical settings. This reflects lack of reliable evidence rather than evidence of no difference. Currently clinicians will need to base decisions about which technique and type of catheter to use on clinical judgment, in conjunction with patients. Differential costs of catheters / techniques may also inform decision making.

In particular, CIC has been shown to have benefits over indwelling catheterisation in the following ways:

- Avoidance of common problems associated with LTC use such as catheter leakage and / or practical management of drainage systems
- Avoidance of complications linked to bacterial biofilm formation, including catheter encrustation and blockage. Strong evidence for reduced risk of CAUTI is less clear.
- Maintenance of some level of bladder capacity and muscle tone by allowing the bladder to fill periodically, compared to free drainage by indwelling catheter.
- Less urethral inflammation (measured by cytology) than urethral indwelling catheterisation (Level of evidence 2/3).
- Lower incidence of bladder calculi than indwelling catheterisation (Level of evidence 2/3).

2. INDWELLING CATHETERISATION

Indwelling catheters (**Figure XII-3**) may be used in the short-term to manage an acute need for controlled bladder drainage or as part of a long-term management strategy (**Table XII-1**).

Catheters may be inserted into the bladder urethrally (UC) or suprapubically (SPC) through an incision

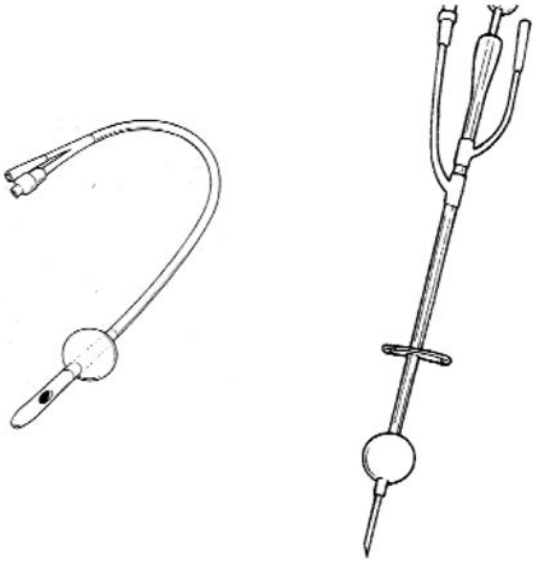


Figure XII-3: A Foley catheter (left) and a suprapubic catheter with a sharp trocar for introducing the catheter (right).

in the abdominal wall. The continued requirement for indwelling catheterization should be reviewed at regular intervals and the catheter removed promptly if no longer necessary, since catheter use is associated with a number of risks. The major complication associated with short-term, indwelling catheters used in acute care, is nosocomial (healthcare acquired) catheter-associated urinary tract infection (CAUTI), which can lead to life-threatening bacteraemia in vulnerable groups and may also contribute to reservoirs of antibiotic resistant microorganisms [187] [122] [259], Long-term catheters (LTC) are also associated with increased risk of CAUTI and a further range of problems including: recurrent blockage due to encrustation by mineral deposits; meatal tissue damage - often caused by excessive weight from heavy drainage bags; frequent bladder spasm with potential expulsion of the catheter; formation of bladder calculi; and potential for long-term neoplastic changes in the bladder (although further long-term studies are needed to establish this risk). Although for some patients an LTC catheter can provide satisfactory management of bladder problems and greater independence, others experience pain and discomfort with a catheter in situ and / or, are distressed by the impact of a catheter on their body image and sexuality. Intermittent catheterisation (See Section XII.1) is less invasive and is generally associated with fewer risks.

a) Quality of Data

Nine Cochrane reviews relating to short and long-term indwelling catheter use were identified. Five reviews on short-term (<14 days or other temporary

short-term use as defined by triallists) catheter issues included: types of urethral catheters for management of short-term voiding problems in hospitalised adults [260]; policies for bladder management[192]; the role of prophylactic antibiotics [221]; use of alpha blockers for acute retention prior to a trial without a catheter [261] and policies for removal of short-term indwelling catheters [262]. The objective of the first review [260] was to determine the effect of type of indwelling urethral catheter on the risk of UTI. Twenty-three trials - comparing different types of standard catheters or a standard catheter with an antiseptic catheter (silver alloy or impregnated with silver oxide), or an antibiotic impregnated catheter (either minocycline and rifampicin, or nitrofurazone) - met the criteria. The reviewers concluded that currently available evidence suggests that silver alloy catheters prevent asymptomatic bacteriuria in the short-term catheterised patient, although trials are generally of poor quality (Level of evidence 2/3). They also recommended that further economic evaluation is required to confirm that reduction of infection compensates for the increased cost of the silver alloy catheters. Catheters impregnated with antibiotics were also beneficial in reducing bacteriuria in hospitalised adults catheterised for less than a week but data were too few for those catheterised longer. However, it is important to note that although bacteriuria is a commonly used outcome measure in CAUTI studies there is much debate over the clinical utility of this measure. Many studies fail to distinguish between asymptomatic bacteriuria and symptomatic infection. This is discussed further in Section XII.2.h.3.

The second review [192] included 14 trials which reported on comparisons between SPC and UC for short term (up to 14 days). Higher relative risks scores were found for UC related to more bacteriuria (RR 2.60; 95% CI 2.12 to 3.18), more frequent re-catheterization (RR 4.12; 95% CI 2.94 to7.56) and increased discomfort (RR 2.98; 95% CI 2.31 to 3.85) (Level of Evidence 1). The third review [221] included six parallel group RCTs and reported weak evidence that antibiotic prophylaxis reduced the rate of symptomatic UTI in female surgical patients, compared to antibiotics given when clinically indicated. The review of policies for catheter removal [262] reported suggestive, but inconclusive, evidence of benefit from midnight removal of the catheter (larger volumes at first void) and shorter hospital stay after early rather than delayed removal.

In the fifth Cochrane review [261] use of alpha blockers prior to a trial without a catheter for acute retention was evaluated. This treatment is believed to relax smooth muscle in the prostate which would improve urine flow and decrease the need for recatheterisation. Five clinical trials were involved, in four trials ranging from 24-72 hours prior to catheter removal in most persons (up to eight days in one trial). In the other study, the drug was given for eight days. Results overall were mixed, with two trials favouring the treatment and two favouring placebo, and thus there was limited but positive evidence that this was helpful. There were some side effects, such as hypotension and headache, but this was similar in the placebo groups. Further research was suggested.

Of the four Cochrane reviews relating to long-term catheter use, a review of 400 articles for comparative methods of using catheters for neurogenic bladder management, updated in 2011 [194] failed to find any trial that met the inclusion criteria. A second review [263] to compare types of indwelling catheter for long-term use (defined as >30 days) found only three trials which met the inclusion criteria. One trial compared antiseptic impregnated catheters with standard catheters and two compared different types of standard catheter. The authors reported ‘an astonishing lack of evidence for this clinically highly relevant problem’. Since the included studies were very small and showed methodological weakness, the authors concluded that the available evidence was insufficient as a reliable basis for practice and catheter choice remains largely based on clinical experience. In the third Cochrane review on ‘urinary catheter policies for long-term bladder drainage’ [264], seven trials met the inclusion criteria. All were small, with wide confidence intervals. No appropriate trials addressed comparisons between: indwelling UC and SPC; UC and intermittent catheterisation; or SPC and intermittent catheterisation. Evidence pertaining to whether antibiotic prophylaxis is better than antibiotics given when clinically indicated, was insufficient as a basis for clinical practice.

A fourth new Cochrane review for long-term catheter care involved washout policies for the management of long-term catheters in adults [265] which examined five trials, four of which were poorly reported or designed. Two crossovers compared group differences not sequential treatments in individuals, and two parallel groups provided limited value. One trial with a strong methodology had a small sample size. No differences were found in three studies in which solutions were compared: saline, acidic, and antibiotic. Unfortunately, there was not enough evidence overall to conclude that washouts were of benefit. Larger size samples in full randomized trials are needed.

There was little research to judge the value of catheter clamping prior to removal, and one (non-Cochrane) systematic review [266] of postoperative clamping in three clinical trials in 224 surgical patients (mostly women) was inconclusive. In two studies, clamping in comparison with free drainage was not effective in reducing UTI (not defined) or retention post removal. Time to first void decreased in one study. Recatheterisation and length of stay were measured in one study each, and were not different between groups. More recently in a trial in Sweden, 113 persons >50 years with short term

catheters post hip fracture were randomized to clamping or free drainage [267]. The primary outcome was the time to normal voiding, with a median of 6 hours (Q14-Q38) in the group with clamping and four hours (Q13–Q37. 25) in the group with free drainage. This difference was not significant, nor were groups different related to recatheterization or length of hospital stay.

Overall long-term catheter care practices remain poorly supported by research evidence. This is at least partially due to difficulties in conducting trials in long-term catheterised populations for a variety of reasons, many of which have been discussed in earlier sections (See Sections XII, XII.1 and XII.1.d).

The impact of long-term catheters on users' quality of life (QoL) is a very important issue which has not been studied adequately. No Cochrane reviews have dealt with this topic directly, although several reviews have included issues with an impact on QoL such as catheter related complications and comfort. One RCT addressed education needs of catheter users. Other studies include a small number of prospective cohort studies, with the remainder being retrospective studies and case series reports, providing evidence at Level 3. Much relevant research uses qualitative research methodologies, aimed at understanding the nature of long-term catheter-related issues and patient concerns. Measures of QoL used commonly rely on a single question of quality of life or satisfaction on a 3- or 10-point scale. Validated QoL instruments, such as SF 36 are not only infrequently used, but are likely to lack sensitivity for the specific issues which concern catheter users. There is one device-specific measure for long-term catheter users [268], recently validated in two small samples for internal consistency reliability and content validity (expert review) [269]. Factor analysis yielded three subscales related to management, interpersonal, and psychosocial issues. Work in this area is continuing.

b) Prevalence of indwelling catheters use

1. Decreasing acute care use

Short-term catheterisation is common in acute care settings, with up to 25% of patients receiving a catheter during their hospital stay [270] [187]. Recently a change in the US, whereby CAUTI will not be reimbursed during hospital stays [271], has triggered a number of studies designed to reduce the use and duration of indwelling catheters in acute care, and subsequently the number of associated infections. A popular approach is a "bundle" in which several evidence-based strategies are grouped and implemented in a system-wide approach. Analysis of cause and effect are incorporated into the bundled activities, and checklists are often used to address the issues in methods (procedures), people, environment, and equipment [272].

In one study [273], in a community hospital's 22 bed intensive care unit (ICU), a bundled approach was used to decrease catheter use with a checklist, a decision algorithm and criteria based guidelines. A fishbone diagram helped the nurses to identify the (historical) reasons for extended catheter device days (duration of use) and to plan the intervention. The device days decreased significantly from 4.72 (SD 7.67) in 124 persons to 2.98 (SD 3.17) in 83 persons, p=0.38, t= -2.10, df 176, n=83). Similar results were found in an inner city ICU with 21 beds [274] with duration of catheter use decreasing from 312 days/month to 239 days/month. CAUTI events decreased as well, from 4.7/month in the 11 previous months, to zero during the six months' intervention. Also, a multidisciplinary team was successful in using a bundled approach and decreased catheter use by 56% and the duration of device days by 71% [275]. In a hospital in Brazil [276], the CAUTI rate went from 10 to 3.3/1000 catheter days after an intervention that bundled several activities in the previous year. Settings in rehabilitation [277] [278] and in an emergency department [279] have also been able to decrease catheter use and CAUTI by effective surveillance and an interdisciplinary approach.

Requiring documentation for the reason for catheter placement is critical to reducing unnecessary use. In one study with emergency room physicians [280] education and guidelines for placement contributed to an increase in appropriate indications for catheter use (72.6% to 82.2% post intervention), and unnecessary catheterizations decreased significantly from16.4% to 13% (p=0.018). Inappropriate catheter use (30%) in a hospital study in Italy with 461 patients [281] was linked with older age, not having had surgery, conscious state, comorbidities, the length of time the catheter had been used, and the hospital ward. In the only randomized (and patient blinded) trial related to interventions to decrease catheter use in acute care [282], automatic stop orders for inappropriate catheter indications were successful in decreasing catheter duration in 392 patients. For those randomized to stop orders, catheter duration was lower at 3.7 days, compared with 5.0 in usual care (mean difference -1.3; 95% CI= -2.1, -0.6). Likewise, inappropriate catheterizations were lower in the stop orders group at 2.2 versus 3.9 in usual care (mean difference -1.7; 95% CI= -2.2,-1.2). CAUTI and recatheterisation rates did not differ.

Simple approaches such as checklists and stop reminders have also been effective in decreasing catheter use. In one study testing a checklist [283] catheter duration decreased significantly in five acute care hospital units from 402 to 380 pre/post intervention (p=0.047), and CAUTI went down from 2.88 to 1.46/1000 catheter days (NS). Compliance with the checklist varied from 50-100% but provider surveys indicated most viewed the checklists as relevant, easy to use, and were satisfied with them. An educational intervention on issues related to infec-

tions and notification of the continued catheter presence [284] also successfully decreased catheter use and the CAUTI rate. A simple chart reminder sticker related to removing the catheter when not needed [285], resulted in a significant increase in appropriate indications and a decrease in CAUTI in a hospital setting.

In a study of an educational strategy to use reminders with or without structured education, Gokula and colleagues (2007) [286] reported a 14% reduction in the number of inappropriately catheterized elderly patients in emergency departments, following a staff education program and the use of an indications checklist attached to each catheter kit. The intervention also enhanced documentation about catheter use. In another study, the total duration of catheter use and number of days of inappropriate catheter use was significantly less for patients randomized to an intervention that required staff in three hospitals in Canada to remove the patient's catheter if six criteria for appropriate catheterization were not met [282]. Saint and colleagues (2005) [287] reported a similar outcome from a simple reminder to assist hospital staff to remember which patients had catheters. Using a pretest-posttest design, two of the four wards were assigned to the intervention group, and two served as controls. The researchers found that of 5,678 patients, the average duration of catheter use decreased by 7.6% in the intervention group and increased by 15.1% in the control group (p=0.007). Similarly, Voss (2009) [288] reported a reduction from 33% catheter use to 15.3% (p=0.0006) in acute care older patients after the implementation of a protocol designed to enhance clinicians awareness of the appropriate use of catheters and the parameters for catheter removal.

A systematic review of reminders and stop orders for catheter use in acute care settings [289] indicated a benefit in the rate of CAUTI, which was reduced by 52% (p=0.001), duration of use decreased by 37%, and 2.61 fewer catheter days' use in treatment versus control groups. Stop orders were more effective than reminders.

Empowering nurses to remove catheters when not indicated was also successful in a quality improvement project [290]. Daily prevalence of catheter use decreased from 24% to 17%. However, in an anonymous survey of 164 nurses [291] 54% said they were not comfortable removing a catheter without a physician's order, but 74% remind the physician daily of the presence of the catheter.

2. Prevalence of catheters and CAUTI

Despite the increase in research in preventing CAUTI, many hospitals do not have systems in place for prevention. Based on a large survey to 600 non-governmental hospitals and 119 VA hospitals in the US [292], only about 1/3 of the respondents stated that they use antimicrobial catheters or bladder scanners, and surveillance data were not tracked for catheter placement by 56%, nor duration of use by 74%. Catheter reminders were used by only 10%.

The prevalence of LTC use in home care or community care settings varies widely and can be more difficult to determine. A large scale survey of 4010 older people (>65 years) receiving home care in 11 European countries, found a mean prevalence of LTC use of 5.4%, ranging from 0% in the Netherlands to 23% in Italy [228]. In another large study of 1004 frail older women living in the community the reported LTC prevalence rate was 38.1% [229]. Duration of use can be for many years. In a US sample of 43 community dwelling long-term catheter users, who each provided data over a six months' period, mean use was 11.7 years (ranging in months from 1-589; median 8.8 years). Twenty persons had used it over 10 years [126].

There is evidence that older patients aged 65 years or more are often catheterised inappropriately [293] [294] [295]. Gokula et al. [294] surveyed a 10% random sample of patient charts from 2845 elderly patients who received an indwelling catheter during hospital admission in one year. Less than half the selected charts recorded an appropriate indication for catheterisation. An explicit reason for catheter insertion was documented in only 13% of charts and there was no written order for catheterisation in 33% of the charts. Only 18% had documented care plans for catheter removal. Expert opinion and experience suggests that even when there is an appropriate clinical reason for initial catheterisation, patients may remain catheterised unnecessarily if medical and nursing staff fail to review ongoing need (Level of Evidence 3). Problems of inappropriate catheter use may be compounded when patients are transferred from one clinical setting to another without adequate information on why the person was catheterised [296]. Wald et al [297] reported that 32% of patients catheterised during treatment for hip fracture in their study were discharged to nursing homes with the catheter still in place.

The prevalence of catheterized patients in nursing homes is generally higher than in people living at home and has been reported to be around 9% in the UK [298], but there may be considerable variation between homes [299]. In nursing homes in the US, it has been estimated that between 7-10% of the residents have an LTC [300], although figures vary from state to state. More recent data from analysis of a US National Nursing Home Survey [301] and a point prevalence study of nursing home-associated infections in the Department of Veterans Affairs nursing home care units [302] demonstrated similar prevalence. Tsan et al. [302] reported a prevalence of 10.7% for indwelling urethral catheters and 2.46% for suprapubic catheters amongst a nursing home population of 11,475 in 133 care home units.

There is some evidence of decreasing rates of urinary catheterisation in some places. A retrospective cohort study of the use of urine collection devices in skilled nursing facilities (SNFs) in five US states examined the characteristics of 57,302 patients who remained in an SNF for one year in 2003 [303]. The prevalence of indwelling catheterisation was 12.6% at admission and 4.5% at annual assessment ($p<0.001$). Paraplegia, quadriplegia, multiple sclerosis and comatose state were strongly associated with LTC use. Male residents were more likely to use a catheter at every assessment, as were obese patients; individuals with diabetes mellitus, renal failure, skin conditions, deep vein thrombosis, aphasia or end-stage disease; and those taking multiple medications.

A qualitative study of catheter use in 14 UK care homes (skilled nursing) [304] found that catheter use was higher in homes which were task-centred rather than patient-centred, and / or where patients were inappropriately given residential care when skilled nursing was actually needed. In contrast, the homes with lower rates of catheter use (6% or < versus 9% or >) were more proactive related to catheter removal (many of which had been "inherited from the hospital"), and they actively promoted toileting and mobility. Both groups had similar staffing and believed their approaches enhanced patient dignity.

Duration of catheter use in home settings varies widely, with a median of 3-4 years and some individuals using them over 20 years [305] [306]. Management regimes for continence problems in older people continue to demonstrate a predominance of containment strategies, using pads and catheters [307] and consequently unwarranted use of LTCs for incontinence continues in many places despite known catheter-associated risks.

In view of the considerable cost, and morbidity and mortality associated with the use of catheters, health services should consider adopting similar successful strategies, incorporate such information into their policies and ensure that education on catheters forms part of staff's continuing education.

c) User characteristics

Short-term catheterisation (usually defined as up to 14 days) is most commonly used:

- During surgical procedures and post-operative care.
- For accurate monitoring of urine output in acute illness.
- Instillation of medication directly into the bladder.
- For relief of acute or chronic urinary retention.

Long-term indwelling catheters - routinely changed and replaced, often over many months or years - may be required to aid those who have difficulty emptying their bladder due to obstruction or neurological disorders, where intermittent catheterisation is not a satisfactory option. LTCs may also be used to provide supportive care for those with severe incontinence who cannot manage otherwise, are terminally ill, or need treatment to heal skin lesions or surgical wounds affected by the presence of urine.

Long-term catheterisation is most commonly used to help manage:

- Bladder outlet obstruction (BOO), where patients are unsuitable for - or waiting for - surgical relief.
- Chronic retention, often as a result of neurological injury or disease (where intermittent catheterisation is not possible).
- Debilitated, paralysed or comatose patients (in presence of skin breakdown and infected pressure ulcers).

Intractable urinary incontinence where catheterisation enhances the patient's quality of life (as a last resort when alternative non-invasive approaches are unsatisfactory or unsuccessful).

d) Routes of catheter insertion

For some patients the insertion of an indwelling catheter suprapubically (SPC) into the bladder, through the abdominal wall, offers advantages over the urethral route (UC). SPC may be necessary following urethral or pelvic trauma but also offers advantages in acute and long-term care. In frail elderly men, and / or those prone to infection e.g. diabetes mellitus, SPC can be preferable to a urethral insertion to avoid urethritis, orchidoepidydimitis and prostatitis [107]. Strategies to support the SPC may be required (e.g anchoring to the abdominal wall with a BioDerm tube holder) to prevent traction and potential displacement of the catheter or balloon [308].

Advantages of SPC compared to UC are:

- Avoidance of risk of urethra trauma to men and women during catheter insertion and withdrawal.
- Avoidance of risk of urethral destruction / necrosis from pressure caused by the weight of poorly supported catheter bags, expulsion of the catheter (particularly in neurologically impaired women), or sitting on the catheter in wheelchair bound women.
- Ease of access to entry site in patients with reduced mobility, who are wheelchair bound, have restricted hip mobility, or experience urethral pain.
- Facilitation of post-surgical trial of voiding (by temporarily clamping the drainage tubing).
- Greater freedom for expression of sexuality, although this may be counteracted by perceptions of altered body image.
- Reduced risk of contamination where faecal incontinence is a problem.

SPC insertion is generally contra-indicated in patients with haematuria of unknown origin, bladder tumour, or small contracted or fibrotic bladders which may have resulted from long-term urethral catheterisation on free drainage. In obese or immobile patients the traditional SPC stoma site may become concealed by an apron of excess anterior abdominal wall fatty tissue which can lead to sub-optimal care by both patient and carer. SPC is an effective and well-tolerated method of bladder management for many SCI patients [309] [310] [311]. In Sheriff et al's study [309] the general level of satisfaction with SPC was very high with 70% of patients awarding a satisfaction score of 9/10 and 95% awarding 7/10 or more. It is of interest to note that in 18% of cases, an SPC was inserted following the request of the patient, having heard about this form of bladder management from others. A review of current literature on SPC in the neuropathic bladder, by Feifer & Corcos [311] identified some notable differences between early studies and more recent reports. Problems and complications of SPC identified in earlier studies of SCI patients were less common in the more recent investigations, in which patients were managed with anti-cholinergics, frequent catheter changes and volume maintenance procedures.

Recent studies demonstrated similar morbidity profiles to clean intermittent catheterisation. In one retrospective study from 2010 [312] comparing 85 persons with neurogenic bladder prior to SPC use, and after a mean of 65.3 (± 48.0) months with SPC, anti-cholinergic medicine and bladder clamping (with a valve) did not seem to be needed to preserve detrusor compliance nor renal function. Bladder capacity did decrease significantly, though, and renal function deteriorated in three persons, two of whom were on anticholinergics and none used clamping. Complications were reported by 62.6%, including recurrent blockage (19.2%), surgery for bladder stones (12.1%), and CAUTI (28%). 3.6% had septicaemia or were hospitalized for CAUTI. In another retrospective study of 179 men with SCI comparing indwelling urethral catheters (UC) and suprapubic catheters (SP) [313] complication rates were similar for UTIs, recurrent bladder/renal calculi and cancer. However, those with UC had higher urethral and scrotal complications and SP users suffered from leakage from the urethra and/or SP tube site. Individualizing care management was suggested.

Although SPC has gained wide acceptance for bladder drainage and many regard SPC insertion as a simple procedure, it is not without risks. The initial insertion of the SPC requires a minor surgical procedure which presents a potential risk of injury to adjacent structures to the bladder, especially the small and large intestines with resultant peritonitis [314] [309]. Other complications of initial SPC insertion include misplacement [315] [316] [317], displacement to the peritoneal cavity and sepsis, [318] and incisional hernia [319] [320]. There are a number of SPC techniques for insertion described in the literature and training models have been developed to facilitate teaching [321]. Some modern catheter insertion kits employ the initial introduction of a guide wire into the bladder, to facilitate accurate positioning of the catheter introducer. However, where patients are at high risk of bowel injury (eg previous abdominal surgery or small fibrotic bladders which do not expand well at cystoscopy), some authorities recommend introduction of the SPC by percutaneous technique using intraoperative ultrasonography combined with flexible cystoscopy [322] [323]. In low risk patients nurse specialists may undertake first insertion of an SPC, according to agreed policy and protocols [324]. Subsequent SPC changes can be competently managed by skilled nurses [325].

e) Catheter characteristics

An effective indwelling catheter should have the following design characteristics:

- Retained in the bladder effectively, yet easily removable without trauma to tissue.
- Soft 'tip' within the bladder to avoid pressure damage to the mucosa.
- Effective drainage while minimising risk of bladder mucosa being 'sucked' into drainage channel.
- Conforms to shape of urethra.

Despite some notable efforts to improve catheter design, the original Foley design has changed very little over the years and remains the most common. However traditional drainage systems may fail to drain the bladder to completion, due to potential outflow obstruction caused by air-locks within the curled, redundant drainage tubing segments. A novel, spiral-shaped, drainage tubing design has recently been reported which appears to optimize flow and minimize residual urine [119]. Adding more eyeholes has been suggested to reduce residual urine [326] and in a case report, leakage [327]. Further evidence of efficacy is awaited.

f) Catheter materials

An ideal catheter material requires the following properties:

- Soft for comfort.
- Causing minimal tissue reaction or friction.
- Sufficiently firm for easy insertion and maintenance of lumen patency in situ.
- Elastic recoil so that an inflated balloon can deflate to almost its original size.
- Resistant to colonisation by micro-organisms and to encrustation by mineral deposits.

Catheters are made of a variety of materials includ-

ing polyvinyl chloride (PVC) or other plastic, latex rubber with or without a coating, silicone or metal. Plastic catheters are relatively cheap to manufacture, have a thin wall and relatively large lumen, and are designed for short-term use (in situ up to 14 days). Latex catheters are restricted to short-term indwelling use (and commonly avoided where possible) because of potential discomfort due to high surface friction, vulnerability to rapid encrustation by mineral deposits from the urine and the implication of latex allergic reactions in the development of urethritis and urethral stricture [328] [329] [330] [331] [332] [333] or anaphylaxis [334].

Attempts to minimise friction during catheterisation and to reduce tissue reactions have led to the coating of latex catheters with tightly bonded materials designed to provide a smoother, less irritant surface which also minimizes absorption of water by the latex (and subsequent changes in internal and external catheter diameters). Polytetrafluoroethylene (PTFE or teflon) coated latex catheters are sometimes used for medium-term use (catheter can remain in situ up to 28 days) but the materials known to cause least friction and tissue reaction are silicone elastomer and hydrophilic polymer-coated catheters, or all-silicone catheters [335] (**Table XII-4**). These materials are therefore recommended for long-term use (i.e. expected to remain in situ for 14 days or more, and changed regularly for a new catheter as part of a long-term strategy of care). LTC materials are also less vulnerable to rapid colonisation by bacteria and encrusting by mineral deposits than short-term catheter materials. There is evidence that silver-alloy coated catheters can help to reduce risks of CAUTI in the short-term (where bacteriuria is used as the outcome measure) (See Section XII.3.a), but no currently available material or surface coating is completely immune to microbial colonisation.

Inflation of silicone catheters with water can sometimes lead to water loss from the balloon over time, [336] with an associated risk of the catheter falling out [337]. Consequently some manufacturers recommend filling the balloon with a 10% aqueous glycerine solution, or to fill the balloon with the full 10mL, knowing that 1/4 to 1/2 could be lost over time [336].

Most catheter materials are suitable for either UC or SPC, however not all UC catheters are also licensed for SPC. Suprapubic catheter removal is sometimes associated with trauma of tracts or stoma site where overgranulation has occurred, with bleeding and patient discomfort [338] [325]. This can be a particular problem with catheter materials such as all-silicone, which are prone to hysteresis, leading to balloon cuffing on deflation. This problem may also occur with hydrophilic coated catheters but is less common [339] [340]. Management of this and other catheter-related problems is considered below in Section XII.2.k.

The main finding of a recent Cochrane Review of types of indwelling urinary catheters for long-term bladder drainage in adults [263] was a remarkable lack of evidence for this clinically, highly relevant problem. Despite consideration of 11,000 abstracts and 74 full papers, only three trials met the inclusion criteria. Since these were very small and showed methodological weakness, the authors concluded that there was insufficient evidence to provide a reliable basis for clinical decision-making and catheter choice remains largely based on clinical experience.

g) Catheter size – catheter gauge, length and balloon size

Indwelling catheters are formed either by building up layers through dipping and coating on a shaped 'former' or by a process of extrusion of a single material. Catheter size is measured in Charrière (Ch) – also called French gauge (Fr) - which refers to the circumference of the catheter shaft in millimetres. Internal diameter varies depending on the manufacturing method, with the extrusion process resulting in a catheter with relatively thinner

Table XII-4: Catheter materials

Duration of catheterisation		Catheter material
Intermittent	Removed immediately after urine drainage.	Plastic: with or without hydrophilic polymer coating. Metal (silver, stainless steel).
Indwelling, short term use	Catheter expected to be *in situ* for < 14 days.	Latex or plastic PTFE-coated latex. Silver-alloy coated (catheter materials recommended for long-term use may also be selected).
Indwelling LTC	Catheter expected to be in situ for 14 days or more (recommended time between catheter changes depends on local catheter policy - may be up to 12 weeks).	Silicone elastomer-coated latex. Hydrophilic polymer-coated latex. All silicone

walls and a larger lumen for the same Charrière size. A size 12Ch catheter made by dipping and coating will have an external diameter of around 4mm and an internal diameter of around 2mm or less. Urinary flow rate is related to the internal diameter of the catheter but 12 -16 Ch catheters (usual sizes for adults) easily drain normal quantities of urine, including larger volumes produced by diuresis [341]. Although larger sizes may be needed following urological procedures where blood clots and other debris are a problem, large catheters are generally associated with increased bladder irritability and spasm [113], and with potential blockage of para-urethral glands and tissue damage, including urethral strictures. Therefore large catheter sizes should be avoided wherever possible. It is not known whether large catheters contribute to CAUTI, but the smallest size to maintain good drainage and prevent urethral and bladder neck trauma is recommended [342] further research may be needed to determine best practices [343]. Small balloon sizes are recommended for all patients (10ml for adults and 2.5-5ml for children) to minimise the risk of discomfort and bladder irritation. Larger balloons tend to sit higher in the bladder with potential for increased residual urine volumes to collect below the catheter eyes. Larger balloons are also associated with increased risk of meatal tissue damage caused by bladder spasm and possible expulsion of the catheter with a fully inflated balloon.

The most common sizes of SPC catheters for adults are also 12-16Ch. Some SPC kits provide a specific catheter in the kit and therefore dictate the sizes available; others allow the insertion of a range of Foley catheters. Since the catheter is inserted into the bladder via an artificial stoma it is possible that slightly larger sizes may be better tolerated than for UC although there is no research evidence to support this.

The standard male length catheter (41-45cm) is available to males and females but a shorter female length (25cm) can be more comfortable and discrete for some women. The female length catheter should not be used for males as inflation of the balloon within the urethra can result in severe trauma. In one case series report [344] six boys, aged < 1 month to 16 years suffered damage to the bulbar or prostatic urethra due to inflation within the urethra. Three required suprapubic catheters, and all healed without further complications. Insertion to the bifurcation of the catheter – that is, until only the inflation and drainage ports were visible - was advised to prevent this. Paediatric catheters are usually approximately 30cm long.

h) LTC–associated risks / problems: catheter-associated urinary tract infection (CAUTI)

The urinary tract is recognised as the commonest site for nosocomial infection in hospitals and nursing homes, accounting for between 21% and 45% of all healthcare-associated infections [345] [346] [65] [347] [302] [348]. National nosocomial infection surveillance systems monitor CAUTIs and provide guidance for benchmarking [349]. The presence of an indwelling catheter is a key risk factor in around 80% of nosocomial UTIs. The risk of bacteriuria increases by 5-8% per day of catheterisation [350] [351] [352] and virtually all LTC patients are likely to be bacteriuric within four weeks [342]. A majority of microorganisms derive from the patient's own colonic and perineal flora or from the hands of health-care personnel during catheter insertion or management [187]. Access is gained in two ways: (1) extraluminally during catheter insertion or via the periurethral space; (2) intraluminally following breaks in the closed system or contamination of urine in the drainage bag. The comparative importance of these routes is difficult to determine, but animal models have demonstrated rapid colonisation via the intraluminal route following a break in the closed system, compared to the extraluminal route (32-48 hours v 72-168 hours respectively) [353]. However, clinical studies have shown that colonisation will occur even when strict infection control practices are adhered to [354].

Indwelling catheters rapidly become colonised by micro-organisms which form a strongly adherent biofilm on catheter and drainage equipment surfaces. Biofilm formation begins by deposition of a conditioning layer of proteins, electrolytes and other organic molecules from the urine [355] which may then mask catheter surface properties designed to inhibit colonisation. Micro-organisms attached to catheter surfaces divide to form micro-colonies, ultimately developing a complex three-dimentional structure, including fluid filled channels through which the biofilm members receive nutrients, diffuse away wastes and send chemical signals to each other [356]. Catheter biofilms commonly comprise mixed communities of micro-organisms embedded in a matrix of host proteins and microbial exopolysaccharides [357], [358] (**Figures XII-4, XII-5 and XII-6**). Microorganisms growing as a biofilm are less susceptible to antimicrobial therapies than free-living organisms and are a major source of resistant, nosocomial pathogens [187] [359] [259]. Decreased susceptibility arises from multiple factors including; physical impairment of diffusion of antimicrobial agents, reduced bacterial growth rates; and local alterations of the micro-environment that may impair activity of the antimicrobial agent [356]. The close proximity of cells within a biofilm can facilitate plasmid exchange and the spread of antimicrobial resistance [355].

1. Antibiotic use

Hospitalized patients are likely to be on antibiotics for other causes than an indwelling catheter, which also might be present. In one study in an acute care setting, [360] catheterized patients on antibiotics

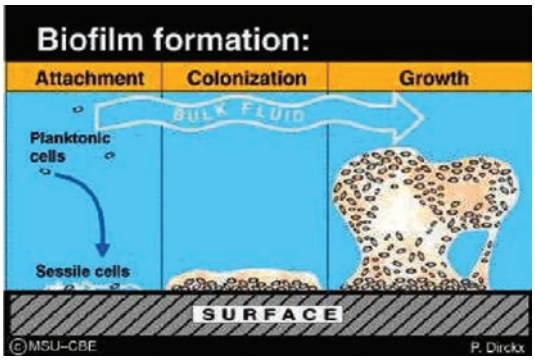


Figure XII-4: Biofilm - 'pillars, mushrooms and water channels' (Reproduced with the permission of Montana University Centre for Biofilm Engineering).

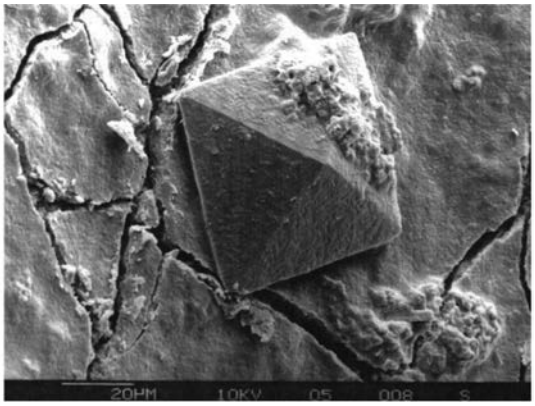


Figure XII-5: Scanning electron micrograph of biofilm.

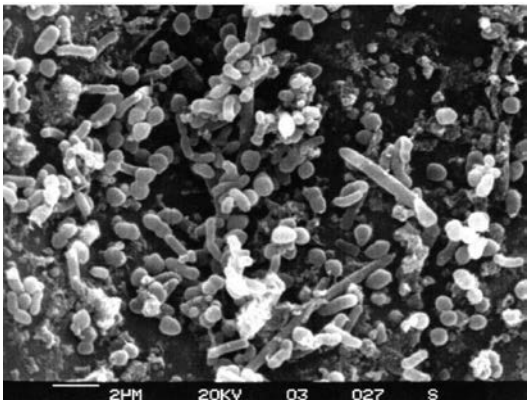


Figure XII-6: SEM of bacteria colonising catheter surface – Proteus mirabilis, Enterococcus faecalis, lactobacillus sp.

for a shorter period of time (< 5 days) were more likely to develop CAUTI than those taking antibiotics longer, and the former should be evaluated for this risk. In a prevalence study in France of antibiotics used to treat hospital acquired infections, [361] urinary tract infection had the highest association with antibiotics use, in particular with fluoroquinolone. The researchers' model predicted that decreasing CAUTI in hospitals with high rates (75th percentile or >) could reduce antibiotic use by 2.1% and 0.4% for fluoroquinolone.

2. Prevalence of CAUTI

The majority of research on the risks of CAUTI has been conducted in acute care settings where catheters usually remain in place for less than 14 days and many patients' health is already compromised by co-morbidities [362]. A series of reports from the International Nosocomial Infection Control Consortium (INICC) provided rates of CAUTI in intensive care unit (ICU), using the methodology of the US National Nosocomial Infections Surveillance system. The rates per 1000 catheter days were: Brazil 9.6 [363] and Peru 5.1 [364]. Overall, in 13 limited resource countries implementing INICC infection control guidelines for education and surveillance (Argentina, Brazil, Colombia, Costa Rica, Cuba, El Salvador,India, Macedonia, Mexico, Morocco, Philippines,Peru, and Turkey) the CAUTI rates dropped from 8.2 to 6.9 per 1000 catheter days [365]. A later report in ICUs in Cyrus, Greece gave a rate of 2.8/1000 catheter days [366]. From the U.S. National Healthcare Safety Network (NHSN) [367] from January 2006 through December 2008, the pooled mean CAUTI rate in ICUs ranged from 3.1 to 7.4 /1000 catheter days, depending on the type of specialty unit. Surveillance was suggested for a minimum of three months, based on a pilot study describing the protocol and surveillance tool used in six hospitals caring for elderly people in Scotland [368].

Less is known about the prevalence of CAUTI in long-term and home care settings or about the potential for reduction of CAUTI and improved cost benefits in the LTC population [352]. Encouragingly, in a recent U.S. study in North Carolina home health and hospice populations, [369] the CAUTI rates have decreased over 11 years of surveillance. The rate of catheter-associated UTI decreased in home health from 4.2/1000 catheter days in 1998 to 0 in 2008, and in hospice patients from 2.35/1000 catheter days in 1999 to 0 in 2008. Infection control specialists trained the persons collecting data, and presumably the rates reflect symptomatic CAUTI. However, in a hospital study of U.S. Veterans with spinal cord injury and disorder, [348] the rate was higher (8.9/1000 catheter days), reflecting greater risk. In a similar population of 100 inpatient and outpatient veterans with chronic catheters, candiduria was present in 17%, and all but one had an indwelling catheter. This was of concern due to the likelihood of reoccurrence of this microorganism [370].

In the multi-national survey of 4010 older people (>65 years) receiving home care in 11 European countries, the risk of a UTI was found to be 6.5 times greater for catheterised individuals than for non-catheterised [371]. Prevalence of a UTI amongst

1004 frail older women living in the community was 21% in catheterized women compared to 10% in non-catheterized subjects (p>0.001) [372]. Furthermore, catheterised subjects were more likely to die within a year (RR1.44; 95% CI 1.01-2.07). Tsan et al's point prevalence survey [302] of Nursing Home acquired infections found 13.2% of 11,475 residents had an indwelling urinary catheter. Of those, 13% of residents with a UC and 9.5% of those with a SPC had a UTI. In catheterised SCI populations the overall rate of urinary tract infection has been quoted as about 2.5 episodes per patient per year [373]. Although randomized trials are lacking there is some evidence of reduced rates of bacteriuria and CAUTI with SPC, condom catheters and intermittent catheterisation compared to UC [373] [374] [302].

Bacteraemia resulting from CAUTI invariably represents a serious complication which may occur in approximately 4% of catheterised patients with bacteriuria in acute care settings [375] [376] [377]. In their review, Saint et al. [375] statistically pooled results from several prospective studies on short-term indwelling catheterization (in which the definition of bacteriuria varied between studies, ranging from >103 cfu/ml to >105 cfu/ml) and estimated (Level of Evidence 2) that:

- 26% of patients (not receiving systemic antibiotics) with a short-term, standard non-coated indwelling catheter in situ for between two and 10 days will develop bacteriuria.
- 72% of patients developing bacteriuria will remain asymptomatic and not require treatment.
- 24% of those developing bacteriuria will develop a symptomatic UTI without bacteraemia.
- 4% with bacteriuria will develop bacteraemia.

This data is interesting since it provides supporting evidence that bacteriuria remains asymptomatic in a majority of catheterised patients. However, it can be difficult to generalize such data from acute care contexts to other practice settings. Unfortunately, few epidemiological studies or comparative catheter evaluations are conducted on long-term catheterised patients in community settings.

3. Outcome measures and criteria for CAUTI

Interpretation of the literature on CAUTI is often confused by the range of definitions and outcome measures used. In this chapter, the terms symptomatic infection and asymptomatic bacteriuria have been employed to distinguish as clearly as possible between symptomatic and asymptomatic conditions. However many studies make little or no distinction between these states, referring to both as infection. This can be particularly confusing when attempting to interpret results in terms of the magnitude of infection-related problems, clinical importance and implications for services and individuals.

Bacteriuria is commonly used as a surrogate outcome measure for the clinically more important outcomes of symptomatic UTI. Although symptomatic infection is far less common than asymptomatic bacteriuria, the frequency of catheter use produces considerable overall morbidity and mortality [378]for patients and high costs to healthcare services [377], often including unnecessary antibiotic drug therapy which may then become a major source of antibiotic resistant pathogens. Asymptomatic bacteriuria can lead on to symptomatic infection, but not necessarily. Questions about the significance of long-term asymptomatic bacteriuria in its own right (e.g. effects of chronic tissue inflammation) are currently unanswered.

In non-catheterised patients the criterion for 'significant' bacteriuria is commonly accepted to be $>10^5$ cfu/ml but since growth of micro-organisms in catheterised patients is rapid, many authorities consider $>10^2$ or 10^3 cfu/ml in a urine sample collected from the sampling port of the catheter, to be indicative [187] [342] [110]. Most definitions of symptomatic UTI [379] are based on those used for non-catheterised patients and include significant bacteriuria. For catheterised patients, these include presence of pyuria (>10wbc/mm3) plus one or more clinical signs and symptoms for which no other aetiology is apparent: fever, suprapubic or flank discomfort, bladder spasm haematuria, changes in mental state, or malaise / lethargy. Pyuria alone is not diagnostic of UTI. [110]. For SCI patients signs and symptoms may also include increasing spasticity and / or worsening autonomic dysreflexia (usually manifested by increase in blood pressure, headache, sweating above the SCI lesion, flushing below the SCI lesion) [380] or a "sense of unease" [110]. Elderly persons may have atypical or generalized symptoms [284]. In a study of the validity, accuracy and predictive value of UTI signs and symptoms in person with SCI using intermittent catheters, [381] cloudy urine had the highest accuracy (83.1%) and leukocytes in the urine was the most sensitive (82.8%). Fever was the most specific (99%) but least sensitive (6.9%) symptom. Moreover, patients might be better at identifying when they do not have UTI, as positive predictive value was 32.6% and negative predictive value was 82.8%.

However, commonly used criteria for symptomatic urinary infection have been questioned by Tambyah and Maki [362] in a prospective study of 1497 newly catheterised patients. No significant difference in reported symptoms of pain, urgency, dysuria and fever was found between patients with a catheter-associated infection and those without, nor was there statistical evidence that peripheral leukocytosis was predictive of infection (p=0.14) (Level of Evidence 2). The criterion for bacteriuria (catheter-associated infection) in this study was >= 10^3 colony forming units (cfu)/ml urine). This finding raises further questions over the selection of the most appropri-

ate outcome measures in studies of CAUTI. Indeed concerns have also been raised over current UTI criteria for non-catheterised populations, particularly for elderly groups, including nursing home residents. Consensus criteria (e.g. Loeb criteria 2001) have been found to be limited in terms of sensitivity, specificity and predictive value by Juthani-Mehta et al. [382] and these authors have called for clearer identification and evaluation of evidence-based clinical criteria associated with laboratory evidence of UTI. A further complication to difficulties in confirming 'best criteria' for UTI and CAUTI is the variation in the clinical and scientific definitions required for specific populations, for research purposes or to meet stipulations for reimbursement from governments and medical agencies. Asymptomatic bacteriuria might be treated inappropriately, as described in a study in which 32% were treated (53 of 164 episodes of bacteriuria) [383] further confounding the definitions of CAUTI that include treatment with antibiotics. It is important that efforts to resolve these issues are progressed as quickly as possible to provide greater clarity in the interpretation of existing research, the design of new studies and the application of clinically important findings.

4. Reducing the risk of CAUTI

Risk factors which are independently predictive of increased risk for CAUTI have been identified in a number of large prospective studies of short-term catheterised patients [187] (**Table XII-5**). There is evidence that females have a substantially higher risk than males (relative risk: RR 2.5-3.7), and 1.3-2.2, p=0.001 in an ICU setting [384]. But the greatest risk is associated with prolonged catheterisation > six days (RR 5.1-6.8). A recent retrospective cohort study of 35,904 undergoing major surgery reported that 86% of patients had a perioperative indwelling catheter [385]. Multivariate analysis showed that postoperative catheterisation for longer than two days was associated with increased risk of UTI.

Use of a preconnected drainage bag may be of value in preventing CAUTI in acute care settings. A prospective study in the UK of 205 patients in three medical wards over two periods, each of about six months' surveillance, [386] compared use of preconnected bags with the usual bags. The CAUTI rate was 41% lower in the group with the preconnected bags, with rates of 37.8/1000 catheter days for the usual bags, compared with 22.4/1000 catheter days in the intervention group (RR 0.59 (0.35–0.99) 0.04.

In Japan, a prospective observational study in five hospitals evaluated risks in persons with catheters 3> days, using a Cox proportional hazards model [387]. Risks were significantly associated with two practices in this study of 555 inpatients, not using a pre-connected closed system (RR 2.35, 95% CI 1.20–4.60, p=0.013) and the lack of daily cleaning of the perineum (RR 2.49, 95% CI 1.32–4.69, p=0.005).

Although there is some evidence to suggest there may be a reduced risk of CAUTI when SPC is employed compared to UC, the data is limited, studies are often small and most catheterisations are for post-operative care in acute care settings. One large scale point prevalence study of nursing home acquired infections in >11,000 residents [302] reported that 9.5% of residents with a SPC had a UTI compared to 13% of those with a UC. These data just fail to demonstrate a statistically significant difference between UC and SPC (one-sided, Fisher's exact test; p=0.066). A review of five published RCTs comparing SPC with urethral catheters

Table XII-5: Risk factors for catheter-associated infection based on prospective studies and use of multivariate statistical modelling (adapted from Maki & Tambyah 2001)[187].

Risk factor	Relative risk
Prolonged catheterisation >6 days	5.1-6.8
Female	2.5-3.7
Catheter insertion outside the operating room	2.0-5.3
Other active sites of infection	2.3-2.4
Diabetes	2.2-2.3
Malnutrition	2.4
Ureteral stent	2.5
Renal insufficiency (creatinine > 2.0mg/dL)	2.1-2.6
Using a catheter to measure urine output	2.0
Improper position of drainage tube (above bladder or sagging below drainage bag)	1.9

following colorectal surgery [388] reported that sample sizes were small, catheters were used short-term and there was no apparent difference in the duration of catheterisation between the two techniques. Significant UTI was defined in different papers as bacteriuria with either $>10^4$ or 10^5 organisms or cfu/ml. Frequency of UTI was less in the SPC group in three of the studies, with no significant difference in the other two. The SPC groups reported less pain and discomfort than the urethral groups and SPC was preferred by those patients who experienced both. The authors concluded that the results favoured SPC over urethral catheterisation as UTIs are reduced, particularly in females, and the ability to attempt normal voiding is facilitated, particularly in males (**Level of Evidence 2**).

Much of the recent research on reduction of risk of CAUTI has centered on the development of catheters with antimicrobial surfaces, such as silver. Silver ions are bactericidal [389], non-toxic to humans when applied topically, and have been used successfully in other areas of infection control such as burn wounds. Silver is also purported to have broad spectrum activity against Gram-positive, Gram-negative, aerobic and anaerobic organisms. Early silver-coatings incorporated silver oxide into the external surface of the catheter material only, but efficacy against CAUTI was limited [390]. Subsequently, silver-alloy coatings were developed to provide an integral coating on both internal and external surfaces and promote a slow release of silver ions. Other developments have been directed towards impregnation of catheter materials with antibiotic or antiseptic agents such as nitrofurazone [391] [392] [393] [394]; minocycline and rifampicin [395]; chlorhexidine, silver sulfadiazine, triclosan [396] and others. Although a large number of studies (both laboratory models and clinical studies) have attempted to examine the potential benefits of antimicrobial catheters, most have used bacteriuria - rather than symptomatic UTI - as a surrogate endpoint. Most reports were either prospective cross-over studies [397] or prospective surveillance of outcomes associated with introduction of new catheter types, in comparison with historical or baseline outcomes associated with previously used catheter types [398] [399] [400]. Almost all have examined short-term catheter use in acute care settings.

A recent Cochrane review [260], designed to determine the effect of type of indwelling urethral catheter on the risk of UTI, examined 23 trials, comparing different types of standard catheters or a standard catheter with an antiseptic catheter (silver alloy or impregnated with silver oxide); or an antibiotic impregnated catheter (either minocycline and rifampicin, or nitrofurazone). The reviewers commented that trials were generally of poor quality but concluded that current evidence suggests silver alloy catheters prevent asymptomatic bacteriuria in the short-term catheterised patient (Level of Evidence 1). They recommended that further economic evaluation is necessary to confirm the extent to which reduction of clinically important infection compensates for the increased cost of the silver alloy catheters. Catheters impregnated with antibiotics were also found to be beneficial in reducing bacteriuria in hospitalised adults catheterised for less than a week, but data were too few for patients catheterised longer.

An earlier systematic review of antimicrobial urinary catheters to prevent CAUTI in hospitalized patients [401] identified 12 randomised or quasi-randomised trials of silver-alloy coated (n=9) or nitrofurazone-coated catheters (n=3) compared to standard silicone or latex catheters. Pre-post study designs were excluded. No study addressed symptomatic UTI and therefore analysis was based on bacteriuria. Although all studies indicated some benefit in prevention or delay of onset of bacteriuria the effect size varied substantially between studies. Variations were related to catheter type, patient characteristics, control group bacteriuria rate and year of publication (i.e prevailing clinical conditions at the time of the study). Post enrolment exclusions, absence of intention to treat analysis, highly selected study samples and lack of data on clinically meaningful end-points, all limited the ability to draw definitive conclusions on efficacy. The authors concluded that, according to fair-quality evidence, antimicrobial catheters can prevent bacteriuria in hospitalized patients during short-term catheterisation (Level of Evidence 1), but trial results are highly context dependent. The relevance of results to other institutions or patient groups depends on the similarities between settings with respect to a range of variables, including: background bacteriuria rate, baseline catheter type, local catheter use and maintenance practices, patient groups and patterns of antimicrobial usage. The authors cautioned that older data may lack current relevance, particularly where background rates of bacteriuria have changed notably in the intervening period. Although there is evidence that antimicrobial-coated catheters prevent bacteriuria during short-term catheterisation, there is a lack of corresponding data to demonstrate clinical benefit [402]. Further well-designed and adequately powered randomised trials, with clinically relevant endpoints are needed to clarify comparative clinical utility and economic value.

In contrast to the majority of trials of silver-coated latex catheters Srinivasan et al [403] found no significant reduction in bacteriuria with silver-impregnated, silicone catheters despite similar performances in vitro. However, outcomes may have been affected by notable differences in the study groups in this prospective, cross-over study. The authors drew attention to the fact that not all silver products are the same and clinical trials of new products remain critically important. Any potential advantages of silver alloy catheters (or other antimicrobial catheters)

for LTC patients remain uncertain, although clinical experience suggests some benefits for individuals with frequent symptomatic infections. It is not known whether argyria (deposition of silver in the skin) may be a potential problem for long-term care patients or whether silver-resistant mutants may be selected by repeated exposure [404] [405].

A common concern over the use of antimicrobial impregnated catheters is that elution of sub-inhibitory levels of the antimicrobial agent into the urine may induce resistance in resident organisms with prolonged catheter use [406]. Antiseptic agents are generally considered more likely to confer resistance to surface colonization than antibiotics and not to select for infection with antimicrobial drug resistant bacteria. Alternative approaches to inhibiting biofilm development include development of catheter surfaces which reduce protein absorption [407]; inflation of the balloon with a biocide solution, such triclosan, which then diffuses throughout the catheter material and into the surrounding area [408] [409]; or efforts to disrupt matrix or glycocalyx components with agents such as heparin [410], and colonization with a competing benign organism. Bacterial interference with E. coli 83972 was attempted in 13 CIC users with SCI, [411] [110], and eight were successfully colonized in 19 three-day attempts. Monthly urine cultures (until colonization was lost in the urine) indicated a reduction in symptomatic UTI rate per year, 0.77 per patient year as compared with 2.27 per patient year prior to the study.

Relatively few studies have examined the cost benefits of different catheters. Those that have tend to rely heavily on assumptions that a certain proportion of patients with bacteriuria will develop the clinically important outcomes of symptomatic UTI or bacteraemia. The focus of economic studies generally falls on acute care settings and, as discussed earlier, it can be difficult to generalise results from one practice setting to another. Practitioners and/or institutions who are considering introducing a new product (e.g. catheter type) for a majority of their patients on the basis of claims of improved cost-effectiveness from clinical research studies, are advised to look carefully at the similarities and differences between their own local practice (and patient groups) compared to that described in the research. Economic studies are frequently required to make assumptions about certain data (e.g. increased length of hospital stay for CAUTI) which is then applied to an economic model. (?Cross ref to economics chapter). Such assumptions may or may not be applicable in local settings.

Numerous trials of oral antibiotics, antimicrobial bladder washes, drainage bag solutions and topical disinfectants all lead to the common conclusion that bacteriuria and UTI may be suppressed temporarily at best, but resistant organisms are highly likely to emerge [357]. The application of devices to secure catheters in place, to prevent a 'to and fro' pistoning effect that could favour invasion of catheter tracts by microorganisms, has been shown to reduce the incidence of catheter-related blood stream infection in central venous catheters. Only one prospective, randomised trial has examined a similar device for urinary catheters (StatLock) [380]. Although the study in 118 SCI patients failed to achieve statistically significant results the authors reported a clinically important reduction in the rate of symptomatic UTI of 45% and called for further larger scale trials. They also noted the polymicrobial nature of infections including the presence of a Candida species in more than 20% of infections.

5. Treating CAUTI: antibiotic use

Some studies have suggested that methenamine hippurate may have a beneficial effect in preventing bacteriuria in patients requiring short-term catheterisation during and post-surgery. However, a Cochrane review [393] designed to address this issue concluded there is not enough reliable evidence to conclusively support its use for urinary prophylaxis and identified a range of methodological limitations in existing studies. Caution is needed in translating research on reducing CAUTIs in short-term catheters to LTCs but treatment of asymptomatic bacteriuria is not recommended in either for either group. Urine cultures should be obtained before initiating treatment to permit selection of specific therapy for the infecting organism and the extensive use of broad spectrum therapy should be avoided [412].

Studies of LTC patients can be difficult given the relatively high proportion of disabled or elderly patients, many of whom are very frail. However, routine use of prophylactic antibiotics in LTC patients is not supported by research evidence and has been shown to favour the emergence of resistant organisms [110]. In a double-blind, cross-over study of 34 elderly nursing home patients with urethral catheters [413] subjects were randomised to receive antibiotic prophylaxis (200mg/day norfloxacin) or placebo for three months, followed by cross-over. Urine cultures were obtained once monthly. Episodes of UTI, catheter-related complications (obstruction, encrustation, leakage, suprapubic pain, inflammation of meatus, haematuria and side effects of treatment were monitored weekly. Symptomatic UTI was defined as bacteriuria $>10^5$ cfu/ml and (i) a temp>38.5^{o}C for two days in the absence of other clinical sources of infection or (ii) flank pain or unexplained mental disturbance or abdominal discomfort. Only 23 patients completed the study and although norfloxacin failed to reduce asymptomatic bacteriuria, there was a significant reduction in symptomatic UTIs (1 v 12, $p<0.02$) and a decrease in catheter-associated complications of obstruction and leakage ($p<0.05$). Of the 11 patients who did not complete the study, six died (of non-infectious causes), one died of septic shock and four were withdrawn. However, norfloxacin

treatment was also strongly associated with the acquisition of gram-positive norfloxacin resistant flora (RR 4.66, 95% CI 2.47-8.80), and there was a rapid recolonisation by norfloxacin-sensitive, gram-negative bacteria on cessation of treatment. Overall the study concluded that norfloxacin failed to prevent bacteriuria in long-term catheterised patients and favoured the emergence of quinalone-resistent organisms, although there were some clinically observable benefits in some patients.

Similarly there is little strong evidence of benefit in prophylactic antibiotics prior to re-catheterisationand it is not routinely recommended [110]. One RCT in which 70 residents in a long-term care home were allocated to a treatment group (1gm IV meropenem given 30 minutes before re-catheterisation) or control group (no antibiotics) showed no significant differences in urine cultures at 3, 7, 14 or 28 days [414].

When catheterised patients are prescribed a course of antibiotics for symptomatic infection a common question from healthcare practitioners is whether the catheter should be changed to a new one prior to starting antibiotics. There are concerns that this may allow time for a new biofilm to become established on the catheter within a few hours (and provide a source of re-infection) before the antibiotics have taken effect. In contrast, the 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America suggest a catheter change if the catheter had been in place for at least two weeks and was still needed. The rationale was that this would facilitate resolution of symptoms and decrease risk of bacteriuria and CAUTI [110]. There is little research to guide practice but in one RCT of 54 nursing home residents managed by long-term catheterisation, subjects were randomised to undergo catheter replacement, or no catheter replacement, before antibiotic intervention for clinical diagnosis of UTI [216]. Clinical outcomes (reduction in polymicrobial counts, time to achieve afebrile status and clinical status at 72 hours) were significantly better among subjects randomised to catheter change immediately before institution of antibiotics (Level of Evidence 2). Replacement of the catheter, in patients suspected of having a UTI, prior to collecting a urine sample for culture and sensitivity testing has also been shown to reduce the number of pathogens identified, the number of antimicrobials prescribed and laboratory costs [415]. There is evidence that certain bacterial strains may be particularly difficult to eradicate. In a prospective study of infection in catheterised nursing home patients a single genotype of P.mirabilis was shown to persist in the urinary tract despite many changes of catheter, periods of non-catheterisation and antibiotic therapy [416].

Cranberry juice has long been advocated as a treatment for urinary tract infection and there is some evidence of decreased symptomatic infections in some study populations, but not in catheterized persons [417]. However current evidence to date is limited to non-catheterised patients and caution needs to be applied in extrapolating results to catheterised patients.

i) LTC-associated risks and problems: recurrent catheter blockage

Recurrent catheter encrustation by mineral deposits, leading to catheter blockage occurs in up to 50% of LTC users, with resultant increased costs to services and patients [418] [419] [420] [421]. Heavy encrustation on external surfaces of the catheter tip and balloon can also cause painful tissue trauma on catheter removal. The major components of encrustation are calcium phosphates and magnesium ammonium phosphate (struvite) (**Figures XII-7 and XII-8**) which precipitate from the urine, most commonly under alkaline conditions.

The precipitation of different ionic species (ie Ca++, Mg++, and phosphates) is influenced by their ionic concentrations in the urine. In addition, the urinary pH at which different ions precipitate from the urine varies, not only for different ions, but also between individuals and at different times [422] [423]. These factors contribute, at least in part, to individual variability in terms of susceptibility to catheter encrustation and time to blockage. Catheterised patients can usually be classified into 'blockers' or 'non-blockers' [418] [424] where 'blockers' are those individuals who experience recurrent catheter blockage within a few days to a few weeks. Early recognition of recurrent 'blockers' facilitates proactive care through appropriate catheter change regimes [424]. Urine from recurrent blockers tends to have a very narrow 'safety margin' between 'voided' urinary pH and the pH at which crystallisation (or nucleation) occurs. This margin is much wider in non-blockers [425]. Precipitates occur most commonly under alkaline conditions caused by the presence of urea-splitting micro-organisms such as Proteus mirabilis, in the catheter biofilm [426] [424] [427] [425].

1. Reducing catheter encrustation – catheter materials

The majority of research on catheter encrustation comprises experimental, laboratory-based studies addressing current and / or potential catheter material surface properties in relation to bacterial adhesion and encrustation. Encrustation may sometimes take place in the absence of infection [428] and is influenced by catheter surface properties, including roughness and irregularity, hydrophobicity and wetability, charge, polymer chemistry and coatings. None of the currently available long-term catheter materials is resistant to biofilm formation and encrustation. In a series of laboratory studies of 18 types of catheter materials, using a model of the catheterised bladder, none resisted biofilm formation by a clinical strain of P.mirabilis [429] [430]. Relative times to catheter blockage were: silver-coated latex 17.7h; hydrogel-coated latex 34h; silicone-coated latex 38h;

Figure XII-7: Section of catheter showing encrustation and blockage.

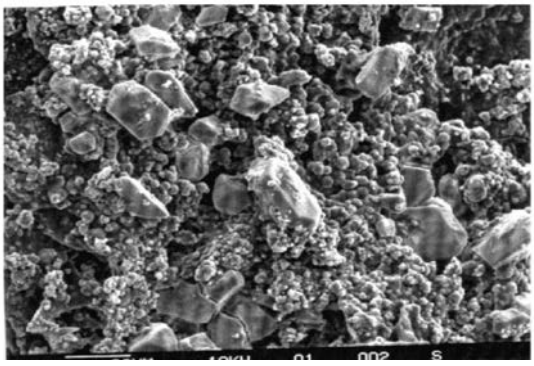


Figure XII-8: SEM of encrusting material - struvite and calcium phosphate.

all-silicone 47h. However, the authors note that the internal diameter of the coated latex catheters was much smaller than for the silicone catheters (1.5mm compared to 2.5mm).

This finding was confirmed [409] in tests with five types of catheters (pure silicone, silicone-coated latex, hydrogel-coated latex, hydrogel/silver-coated latex, and nitrofurazone silicone) colonized with P. mirabilis 108 cfu/mL and a urine pH of 8.5 All had heavy encrustation by 18 h. and were blocked within 40 h. There are implications for coated catheters, such as silver, because the bacteria can continue to grow even when attached to the crystalline biofilm, which shields them from the silver. To keep the pH from rising, antimicrobials need to get into the urine.

Targeting P. mirabilis infection for treatment as soon as it is introduced into the urinary tract may be beneficial in preventing recurrent encrustation and blockage [431]. While this organism, which is harboured in the intestines, may not cause problems in the urinary tract of a healthy person, it has many characteristics that negatively impact the bladder of a catheterized person who has an already inflammatory process taking place. These include: four adhesins that help make it stick to the bladder and catheter, a protective capsule, several secretions that promote extraction of host nutrients, quick migration capacity, and a powerful urease [431]. The ability of P.mirabilis to evade the host's immune response make it a very difficult organism to treat. For example, a structure in the membrane called LPS contributes to virulence and can cause hypotension, fever, DIC and shock. Another component (migration factor Cmf] improves swarming [432].

Although it is not possible to examine the effects of polymer surface properties on microbial adhesion and formation of catheter encrustation in detail here, recent studies have shown that strongly electron donating surfaces are less prone to adherence by P.mirabilis than more hydrophobic materials [433]. Some copolymer, polyurethane blends are associated with less microbial adherence and improved resistance to encrustation in an artificial bladder model [434]. The effect of iontophoresis produced by passing an electric current through silver electrodes attached to catheters has also been shown to inhibit bacterial growth [435]. Another potentially promising innovation is the use of the antiseptic agent triclosan in the catheter balloon [408] [436] [437]. In laboratory models of the catheterised bladder infected with P.mirabilis, silicone and latex-based catheters, with balloons inflated with triclosan, drained freely for seven days compared to 24h for controls inflated with water. Triclosan became impregnated throughout the silicone catheter material and strongly inhibited the formation of the crystalline biofilm. However, latex-based catheters required a higher concentration of triclosan (>1mg/ml) than silicone catheters to produce similar inhibitory effects on P. mirabilis. Diffusion through the latex balloon occurred but the latex-based catheter did not become impregnated with triclosan throughout. The potential benefits of triclosan in catheter balloons now needs to be tested in clinical trials but it is also important to note that not all microbial species responsible for CAUTIs are sensitive to this biocide and emergence of resistant strains is a common concern [437].

2. Reducing catheter encrustation – interventions

A number of studies have employed in vitro models of the catheterised bladder to examine the influence of urinary composition on bacteria growth and encrustation, and the ability of acidic irrigations to reduce encrustation build up. There is good evidence from laboratory studies that increased fluid consumption (leading to lower concentration of encrustation components) increases the time to catheter

blockage [438]. Increasing citrate concentration in fluid intake and urinary output (eg through drinking orange juice or other fruit juices such as lemon or lime) has also been shown to increase time to catheter blockage (see below). Cranberry juice has frequently been advocated to reduce UTIs, microbial adherence and biofilm development but an in vitro study by Morris and Stickler [439] drinking cranberry juice did not produce urine which was inhibitory to the development of P.mirabilis biofims and catheter blockage, although increased fluid intake was beneficial. Although some studies have claimed drinking cranberry juice can decrease urinary pH in healthy volunteers [440], this is unlikely to be accomplished in catheterised patients, in the presence of continued ammonia production by the action of urease-producing micro-organisms [441].

Urease inhibitors, including acetohydroxamic acid (1.0mg/ml) and fluorofamide (1.0microg/ml), have been shown to restrict the increase in urinary pH of P.mirabilis infected urine from 9.1 to 7.6, in a simple physical model of the catheterised bladder [430]. Significant reductions in precipitation of calcium and magnesium salts were also noted but the impact of possible side-effects remains unclear, and therefore clinical potential is uncertain. Clinical studies on the prevention or management of catheter encrustation are extremely limited and only two relevant studies addressing the use of urease-inhibitors were identified. One early clinical study [442] examined oral administration of a urease inhibitor (acetohydroxamic acid) to five patients who required frequent catheter changes (>1 every 2 weeks) due to encrustation and blockage. The dose was based on body weight (eg. 250mg three times daily for patients between 50-70kg). The degree of encrustation decreased significantly during therapy ($p<0.05$) and the authors reported minimal adverse side effects experienced by patients, but acknowledged the potential for more severe side effects to occur. A subsequent double-blind, RCT of acetohydroxamic acid in the palliative treatment of infection-induced urinary calculi, demonstrated lowered urinary pH in urine infected with P.mirabilis but the side effects were unacceptable to patients [443] (Level of Evidence 1).

An alternative approach to reducing catheter encrustation, aimed at increasing the 'safety margin' between urinary pH and the nucleation pH (pHn) (i.e. the pH at which crystals of calcium and magnesium are formed in the urine) warrants further clinical investigation. In laboratory studies using models of the catheterised bladder, the pHn of the urine was shown to increase when urine concentration was decreased and also by addition of citrate to the urine [438]. In models supplied with urine containing citrate at 1.5mg/ml or above, catheter drained freely for the seven day experimental period. Drinking 500ml pure orange juice per day can achieve concentrations of citrate of up to 1.2mg/ml urine [423] and further clinical evaluation of the effects of increasing a patient's fluid intake with citrate containing drinks is awaited. Viable cell counts of P.mirabilis in the model suggest that results were unlikely to be due to direct effects of citrate on the growth of metabolism of P.mirabilis in the catheter biofilm, but rather on the process of mineral crystallization.

Recent research provides more evidence. In a recent randomized six week crossover trial of citrated drinks in 24 persons with catheter blockage [444], it was demonstrated that the pHn could be significantly increased. The highest level of change was with lemon juice, with a "safety margin" of 0.84 (95% CI 0.63, 1.04), followed by fluid intake 0.57 (95% CI 0.37, 0.78), and potassium citrate 0.41 (95% CI 0.20, 0.61). Overall, the safety margin for the drinks was significant ($p<0.001$) when controlling for the three groups. Each participant, who had experienced at least three blockages within four weeks previously, received all three drinks. Baseline 24 hour urines were obtained after each week, allowing for a washout period between the one week drink consumption for each arm of the study. The lemon juice concentration was 60mL/1 litre of water, potassium citrate was 6 g/1 litre, and the fluid intake was also 1 litre additional. Participants were instructed to consume the drinks each day in addition to their usual fluid intake and they tracked their intake and output during the study. This study provides additional evidence that optimal and consistent levels of fluid intake could minimize catheter blockage or increase the interval between changes, in persons with persistent encrustation and blockage.

The reduction of encrustation and corresponding extension of 'catheter life' by regular instillation of an acidic catheter maintenance solution into the catheter has been advocated by some researchers, particularly where frequent catheter changes for recurrent blockage are difficult and / or unacceptable to patients. Solution G (Suby G) and Solution R (Table XII-5) have been shown to be effective in in vitro models of the catheterised bladder [445] [446] [447] and in vitro models of struvite stone chemolysis [448]. In response to concerns over potential damage to the bladder mucosa from acidic catheter maintenance solutions, Getliffe et al. [446] advocate the use of small volumes of solution so that less enters the bladder. Under controlled laboratory conditions smaller volumes of acidic solutions (Suby G) (50ml), retained in the catheter for 15 minutes, were shown to be as effective as the commonly available commercial standard of 100ml. Getliffe et al. also showed that two sequential washouts with 50ml were more effective than a single washout.

There is relatively little clinical evidence to draw on in this area and outcomes remain to be tested in well-controlled clinical trials. Most clinical studies are small-scale and descriptive although both Getliffe [424] and Kunin et al. [418] compared groups of 'blockers' and non-blockers' to identify

characteristics of recurrent 'blockers'. One small-scale, comparative trial of Suby G, Solution R and saline catheter 'washouts' in 14 older female patients [449] reported a higher incidence of red-cells in the retrieved washout fluid with Suby G compared to saline (mean incidence of 28% and 14%, respectively. However, increased shedding of uro-epithelial cells was present in the retrieved washout from all three solutions suggesting this was at least partially related to the physical process of administration. This issue was previously raised by Elliot et al. [450] who also demonstrated increased uroepithelial shedding following washouts with up to 60ml saline 0.9%; chlorhexidine 0.02% or noxythiolin 2.5%.

A more recent RCT with 73 community dwelling individuals, which aimed to compare weekly catheter flushes with saline or an acidic solution, with no flushes, reported the mean time until catheter removal was very similar between groups. Importantly, there was no evidence of detrimental effects, such as increased risk of symptomatic infection, from breaking the closed system in order to apply catheter flushes. Urinary pH did not change over the study time; at baseline the mean was 6.3 (SD 1.04), range 5-8.5. However the study was underpowered and subjects were only followed for a maximum of eight weeks, or until the catheter was changed three times, or a symptomatic UTI developed. There were considerable difficulties with recruitment of patients and target numbers fell short within each group (Level of Evidence 2) [358). A sample of 400 per group, 1200 in total, was estimated posthoc, as giving sufficient power for future research in this area [451]. Other clinical studies have focused on chemolysis of infection stones (principally composed of struvite). Stronger acidic solutions such as Solution R have been shown to dissolve fragments of struvite renal calculi following lithotripsy [452] but potential benefits may be outweighed by the greater risk of inflammatory tissue reactions when used as a catheter maintenance solution. Renacidin solution is approved for kidney stone disintegration in the US but although it may be effective for recurrent catheter blockers, there is no published research evidence of its use in this group.

Overall, methodological issues make it difficult to draw robust conclusions on the effectiveness of acidic solutions in managing catheter blockage. It is unlikely that any currently available strategies will completely prevent catheter encrustation and a more practical aim is to extend catheter life to a period which is acceptable to users and manageable by healthcare professionals. Early detection of impending blockage by determination of usual length of catheter-life [424] or by application of a sensor device designed to detect early stages of P. mirabilis biofilm formation [453] are likely to remain the main stays of management.

j) LTC-associated risks and problems: urethral trauma, bladder calculi and bladder cancer

1. Urethral trauma

Urethral trauma and discomfort can occur during catheterisation but may be minimised by using a sterile lubricant or anaesthetic gel [454], however clinical practice remains variable. More studies have considered the use of lubricants for male catheterisation but few have considered the procedure for women or for supra-pubic catheterisation [455]. A recent randomised, double-blind study with 62 alert, cooperative females requiring urethral catheterisation, demonstrated that the group receiving lignocaine gel had a significantly lower median procedural pain score compared to the group receiving a water-based lubricating gel [456]. It is not clear whether cleaning the urinary meatus prior to insertion is needed, based on two small trials (Level of Evidence II). In one study, 0.05% chlorhexidine gluconate or sterile water was tested in a home care sample (N=20), with four urine specimens cultured over two weeks. No difference was found, and no one developed a symptomatic CAUTI [457].In the other study of 60 women receiving outpatient gynaecological surgery,[458] povidone-iodine was compared with water. No significant differences in bacteriuria or symptomatic CAUTI were found in comparing urine samples just prior to insertion and 24 hours later.

2. Bladder calculi

Most long-term follow up studies of LTC use have addressed SCI populations. Indwelling catheters (UC and SPC) have been significantly associated with increased risk of bladder calculi formation in SCI patients, compared to intermittent catheterisation [460] [235]. In a retrospective cohort study of 457 patients, controlled for variable follow up times by regression analysis, both UC and SPC were significantly associated with increased risk of bladder calculi formation compared to intermittent catheterisation IC (hazard ratio 10.5; $p<0.0005$ and 12.8; $p<0.0005$) respectively [461]. This increased risk was independent of age, sex, level and degree of injury but calculi were no more likely to form with SPC than UC (hazard ratio 1.2, $p=0.6$). Another case series of SPC in 118 patients with neurogenic bladders [462] found common complications were bladder calculi (25%), (particularly associated with high urinary pH) and urethral leakage (10%). Bladder calculi-free rates at five and 10 years were 77% and 64% respectively, falling to 50% at 20 years.

Where SPC has been compared to CIC the main difference appears to be in a lower incidence of bladder calculi in the CIC group. A prospective comparison of long-term outcomes between 34 quadriplegic patients managed by SPC (mean period 8.6 years) and 27 paraplegic patients managed with CIC (mean period 9.9 years) reported no significant

difference between groups in respect of symptomatic UTI, renal stone, degree of bother and overall satisfaction [310] but there was a significantly increased incidence of bladder stones in the SPC group. However a recent review of current literature [311] (56 studies), concluded there were variations between older and more recent studies. More recent studies showed morbidity profiles to be similar for SPC and CIC, where patients were managed by anticholinergic medications, frequent catheter changes and volume maintenance procedures. A dedicated catheter clinic established to aid the management of patients having problems with LTC, reported the majority of patients were elderly with chronic disabilities. A significant proportion of those with catheter encrustation and blockage (45% of 147 patients) were shown to have formed bladder calculi [463].

3. Bladder cancer

A number of retrospective, cohort reports of SCI patients have linked bladder cancer with long-term indwelling catheterisation [464] [465] [466]. The reported incidence of squamous cell and transitional cell carcinoma associated with chronic indwelling catheterisation varies widely between studies but Groah et al. [466] in their follow-up of 3670 subjects, calculated that patients with SCI and an indwelling catheter were 25 times more likely to develop bladder cancer than the general population (Level of Evidence 3). For SCI patients without an indwelling catheter, the risk of bladder cancer was 15 times that of the general population. Since SCI patients are already at increased risk of developing bladder cancer compared to non-SCI groups, the influence of an indwelling catheter on bladder cancer requires further clarification, including the potential relationship between duration of catheterisation and cancer development. Bladder calculi have been identified as an independent risk factor for bladder cancer by some authors (464].

Most reports have grouped UC and SPC together as indwelling catheters but a small number of case study reports have drawn attention to long-term risks of carcinoma within the cystostomy tract with SPC, with or without further extension into the bladder [467] [468] [469]. However, in a retrospective analysis of screening biopsies for bladder malignancy in 36 patients with SPC for more than 12 years, Hamid et al. [470] found no tumours in the screened group although histological findings were frequently abnormal (Level of Evidence 2). These authors raise concerns over the interpretation of screening cystoscopy and biopsy in this population and note the importance of the distinguishing between histological changes and confirmed cancers when interpreting study results. Recently published guidance on management and prevention of catheter-associated urinary tract infection, based on an extensive survey of the literature, includes a recommendation that patients with urethral catheters in place for 10 years or more should be screened annually for bladder cancer [471] (Grade of Recommendation C).

k) Catheter management strategies

Although guidelines and protocols for catheter-care practices are abundant, relatively few practices are supported by research evidence and even fewer by evidence from randomized controlled trials. For example, in the 'Guidelines for prevention of healthcare associated infections in primary and community care' commissioned by the UK's National Institute for Clinical Excellence [472], of 29 recommendations relating to urinary catheterisation only six were Grade A (directly based on Level 1 evidence); with one each at Grades B and C. The remaining 21 were all grade D, being based on evidence from expert groups or clinical opinion.

1. Guidelines

In 2009, the U.S. Healthcare Infection Control Practices Advisory Committee issued through the Centers for Disease Control and Prevention (CDC) updated Guideline for Prevention of Catheter Associated Urinary Tract Infections [342]. This guideline, which updated the 1982 Guideline, expanded information about catheter related issues, including intermittent, condom, suprapubic, and chronically catheterised long-term users. The recommendations made by this committee for preventing catheter-associated urinary tract infections, based on systematic review of the best available evidence, address the following issues:

- who should receive an indwelling urinary catheter
- catheter insertion
- catheter maintenance
- quality improvement programs to achieve appropriate placement, care, and removal of catheters
- administrative infrastructure required
- surveillance strategies

This new guideline recommended selected practices at grade B based on level of evidence of 1 or 2. Therefore, many topics were judged as "no recommendation/unresolved issue" due to a lack of evidence.

2. Quality indicators and regulator initiatives

It is well established that guidelines alone do not change practice. Further efforts should be directed to disseminating evidence-based guidelines about catheter care through education and the use of quality indicators and regulatory initiatives.

Regulation that is accompanied by the use of evidence based quality indicators has a powerful influence on the quality of care. Quality indicators are defined as quantitative measures reflecting a professional

care standard which are used as guides to monitor and evaluate the quality of important patient care and support service activities. The ACOVE (Assessing Care of Vulnerable Elders) suite of quality indicators has been designed to measure the quality of care for vulnerable elders [473]. It incorporates one quality indicator to guide measurement of the quality of care related to catheter use.

"IF a VE has clinically significant urinary retention, and a long-term (> 1 month) urethral catheter is placed, THEN there should be documentation of justification for its use, BECAUSE treatment of certain underlying causes(s) of urinaryretention (e.g., treatment of constipation or bladder outlet obstruction) may carry less risk than long-term urinary catheterization" [473].

Another attempt to ensure the appropriate use of catheters is the use of assessment protocols. For example, regulation for long-term care settings in the USA mandates that all newly admitted Medicare/Medicaid funded residents receive an assessment using a standardized form called the Minimum Data Set (MDS). A further level of assessment is triggered when/if a resident is newly incontinent and the Resident Assessment Instrument Minimum Data Set is completed (RAI-MDS). This assessment information in turn, acts as a prompt for staff to design an individualized care plan based on direct contact with residents, appropriate staff, and through use of observation, interviews and record reviews. The MDS and RAI are now used in a number of other countries, including Canada and Iceland, and other countries have developed their own assessment instruments. Ideally, these assessment instruments should prompt staff to enquire about whether the residents' catheter is medically warranted, and to identify catheter related problems, and care plans should contain information about an individualized catheter care plan (including the frequency of catheter changes and ongoing maintenance). This assessment process is strengthened in the USA by its link to quality indicators. Specifically, long-term care facilities are required to use information from the residents' comprehensive assessment to provide assurances that:

- Catheters are used for only medically valid reasons;
- Catheters are removed as soon as clinically warranted;
- Efforts are applied to restore or improve bladder function as much as possible; and
- Efforts are made to prevent infection while the catheter is inserted (U.S Dept of Health and Human Services, 2004).

It remains to be seen if these measures will reduce catheter rates in long-term care, and how they will impact day-to-day catheter use and catheter care. However, similar regulatory approaches should be considered by government and health agencies in other countries.

3. Catheter change procedures and catheter comfort

Indwelling catheters can cause substantial patient discomfort but although anecdotal information on the discomfort experienced by many catheterised patients is readily available, there is a general lack of published evidence from research studies. Further investigation and guidance to practitioners is needed. Catheter-related pain or discomfort can occur as the catheter is passed, in situ and on removal. Local anaesthetic lubricant gels are commonly used to aid the insertion of indwelling catheters in males and protect the sensitive urothelium from trauma [474]. Similar use of anaesthetic gels is generally recommended for females although the procedure may be less consistent in some places and where only small amounts of lubricant are applied to the catheter tip this may be insufficient to coat the urethra adequately. There is little research evidence to underpin clinical practice in this area although the NICE guidelines on infection control [472] recommend: 'an appropriate lubricant from a single–use container should be used during catheterisation to minimise trauma and infection'. The choice of lubricating gel is usually left to practitioners but not all gels containing anaesthetic agents (eg lidocaine) are suitable for both urethral and suprapubic use. One prospective, randomized, double-blind, controlled trial of plain lubricant versus lidocaine gel prior to female catheterisation in an accident and emergency department found no significant differences in pain ratings, based on lubricant type or catheter size amongst 100 women recruited to the trial [475]. Anaesthetic gels may be contraindicated in patients with damaged or bleeding urethral membranes and should be used with caution in those with cardiac conditions, hepatic insufficiency and epilepsy [476]. Lubricants which contain chlorhexidine have been reported to trigger anaphylaxis in a small number of patients during catheter insertion and consequently a careful history is required to screen for sensitivities [477] [96].

In a study with 45 infants (2-24 months) who needed urethral catheterization, random assignment was made to either a topical lubricant (control), topical and intraurethral lubricants, or topical and intraurethral lidocaines [478].Infants with the lidocaine had less distress, but the lidocaine did not eliminate the distress totally.

Catheterization in males can be difficult at times, and different approaches can be used, including a Coude catheter, various guide wires or filiform catheters, and other techniques performed by urologists. Research in this area is needed to compare different practices and associated risks [479].

Catheters can be painful when in situ. In one study at a US Veterans Affairs Medical Centre, 42% of

catheterised patients reported it was uncomfortable, with 48% complaining it was painful, and 61% stated it restricted their activities of daily living [107]. In one small sample of 43 community dwelling persons with long-term catheters, pain was reported by 24 (54%) [126]. Causes of pain were bladder spasms, position of the catheter, or related to catheter changes. Three had pain all the time, but 21 of 24 persons had it intermittently. If bladder spasm is the cause of pain when a catheter is in situ a low dose of an anticholinergic medication can help [480]. Other helpful approaches include treating constipation if present, ensuring that the catheter is the smallest size to provide adequate drainage, and ensuring that the drainage bag is well supported to prevent dragging on the catheter. Attention to the catheter position is needed to prevent kinks or twists in tubing and ensurethat the catheter straps are not blocking urine flow [481]. Blockage in urine flow can cause bladder distension resulting in increases in hydrostatic pressure and bleeding points which open the way to bacteria, already present, to cause a symptomatic infection [210].

Bladder discomfort related to an indwelling catheter can exacerbate post-operative pain by mimicking overactive bladder syndrome that is resistant to conventional opioid therapy. Sub-lingual oxybutinin has been shown to be an effective treatment for pain after radical retropubic prostatectomy, with significant reduction in other pain relief requirements [482]. Cuffing of the catheter material on balloon deflation (see below) and / or encrustation of the catheter by mineral deposits may cause pain during catheter removal. Encrustation is discussed further in Section 12.2.9 and management of these problems is also discussed below.

4. Education of healthcare providers

Educational approaches should ensure that all healthcare practitioners have the necessary knowledge and skills to care for individuals with a catheter. Some research however, points to gaps in healthcare practitioners' knowledge about what catheter to select, and how to minimize and manage ongoing problems[483]. Mody and colleagues (2010) [484] assessed nursing home healthcare workers' knowledge and awareness of recommended catheter care practices, and found significant discrepancies between their knowledge and research-based recommendations. Respondents were drawn from seven community-based nursing homes in the USA and included nurses and nurse aides

Twin surveys were sent to healthcare providers in Minnesota to determine their level of knowledge about catheter use. The physicians (N=635) reflected awareness of the indications for catheter use, and about 1/3 said they remove them sooner. However, about 30% were unsure about how to prevent UTI [485]. Nurses (N=370) were aware of catheter indications, but some were likely to approve of catheter use in the ICU (for whatever reason) and of the value of silver coatings on catheters [485].Both studies had low response rates, of 9% and 4% physicians and nurses, respectively. Another survey to 333 persons, (70% RNs and 27% unlicensed assistants) indicated that there was a need for more education related to catheters [486]. Incorrect practices involved not securing the catheter (75%) and not knowing when to replace the catheter (74%). The response rate was 54%, and about half of those surveyed had less than two years work experience.

An audit of education given to nursing students in Greece indicated that there was a need to upgrade teaching methods [487]. Proficiency was impaired by a lack of attention to preparing the patient (including emotional and practical aspects), old textbooks, outworn traditions, little or no instruction on troubleshooting and a lack of sophisticated methods for teaching (e.g. DVDs showing the procedure).

An audit of adherence to standards of nursing care in one UK Trust related to catheter practices in patients' homes [488]. All nurses surveyed (N=25) indicated they would change the catheter every 12 weeks unless there was a reason to do this more often; no data were provided on the percentage with 12 week changes. Though a closed system was advocated by all nurses, washouts were performed by 75% and sampling ports for urine samples were used by 28%, and the rest used a clean drainage bag. A similar audit was conducted in a hospital setting [489]. Continuing catheter care was well documented at 98%, but 11% were missing details on insertion.

5. Catheter change frequency

Protocols on indwelling catheter change frequency vary widely from monthly to up to three months if the catheter is trouble-free. In the absence of clear supporting evidence this remains an area of controversy amongst clinicians with advocates of early change believing this to reduce the incidence of complications while others argue that frequent changes increase the risk of infection, trauma and long-term histological changes. However, very sparse evidence suggests that CAUTI might be less when the catheter is changed every 4-6 weeks, rather than only when it blocks, or with planned changes of every two weeks [490].

SPC changes can be competently managed by skilled nurses [325], often in the patient's own home, but the new catheter should be inserted as quickly as possible whilst the track is still easy to follow. A delay of only a few minutes can result in partial obliteration of the tract [491]. It is also possible to insert the new catheter too far through the bladder so it enters the urethra with resultant trauma when attempts to inflate the balloon are made. Careful observation of the length of catheter external to the abdomen and the angle of protrusion prior to catheter change can

help to ensure correct positioning of the new catheter [492]. Dressings around the stoma site are not normally required unless there is excessive discharge, causing staining and / or sticking to clothing.

While nurses do not usually order catheter insertions, and there may be times when delay in a clinically appropriate catheterisation is harmful to certain patients. A new protocol and algorithm was thus developed by nurses, physicians and other key stakeholders in an orthopaedic unit of a large urban hospital to facilitate catheter insertion in certain defined situations [493]. Indications, such as spinal column injury, and contraindications were depicted in a diagram to identify when to stop, consider the issues (e.g., neutropenia), and when to insert the catheter.

Urinary catheter 'deflation cuff' formation can be a problem in both SPC and UC, causing difficulty in removal and great discomfort to patients. Evidence suggests deflation cuff formation can be a particular problem for all-silicone SPCs. A retrospective study of 113 patients cared for by community nurses showed that 30% of nurses had experienced problems changing catheters in the previous 12 months [494]. In vitro studies have confirmed increased retention force and resistance to withdrawal caused by cuff formation and although cuffs can form with other catheter materials (eg hydrogel coated-latex) the retention force is less than with all-silicone material [339]. It has been suggested that slow deflation may enhance the probability of the silicone balloon returning to its pre-inflation shape [340]. Alternatively, reinsertion of 0.5-1ml water is sufficient to fill the catheter inflation lumen and eliminate the balloon cuff. Subsequent use of lubrication with gentle removal of the catheter has been well-tolerated by patients and produced virtually no trauma.

6. Personal hygiene and infection control

Meatal cleansing by simple washing with soap and water during routine bathing or showering is recommended (Level of Evidence 1) [495] [496]. No consistent reduction in bacteriuria has been demonstrated by any other meatal cleansing regimes, using povidone-iodine solution or cream, chlorhexidine, polymicrobial creams, 1% silver sulfadiazine or antiseptic lubricating gels, compared to routine bathing or showering [374] [122]. Effective handwashing by healthcare professionals, carers and patients, before and after handling catheters and drainage equipment is generally accepted to be the most important component of any infection control strategy. Healthcare professionals and formal carers should also wear gloves. Catheters and drainage equipment are commonly supported in position by tapes, Velcro and other securing devices (eg CathSecure, StatLock)

More securement devices are now on the market providing choices for long-term users, in particular. Consideration should be given to usual activity, clothing, size of the person (e.g. thighs) and the weight of the bag it would support. All, but especially those using adhesives, need to be comfortable, easy to use, and gentle to the skin [497].These securement devices are designed to control post-operative bleeding, maintain surgical anastomoses in the lower urinary tract, and prevent urethral erosion or trauma and accidental dislodgement from traction [498]. The importance of these in reducing risks of CAUTI and the mechanism involved are not well-established [380] (See also section XII.2.h).

7. Urine collection – catheter valves

Urine may drain continuously from the bladder into a drainage bag attached to the catheter (See Section XIII) or intermittently via a catheter valve. The valve is a small device connected to the catheter outlet in place of a bag. Closure and opening the valve allows bladder filling and intermittent drainage rather than continuous drainage into a bag. Valves are available in a variety of designs (**Figure XII-9**) ranging from simple inexpensive types used for up to a week, to more expensive, complex, forms which last longer and which may permit one handed action. However, valves are not available or licensed in all countries.

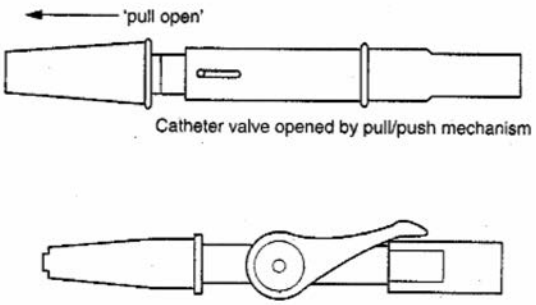


Figure XII-9: Example catheter valves.

Most valve designs can be attached to a drainage bag at night to allow free drainage while the patient sleeps. A valve can provide a discreet alternative to conventional urine drainage bags and may offer improved maintenance of bladder tone and capacity for appropriate patients. A spigot is not a suitable alternative to a valve since it must be removed from the catheter to allow drainage thereby breaking the 'closed system'. Patients must be able to manipulate the valve mechanism and empty the bladder regularly to avoid overfilling, with accompanying risks of back pressure on the upper urinary tract. Valves are generally inappropriate for patients with poor manual dexterity, poor bladder capacity, detrusor overactivity, ureteric reflux, renal impairment or cognitive impairment. There is relatively little research-based literature on catheter valves with much of the evidence supporting beneficial effects derived from the level of expert opinion. Concerns

over possible increased risk of infection associated with valves have not been realised although there is a paucity of research in this area. A lack of knowledge on valves may interfere with their use in appropriate situations; therefore, a full assessment is required to determine whether the person is a good candidate for a catheter valve using a systematic process, such as an algorithm [499].

The flushing mechanism resulting from bladder filling and emptying may be expected to contribute to reduction in problems of encrustation and blockage. One study was found that provides new evidence as to how a catheter valve might do this [500]. The laboratory study involved four experiments with a bladder model and artificial urine cultured with Proteus mirabilis. Manual valves were opened every two or four hours with continuous drainage at night, followed by experiments with automatic valves timed to open for five minutes every two to four hours around the clock for seven days. All experiments were compared with continuous drainage of urine. Analysis of variance showed that all models controlled by valves during the daytime (12 h) took significantly more time to block (62.6 versus 35.9 h, p=0.039) than 24 hour continuous drainage. Experiments were done with automatic valves which ran 24 hours day every two or four hours, and time to blockage extended to 119.8 h versus. 50.7 h, and 159.8 hversus. 44.7 h, respectively.

There is stronger evidence of benefits in terms of patient comfort and independence since this is a common finding in most studies. Five studies comparing a catheter valve with standard drainage (leg bag) were identified: three were cross-over designs, with 28, 16 and 18 subjects respectively [501] [502] [503] (Level of Evidence 3); two randomized their sample of 100 subjects to either catheter valve or standard drainage [504] [505] (Level of Evidence 2). None of the studies identified any significant difference in urinary tract infection and a majority found a high level of preference or acceptability of catheter valves (>72%). There were no differences in reported incidence of bladder spasms or discomfort; however, there was a higher incidence of nocturnal frequency and episodes of bypassing with valves. It was suggested that a combination of a valve during the day and free drainage at night through an open valve connected to a drainage bag could be an appropriate management strategy.

Several studies have evaluated a single valve design [506] [507] but only one has compared a broad range of valve designs [508]. Fader et al undertook a comparative evaluation of the seven catheter valves available on the UK market in 1996. Each valve type was tested for one week by between 19 and 36 subjects, followed by completion of a product evaluation questionnaire. Performance scores (and costs) varied widely between products but critical characteristics were: being easy to manipulate, leak-free, and inconspicuous. The authors concluded that prescribers need to be aware of the strengths and limitations of different valves for appropriate product selection (Level of Evidence 3). A more recent development concerns the design of a prototype, novel, automatic valve system for LTC patients [509] which may be helpful for patients who lack sufficient dexterity to manage a manual valve. In summary:

- Catheter valves provide a well-accepted system of bladder emptying for suitable patients who are able to manipulate the valve mechanism and empty the bladder regularly to avoid overfilling (Level of Evidence 2).
- There is no evidence of increased risk of urinary tract infection with valves compared to conventional drainage systems (Level of Evidence 2).
- Valves may promote maintenance of bladder tone and capacity (Level of evidence 4).

8. Maintaining effective catheter drainage

Use of urinary catheters is rarely completely trouble-free. Catheter drainage can be compromised by a variety of factors from simple causes such as kinked tubing or the position of the drainage bag, to bladder spasm, pressure of a constipated bowel on the adjacent urethra, suction of bladder mucosa into the catheter eye, or blockage by blood clots, mucous or encrustations formed by deposits of mineral salts. The algorithms in **Figures XII -10 to XII-12** combine current evidence-based knowledge and expert opinion to provide some guidance on troubleshooting common problems.

9. Recurrent catheter encrustation and blockage

Factors affecting persistent catheter encrustation leading to recurrent blockage have been discussed earlier in section XII.2.i. The day to day management of recurrent catheter encrustation and blockage is largely a nursing responsibility but there are few options available. Maintenance of dilute urine by a suitably high level of fluid intake has been shown to reduce encrustation in laboratory studies [438] and increased urinary citrate concentration produced by drinking orange juice or other fruit juices may also be beneficial [438]. However the amounts required may be relatively high and clinical studies are needed to assess benefits and possible detrimental side effects e.g on bowel behaviour. Use of a catheter valve in suitable patients may also help reduce build up of encrustation by facilitating periodic flushing but clinical evidence is currently unavailable. In a majority of patients a characteristic pattern of ‘catheter life’ can be identified with careful record-keeping of three or more catheter episodes [424] [418] [510]. This may allow pro-active strategies of care designed to change the catheter before likely blockage. However, very frequent catheter changes can be unsuccessful or

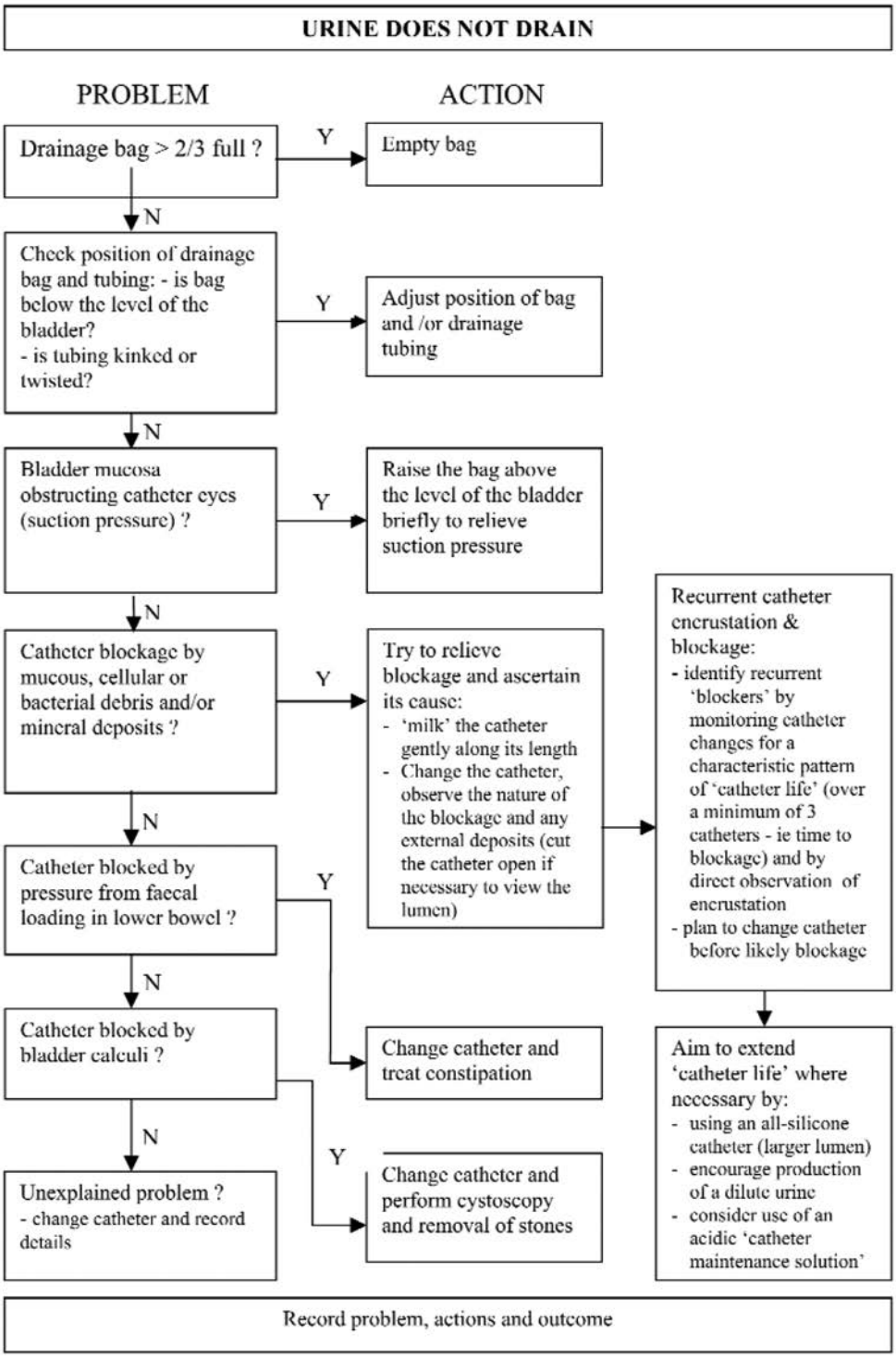


Figure XII-10: Troubleshooting long-term catheter problems: urine does not drain (N = No; Y = Yes). (Always have a spare catheter available)

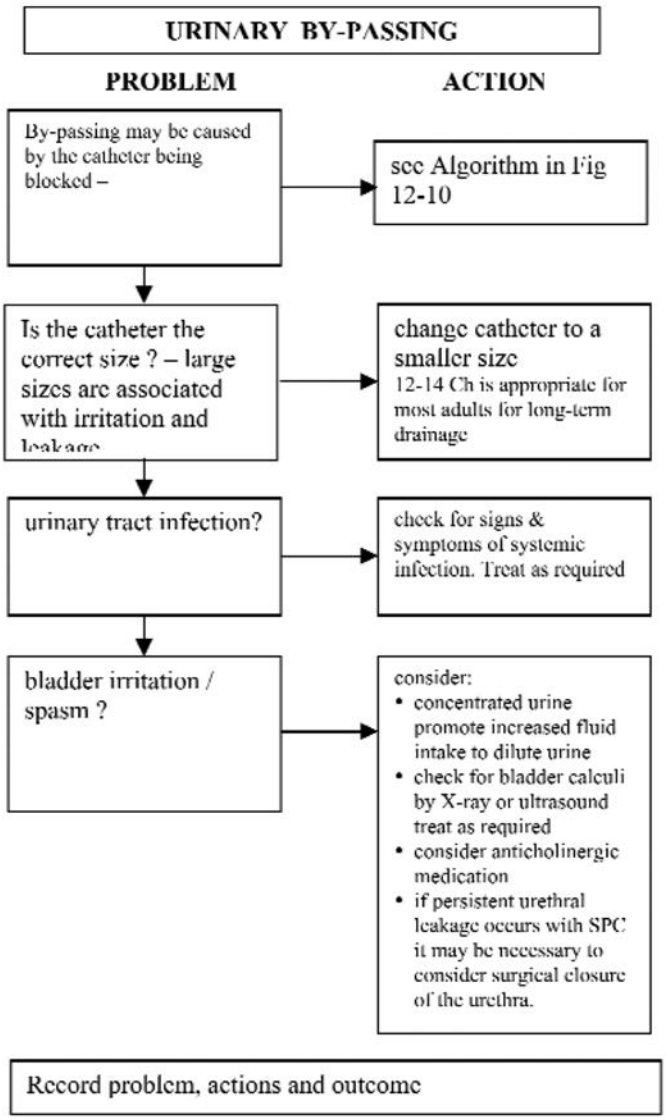


Figure XII-11: Troubleshooting long-term catheter problems: urinary by-passing.

unacceptable for some patients, as well as being costly in terms of health service resources [420]. In a study of planned catheter changes [511], based on observation of the intervals for three changes,urinary pH, and visual encrustation, unplanned changes decreased significantly from 46 the year prior (n=39) to 30 during the 12 months post intervention (n=21, p<0.01). The major impact on quality of life related to catheter problems decreased from 39% to 5%, though satisfaction with care management did not change much.

An alternative strategy is the regular prophylactic instillation or irrigation of the catheter with an acidic 'catheter maintenance' solution to dissolve mineral deposits. In older literature the term 'bladder washout' appears but as the aim is to wash the catheter, rather than the bladder, 'catheter maintenance solution' is a more appropriate term. A range of commercially available catheter-maintenance solutions is indicated in **Table 12-6**, although these are not necessarily available in all countries. Support for irrigations is strongly divided between those claiming benefit for specific patients who experience very frequent blockage and those who consider any break to the closed system to increase risks of infection. Research evidence is primarily derived from laboratory models of the catheterised bladder. The few clinical studies which have addressed this issue have been limited by methodological deficits and small sample size.

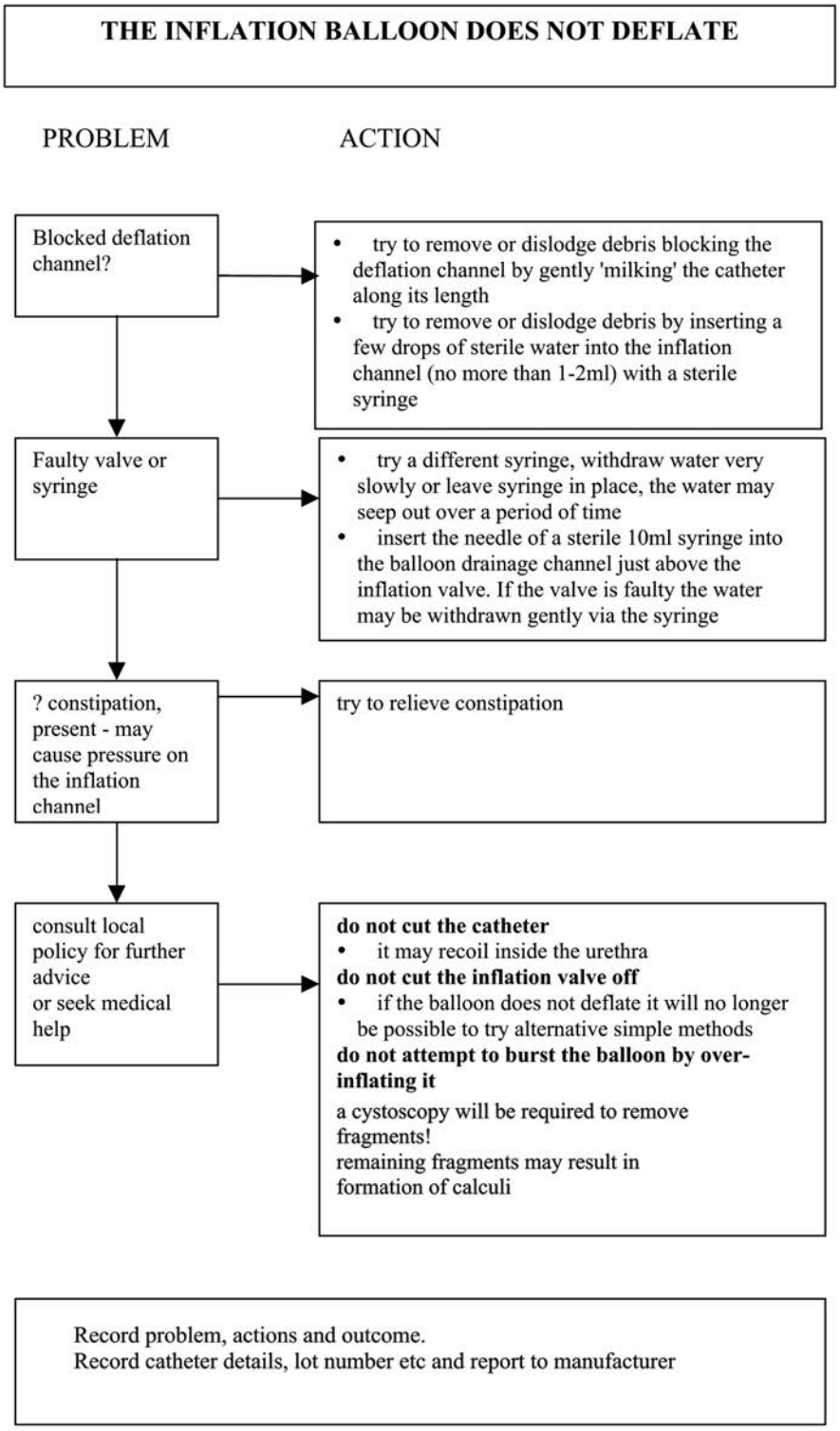


Figure XII-12: Troubleshooting long-term catheter problems: the inflation balloon does not deflate.

Table XII-6: Catheter maintenance solutions

Suby G or Solution G[1]	3.23% citric acid solution, pH 4, containing magnesium oxide to minimise tissue irritation, aimed at reducing encrustation. Used where routine catheter maintenance is required to reduce build up of encrustations.
Solution R[1]	6% citric acid solution, pH 2, containing magnesium carbonate, aimed at dissolving encrustations. A stronger acid than Suby G and therefore not recommended for frequent, regular use.
Renacidin[R2]	A citric acid solution, pH 3.5-4.2, containing glucono-delta-lactone to minimise tissue irritation and magnesium carbonate, aimed at reducing encrustation.
Mandelic acid 1%[1]	An acidic solution, pH 2, aimed at inhibiting the growth of urease-producers. A stronger acid which is not commonly used to reduce catheter encrustations
Saline 0.9%[1,3]	A neutral solution, pH 7, recommended for flushing of debris and small blood clots. Neutral pH solutions will not dissolve catheter encrustations.
Chlorhexidine 0.02%[1]	An antiseptic solution aimed at preventing or reducing bacterial growth, in particular E. coli and Klebsiella species (but will not prevent biofilm formation on long-term catheters)

[1] Available in the UK pre-packed in a sterile delivery devices designed for instillation into a urinary catheter.
[2] Renacidin[R] is approved in the USA for kidney stone disintegration only. Although it may be effective in certain situations for persistent catheter blockers, there are no supporting studies.

- **Saline is widely available**

I) Levels of evidence relating to catheter-associated risks and complications

- All currently available catheter materials are subject to bacterial biofilm formation (**Level of Evidence 1**).
- Silver alloy coated catheters are associated with a statistically significant reduction in incidence of asymptomatic bacteriuria in short-term catheterised, hospitalized adults (studies of varying quality included) (**Level of Evidence 1**). There is less robust data to show that silver-alloy catheters reduce symptomatic infection (**Level of evidence 4**). Silver oxide coated catheters are not associated with a statistically significant reduction in bacteriuria (**Level of Evidence 2**).
- Antimicrobial catheters can prevent bacteriuria in hospitalized patients during short-term catheterization (<14days) (**Level of Evidence 1**). Trial results are highly context dependent and the effectiveness of specific antimicrobial preparations may be limited to specific groups of microorganisms. Potential toxicity and / or antimicrobial resistance is unknown (**Level of Evidence 2**).
- There is little evidence to guide the precise timing of antibiotic cover (when required) for catheter change. One study has shown that clinical outcomes (i.e. reduction in polymicrobial counts in urine, time to achieve afebrile status and clinical status at 72 hours) are significantly better among subjects randomised to catheter change immediately before institution of antibiotics (**Level of Evidence 2**).
- A majority of health services have clear policies on the use of antibiotics, designed to limit unnecessary use. Current evidence does not support routine use of antibiotic cover during catheter changes unless the patient's condition renders them particularly at risk (**Level of evidence 4**).
- Meatal cleansing by simple washing with soap and water (i.e. not with antimicrobial agents) during routine bathing or showering is recommended (**Level of Evidence 1**).
- Recurrent urinary catheter blockage caused by encrustation occurs in 40-50% of all long-term catheterised patients (**Level of Evidence 2**). In the majority a characteristic pattern of 'catheter life' can be identified (**Level of Evidence 3**).
- Evidence from in vitro models of the catheterised bladder indicates that i) dilute urine; ii) high urine citrate content (> 1.5mg/mL) reduce risk of blockage (**Level of Evidence 2**).
- Evidence from in vitro models of the catheterised bladder indicates that acidic 'catheter maintenance'

solutions may have a role in dissolving encrustations in persistent blockers (**Level of Evidence 2**). There is insufficient evidence from RCTs to assign an in vivo level of evidence.

- Suprapubic catheterisation (SPC) is an appropriate alternative to urethral catheterization for many patients following appropriate risk assessment (**Level of Evidence 1**).
- There is some evidence for a reduction in catheter-associated infection in SPC use during short-term catheterisation (**Level of Evidence 2**), compared to urethral catheter insertion. However, there is no corresponding evidence for long-term catheterisation.
- Patient comfort, quality of life and satisfaction with SPC is generally good compared to urethral catheters (**Level of Evidence 1**).
- Catheter valves provide a well-accepted system of bladder emptying for suitable patients who are able to manipulate the valve mechanism and empty the bladder regularly to avoid overfilling (**Level of Evidence 2**).
- There is no evidence of increased risk of urinary tract infection with valves compared to conventional drainage systems (**Level of Evidence 2**).

m) Urinary catheters versus other care strategies

Very few studies have compared urinary catheterisation with other strategies to manage urinary incontinence, not least because of the difficulties in recruiting to and conducting robust trials. For male patients who do not have problems with retention of urine external urine collection systems are an option (See Sections VII, VIII and IX). One recent prospective, randomized, unblinded, controlled trial on men >40years in a US Veterans Affairs Medical Centre reported that the use of condom catheters was less likely to be associated with bacteriuria, symptomatic UTI or death than the use of indwelling catheters [101]. Patients reported that condom catheters were more comfortable (P=0.02) and less painful (P=0.02) than indwelling catheters.

A small number of studies have attempted to examine preferences for different urinary incontinence treatments in long-term care. In a descriptive, comparative study of preferences for treatments for frail older adults, residents in long-term care facilities were interviewed and groups likely to serve as proxy decision makers were surveyed (family members of residents and nursing staff) [512]. Forced choice comparisons of continence treatments were measured. Although there was wide variation within and between groups, most preferred non-invasive strategies (diapers and prompted voiding) to invasive strategies including indwelling catheterisation. Older adults stated they would choose a treatment based, in part, on feeling dry, being natural, not causing embarrassment, being easy, and not resulting in dependence. Similar results, showing urinary catheterisation as the least favoured choice, were found in a study of 117 medical inpatients aged 80 years or over, their physicians, nurses and family members [513].

3. CATHETER-RELATED QUALITY OF LIFE

Use of a LTC is often a last choice for bladder management when other options such as CIC, for males a sheath (condom) catheter, or other voiding treatments like Credé procedure, are either unsatisfactory or no longer practical. Catheter users must deal with a variety of problems that disrupt their daily activities and negatively affect QoL, such as CAUTI, blockage, leakage and catheter dislodgment. In addition, the visibility of a catheter or drainage bag can contribute to shame or stigma, and urine odour can be embarrassing. A catheter can also be a reminder of vulnerability associated with illness / mortality and a symbol of a loss in control of bodily function. Yet catheter users also acknowledge catheter-associated benefits of freedom from wetness, convenience, and utility in promoting urine drainage. While this section focuses on long-term catheter use, even short-term catheters can have a detrimental impact on QoL. For instance in a study of short term catheter use prior to surgery for acute urinary retention, leaking, blocking, urgency, and pain at the penis or during erection were all reported [514].

Studies of QoL issues commonly utilise qualitative research methodologies, such as phenomenology or grounded theory approaches (see also Section XII.1.e). In-depth interviews with catheter-users and carers provide important insights into aspects of 'living with a catheter' and contribute research based evidence to support development of effective care strategies. Measurement of QoL and the impact of factors which may affect it is complex. Most validated QoL instruments fall into one of two groups: i) generic measures designed to encompass domains including physical, mental and social wellbeing; ii) disease specific measures designed to measure change in QoL resulting from treatment. For those people whose urinary symptoms are managed by products or devices, including catheter users, it is particularly difficult to assess the impact of the product on QoL. This is partially because changes are more likely to be related to improved management of ongoing symptoms rather than actual change in symptoms, and partially because QoL is also dependent on the underlying disease process.

Much of the literature on LTC use involves people with neurogenic bladder, particularly those with spinal cord injury (SCI) or multiple sclerosis (MS). Thus, QoL in catheter users must be considered from a perspective of how the disease and the device affect the individual's life. For instance, in one postal survey of 230 people with SCI, the factors

which had most impact on QoL were social activities and accomplishments, including employment, attending school, and other activities. There was no association between QoL and different bladder drainage methods [515]. A particular problem for people with spinal cord injury or disease is autonomic dysreflexia (AD), an autonomic nervous system syndrome causing symptoms which include severe hypertension, headache and sweating. A blocked urinary catheter can be a common cause. AD can be a serious problem requiring emergency medical attention, but lack of knowledge and awareness of the risks by some health care providers can cause high levels of anxiety for SCI patients [516] [305] (Level of Evidence 3).

There is currently one instrument measuring quality of life in people with indwelling urinary catheters [269] though this measure was validated in two small samples. Further development and validation are ongoing in the US and in the UK (Level of Evidence 3).

The published literature addressing QoL in catheter-users is small, and is commonly limited to reports addressing levels of satisfaction with a device. Studies which include a broader perspective of QoL are discussed below under the following headings: changes in bladder management, embarrassment, sexuality, catheter-related pain, catheter adjustment, and self-management.

a) Changes in Bladder Management

Changes in bladder management are often made to promote QoL but there are trade offs that require weighing up the pros and cons of various methods. People sometimes switch from CIC to an indwelling catheter - despite the inherent problems with an indwelling catheter -because quality of life might be improved. In particular, women with cervical spinal cord injury (SCI) may need an indwelling catheter because of difficulties in transferring to the toilet, limited hand dexterity, or dependence on caregivers [517]. Moreover, many people have used different bladder drainage methods over time. In one study, of 30 long-term catheter users, 80% of the sample had used another form, and 33% had used two or three different types [518]. In another small study with a sample of 11, 100% had used another method, and 27% had used two or three other types [306]. Reasons for non-compliance with CIC in relation to QoL or satisfaction have been addressed in Section XII.1.e and in some studies comparing drainage methods (Level of Evidence 3).

Two studies provided additional evidence of how changes in bladder drainage methods are made to improve their quality of life. In a retrospective study assessing compliance with bladder management, 50 new spinal cord injury (SCI) patient records were reviewed after admission, discharge, and follow up from 1994-1997 [517]. Of 38 patients on IC at hospital discharge, 20 (52%) were back to UC at follow up. Six of 10 females on IC had resumed UC. Reasons for not continuing with IC were: the need to depend on caregivers, poor hand functioning, spasticity, incontinence (despite anticholinergic drugs), and for females with cervical injury, toileting inconvenience (Level of Evidence 3). In contrast, a retrospective chart review and follow up questionnaire was used with 236 SCI injured people (at least 10 years post injury) between 1956-1990 [519]. An 85% response rate was achieved in the sample, with 82% males who had tetraplegia (47%) or paraplegia (53%). Although 46% changed their bladder management method over time and 28% considered the method a problem, in 58% of those who had tetraplegia, the use of CIC went up from 11% at discharge to 36%. Suprapubic tapping decreased from 57% to 31% and Crede increased from 5% to 19%. CIC alone, or with other methods, was the most common method (Level of Evidence 2).

b) Embarrassment

Embarrassment and a sense of lack of bladder control are two major catheter-related issues that are ongoing problems for many people. In one study at a US Veterans Affairs Medical Centre, 30% of catheterised patients surveyed found the indwelling catheter embarrassing, and 61% stated it restricted their activities of daily living [107]. The catheter is placed in a position in the body normally considered 'private', yet health care providers frequently need access to the site to provide care. Also, the force of urine flow is something that catheter users must deal with on a daily basis. In a qualitative phenomenological study of 14 people with long-term catheters, people told stories of how getting wet in public was embarrassing and how the force of the urine was like water that had built up pressure [516]. They used the metaphor of "flowing water" to describe the force of urine flow, the weight of the drainage bag, and the sound of urine sloshing around in the bag.

Living with the catheter was described in one qualitative study [305] as a swing back and forth between stigma, when it contributed to embarrassment or shame, and acceptance when it was working right and did not cause problems. The catheter became a source of embarrassment during catheter changes, bag emptying, and when it leaked or spilled in public. Individuals used planning and great care when going out (e.g. mapping out the toilets) to prevent urine accidents. They were bothered also by their lack of bodily control, the monotonous care, and how it was a reminder of their condition and mortality (**Level of Evidence 3**).

Catheter related embarrassment is a common experience stemming from exposure to the opposite sex, the visibility of the urine bag, and unpredictability of urine accidents [520] [521] [305]. Breeches in privacy were identified in two qualitative studies of the lived experience of catheter use [522]

[523] [305] [524]. To care providers, catheters may seem commonplace, but male / female sensitivities may occur during catheter care, particularly catheter changes, including men who are embarrassed by a female care provider [520]. Embarrassment can be minimized by providing privacy during catheter changes and same sex care providers when possible [522] [305] [523]. Acknowledging the embarrassment that exists if the nurse is of the opposite sex paradoxically may diminish the vulnerability [305]. Humour is often used by care providers, catheter users, and caregivers, and a professional approach by the health care provider may help the catheter user accept the situation [522] [305] [523] (**Level of Evidence 3**).

A few studies have examined QoL issues related to practical aspects of living with the catheter, such as managing the drainage bag (See Section VIII). While most people who are self-caring cope with the management of their catheter drainage system, many find them restrictive and report a negative impact on QoL. In a small pilot study based on a postal questionnaire to LTC catheter users (n=59) [525] almost 25% of respondents stated that wearing a bag had a major negative affect on everyday living. Concealment of the bag was one of the most important concerns raised (89%). Keeping the urine drainage bag covered and its visibility minimized can help reduce embarrassment and the stigma related to using a catheter. The visibility of the bag can be considered demeaning and it exemplifies a loss of bladder control [305] [523]. Moreover, if a bag is unreliable, and springs a leak for instance, it contributes to vulnerability. Even using a catheter for a short time can be an assault to one's dignity. In a study in post-operative short-term catheter use, people complained about feeling "on display" and objectified [522] (**Level of Evidence 3**).

c) Sexuality

In a study of experiences of 25 men with prostate cancer, many of whom were treated with a urinary catheter, subjects reported the catheter contributed to feelings of shame, excess hospital visits for complications, and with other treatments for cancer, an end to sexual activity [526]. Men viewed healthcare professionals as having responsibility for medical decisions and they alone felt responsible for the catheter, micturition, and sexual life (**Level of Evidence 3**).

Issues related to sexuality were dominant in several other studies. Using a catheter compounded changes in sexual life caused by illness or injury [521] [524]. In one study, catheter users complained that care providers did not provide enough information about sexuality and how to adapt to a catheter [524]. Despite some care provider's reluctance to address these issues, sexual health should be a part of assessments [527], and information about sexual activity should be provided proactively, while recognizing that some catheter users will wish to engage in sexual intercourse and others will not (**Level of Evidence 3-4**).

In a study of 20 men in Nigeria with prostate-related obstruction, who used an indwelling catheter from 1-36 months, [528], negative changes in self-esteem and sexuality (manhood) were reported. However, family and friends were instrumental in providing support and encouragement, including financial help and transportation to the hospital. The underlying disease may also impact on sexuality. For instance, a urinary catheter complicates sexual activity in people with spinal cord injury (SCI). Moreover, men may have changes in sexual performance related to ejaculation, erectile function, and arousal [529]. For females with SCI, experimenting with positions, lubrication, and preventing spasticity may be helpful in sexual activity [529] (Level of Evidence 2). For people with SCI, sex-related autonomic dysreflexia (AD) occurs most often in people who suffer from AD during bladder or bowel care [530] (Level of Evidence 2). Autonomic dysreflexia is an autonomic nervous system syndrome that occurs in people with spinal cord injury or disease. Symptoms include severe hypertension and excruciating headache as well as sweating and goosebumps. It can be a serious problem—even life-threatening--requiring emergency medical attention, yet it is sometimes ignored or disregarded by health care providers [516]. A blocked catheter is also a frequent cause of AD. In a qualitative study [524], several people complained that care providers did not know much about AD and often dismissed their anxiety and concerns (**Level of Evidence 3**).

Promoting sexual health for persons with catheters [531] requires awareness of self (especially in relation to sexuality), training for health care providers, open communication, and advocacy for and validation of patients'experiences.

d) Catheter-related Pain

Pain related to catheter use is not always recognized although anecdotal information suggests that many people find a urethral catheter uncomfortable (see also Section XII.2 k.3 on catheter comfort and catheter change procedures). In Saint et al's study [107] 90% of catheterised patients surveyed reported they found the indwelling catheter uncomfortable or painful, and in a study of 43 community dwelling persons [126] 54% reported catheter-associated pain, and in a sample of 20 men who used a catheter for prostate obstruction, 35% had pain [528]. Sometimes women complained about the pain because of sitting on the catheter or sores in the vaginal area [516], however it is unclear whether sores or skin irritation are related to latex sensitivity, friction, or wetness or a combination. Bladder spasms, CAUTIs, blockage, and dislodgement can all contribute to catheter-associated pain, as well as insertion and removal procedures [532] [523] [516]

(**Level of Evidence 3**). Pain arising from AD in SCI patients can result from catheter blockage and has been discussed above.

e) Adjustment to a Catheter

Adjusting to living with a catheter may take a considerable time. In Roe's study [533] participants reported it had taken them up to a year. Similar lengths of time are commonly reported in anecdotal evidence. An educational booklet for catheter wearers has been shown to significantly improve knowledge and acceptance of the catheter [534]. Though the implications for this type of intervention are positive (Level of Evidence 1-2), the sample was small (n=45) and the study has not been replicated. The core category identified in a study using a grounded theory approach to examine older people's experiences of living with a LTC was 'all about acceptance'. Two further categories defined as 'at ease' and 'unease' reflected the extremes of their experience and these were mediated by 'interaction with others' [535]. The presence of a catheter can affect the individual's view of their own body and such shifts in body image can cause some people to exclude themselves socially. New catheter users (both urethral and suprapubic) may resist the "intrusion of the catheter" prior to acknowledging the need for it [536]. Qualitative studies have shown that although some people felt ill prepared for a catheter, and even viewed it as distasteful, most learned to accept the device over time [536] [523]. Catheter-users have described their changed perceptions of the body and of how they learned to pay attention to urine flow to prevent catheter related problems. Though most acknowledged feeling vulnerable because of disruptions caused by the catheter, they noted also that keeping urine flowing was critical to their wellbeing [537] (Level of Evidence 3).

Health care providers need to provide proactive support and education about the catheter and its care, particularly since some catheter users are uncomfortable in asking for help or support. Male / female sensitivities can interfere; for example, a woman might be disinclined to talk about her catheter with her son [536] [523] (Level of Evidence 3).

Guiding and supporting an individual's adjustment to living with a catheter involves promoting dignity, supporting the changed body image so that the catheter becomes a part of self (and almost not noticed), and learning self-management and self-care, and in planning for active life in the community. It is essential that catheter users know how to select suitable equipment. Simple advice such as not using a coloured catheter in the summer when white clothing would allow it to show can be very helpful. Knowing where toilets are and planning for outings (rehearsing) can prevent urine accidents [516] (Level of Evidence 3). Ambulatory females who use a belly bag need to face the toilet when emptying the bag. Since this position is associated with male toileting rather than female it can sometimes cause embarrassment. Some women may prefer to use a unisex toilet where possible.

While adjustment takes time, emotional distress with the catheter can swing back into the picture at any time if problems develop. Depending on whether the device is working well or not, people can move back and forth between acceptance and estrangement from the catheter [305] when the problem in the background emerges and brings the issue once again to the foreground [538] (Level of Evidence 3). Learning to live with a catheter involves recognizing that the benefits can outweigh the problems [524], watching for signs of problems, and adjusting to the interpersonal and sexual changes [536] (Level of Evidence 3).

f) Self-management

Self-monitoring, a component of self-management, involves awareness of what to notice and related measurements or observations [539]. Self-monitoring urine flow was found to be helpful in preventing or minimizing catheter-related problems in a pilot study with 11 community-based individuals over a six months' time [306]. In this study, a 3-day urinary diary of intake and output was combined with an educational program, individualized to the interests of participants. Most participants said they learned to pay attention to urine flow, through observing continuous drainage into the drainage bag, increased awareness of the urine colour, position of the catheter, and by monitoring the consistency of their fluid intake [306]. Health care providers can help catheter users to learn to manage their catheter themselves, (i.e. self-care) by identifying where they are in the process of learning self-care and by working with them [536] (Level of Evidence 3).

g) Summary

Most published studies of patients with indwelling catheters have focussed on short-term catheters (< 14 days) in hospitalised patients and relatively few have compared different modes of catheterisation (urethral, suprapubic, intermittent). The main subject of research on catheter use has been the risk of catheter-associated infection and the surrogate outcome measure of bacteriuria (asymptomatic) is commonly employed. However, there are important questions over the appropriateness of this as an outcome measure. Although there is clear evidence to support a small proportion of catheter care procedures (indicated below) the majority of procedures are based on clinical experience and expert opinion. Long-term studies are difficult to carry out for a variety of reasons (not least the frailty of many long-term catheterised patients) and there are relatively fewer studies based on community dwelling patients. RCTs may not be the most appropriate or pragmatic design for these groups. Although there are now a number of Cochrane reviews relating to

long-term catheter use it is clear that the quality of studies available frequently precludes drawing robust conclusions.

The published literature on SPC use is still relatively small, with much of it based on single centre cohort or case studies, or on short-term post-operative care following surgical procedures (not necessarily related to lower urinary tract symptoms). The majority of reports on SPC for long-term bladder drainage focus on the management of neurogenic bladder. Robust conclusions are often difficult to reach given the relatively short follow-up time frame of many studies and the lack of precise definitions of key outcome measures such as measurement of infection. Overall the risks associated with short and long-term use of indwelling catheters are common to both urethral and SPC insertions, including CAUTI, tissue trauma, catheter encrustation leading to blockage, formation of bladder calculi and histological changes.

Quality of life measures, including evaluation of psychometrics, need to be developed further and tested in this population, which may have different needs than others with incontinence. Studies of incontinent people that include catheter users should present data in ways that give the reader information about this sub-population. Sensitivity and a proactive stance from care providers could prevent or minimize some of the stigmatizing effects of the catheter, including those related to privacy needs, dignity, and sexuality. Further product development may help catheter users attain a higher quality of life. Additional research on the effects of self-management/self-care may provide direction for teaching that could contribute to a higher quality of life for catheter users.

4. OVERALL RECOMMENDATIONS RELATING TO CATHETERS

a) Intermittent catheters

- Clean intermittent catheterisation (CIC) is a treatment of choice for those with ongoing bladder emptying problems and residual urine > 100ml who are able to manage the technique (**Grade of Recommendation A**).
- CIC technique can be taught to all ages of people with appropriate motivation and manual dexterity (or to a carer where this is acceptable to both parties). Appropriate education and ongoing support is needed (**Grade of Recommendation C/D**).
- Frequency of catheterisation needs to be based on individual need, to prevent over-filling of bladder (**Grade of Recommendation C**).
- An external lubricant or lubricant-coated catheter is recommended to minimise urethral trauma (**Grade of Recommendation C**).
- CIC users may benefit from access to different catheters or catheter-packs for different purposes (eg ease of use may be particular important when at work or in public) (**Grade of Recommendation C**)

b) Indwelling catheters

- Indwelling catheters should only be used after alternative management strategies have been considered and rejected as unsatisfactory (**Grade of Recommendation A**).
- Duration of catheterisation should be minimal (**Grade of Recommendation A**).
- A closed drainage system should be maintained to reduce risk of catheter-associated infection (**Grade of Recommendation A**).
- Asymptomatic bacteriuria should NOT be treated with antibiotics (unless urological instrumentation is planned) (**Grade of Recommendation B**).
- Routine urine culture in an asymptomatic patient is not recommended (**Grade of Recommendation C**).
- Silver-alloy catheters should be considered for short-term catheterised patients to reduce the risk of catheter-associated infection (**Grade of Recommendation A)** but further economic evaluations are required to determine cost-benefit to institutions.
- Catheter materials designed for long-term use (all-silicone, silicone or hydrogel-coating) should be used where a catheter is expected to be used long-term (i.e. >14days) (**Grade of Recommendation B**).
- Meatal cleansing with plain soap and water (not with antimicrobial agents) is recommended (**Grade of Recommendation A**).
- Addition of disinfectants to drainage bags, bladder irrigation and antibiotic prophylaxis are NOT recommended as routine infection-control measure (**Grade of Recommendation A**).
- If an indwelling catheter is being considered, SPC should be considered alongside UC, following appropriate risk assessment (**Grade of Recommendation B**).
- UC and SPC insertion should be carried out only by appropriately trained and skilled practitioners using aseptic technique (**Grade of Recommendation C**).
- UC and SPC catheters and drainage bags should be adequately supported to prevent meatal or cystostomy damage from traction (**Grade of Recommendation C**).

- In patients with recurrent catheter encrustation and blockage, careful monitoring should be undertaken to identify a characteristic pattern of 'catheter life' and instigate pre-emptive catheter changes prior to likely blockage (**Grade of Recommendation C**).

c) Catheter valves

- A catheter valve can provide an effective means of catheter drainage following appropriate patient assessment (**Grade of Recommendation B**).
- A combination of a valve during the day and free drainage at night through an open valve connected to a drainage bag could be an appropriate management strategy (**Grade of Recommendation D).**

5. PRIORITIES FOR RESEARCH

a) General

- Despite much published research (primarily on short-term catheter use in acute care settings), catheter studies have been hampered by methodological weaknesses. There is a need for agreement on key criteria to permit robust comparisons between studies: (i) criteria for symptomatic UTI, (ii) significant bacteriuria in a catheterised patient and its clinical/research usefulness (iii) standardised time frames for following patients in studies of catheter-associated infection eg 48h, 5 days, 7 days, 14 days 21 days etc (iv) documentation of the use of antibiotics prior to and during a study eg preoperatively in surgery or commencement of antibiotics for other conditions during the study, (v) patient follow-up to include post catheter removal.
- A standardised definition of UTI should be adopted as the primary outcome variable. At present the most recent CDC/NHSN surveillance definition of health care-associated UTI is an example [379]. Although criteria for both symptomatic UTI and asymptomatic bacteriuria are defined by the CDC/NHSN, it should be recognised that definitions are applicable to non-catheterised populations and specific to acute care settings and additional definitions apply to catheterized patients [342].
- Moreover, definitions which distinguish between asymptomatic and symptomatic infection in catheterized patients can be prone to coding errors. Inappropriately treated asymptomatic bacteriuria confounds the errors [540] and contributes to a lack in knowledge of effective ways to treat symptomatic CAUTI [541].
- Better adherence to CONSORT guidelines [542] eg double blind randomization with appropriate power calculations, intention to treat analysis with inclusion of study drop-outs
- Need for clinical studies which are adequately powered to detect differences in clinically and economically important endpoints in preference to (or in addition to) more easily measured surrogate endpoints such as bacteriuria.
- Comparative studies of different patient groups eg. males and females, different age groups, patients at home and those in institutional care, including patients' comfort, satisfaction and quality of life measures.
- Further research on the development of biomaterials that resist microbial adherence and biofilm formation and /or prevent catheter-associated bacteriuria in both long-term and short-term catheter users.
- Further efforts aimed at reduction of short and LTC use, particularly acute care and nursing home populations. Targeted areas to include evaluation and management of skin problems, and alternative measures for people with diabetes mellitus, obesity and communication problems.

b) Intermittent catheters

There is lack of evidence demonstrating the effectiveness of any particular catheter type, technique or strategy. Variations in clinical practice and growth in the use of single-use catheters (particularly coated catheters) with associated increased costs mean that large, well-designed, parallel group RCTs are needed. RCTs are difficult to conduct in this area and must focus on the most important pragmatic questions, for both clinical and cost-effective reasons. Key issues are identified below.

- What evidence is there that coated (single-use) catheters are superior to uncoated (multi-use) catheters and in what ways (e.g infection, comfort, convenience)? Further studies are needed on the risks / benefits of single use catheterisation (new catheter used at each insertion) versus single patient use (patient cleans, stores and re-uses the same catheter for several days) for patients whose long-term bladder management is by CIC.
- To assist assessment of cost-effectiveness, it is recommended that patient acceptability / satisfaction with procedure and a measure of health state utility are measured for different situations (e.g. at home and when away from home) as a secondary outcome variable.

c) Indwelling catheters

- Epidemiological studies of CAUTI in LTC use in community care settings.
- Better prospective data on long-term sequalae of indwelling catheter use, eg ongoing symptoms, strictures, calculi, bladder cancer.

- Studies comparing catheterisation techniques eg CIC, suprapubic and urethral catheters, on CAUTI and other risks or potential benefits
- Studies to determine whether the frequency of regular re-catheterisation make a difference to CAUTI and other complications
- Studies to ascertain if there are detrimental effects on bladder tissue from persistent asymptomatic bacteriuria in long-term catheterised patients.
- Clinical evaluation of strategies to reduce recurrent catheter encrustation and blockage, including maintaining a dilute urine, increased level of urinary citrate, role of acidic 'catheter maintenance' solutions.
- Further development of catheter materials resistant to microbial biofilm formation, new approaches to disruption of the biofilm, or alternatives to catheterisation.

d) Catheter valves

- Clinical investigation of effect of catheter valves on incidence and frequency of catheter encrustation and blockage.
- Cost-effectiveness studies of disposable versus re-useable valves.
- Studies designed to demonstrate if catheter valves promote maintenance of bladder tone and capacity.
- Further examination of combination management strategies such as valve during the day and free drainage overnight.

e) Quality of life

- Identification of appropriate quality of life indicators/ criteria and measures for catheterised patients.
- Development of a quality of life measurement instrument including both subjective measures and objective measures, including factors such as: frequency of catheter blockage, catheter-associated infection, hospitalization, unplanned catheter changes, adequacy of equipment, knowledge about self care, interaction with caregivers in catheter management.
- Case study analyses to maximise evidence gained through clinical experience and expert opinion, particularly where opportunities for formal research are likely to be unrealistic.

XIII. PRODUCTS FOR PREVENTING OR CONTAINING FAECAL INCONTINENCE

The broader issues of conservative management of faecal incontinence are dealt with comprehensively in chapter 16 while this chapter deals with products for preventing or managing faecal incontinence. They fall into three main categories:

- Products that aim either to prevent or contain leaked stool.
- Products that seek to prevent or mask the offensive odour that occurs from leaked stool or flatus.
- Products for preventing or treating perianal skin damage associated with faecal incontinence (one of the primary complications of faecal incontinence and an important part of care).

Products dealing with skin health and odour are covered in Sections XIV and XV, respectively, while products for preventing or containing faecal incontinence are covered in this section (apart from absorbent pads, which are included in Section VI).

1. PRODUCTS TO PREVENT OR CONTAIN LEAKED STOOL

There is little knowledge about product management for people suffering with faecal incontinence. Peden-McAlpine et al. (2008) [543] show in their study the experiences of ten women with faecal incontinence. They show how a number of strategies, such as: bathroom rituals, eating habits or fiber supplements belong to the management strategies of the affected, so that they may actively participate in a normal public life. The use of aids is also a major strategy as Bliss et al. (2011) [544] also show. More than 1/3 of those questioned (189 participants) would no longer pursue their activities, when they had no aids at their disposal. Thereby, those who suffer seriously with faecal incontinence resort to absorbent aids, particularly to pantiliners from the range of feminine hygiene products. First and foremost of importance for the study participants was odour control, however, when asked about their satisfaction with various aspects of the product, they ranked odour control as the worst.

Products fall into three groups:

- Plugs to prevent leakage of faeces.
- Devices to channel faeces from the rectum into a storage container.
- Absorbent pads to contain leaked faeces (see Section 6).

An anal plug (**Figure XIII-1**) consists of a foam, cup-shaped plug that is collapsed and held by a film for insertion; the plug opens when the film comes in contact with the moist rectal mucosa [545] [546]. It is inserted like a suppository using a lubricant gel. It has a string for removal or it can be expelled by raising intra-abdominal pressure and pushing like during normal defaecation. The anal plug has been used mainly by community living people, both adults and children, who are independent in managing faecal incontinence and toileting. Another type

of experimental anal plug consists of a balloon at the end of a catheter connected to a notification device. The catheter is intended to be inserted into the rectum by the user and the inflated balloon acts as the anal plug; there are also vent holes on the distal tip of the catheter (**Figure XIII-2**). The disposable, double lumen, balloon-cuffed rubber catheter has an infra-red photo-interrupter sensor that is connected to a pager [547]. When faeces enter the rectum, a photosensor signal is sent to the pager which then notifies the person to inflate the balloon. Before a bowel movement, the balloon is deflated and the catheter is withdrawn. To prevent ischemic bowel damage, patients are advised to deflate the balloon for 10-15 min every 3-4 hours.

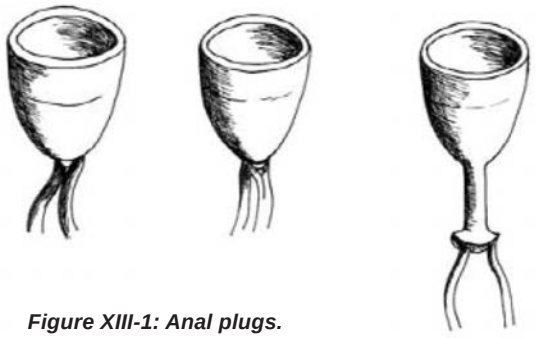


Figure XIII-1: Anal plugs.

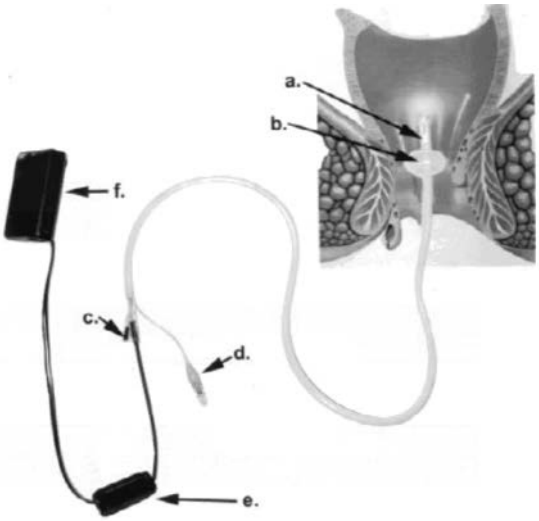


Figure XIII-2: Procon anal plug with infra-red photo-interrupter sensor and pager. (Reproduced with the permission of Wiley-Blackwell Publishing)

a: infrared photo-interrupter sensor and flatus vent holes incorporated into the catheter
b: 20 cc air cuff (similar to a regular bladder catheter)
c: flatus venting charcoal filter
d: cuff fill valve
e: monitor connector
f: monitor that resembles a "beeper" or pager

By contrast, devices for channelling faeces from the rectum to a storage container are used primarily by people who are acutely ill, critically ill, confined to bed, or in long-term care institutions and receive assistance in incontinence management and toileting by caregivers [548] [549] [550] [551] [552]. These devices do not prevent faecal incontinence and are used primarily for preventing or treating skin damage associated with faecal incontinence. They include rectal tubes, catheters, trumpets, and pouches.

Rectal tubes and catheters are inserted into the rectum and drain faeces through openings at their proximal end into a collection bag (**Figure XIII-3**). Sometimes a balloon slightly distal to the proximal tip is inflated with the aim of preventing leakage of faeces around the catheter and to retard inadvertent expulsion of the tube during defaecation [549]. This arrangement works best with liquid stool which is most likely to be able to flow without blocking the drainage lumen [553] [552]. Bowel management programs often include daily saline irrigations through the rectal catheter to maintain liquid consistency of stool and catheter patency. Differing amounts and frequency of irrigation have been reported (300 to 900 ml). Cutting the tip of the catheter off at an angle to facilitate drainage of stool of thicker consistency has been reported [554]. A rectal tube / catheter is contraindicated in patients who have intestinal mucosal disease, immunosuppression, gastrointestinal bleeding or bleeding tendencies, recent myocardial infarction or prostate surgery [555] [554]. Use of a rectal tube with or without inflating the balloon is controversial because of concerns of perforating the rectum, damaging the anal sphincter or rectal mucosa, stimulating intestinal secretion worsening diarrhoea and thus incontinence [553] [554] [556]. Critically ill patients, who often receive a rectal tube, may be at greater risk for intestinal ischemia and rectal damage because they experience shunting of blood from the gastrointestinal tract during shock or low perfusion states.

A rectal trumpet is a nasopharyngeal airway that is inserted into the rectum and connected to a collection bag at its distal end. The flange end of the trumpet is inserted into the rectum [557] (**Figure XIII-4**). A possible advantage of the rectal trumpet over a rectal tube is that it is shorter and has less contact with the rectal mucosa, so limiting the area of possible damage. Other limitations are similar to those for the rectal tube / catheter regarding risk of expulsion from forceful valsalva movements and dislodging during linen changes or from tugging on the collection bag [557]. Nasopharyngeal airways that can be used as a rectal trumpet are produced by several manufacturers.

An external anal pouch consists of a pliable wafer, which has an opening at its centre, an adhesive on the body side, and a collection bag on the other. The wafer adheres to the perianal skin (**Figure XIII-5**).

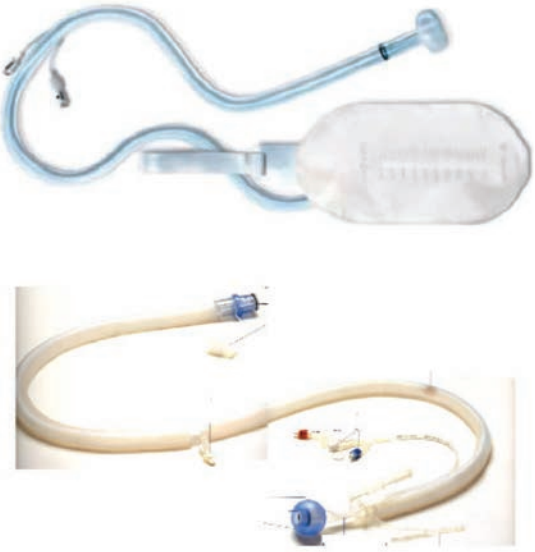


Figure XIII-3: Rectal catheters; Flexiseal Fecal Management System, Convatec (Nordic Capital Fund VII and Avista Capital Partners); Princeton, NJ (top); and Zassi Bowel Management System, Hollister, Inc. Libertyville, IL (bottom).

Figure XIII-4: A rectal trumpet.

The bag has a resealable port at its distal end through which faeces can be drained without the need to remove the wafer from the skin. The port can also be connected to a larger, gravity drainage bag. Some pouches have a small folded flap that allows flatus to escape so that it doesn't inflate and rupture the bag. The pouch avoids the risks of rectal or sphincter damage associated with the rectal tube or trumpet. If used without the additional drainage bag, it can collect leaked stool of any consistency without clogging. A limitation of the rectal pouch is difficulty in applying it on people who have a small space or severe oedema between the anus and vagina or scrotum. Other reported disadvantages include difficulties in maintaining the seal (especially when the perianal skin is already damaged); break of the seal when repositioning the patient; and skin tears by traumatic removal of the adhesive [557] [551].

An intra-anal stool bag is composed of a latex bag (20cm non-extended, to 26cm extended) that is inserted into the anus and an adhesive attachment (10 cm in diameter) applied perianally [558] (**Figure XIII-6**). There is a cut-out on the ventral urinary side of the adhesive wafer.

Aspects of patient assessment that are relevant to products to prevent or contain leaked stool include the following: a) physical characteristics (e.g. some anal plugs may be too large to fit smaller sized children), b) dexterity (e.g. some degree is needed to insert or remove an anal plug), c) mobility (e.g. rectal catheters are mainly used for patients who are in bed versus ambulatory), d) nature of incontinence (e.g. bowel catheters will require irrigation when stool consistency is not loose or liquid in order to remain patent; and e) personal priority and lifestyle (e.g., some persons will wear an anal plug on certain occasions such as when swimming, despite discomfort).

2. QUALITY OF DATA

Since the previous review there have been two observational studies in which the anal plug has been evaluated. One study was of adults [559] and

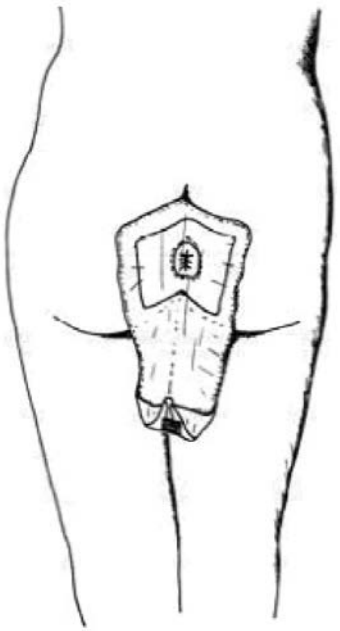


Figure XIII-5: An anal pouch.

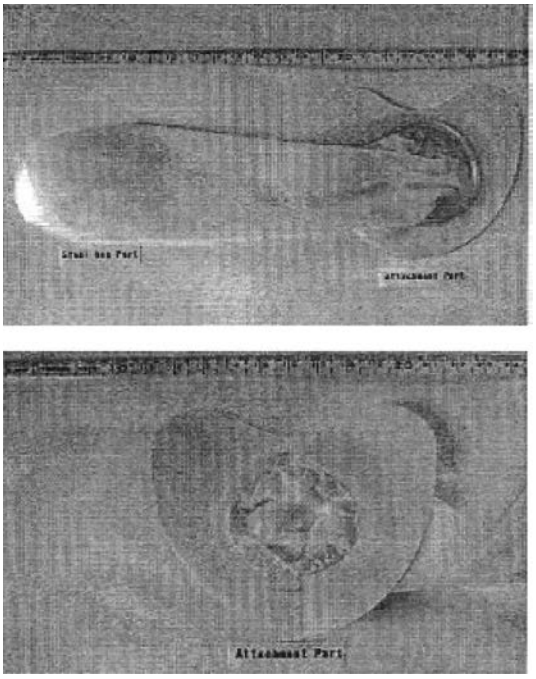


Figure XIII-6: Interanal stool bag (left) and Outer attachment wafer of Interanal stool bag (right). (Reproduced with the permission of Wiley- Blackwell Publishing)

the other of children [560] bringing the total number of published evaluations of anal plugs for controlling faecal incontinence to ten. There was one study of the anal catheter plug (Procon, AnaTech, El Paso, TX). Six reports included children of which two studied children exclusively [561] [562]. The study designs were one randomized clinical trial, four repeated measures (cross-over), one pre-post design, two prospective cohort studies, one cross-sectional survey, one case series, and one case report. One study did not specify the manufacturer of the anal plug studied [560], one study [561] compared plugs of two manufacturers (Coloplast, Denmark and Med.SSE-System, Germany) and all other studies of anal plugs evaluated products from the same manufacturer (Coloplast). There has also been one published evaluation of a rectal trumpet using a case series design [557] and one each of an external anal pouch and an intra-anal stool bag in which no comparison group or pre-post measures were included.

3. RESULTS

a) Anal Plugs

Most evaluations of anal plugs have involved relatively small cohorts of ambulatory subjects. The largest sample had 48 subjects and 26 of 31 persons in the intervention group who wore the anal plug completed the study [563]. The aetiologies of faecal incontinence varied across studies and included spina bifida, imperforate anus, spinal injury, post-surgical incontinence, sphincteric injury, and obstetric trauma. Faecal incontinence was measured by self-report using a daily stool diary in six studies [563] [562] [547] [545] [546] [564]. A questionnaire /survey was used in one descriptive [565] and one repeated measures study [561]. The main reported outcome measures were: the number of episodes of faecal incontinence per number of anal plugs used due to self removal or need for defecation [545]; the number of patients experiencing no faecal incontinence [564] [562] [561] [546] [560] or improved faecal incontinence [546] while using the plug; score on a 10-point visual analogue scale for control of faecal leakage, [559]; the number of patients able to retain 150 ml of viscous fluid while using the plug [564]; and the change in a faecal incontinence severity score [563] [547]. The percentage of participants lost to follow-up ranged from 10% [545] to 80% [564].

The effectiveness of the plug in preventing faecal incontinence in adults ranged from 83% [564] to 38% [562] (Level of Evidence 3). Bond et al [563] conducted a randomized clinical trial of the effectiveness of an anal plug that included 31 adults and children with spina bifida in the treatment group and 17 adults and children in a control group; 84% of the treatment group and 100% of the control group completed 12 months of follow-up. There was no statistical difference in the faecal incontinence severity score between the group wearing an anal plug and the one that did not; however, the study was determined to be underpowered to detect differences. Norton and Kamm [546] compared two anal plugs for two weeks each in random order in a cross-over design. Of the 20 adults (16 female) participating, 10 (50%) were continent, and 9 (45%) withdrew after trying the first plug. Three anal plugs were compared by 10 adults for one week each in a cross-over design in an earlier study by Mortensen and Humphreys [545]. Continence was achieved in 83% of anal plug uses overall. Faecal incontinence occurred in 18%, 19% and 15% of uses when Plug 1, 2 or 3 were worn, respectively. Only one subject withdrew from the study. In a pre-post comparison of an anal catheter plug, seven of 18 adults (39%) with various aetiologies of faecal incontinence and a Cleveland Clinic FI severity score >7 completed a 14-day wear period [547]. The mean (standard deviation (sd)) faecal incontinence score during wear of the anal plug (5.2 (3.0)) was less than half that before its use (12.7 (3.6)). Thirty middle-aged patients (aged 63 (52-70) years (mean (range)) with intractable FI of various aetiologies tested the anal plug for three weeks; the score for control of faecal leakage on a visual analogue scale (1= very poor to 10= extremely good) was 9 (median) after 1 and 3 weeks of using the plug [559]. Christiansen & Roed-Petersen [564] reported that 86% of persons were able to retain 150 ml of viscous fluid while an anal plug was inserted.

In the study of children only, 38 children (ages six to 15 years) after anorectal malformation repair compared two anal plugs (one made of polyurethane and one of polyvinyl alcohol) for three weeks each in random order in a cross-over design. Approximately two-thirds (61%) completed the study. Twelve children (32%) were completely continent using either plug and five (13%) reported "total failure." Two or fewer soiling accidents occurred in 74% using the polyurethane plug, and in 65% using the polyvinyl alcohol plug [561].

In a study of 20 children and adults with spina bifida, average age 12 years (range = 4-29 years), the weekly number of episodes of FI soiling decreased from 4 (0-28) to 0 (0-8) (median (range)) after using the anal plug [560].A survey of adults and children showed that a higher percentage of children tolerated using an anal plug over a longer period of time [565]. Five of eight (63%) adult survey respondents who had faecal incontinence of various aetiologies stopped using an anal plug immediately while three used it periodically for 12 to 20 months. Two of seven child respondents stopped anal plug use immediately while five (71%) used it weekly for an average of 2.5 years.

The most common reported problems associated with wearing an anal plug included discomfort and failure to retain the plug. Despite efficacy, approximately two-thirds of the subjects in two studies [564] [546] said they would not continue to wear the plug due to discomfort. Discomfort occurred in 10% to 12% of the times that one of the three anal plugs were worn in another study [545]. In more recent studies, 23% and 33% of subjects reported discomfort [563] [560]and 23-25% withdrewfrom studies because of pain [562] or discomfort[560]. More men than women withdrew from one study because of discomfort [559]. Adults who experience discomfort do not seem to adapt over time [559]. After three weeks of wear, adults reported a score on a ten-point visual analogue scale for comfort while inserting the anal plug was 7 (5-9) and while removing it was 8 (7-10) (median (range)). There was no association between comfort of the plug and anorectal sensitivity during anal-rectal physiology tests in adults [546]. Children seem to experience less discomfort than adults while wearing the anal plug. [561] [559]. Approximately 20% of children reported that insertion of the polyvinyl alcohol plug was painful while 17% found removal of the polyurethane plug to be painful; one child experienced bleeding on removal of this second plug. Rectal bleeding also occurred in adults but infrequently [545].

Failure to retain the anal plug was reported by 13% of subjects in two studies [563] [562] and was noted by one child in the paediatric study as a reason for withdrawal [561]. The size of any plug tested was too large for six children in one study [561]. Twenty-seven of 30 adult subjects preferred a small size anal plug [559]. Other tolerance problems were fairly uncommon. In one study, adults rated all three anal plugs that were evaluated as relatively easy to insert. Two plugs were difficult to remove in only 5% and 6% of uses, respectively, while the third was difficult to remove in 23% of uses [545]. Other reported problems were feeling a need to defecate [546], inconvenience or difficulty in managing [546] [547], and local irritation [565].

b) Rectal Trumpet

One case series study evaluated the use of a rectal trumpet in 22 acutely or critically ill patients with faecal incontinence and perineal skin damage [557]. For 90% of the subjects, the skin damage had been caused by wearing a rectal pouch immediately prior to the study. Subjects used the trumpet for periods varying between 36 hours and 16 days (mean 6.5 days; sd 4.4 days). The reasons for any discontinuation of use were reported. Outcome was determined using a daily questionnaire completed by patients' nurses and the health of the perianal skin was noted by subjective assessment. No standardised definitions or criteria for restoration of skin integrity or healing of skin damage were reported. Two subjects were lost to follow up. Faeces were successfully diverted to and contained by the collection bag in all patients. Recovery from skin damage was reported in 7 (39%) patients and partial healing of skin in the remaining 11 (61%). Discomfort on insertion was noted for 41% of subjects (Level of Evidence 3).

c) Rectal Catheter Systems

Closed rectal catheter and collection bag systems specifically designed for extended use and diversion of faeces are commercially available, primarily for acutely-ill or bed-ridden patients (Flexi-Seal™ and Flexi-Seal™ Signal™ Faecal Management System, Convatec A Bristol Myers Squibb Company; Princeton, NJ; Actiflo Indwellling Bowel Catheter (formerly Zassi® Bowel Management System); Hollister, Inc., Libertyville, IL; Dignicare® and Dignishield™ Stool Management Systems, Bard Medical). The catheters of these systems typically contain a retention cuff that collapses to assist with insertion (US FDA approved for up to 29 days) and a port for irrigation. In one system (Acti-flo) there is also a collapsible zone below the cuff that resides in the anus to allow normal anal sphincter function during use and a second port for sampling intestinal fluid. A third catheter has an inner balloon that can be inflated to serve as an anal plug to promote retention of an enema, for instance (Kim, US Patent 5 569 216, apparently not currently commercially available).

Six studies evaluated use of a rectal catheter system. Three studies used one type of catheter while the other three studies used three different types of systems. One study was of children [566]. The designs included a prospective single cohort in four studies [548] [567] [549] [566], a pre-post descriptive design[568], and a retrospective case-matched

pre-post design [569]. The largest sample size was 106 in the retrospective chart review whereas sample sizes in the prospective studies were relatively small, ranging from 20 to 42 subjects. In the studies of adults, subjects were burn patients in two studies [567] [569] and acutely or critically-ill patients in three studies [548] [568] [549]. In three studies, irrigation of the catheter with saline, a combination of lactulose and saline irrigation or use of an enema was used to keep the stool liquid and the rectal catheter patent [567] [569] [549].

In only two studies was the effectiveness of the rectal catheter system in reducing faecal incontinence reported (Level of Evidence 3). In the one paediatric study, 31 children (11 females) participated. Eight families refused to stop using the rectal catheter to complete an incontinence diary without use of a catheter. Two children had balloon extrusions and three were noncompliant resulting in their study withdrawal. The mean number of daily faecal incontinence episodes as reported on a daily diary decreased from 3 to 1.5 in males and from 1.6 to 1.1 in females ($p<0.05$ for both) [566]. Three children experienced no improvement of faecal incontinence. In the one adult study, 39 of 42 subjects (62% female) with diarrhoea in intensive care units in seven hospitals completed the study. There was up to 29 days of follow-up. Varying degrees and types of leakage around the rectal catheter were reported in 71% of 198 assessments; 35% of these leakages extended to pads on the bed or beyond [548]. Seven (17%) of subjects had difficulty retaining the rectal catheter. Section 6.11 discusses use of a small gauze dressing for absorbing small amounts of stool leakage and a moisture barrier as skin protective strategies that might also help prevent damage from stool leakage around a rectal catheter. Skin damage from the tape holding the catheter in place and rectal bleeding are other reported but uncommon complications [567] [548].

The effect of a rectal catheter on various outcomes associated with stool leakage has also been studied. Two studies reported costs savings in terms of reducing laundering of soiled bed linens. One study reported that the number of bed linen changes in burn patients with diarrhoea decreased eight-fold and dressing changes in hospitalized or burn patients decreased in half after a bowel system was introduced [567]. A multi-site study of 146 bedridden patients in the U.S. showed that one catheter (Hollister, Inc) reduced the rate of bed linen changes (1.2 changes per day) more than another (1.7 per day) (Convatec). Estimates of cost savings based on staff time and laundry costs was almost $14 USD per patient per day [570].

Other outcome measures of rectal catheter use included urinary tract infections, incidence of skin / soft tissue damage or infections, prevalence of pressure ulcers, and number of linen changes (Level of Evidence 3/4). In a retrospective review of medical records, approximately twice as many burn patients had skin / soft tissue or urinary tract infections before a bowel catheter system was introduced than after ($p<0.01$) [569]. A prospective study of acutely and critically-ill patients showed that 41% who had normal skin in the perineum or buttocks at baseline maintained normal skin during use of the bowel catheter, 44% with some degree of skin damage improved, and 8% had worsened skin condition [548]. The percentage of intensive care unit patients with a stage II or greater pressure ulcer was observed to be less at nine months after use of a bowel catheter was introduced. The total number of patients observed was not reported. The length of time during which the prevalence of pressure ulcers was determined prior to catheter use was also not reported [568].

The condition of the rectal mucosa was observed endoscopically in 40 patients total across three studies; the evaluations were not blinded or independent and did not use a rating scale [548] [567] [549]. All endoscopic observations were reported as being normal after rectal catheter use. Few complications associated with use of the rectal catheter system were reported in one study. Leakage around the rectal catheter seemed to be the most frequent problem. Catheter expulsion occurred in a small number of patients and skin damage from trying to secure the tube occurred only in one patient. Altered rectal sphincter function occurred using one of the catheters [549]. As the catheters are used more widely in clinical practice, there are more case reports of complications including rectal or lower gastrointestinal bleeding and need for blood replacement, mucosal pressure necrosis, fistula, and autonomic dysreflexia [571] [572] [573] MAUDE http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm. (Level of Evidence 3).

d) Anal Pouch

One case series study evaluated the use of an external anal pouch (Technoline, Concordia, Moderna, Italy) in 120 nursing home or hospitalized patients (65 men, 55 women, ages 45-96 years) [574]. The nursing home residents (n = 92) were bedridden and had faecal and urinary incontinence or were treated for constipation for rectal enemas that drained into the pouch. Ten had a pressure ulcer. They used the pouch for four weeks or more. Acute care patients (n = 28, of which 10 were in the intensive care unit) had diarrhoea and were temporarily bedridden. Forty-five patients who had surgery of the perineal area received a pouch to collect post-surgical drainage for up to three days. In the nursing home residents free of pressure ulcers, no new ulcers developed. In those with a pressure ulcer, healing occurred in five residents, ulcer diameter was reduced by 50% in three residents, and there was less than 50% reduction in two residents. Of the nursing home and acute

care participants, 77% found the pouch comfortable and 75% thought it was better than a sanitary napkin. Seventy-seven percent of the nurses thought the anal pouch was easy to apply and 78% thought is easy to remove. Reported complications included moderate pain on removal in 18 (15%) patients in the nursing home or acute care (Level of Evidence 3).

An internal anal stool bag (Terumo Corp., Tokyo, Japan) was applied to five bedridden patients (3 female, 2 male) aged 68-90 years [558]. Persons were administered a biscodyl suppository prior to insertion of the stool bag into the anus to control excretion of faeces. The bag was successful in collecting stool 50% of the time (Level of Evidence 3). The bag was removed after each stool was collected.

Bliss and Savik (2008) [88] carried out a study, to examine the use of a surgical dressing to absorb a small leak of feces. These anorectal dressings can be placed between the buttocks. Of 28 people who had faecal incontinence, 27 had used the dressing and 23 of them wanted to continue to use it. 79% reported no skin complications, and 80% of the participants rated their confidence in its effectiveness as very good to good. Use of the dressing lessened anxiety about faecal soiling in 81% and was thought to improve quality of life in 76%. The authors stated that new types of absorbent products will become available.

4. SUMMARY

- An anal plug can successfully prevent faecal incontinence but it is associated with high levels of discomfort, more so in adults than children (Level of Evidence 3).
- A rectal catheter system diverts faeces to a collection bag and promotes healing of damaged perineal skin but requires liquid stool consistency to remain patent. Some catheter systems enable irrigation of the rectum to maintain liquid stool consistency.
- Non-blinded and non-independent endoscopic observations suggest the rectal catheter does not cause rectal mucosal damage during the recommended length of use (≤ 29 d in the US). As rectal catheter usage increases in clinical practice, case reports of complications have become evident; among the common ones reported are perianal skin damage, rectal bleeding, and mucosal pressure necrosis. (Level of Evidence 3).
- A rectal trumpet can successfully channel faeces to a collection bag and there is some evidence that it can thereby enable damaged perianal skin to recover but it has been associated with discomfort and its safety has not been determined (Level of Evidence 3).
- An external anal pouch and an internal anal bag can be used to collect stool (Level of Evidence 3) but the adhesive wafers used to adhere them can cause skin damage upon removal. The internal anal bag has been primarily used when a bowel movement is induced using a suppository.

5. RECOMMENDATIONS

- Anal plugs may be tried but many patients are likely to use them on a limited basis or reject them due to discomfort (Grade of Recommendation C).
- The use of a rectal trumpet (i.e. a nasopharyngel tube inserted into the rectum) in patients with loose / liquid stool consistency offers an alternative to the rectal pouch when pouch adherence is a problem and may preserve perianal skin integrity or facilitate healing (Grade of Recommendation C). The safety of the rectal trumpet has not been determined, but it suggests a lower risk due to its shorter length than a standard, longer rectal tube (Grade of Recommendation C).
- Use of a standard rectal tube with and without an inflatable balloon for faecal diversion is indicated primarily for non-ambulatory patients with liquid stools (Grade of Recommendation C).
- Use of an anal pouch attached to a drainage catheter to divert liquid stool is recommended, but there is a risk of skin damage. For this reason it is not recommended in cases where skin is already damaged or the need for faecal diversion is less acute (e.g. where stool is more formed) (Grade of Recommendation C).

6. PRIORITIES FOR RESEARCH

- Development of an anal plug that is more comfortable and tolerable.
- More rigorous evaluation of anal plugs using larger subject cohorts and more objective outcome measures over longer periods of use.
- More rigorous evaluation of rectal tubes / catheters and trumpets using larger subject cohorts and more objective outcome measures (e.g. for assessing health of the rectal mucosa) over longer periods of use.
- Development and evaluation of an external anal pouch that is easy to apply and remove, adheres to skin better and, perhaps, even promotes healing of damaged skin to which it would be applied. Further evaluation of an internal stool bag with similar adherent properties (as recommended for the external anal pouch) is needed.

XIV. SKIN HEALTH AND CONTINENCE PRODUCTS

1. BACKGROUND

The skin of an incontinent individual will be regularly exposed to contact with urine and / or fae-

ces and damage to the skin is the main physical health consequence of urinary and faecal incontinence. The majority of current knowledge about the effects of urine and faeces on skin has been obtained from studies with pads or pad materials on animals, healthy infants, and on body areas such as the forearm or back of adults. Where clinical trials have been conducted, they have usually been on infants and rarely on adults using pads. Skin irritation within the pad occlusion area is usually termed diaper dermatitis in infants. In adults the term perineal dermatitis (PD) has commonly been used, but more recently it has been proposed that incontinence-associated dermatitis (IAD) is a better term because affected skin areas are not confined to the perineum [575] [576]. A consensus panel in 2005 defined IAD as 'erythema and oedema of the surface of the skin, sometimes accompanied by bullae with serous exudate, erosion, or secondary cutaneous infection [577] and this term and definition has been widely used since then [578] [575] [579]. More recently IAD has been classed as a sub-category of 'moisture-associated skin damage' (MASD) which includes intertriginous dermatitis and peristomal and periwound moisture-associated dermatitis [579] [580].

Literature reviews and consensus papers

There has been considerable interest in IAD over the last few years, particularly with regard to its definition and aetiology and there have been three review/consensus papers on the subject [578] [575] [579] and one focusing on the prevention and treatment of IAD [581].

a) The role of urine and faeces in skin irritation

Prolonged exposure to water alone has been shown to cause hydration dermatitis [582] [583] and prolonged occlusion of the skin (as within a continence product) has been demonstrated to reduce skin barrier function [584] and significantly raise microbial counts and pH [585] [586]. Repeated wetting and drying makes the skin more vulnerable to substances that are usually innocuous, e.g., bile salts [587] [588]. A product that simply maintains wet and occluded skin (even without the additional constituents of urine and faeces) is therefore likely to cause skin irritation and increase skin permeability to other irritants.

Using a hairless mouse model Buckingham and Berg [589] examined the role of faeces in the aetiology of diaper dermatitis. They identified proteases and lipases as the major irritants and noted that these faecal enzymes not only irritated the skin directly but also increased the susceptibility of the skin to other irritants such as bile salts. The irritant effect of faeces was virtually eliminated by heating, which destroys enzymes, and was restored by the replacement of specific enzymes [e.g. lipase and protease). Skin damage appeared dependent on the concentration and length of exposure to enzymes in faeces [590].

A similar mouse model was used by the same researchers to examine the role of urine in the aetiology of diaper dermatitis [588]. They found that the irritant potential of urine by itself was minimal over short periods (48 hours) but after continuous exposure (10 days), skin damage became apparent. The researchers also measured skin permeability and found that continuous exposure to urine greatly increased skin permeability (more than 15 fold) compared to occluded skin or skin exposed only to water.

However, the combination of urine and faeces caused significantly higher levels of irritation than urine or faeces alone. The authors concluded that the presence of faecal urease results in the break down of urinary urea causing an increase in pH, which increases the activities of faecal proteases and lipases leading to skin irritation. The role of microorganisms - which comprise approximately 50% of the solid component of faeces - in skin damage is unresolved. Microorganisms on the skin of infants with and without diaper dermatitis were similar [591]. Zimmerer [592] sampled the microflora of the skin after pre-loading with pre-wetted patches containing urine and found that the microbial counts were significantly higher for wet patches relative to the dry patch controls. It was nearly impossible to establish infection with the opportunistic organism, Candida albicans, on normal skin without complete occlusion of the site [593]. Therefore, it is thought that bacterial or fungal infection is secondary to alterations in the skin barrier that allow penetration of the microorganisms [594].

Zimmerer et al. [592] examined the role of skin wetness in the development of diaper dermatitis by using the volar forearms of adult volunteers. They aimed to determine the effects of wet and dry diaper materials on skin health with respect to friction, abrasion damage, permeability and microbial growth. Pre-wetted patches of baby diapers were placed on the volar forearms of adults for two hours and then the skin was subjected to friction and abrasion. The coefficient of friction for the 'wet' skin was significantly higher than for 'dry' skin although increased fluid loading of wet patches did not further increase skin friction. Similarly, skin hydrated with a wet patch showed a significant increase in skin abrasion damage relative to a dry patch. Again, variations in the fluid loading of the patch did not produce significant changes in abrasion damage.

Although the volar forearm is most commonly used for skin experimentation, it has not been shown to be a valid model for the skin exposed to an incontinence pad, i.e. buttocks and groins. Schnetz and colleagues [595] demonstrated that trans-epidermal water loss (TEWL) measurements (used to measure both skin barrier function and excess water in the skin) from the volar forearm did not correlate with those taken from the face, although the left and

right side of the face showed good correlation. The researchers concluded that TEWL measurements for the study of facial cosmetics should be taken from the face rather than the forearm. Similarly, studies using the volar forearm may not be valid for the buttocks and groin. Skin in the perianal area was shown to be more sensitive to faecal irritation than that on the inner arm [596].

Recently Fader and colleagues (2010, 2011) [597] [598] reviewed the literature on measurement of TEWL for assessment of overhydrated skin and found that there was a lack of standardization in all components of the method including the analysis and interpretation of findings [597] and they describe the development and testing of a more valid and robust method and compare measurements made on younger and older women and on volar forearm and hip skin. The authors conclude that age did not significantly affect measurements but those made on the hip were consistently higher and more variable than those made on the forearm. It is recommended that the forearm is used for future work.

Berg [588] analysed the aetiological factors contributing to infant diaper dermatitis and developed a model (**Figure XIV-1**) to show its development and resolution. However, the applicability of this model to adults with incontinence has not been tested, and other factors such as low mobility and prolonged pressure - which are common in frail, older adults - are not accounted for in this model. In addition, this model assumes the presence of urinary and faecal incontinence, which is much less common in adult populations than urinary incontinence alone.

b) Prevalence of incontinence-associated dermatitis / perineal dermatitis

Incontinence-associated dermatitis (IAD) has been defined most recently as "an inflammation of the skin occurring with or without erosian or secondary cutaneous infection". Perineal dermatitis (PD) is an inflammation of the skin characterized by redness, tissue breakdown or denudement, vesiculation, oozing, crusting, soreness, itching, and in its more severe form, pain and fungal patches [599] [600] [575] within the pad area. In the largest study of assessment records of more than 59,000 residents in 510 nursing homes located in 31 US states, Bliss et al. [601] reported a prevalence of perineal dermatitis of nearly 6%. In studies with smaller sample sizes and other populations, perineal dermatitis (**Table** XIV-1) has been shown to affect about a quarter to a half of patients.

Recently there has been further clinical evidence supporting the role of faeces in the development of IAD. Bliss et al (2011) [544] studied the development of IAD in 45 criticially ill adults in three critical care units. Most (76%) were male and all were free of IAD at the start of the study. IAD developed in 36% of patients and the median time to onset was 4 days (range 1-6). Severe IAD (denudement) occurred in 9% of the observed time. Frequent incontinence of loose or liquid stools and diminished cognitive awareness were significant independent risk factors for development of IAD sooner.

Shigeta and colleagues (2011) [610] studied the skin of 100 older Japanese patients in a nursing

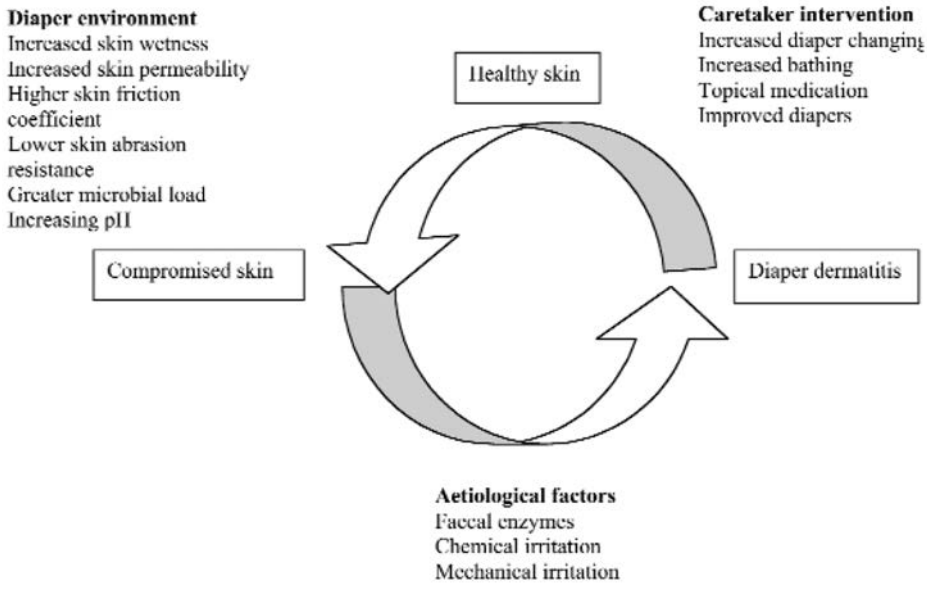


Figure XIV-1: Berg's model of diaper dermatitis (1987).

Table XIV-1: Studies reporting the prevalence of incontinence-associated dermatitis

Authors	Sample	Prevalence of dermatitis (%)
Lyder et al., 1992 [602]	15 older people: hospital psychogeriatric wards	33
Keller et al., 1990 [603]	95 older people: long stay	53
Brown, 1994 [22]	166 adults (acute medical wards)	35
Bale et al., 2004 [604]	79 nursing home residents	25
Zehrer et al., 2005 [605]	398 nursing home residents on a skin damage prevention regimen	4
Bliss, Savik et al., 2006 [601]	59,558 nursing home residents	5.7
Bliss, Zehrer et al., 2006 [601]	1,918 nursing home residents on a skin damage prevention program	3.5
Ehman et al., 2006 [606]	45 adult intensive care unit patients	36
Junkin et al., 2008 [607]	698 paediatric and adult hospitalized patients	20
Shigeta et al., 2008[608]	100 older Japanese patients in a nursing home	36
Beeckman et al., 2011[609]	141 long-term care patients	22.5

home who had faecal and/or urinary incontinence and wore absorbent products. Multivariate logistic regression analysis showed that the presence of diarrhea was an independent risk factor.

Bliss et al. [611] prospectively investigated the development of IAD using assessment data of 1,850 elders who were free of IAD at admission to a nursing home. The preliminary report showed that at three months after admission, faecal incontinence alone and double incontinence were significant predictors of IAD, but urinary incontinence alone was not a significant risk. The prevalence of IAD appears to be influenced not only by the type of patient (nursing home versus hospitalized) but also by the type of incontinence and whether or not a skin damage prevention program is followed.

Measurement of IAD

There is no widely available valid or reliable tool for the assessment of PD / IAD although four instruments have been published [614] [615] [601] [617]. One of these tools, the Perineal Assessment Tool, despite its name, is an instrument primarily for assessing the risk of IAD (versus assessing skin health) and it has been described and used by its developer as such [616]. The most recently published tool [617] has been subject to internal validation and determines degree of redness, amount of skin loss and presence of rash on 13 body locations; a revised version for dark-toned skin is also being tested. Most researchers have reported ratings of colour changes (degree of erythema) based on visual inspection, which may be confounded by the presence of reactive hyperaemia on areas subject to pressure (particularly the buttocks, hips and sacrum). In some studies (mainly those finding higher proportions of IAD) trained staff or researchers have been utilised to carry out skin inspections at pre-specified times and in others (mainly those finding lower proportions of IAD) the usual care staff have been asked to report skin problems or written records have been used; this may explain the wide range of prevalence reported.

Few studies report the severity of PD. In a prospective surveillance study of 981 nursing home residents with incontinence of urine and/or stool over six weeks, the most common anatomical locations of PD were the buttocks (73% of those with PD) and perianal area (70%) followed by the genitalia, scrotum and groin (36%) and thighs (24%) with the smallest percentage near the sacrum (9%). Approximately one-third of residents had PD in more than one location. Mild PD was by far the most common (69% of residents); severe PD affected only 8% of residents [616].

c) Pressure ulcers and incontinence

The role of urinary and faecal incontinence in the development of pressure ulcers is uncertain. Studies aiming to identify risk factors for the development of pressure ulcers have generally found that the presence of both urinary and faecal incontinence was a risk [617] [618] [619] [620], but some studies have only found faecal rather than urinary incontinence to be a risk factor [621] [622]. Pressure ulcer risk assessment scales all have a sub-scale of incontinence or moisture-level, and the main mechanism for the development of pressure ulcers has been thought to be the increased friction and increased vulnerability to abrasion of wet skin.

Some researchers have used pressure ulcer classification systems, such as those published by the National Pressure Ulcer Advisory Panel (NPUAP) or the European Pressure Ulcer Advisory Panel (EPUAP), to measure skin health. The validity and reliability of most of these tools have not been established. Doughty et al [623] and Bethell [624] described numerous other limitations of pressure ulcer staging systems and despite recent revisions of the NPAUP and EPUAP staging systems, many of the shortcomings still apply. The reliability of the EPUAP staging score (which is a modified version of the NPUAP score) has been tested recently in three studies using photographs of pressure ulcers. These photographs included 'moisture lesions' (defined as lesions resulting from prolonged exposure of the skin to excessive fluid because of urinary or faecal incontinence, profuse sweating or wound exudate). A high degree of reliability for classification of moisture lesions was found amongst 44 pressure ulcer experts (Kappa =0.80) [625]. However, inter-rater reliability was found to be much worse (Kappa = 0.37) when photographs were viewed by 473 non-expert nurses [626] and subsequently in

a European study of 1,452 non-expert nurses from five European countries (Kappa = 0.36). The authors concluded that better descriptors needed to be incorporated into the EPUAP system and more education was needed.

An education tool aimed at improving skills in pressure ulcer classification (the PUCLAS education tool) was developed by a workgroup of the EPUAP and was tested by Beeckman and colleagues [627] in a randomised controlled trial. 1217 nurses from Belgium, the Netherlands, UK and Portugal participated. At baseline 45% of skin photographs were classified correctly and results were significantly improved in the intervention group who received the PUCLAS education tool (63% classified correctly) compared to the control group (53% classified correctly). Furthermore the proportion of correct assessments for IAD was 71% in the intervention group and 36% in the control group. The authors conclude that the PUCLAS tool improved pressure ulcer classification.

However there is still debate regarding the validity of separately classifying IAD from pressure ulcers particularly when skin damage occurs over bony prominences. To investigate the validity of classifying moisture lesions, Houwing et al. [628] examined the histology of 14 biopsy samples of damaged patient skin. Skin damage was classified using the EPUAP system: 12 were moisture lesions, one was a grade 4 pressure ulcer (extensive tissue destruction / necrosis) and one was a combination of a moisture lesion and a grade 1 pressure lesion (non-blanchable erythema). Both pressure ulcers had a histological pattern suggesting ischemic pathology; the histology of the moisture lesions, however, was either of an ischemic or irritation pattern. Because of the overlap in histology patterns of some of the moisture lesions and the pressure ulcers, the authors concluded that there is no justification for classifying moisture lesions separately from pressure ulcer lesions.` This finding requires further study as there are several limitations of their study. First, the true aetiology of the skin damage and the veracity of the EPUAP classification were not determined; some moisture lesions seem to be partially over a bony prominence so that a mix of pressure and moisture damage cannot be ruled out, which might explain the mixed histology patterns. Secondly, the moisture lesions and the pressure ulcer were both described as having blanchable erythema.

Identification of moisture lesions as distinct from pressure ulcers is sought as a way to solve the tension between inadequate prevention / treatment of a pressure ulcer and inappropriate use of costly prevention relieving devices / measures. It is also of importance in determining care quality. Pressure ulcers are deemed as quality indicators in many countries and are considered to be preventable. Facilities may not be allowed to charge for the care and treatment of patients who develop pressure ulcers and may also be fined. The 'correct' classification of IAD and pressure ulcers therefore has financial and reputational implications.

Fader et al. [629], examined the effects of absorbent continence pads on mattress interface pressures using an articulated model or "phantom" as the subject and found that the presence of a pad significantly and substantially (around 20%) increased the peak pressures recorded between the buttocks and the pad / mattress. Peak pressures were frequently found at the locations of pad creases and it was considered that pad folding and compression may contribute to raised interface pressures. It is therefore possible that continence product use contributes to the formation of pressure ulcers by raising interface pressures.

Black et al. (2011) [579] have categorized IAD as distinct from pressure ulcers as shown in **Table XIV.2**

2. CLINICAL STUDIES OF THE IMPACT OF PRODUCTS AND PRODUCT MATERIALS ON SKIN HEALTH

In the 1980s, product manufacturers introduced diapers with super-absorbent polymers (SAP), which were designed to reduce skin wetness, buffer pH and reduce urine / faecal contact in order to help prevent diaper dermatitis. This led to clinical and laboratory studies to evaluate the efficacy of diapers with different materials, in particular, super-absorbent polymers (SAP) compared to those without, and compared to conventional washable diapers.

a) Quality of data

There are three types of studies testing the effects of different products or product materials on skin health: (i) clinical trials of normal infants wearing diapers; (ii) laboratory wet patch testing of adult forearms with diaper or continence pad patches; and (iii) clinical trials of adult absorbent pads containing different materials. The infant diaper studies were randomised controlled trials with large samples and blind measurement of outcomes. It should be noted that these studies were carried out by industry-employed staff. The infant and laboratory studies used a probe comprising two hygrosensors and thermistors (an evaporimeter) placed on the 'wet' skin to measure trans-epidermal water loss (TEWL), an indicator of skin hydration level. However, there is uncertainty about the optimum procedures for measuring TEWL, and different procedures and outcomes were used in the studies, making it difficult to compare results. Probably the most important threat to the validity of these studies is the selection of products or materials used in the study. None of the studies adequately described the products used - in particular, regarding their total absorbency. Thus it is possible that an alternative explanation for the fairly consistent findings that disposable pads with

Table XIV-2: Differentiation of IAD Versus Stage I and II Pressure Ulcers

Factors	IAD	Stage I Pressure Ulcers	Stage II Pressure Ulcers
History of condition	Exposure to urine or stool	Exposure to pressure, shear and/or microclimate from immobility or inactivity	Exposure to pressure, shear and/or microclimate from immobility or inactivity
Location of affected skin	Skin folds in areas where urine or stool can accumulate	Skin usually over bony prominences or exposed to other external pressure (eg, medical device)	Skin usually over bony prominences or exposed to other external pressure (eg, medical device)
Colour of wound bed	Shiny, red, glistening, no slough in wound bed	Nonblanchable erythema of intact skin	Shiny pink or red open wound, no slough in wound bed
Colour of periwound tissue	Red, irritated, edematous	Normal for race/ethnicity, edema may be palpable	Normal for race/ethnicity, edema may be palpable
Characteristics of involved area	Blotchy, not uniform in appearance	Tend to be single areas of erythema	Tend to be single ulcers with distinct ulcer wound margin
Pain	Burning, itching and tingling	Sharp pain, usually no itching; pain may intensify when patient is initially moved off of injured areas	Sharp pain, usually no itching; pain may intensify when patient is initially moved off of injured areas
Odour	Urine, faecal odour	None	None unless infected and then may have odour of infecting organism
Other	Candidiasis common (seen as satellite lesions)	Redness tends to resolve with offloading or repositioning of device	Ulcer bed is shallow and heals through epithelialization

SAP perform better on skin outcome measures may be that those with SAP simply had greater absorbency than those without.

b) Results

1. Clinical studies of infant diapers

Campbell and colleagues [630] conducted four clinical studies involving 1,614 infants randomly assigned to either disposable diapers with SAP, disposable diapers without SAP or washable cloth diapers. Disposable diapers with SAP were associated with significantly reduced skin wetness as measured by TEWL, lower pH and lower ratings of diaper dermatitis when compared to the two other diaper products (Level of Evidence 2).

Lane et al., [631] randomised disposable diapers without SAP and disposable diapers with SAP to 149 newborn infants and assessed their skin condition seven times over a 14 week period. Skin rash ratings were significantly lower for infants wearing diapers with SAP at only one time period (14 weeks) (Level of Evidence 2).

Davis and colleagues [632] assessed 150 infants over 15 weeks in a cross-over study involving four different disposable diaper types, two with different levels of SAP and two with different levels of fluff pulp only. Both diapers containing SAP were associated with significantly less skin wetness and significantly lower pH. Clinical skin ratings showed significantly lower ratings for the SAP-containing pads compared to the lower weight fluff pulp pad, but not compared to the higher weight fluff pad (Level of Evidence 2).

2. Laboratory studies of diaper patches

Wilson and Dallas [633] used the adult normal volar forearm skin model to compare patches taken from 16 different infant diapers. They found that disposable diapers containing SAP left the skin significantly drier than washable diapers and disposable diapers without SAP ($p<0.01$). Disposable diapers without SAP did not differ significantly from reusable diapers and there were no significant differences between products within any of the three groupings (Level of Evidence 2).

However, in a subsequent study involving 20 disposable and washable adult incontinence pads incorporating a similar range of materials to the baby diaper study Dallas and Wilson [634] found significant differences between products within each of the three product groupings but not between groupings (Level of Evidence 2). Grove et al. [635] used a similar approach to compare three infant diapers and found a significant difference in skin wetness between two that contained similar quantities of SAP ($p<0.001$). The one in which the SAP was in a layer near the water-proof backing kept the skin dryer than that in which it was near the coverstock. The third diaper – which had a microporous (breathable) backing kept the skin significantly dryer than each of the other two ($p<0.001$) (Level of Evidence 2).

3. Clinical studies of adult absorbent products

There has been one clinical study of adult incontinent patients comparing underpads with and without SAP, diapers with and without SAP and washable cloth underpads and which used skin condition as the primary outcome variable [22]. This study included 166 incontinent patients (urine, faeces or both) from three acute care facilities who were divided into the five groups. It is unclear whether randomisation to group occurred by patient or by facility. One facility used the washable cloth underpads only for their patients. Other patients tested either diapers or underpads and crossed-over from without SAP to with SAP products after six weeks. Skin measurements were made for colour, integrity and symptoms using rating scales. Both blind and non-blind measurements were made.

Findings were rather complex and difficult to interpret and no corrections for multiple comparisons

appear to have been made. Overall there were no differences in skin measurements between the diaper and underpad groups but - for some measurement sub-groups - differences were found with mean colour scores being significantly higher (worse) in the without-SAP diaper group and the washable cloth underpad group. Blinded 'worst' skin colour scores were highest for without-SAP diapers and washable cloth underpads and lowest for with-SAP products. Overall the findings supported the favourable effects of SAP on skin health but, as with the infant diaper studies, total absorbency of the products was not reported (Level of Evidence 2).

Hu et al. [66] randomised an unnamed range of disposable insert pads with mesh pants to 34 nursing home residents who were matched (based on incontinence severity) with 34 residents who received the usual reusable cloth diaper product. Skin condition was rated at baseline and after the five week intervention period by a blinded nurse researcher. Skin condition was reported to be significantly better in the disposable pad group (Level of Evidence 2).

More recently Beguin and colleagues (2010) [636] tested a modified diaper design (incorporating a top layer of specialised cellulose – beneath the top sheet – to maintain skin pH, and air-permeable side panels to minimise skin occlusion) in a small study of 12 patients using a pre-post test design. Skin pH was significantly lower when patients used the modified diaper and 8 out of 12 patients had resolution of pre-existing skin lesions. A larger more robust trial would be needed to establish any important clinical benefit.

3. CLINICAL STUDIES OF SKIN-CARE PRODUCTS AND NURSING PRACTICES TO MAINTAIN OR IMPROVE SKIN HEALTH

The skin of incontinent people requires frequent cleansing to remove urine and / or faeces. Soap and water is in common use [637] but it is known that repeated exposure to anionic surfactants (common in soaps) results in skin irritation [638] [639]. In addition, the action of washing is also considered likely to contribute to mechanical damage of the stratum corneum.

Cleansing of skin soiled with urine and / or faeces should occur immediately if possible or promptly after episodes of incontinence [640] [641] [642] [643] [644] [579] [575]. In addition, an individualized schedule for cleansing the perineum according to patients' needs or preferences [645] [646] [575] [579] or at routine intervals, such as daily or at bath time [647] [576] [640] [642] [648] has been recommended (Level of Evidence 3).

The practice of cleansing or wiping the perineum front to back is recommended as standard practice in the literature - particularly for women [649] [650] [651] [652] [653]; this recommendation is based on the physiological rationale of lowering presumed risk of contaminating the urethra with faecal bacteria and subsequent urinary tract infection [653]. One retrospective study of pregnant women found a significantly higher association of urinary tract infections in women who self-reported they wiped back to front (25.8%) than among those who wiped front to back (18.5%) [654] (Level of Evidence 2).

To minimize friction damage of the skin during the perineal cleansing process, gentle cleansing and patting dry the skin [655] [656] rather than rubbing or using a soft cloth is recommended by clinical experts [616] [657] [576] [643] [644] [658] [659] [659] (Level of evidence 4).

However there is some evidence that drying the skin by patting may be less effective than gentle towel drying or drying with a hair dryer [660]. Damp skin is more vulnerable to friction damage and special care may therefore be needed to ensure that the skin is dry. For already damage skin, there are clinical anecdotes of using a small hand-held hair-dryer set on a low and cool setting rather than drying with a cloth. Further research into cleaning and drying techniques and products is encouraged.

Alternative cleansers are available which have been formulated with the intention of overcoming some of the limitations of soap and water. Although overhydration of skin is detrimental, an excessively dry stratum corneum develops cracks and fissures and can be as ineffective a barrier as an over hydrated one [583]. Soap has a high pH (9.5-11) [661] and under laboratory conditions skin that has been exposed to high pH solutions has been found to have increased stratum corneum swelling and other signs of skin damage. However, there is a lack of controlled clinical trials comparing standard (high pH) soap with pH neutral soap or cleansers.

Many modern cleansers are designed to be used without water [i.e. 'no-rinse') and are designed to provide a less aggressive skin environment than soap (e.g. lower pH) but this may compromise their effectiveness in cleaning the skin of urine and faeces. This question has been addressed by Ronner et al, (2010) [662] who compared soap and water and a no-rinse cleanser in terms of their ability to remove escherichia coli and staphylococcus aureus. This laboratory study employed volunteer volar forearms and found low level and comparable levels of residual bacteria on the skin.

The use of topical products aiming to prevent or treat skin irritation is common but there is a lack of standardisation in definitions and descriptions of products, which makes comparisons difficult. Products such as 'moisturisers' or 'barriers' may be applied to the skin after cleansing, and some cleansers also incorporate moisturisers. The aim of moisturisers (also known as emollients) is to hydrate the skin by reducing trans-epidermal water loss through occlusion (e.g. petrolatum), by drawing

water into the stratum corneum by the addition of a humectant (a hygroscopic substance, e.g. glycerol) or by adding water in the applied water-miscible product. These modes of action are often combined in the same product, but there are exceptions - such as petrolatum - which only work by occlusion [663]. Some products are designed specifically to prevent penetration of water into the stratum corneum ('barrier' products) such as liquid skin sealants containing polymers, and may allow trans-epidermal water loss whilst preventing external water penetration. Simple occlusive products such as petrolatum may also act as barrier products to water but also occlude trans-epidermal water loss.

The application of skin barriers is recommended on areas that would come in contact with leaked urine and / or faeces. In general these areas include the buttocks and perianal area, groin, and inner thighs. Community-living persons report leaking small amounts of faeces that remain between the buttocks. Clinically, nursing staff have observed seepage of faeces around a rectal catheter in hospitalized patients. In both groups, perianal skin protection is important, and skin barriers are recommended (Level of evidence 4).

Topical creams are commonly used to prevent and treat dermatitis but controlled experiments to assess efficacy on human and animal skin have produced equivocal results. Ghadially et al. [663] showed that barrier recovery (measured by TEWL) on experimentally irritated skin was accelerated by the application of petrolatum and De Paepe K et al. [664] showed similar results using a different moisturising cream. Hannuksela and Kinnunen [665] showed that treatment with moisturisers prevented the development of irritation in an experiment involving frequent skin washing with liquid detergent. However, Gabard [666] was unable to demonstrate significant acceleration of barrier recovery to chronically irritated skin following application of different moisturisers using a chronic irritation model and also found that some creams enhanced irritation.

The efficacy of barrier products in preventing water penetration of the skin has been tested in laboratory settings. Vinson and Proch [667] applied wet patches with a water-soluble marker to skin coated with three different barrier products and measured dye extracted from the skin by absorbance spectrophotometry. One multiple barrier product performed significantly better than a petrolatum-based and an allantoin-based protectant. Waring and Hoggarth [668] used a Chromameter to measure skin colour change after staining skin with a water-soluble dye, covering it with a barrier product and washing the skin. Petrolatum products were found to be more effective barriers than dimethicone-based products. In a later study, Hoggarth et al. [669] investigated the barrier function and skin hydration properties of six skin protectants when applied to the volar forearms of 18 healthy volunteers. The researchers found that each had different performance properties with the water-in-oil products containing petrolatum performing better than the oil-in-water products containing dimethicone for protection against irritation or maceration. However the dimethicone products had higher hydration properties compared to the petrolatum products. Overall the water-in-oil petrolatum-based product was the only product to be efficacious for all performance variables. A limitation of some petrolatum-based moisture barriers compared to a non-alcohol barrier film for individuals wearing absorbent pads or briefs is that the petrolatum-based products have been shown to transfer from the skin onto the absorbent product and reduce fluid update by 54% to 90%. [605]. However this has not been tested in clinical trials and the effects of different topical products on the leakage performance of absorbent pads is unknown.

Other practices that may affect skin health include frequency of pad changing. Increasing pad changing may reduce skin wetness by application of a dry pad and may therefore benefit skin health. Increased pad changing is commonly recommended to prevent or treat dermatitis particularly in infants [670] Level of Evidence 4.

a) Quality of data

Several studies of skin cleansing and / or moisturising / barrier products to prevent perineal dermatitis have been limited by being uncontrolled [614] [671] [604] [672] and of small size and lacking adequate power calculations [673] [674] [602], or not including any clinical outcome measures [673]. Measurement of dermatitis may also have been compromised by reactive hyperaemia on skin areas subject to pressure. Only four randomised controlled trials of a skin cleansing regimes to prevent perineal dermatitis could be found, and two RCTs of products to treat dermatitis. Two trials focused on the costs of barrier products use. In addition there was one randomised crossover trial of pad changing frequency.

b) Results

1. Skin cleansing / moisturising products to prevent dermatitis

Byers et al. [673] compared four different cleansing / moisturising regimes including soap and water using a multiple cross-over design. Despite having a very small sample size (n = 12 elderly women) they found statistically significant differences in TEWL, pH and erythema between some of the regimes, and soap and water was found to be the least effective product for skin health. No clinical outcomes were measured and differences in outcomes were small (Level of Evidence 2).

Beeckman et al, 2011 [609] randomised 141 nursing home residents to receive standard cleansing with pH neutral soap and water with the use of a

3-in-1 perineal care washcloth impregnated with a 3% dimethicone skin protectant over a period of 120 days. Skin health was measured using the IAD skin condition assessment tool. Although no differences in the severity of IAD were found there were substantial differences in prevalence of IAD (experimental: 8.1% versus control: 27.1%, F = 3.1, p=0.003) (Level of Evidence 2).

Cleansing products

Cooper and Gray [657] randomised 93 long-term elderly subjects to skin cleansing with soap and water or with a foam cleanser over a 14 day period and blindly assessed perineal skin photographs at zero, seven and 14 days. The skin of 37% of subjects using soap and water remained 'healthy' compared to 66% of subjects using the foam cleanser. However, statistical analysis was not carried out (Level of Evidence 3).

Lewis-Byers et al. [658] randomised 32 nursing home residents with incontinence to a soap and water or no-rinse cleanser regime over a period of three weeks. No significant differences in skin condition were found but no power calculations were included (Level of Evidence 3).

Taken together, the evidence from these trials indicate that specialised cleansers may be better than soap and water for skin health, although there is still a need for further robust clinical trials. Reported staff opinion tends to favour specialised cleansers rather than soap and water and there may also be cost savings [614] [673] [674] [658] although the reliability and validity of the health economic analyses carried out to date has been questioned by Beeckman (2009) [581].

Costs of barrier products to prevent dermatitis

Zehrer et al. [605] compared the cost and efficacy of three incontinence skin barrier products in 250 nursing home residents from four facilities. A polymer-based barrier film was used either once daily or three times weekly, and one of two petrolatum ointments was used after each episode of incontinence. Residents were monitored for skin damage for six months. There were no significant differences in effectiveness among the various barrier film and ointment protocols of care. Time and motion measures were used to determine the costs of the products and associated nursing labour. Daily cost of barrier product ranged from $0.17 for the barrier film applied three times per week to $0.76 for a petrolatum ointment applied after each incontinent episode. When nursing staff labour to apply the barrier products was included in the cost analysis, costs increased from $0.26 per day for the less frequently applied barrier film to $1.40 per day for the more frequently applied petrolatum ointments (Level of Evidence 3).

Bliss et al. [616] randomly selected 16 nursing homes to compare the cost and effectiveness of four skin damage prevention regimens. In three of the four skin prevention regimens, a moisture barrier ointment or cream of different compositions (43% petrolatum; 98% petrolatum; and 12% zinc oxide + 1% dimethicone) was applied after each episode of incontinence, while in the fourth, a polymer-based alcohol-free barrier film was applied three times per week. All regimens used a pH-balanced, moisturizing cleanser of the same manufacturer as the barrier. Time and motion measures were documented for the amount of skin care products used, the number, type, and time of caregivers performing IAD prevention care, and the number and type of supplies used. Compared to the three regimens in which a barrier was applied after each episode of incontinence, the use of a regimen in which a barrier film was applied three times weekly had significantly lower costs for the barrier product, labour associated with barrier application, and total cost which included products, labour, and supplies. There were also savings in total product (cleanser and barrier) and total labour costs. The total cost was lowest for the regimen using the barrier film compared to the other regimens in which a barrier needed to be applied after each episode of incontinence. The total cost savings ranged from $ 0.40 to $0.85 per episode of incontinence (Level of Evidence 2).

Although both these studies demonstrated cost savings when using barrier-film products such savings are dependent on relatively infrequent application of the barrier-film product. This may be achieved by assigning product application to care staff on particular shifts but uncontrolled use of such products may be expensive.

2. Skin products to treat dermatitis

In a double blind controlled trial of 64 subjects, Anthony et al. [675] compared the efficacy of cream formulated to treat dermatitis (Sudocrem) with zinc cream BP. Thirty subjects showed inflammatory lesions of the buttocks and a significantly greater proportion of subjects allocated to Sudocrem showed reduction in skin redness at both seven days and 14 days. No differences were found in the prevention of inflammatory lesions between the two groups. Skin measurements were made over the ischial tuberosities but the effect of reactive hyperaemia was not accounted for. There was no control group receiving no skin treatment and therefore it was not possible to establish the efficacy of using cream as treatment per se (Level of Evidence 2).

Baatenburg de Jong & Admiraal [676] determined the cost of treating moderate to severe IAD in 39 nursing home patients in the Netherlands randomly assigned to treatment with a non-stinging barrier film or zinc oxide oil. The barrier film was applied every 48 - 72 hours for less severe skin damage and 24 - 48 hours for more severe damage. Zinc oxide oil was applied twice per day and after each episode of incontinence. Both barriers reduced IAD but the no-sting barrier film was significantly associated

with reduced severity of skin redness and skin loss, although skin assessments were not blinded. The cost per day of the nursing staff labour in the regimen using the barrier film was €68.58 (sd = € 23.61) compared to €88.20 (sd = €22.88) in the regimen using the zinc oxide oil The total cost (including barrier, labor and supplies) per day of the regimen using the barrier film (€76.13, sd = €25.48) was also less than for the regimen using the zinc oxide oil (€102.96, sd = €23.25) (Level of Evidence 2).

3. Pad changing frequency

Fader et al. [629] investigated the effect of different frequency of night-time pad changing on 81 incontinent nursing / residential home subjects from 20 homes. Following a two week baseline period, subjects were randomised by home to pad changing at 22.00 and 06.00 for four weeks followed by 22.00, 02.00 and 06.00 for four weeks, or vice versa. Blinded skin measurements of instrumental erythema (using an erythema meter), visual rating, trans-epidermal water loss and pH were made at baseline and during the last two weeks of each regime with instrumental erythema measurements used as the primary outcome variable. Trans-epidermal water loss measurements were significantly higher when pads were changed less frequently (22.00 and 06.00) indicating that skin was wetter. No other significant differences were found. However, five subjects developed stage II pressure ulcers in the less frequent pad changing regime compared to none in the frequent pad changing regime. Although more frequent pad changing did not demonstrate less dermatitis / erythema, the pressure ulcer findings - though non-significant - make it unwise to conclude that less frequent pad changing does not damage skin health (Level of Evidence 2).

4. SUMMARY

- Incontinence-associated dermatitis is a common problem amongst absorbent product users (**Level of Evidence 2**).
- Skin wetness overhydrates skin and potentiates the effects of other irritants (**Level of Evidence 2**).
- Faecal incontinence is more irritating than urinary incontinence, but the combined effects of urine and faeces are particularly damaging to skin (**Level of Evidence 2**).
- Absorbent pads containing super absorbent polymers are associated with reduced skin wetness (**Level of Evidence 3**).
- Wet skin is more vulnerable to friction and abrasion injury (**Level of Evidence 2**).
- Pressure ulcers are associated with urinary and faecal incontinence (**Level of Evidence 2**).
- Bodyworn absorbent products may raise interface pressures measured under the buttocks (**Level of Evidence 3**).
- There are indications that skin cleansers may be more cost-effective than soap and water (**Level of Evidence 3**) and may be better for skin health (**Level of Evidence 2**).
- Barrier skin products may impede water penetration into the stratum corneum (**Level of Evidence 3**).
- A regular and structured skin care regimen using topical preparations such as moisturisers or barrier creams is associated with a low incidence of perineal dermatitis (**Level of evidence 4**).
- More frequent pad changing has not been shown to prevent dermatitis, but less frequent pad changes may be associated with pressure ulcers (**Level of Evidence 3**).

5. RECOMMENDATIONS

- Absorbent pads with SAP should be selected in preference to those without (**Grade of Recommendation B**).
- Absorbent pads should be changed regularly to minimise skin wetness (**Grade of Recommendation C**).
- Patients with faecal or double incontinence should be changed as soon as possible after incontinence has occurred to prevent the development of dermatitis from protease and lipase activity (**Grade of Recommendation B**).
- Patients should be washed gently at times of pad change with either soap and water or cleansers. Cleanser may be less time-consuming than soap and water (**Grade of Recommendation C**).
- Skin barrier products should be applied to areas that potentially come in contact with leaked urine and / or faeces (**Grade of Recommendation D**)
- Barrier products may be applied to skin within the pad area to reduce water penetration of the skin (**Grade of Recommendation C**).
- Buttock and sacral areas should be protected using topical skin barrier products, containment products or diversion devices in patients vulnerable to IAD or pressure ulcers (**Grade of Recommendation C**).

6. PRIORITIES FOR RESEARCH

- Controlled randomized trials that investigate the effectiveness of skin care products or skin care regimes to prevent or treat perineal skin damage due to urinary and faecal incontinence are recommended. Trials which

aim to test the comparative effects of different cleansing regimes, different barrier products and use of barrier products compared to careful cleansing are needed in particular. Such studies should determine appropriate sample sizes using power analyses. Analyses need to be powered to distinguish effects on participants with faecal or double incontinence. Objective measures from instruments, standardized clinical assessments, and patient symptom ratings should be included.

- Laboratory-based studies on healthy volunteers are recommended to help select products and establish potential efficacy of products before undertaking RCTs.
- Further work is needed to examine the relationship between IAD and pressure ulcers, in particular the potential and/or methods to discriminate between them, including use of biomarkers and technology.
- Studies to identify markers or ways of discriminating between pressure ulcers and IAD are required. Trials to test the comparative effectiveness of different skin cleansing regimes are needed as are trials to determine whether skin barrier products deliver benefits over careful cleansing alone and, if they do, which work best.

XV. ODOUR CONTROL PRODUCTS

Fear of smelling is a major concern that preoccupies many people suffering from incontinence and it is an issue that has been raised in several qualitative studies that have explored the subjective opinion of the patient eg [677] [678] [5]. Accordingly, there is a demand for products which will mask odour or, preferably, prevent it.

1. PRODUCTS FOR URINARY INCONTINENCE

Fresh, infection-free urine smells only slightly but bacterial action on urea over time yields pungent smelling ammonia.

A variety of anti-microbial solutions are available for washing such products as hand-held urinals or for treating urine spillage onto soft furnishings such as carpets. They aim to prevent smell by destroying the bacteria responsible for break down of urea. There are no robust published studies that have sought to evaluate such products. Another approach is to mask the smell of stale urine using a strong but (hopefully) pleasant smelling liquid. There are no robust published studies on such products either but anecdotal evidence suggests that, in time, the masking smell comes to be associated with the incontinence that it is intended to disguise. Several companies supply products (washable bedpads, carpets, chairs, clothing and bed linen) made with fabrics that have been treated with anti-microbial agents intended to reduce the smell of any urine on or in them. However, again, there have been no robust published studies to investigate efficacy.

One of the 12 disposable bodyworn pads for lightly incontinent women evaluated by Clarke-O'Neill et al. [18] was treated with a lavender scent but it was not found to perform significantly better than the other products in terms of preventing smell. However, the scent was appreciated by 18% of the 50 test subjects, who commented favourably on it.

2. PRODUCTS FOR FAECAL INCONTINENCE

Odour associated with faecal incontinence may occur from involuntarily leaked stool or flatus. In a study with subjects eating a self-selected diet, Moore et al. [679] identified the volatile chemicals primarily responsible for faecal odours as the methyl sulphides: methanethiol, dimethyl disulphide, and dimethyl trisulphide. Hydrogen sulphide was thought to make a smaller contribution. In a subsequent study with persons consuming a bolus of pinto beans and lactulose (a non-absorbable carbohydrate) Suarez et al. [680] attributed the odour of flatus to the sulphur compounds, hydrogen sulphide, methanethiol, and dimethyl sulphide. The intensity of the odour in flatus was related to the concentration of the sulphur-containing compounds: the ability of the human nose to recognise malodorous odour appears to be related to the amount of gas expelled [680]. Different states of health and gastrointestinal function, diet composition, relative concentrations of sulphide gases and, possibly, short chain fatty acids or ammonia are expected to contribute to the odour of faeces and flatus [679] and [680].

There are several commercially available devices that are designed to absorb the odour of flatus. One such product originally called the "Toot Trapper" and renamed the "Flatulence Filter" (UltraTech products, Inc., Houston, TX, USA) is a cushion or pad (which can be placed directly against the anus) that is lined with activated charcoal. Both the cushion and pad are encased in either a washable or a disposable cover. There are similar products by other manufacturers (e.g., Flat-D by Flat-D Innovations, Inc., Iowa, USA and GasMedic and GasBGon by Dairiair and manufactured by ECVC, Greenville, NC, USA). Pads comprising fabric covered activated charcoal that can be worn next to the anus or attached to a brief (GasMedic underair pad by Dairiair and Flat-D, Flat-D Innovations, Inc., Cedar Rapids, IA). There is also underwear (briefs) entirely made of covered activated carbon cloth (Underease protective underwear (UltraTech Products, Inc., Houston, TX). Ohge at el. [681] compared the effectiveness of

11 devices containing activated carbon in six normal adults (50% female) under controlled conditions in absorbing odoriferous rectal gases. Five types of seat cushions, four types of pads, and two types of briefs (one that held a pad next to the anus and one made of activated carbon fiber fabric) were tested. A mixture gas comprising 100 ml of nitrogen with traces of hydrogen sulphide (40 ppm), methylmercaptan (40 ppm) and hydrogen (5,000 ppm) was instilled into the rectum of the subjects via a rectal tube. Since hydrogen does not react with charcoal, the amount of unabsorbed sulphide was determined from the ratio of sulphide to hydrogen collected from the pantaloons relative to the ratio in the instilled gas. The subjects wore mylar pantaloons that were sealed at the thighs and waist with elastic bandages to reduce convection to the air.

The subjects' clothing, apart from any device, absorbed approximately 22% of sulphide gas. The cushions absorbed an amount comparable to usual clothing, 20%. The various pads and the brief with an attached pad held near the anus absorbed 55-77% of the rectal gas. The underwear made of charcoal fabric was the most effective and removed nearly all (95-99%) of the sulphide gas. The charcoal fabric briefs are reusable and the charcoal is allegedly regenerable with heat. There are no reports of any odour absorbing devices being evaluated in persons with faecal incontinence. In vitro studies showed that each device had the capability of absorbing the rectal gases and that their performance efficiency depended on contact between the charcoal element and gas. Briefs entirely made of activated charcoal fabric appear to provide the greatest surface area for contact with malodorous rectal gas. The absorption of odorous gas by clothing suggests that washing outer clothing as well as underwear is important to reduce odour.

Some products aim to reduce the amount of malodorous flatus that is produced. Administration of the probiotic, Lactobacillus plantarum, (5 x 10^7 cfu/ml) in a randomized trial of 60 patients with IBS significantly reduced flatulence (by half in 44% of patients). Only 18% of the placebo group reported reductions of flatulence [682]. Although administration of charcoal, yucca and zinc acetate reduced the percentage of episodes of malodorous gas [683], there are inconsistent findings about reductions in flatulence from ingesting activated charcoal in humans [165] [684]. Two clinical trials involving small sample sizes (19 and eight persons, respectively) showed that the over-the-counter product, Beano, which contains α-galactosidase, reduced flatus frequency in normal persons following the ingestion of beans [685] [686]. A significant reduction in cumulative breath hydrogen excretion over an 8-hour period after α-galactosidase versus placebo suggests α-galactosidase reduces flatus production [686]. Although Ganiats et al., 1994 [685] reported a significant decrease in flatus using 240 galactosidic units (GalU), Di Stefano reported that effects of 1200 GalU but not 300 GalU were significantly different from placebo. One GalU is the amount of galactosidase that releases 1 μmol of galactose from its substrate in one minute [686]. Differences in the test diet or lack of adequate statistical power may explain these differences since neither study reported a power analysis. Although a reduction in the amount of intestinal gas produced may decrease the volume of odour, it may not decrease its potency or perceived odour.

A few products are available that aim to prevent, absorb, or control odour associated with involuntarily leaked stool or flatus associated with faecal incontinence. These include cushions and pads that absorb odour as well as probiotics and enzymes, which aim to reduce production of malodorous gas.

3. RECOMMENDATIONS

- Briefs made of activated charcoal fabric are recommended over pads or cushions containing activated charcoal for absorbing odoriferous rectal gas (**Grade of Recommendation C**).
- Since some pads absorb up to 75% of gas, there may be value in offering patients who have smaller amounts of gas the opportunity to compare pads and briefs for themselves. (**Grade of Recommendation D**).
- For those persons experiencing stool leakage due to flatus, over-the-counter α-galactosidase containing products, which reduce flatus frequency, can be tried in an attempt to reduce FI frequency (**Grade of Recommendation B**).
- Washing of outer as well as under clothing after flatus is recommended to reduce odour due to absorption of gas by clothing (**Grade of recommendation of C**).

4. PRIORITIES FOR RESEARCH

- Investigation of whether probiotics or changes in dietary intake can modulate or reduce the odour of flatulence or leaked faeces.
- Development of an absorbent product that can reduce the odour of leaked faeces while protecting the skin.
- Investigation of the efficacy of anti-microbial agents in textile products (soft furnishings and bedding) for reducing odour associated with urinary and faecal incontinence.

REFERENCES

1. Fonda D, Abrams P. Cure sometimes, help always--a "continence paradigm" for all ages and conditions. Neurourol Urodyn 2006;25(3):290-2.
2. Cottenden A, Bliss D, Fader M, Getliffe K, Paterson J, Herreras H, et al. Management with continence products. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. 3rd International Consultation on Incontinence. Health Publications Ltd; 2005.
3. Paterson J. Stigma associated with post-prostatectomy urinary incontinence. Journal of Wound, Ostomy and Continence Nursing 2000;27(3):168-73.
4. Mitteness LS, Barker JC. Stigmatizing a "normal" condition: urinary incontinence in late life. Med Anthropol Q 1995 Jun;9(2):188-210.
5. Paterson J, Dunn S, Kowanko I, van LA, Stein I, Pretty L. Selection of continence products: perspectives of people who have incontinence and their carers. Disability & Rehabilitation 25(17):955-63, 2003 Sep 2.
6. Gibb H, Wong G. How to choose: nurses' judgements of the effectiveness of a range of currently marketed continence aids. J Clin Nurs 1994 Mar;3(2):77-86.
7. Proudfoot LM, Farmer ES, McIntosh JB. Testing incontinence pads using single-case research designs. Br J Nurs 1994 Apr 14;3(7):316, 318-20, 322.
8. Shaw C, Tansey R, Jackson C, Hyde C, Allan R. Barriers to help seeking in people with urinary symptoms. Fam Pract 2001 Feb;18(1):48-52.
9. Hocking C. Function or feelings: factors in abandonment of assistive devices. Technology and Disability 1999;(11):3-11.
10. Low J. Negotiating identities, negotiating environments: an interpretation of the experiences of students with disabilities. 1996;11(2):235-248. Disability and society 1996;11(2):235-48.
11. Phillips B, Zhao H. Predictors of assistive technology abandonment. Assist Technol 1993;5(1):36-45.
12. McMillen A-M, Soderberg S. Disabled persons' experience of dependence on assistive devices. Scandinavian Journal of Occupational Therapy 2002;(9):176-83.
13. Koch T, Kralik D, Eastwood S, Schofield A. Breaking the silence: women living with multiple sclerosis and urinary incontinence. Int J Nurs Pract 2001 Feb;7(1):16-23.
14. Fader M, Cottenden A, Brooks R. The CPE network: creating an evidence base for continence product selection. J Wound Ostomy Continence Nurs 2001 Mar;28(2):106-12.
15. Clancy B, Malone-Lee J. Reducing the leakage of bodyworn incontinence pads. J Adv Nurs 1991 Feb;16(2):187-93.
16. Thornburn P, Fader M, Dean G, Brooks R, Cottenden A. Improving the performance of small incontinence pads: a study of "wet comfort". J Wound Ostomy Continence Nurs 1997 Jul;24(4):219-25.
17. Armitage P, Berry G. Statistical methods in medical research. 3rd ed. Oxford; 1994.
18. Clarke-O'Neill S, Pettersson L, Fader M, Cottenden A, Brooks R. A multicenter comparative evaluation: disposable pads for women with light incontinence. Journal of Wound, Ostomy, & Continence Nursing 31(1):32-42, 2004 Jan;-Feb.
19. Getliffe K, Fader M, Cottenden A, Jamieson K, Green N. Absorbent products for incontinence: 'treatment effects' and impact on quality of life. Journal of Clinical Nursing 16(10):1936-45, 2007 Oct.
20. Macaulay M, Clarke-ONeill S, Fader M, Pettersson L, Cottenden A. Are washable absorbents effective at containing urinary incontinence? Nursing Times 100(12):58-62, 2004 Mar 23;-29.
21. Fader M, Pettersson L, Dean G, Brooks R, Cottenden AM, Malone-Lee J. Sheaths for urinary incontinence: a randomized crossover trial. BJU Int 2001 Sep;88(4):367-72.
22. Brown DS. Diapers and underpads, Part 1: Skin integrity outcomes. Ostomy Wound Manage 1994 Nov;40(9):20-6, 28.
23. Fader M, Pettersson L, Dean G, Brooks R, Cottenden A. The selection of female urinals: results of a multicentre evaluation. Br J Nurs 1999 Jul 22;8(14):918-5.
24. McIntosh J. A guide to female urinals. Nurs Times 2001 Feb 8;97(6):VII-VIX.
25. Macaulay M, Clarke-O'Neill S, Cottenden A, Fader M, van den HE, Jowitt F. Female urinals for women with impaired mobility. Nursing Times 102(42):42-3, 45, 47, 2006 Oct 17;-23.
26. Vickerman J. The benefits of a lending library for female urinals. Nursing Times 99(44):56-7, 2003 Nov 4;-10.
27. Vickerman J. Selecting urinals for male patients. Nursing Times 102(19):47-8, 2006 May 9;-15.
28. Macaulay M, van den HE, Jowitt F, Clarke-O'Neill S, Kardas P, Blijham N, et al. A noninvasive continence management system: development and evaluation of a novel toileting device for women. Journal of Wound, Ostomy, & Continence Nursing 34(6):641-8, 2007 Nov;-Dec.
29. Pomfret I, Vickerman J, Tonge P. Introducing a handheld urinal service in secondary care. Nursing Times 101(18):68, 70-1, 2005 May 3;-9.
30. Matsumoto M, Inoue K. Predictors of institutionalization in elderly people living at home: the impact of incontinence and commode use in rural Japan. J Cross Cult Gerontol 2007 Dec;22(4):421-32.
31. Fader M. Access to toilets and toileting. In: Potter J, Norton C, Cottenden C, editors. Bowel care in older people: research and practice.London: Royal College of Physicians; 2002.
32. Nazarko L. Commode design for frail and disabled people. Prof Nurse 1995 Nov;11(2):95-7.
33. Medical Devices Agency. Basic commodes: a comparative evaluation. 1994.
34. Fader MJ, Pettersson L, Clinton L, Dean G, Brooks R, Cottenden A. Basic commodes: a comparative evaluation. Medical Devices Agency; 2004. Report No.: A5.
35. Ballinger C, Pain H, Pascoe J, Gore S. Choosing a commode for the ward environment. Br J Nurs 1996 Apr 25;5(8):485-500.
36. Gillan J. Seat of the motions. Nursing Times 1999;95:26.
37. Bucior H, Cochrane J. Lifting the lid: a clinical audit on commode cleaning. Journal of Infection Prevention 2010.
38. Naylor JR, Mulley GP. Commodes: inconvenient conveniences. BMJ 1993 Nov 13;307(6914):1258-60.
39. Nelson A, Malassigne P, Amerson T, Saltzstein R, Binard J. Descriptive study of bowel care practices and equipment in spinal cord injury. SCI Nurs 1993 Jun;10(2):65-7.
40. Malassigne P, Nelson A, Amerson T, Salzstein R, Binard J. Toward the design of a new bowel care chair for the spinal cord injured: a pilot study. SCI Nurs 1993 Aug;10(3):84-90.
41. Nelson AL, Malassigne P, Murray J. Comparison of seat pressures on three bowel care/shower chairs in spinal cord injury. SCI Nurs 1994 Dec;11(4):105-7.
42. Malassigne P, Nelson AL, Cors MW, Amerson T. Design of the advanced commode-shower chair for spinal cord injured individuals. Journal of rehabilitiation research and development 1995;37:373-82.
43. Wells M. Managing urinary incontinence with BioDerm external continence device. British Journal of Nursing 2008.
44. MacIntosh J. Realising the potential of urinals for women. Journal of Community Nursing 1998;12(8):14-8.
45. Fader M, Barnes E, Malone-Lee J, Cottenden A. Continence. Choosing the right garment. Nurs Times 1987 Apr 15;83(15):78-85.

46. Teunissen TAM, Lagro-Janssen ALM. Sex differences in the use of absorbent (incontinence) pads in independently living elderly people: do men receive less care? Int J Clin Pract 2009.

47. Chartier-Kastler E, Ballanger P, Petit J, Fourmarier M, Bart S, Ragni-Ghazarossian E, et al. Randomized, crossover study evaluating patient preference and the impact on quality of life or urisheaths versus absorbent products in incontinent men. BJU International 2011.

48. Cottenden AM, Fader MJ, Pettersson L, Clinton L, Dean GE, Malone-Lee J, et al. Disposable, shaped bodyworn pads with pants for heavy incontinence. London, UK: Medical Devices Agency; 1998. Report No.: IN1.

49. Clarke-O'Neill S, Fader MJ, Pettersson L, Clinton L, Dean G, Malone-Lee J, et al. Disposable pads for light incontinence. London, UK: Medical Devices Agency; 2002. Report No.: IN9.

50. Omli R, Skotnes LH, Romild U, Bakke A, Mykletun A, Kuhry E. Pad per day usage, urinary incontinence and urinary tract infections in nursing home residents. Age & Ageing 2010.

51. Hellstrom L, Ekelund P, Larsson M, Milsom I. Adapting incontinent patients incontinence aids to their leakage volumes. Scand J Caring Sci 1993;7(2):67-71.

52. Aumônier S, Collins M. Life cycle assessment of disposable and reusable nappies in the UK. London: Environmental Agency; 2005.

53. International Standards Organization. ISO 11948-1: Urine-absorbing aids Part 1: Whole product testing. Geneva: International Standards Organization; 1996. 1996.

54. Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, et al. Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product designs. Health Technol Assess 2008 Jul;12(29):iii-185.

55. Fader M, Cottenden AM, Getliffe K. Absorbent products for light urinary incontinence in women. Cochrane Database of Systematic Reviews 2007.

56. Clarke-O'Neill S, Pettersson L, Fader M, Dean G, Brooks R, Cottenden A. A multicentre comparative evaluation: washable pants with an integral pad for light incontinence. J Clin Nurs 2002 Jan;11(1):79-89.

57. Baker J, Norton P. Evaluation of absorbent products for women with mild to moderate urinary incontinence. Appl Nurs Res 1996 Feb;9(1):29-33.

58. Erekson EA, Meyer SA, Melick C, McLennan MT. Incontinence pads: recommending the best product-based wetback performance and price. Int Urogynecol J 2008.

59. Macaulay M, Pettersson L, Fader M, Brooks R, Cottenden A. Absorbent products for men with light incontinence: an evaluation. UK: Medical Devices Agency; 2005.

60. Brink CA. Absorbent pads, garments, and management strategies. J Am Geriatr Soc 1990 Mar;38(3):368-73.

61. Beber CR. Freedom for the incontinent. Am J Nurs 1980 Mar;80(3):482-4.

62. Grant R. Washable pads or disposable diapers? Geriatr Nurs 1982 Jul;3(4):248-51.

63. Haeker S. What's best--reusable or disposable incontinence products? Text Rent 1986 May;69(9):86-91.

64. Dolman M. Continence. The cost of incontinence. Nurs Times 1988 Aug 3;84(31):67-9.

65. Prevalence of hospital-acquired infections in Spain. EPINE Working Group. J Hosp Infect 1992 Jan;20(1):1-13.

66. Hu TW, Kaltreider DL, Igou J. The cost-effectiveness of disposable versus reusable diapers. A controlled experiment in a nursing home. J Gerontol Nurs 1990 Feb;16(2):19-24.

67. Harper DW, O'Hara PA, Lareau J, Cass J, Black EK, Stewart S, et al. Reusable versus disposable incontinent briefs: a multiperspective crossover clinical trial. Journal of Applied Gerontology 1995;14(4):391-407.

68. Merrett S, Adams L, Jordan J. Incontinence research provides some answers. Aust Nurses J 1988 Aug;18(2):17-8.

69. Brown DS. Diapers and underpads, Part 2: Cost outcomes. Ostomy Wound Manage 1994 Nov;40(9):34-6, 38, 40.

70. Hu TW, Kaltreider DL, Igou J. Incontinence products: which is best? Geriatr Nurs 1989 Jul;10(4):184-6.

71. Hu TW, Kaltreider DL, Igou JF. Disposable versus reusÐ able incontinent products: a controlled cost-effectiveness experiment. Ostomy Wound Manage 1988;21:46-53.

72. Fader MJ, Pettersson L, Clinton L, Dean GE, Brooks RD, Cottenden AM. Disability Equipment Assessment Report, Disposable, shaped bodyworn pads with pants for heavy incontinence: an evaluation. Medical Devices Agency (UK); 1998. Report No.: IN.1.

73. Fader MJ, Pettersson L, Clinton L, Dean GE, Brooks RD, Cottenden AM. Disability Equipment Assessment Report, All-in-one disposable bodyworn pads for heavy incontinence. Medical Devices Agency (UK); 1999. Report No.: IN.4.

74. Cottenden AM, Ledger DJ. Predicting the leakage performance of bodyworn disposable incontinence pads using laboratory tests. J Biomed Eng 1993 May;15(3):212-20.

75. Cottenden AM, Fader MJ, Pettersson L, Brooks RJ. How well does ISO 11948-1 (the Rothwell method) for measuring the absorption capacity of incontinence pads in the laboratory correlate with clinical pad performance. Medical Engineering & Physics 25(7):603-13, 2003 Sep.

76. Cottenden AM, Rothwell JG, Leander H, Grau C, Brooks RJ. An investigation of the repeatability and reproducibility of ISO 11948-1 (the Rothwell method) for measuring the absorption capacity of incontinence pads. Med Eng Phys 2002 Mar;24(2):159-63.

77. Henderson DJ, Rogers WF. Hospital trials of incontinence underpads. Nurs Times 1971 Feb 4;67(5):141-3.

78. Thornburn P, Cottenden A, Ledger D. Continence. Undercover trials. Nurs Times 1992 Mar 25;88(13):72-8.

79. Bradbury SM. Incontinence pads and clostridium infection. J Hosp Infect 1985 Mar;6(1):115.

80. Leigh DA, Petch VJ. Sterility of incontinence pads and sheets. J Hosp Infect 1987 Jan;9(1):91-3.

81. Sprott MS, Kearns AM, Keenlyside D. A microbiological study of absorbent pads. J Hosp Infect 1988 Aug;12(2):125-9.

82. Stansfield R, Caudle S. Bacillus cereus and orthopaedic surgical wound infection associated with incontinence pads manufactured from virgin wood pulp. J Hosp Infect 1997 Dec;37(4):336-8.

83. Cottenden AM. Aids and appliances for incontinence. The promotion and management of continence. Prentice Hall; 1992.

84. Leiby DM, Shanahan N. Clinical study: assessing the performance and skin environments of two reusable underpads. Ostomy Wound Manage 1994 Oct;40(8):30-7.

85. Cottenden AM, Moore KN, Fader MJ, Cremer AW. Is there a risk of cross-infection from laundered reusable bedpads? Br J Nurs 1999 Sep 23;8(17):1161-3.

86. Lukeman D. Mainly children: childhood enuresis and encopresis. In: Getliffe K, Dolman M, Tindall B, editors. Promoting continence: A clinical and research resource. London: Bailliere Tindall; 1997. p. 138.

87. Macaulay M, Pettersson L, Fader M, Brooks R, Cottenden A. A multicenter evaluation of absorbent products for children with incontinence and disabilities. Journal of Wound, Ostomy, & Continence Nursing 31(4):235-44, 2004 Jul;-Aug.

88. Bliss DZ, Savik K. Use of an absorbent dressing specifically for fecal incontinence. Journal of Wound, Ostomy, & Continence Nursing 35(2):221-8, 2008 Mar;-Apr.

89. Potter PJ. Disordered control of the urinary bladder after

human spinal cord injury: what are the problems? Prog Brain Res 2006;152:51-7.

90. Pomfret I. Penile sheaths: a guide to selection and fitting. Journal of Community Nursing 2006;20(11):14-8.

91. Bycroft J, Hamid R, Shah PJ. Penile erosion in spinal cord injury--an important lesson. Spinal Cord 41(11):643-4, 2003 Nov.

92. Fetsch JF, Davis CJ, Jr., Hallman JR, Chung LS, Lupton GP, Sesterhenn IA. Lymphedematous fibroepithelial polyps of the glans penis and prepuce: a clinicopathologic study of 7 cases demonstrating a strong association with chronic condom catheter use. Hum Pathol 2004 Feb;35(2):190-5.

93. Potter J. Male urinary incontinence-could penile sheaths be the answer? Journal of Community Nursing 2007;21(5):4042.

94. Pemberton P, Brooks A, Eriksen CM, Frost S, Graham S, Greenman L, et al. A comparative study of two types of urinary sheath. Nursing Times 102(7):36-41, 2006 Feb 14;-20.

95. Golji H. Complications of external condom drainage. Paraplegia 1981;19(3):189-97.

96. Jayachandran S, Mooppan UM, Kim H. Complications from external (condom) urinary drainage devices. Urology 1985 Jan;25(1):31-4.

97. Hirsh DD, Fainstein V, Musher DM. Do condom catheter collecting systems cause urinary tract infection? JAMA 1979 Jul 27;242(4):340-1.

98. Johnson JR, Roberts PL, Olsen RJ, Moyer KA, Stamm WE. Prevention of catheter-associated urinary tract infection with a silver oxide-coated urinary catheter: clinical and microbiologic correlates. J Infect Dis 1990 Nov;162(5):1145-50.

99. Ouslander JG, Greengold B, Chen S. External catheter use and urinary tract infections among incontinent male nursing home patients. J Am Geriatr Soc 1987 Dec;35(12):1063-70.

100. Al-Awadhi NM, Al-Brahim N, Ahmad MS, Yordanov E. Giant fibroepithelial polyp of the penis associated with long-term use of condom catheter. Case report and literature review. Canadian Journal of Urology 14(4):3656-9, 2007 Aug.

101. Saint S, Kaufman SR, Rogers MA, Baker PD, Ossenkop K, Lipsky BA. Condom versus indwelling urinary catheters: a randomized trial. Journal of the American Geriatrics Society 54(7):1055-61, 2006 Jul.

102. Nichols T, Balis N. Male External Urinary Catheter Design Survey. 2000 Jun 4; 2000.

103. Peifer DJ, Hanover RY. Clinical evaluation of the easy-flow catheter. J Rehabil Res Dev 1997 Apr;34(2):215-9.

104. Thelwell S, Symon C, Gay S, Dean G, Cottenden A, Feneley R. Penile sheaths: a comparative evaluation. UK: Medical Devices Agency; 1995 Nov. Report No.: A15.

105. Watson R, Kuhn M. The influence of component parts on the performance of urinary sheath systems. J Adv Nurs 1990 Apr;15(4):417-22.

106. Goldyn V, Buck R, Chenelly S. Two incontinence management devices: the benefits of the “incontinence bag” and the freedom catheter. Ostomy Wound Manage 1992 Mar;38(2):28-35.

107. Saint S, Lipsky BA, Baker PD, McDonald LL, Ossenkop K. Urinary catheters: what type do men and their nurses prefer? J Am Geriatr Soc 1999 Dec;47(12):1453-7.

108. Pomfret I. Back to basics: urinary sheaths. Journal of Community Nursing 2003;17(10).

109. Pomfret IJ. Catheters: design, selection and management. Br J Nurs 1996 Feb 22;5(4):245-51.

110. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the infectious diseases society of America. Clinical Infectious Diseases 2010.

111. Garcia MM, Gulati S, Liepmann D. Traditional Foley drainage systems-do they drain the bladder? J Urol 2007;177(1):203-7.

112. Pinar K, Moore KN, Smits E, Murphy K, Schopflocher D. Leg Bag Comparison Reported Skin Health, Comfort, and Satisfaction. Journal of Wound, Ostomy and Continence Nursing 2009.

113. Kennedy AP, Brocklehurst JC, Lye MD. Factors related to the problems of long-term catheterization. J Adv Nurs 1983 May;8(3):207-12.

114. Wilson M, Coates D. Infection control and urine drainage bag design. Prof Nurse 1996 Jan;11(4):245-9, 251.

115. Fader M, Thelwell S, Symon C, Gay S, Cottenden A, Dean G, et al. Sterile 500ml leg bags for urine drainage: a multi-centre comparative evaluation. UK: Medical Devices Agency; 1996 Feb. Report No.: A20.

116. Fader M, Pettersson L, Clinton L, Dean G, Brooks R, Cottenden A. Non-sterile 500ml - 700ml leg bags for urine drainage: an evaluation. UK: Medical Devices Agency; 1999 Feb. Report No.: IN2.

117. Thelwell S, Symon C, Gay S, Cottenden A, Feneley R. Continence. Systems for leg bags. Nurs Times 1995 Apr 19;91(16):62-4.

118. Munnings LJ, Cawood CD. Clinical study of a new urine collection bag. Urologic Nursing 23(4):287-91, 2003 Aug.

119. Garcia MF, Knight SL, Greenwell T, Mundy AR, Craggs MD. “Flowsecure” artificial urinary sphincter: a new adjustable artificial urinary sphincter concept with conditional occlusion for stress urinary incontinence]. [Spanish]. Actas Urologicas Espanolas 31(7):752-8, 2007 Jul;-Aug.

120. Wong ES. Guideline for prevention of catheter-associated urinary tract infections. Am J Infect Control 1983 Feb;11(1):28-36.

121. Lowthian P. The dangers of long-term catheter drainage. Br J Nurs 1998 Apr 9;7(7):366-8, 370, 372.

122. Pratt RJ, Pellowe CM, Wilson JA, Loveday HP, Harper PJ, Jones SR, et al. epic2: National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. J Hosp Infect 2007 Feb;65 Suppl 1:S1-64.

123. Roe BH, Reid FJ, Brocklehurst JC. Comparison of four urine drainage systems. J Adv Nurs 1988 May;13(3):374-82.

124. Platt R, Polk BF, Murdock B, Rosner B. Reduction of mortality associated with nosocomial urinary tract infection. Lancet 1983 Apr 23;1(8330):893-7.

125. Rogers J, Norkett D, Bracegirdle P, Dowsett AB, Walker JT, Brooks T. Examination of biofilm formation and risk of infection associated with the use of urinary catheters with leg bags. The Journal of Hospital Infection 1996.

126. Wilde MH, Brasch J, Getliffe K, Brown KA, McMahon JM, Smith JA, et al. Study on the use of long-term urinary catheters in community-dwelling individuals. Journal of Wound, Ostomy and Continence Nursing 2010.

127. Keerasuntonpong A, Thearawiboon W, Panthawanan A, Judaeng T, Kachintorn K, Jintanotaitavorn D, et al. Incidence of urinary tract infections in patients with short-term indwelling urethral catheters: a comparison between a 3-day urinary drainage bag change and no change regimens. Am J Infect Control 2003 Feb;31(1):9-12.

128. Hardyck C, Petrinovich L. Reducing urinary tract infections in catheterized patients. Ostomy Wound Management 1998.

129. Thompson RL, Haley CE, Searcy MA, Guenthner SM, Kaiser DL, Groschel DH, et al. Catheter-associated bacteriuria. Failure to reduce attack rates using periodic instillations of a disinfectant into urinary drainage systems. JAMA 1984 Feb 10;251(6):747-51.

130. Lo E, Nicolle L, Classen D, Arias KM, Podgorny K, Anderson DJ, et al. Strategies to prevent catheter-associated urinary tract infections in acute care hospitals. Infection Control & Hospital Epidemiology 2008.

131. Smith PW, Bennett G, Bradley S, Drinka P, Lautenbach E, Marx J, et al. SHEA/APIC guideline: infection prevention and control in the long-term care facility. Infection Control & Hospital Epidemiology 2008.

132. Ostaszkiewicz J, Paterson J. Nurses' Advice Regarding Sterile or Clean Urinary Drainage Bags for Individuals With a Long-term Indwelling Urinary Catheter. Journal of Wound, Ostomy, & Continence Nursing 2012.

133. Madigan E, Neff DF. Care of patients with long-term indwelling urinary catheters. Online Journal of Issues in Nursing 8(3):7, 2003.

134. Dille CA, Kirchhoff KT, Sullivan JJ, Larson E. Increasing the wearing time of vinyl urinary drainage bags by decontamination with bleach. Arch Phys Med Rehabil 1993 Apr;74(4):431-7.

135. Hashisaki P, Swenson J, Mooney B, Epstein B, Bowcutt C. Decontamination of urinary bags for rehabilitation patients. Arch Phys Med Rehabil 2012.

136. Rooney M. Impacting health care: study of a reusable urinary drainage system. SCI Nurs 1994 Mar;11(1):16-8.

137. Glenister H. The journal of infection control nursing. The passage of infection. Nurs Times 1987 Jun 3;83(22):68-73.

138. Wenzler-Rottele S, Dettenkofer M, Schmidt-Eisenlohr E, Gregersen A, Schulte-Monting J, Tvede M. Comparison in a laboratory model between the performance of a urinary closed system bag with double non-return valve and that of a single valve system. Infection 34(4):214-8, 2006 Aug.

139. Tsumura H, Satoh T, Kurosaka S, Fujita T, Matsumoto K, Baba S. Clinical characteristics in patients with purple urine bag syndrome. Hinyokika Kiyo Acta Urologica Japonica 2008.

140. Mantani N, Ochiai H, Imanishi N, Kogure T, Terasawa K, Tamura J. A case-control study of purple urine bag syndrome in geriatric wards. J Infect Chemother 2003 Mar;9(1):53-7.

141. Jones S, Brooks A, Foxley S, Dunkin J. Care of urinary catheters and drainage systems. Nursing Times 103(42):48-50, 2007 Oct 16;-22.

142. Hudson L, McNicoll D. Simpla Plus leg bag: approval by the National Customer Group. British Journal of Nursing 12(8):505-6, 508-10, 2003 Apr 24;-May.

143. Pieper B, Cleland V, Johnson DE, O'Reilly JL. Inventing urine incontinence devices for women. Image J Nurs Sch 1989;21(4):205-9.

144. Lipp A SCGK. Mechanical devices for urinary incontinence in women. Cochrane Database of Systematic Reviews 2011.

145. Eckford SD, Jackson SR, Lewis PA, Abrams P. The continence control pad--a new external urethral occlusion device in the management of stress incontinence. Br J Urol 1996 Apr;77(4):538-40.

146. Brubaker L, Harris T, Gleason D, Newman D, North B. The external urethral barrier for stress incontinence: a multicenter trial of safety and efficacy. Miniguard Investigators Group. Obstet Gynecol 1999 Jun;93(6):932-7.

147. Versi E, Harvey MA. Efficacy of an external urethral device in women with genuine stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1998;9(5):271-4.

148. Moore KH, Simons A, Dowell C, Bryant C, Prashar S. Efficacy and user acceptability of the urethral occlusive device in women with urinary incontinence. J Urol 1999 Aug;162(2):464-8.

149. Tincello DG, Bolderson J, Richmond DH. Preliminary experience with a urinary control device in the management of women with genuine stress incontinence. Br J Urol 1997 Nov;80(5):752-6.

150. Tincello DG, Adams EJ, Bolderson J, Richmond DH. A urinary control device for management of female stress incontinence. Obstet Gynecol 2000 Mar;95(3):417-20.

151. Bellin P, Smith J, Poll W, Bogojavlensky S, Knoll D, Childs S, et al. Results of a multicenter trial of the CapSure (Re/Stor) Continence shield on women with stress urinary incontinence. Urology 1998 May;51(5):697-706.

152. Shinopulos NM, Dann JA, Smith JJ, III. Patient selection and education for use of the CapSure (Re/Stor) continence shield. Urol Nurs 1999 Jun;19(2):135-40.

153. Dunn M, Brandt D, Nygaard I. Treatment of exercise incontinence with a urethral insert: a pilot study. The Physician and Sports Medicine 2002 Jan;30(1).

154. Balmforth J, Cardozo LD. Trends toward less invasive treatment of female stress urinary incontinence. Urology 2003 Oct;62(4 Suppl 1):52-60.

155. Nielsen KK, Walter S, Maegaard E, Kromann-Andersen B. The urethral plug II: an alternative treatment in women with genuine urinary stress incontinence. Br J Urol 1993 Oct;72(4):428-32.

156. Nielsen K, Walter S, Maegaard E, Kromann-Andersen B. The urethral plug : an alternative treatment of women with urinary stress incontinence. (Danish). Ugeskrift for Laeger 1995;157(22):3194-7.

157. Peschers U, Zen RF, Schaer GN, Schussler B. [The VIVA urethral plug: a sensible expansion of the spectrum for conservative therapy of urinary stress incontinence?]. Geburtshilfe Frauenheilkd 1996 Mar;56(3):118-23.

158. Staskin D, Bavendam T, Miller J, Davila GW, Diokno A, Knapp P, et al. Effectiveness of a urinary control insert in the management of stress urinary incontinence: early results of a multicenter study. Urology 1996 May;47(5):629-36.

159. Miller JL, Bavendam T. Treatment with the Reliance urinary control insert: one-year experience. J Endourol 1996 Jun;10(3):287-92.

160. Sand PK, Staskin D, Miller J, Diokno A, Sant GR, Davila GW, et al. Effect of a urinary control insert on quality of life in incontinent women. Int Urogynecol J Pelvic Floor Dysfunct 1999;10(2):100-5.

161. Robinson J. Purple urinary bag syndrome: a harmless but alarming problem. British Journal of Community Nursing 8(6):263-6, 2003 Jun.

162. Boos K, Anders K, Hextall A, Tooz-Hobson P, Cardozo L. Randomised trial of Reliance versus FemAssist devices in the management of genuine stress incontinence. Neurourology & Urodynamics 1998;17(4):455-6.

163. Nygaard I. Prevention of exercise incontinence with mechanical devices. J Reprod Med 1995 Feb;40(2):89-94.

164. Realini JP, Walters MD. Vaginal diaphragm rings in the treatment of stress urinary incontinence. J Am Board Fam Pract 1990 Apr;3(2):99-103.

165. Suarez GM, Baum NH, Jacobs J. Use of standard contraceptive diaphragm in management of stress urinary incontinence. Urology 1991 Feb;37(2):119-22.

166. Bhatia NN, Bergman A. Pessary test in women with urinary incontinence. Obstet Gynecol 1985 Feb;65(2):220-6.

167. Richter HE, Burgio K, Brubaker L, Nygaard IE, Ye W, Weidner A, et al. A Trial of Continence Pessary versus Behavioral Therapy versus Combined Therapy for Stress Incontinence. Obstet Gynecol 2010.

168. Cameron A, Wallner L, Tate DG, Sarma S, Rodriguez G, Clemens JQ. Bladder management after spinal cord injury in the United States 1972 to 2005. Journal of Urology 2010.

169. Gorti M, Hudelist G, Simons A. Evaluation of vaginal pessary management: a UK-based survey. Journal of Obstetrics and Gynaecology 2009.

170. Biswas NC. A silastic vaginal device for the treatment of genuine stress incontinence. Neurourology & Urodynamics 1988;(7):271-2.

171. Davila GW, Neal D, Horbach N, Peacher J, Doughtie JD, Karram M. A bladder-neck support prosthesis for women with stress and mixed incontinence. Obstet Gynecol 1999 Jun;93(6):938-42.

172. Kondo A, Yokoyama E, Koshiba K, Fukui J, Gotoh M, Yoshikawa Y, et al. Bladder neck support prosthesis: a nonoperative treatment for stress or mixed urinary incontinence. J Urol 1997 Mar;157(3):824-7.

173. Morris A, Moore KH. The Contiform incontinence device - efficacy and patient acceptability. Int Urogynecol J Pelvic Floor Dysfunct 2003.

174. Allen WA, Leek H, Izurieta A, Moore KH. Update: the 'Contiform' intravaginal device in four sizes for the treatment of stress incontinence. International Urogynaecology Journal and Pelvic Floor Dysfunction 2008.

175. Thyssen H, Lose G. New disposable vaginal device (continence guard) in the treatment of female stress incontinence. Design, efficacy and short term safety. Acta Obstet Gynecol Scand 1996 Feb;75(2):170-3.

176. Thyssen H, Sander P, Lose G. A vaginal device (continence guard) in the management of urge incontinence in women. Int Urogynecol J Pelvic Floor Dysfunct 1999;10(4):219-22.

177. Sander P, Thyssen H, Lose G, Andersen JT. Effect of a vaginal device on quality of life with urinary stress incontinence. Obstet Gynecol 1999 Mar;93(3):407-11.

178. Hahn I, Milsom I. Treatment of female stress urinary incontinence with a new anatomically shaped vaginal device (Conveen Continence Guard). Br J Urol 1996 May;77(5):711-5.

179. Thyssen H, Bidmead J, Lose G, Moller BK, Dwyer P, Cardozo L. A new intravaginal device for stress incontinence in women. BJU Int 2001 Dec;88(9):889-92.

180. Glavind K. Use of a vaginal sponge during aerobic exercises in patients with stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1997;8(6):351-3.

181. Ziv E, Stanton SL, Abarbanel J. Significant improvement in the quality of life in women treated with a novel disposable intravaginal device for stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2009.

182. Farage M, Aronstein W, Miller KW, Karram M, Katz M, Hertzman B. A Disposable Intravaginal Device for the Management of Stress Urinary Incontinence. The open women's health journal 2011.

183. Ziv E, Stanton SL, Abarbanel J. Efficacy and safety of a novel disposable intravaginal device for treating stress urinary incontinence. American Journal of Obstetrics & Gynecology 2008.

184. Chye PLH. The management of post prostatecetomy incontinence. 1990.

185. Fantl JA, Newman D, Colling J. Managing Acute and Chronic Urinary Incontinence. Clinical Prcatice Guideline. 1996. Report No.: 2.

186. Moore KN, Schieman S, Ackerman T, Dzus HY, Metcalfe JB, Voaklander DC. Assessing comfort, safety, and patient satisfaction with three commonly used penile compression devices. Urology 63(1):150-4, 2004 Jan.

187. Maki DG, Tambyah PA. Engineering out the risk for infection with urinary catheters. Emerg Infect Dis 2001 Mar;7(2):342-7.

188. Lapides J, Diokno AC, Silber SJ, Lowe BS. Clean, intermittent self-catheterization in the treatment of urinary tract disease. Trans Am Assoc Genitourin Surg 1971;63:92-6.

189. Eckstein HB. Intermittent Catheterisation of the bladder in patients with neuropathic incontinence of urine. Z Kinderchir Grenzgeb 1979 Dec;28(4):408-12.

190. Bray L, Sanders C. Teaching children and young people intermittent self-catheterization. Urol Nurs 2007 Jun;27(3):203-9, 242.

191. Moore KN, Fader M, Getliffe K. Long-term bladder management by intermittent catheterisation in adults and children. Cochrane Database Syst Rev 2007;(4):CD006008.

192. Niel-Weise BS, van den Broek PJ. Urinary catheter policies for short-term bladder drainage in adults. Cochrane Database of Systematic Reviews (3):CD004203, 2005.

193. Niel-Weise BS, van den Broek PJ. Urinary catheter policies for short-term bladder drainage in adults. Cochrane Database of Systematic Reviews (3):CD004203, 2005.

194. Jamison J, Maguire S, McCann J. Catheter policies for management of long term voiding problems in adults with neurogenic bladder disorders (Cochrane Review). The Cochrane Library 2011;(4).

195. Fowler C. Bladder Problems. Letchworth, UK: MS Research Trust; 1998.

196. Burgdorfer H, Heidler H, Madersbacher H. Manual neurourology and spinal cord lesion: guidelines for urological care of spinal cord injury patient. Parco-Pharma Gmbh 1987.

197. Orikasa S, Koyanagi T, Motomura M, Kudo T, Togashi M. Experience with non-sterile intermittent self-catheterization. J Urol 1976 Feb;115(2):141-2.

198. Carver M. Adaptive Equipment to Assist With One-Handed Intermittent Self-Catheterization: A Case Study of a Patient With Multiple Brain Injuries. The American Journal of Occupational Therapy 2012.

199. Vahter L, Zopp L, Kreegipuu M, Kool P, Talvik T, Gross-Paju K. Clean intermittent self-catheterization in persons with multiple sclerosis: the influence of cognitive dysfunction. Multiple Sclerosis 2008.

200. Pohl HG, Bauer SB, Borer JG, Diamond DA, Kelly MD, Grant R, et al. The outcome of voiding dysfunction managed with clean intermittent catheterization in neurologically and anatomically normal children. BJU Int 2002 Jun;89(9):923-7.

201. Pilloni S, Krhut J, Mair D, Madersbacher H, Kessler TM. Intermittent catheterisation in older people: a valuable alternative to an indwelling catheter? Age Ageing 2005 Jan;34(1):57-60.

202. Cutright J. The effect of the bladder scanner policy on the number of urinary catheters inserted. Journal of Wound, Ostomy and Continence Nursing 2011.

203. Witjes JA, Del Popolo G, Marberger M., Jonsson O, Kaps HP, Chapple CR. A Multicenter, Double-Blind, Randomized, Parallel Group Study Comparing Polyvinyl Chloride and Polyvinyl Chloride-Free Catheter Materials. The Journal of Urology 2009.

204. Gray M. Are all urethral catheters created equal? Journal of Urology 2009.

205. Howard M. U.S. Medicare policy change in catheter guidelines Improves patient care in home and hospice setting. Caring 2009.

206. Wilde MH, Brasch J, Yi Zhang. A qualitative descriptive study of self-management issues in people with long-term intermittent urinary catheters. Journal of Advanced Nursing 2011.

207. Biering-Sorensen F, HansenH, Nielsen PN, Looms D. Residual urine after intermittent catheterization in females using two different catheters. Scandinavian Journal of Urology & Nephrology 2007.

208. De Ridder DJ, Everaert K, Fernandez LG, Valero JV, Duran AB, Abrisqueta ML, et al. Intermittent catheterisation with hydrophilic-coated catheters (SpeediCath) reduces the risk of clinical urinary tract infection in spinal cord injured patients: a prospective randomised parallel comparative trial. Eur Urol 2005 Dec;48(6):991-5.

209. Wyndaele JJ. Intermittent catheterization: which is the optimal technique? Spinal Cord 2002 Sep;40(9):432-7.

210. Lapides J, Diokno AC, Lowe BS, Kalish MD. Followup on unsterile intermittent self-catheterization. J Urol 1974 Feb;111(2):184-7.

211. Dromerick AW, Edwards DF. Relation of postvoid residual to urinary tract infection during stroke rehabilitation. Arch Phys Med Rehabil 2003 Sep;84(9):1369-72.

212. Campbell JB, Moore KN, Voaklander DC, Mix LW. Complications associated with clean intermittent catheterization in children with spina bifida. J Urol 2004 Jun;171(6 Pt 1):2420-2.

213. Ku JH, Jung TY, Lee JK, Park WH, Shim HB. Influence of bladder management on epididymo-orchitis in patients with spinal cord injury: clean intermittent catheterization is a risk factor for epididymo-orchitis. Spinal Cord 2006 Mar;44(3):165-9.

214. Cameron A, Wallner L, Forcheimer M, Clemens JQ, Dunn RL, Rodriguez G, et al. Medical and psychosocial complications associated with method of bladder management after traumatic spinal cord injury. Arch Phys Med Rehabil 2011.

215. Zegers BSHJ, Winkler-Seinstra PLH, Uiterwaal CSPM, de Jong TVPM, Kimpen JLL, de Jong-de Vos van Steenwijk CCE. Urinary tract infections in children with spina bifida: an inventory of 41 European centers. Pediatric Nephrology 2008.

216. Raz R, Schiller D, Nicolle LE. Chronic indwelling catheter replacement before antimicrobial therapy for symptomatic urinary tract infection. J Urol 2000 Oct;164(4):1254-8.

217. Biering-Sorensen F, Nielans HM, Dorflinger T, Sorensen B. Urological situation five years after spinal cord injury. Scand J Urol Nephrol 1999 Jun;33(3):157-61.

218. Penders J, Huylenbroeck AA, Everaert K, Van LM, Verschraegen GL. Urinary infections in patients with spinal cord injury. Spinal Cord 2003 Oct;41(10):549-52.

219. Cardenas DD, Hoffman JM. Hydrophilic catheters versus noncoated catheters for reducing the incidence of urinary tract infections: a randomized controlled trial. Arch Phys Med Rehabil 2012.

220. Cardenas DD, Moore KN, Dannels-McClure A, Scelza WM, Graves DE, Brooks M, et al. Intermittent catheteriM zation with a hydrophilic-coated catheter delays urinary tract infections in acute spinal cord injury: a prospective, randomized, multicenter trial. PM&R The journal of injury, function and rehabilitation 2011.

221 . Niel-Weise BS, van den Broek PJ. Antibiotic policies for short-term catheter bladder drainage in adults. Cochrane Database Syst Rev 2005;(3):CD005428.

222. Woodbury MG, Hayes KC, Askes HK. Intermittent catheterization practices following spinal cord injury: a national survey. Can J Urol 2008 Jun;15(3):4065-71.

223. Schlager TA, Anderson S, Trudell J, Hendley JO. Effect of cranberry juice on bacteriuria in children with neurogenic bladder receiving intermittent catheterization. J Pediatr 1999 Dec;135(6):698-702.

224. Waites KB, Canupp KC, Armstrong S, DeVivo MJ. Effect of cranberry extract on bacteriuria and pyuria in persons with neurogenic bladder secondary to spinal cord injury. J Spinal Cord Med 2004;27(1):35-40.

225. Wyndaele JJ, Maes D. Clean intermittent self-catheterization: a 12-year followup. J Urol 1990 May;143(5):906-8.

226. Perrouin-Verbe B, Labat JJ, Richard I, Mauduyt de IG, I, Buzelin JM, Mathe JF. Clean intermittent catheterisation from the acute period in spinal cord injury patients. Long term evaluation of urethral and genital tolerance. Paraplegia 1995 Nov;33(11):619-24.

227. Webb RJ, Lawson AL, Neal DE. Clean intermittent self-catheterisation in 172 adults. Br J Urol 1990 Jan;65(1):20-3.

228. Stensballe J, Looms D, Nielsen PN, Tvede M. Hydrophilic-coated catheters for intermittent catheterisation reduce urethral micro trauma: a prospective, randomised, participant-blinded, crossover study of three different types of catheters. Eur Urol 2005 Dec;48(6):978-83.

229. Vapnek JM, Maynard FM, Kim J. A prospective randomized trial of the LoFric hydrophilic coated catheter versus conventional plastic catheter for clean intermittent catheterization. J Urol 2003 Mar;169(3):994-8.

230. Sutherland RS, Kogan BA, Baskin LS, Mevorach RA. Clean intermittent catheterization in boys using the LoFric catheter. J Urol 1996 Dec;156(6):2041-3.

231. Michielsen DP, Wyndaele JJ. Management of false passages in patients practising clean intermittent self catheterisation. Spinal Cord 1999 Mar;37(3):201-3.

232. Vaidyanathan S, Soni BM, Dundas S, Krishnan KR. Urethral cytology in spinal cord injury patients performing intermittent catheterisation. Paraplegia 1994 Jul;32(7):493-500.

233. Lindehall B, Abrahamsson K, Jodal U, Olsson I, Sillen U. Complications of clean intermittent catheterization in young females with myelomeningocele: 10 to 19 years of followup. J Urol 2007 Sep;178(3 Pt 1):1053-5.

234. Hedlund H, Hjelmas K, Jonsson O, Klarskov P, Talja M. Hydrophilic versus non-coated catheters for intermittent catheterization. Scand J Urol Nephrol 2001 Feb;35(1):49-53.

235. Chen Y, DeVivo MJ, Lloyd LK. Bladder stone incidence in persons with spinal cord injury: determinants and trends, 1973-1996. Urology 2001 Nov;58(5):665-70.

236. Barroso U, Jednak R, Fleming P, Barthold JS, Gonzalez R. Bladder calculi in children who perform clean intermittent catheterization. BJU Int 2000 May;85(7):879-84.

237. Casey R, Cullen I, Crotty T, Quinlan D. Intermittent self-catheterization and the risk of squamous cell cancer of the bladder: An emerging clinical entity? Canadian Urological Association Journal 2009.

238. van AT, Holleman G, Cobussen-Boekhorst H, Arts R, Heesakkers J. Adherence to clean intermittent self-catheterization procedures: determinants explored. J Clin Nurs 2008 Feb;17(3):394-402.

239. Logan K, Shaw C, Webber I, Samuel S, Broome L. Patients' experiences of learning clean intermittent self-catheterization: a qualitative study. J Adv Nurs 2008 Apr;62(1):32-40.

240. Ramm D, Kane R. A qualitative study exploring the emotional responses of female patients learning to perform clean intermittent self-catheterisation. Journal of Clinical Nursing 2011.

241. Shaw C, Logan K, Webber I, Broome L, Samuel S. Effect of clean intermittent self-catheterization on quality of life: a qualitative study. J Adv Nurs 2008 Mar;61(6):641-50.

242. Vaidyanathan S, Soni BM, Singh G, Oo T, Hughes PL. Barriers to implementing intermittent catheterisation in spinal cord injury patients in Northwest Regional Spinal Injuries Centre, Southport, U.K. ScientificWorldJournal 2011.

243. Pannek J, Kullik B. Does optimizing bladder management equal optimizing quality of life? Correlation between health-related quality of life and urodynamic parameters in patients with spinal cord lesions. Urology 2009.

244. Lindehall B, Moller A, Hjalmas K, Jodal U, Abrahamsson K. Psychosocial factors in teenagers and young adults with myelomeningocele and clean intermittent catheterization. Scand J Urol Nephrol 2008.

245. Brillhart B. Internet education for spinal cord injury patients: Focus on urinary management. Rehabil Nurs 2007.

246. Kovindha A, Mai WN, Madersbacher H. Reused silicone catheter for clean intermittent catheterization (CIC): is it safe for spinal cord-injured (SCI) men? Spinal Cord 2004 Nov;42(11):638-42.

247. Kurtz MJ, Van ZK, Burns JL. Comparison study of home catheter cleaning methods. Rehabil Nurs 1995 Jul;20(4):212-4, 217.

248. Lavallee DJ, Lapierre NM, Henwood PK, Pivik JR, Best M, Springthorpe versus, et al. Catheter cleaning for re-use in intermittent catheterization: new light on an old problem. SCI Nurs 1995 Mar;12(1):10-2.

249. Sherbondy AL, Cooper CS, Kalinowski SE, Boyt MA, Hawtrey CE. Variability in catheter microwave sterilization techniques in a single clinic population. J Urol 2002 Aug;168(2):562-4.

250. Sekiguchi Y, Yao Y, Ohko Y, Tanaka K, Ishido T, Fujishima A, et al. Self-sterilizing catheters with titanium dioxide photocatalyst thin films for clean intermittent catheterization: basis and study of clinical use. Int J Urol 2007 May;14(5):426-30.

251. Shekelle PG, Morton SC, Clark KA, Pathak M, Vickrey BG. Systematic review of risk factors for urinary tract infection in adults with spinal cord dysfunction. J Spinal Cord Med 1999;22(4):258-72.

252. Johansson I, Athlin E, Frykholm L, Bolinder H, Larsson G. Intermittent versus indwelling catheters for older patients with hip fractures. J Clin Nurs 2002 Sep;11(5):651-6.

253. Turi MH, Hanif S, Fasih Q, Shaikh MA. Proportion of complications in patients practicing clean intermittent self-catheterization (CISC) versus indwelling catheter. J Pak Med Assoc 2006 Sep;56(9):401-4.

254. Patel MI, Watts W, Grant A. The optimal form of urinary drainage after acute retention of urine. BJU Int 2001 Jul;88(1):26-9.

255. Tang MW, Kwok TC, Hui E, Woo J. Intermittent versus indwelling urinary catheterization in older female patients. Maturitas 53(3):274-81, 2006 Feb 20.

256. Dixon L, Dolan L, Brown K, Hilton P. RCT of urethral vesus suprapubic catheterization. British Journal of Nursing 2010.

257. Naik R, Maughan K, Nordin A, Lopes A, Godfrey KA, Hatem MH. A prospective randomised controlled trial of intermittent self-catheterisation versus supra-pubic catheterisation for post-operative bladder care following radical hysterectomy. Gynecologic Oncology 99(2):437-42, 2005 Nov.

258. Bothig R, Hirschfeld S, Thietje R. Quality of life and urological morbidity in tetraplegics with artificial ventilation managed with suprapubic or intermittent catheterisation. Spinal Cord 2012.

259. Mody L, Maheshwari S, Galecki A, Kauffman CA, Bradley SF. Indwelling device use and antibiotic resistance in nursing homes: identifying a high-risk group. J Am Geriatr Soc 2007 Dec;55(12):1921-6.

260. Schumm K, Lam TBL. Types of Urethral Catheters for Management of Short-Term Voiding Problems in Hospitalized Adults: A Short Version Cochrane Review. Neurourology & Urodynamics 2008.

261. Zeif H, Subramonian K. Alpha blockers prior to removal of a catheter for acute urinary retention in adult men. Cochrane Database of Systematic Reviews 2009.

262. Griffiths R, Fernandez R. Policies for the removal of short-term indwelling urethral catheters. Cochrane Database of Systematic Reviews (2):CD004011, 2007.

263. Jahn P, Preuss M, Kernig A, Seifert-Huhmer A, Langer G. Types of indwelling urinary catheters for long-term bladder drainage in adults. Cochrane Database of Systematic Reviews (3):CD004997, 2007.

264. Niel-Weise BS, van den Broek PJ. Urinary catheter policies for long-term bladder drainage. Cochrane Database of Systematic Reviews (1):CD004201, 2005.

265. Hagen S, Sinclair L, Cross S. Washout policies in long-term indwelling urinary catheterisation in adults. Cochrane Database of Systematic Reviews 2010.

266. Fernandez R, Griffiths R. Clamping short-term indwelling catheters: a systematic review of the evidence. Journal of Wound, Ostomy, & Continence Nursing 2005.

267. Nyman MH, Johansson J, Gustafsson M. A randomised controlled trial on the effect of clamping the indwelling urinary catheter in patients with hip fracture. Journal of Clinical Nursing 2010.

268. relate with generic health-related quality of life and objective incontinence severity in women with stress urinary incontinence? Neurourology & Urodynamics 25(4):324-9; discussion 330, 2006.

269. Wilde M, Getliffe K, Brasch J, Mcmahon J, Anson E, Tu X. A new urinary catheter-related quality of life instrument for adults. Neurourology & Urodynamics 2010.

270. Saint S, Chenoweth CE. Biofilms and catheter-associated urinary tract infections. Infect Dis Clin North Am 2003 Jun;17(2):411-32.

271. Saint S, Meddings JA, Calfee D, Kowalski CP, Krein SL. Catheter-associated urinary tract infection and the Medicare rule changes. Annals of Internal Medicine 2009.

272. Curran E, Murdoch H. Aiming to reduce catheter associated urinary tract infections (CAUTI) by adopting a checklist and bundle to achieve sustained system improvements. Journal of Infection Prevention 2009.

273. Reilly L, Sullivan P, Ninni S, Fochesto D, Williams K, Fetherman B. Reducing foley catheter device days in an intensive care unit: using the evidence to change practice. AACN Advanced Critical Care 2006.

274. Elpern EH, Killeen K, Ketchem A, Wiley A, Patel G, Lateef O. Reducing use of indwelling urinary catheters and associated urinary tract infections. American Journal of Critical Care 2009.

275. Andreessen L, Wilde MH, Herendeen P. Preventing catheter-associated urinary tract infections in acute care: the bundle approach. journal of nursing care quality 2012.

276. Silva CV, Gonçalves P, Toniolo AR, Guastelli LR, Ribeiro Macedo RC, Moura DF, et al. Successful Strategies to Prevent Catheter-Associated Urinary Tract Infections in Critically Ill Patients using a Quality Tool. American Journal of Infection Control 2011.

277. Salamon L. Catheter associated urinary tract infections: A nurse-sensitive indicator in an inpatient rehabilitation program. Rehabil Nurs 2009.

278. Pischke VL, Salamon L, Reynolds S. Catheter-Associated Urinary Tract Infection (CAUTI) Surveillance in an Inpatient Rehabilitation (Rehab) Program: Baseline Data and Post Intervention Success. American Journal of Infection Control 2008.

279. Patrizzi K, Fasnacht A, Manno M. A collaborative, nurse-driven initiative to reduce hospital-acquired urinary tract infections. Journal of Emergency Nursing 2009.

280. Fakih MG, Pena ME, Shemes S, Rey J, Berriel-Cass D, Szpunar SM, et al. Effect of establishing guidelines on appropriate urinary catheter placement. Acad Emerg Med 2010.

281. Raffaele G, Bianco A, Aiello M, Pavia M. Appropriateness of use of indwelling urinary tract catheters in hospitalized patients in Italy. Infect Control Hosp Epidemiol 2008.

282. Loeb M, Hunt D, O'Halloran K, Carusone SC, Dafoe N, Walter SD. Stop orders to reduce inappropriate urinary catheterization in hospitalized patients: a randomized controlled trial. Journal of General Internal Medicine 23(6):816-20, 2008 Jun.

283. Fuchs MA, Sexton DJ, Thornlow DK, Champagne MT. Evaluation of an evidence-based, nurse-driven checklist to prevent hospital-acquired catheter- associated urinary tract infections in intensive care units. journal of nursing care quality 2011.

284. Smith SL. Effect of an educational intervention on hospital acquired urinary tract infection rates. 2009.

285. Bruminhent J, Keegan M, Lakhani A, Roberts IM, Passalacqua J. Effectiveness of a simple intervention for prevention of catheter-associated urinary tract infections in a community teaching hospital. American Journal of Infection Control 2010.

286. Gokula RM, Smith MA, Hickner J. Emergency room staff education and use of a urinary catheter indication sheet improves appropriate use of foley catheters. American Journal of Infection Control 35(9):589-93, 2007 Nov.

287. Saint S, Kaufman SR, Thompson M, Rogers MA, Che-

noweth CE. A reminder reduces urinary catheterization in hospitalized patients. Joint Commission Journal on Quality & Patient Safety 31(8):455-62, 2005 Aug.

288. Voss A. Incidence and duration of urinary catheters in hospitalized older adults: before and after implementing a geriatric protocol. Journal of Gerontological Nursing 2012.

289. Meddings J, Rogers MA, Macy M, Saint S. Systematic review and meta-analysis: reminder systems to reduce catheter-associated urinary tract infections and urinary catheter use in hospitalized patients. Clinical Infectious Diseases 2010.

290. Gotelli JM, Merryman P, Carr C, McElveen L, Epperson C, Bynum D. A quality improvement project to reduce the complications associated with indwelling urinary catheters. Urologic Nursing 2008.

291. Arentzen J. Does a Nurse-Driven Protocol for Urinary Catheter Removal Empower Nurses to Remove Urinary Catheters Without a Physician Order? American Journal of Infection Control 2011.

292. Saint S, Kowalski CP, Kaufman SR, Hofer TP, Kauffman CA, Olmsted RN, et al. Preventing hospital-acquired urinary tract infection in the United States: a national study. Clinical Infectious Diseases 2008.

293. Gardam MA, Amihod B, Orenstein P, Consolacion N, Miller MA. Overutilization of indwelling urinary catheters and the development of nosocomial urinary tract infections. Clin Perform Qual Health Care 1998 Jul;6(3):99-102.

294. Gokula RR, Hickner JA, Smith MA. Inappropriate use of urinary catheters in elderly patients at a midwestern community teaching hospital. Am J Infect Control 2004 Jun;32(4):196-9.

295. Holroyd-Leduc JM, Sen S, Bertenthal D, Sands LP, Palmer RM, Kresevic DM, et al. The relationship of indwelling urinary catheters to death, length of hospital stay, functional decline, and nursing home admission in hospitalized older medical patients. J Am Geriatr Soc 2007 Feb;55(2):227-33.

296. Brennan ML, Evans A. Why catheterize?: audit findings on the use of urinary catheters. Br J Nurs 2001 May 10;10(9):580-90.

297. Wald H, Epstein A, Kramer A. Extended use of indwelling urinary catheters in postoperative hip fracture patients. Medical Care 43(10):1009-17, 2005 Oct.

298. McNulty C, Freeman E, Smith G, Gunn K, Foy C, Tompkins D, et al. Prevalence of urinary catheterization in UK nursing homes. Journal of Hospital Infection 55(2):119-23, 2003 Oct.

299. Clarke-O'Neill S, Fader MJ, Pettersson L, Cottenden AM. Disability Equipment Assessment Report: A survey of continence products use in residential settings. Medical Devices Agency (UK); 2003. Report No.: IN.10.

300. Kunin CM, Chin QF, Chambers S. Morbidity and mortality associated with indwelling urinary catheters in elderly patients in a nursing home--confounding due to the presence of associated diseases. J Am Geriatr Soc 1987 Nov;35(11):1001-6.

301. Anger J, Saigal C, Pace J, Rodriguez L, Litwin M. True prevalence of urinary incontinence among female nursing home residents. Urology 2006;67:281-7.

302. Tsan L, Davis C, Langberg R, Hojlo C, Pierce J, Miller M, et al. Prevalence of nursing home-associated infections in the Department of Veterans Affairs nursing home care units. Am J Infect Control 2008 Apr;36(3):173-9.

303. Rogers MA, Mody L, Kauffman SR, Fries BE, McMahon LF, Saint S. Use of urinary collection devices in skilled nursing facilities in five states. Journal of the American Geriatrics Society 2008.

304. McNulty C, Bowen J, Howell-Jones R, Walker M, Freeman E. Exploring reasons for variation in urinary catheterisation prevalence in care homes: A qualitative study. Age & Ageing 2008.

305. Wilde MH. Life with an indwelling urinary catheter: the dialectic of stigma and acceptance. Qualitative Health Research 13(9):1189-204, 2003 Nov.

306. Wilde MH, Brasch J. A pilot study of self-monitoring urine flow in people with long-term urinary catheters. Res Nurs Health 2008 Oct;31(5):490-500.

307. Wagg A, Peel P, Potter J, Lowe D. Report of the National Audit of Continence Care for Older people (65 years and above) in England Wales and Northern Ireland. Royal College of Physicians, London; 2006.

308. Vaidyanathan S, Hughes PL, Soni BM. Unusual complition of suprapubic cystostomy in a male patient with tetraplegia: traction on Foley catheter leading to extrusion of Foley balloon from urinary bladder and suprapubic urinary fistula--importance of securely anchoring suprapubic catheter with adhesive tape or BioDerm tube holder. ScientificWorldJournal 2007;7:1575-8.

309. Sheriff MK, Foley S, McFarlane J, Nauth-Misir R, Craggs M, Shah PJ. Long-term suprapubic catheterisation: clinical outcome and satisfaction survey. Spinal Cord 1998 Mar;36(3):171-6.

310. Mitsui T, Minami K, Furuno T, Morita H, Koyanagi T. Is suprapubic cystostomy an optimal urinary management in high quadriplegics?. A comparative study of suprapubic cystostomy and clean intermittent catheterization. Eur Urol 2000 Oct;38(4):434-8.

311. Feifer A, Corcos J. Contemporary role of suprapubic cystostomy in treatment of neuropathic bladder dysfunction in spinal cord injured patients. Neurourol Urodyn 2008;27(6):475-9.

312. Pannek J, Gocking K, Bersch U. To clamp or not to clamp? Bladder management by suprapubic catheterization in patients with neurogenic bladder dysfunction. World Journal of Urology 2010.

313. Katsumi HK, Kalisvaart JF, Ronningen LD, Hovey RM. Urethral versus suprapubic catheter: choosing the best bladder management for male spinal cord injury patients with indwelling catheters. Spinal Cord 2010.

314. Heit M. Infectious peritonitis complicating suprapubic catheter removal. Int Urogynecol J Pelvic Floor Dysfunct 1997;8(1):47-9.

315. Ahluwalia RS, Johal N, Kouriefs C, Kooiman G, Montgomery BS, Plail RO. The surgical risk of suprapubic catheter insertion and long-term sequelae. Ann R Coll Surg Engl 2006 Mar;88(2):210-3.

316. Hamid R, Peters J, Shah PJ. Pitfall in insertion of suprapubic catheter in patients with spinal cord injuries. Spinal Cord 2002 Oct;40(10):542-3.

317. Goldblum D, Brugger JJ. Bowel obstruction caused by dislocation of a suprapubic catheter. Surg Endosc 1999 Mar;13(3):283-4.

318. Huang JG, Brough SJ, Jensen RS, Monsour MJ. Suprapubic catheter displacement: a forgotten phenomenon. Emergency Medicine Australasia 2010.

319. Mehta A, Makris A, Saad A, Callaghan PS. Incisional hernia after suprapubic catheter insertion. BJU Int 1999 Sep;84(4):526-7.

320. Lobel RW, Sand PK. Incisional hernia after suprapubic catheterization. Obstet Gynecol 1997 May;89(5 Pt 2):844-6.

321. Shergill IS, Shaikh T, Arya M, Junaid I. A training model for suprapubic catheter insertion: the UroEmerge suprapubic catheter model. Urology 2008 Jul;72(1):196-7.

322. Lawrentschuk N, Lee D, Marriott P, Russell JM. Suprapubic stab cystostomy: a safer technique. Urology 2003 Nov;62(5):932-4.

323. Aguilera PA, Choi T, Durham BA. Ultrasound-guided suprapubic cystostomy catheter placement in the emergency department. J Emerg Med 2004 Apr;26(3):319-21.

324. Gujral S, Kirkwood L, Hinchliffe A. Suprapubic catheterization: a suitable procedure for clinical nurse specialists in selected patients. BJU Int 1999 Jun;83(9):954-6.

325. Anderson PJ, Walsh JM, Louey MA, Meade C, Fairbrother G. Comparing first and subsequent suprapubic catheter change: complications and costs. Urol Nurs 2002 Oct;22(5):324-30.

326. Barford JMT, Coates ARM. The pathogenesis of catheter-associated urinary tract infection. Journal of Infection Prevention 2009.

327. Silver JR. Case report by RN Mohapatra: urine leakage in persons with spinal cord injury and using long-term Foley catheters: a simple solution. Spinal Cord 2010.

328. Cox AJ, Millington RS, Hukins DW, Sutton TM. Resistance of conformable indwelling urinary catheters to encrustation. Biomater Artif Cells Artif Organs 1989;17(4):429-35.

329. Ruutu M, Alfthan O, Heikkinen L, Jarvinen A, Lehtonen T, Merikallio E, et al. «Epidemic» of acute urethral stricture after open-heart surgery. Lancet 1982 Jan 23;1(8265):218.

330. Ruutu M, Alfthan O, Talja M, Andersson LC. Cytotoxicity of latex urinary catheters. Br J Urol 1985 Feb;57(1):82-7.

331. Nacey JN, Tulloch AG, Ferguson AF. Catheter-induced urethritis: a comparison between latex and silicone catheters in a prospective clinical trial. Br J Urol 1985 Jun;57(3):325-8.

332. Pariente JL, Bordenave L, Jacob F, Bareille R, Baquey C, Le GM. Cytotoxicity assessment of latex urinary catheters on cultured human urothelial cells. Eur Urol 2000 Nov;38(5):640-3.

333. Crippa M, Belleri L, Mistrello G, Tedoldi C, Alessio L. Prevention of latex allergy among health care workers and in the general population: latex protein content in devices commonly used in hospitals and general practice. Int Arch Occup Environ Health 2006 Aug;79(7):550-7.

334. Shenot P, Rivas DA, Kalman DD, Staas WE, Jr., Chancellor MB. Latex allergy manifested in urological surgery and care of adult spinal cord injured patients. Arch Phys Med Rehabil 1994 Nov;75(11):1263-5.

335. Talja M, Korpela A, Jarvi K. Comparison of urethral reaction to full silicone, hydrogen-coated and siliconised latex catheters. Br J Urol 1990 Dec;66(6):652-7.

336. Anderson R. Pilot study to assess silicone indwelling urinary catheter change regimens. Australian and New Zealand Continence Journal 2010.

337. Barnes KE, Malone-Lee J. Long-term catheter management: minimizing the problem of premature replacement due to balloon deflation. Journal of Advanced Nursing 1986;11(3):303-7.

338. Jannings W, Kelly M. Difficulty in removing suprapubic urinary catheters in home based patients: a comparative descriptive study. Aust J Adv Nurs 2001 Dec;19(2):20-5.

339. Parkin J, Scanlan J, Woolley M, Grover D, Evans A, Feneley RC. Urinary catheter 'deflation cuff' formation: clinical audit and quantitative in vitro analysis. BJU Int 2002 Nov;90(7):666-71.

340. Gonzalgo ML, Walsh PC. Balloon cuffing and management of the entrapped Foley catheter. Urology 2003 Apr;61(4):825-7.

341. Ebner A, Madersbacher H, Schober F, Marbeger H. Hydrodynamic properties of Foley catheters and its clinical relevance. 1985 p. 217-8.

342. Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA. Guideline for prevention of catheter-associated urinary tract infections 2009. Infection Control & Hospital Epidemiology 2010.

343. Parker D, Callan L, Harwood J, Thompson DL, Wilde M, Gray M. Nursing interventions to reduce the risk of catheter-associated urinary tract infection. Part 1: catheter selection. Journal of Wound, Ostomy and Continence Nursing 2009.

344. D'Cruz R, Soundappan SS, Cass DT, Smith G. Catheter balloon-related urethral trauma in children. Journal of Pediatrics & Child Health 2009.

345. Plowman R, Graves N, Griffin M, Swan A, Cookson B, Taylor L. The socio-economic burden of hospital-acquired infection. London: Public Health Laboratory Service; 1999.

346. Stamm WE. Urinary tract infections. Lippincott-Raven, Philadelphia.; 1998.

347. Sartor C, Sambuc R, Bimar MC, Gulian C, De MP. Prevalence surveys of nosocomial infections using a random sampling method in Marseille hospitals. J Hosp Infect 1995 Mar;29(3):209-16.

348. Evans CT, LaVela SL, Weaver FM, Priebe M, Sandford P, Niemiec P, et al. Epidemiology of hospital-acquired infections in veterans with spinal cord injury and disorder. Infect Control Hosp Epidemiol 2008.

349. Edwards JR, Peterson KD, Andrus ML, Tolson JS, Goulding JS, Dudeck MA, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2006, issued June 2007. Am J Infect Control 2007 Jun;35(5):290-301.

350. Mulhall AB, Chapman RG, Crow RA. Bacteriuria during indwelling urethral catheterization. J Hosp Infect 1988 Apr;11(3):253-62.

351. Stamm WE. Catheter-associated urinary tract infections: epidemiology, pathogenesis, and prevention. Am J Med 1991 Sep 16;91(3B):65S-71S.

352. Nicolle LE. The chronic indwelling catheter and urinary infection in long-term-care facility residents. Infect Control Hosp Epidemiol 2001 May;22(5):316-21.

353. Nickel JC, Grant SK, Costerton JW. Catheter-associated bacteriuria. An experimental study. Urology 1985 Oct;26(4):369-75.

354. Garibaldi RA, Burke JP, Dickman ML, Smith CB. Factors predisposing to bacteriuria during indwelling urethral catheterization. N Engl J Med 1974 Aug 1;291(5):215-9.

355. Watnick P, Kolter R. Biofilm, city of microbes. J Bacteriol 2000 May;182(10):2675-9.

356. Donlan RM. Biofilm formation: a clinically relevant microbiological process. Clin Infect Dis 2001 Oct 15;33(8):1387-92.

357. Trautner BW, Darouiche RO. Role of biofilm in catheter-associated urinary tract infection. Am J Infect Control 2004 May;32(3):177-83.

358. Nickel JC, Costerton JW, McLean RJ, Olson M. Bacterial biofilms: influence on the pathogenesis, diagnosis and treatment of urinary tract infections. J Antimicrob Chemother 1994 May;33 Suppl A:31-41.

359. Stickler D, Dolman J, Rolfe S, Chawla J. Activity of antiseptics against Escherichia coli growing as biofilms on silicone surfaces. Eur J Clin Microbiol Infect Dis 1989 Nov;8(11):974-8.

360. Utsumi M, Yamada M, Nishi I, Nabetani Y, Asari S, Tomono K, et al. Adjustment for antibiotic exposure level in catheter-associated urinary tract infections. Journal of Hospital Infection 2008.

361. Amadeo B, Dumartin C, Venier AG, Fourrier-Réglat A, Coignard B, Rogues AM. Factors associated with the prevalence of antibiotic use for the treatment of hospital-acquired infections at 393 French hospitals: a regional variation analysis. Infection Control & Hospital Epidemiology 2011.

362. Tambyah PA, Maki DG. Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1,497 catheterized patients. Arch Intern Med 2000 Mar 13;160(5):678-82.

363. Salomao R, Rosenthal VD, Grimberg G, Nouer S, Blecher S, Buchner-Ferreira S, et al. Device-associated infection rates in intensive care units of Brazilian hospitals: findings of the International Nosocomial Infection Control Consortium. Revista Panamericana de Salud Publica 2008.

364. Cuellar LE, Fernandez-Maldonado E, Rosenthal VD, Castaneda-Sabogal A, Rosales R, Mayorga-Espichan MJ, et al. Device-associated infection rates and mortality in intensive care units of Peruvian hospitals: findings of the

International Nosocomial Infection Control Consortium. Pan Am Journal of Public Health 2008.

365. Rosenthal VD. Device-associated nosocomial infections in limited-resources countries: findings of the International Nosocomial Infection Control Consortium (INICC). American Journal of Infection Control 2008.

366. Gikas A, Roumbelaki M, Bagatzouni-Pieridou D, Alexandrou M, Zinieri V, Dimitriadis I, et al. Device-associated infections in the intensive care units of Cyprus: results of the first national incidence study. Infection 2010.

367. Edwards JR, Peterson KD, Andrus ML, Dudeck MA, Pollock DA, Horan TC, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2006 through 2007, issued November 2008. Am J Infect Control 2009.

368. Mullings A, Murdoch F, Reilly J. Catheter associated urinary tract infection within care of the elderly facilities: results from a Scottish pilot study. Journal of Infection Prevention 2011.

369. Weber DJ, Brown V, Huslage K, Sickbert-Bennett E, Rutala WA. Device-related infections in home health care and hospice: infection rates, 1998-2008. Infect Control Hosp Epidemiol 2009.

370. Goetz LL, Howard M, Cipher D, Revankar SG. Occurrence of candiduria in a population of chronically catheterized patients with spinal cord injury. Spinal Cord 2010.

371. Sorbye LW, Finne-Soveri H, Ljunggren G, Topinkova E, Bernabei R. Indwelling catheter use in home care: elderly, aged 65+, in 11 different countries in Europe. Age Ageing 2005 Jul;34(4):377-81.

372. Landi F, Cesari M, Onder G, Zamboni V, Barillaro C, Lattanzio F, et al. Indwelling urethral catheter and mortality in frail elderly women living in community. Neurourol Urodyn 2004;23(7):697-701.

373. Siroky MB. Pathogenesis of bacteriuria and infection in the spinal cord injured patient. Am J Med 2002 Jul 8;113 Suppl 1A:67S-79S.

374. Saint S, Lipsky BA. Preventing catheter-related bacteriuria: should we? Can we? How? Arch Intern Med 1999 Apr 26;159(8):800-8.

375. Saint S, Veenstra DL, Lipsky BA. The clinical and economic consequences of nosocomial central venous catheter-related infection: are antimicrobial catheters useful? Infect Control Hosp Epidemiol 2000 Jun;21(6):375-80.

376. Saint S, Veenstra DL, Sullivan SD, Chenoweth C, Fendrick AM. The potential clinical and economic benefits of silver alloy urinary catheters in preventing urinary tract infection. Arch Intern Med 2000 Sep 25;160(17):2670-5.

377. Tambyah PA, Maki DG. The relationship between pyuria and infection in patients with indwelling urinary catheters: a prospective study of 761 patients. Arch Intern Med 2000 Mar 13;160(5):673-7.

378. Chant C, Smith OM, Marshall JC, Friedrich JO. Relationship of catheter-associated urinary tract infection to mortality and length of stay in critically ill patients: A systematic review and meta-analysis of observational studies. Critical Care Medicine 2011.

379. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008 Jun;36(5):309-32.

380. Darouiche RO, Goetz L, Kaldis T, Cerra-Stewart C, AlSharif A, Priebe M. Impact of StatLock securing device on symptomatic catheter-related urinary tract infection: a prospective, randomized, multicenter clinical trial. Am J Infect Control 2006 Nov;34(9):555-60.

381. Massa LM, Hoffman JM, Cardenas DD. Validity, accuracy, and predictive value of urinary tract infection signs and symptoms in individuals with spinal cord injury on intermittent catheterization. Journal of Spinal Cord Medicine 2009.

382. Juthani-Mehta M, Tinetti M, Perrelli E, Towle V, Van Ness PH, Quagliarello V. Diagnostic accuracy of criteria for urinary tract infection in a cohort of nursing home residents. J Am Geriatr Soc 2007 Jul;55(7):1072-7.

383. Cope M, Cevallos ME, Cadle RM, Darouiche RO, Musher DM, Trautner BW. Inappropriate treatment of catheter-associated asymptomatic bacteriuria in a tertiary care hospital. Clinical Infectious Diseases 2009.

384. Talaat M, Hafez S, Saied T, Elfeky R, El-Shoubary W, Pimentel G. Surveillance of catheter-associated urinary tract infection in 4 intensive care units at Alexandria university hospitals in Egypt. American Journal of Infection Control 2010.

385. Wald HL, Ma A, Bratzler DW, Kramer AM. Indwelling urinary catheter use in the postoperative period: analysis of the national surgical infection prevention project data. Archives of Surgery 143(6):551-7, 2008 Jun.

385. Madeo M, Barr B, Owen E. A study to determine whether the use of a preconnect urinary catheter system reduces the incidence of nosocomial urinary tract infections. Journal of Infection Prevention 2009.

387. Tsuchida T, Makimoto K, Ohsako S, Fujino M, Kaneda M, Miyazaki T, et al. Relationship between catheter care and catheter-associated urinary tract infection at Japanese general hospitals: a prospective observational study. International Journal of Nursing Studies 2008.

388. Branagan GW, Moran BJ. Published evidence favors the use of suprapubic catheters in pelvic colorectal surgery. Dis Colon Rectum 2002 Aug;45(8):1104-8.

389. Fox CL, Jr., Modak SM. Mechanism of silver sulfadiazine action on burn wound infections. Antimicrob Agents Chemother 1974 Jun;5(6):582-8.

390. Brosnahan J, Jull A, Tracy C. Types of urethral catheters for management of short-term voiding problems in hospitalised adults. Cochrane Database Syst Rev 2004;(1):CD004013.

391. Maki DG, Knasinski V, Halvorson KT, Tambyah PA. A novel silver hydrogel-impregnated indwelling catheter reduces catheter-related urinary tract infections. A prospective double-blind trial. Infect Control Hosp Epidemiol 1998;19:682.

392. Al-Habdan I, Sadat-Ali M, Corea JR, Al-Othman A, Kamal BA, Shriyan DS. Assessment of nosocomial urinary tract infections in orthopaedic patients: a prospective and comparative study using two different catheters. Int Surg 2003 Jul;88(3):152-4.

393. Lee B, Bhuta T, Craig J, Simpson J. Methenamine hippurate for preventing urinary tract infections (Cochrane Review). The Cochrane Library 2004;(4).

394. Stensballe J, Tvede M, Looms D, Lippert FK, Dahl B, Tonnesen E, et al. Infection risk with nitrofurazone-impregnated urinary catheters in trauma patients: a randomized trial. Ann Intern Med 2007 Sep 4;147(5):285-93.

395. Darouiche RO, Smith JA, Jr., Hanna H, Dhabuwala CB, Steiner MS, Babaian RJ, et al. Efficacy of antimicrobial-impregnated bladder catheters in reducing catheter-associated bacteriuria: a prospective, randomized, multicenter clinical trial. Urology 1999 Dec;54(6):976-81.

396. Gaonkar TA, Sampath LA, Modak SM. Evaluation of the antimicrobial efficacy of urinary catheters impregnated with antiseptics in an in vitro urinary tract model. Infect Control Hosp Epidemiol 2003 Jul;24(7):506-13.

397. Karchmer TB, Giannetta ET, Muto CA, Strain BA, Farr BM. A randomized crossover study of silver-coated urinary catheters in hospitalized patients. Arch Intern Med 2000 Nov 27;160(21):3294-8.

398. Rupp ME, Fitzgerald T, Marion N, Helget V, Puumala S, Anderson JR, et al. Effect of silver-coated urinary catheters: efficacy, cost-effectiveness, and antimicrobial resistance. American Journal of Infection Control 32(8):445-50, 2004 Dec.

399. Lai KK, Fontecchio SA. Use of silver-hydrogel urinary

catheters on the incidence of catheter-associated urinary tract infections in hospitalized patients. Am J Infect Control 2002 Jun;30(4):221-5.

400. Bologna RA, Tu LM, Polansky M, Fraimow HD, Gordon DA, Whitmore KE. Hydrogel/silver ion-coated urinary catheter reduces nosocomial urinary tract infection rates in intensive care unit patients: a multicenter study. Urology 1999 Dec;54(6):982-7.

401. Johnson JR, Kuskowski MA, Wilt TJ. Systematic review: antimicrobial urinary catheters to prevent catheter-associated urinary tract infection in hospitalized patients. Annals of Internal Medicine 144(2):116-26, 2006 Jan 17.

402. Drekonja DM, Kuskowski MA, Wilt TJ, Johnson JR. Antimicrobial urinary catheters: a systematic review. Expert Rev Med Devices 2008 Jul;5(4):495-506.

403. Srinivasan A, Karchmer T, Richards A, Song X, Perl TM. A prospective trial of a novel, silicone-based, silver-coated foley catheter for the prevention of nosocomial urinary tract infections. Infect Control Hosp Epidemiol 2006 Jan;27(1):38-43.

404. Kunin CM. Nosocomial urinary tract infections and the indwelling catheter: what is new and what is true? Chest 2001 Jul;120(1):10-2.

405. Li X-Z, Nikaido H, Williams KE. Silver-resistant mutants of Escherichia coli display efflux of Ag + and are deficient in porins. J Bacteriol 1997;179:6127-32.

406. Stickler DJ. Susceptibility of antibiotic-resistant Gram-negative bacteria to biocides: a perspective from the study of catheter biofilms. J Appl Microbiol 2002;92 Suppl:163S-70S.

407. Shu-Hua Y, Yu-Sheng J, Feng-Huei L. Chitosan/poly(vinyl alcohol) blending hydrogel coating improves the surface characteristics of segmented polyurethane urethral catheters. J Biomedical Material Research Part B:Applied Biomaterials 2007;83(2):304-13.

408. Jones GL, Muller CT, O'Reilly M, Stickler DJ. Effect of triclosan on the development of bacterial biofilms by urinary tract pathogens on urinary catheters. Journal of Antimicrobial Chemotherapy 57(2):266-72, 2006 Feb.

409. Stickler DJ, Morgan SD. Observations on the development of the crystalline bacterial biofilms that encrust and block Foley catheters. Journal of Hospital Infection 2008.

410. Tenke P, Riedl CR, Jones GL, Williams GJ, Stickler D, Nagy E. Bacterial biofilm formation on urologic devices and heparin coating as preventive strategy. Int J Antimicrob Agents 2004 Mar;23 Suppl 1:S67-S74.

411. Prasad A, Cevallos ME, Riosa S, Darouiche RO, Trautner BW. A bacterial interference strategy for prevention of UTI in persons practicing intermittent catheterization. Spinal Cord 2009.

412. Nicolle LE. Resistant pathogens in urinary tract infections. J Am Geriatr Soc 2002 Jul;50(7 Suppl):S230-S235.

413. Rutschmann OT, Zwahlen A. Use of norfloxacin for prevention of symptomatic urinary tract infection in chronically catheterized patients. Eur J Clin Microbiol Infect Dis 1995 May;14(5):441-4.

414. Firestein M, Mendelson G, Gronich D, Granot D, Ben-Israel J, Raz R. Can Antibiotic Use During Routine Replacement of Long-Term Urinary Catheter Prevent Bacteriuria? Infectious Diseases in Clinical Practice 2001 Mar;3(3):133-5.

415. Shah PS, Cannon JP, Sullivan CL, Nemchausky B, Pachucki CT. Controlling antimicrobial use and decreasing microbiological laboratory tests for urinary tract infections in spinal-cord-injury patients with chronic indwelling catheters. Am J Health Syst Pharm 2005 Jan 1;62(1):74-7.

416. Sabbuba NA, Mahenthiralingam E, Stickler DJ. Molecular epidemiology of Proteus mirabilis infections of the catheterized urinary tract. J Clin Microbiol 2003 Nov;41(11):4961-5.

417. Jepson RG, Mihaljevic L, Craig J. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev 2008;(1):CD001321.

418. Kunin CM, Chin QF, Chambers S. Formation of encrustations on indwelling urinary catheters in the elderly: a comparison of different types of catheter materials in «blockers» and «nonblockers». J Urol 1987 Oct;138(4):899-902.

419. Getliffe KA. The use of bladder wash-outs to reduce urinary catheter encrustation. Br J Urol 1994 Jun;73(6):696-700.

420. Kohler-Ockmore J, Feneley RC. Long-term catheterization of the bladder: prevalence and morbidity. Br J Urol 1996 Mar;77(3):347-51.

421. Getliffe K. Managing recurrent urinary catheter blockage: problems, promises, and practicalities. Journal of Wound, Ostomy, & Continence Nursing 30(3):146-51, 2003 May.

422. Mathur S, Suller MT, Stickler DJ, Feneley RC. Factors affecting crystal precipitation from urine in individuals with long-term urinary catheters colonized with urease-positive bacterial species. Urological Research 34(3):173-7, 2006 Jun.

423. Suller MT, Anthony VJ, Mathur S, Feneley RC, Greenman J, Stickler DJ. Factors modulating the pH at which calcium and magnesium phosphates precipitate from human urine. Urol Res 2005 Aug;33(4):254-60.

424. Getliffe KA. The characteristics and management of patients with recurrent blockage of long-term urinary catheters. J Adv Nurs 1994 Jul;20(1):140-9.

425. Choong SK, Hallson P, Whitfield HN, Fry CH. The physicochemical basis of urinary catheter encrustation. BJU Int 1999 May;83(7):770-5.

426. Cox AJ, Harries JE, Hukins DW, Kennedy AP, Sutton TM. Calcium phosphate in catheter encrustation. Br J Urol 1987 Feb;59(2):159-63.

427. Stickler DJ, Zimakoff J. Complications of urinary tract infections associated with devices used for long-term bladder management. J Hosp Infect 1994 Nov;28(3):177-94.

428. Choong SK, Whitfield HN. Urinary encrustation of alloplastic materials. J Endourol 2000 Feb;14(1):19-23.

429. Morris NS, Stickler DJ, Winters C. Which indwelling urethral catheters resist encrustation by Proteus mirabilis biofilms? Br J Urol 1997 Jul;80(1):58-63.

430. Morris NS, Stickler DJ. Encrustation of indwelling urethral catheters by Proteus mirabilis biofilms growing in human urine. J Hosp Infect 1998 Jul;39(3):227-34.

431. Stickler DJ, Feneley RCL. The encrustation and blockage of long-term indwelling bladder catheters: a way forward in prevention and control. Spinal Cord 2010.

432. Jacobsen SM, Stickler DJ, Mobley HL, Shirtliff ME. Complicated catheter-associated urinary tract infections due to escherichia coli and proteus mirabilis. Clinical Microbiology Reviews 2008.

433. Downer A, Morris N, Feast WJ, Stickler D. Polymer surface properties and their effect on the adhesion of Proteus mirabilis. Proc Inst Mech Eng [H] 2003;217(4):279-89.

434. Park JH, Cho YW, Kwon IC, Jeong SY, Bae YH. Assessment of PEO/PTMO multiblock copolymer/segmented polyurethane blends as coating materials for urinary catheters: in vitro bacterial adhesion and encrustation behavior. Biomaterials 2002 Oct;23(19):3991-4000.

435. Chakravarti A, Gangodawila S, Long MJ, Morris NS, Blacklock AR, Stickler DJ. An electrified catheter to resist encrustation by Proteus mirabilis biofilm. J Urol 2005 Sep;174(3):1129-32.

436. Williams GJ, Stickler DJ. Some observations on the diffusion of antimicrobial agents through the retention balloons of foley catheters. J Urol 2007 Aug;178(2):697-701.

437. Stickler DJ, Jones GL. Reduced Susceptibility of Proteus mirabilis to triclosan. Antimicrob Agents Chemother 2008 Mar;52(3):991-4.

438. Stickler DJ, Morgan SD. Modulation of crystalline Proteus

mirabilis biofilm development on urinary catheters. Journal of Medical Microbiology 55(Pt 5):489-94, 2006 May.

439. Morris NS, Stickler DJ. Does drinking cranberry juice produce urine inhibitory to the development of crystalline, catheter-blocking Proteus mirabilis biofilms? BJU Int 2001 Aug;88(3):192-7.

440. Kessler T, Jansen B, Hesse A. Effect of blackcurrant-, cranberry- and plum juice consumption on risk factors associated with kidney stone formation. Eur J Clin Nutr 2002 Oct;56(10):1020-3.

441. Bibby JM, Cox AJ, Hukins DW. Feasibility of preventing encrustation of urinary catheters. Cells and Materials 1995;2:183-95.

442. Burns JR, Gauthier JF. Prevention of urinary catheter incrustations by acetohydroxamic acid. J Urol 1984 Sep;132(3):455-6.

443. Gleeson MJ, Cunnane G, Grainger R. Spontaneous perforation of an augmented bladder. Br J Urol 1991 Dec;68(6):655.

444. Khan A, Housami F, Melotti R, Timoney A, Stickler D. Strategy to Control Catheter Encrustation With Citrated Drinks: A Randomized Crossover Study. The Journal of Urology 2010.

445. Getliffe K. Care of urinary catheters. Elder Care 1996 Apr;8(2):23-6.

446. Getliffe KA, Hughes SC, Le CM. The dissolution of urinary catheter encrustation. BJU Int 2000 Jan;85(1):60-4.

447. Hesse A, Nolde A, Klump B, Marklein G, Tuschewitzki GJ. In vitro investigations into the formation and dissolution of infection-induced catheter encrustations. Br J Urol 1992 Oct;70(4):429-34.

448. Jacobs D, Heimbach D, Hesse A. Chemolysis of struvite stones by acidification of artificial urine--an in vitro study. Scand J Urol Nephrol 2001 Oct;35(5):345-9.

449. Kennedy AP, Brocklehurst JC, Robinson JM, Faragher EB. Assessment of the use of bladder washouts/instillations in patients with long-term indwelling catheters. Br J Urol 1992 Dec;70(6):610-5.

450. Elliot S, Striker LJ, Doi T, Linehan WM, Striker GE. Hepatoma G2 conditioned medium facilitates early outgrowth of endothelial cells from isolated glomeruli. Kidney Int 1989 May;35(5):1245-8.

451. Moore KN, Hunter KF, McGinnis R, Bacsu C, Fader M, Gray M, et al. Do catheter washouts extend patency time in long-term indwelling urethral catheters? A randomized controlled trial of acidic washout solution, normal saline washout, or standard care. Journal of Wound, Ostomy and Continence Nursing 2009.

452. Holden D, Rao PN. Management of staghorn stones using a combination of lithotripsy, percutaneous nephrolithotomy and Solution R irrigation. Br J Urol 1991 Jan;67(1):13-7.

453. Stickler DJ, Jones SM, Adusei GO, Waters MG. A sensor to detect the early stages in the development of crystalline Proteus mirabilis biofilm on indwelling bladder catheters. J Clin Microbiol 2006 Apr;44(4):1540-2.

454. Department of Health (UK). Guidelines for preventing infections associated with the insertion and maintenance of short-term indwelling urehral catheters in acute care. J Hosp Infect 2001;47:39-46.

455. Ogden V. Anaesthetic gel insertion during male catheterization. J Community Nursing 2003;17(1):4-8.

456. Chung C, Chu M, Paoloni R, O'Brien MJ, Demel T. Comparison of lignocaine and water-based lubricating gels for female urethral catheterization: a randomized controlled trial. Emerg Med Australas 2007 Aug;19(4):315-9.

457. Cheung K, Leung P, Wong Y, To O, Yeung Y, Chan M, et al. Water versus antiseptic periurethral cleansing before catheterization among home care patients: a randomized controlled trial. American Journal of Infection Control 2008.

458. Nasiriani K, Kalani Z, Farnia F, Motavasslian M, Nasiriani F, Engberg S. Comparison of the Effect of Water versus Povidone-Iodine Solution for Periurethral Cleaning in Women Requiring an Indwelling Catheter Prior to Gynecologic Surgery. Urol Nurs 2009.

459. Gormley E. Vaginal flap urethroplasty for female urethral stricture disease. Neurourol Urodyn 2010.

460. Donnellan SM, Bolton DM. The impact of contemporary bladder management techniques on struvite calculi associated with spinal cord injury. BJU Int 1999 Aug;84(3):280-5.

461. Ord J, Lunn D, Reynard J. Bladder management and risk of bladder stone formation in spinal cord injured patients. J Urol 2003 Nov;170(5):1734-7.

462. Nomura S, Ishido T, Teranishi J, Makiyama K. Long-term analysis of suprapubic cystostomy drainage in patients with neurogenic bladder. Urol Int 2000;65(4):185-9.

463. Khan AA, Mathur S, Feneley R, Timoney AG. Developing a strategy to reduce the high morbidity of patients with long-term urinary catheters: the BioMed catheter research clinic. BJU Int 2007 Dec;100(6):1298-301.

464. Stonehill WH, Dmochowski RR, Patterson AL, Cox CE. Risk factors for bladder tumors in spinal cord injury patients. J Urol 1996 Apr;155(4):1248-50.

465. West DA, Cummings JM, Longo WE, Virgo KS, Johnson FE, Parra RO. Role of chronic catheterization in the development of bladder cancer in patients with spinal cord injury. Urology 1999 Feb;53(2):292-7.

466. Groah SL, Weitzenkamp DA, Lammertse DP, Whiteneck GG, Lezotte DC, Hamman RF. Excess risk of bladder cancer in spinal cord injury: evidence for an association between indwelling catheter use and bladder cancer. Arch Phys Med Rehabil 2002 Mar;83(3):346-51.

467. Schaafsma RJ, Delaere KP, Theunissen PH. Squamous cell carcinoma of suprapubic cystostomy tract without bladder involvement. Spinal Cord 1999 May;37(5):373-4.

468. Berge B, Heicappell R, Steiner U, Miller K. Urothelial carcinoma in a suprapubic cystostomy tract 27 years after tube removal. J Urol 1999 Sep;162(3 Pt 1):797-8.

469. Blake PA, Kim CO, Lopez AE, Krongrad A. Verrucous carcinoma of a suprapubic cystostomy track. J Urol 1996 Jul;156(1):174.

470. Hamid R, Bycroft J, Arya M, Shah PJ. Screening cystoscopy and biopsy in patients with neuropathic bladder and chronic suprapubic indwelling catheters: is it valid? J Urol 2003 Aug;170(2 Pt 1):425-7.

471. Tenke P, Kovacs B, Bjerklund Johansen TE, Matsumoto T, Tambyah PA, Naber KG. European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. Int J Antimicrob Agents 2008 Feb;31 Suppl 1:S68-S78.

472. NICE. Infection Control: prevention of heathcare associated infection in primary and community care. National Institute for Clinical Effectiveness London 2003.

473. Fung C, Spencer B, Eslami M, Crandall C. Quality indicators for the screening and care of urinary incontinence in vulnerable elders. Journal of American Geriatric Society 2007.

474. Muctar S. The importance of a lubricant in transurethral interventions. Urologie (B) 1991;(31):153-5.

475. Tanabe P, Steinmann R, Anderson J, Johnson D, Metcalf S, Ring-Hurn E. Factors affecting pain scores during female urethral catheterization. Acad Emerg Med 2004 Jun;11(6):699-702.

476. British National Formulary. London: British Medical Association and Royal Pharmaceutical Society of great Britain; 2007. Report No.: 54.

477. Ebo DG, Bridts CH, Stevens WJ. Anaphylaxis to an urethral lubricant: chlorhexidine as the "hidden" allergen. Acta Clin Belg 2004 Nov;59(6):358-60.

478. Mularoni PP, Cohen LL, DeGuzman M, Mennuti-Washburn J, Greenwald M, Simon HK. A randomized clinical trial of lidocaine gel for reducing infant distress during urethral catheterization. Pediatric Emergency Care 2009.

479. Villanueva C, Hemstreet GP. Difficult male urethral catheterization: a review of different approaches. Journal of the Brazilian Society of Urology 2008.

480. Agarwal A, Dhiraaj S, Singhal V, Kapoor R, Tandon M. Comparison of efficacy of oxybutynin and tolterodine for prevention of catheter related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study. Br J Anaesth 2006 Mar;96(3):377-80.

481. Mitchell N. Long term urinary catheter problems: a flow chart to aid management. British Journal of Community Nursing 13(1):6, 8, 10-2, 2008 Jan.

482. Tauzin-Fin P, Sesay M, Svartz L, Krol-Houdek MC, Maurette P. Sublingual oxybutynin reduces postoperative pain related to indwelling bladder catheter after radical retropubic prostatectomy. Br J Anaesth 2007 Oct;99(4):572-5.

483. Fleming AA, Day J, Glanfield L. Registered nurse management of urinary catheters in a rehabilitation and long-term care hospital. International Journal of Nursing Practice 2000.

484. Mody L, Saint S, Galecki A, Chen S, Krein SL. Knowledge of evidence-based urinary catheter care practice recommendations among healthcare workers in nursing homes. Journal of the American Geriatrics Society 2010.

485. Drekonja DM, Kuskowski MA, Johnson JR. Internet survey of Foley catheter practices and knowledge among Minnesota nurses. American Journal of Infection Control 2010.

486. Singson K, Murphy S, Merrill KC. Nurses' Knowledge and Compliance to Catheter Associated Urinary Tract Infection Prevention Bundle: A Baseline Survey. American Journal of Infection Control 2011.

487. Theofanidis D, Fountouki A. Bladder catheterization in greek nursing education: an audit of the skills taught. Nurse Education Today 2011.

488. Kneil C, Pellow H, Potter J. Long-term urethral catheter audit in patients' own homes. Journal of Infection Prevention 2009.

489. Bhardwaj R, Pickard R, Rees J. Documented adherence to standards and guidelines: an audit. British Journal of Nursing 2010.

490. Willson M, Wilde M, Webb M, Thompson D, Parker D, Harwood J, et al. Nursing interventions to reduce the risk of catheter-associated urinary tract infection: part 2: staff education, monitoring, and care techniques. Journal of Wound, Ostomy and Continence Nursing 2009.

491. Iacovou JW. Supra-pubic catheterisation of the urinary bladder. Hospital Update 1994;March:159-62.

492. Vaidyanathan S, Hughes PL, Oo T, Soni BM. Long catheter sign: a reliable bedside sign of incorrect positioning of foley catheter in male spinal cord injury patients. Cases J 2008;1(1):43.

493. Heaney F. Nurse decision to insert a urinary catheter in a female patient in orthopaedic speciality: The development of a protocol to guide care. International Journal of Orthopaedic and Trauma Nursing 2011.

494. Evans D. Faecal incontinence products and quality of life. Nursing Times 102(2):44-5, 47, 2006 Jan 10;-16.

495. Burke JP, Garibaldi RA, Britt MR, Jacobson JA, Conti M, Alling DW. Prevention of catheter-associated urinary tract infections. Efficacy of daily meatal care regimens. Am J Med 1981 Mar;70(3):655-8.

496. Gray M. What nursing interventions reduce the risk of symptomatic urinary tract infection in the patient with an indwelling catheter? J Wound Ostomy Continence Nurs 2004 Jan;31(1):3-13.

497. Fisher J. The importance of effective catheter securement. British Journal of Nursing 2010.

498. Gray ML. Securing the indwelling catheter. American Journal of Nursing 2008.

499. Gibney L. Offering patients a choice of urinary catheter drainage system. British Journal of Nursing (BJN) 2010.

500. Sabbuba NA, Stickler DJ, Long MJ, Dong Z, Short TD, Feneley RJ. Does the valve regulated release of urine from the bladder decrease encrustation and blockage of indwelling catheters by crystalline proteus mirabilis biofilms? Journal of Urology 173(1):262-6, 2005 Jan.

501. Woods M, McCreanor J, Aitchison M. An assessment of urethral catheter valves. Prof Nurse 1999 Apr;14(7):472-4.

502. Rowley P, German K, Kumar U, Stone D, Stone V, Blackford HN. A randomized cross-over study comparing the catheter valve with the leg bag in male patients with urethral catheters. 1995.

503. German K, Rowley P, Stone D, Kumar U, Blackford HN. A randomized cross-over study comparing the use of a catheter valve and a leg-bag in urethrally catheterized male patients. Br J Urol 1997 Jan;79(1):96-8.

504. Lewington C, Morgan M, Noone P, Kaisary AV. The value of catheter valve use in long-term bladder drainage. 1989.

505. Wilson C, Sandhu SS, Kaisary AV. A prospective randomized study comparing a catheter-valve with a standard drainage system. Br J Urol 1997 Dec;80(6):915-7.

506. Doherty W. The Sims Portex Catheter Valve: an alternative to the leg bag. Br J Nurs 1999 Apr 8;8(7):459-62.

507. Addison R. Catheter valves: a special focus on the Bard Flip-Flo catheter. Br J Nurs 1999 May 13;8(9):576-80.

508. Fader M, Pettersson L, Brooks R, Dean G, Wells M, Cottenden A, et al. A multicentre comparative evaluation of catheter valves. Br J Nurs 1997 Apr 10;6(7):359, 362-59, 367.

509. Lee SM, Short TD, Unsworth A. Design and development of a novel, automatic valve system for long-term catheterised urinary incontinence patients. Proceedings of the Institution of Mechanical Engineers Part H - Journal of Engineering in Medicine 2007;221(6):665-7.

510. Norberg B, Norberg A, Parkhede U. The spontaneous variation of catheter life in long-stay geriatric inpatients with indwelling catheters. Gerontology 1983;29(5):332-5.

511. Miles G, Schroeder J. An evidence-based approach to urinary catheter changes. British Journal of Community Nursing 2009.

512. Johnson TM, Ouslander JG, Uman GC, Schnelle JF. Urinary incontinence treatment preferences in long-term care. J Am Geriatr Soc 2001 Jun;49(6):710-8.

513. Pfisterer MH, Johnson TM, Jenetzky E, Hauer K, Oster P. Geriatric patients' preferences for treatment of urinary incontinence: a study of hospitalized, cognitively competent adults aged 80 and older. J Am Geriatr Soc 2007 Dec;55(12):2016-22.

514. Khoubehi B, Watkin NA, Mee AD, Ogden CW. Morbidity and the impact on daily activities associated with catheter drainage after acute urinary retention. BJU Int 2000 Jun;85(9):1033-6.

515. Brillhart B. Studying the quality of life and life satisfaction among persons with spinal cord injury undergoing urinary management. Rehabil Nurs 2004 Jul;29(4):122-6.

516. Wilde MH. Understanding urinary catheter problems from the patient's point of view. Home Healthc Nurse 2002 Jul;20(7):449-55.

517. Yavuzer G, Gok H, Tuncer S, Soygur T, Arikan N, Arasil T. Compliance with bladder management in spinal cord injury patients. Spinal Cord 2000 Dec;38(12):762-5.

518. Wilde MH, Dougherty MC. Awareness of urine flow in people with long-term urinary catheters. Journal of Wound, Ostomy, & Continence Nursing 33(2):164-74; discussion 174-5, 2006 Mar;-Apr.

519. Hansen RB, Biering-Sorensen F, Kristensen JK. Bladder emptying over a period of 10-45 years after a traumatic spinal cord injury. Spinal Cord 2004 Nov;42(11):631-7.

520. Pateman B, Johnson M. Men's lived experiences following transurethral prostatectomy for benign prostatic hypertrophy. J Adv Nurs 2000 Jan;31(1):51-8.

521. Seymour W. Coping with embarrassment: bodily continence. Remaking the body: Rehabilitation and change. London: Routledge; 1998. p. 154-76.

522. Baillie L. The impact of urological conditions on patient's dignity. International Journal of Urological Nursing 2007;1(1):27-35.

523. Sweeney A, Harrington A, Button D. Suprapubic catheters--a shared understanding, from the other side looking in. J Wound Ostomy Continence Nurs 2007 Jul;34(4):418-24.

524. Wilde MH, Cameron BL. Meanings and practical knowledge of people with long-term urinary catheters. Journal of Wound, Ostomy, & Continence Nursing 30(1):33-40; discussion 40-3, 2003 Jan.

525. Fraczyk L, Godfrey H, Feneley R. A pilot study of users' experiences of urinary catheter drainage bags. Br J Community Nurs 2003 Mar;8(3):104-11.

526. Jakobsson L, Hallberg IR, Loven L. Experiences of micturition problems, indwelling catheter treatment and sexual life consequences in men with prostate cancer. J Adv Nurs 2000 Jan;31(1):59-67.

527. Hampton S. Male genitourinary health. A guide to male catheterization and sexuality and quality of life. British Journal of Nursing (BJN) 2005;14(7):376.

528. Adejumo P. Acute urinary retention and indwelling Urethral Catheters: A qualitative study of men with obstructive prostate enlargement. West African Journal of Nursing 2008.

529. Anderson KD, Borisoff JF, Johnson RD, Stiens SA, Elliott SL. Spinal cord injury influences psychogenic as well as physical components of female sexual ability. Spinal Cord 2007 May;45(5):349-59.

530. Anderson KD, Borisoff JF, Johnson RD, Stiens SA, Elliott SL. The impact of spinal cord injury on sexual function: concerns of the general population. Spinal Cord 2007 May;45(5):328-37.

531. Bostock N, Kralik D. Sexual health and living with a urinary catheter. Australian and New Zealand Continence Journal 2008.

532. Wilson M. Causes and management of indwelling urinary catheter-related pain. British Journal of Nursing 17(4):232-9, 2008 Feb 28;-Mar.

533. Roe B. Long--term catheter care in the community. Nurs Times 1989 Sep 6;85(36):43-4.

534. Roe BH. Study of the effects of education on patients' knowledge and acceptance of their indwelling urethral catheters. J Adv Nurs 1990 Feb;15(2):223-31.

535. Godfrey H. Living with a long-term urinary catheter: older people's experiences. J Adv Nurs 2008 Apr;62(2):180-90.

536. Kralik D, Seymour L, Eastwood S, Koch T. Managing the self: living with an indwelling urinary catheter. Journal of Clinical Nursing 16(7B):177-85, 2007 Jul.

537. Wilde MH. Urine flowing: a phenomenological study of living with a urinary catheter. Res Nurs Health 2002 Feb;25(1):14-24.

538. Paterson BL. The shifting perspectives model of chronic illness. J Nurs Scholarsh 2001;33(1):21-6.

539. Wilde MH, Garvin S. A concept analysis of self-monitoring. J Adv Nurs 2007 Feb;57(3):339-50.

540. Marx J, Gama J. Resolving Conflicts Between Administrative Data and CDC/NHSN Surveillance Definitions of Catheter Associated Urinary Tract Infection (CA-UTI). American Journal of Infection Control 2011.

541. Trautner BW. Management of catheter-associated urinary tract infection. Current Opinion in Infectious Diseases 2010.

542. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001 Apr 17;134(8):663-94.

543. Peden-McAlpine C, Bliss D, Hill J. The experience of community-living women managing fecal incontinence. Western Journal of Nursing Research 2008.

544. Bliss D, Lewis J, Hasselman K, Savik K, Lowry A, Whitebird R. Use and Evaluation of Disposable Absorbent Products for Managing Fecal Incontinence by Community-Living People. Journal of Wound, Ostomy and Continence Nursing 2011.

545. Mortensen N, Humphreys MS. The anal continence plug: a disposable device for patients with anorectal incontinence. Lancet 1991 Aug 3;338(8762):295-7.

546. Norton C, Kamm MA. Anal plug for faecal incontinence. Colorectal Dis 2001 Sep;3(5):323-7.

547. Giamundo P, Welber A, Weiss EG, Vernava AM, III, Nogueras JJ, Wexner SD. The procon incontinence device: a new nonsurgical approach to preventing episodes of fecal incontinence. Am J Gastroenterol 2002 Sep;97(9):2328-32.

548. Padmanabhan A, Stern M, Wishin J, Mangino M, Richey K, DeSane M, et al. Clinical evaluation of a flexible fecal incontinence management system. American Journal of Critical Care 16(4):384-93, 2007 Jul.

549. Kim J, Shim MC, Choi BY, Ahn SH, Jang SH, Shin HJ. Clinical application of continent anal plug in bedridden patients with intractable diarrhea. Dis Colon Rectum 2001 Aug;44(8):1162-7.

550. Duso S. Product notebook: a new fecal containment device. A case study describing one use of the Bard FCD fecal containment device. Ostomy Wound Manage 1992 Jun;38(5):38-41.

551. Hanlon M, Cofone E. Patient with frequent liquid stools resulting in a chemical dermatitis and a perianal ulcer. J Wound Ostomy Continence Nurs 1996 May;23(3):174-7.

552. Ross V. The fecal containment device: one answer to a dreaded procedure. Ostomy Wound Manage 1993 Sep;39(7):42-4, 46.

553. Freedman P. The rectal pouch: a safer alternative to rectal tubes. Am J Nurs 1991 May;91(5):105-6.

554. Bosley C. Three methods of stool management for patients with diarrhea. Ostomy Wound Manage 1994 Jan;40(1):52-7.

555. Beitz JM. Fecal incontinence in acutely and critically ill patients: options in management. Ostomy Wound Management 52(12):56-8, 60, 62-6, 2006 Dec.

556. Rainville N. Does a foley belong in the rectum? Am J Nurs 1987;87(2):175.

557. Grogan TA, Kramer DJ. The rectal trumpet: use of a nasopharyngeal airway to contain fecal incontinence in critically ill patients. J Wound Ostomy Continence Nurs 2002 Jul;29(4):193-201.

558. Fujii M, Sato TN, Ohrui T, Sato T, Sasaki H. Interanal stool bag for the bedridden elderly with pressure ulcer. Geriatrics & Gerontology International, 2004;4(2):120-2.

559. Chew MH, Quah HM, Ooi BS, Lim JF, Ho KS, Tang CL, et al. A prospective study assessing anal plug for containment of faecal soilage and incontinence. Colorectal Dis 2007.

560. Shoshan L, Ben-Zvi D, Katz-Leurer M. Use of the Anal Plug in the Treatment of Fecal Incontinence in Patients With Meningomyelocele. Journal of Pediatric Nursing 2008.

561. Pfrommer W, Holschneider AM, Loffler N, Schauff B, Ure BM. A new polyurethane anal plug in the treatment of incontinence after anal atresia repair. Eur J Pediatr Surg 2000 Jun;10(3):186-90.

562. Van WM, Van BS, Van LE, Hoebeke P. Is an anal plug use-

ful in the treatment of fecal incontinence in children with spina bifida or anal atresia? Journal of Urology 176(1):342-4, 2006 Jul.

563. Bond C, Youngson G, MacPherson I, Garrett A, Bain N, Donald S, et al. Anal plugs for the management of fecal incontinence in children and adults: a randomized control trial. Journal of Clinical Gastroenterology 41(1):45-53, 2007 Jan.

564. Christiansen J, Roed-Petersen K. Clinical assessment of the anal continence plug. Dis Colon Rectum 1993 Aug;36(8):740-2.

565. Cazemier M, Felt-Bersma RJ, Mulder CJ. Anal plugs and retrograde colonic irrigation are helpful in fecal incontinence or constipation. World Journal of Gastroenterology 13(22):3101-5, 2007 Jun 14.

566. Blair GK, Djonlic K, Fraser GC, Arnold WD, Murphy JJ, Irwin B. The bowel management tube: an effective means for controlling fecal incontinence. J Pediatr Surg 1992 Oct;27(10):1269-72.

567. Keshava A, Renwick A, Stewart P, Pilley A. A nonsurgical means of fecal diversion: the Zassi Bowel Management System. Dis Colon Rectum 2007 Jul;50(7):1017-22.

568. Benoit RA, Jr., Watts C. The effect of a pressure ulcer prevention program and the bowel management system in reducing pressure ulcer prevalence in an ICU setting. Journal of Wound, Ostomy, & Continence Nursing 34(2):163-75; quiz 176-7, 2007 Mar;-Apr.

569. Echols J, Friedman BC, Mullins RF, Hassan Z, Shaver JR, Brandigi C, et al. Clinical utility and economic impact of introducing a bowel management system. Journal of Wound, Ostomy, & Continence Nursing 34(6):664-70, 2007 Nov;-Dec.

570. Kowal-Vern A, Poulakidas S, Barnett B, Conway D, Culver D, Ferrari M, et al. Fecal Containment in Bedridden Patients: Economic Impact of 2 Commercial Bowel Catheter Systems. American Journal of Critical Care 2009.

571. Page BP, Boyce SA, Deans C, Camilleri-Brennan J. Significant Rectal Bleeding as a Complication of a Fecal Collecting Device: Report of a Case. Diseases of the Colon & Rectum 2008.

572. Bright E, Fishwick G, Berry D, Thomas M. Indwelling bowel management system as a cause of life-threatening rectal bleeding. Case reports in gastroenterology 2008.

573. Safaz I, Kesikburun S, Omac OK, Tugcu I, Alaca R. Autonomic Dysreflexia as a Complication of a Fecal Management System in a Man With Tetraplegia. Journal of Spinal Cord Medicine 2010.

574. Palmieri B, Benuzzi G, Bellini N. The anal bag: a modern approach to fecal incontinence management. Ostomy Wound Management 51(12):44-52, 2005 Dec.

575. Gray M, Beeckman D, Bliss D, Fader M, Logan S, Junkin J, et al. Incontinence-associated dermatitis: a comprehensive review and update. Journal of Wound, Ostomy, & Continence Nursing 2012.

576. Gray M, Bliss DZ, Doughty DB, Ermer-Seltun J, Kennedy-Evans KL, Palmer MH. Incontinence-associated dermatitis: a consensus. Journal of Wound, Ostomy, & Continence Nursing 34(1):45-54; quiz 55-6, 2007 Jan;-Feb.

577. Gray M, Bliss DZ, Doughty DB, Ermer-Seltun J, Kennedy-Evans KL, Palmer MH. Incontinence-associated dermatitis: a consensus. Journal of Wound, Ostomy, & Continence Nursing 34(1):45-54; quiz 55-6, 2007 Jan;-Feb.

578. Gray M, Black JM, Baharestani MM, Bliss D, Colwell JC, Goldberg M, et al. Moisture-associated skin damage: overview and pathophysiology. Journal of Wound, Ostomy and Continence Nursing 2011.

579. Black JM, Gray M, Bliss D, Kennedy-Evans KL, Logan S, Baharestani MM, et al. MASD Part 2: Incontinence-Associated Dermatitis and Intertriginous Dermatitis A Consensus. Journal of Wound, Ostomy and Continence Nursing 2011.

580. Colwell JC, Ratliff C, Goldberg M, Baharestani MM, Bliss DZ, Gray M, et al. MASD part 3: peristomal moisture- associated dermatitis and periwound moisture-associated dermatitis: a consensus. Journal of Wound, Ostomy and Continence Nursing 2011.

581. Beeckman D, Schoonhoven L, Verhaeghe S, Heyneman A, Defloor T. Prevention and treatment of incontinence-associated dermatitis: literature review. Journal of Advanced Nursing 2009.

582. Kligman AM. Hydration injury to human skin. In: Elsner P, Berardesca E, Maibach H, editors. Bioengineering of the skin: water and the stratum corneum. CRC Press; 1994.

583. Tsai TF, Maibach HI. How irritant is water? An overview. Contact Dermatitis 1999 Dec;41(6):311-4.

584. Fluhr JW, Gloor M, Lehmann L, Lazzerini S, Distante F, Berardesca E. Glycerol accelerates recovery of barrier function in vivo. Acta Derm Venereol 1999 Nov;79(6):418-21.

585. Faergemann J, Aly R, Wilson DR, Maibach HI. Skin occlusion: effect on Pityrosporum orbiculare, skin PCO2, pH, transepidermal water loss, and water content. Arch Dermatol Res 1983;275(6):383-7.

586. Aly R, Shirley C, Cunico B, Maibach HI. Effect of prolonged occlusion on the microbial flora, pH, carbon dioxide and transepidermal water loss on human skin. J Invest Dermatol 1978 Dec;71(6):378-81.

587. Suskind RR, Ishihara M. The effects of wetting on cutaneous vulnerability. Arch Environ Health 1965 Oct;11(4):529-37.

588. Berg RW, Buckingham KW, Stewart RL. Etiologic factors in diaper dermatitis: the role of urine. Pediatr Dermatol 1986 Feb;3(2):102-6.

589. Buckingham KW, Berg RW. Etiologic factors in diaper dermatitis: the role of feces. Pediatr Dermatol 1986.

590. Andersen P, Bucher A, Saeed I, Lee P, Davis J, Maibach HI. Faecal enzymes: in vivo human skin irritation. Contact Dermatitis 1994.

591. Leyden J. Diaper dermatitis. Dermatologic Clinics 1986.

592. Zimmerer R, Lawson K, Calvert C. The effects of wearing diapers on skin. Pediatr Dermatol 1986.

593. Maibach HI, Kligman AM. The biology of experimental human cutaneous moniliasis (Candida albicans). Archives of Dermatology 1962.

594. Faria D, Shwayder T, Krull E. Perineal skin injury: extrinsic environmental risk factors. Ostomy Wound Management 1996.

595. Schnetz E, Kuss O, Schmitt J, Diepgen T, Kuhn M, Fartasch M. Intra-and inter-individual variations in transepidermal water loss on the face: facial locations for bioengineering studies. Contact Dermatitis 1999.

596. Caplan R. The irritant role of feces in the genesis of perianal itch. Gastroenterology 1966.

597. Fader M, Clarke-O'Neill S, Wong W, Runeman B, Farbrot A, Cottenden A. Review of methods used for quantifying excess water in over-hydrated skin using evaporimetry. Skin Research and Technology 2010.

598. Fader M, Clarke-O'Neill S, Wong W, Runeman B, Farbrot A, Cottenden A. Development and preliminary testing of a standardized method for quantifying excess water in over-hydrated skin using evaporimetry. Physiological Measurement 2011.

599. Brown DS. Perineal dermatitis: can we measure it? Ostomy Wound Management 1993;39(7):28-30-32.

600. Gray M, Jones DP. The effect of different formulations of equivalent active ingredients on the performance of two topical wound treatment products. Ostomy Wound Management 50(3):34-8, 40, 42-4, 2004 Mar.

601. Bliss DZ, Savik K, Harms S, Fan Q, Wyman JF. Prevalence and correlates of perineal dermatitis in nursing home residents. Nursing Research 55(4):243-51, 2006 Jul;-Aug.

602. Lyder C, Clemes-Lowrance C, Davis A, Sullivan L, Zucker A. Structured skin care regimen to prevent perineal dermatitis in the elderly. Journal of ET Nursing 1992.

603. Keller P, Sinkovic S, Miles S. Skin dryness: a major factor in reducing incontinence dermatitis. Ostomy Wound Management 1990.

604. Bale S, Tebble N, Jones V, Price P. The benefits of implementing a new skin care protocol in nursing homes. J Tissue Viability 2004 Apr;14(2):44-50.

605. Zehrer CL, Newman DK, Grove GL, Lutz JB. Assessment of diaper-clogging potential of petrolatum moisture barriers. Ostomy Wound Management 51(12):54-8, 2005 Dec.

606. Ehman S, Thorson M, Lebak K, Bliss D, Savik K, Beilman G. Development of Perineal Dermatitis in Critically Ill Adults with Fecal Incontinence. American Journal of Critical Care 2006;15(3):333.

607. Junkin J, Selekof JL. Prevalence of incontinence and associated skin injury in the acute care inpatient. Journal of Wound, Ostomy, & Continence Nursing 34(3):260-9, 2007 May;-Jun.

608. Shigeta Y, Nakagami G, Sanada H, Oba M, Fujukawa J, Konya C, et al. Exploring the relationship between skin property and absorbent pad environment. Journal of Clinical Nursing 2008.

609. Beeckman D, Verhaeghe S, Defloor T, Schoonhoven L, Vanderwee K. A 3-in-1 Perineal Care Washcloth Impregnated With Dimethicone 3% Versus Water and pH Neutral Soap to Prevent and Treat Incontinence-Associated Dermatitis. Journal of Wound, Ostomy and Continence Nursing 2011.

610. Shigeta Y, Nakagami G, Sanada H, Konya C, Sugama J. Factors influencing intact skin in women with incontinence using absorbent products: results of a cross-sectional, comparative study. Ostomy Wound Management 2010.

511. Bliss DZ, Savik K, Fan Q, Harms S. Risks for perineal dermatitis in nursing home elders: A prospective analysis. Gerontologist 2003.

612. Nix DH. Validity and reliability of the Perineal Assessment Tool. Ostomy Wound Manage 2002 Feb;48(2):43-9.

613. Kennedy KL, Lutz L. Comparison of the efficacy and cost-effectivenes of three skin protectants in the management of incontinent dermatitis. 1996.

614. Warshaw E, Nix D, Kula J, Markon CE. Clinical and cost effectiveness of a cleanser protectant lotion for treatment of perineal skin breakdown in low-risk patients with incontinence. Ostomy Wound Manage 2002 Jun;48(6):44-51.

615. Borchert K, Bliss D, Savik K, Radosevich DM. The incontinence-associated dermatitis and its severity instrument: development and validation. Journal of Wound, Ostomy, & Continence Nursing 2010.

616. Bliss D., Zehrer C, Savik K, Thayer D, Smith G. Incontinence-associated skin damage in nursing home residents: a secondary analysis of a prospective, multicenter study. Ostomy Wound Management 52(12):46-55, 2006 Dec.

617. Maklebust J, Magnan M. Risk factors associated with having a pressure ulcer: a secondary data analysis. Advances in Wound Care 1994.

618. Watret L. Using a case-mix-adjusted pressure sore incidence study in a surgical directorate to improve patient outcomes in pressure ulcer prevention. Journal of Tissue Viability 1999.

619. Brandeis G, Ooi W, Hossain M, Morris J, Lipsitz L. A longitudinal study of risk factors associated with the formation of pressure ulcers in nursing homes. Journal of the American Geriatrics Society 1994.

620. Bergquist S, Frantz R. Pressure ulcers in community-based older adults receiving home health care. Prevalence, incidence, and associated risk factors. Advances in Wound Care 1999.

621. Theaker C, Mannan M, Ives N, Soni N. Risk factors for pressure sores in the critically ill. Anaesthesia 2000.

622. Spector W, Fortinsky R. Pressure ulcer prevalence in Ohio nursing homes: clinical and facility correlates. Journal of aging and health 1998.

623. Doughty D, Ramundo J, Bonham P, Beitz J, Erwin-Toth P, Anderson R, et al. Issues and challenges in staging of pressure ulcers. J Wound Ostomy Continence Nurs 2006 Mar;33(2):125-30.

624. Bethell E. Controversies in classifying and assessing grade I pressure ulcers. J Wound Care 2003 Jan;12(1):33-6.

625. Defloor T, Schoonhoven L. Inter-rater reliability of the EPUAP pressure ulcer classification system using photographs. J Clin Nurs 2004 Nov;13(8):952-9.

626. Defloor T, Schoonhoven L, Katrien V, Weststrate J, Myny D. Reliability of the European Pressure Ulcer Advisory Panel classification system. J Adv Nurs 2006 Apr;54(2):189-98.

627. Beeckman D, Defloor T, Verhaeghe S, Vanderwee K, Demarre L, Schoonhoven L. What is the most effective method of preventing and treating incontinence associated dermatitis? Nursing Times 2010.

628. Houwing RH, Arends JW, Canninga-van Dijk MR, Koopman E, Haalboom JR. Is the distinction between superficial pressure ulcers and moisture lesions justifiable? A clinical-pathologic study. Skinmed 2007 May;6(3):113-7.

629. Fader M, Clarke-O'Neill S, Cook D, Dean G, Brooks R, Cottenden A, et al. Management of night-time urinary incontinence in residential settings for older people: an investigation into the effects of different pad changing regimes on skin health. Journal of Clinical Nursing 12(3):374-86, 2003 May.

630. Campbell R, Seymour J, Stone L, Milligan M. Clinical studies with disposable diapers containing absorbent gelling materials: evaluation of effects on infant skin condition. Journal of the American Academy of Dermatology 1987.

631. Lane A, Rehder P, Helm K. Evaluations of diapers containing absorbent gelling material with conventional disposable diapers in newborn infants. American Journal of Diseases in Children 1990.

632. Davis J, Leyden J, Grove GL, Raynor W. Comparison of disposable diapers with fluff absorbent and fluff plus absorbent polymers: effects on skin hydration, skin pH, and diaper dermatitis. Pediatr Dermatol 1989.

633. Wilson P, Dallas M. Diaper performance: maintenance of healthy skin. Pediatr Dermatol 1990.

634. Dallas M, Wilson P. Adult incontinence products: performance eveluation on healthy skin. INDA Journal of Nonwovens Research 1992.

635. Grove GL, Lemmen J, Garafalo M, Akin F. Assessment of skin hydration caused by diapers and incontinence articles. Current Problems in Dermatology 1998.

636. Beguin AM, Malaquin-Pavan E, Guihaire C, Hallet-Lezy AM, Souchon S, Homann V, et al. Improving diaper design to address incontinence associated dermatitis. BMC Geriatrics 2010.

637. Skewes S. Bathing: it's a tough job! Journal of Gerontological Nursing 1997.

638. Van der Valk P, Maibach HI. A functional study of the skin barrier to evaporative water loss by means of repeated cellophane-tape stripping. Clinical and experimental dermatology 1990.

639. Klein G, Grubauer G, Fritsch P. The influence of daily dishwashing with synthetic detergent on human skin. British Journal of Dermatology 1992.

640. AHRQ. Pressure ulcers in adults: Prediction and prevention (AHCPR publication no. 92-0047). 1992.

641. Gray M, Ratliff C, Donovan A. Perineal skin care for the incontinent patient. Adv Skin Wound Care 2002 Jul;15(4):170-5.

642. Gray M. Incontinence-related skin damage: essential knowledge. Ostomy Wound Management 53(12):28-32, 2007 Dec.

643. Lekan-Rutledge D, Doughty D, Moore KN, Wooldridge L. Promoting social continence: products and devices in the management of urinary incontinence. Urol Nurs 2003 Dec;23(6):416-28, 458.

644. Nix D, Ermer-Seltun J. A review of perineal skin care protocols and skin barrier product use. Ostomy Wound Management 50(12):59-67, 2004 Dec.

645. Fiers SA. Breaking the cycle: the etiology of incontinence dermatitis and evaluating and using skin care products. Ostomy Wound Manage 1996 Apr;42(3):32-40, passim.

646. Hess CT. Fundamental strategies for skin care. Ostomy/Wound Management, 1997;43(8):32-41.

647. Brown DS, Small S, Jones D. Standardizing skin care across settings. Ostomy Wound Manage 1995 Nov;41(10):40-3.

648. Gray M. Incontinence-related skin damage: essential knowledge. Ostomy Wound Management 53(12):28-32, 2007 Dec.

649. Jackson MA. Evidence-based practice for evaluation and management of female urinary tract infection. Urologic Nursing 2007;27(2):133-6.

650. Hurlow JSDA. An opportunity for WOC nurses. Journal of Wound, Ostomy, and Continence Nursing 2006;33:296-304.

651. Leiner S. Recurrent urinary tract infections in otherwise healthy adult women. Nurse Practitioner 1995;20(2):48-56.

652. Naish W, Hallam M. Urinary tract infection: diagnosis and management for nurses. Nurs Stand 2007 Feb 14;21(23):50-7.

653. Stapleton A, Stamm WE. Prevention of urinary tract infection. Infect Dis Clin North Am 1997 Sep;11(3):719-33.

654. Persad S, Watermeyer S, Griffiths A, Cherian B, Evans J. Association between urinary tract infection and post-micturition wiping habit. Acta Obstet Gynecol Scand 2006;85(11):1395-6.

655. Le Lievre S. Skin care for older people with incontinence. Elderly Care 2000;11(10):36-8.

656. Pasceri P. Utilizing a prevention and treatment protocol for skin breakdown secondary to urinary incontinence. Ostomy Wound Manage 1991 Sep;36:66-9.

657. Cooper P, Gray D. Comparison of two skin care regimes for incontinence. Br J Nurs 2001 Mar;10(6 Suppl):S6, S8, S10.

658. Lewis-Byers K, Thayer D. An evaluation of two incontinence skin care protocols in a long-term care setting. Ostomy Wound Manage 2002 Dec;48(12):44-51.

659. Nix D, Ermer-Seltun J. A review of perineal skin care protocols and skin barrier product use. Ostomy Wound Management 50(12):59-67, 2004 Dec.

660. Voegeli D. The effect of washing and drying practices on skin barrier function. J Wound Ostomy Continence Nurs 2008 Jan;35(1):84-90.

661. Abbas S, Goldberg JW, Massaro M. Personal cleanser technology and clinical performance. Dermatologic Therapy 2004.

662. Ronner AC, Berland CR, Runeman B, Kaijser B. The Hygienic Effectiveness of 2 Different Skin Cleansing Procedures. Journal of Wound, Ostomy and Continence Nursing 2010.

663. Ghadially R, Halkier-Sorensen L, Elias P. Effects of petrolatum on stratum corneum structure and function. Journal of the American Academy of Dermatology 1992.

664. De Paepe K, Hachem J, Vanpee E, Goossens A, Germaux M, Lachapelle J, et al. Beneficial effects of a skin tolerance-tested moisturizing cream on the barrier function in experimentally-elicited irritant and allergic contact dermatitis. Contact Dermatitis 2001.

665. Hannuksela A, Kinnunen T. Moisturizers prevent irritant dermatitis. Acta Derm Venereol 1992.

666. Gabard B. Testing the efficacy of moisturisers. In: Elsner P, Berardesca E, Maibach H, editors. Bioengineering of the skin:water and the stratum corneum. 1994.

667. Vinson J, Proch J. Inhibition of moisture penetration to the skin by a novel incontinence barrier product. Journal of Wound, Ostomy and Continence Nursing 1998.

668. Waring M, Hoggarth A. The measurement of skin barrier product efficacy. Journal of Wound, Ostomy and Continence Nursing 2004.

669. Hoggarth A, Waring M, Alexander J, Greenwood A, Callaghan T. A controlled, three-part trial to investigate the barrier function and skin hydration properties of six skin protectants. Ostomy Wound Manage 2005 Dec;51(12):30-42.

670. Berg RW. Etiologic factors in diaper dermatitis: a model for development of improved diapers. Pediatrician 1987.

671. Dealey C. Pressure sores and incontinence: a study evaluating the use of topical agents in skin care. Journal of Wound Care 1995.

672. Hunter S, Anderson J, Hanson D, Thompson P, Langemo D, Klug MG. Clinical trial of a prevention and treatment protocol for skin breakdown in two nursing homes.[erratum appears in J Wound Ostomy Continence Nurs. 2003 Nov;30(6):350]. Journal of Wound, Ostomy, & Continence Nursing 30(5):250-8, 2003 Sep.

673. Byers PH, Ryan PA, Regan MB, Shields A, Carta SG. Effects of incontinence care cleansing regimens on skin integrity. J Wound Ostomy Continence Nurs 1995 Jul;22(4):187-92.

674. Whittingham K, May S. Cleansing regimens for continence care. Prof Nurse 1998 Dec;14(3):167-72.

675. Anthony D, Barnes E, Malone-Lee J, Pluck R. A clinical study of Sudocrem in the management of dermatitis due to the physical stress of incontinence in a geriatric population. Journal of Advanced Nursing 1987.

676. Baatenburg de JH, Admiraal H. Comparing cost per use of 3M Cavilon No Sting Barrier Film with zinc oxide oil in incontinent patients. J Wound Care 2004 Oct;13(9):398-400.

677. Ashworth PD, Hagan MT. The meaning of incontinence: a qualitative study of non-geriatric urinary incontinence sufferers. J Adv Nurs 1993 Sep;18(9):1415-23.

678. Roe B, May C. Incontinence and sexuality: findings from a qualitative perspective. Journal of Advanced Nursing 1999.

679. Moore J, Jessop L, Osborne D. Gas-chromatographic and mass-spectrometric analysis of the odor of human feces. Gastroenterology 1987.

680. Suarez F, Springfield J, Levitt MD. Identification of gases responsible for the odour of human flatus and evaluation of a device purported to reduce this odour. Gut 1998.

681. Ohge H, Furne JK, Springfield J, Ringwala S, Levitt MD. Effectiveness of devices purported to reduce flatus odor. Am J Gastroenterol 2005 Feb;100(2):397-400.

682. Nobaek S, Johansson M, Molin G, Ahrne S, Jeppsson B. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. American Journal of Gastroenterology 2000.

683. Giffard CJ, Collins SB, Stoodley NC, Butterwick RF, Batt RM. Administration of charcoal, Yucca schidigera, and zinc acetate to reduce malodorous flatulence in dogs. J Am Vet Med Assoc 2001 Mar 15;218(6):892-6.

684. Hall RJ, Thompson H, Strother A. Effects of orally administered activated charcoal on intestinal gas. American Journal of Gastroenterology 1981.

685. Ganiats TG, Norcross WA, Halverson AL, Burford PA, Palinkas LA. Does Beano prevent gas? A double-blind crossover study of oral alpha-galactosidase to treat dietary oligosaccharide intolerance. J Fam Pract 1994 Nov;39(5):441-5.

686. Di SM, Miceli E, Gotti S, Missanelli A, Mazzocchi S, Corazza GR. The effect of oral alpha-galactosidase on intestinal gas production and gas-related symptoms. Dig Dis Sci 2007 Jan;52(1):78-83.

Committee 21

Continence Promotion, Education & Primary Prevention

Chair

Diane K. Newman, (USA)

Members

Brian Buckley, (UK/Ireland)

Deborah Gordon, (Australia)

Tomas L. Griebling, (USA)

Leigh E. Petty, (Australia)

Kefang Wang, (China)

Consultant

Cheryle Gartley (USA)

Nancy Norton (USA)

CONTENTS

I. LITERATURE SEARCH

II. INTRODUCTION

III. CONTINENCE PROMOTION AND AWARENESS

1. BACKGROUND
2. RAISING AWARENESS AND UNDERSTANDING
3. HELP-SEEKING (CARE-SEEKING) BEHAVIOR
4. CONTINENCE PROMOTION PROGRAM
5. RECOMMENDATIONS

IV. CONTINENCE ADVOCACY

1. BACKGROUND
2. CONTINENCE ADVOCACY WORLDWIDE
3. RECOMMENDATIONS

V. SERVICE DELIVERY, MODELS AND ACCESSING CARE

1. BACKGROUND
2. NEED FOR SERVICES
3. MODELS OF CARE
4. RECOMMENDATIONS

VI. PROFESSIONAL EDUCATION

1. BACKGROUND
2. MEDICAL EDUCATION
3. NURSING PROFESSIONALS
4. PHYSIOTHERAPY AND OTHER ALLIED HEALTH PROFESSIONALS
5. IMPACT OF CLINICAL GUIDELINES
6. RECOMMENDATIONS

VII. PRIMARY PREVENTION

1. BACKGROUND
2. POPULATION BASED PREVENTION
3. PREVENTION OF UI IN OLDER ADULTS
4. PREVENTION OF FAECAL INCONTINENCE
5. RECOMMENDATIONS

REFERENCES

APPENDIX1- Directory of Continence Organisations

LIST OF ABBREVIATIONS

APRN	Advanced practice registered nurse
BBF	Bladder and Bowel Foundation
BPS	Bladder pain syndrome
CFA	Continence Foundation of Australia
CNA	Continence nurse advisor
CNP	Continence nurse practitioner
CPC	Continence Promotion Committee
FI	Faecal incontinence
GP	General practitioner
HSB	Help-seeking behaviour
IC	Interstitial cystitis
ICI	International Consultation on Incontinence
ICS	International Continence Society
IFFGD	International Foundation for Functional Gastrointestinal Disorders
LUTS	Lower urinary tract symptoms
NA	Nursing assistant
NAFC	National Association For Continence
NCA	Nurse continence advisor
NIH	National Institute of Health
NH	Nursing home
OAB	Overactive bladder
POP	Pelvic organ prolapse
RCT	randomized, controlled study
QoL	Quality of life
PFMT	Pelvic floor muscle training
PT	Physical therapist or physiotherapist
UI	Urinary incontinence

Continence Promotion, Education & Primary Prevention

Diane K. Newman,
Brian Buckley, Deborah Gordon, Tomas L. Griebling,
Leigh E. Petty, Kefang Wang

Consultant
Cheryle Gartley, Nancy Norton

I. LITERATURE SEARCH

A systematic review of the literature using online databases Scopus, Medline/Pubmed, Embase, Biosis, Cinahl, Pychinfo, Psychlit, ERIC, Cochrane Library, Web of Knowledge, and CNKI (China National Knowledge Infrastructure) was conducted. The focuses of the searches were from 2008 to March 1, 2012, although literature from the preceding 15 years was also searched to ensure thorough coverage. The following search terms were used in various combination: awareness, consumer, education, urinary incontinence, faecal incontinence, incontinence, continence, continence awareness, continence promotion, health education, public education, population-based prevention, health promotion, help-seeking, care seeking, continence nurse, continence advisor, public awareness, prevention, primary prevention, pelvic organ prolapse, interstitial cystitis, bladder pain syndrome, painful bladder syndrome, allied health care professionals, self-care practices, outcome measures. There was significant overlap between the searches made on different databases, as would be expected. Non-English language guideline references were noted, but excluded from the review unless they contained an English-language abstract providing sufficient information.

II. INTRODUCTION

Continence promotion, education and primary prevention involves informing and educating the public and health care professionals that urinary and fecal incontinence can often be prevented, can be treated successfully in most cases, and can always be managed. Other bladder disorders, with links to incontinence, such as bladder pain syndrome/interstitial cystitis and pelvic organ prolapse, can also be treated and managed successfully and are often included in continence awareness programs. The Fourth International Consultation on Incontinence (ICI) Continence Promotion, Education & Primary Prevention Committee stressed the importance of all health care professionals promoting primary prevention of incontinence [1]. It was acknowledged that this would require raising the level of community awareness, providing public education as well as addressing health care professionals' education. While some advances have been made, these strategies remain a priority.

Taboos surrounding disorders of the bladder and bowel are gradually lifting in most cultures [2]. Two decades ago it was almost impossible to discuss urinary incontinence in the media. Today, in many countries, government funded initiatives and practice guidelines have been developed in the area of urinary and faecal incontinence [1,3,4]. Around the world, expert panels have suggested that urinary and fecal incontinence be combined through a multidisciplinary approach to further research priorities. Thus, there have been advances in promoting awareness of both of these conditions. Popular magazines, local and national papers, radio, and television, regularly cover topics of men and women relating to urinary incontinence in most developed countries. Many countries have run national or local public awareness campaigns, often spearheaded by a national continence organization. Many also have confidential "help lines," which can be accessed anonymously. The internet provides a convenient source of health information for a growing number of consumers. Some experts believe that persons with incontinence might get valuable advice and comfort by using interactive services such as internet "chat rooms." However, in many developing countries, accessible public information and campaigns relating to continence are limited or non-existent. Though information may be available in principle on the internet, access to the internet may itself be limited.

This chapter updates previous ICI chapters on four areas: continence awareness and promotion, service delivery, professional education, and primary prevention along with the recommendations in each area. The majority of information available relates primarily to urinary incontinence (UI) and faecal incontinence (FI) and less to bladder pain syndrome/interstitial cystitis (BPS/IC) and pelvic organ prolapse (POP). The first section reviews continence awareness by discussing health promotion and help-seeking (care-

seeking) behaviors (HSB) for these conditions. It is evident that progress has been made in the promotion of continence on a worldwide basis, but not much has changed in HSB for these disorders. There is a lack of evidence on translating awareness into behavioral change and on what triggers HSB. Information is provided on continence promotion programs and advocacy through worldwide organizations. Although there is a great deal of published information on building public and health care professional awareness of incontinence, there is minimal information on the effectiveness of changing public and professional attitudes and knowledge about it. The second section discusses service delivery and models of continence care. The third topic reviewed is the education of professionals in these areas (UI, FI, BPS/IC and POP) including the development and use of medical guidelines and care pathways. Finally, since these conditions are prevalent but often ignored by sufferers and professionals, the fourth and final topic addressed is population-based primary prevention research. There is a need for further research to substantiate the benefits of primary preventative strategies, including long term follow-up. The committee found more information about initiatives in all of these areas but very little evidence-based research to support the effectiveness of the initiatives or care.

III. CONTINENCE PROMOTION AND AWARENESS

1. BACKGROUND

Health promotion was defined by the Ottawa Charter for Health Promotion in 1986 as "the process of enabling people to increase control over and to improve their health."[5] Hence, health promotion is an important factor in primary, secondary and tertiary prevention efforts directed at individuals, communities and populations with, or at risk of developing, incontinence.

Efforts to promote continence awareness may be enhanced by adopting evidence based theories and methods from the field of health promotion. Health promotion frameworks can be used to plan and evaluate the effectiveness of strategies and programs used to promote continence. When planning health promotion interventions, consideration needs to be given to the demographic features of target groups including age, gender, culture, language and socioeconomic background [6].

2. RAISING AWARENESS AND UNDERSTANDING

The main reason to educate consumers – individuals with, or at risk of, incontinence and their family members or informal caregivers – is to increase awareness of incontinence and the benefits of prevention and management, with goals of eliminating stigma, promoting help-seeking, and reducing suffering [7,8,9]. While in some countries there is strong governmental support, much of the health promotion effort related to continence issues is undertaken by the many professional bodies, non-governmental continence organizations, and advocacy groups listed in Appendix I. Health education activities can involve educational, health-care, and community service providers, and may include a range of components including materials that are accessible, comprehensible, trustworthy, and culturally sensitive, formal and informal health advice systems such as including a hotline, online support and health care professional learning systems [10].

Consumer education is a critical component of effective continence promotion. This includes both general information about UI[11] and methods to identify potentially modifiable risk factors for UI [12]. Patients with UI have a wide variety of ideas and attitudes about why they leak urine [13]. Knowledge about specific aspects of UI is often limited, indicating an area for improved consumer education.

Consumer knowledge about FI is also generally limited. A recent study found that many patients had a significant emotional component to their experience of FI and that knowledge about the terms used to describe the condition was often limited [14]. A United States (USA) Public Broadcast (PBS) Second Opinion medical television program was develop to educate consumers about FI and attempts to dispel the stigma of this condition (www.iptv.org/video/detail.cfm/12719/sopt_20101018_fecal_incontinence_apt).

The Internet is frequently searched for health information, and coverage of relevant health topics is growing. This method of acquiring health information is widely accessible, anonymous and informal, with estimates indicating that around 20% of USA adults use the internet for this purpose [15]. Since one-quarter of adults do not go online, the percentage of health information seekers is 59% among the total U.S. adult population (http://pewinternet.org/Reports/2011/HealthTopics/Summary-of-Findings/Looking-for-health-information.aspx). Thus, accessing information about incontinence has become much easier in the age of digital technology, especially for internet users with a higher literacy level [10]. A 2011 Google search for "urinary incontinence" and "faecal incontinence" yielded about 4.8 million and 311,000 websites respectively; "interstitial cystitis" - 2.2 million sites, "bladder pain syndrome" – 105,000 sites and "pelvic organ prolapse" – 382,000 sites. These figures are all two to three times greater than a similar search in 2008. Many of the sites were related to non-government organizations such as the International Continence Society (ICS), the National Association For Continence (NAFC), the Simon Foundation, the Interstitial Cystitis Association (ICA), and the International Foundation for Functional Gastrointestinal Disorders (IFFGD).

In light of the reluctance of those affected by stigmatized illnesses such as incontinence to seek treatment or to ask health care professionals for information, the Internet may prove to be a useful tool for consumer education and public health outreach [16,17]. In a national survey of internet users in the USA, Berger et al[18] found a trend among people with a stigmatized illness such as UI to be more likely to report that internet use increased their communication with a health care provider and utilization of health care. The quality of these materials can vary widely and providers should help interested patients to navigate resources that provide accurate information. A recent study showed that most websites that provide UI information are not certified by any accrediting body [19]. There were also differences observed between sites run by professional organizations, educational and government agencies, and companies either for profit or non-profit.

Among those who do not use the Internet, 60% are aware of publicly available Internet access points within their community [20]. However, people with low levels of education and low socioeconomic status are less likely to use the Internet [21]. Research has questioned the quality of continence information on the internet and suggested that validation is needed [22]. Healthcare professionals can assist patients in finding reliable information sources by providing details of reputable web sites [23].

The Internet has changed the way many people access health information, and has much to offer as a means of health education and raising awareness. But Internet access is far from universal, especially in developing nations and among older and poorer sections of society in developed nations. Thus, it is important that more traditional awareness-raising and education methods are still used, such as information posters, leaflets and booklets distributed through health outlets such as clinics and pharmacies, and articles in the popular media. In both developing nations and in countries with limited health systems and dispersed populations, more innovative techniques have been successfully used for health education, such as dissemination of information through community nursing infrastructures and lay health workers.

Social network sites may be the future source of information for consumers. Sajadi and Goldman[24] used the word “incontinence” to search for information on Facebook, Twitter, and YouTube, to evaluate its usefulness. Their conclusion was that social networks have insufficient useful incontinence content, especially from healthcare professionals and incontinence organisations. However, they recommended that medical professionals and societies target these avenues to reach and educate consumers.

3. HELP-SEEKING (CARE-SEEKING) BEHAVIOR

Estimating the prevalence of continence problems is difficult due to different definitions of incontinence, different populations and different data collection strategies,[25] and this lack of clarity regarding baseline prevalence of incontinence undermines efforts to determine the proportion of those affected that seek help. Despite the considerable impact of both UI and FI on quality of life (QoL), it is clear that many people never seek help for their incontinence, although the precise level of under-reporting is difficult to determine [26,27]. Perhaps of more concern is a recent comparison of HSBs in two surveys conducted sixteen years apart (1991 and 2007) which revealed that there had been virtually no increase in the proportion of women seeking help for lower urinary tract symptoms (LUTS) [28].

Qualitative research has described a process that takes place and influences the decision to seek treatment (or not), whereby consumers affected by incontinence, or other chronic, non-life-threatening conditions, weigh the perceived costs and benefits of treatment (in terms of discomfort and inconvenience as well as financially) against the effect of the condition on QoL [29].

Instead of seeking care, individuals with UI and FI alter their lifestyle and develop elaborate “self-care” practices (e.g., stopping exercising, use of protective products, dietary and fluid changes) to conceal and/or mange symptoms and improve QoL [30,31,32,33]. Data from focus groups of women showed self-reliance and the development of personalized strategies to alleviate symptoms [34]. Some patients have been known to make major changes in their lives (e.g., quitting their jobs). Surveys have also revealed extensive use of coping mechanisms for overactive bladder (OAB) symptoms of urgency and frequency (e.g., toilet mapping) [35].

Several studies have estimated levels of help-seeking for specific consumer groups. An integrative literature review of HSB for UI symptoms among non-institutionalized women of all ages indicated that less than 38% of women sought help for their UI symptoms [36]. Age, type, and severity of UI, and embarrassment have been found to be significantly related to seeking care [37,38,39].

Kinchen and colleagues [26] noted that women with UI waited more than a year before seeking help from a health care provider or professional [26]. This delay is in line with a European survey that reported that consumers wait from 2 to 11 or more years before seeking treatment [40]. Huang et al[41] reported that fewer than 50% of women in the USA with clinically significant UI reported seeking treatment. This was despite the fact that all women in this study had health insurance to cover such services and had continuous access to a primary care provider. Only 12% of women with UI attending obstetric and gynaecology clinics in Turkey had sought help for their incontinence [42]. Shaw and colleagues[43] surveyed adult women attending primary care practices in United Kingdom (UK) and of those who noted UI symptoms (n=3273), only 15.8% of women with

stress UI, 32.3% of those with urge UI, and 33.7% with mixed UI had sought help for urinary symptoms during the preceding 12 months. Rizk[44] found that of women affected by UI in the United Arab Emirates (UAE), only 30.9% had sought medical advice.

Surveys of individuals with FI also indicate a lack of HSB. In 2010, the IFFGD conducted an online survey to help explain what it is like to live with and manage FI from the point of view of those who experience the condition (http://www.aboutincontinence.org/pdfs/319-IFFGD%20Incontinence%20Survey%20(9-11).pdf). A total of 142 individuals completed the survey, responders were recruited primarily from the IFFGD websites. Ninety-seven (68%) of the survey responders indicated they had never been diagnosed by a physician, giving reasons such as "too embarrassed to bring it up" and "feel I can manage the condition on my own." Of the 32% who had mentioned their FI problems to a physician, the physician implied there is not much to be done about it or it is a normal part of aging.

a) Barriers to seeking care

Understanding the barriers and reasons why people do or do not seek treatment for incontinence is hampered by the ethnic homogeneity of the existing data, which has been derived mostly from white populations, and there is a lack of comparisons with ethnic and minority populations. The strategies for promoting HSB need to be culturally appropriate to the populations of interest [45,46,47]. Rates of HSB for UI amongst minority groups may relate to a number of factors such as access to care, socioeconomic factors and access to or comprehension of health education campaigns or materials [48,49,50].

Help-seeking behaviour is dependent upon awareness and understanding [51] and lack of knowledge has been a significant barrier to people seeking help for continence issues. Furthermore, HSB for UI, FI, BPS and POP may be different depending on the person's culture, ethnicity, gender and socioeconomic groups.

Questionnaires have been developed and validated which can be used to assess consumer knowledge about UI and POP [52]. In 2008, a study (n = 126) found that white women had greater knowledge of UI than non-white women while both groups of women had higher levels of knowledge of UI compared to POP [53]. Using this instrument, research has shown that there appear to be important differences in health literacy about these conditions in different racial and ethnic groups.

Another study found that Korean American women living in America tend to rely on information and social support from family and friends rather than seeking professional advice for UI [54]. The women in this study sought help less frequently, had less knowledge and more negative attitudes towards UI than other community members. It was suggested that these factors influenced help-seeking in this group of women [55].

In certain parts of the world, cultural factors can affect the experience of incontinence and HSB and the gender of the health care provider may be a barrier. Knowledge of continence issues in UAE women was researched by Rizk and Hassan [56]. It was found that UAE women perceive continence problems to be neurological or "senile" disorders rather than related to childbirth or menopause. Quantitative data was derived from a community-based descriptive cross-sectional study conducted in Sri Lanka from 2006 to 2007 with 1,718 married women, aged 15-49, of whom 9.8% reported problems of stress UI [57]. Although incontinence affected outdoor activities, sexual life, and sense of wellbeing, women did not consider it a health problem, rarely discussed it with others, and rarely sought treatment. Barriers to help-seeking included fear of vaginal examination, shame and embarrassment, and belief that stress UI was a natural consequence of aging and childbirth. Within all cultures, embarrassment or shyness may prevent some women from seeking care for UI [58,59,60,61]. These have been shown to impact help-seeking in Middle Eastern women, where both UI and FI are underreported. In the UAE, cultural attitudes and inadequate public knowledge, and male health care providers have been identified as barriers to seeking health care for women, despite the effect on QoL. Rizk[44] found that women affected by UI in the UAE, were troubled by their inability to pray (90%) and to have sexual intercourse (33.3%). Saleh[62] found similar results when surveying women in Qatar who reported that UI interfered with their ability to pray (64%) because of lack of cleanliness and need to void, and 47% reported that UI interfered with marital relationships. El-Azab and colleagues[63] found that encouragement from husbands, severe UI and the desire to be able to pray were associated with an increased likelihood of HSB [63].

Rizk and colleagues (2001) investigated the prevalence and HSB of UAE women with FI (n = 400, mean age 37.9) and also found that many did not seek medical advice because they were too embarrassed to consult their physician and preferred to discuss the difficulty with friends (64.7 %), assumed that FI would resolve spontaneously (47.1 %), felt it was normal (31.3 %), or they chose self-treatment as a result of low expectations of medical care (23.5 %). As with UI, women with FI were bothered by the inability to pray (92.2 %) and to have sexual intercourse (43.1 %).

These studies reinforce the need for different strategies to be targeted to cultural and minority groups with low levels of HSB for UI and FI. In addition, public education efforts related to UI should not just focus on older adults [64]. An earlier study of high-school and college age athletes in the USA found that more than 25% of the young women surveyed

experienced UI during strenuous physical activity, but 90% had never reported their symptoms to anyone [65]. A recent study of nulliparous female athletes also found that young women have low levels of HSB for UI [66]. This study found that UI issues occurred particularly during training and to a lesser extent, during competition in women of varying competitive levels ranging from high school to elite level athletes. The prevalence rates of UI in nulliparous women in recent studies have varied from 28% to 52% and are influenced by the type of athletic activity. A 2011 study found a lower prevalence rate of UI in women playing volleyball compared to higher rates occurring in women performing track and field, soccer and gymnastics [66].

Barriers to seeking help for continence issues that have been frequently identified in the literature include embarrassment, social stigma and the mistaken belief that incontinence is inevitable, untreatable, and/or a normal part of aging [67]. The authors of a Swedish study suspected that lack of knowledge, worries about different procedures and negative expectations may be important factors in reducing the desire to seek treatment among even those most severely affected [68]. Embarrassment and fear of humiliation have been identified as the major factor influencing reluctance to seek help among women with long-term UI [69]. Among women affected by UI in the UAE, reasons for not seeking help included embarrassment (38.2%), choice of self-treatment because of low expectations from medical care (38.2%) and assuming that UI is normal (23.3%) [44]. Among women with gynaecological cancers who experience concomitant LUTS, the failure to seek help for the latter symptoms has been attributed to a perception that the LUTS were not serious enough symptoms to warrant attention and lack of awareness of treatment options [70].

Advice given by physicians can affect a patient's ability to change health behaviours [71]. Opportunities to promote continence can present themselves during other health screening activities (e.g., yearly physical examination) [72]. While health care professionals may enable people to seek help, those who have a lack of interest in incontinence can negatively affect HSB in consumers [73,74].

Other initiatives to promote HSB can include providing written information [75]. Continence health promotion information provided in a brochure [76] and in a computer based program,[77] have been found to improve HSB. However, language, level of education and cultural factors may also be barriers to seeking help [78]. Consideration should be given to health literacy in target populations and this will affect the ability to read and understand health information in written formats. Poor health literacy results in lower rates of health seeking behavior [79].

The Boston Area Community Health (BACH)[80] population-based random epidemiological survey of urologic symptoms (n=5503) indicated that the stigma of UI also includes other LUTS. They reported that OAB symptoms of urgency and frequency were linked to social interruption, loss of socially-expected control of the body, not understanding the nature of the bladder problem, and the need to mix private behavior and public space. The stigma of OAB and UI was correlated to whether the problem was perceptible (i.e., odor, or observation of trips to the bathroom or soiled clothes) or concealed. Men reported feeling stigmatized for being seen making frequent trips to the bathroom and feared being viewed as impotent. Women feared being stigmatized based on having an unclean body and a compromised social identity. Like others, Hispanic individuals wanted to keep urinary symptoms a secret from others.

Surprisingly, the perception that incontinence is not important or serious enough to warrant treatment has even been found to affect HSBs in women with recurrent UI following surgery for UI and POP [81]. Women with POP have also reported that fear and embarrassment are barriers to seeking help. Symptoms such as nocturia have been linked with serious consequences such as falls and associated morbidity in older adults. Bladder and bowel incontinence is a deviation from social norms, which in most cultures there are defined complex and sensitive rules and behaviours for bladder and bowel emptying [82,83]. If incontinence occurs in adulthood, it can cause a decrease in self-esteem and feelings of not being "normal."[84] These perceptions, which can affect help-seeking, are shared by the public as well as by many health care providers [85].

b) Gender-specific disparity

The impact of UI may also differ depending on gender but little is known about gender differences in HSB. Teunissen and colleagues [86] interviewed independently living patients (56 men, 314 women) 60 years and older with uncomplicated UI. Men reported higher impact scores than women, despite the fact that incontinence was less severe in men. The most important effect of incontinence reported in men was ''being out of control," while most women considered ''feeling compelled to take several precautions'' to be the most important consequence of UI. Researchers in Egypt interviewed 353 patients attending clinics at hospitals in Alexandria, Egypt [87]. They found differences in men and women as women suffered from at least one negative impact on their social lives compared to men. The impact of symptoms on QoL appeared to be the main trigger for seeking help for UI in both men and women. Women had fewer hospital admissions and hospital days and less use of diagnostic procedures and surgery.

There is very limited data on ways to improve men's awareness of bladder and bowel health [88]. Gender specific health disparity may exist as men tend to be less proactive in HSB for UI. There is a need

for gender specific strategies to address this [89]. Men with LUTS have been found to seek help less frequently than women [90]. Consumer surveys conducted over a 5-year period by the USA continence advocacy group, the NAFC, indicated that only 26% of respondents (18% of men and 33% of women) reporting bladder control symptoms had discussed them with a doctor [91]. However, a study into the prevalence of UI in men in the USA found that while a low proportion of men with continence issues sought help, those who did, consulted their doctor within 12 months of the onset of symptoms, a shorter period than the length of time taken by women to seek help [92]. Men are more likely to seek help for LUTS if they have had advice from others or received information in the media, rather than seeking help as a result of their symptoms [93].

In certain parts of the world, the gender of the health care provider may be a barrier. Doshani et al[94] explored views and experiences of South Asian Indian women with UI and found that feelings of embarrassment were present, especially with male health care providers.

c) Symptom impact and bother

The level of perceived bother (physical, emotional and/or economic) associated with incontinence also affects HSBs. A number of studies have found that those affected by incontinence are not necessarily so bothered by it as to want to seek professional help. In Japan, it has been found that 55% of elderly incontinent people do not consider incontinence a bother [95]. Of women with UI attending obstetric and gynaecology clinics in Turkey, 53% were found not to be bothered by their incontinence [42]. In a population-based study in Sweden (a supplement to a comprehensive survey of public health and general living conditions), a postal questionnaire comprised of 12 questions on UI received a response rate of 64.5% from 15,360 randomly selected residents (aged 18–79 years) [68]. The prevalence of UI was 19% (when defined as “any leakage”) and most considered their problems to be minor. Only 18% of those with UI desired treatment. Of the 17% who had reported severe problems that interfered with daily life, 42% did not want treatment. A recent study by Visser and colleagues[39] showed that older adult women, who did not consult a general practitioner (GP) about incontinence symptoms, were more often younger and had lower levels of distress due to their urogynaecological symptoms, but the main reason for not seeking help was they did not consider their symptoms to be severe enough [39]. An internet survey in the USA, the UK and Sweden, noted that in men and women who reported LUTS less than a third of respondents reported seeking treatment [96]. Rates of bother were greatest for those who reported multiple storage, voiding and post-micturition LUTS (men 83%, women 89%) and correlates of treatment seeking across genders included bother due to weak stream, incomplete emptying, perceived daytime frequency, nocturia and urgency.

With chronic problems like UI, FI, POP and BPS/IC, it is important to understand what triggers the consumer to consult a health care provider [83]. Yet factors that lead those affected to seek help for continence issues remain less well researched than those that prevent help seeking. Women with stress UI are more likely to seek help when there is severe leakage that is having a significant impact on their QoL [97]. The importance of the effect of UI on QoL is supported by Brazilian research [98]. An American study suggests that worsening severity of UI, along with increasing age and not being obese, were associated with an increased likelihood of help seeking [99]. Older people may be keen to seek help if they are concerned that a health issue, such as incontinence, impacts on their ability to remain independent and living in the community [100].

In conclusion, the most commonly reported reasons for not seeking help for incontinence are lack of knowledge and awareness, embarrassment, a perception that incontinence is not sufficiently important to warrant treatment or is “normal” either at certain stages of life or in association with childbirth or certain illnesses, and low expectations of the effectiveness of treatments offered. The more serious the impact of incontinence is on QoL, the greater the likelihood of seeking help, but this will be balanced against the perceived disadvantages of treatment in terms of cost, discomfort or inconvenience.

4. CONTINENCE PROMOTION PROGRAMS

Continence promotion programs vary across countries and cultures, but share the same aim of increasing awareness and understanding of incontinence. Efforts to raise awareness of continence issues need to consider the following:

Target population - Continence promotion programs need to consider age, gender and culture of target populations. It is necessary to consult with target groups when planning programs in order to meet the needs of these groups and to enhance HSB [101].

Target issues - A continence promotion program needs to address risk factors and management options in different target groups. Community-based interactive continence promotion workshops conducted in a recent cohort study in Canada were shown to be well-received by participants and the interventions changed knowledge, attitudes, skills, and appeared to increase rates of HSBs [102]. A similar study showed that improved understanding about UI and POP was associated with improved QoL scores among women who attended a nurse-led educational workshop [103].

Promotional material – Newman [104] reported on a mail survey of 1,500 women, noting that most of the 422 respondents wanted more information regarding UI, and while they may not be equipped to fully

understand the problem, they expect doctors, nurses, medical professionals, retail outlets, medical supply companies, and mail order houses to provide the information, including information through consumer advertising.

Communication and expectations – Health care professionals may launch campaigns or seminars to increase practice revenues. Commercial companies often fund public campaigns in order to sell their products, whereas continence organizations may be driven by missionary zeal or organizational growth. Regardless of motivation, care should be taken to avoid raising public expectations beyond what the services or products can deliver [105].

a) Creating public awareness

In the area of UI, building awareness among the general public has usually been attempted via the media. The USA National Institutes of Health, in partnership with the American Urogynecological Society, American Urological Association, American Foundation for Urologic Disease, NAFC, Society of Urologic Nurses and Associates and the Simon Foundation for Continence, launched a national awareness campaign in 1997. The Let's Talk About Bladder Control for Women awareness campaign (http://kidney.niddk.nih.gov/kudiseases/pubs/bcw_ez/index.htm) offered easy-to-read booklets explaining the symptoms, types and causes of poor bladder control, as well as treatment options. The materials were designed to encourage and enhance communication between and among women and their health care providers. Free consumer and health care provider kits were available through a toll-free phone number. In 2007, the USA National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH) State of the Science Conference Statement on Prevention and Fecal and Urinary Incontinence in Adults paved the way for the 2011 national campaign, Let's Talk about Bowel Control (www.bowelcontrol.nih.gov). In 2001, the NAFC in the USA produced and disseminated continence awareness public service announcements (PSAs) to 380 television media markets, including Hispanic outlets. In the UK, the Bladder and Bowel Foundation (BBF), supported by the pharmaceutical industry, has conducted a lengthy campaign to raise awareness of OAB and to encourage HSBs (www.bladderandbowelfoundation.org/?p=1550). The campaign has featured advertisement of a toll-free information line on television, in the print media and on public transport. The BBF also provides informational leaflets on a variety of continence-related topics and a website containing a great deal of information as well as a directory through which visitors can locate their nearest continence professionals and clinics. Another UK organization, Education and Resources for Improving Childhood Continence (ERIC), offers courses for school nurses on how to deal with school children with UI, as well as children with medical issues (http://www.telegraph.co.uk/education/primaryeducation/5956231/Pupils-start-school-still-in-nappies.html). In Australia, the government has provided a high level of support to continence promotion activities via the National Continence Program [106,107,108]. These are just a few examples of campaigns conducted by organizations to bring awareness to lower urinary tract conditions.

Media campaigns should use multiple channels to ensure the broadest coverage [109]. Channels can include print media, television and radio, while the Internet, phones, and other mobile devices are also effective outreach channels [110]. Specialised age and health publications offer potentially valuable channels for dissemination of continence advice. At a more local level, a useful channel for dissemination can be the use of posters and brochures placed in medical offices, hospitals, seniors' centres, pharmacies and churches and direct presentations to the public, such as at senior citizen's centres [111] or retirement communities [112]. In many cultures, an effective strategy for reaching the public is through an informed journalist. Journalists often use a "media hook," an interesting story that will take priority over other news on the television, radio or newspaper. In addition, having a spokesperson affected by incontinence or finding a celebrity who is willing to speak for the cause can help [82]. These individuals can act as "influence leaders."

The Japan Continence Action Society held a "Toll Free Telephone Clinic" and callers were asked how they heard about the line. The responses in 2006 were: 30% from television, 16% from the web, 11% from a newspaper, 9% from a book, 6% from a friend, 5% from a brochure, 3% from a magazine and 20% other and/or unknown. A UK campaign [113] found that newspapers were by far the most common source of information, followed by radio. However, with the growth of the Internet and social media, print campaigns may no longer be the most effective avenue for awareness.

Roe [114] suggested that local initiatives on the availability of services and how to access them, as well as health education information on UI, may be particularly effective in raising public awareness and should supplement national campaigns. Awareness raising materials include pamphlets, self-care instructions, visual aids, pictographs, posters, banners, decals and advertisements in newspapers, magazines, newsletters, CD and films. Muller [115] believed that the change related to increased public awareness and HSB for continence care is likely to fuel the demand for innovation in technology and products. The Simon Foundation for Continence developed an innovative community education initiative, The Bladder Health Mobile. The goal of this initiative was to provide education, increase public awareness, and promote early diagnosis and proper treatment of UI and other bladder control problems [116]. However, it was never launched due to a lack of funding.

Health literacy related to UI is an important issue,

and is a potential target for additional consumer education. Raising awareness of health problems and providing information on terms used to describe symptoms assists in promoting HSB [117]. The words "continence" or "incontinence," "interstitial cystitis," or "painful bladder syndrome," or bladder pain syndrome and "pelvic organ prolapse" are poorly understood [118] and simpler terms may achieve greater public recognition in many languages and cultures. The use of "overactive bladder" in advertising has increased reporting of the condition to primary care professionals in the USA. Palmer and Newman [74] reported on a USA health promotion project conducted in 2000 to determine the needs of senior citizens concerning bladder control issues. Focus groups of older adults attending health seminars in urban, community and church settings were conducted. The primary objective of the project was to determine the understanding of older adults in the areas of general health and their beliefs surrounding the problem of UI. The 82 participants were predominantly African-American women representing all socio-economic levels. Seniors expressed confusion when asked if "overactive bladder, bladder control issues and UI" were the same condition. An evaluation of Australia's National Continence Management Strategy in 2006 noted that recognition of the barriers to help-seeking and identification of the most appropriate terminology and key messages would strengthen awareness raising strategies [106,119].

In the UK, campaigns and consumer literature often avoid clinical terms in favor of lay terms that focus on the need to go to the toilet often, worrying that one may not make it to the toilet on time or have "leaking" of urine or feces. In the area of bowel disorders such as FI, it is felt that people find it difficult to find the right words to discuss their symptoms [85]. The IFFGD in the USA has found that people will often report having diarrhea to their physician. If the physician or nurse does not question the patient any further regarding the ability to control gas, liquid or solid stool, the incontinence may not be discovered.

Lack of understanding about terminology and physiology may lead to difficulties with communication between patients and providers. A survey of 138 women attending continence clinics in the UK, Australia, and Italy found that over 20% of women were unsure of the meaning of basic continence terminology commonly used by health care providers [120]. Terms tested in this study included "daytime frequency, nocturia, urgency, urge UI, stress UI, and hesitancy." Two recent studies highlight the confusion and lack of knowledge about LUTS. Smith and colleagues [121] study of focus groups with women who experienced OAB, showed that there were high levels of misunderstanding about symptoms and physiology, and miscommunication between patients and providers. The finding was more pronounced among the older women in this study. Senejian and colleagues[118] corroborated this finding and recommended that public health campaigns about UI and other pelvic floor disorders need to use terminology targeted to the basic understanding of consumers.

Some researchers have targeted health literacy of patients undergoing urodynamic testing [122]. Theoretically, this may help to improve understanding of the procedure and reduce patient anxiety. This particular study did not reveal significant differences in overall satisfaction between the group that received this additional information and those who did not. A similar study revealed that after reading this type of material, most women (78.1%) felt they understood the indications for urodynamic testing [123]. However, fewer felt they understood what the procedures would involve (68.2%) or that they had enough information about the tests (64.9%). Many patients still expressed anxiety or embarrassment about the procedure. Additional research will be needed to determine how best to deliver this type of information to improve patient experiences.

b) Program evaluation

Evaluating the effectiveness of health promotion programs is notoriously difficult. Evaluation methods should be established prior to developing the continence promotion program. Evaluation should include quantitative measurements and qualitative measures. Open-ended questions may be more sensitive than "direct satisfaction" questions [124]. Health promotion evaluation methods include process evaluation, impact evaluation and outcome evaluation.

Research-based evidence for the effectiveness of programs aimed at raising awareness of continence issues or at improving help-seeking behaviors is rare [125]. A number of studies have considered the effectiveness of leaflets or brochures in raising awareness of UI and of treatment options and while generally supportive of such information, the evidence is contradictory in some areas and far from conclusive. In a good quality study of 1,175 participants, Wagg et al [126] reported that a self-help standard treatment leaflet is as effective as structured help from a continence nurse in reducing bothersome urinary symptoms in women. A small Australian study considered an information leaflet to have influenced the HSBs of people with UI who had received it, but these were people who were identified in a primary care setting and had already reported a UI problem [127]. A similar study found that individuals given a continence education package, which included a Continence Educational Brochure, helped to improve the health-seeking behaviours of participants who were bothered by UI symptoms [128]. Within 3 months following the education, of the 111 participants who were bothered by UI symptoms, 49 participants (44.1%) indicated that they had discussed the issue of bladder or bowel problems with a health care professional, but this could have been either directly because of the information contained in the brochure or because of

information contained in the leaflet. But there is research that indicates that education alone may not improve a person's understanding or experience with specific medical care. A study that investigated the effectiveness of detailed educational materials, about the urodynamic tests given to women undergoing these investigations, did not significantly improve their experience [129]. A Swedish population-based study found that the distribution of a brochure on UI to the general public was well received and can be an efficient method to spread knowledge and encourage self-management [130].

In France, the effect of direct health education was evaluated in a randomized study in sheltered accommodation for the elderly [131]. Twenty centers were randomized to either a single one-hour health information meeting or control group. During a 30-minute talk, a nurse encouraged people to visit a physician if they had urinary problems. A questionnaire three months later found that the experimental group was much more likely to have had treatment if they were incontinent (41% vs. 13% controls). Similarly, knowledge and symptoms were found to have significantly improved three months after a 2.5 hour nurse-led workshop for women with UI and POP [132].

A health promotion project called 'Dry Expectations' was developed and implemented in six ethnically diverse, predominantly minority, and inner city senior centres in the USA in 1996 [111]. The program was designed to address an older population. The project consisted of three phases: orientation and training of key staff members/peer educators at the centres (train-the-trainer model); educating seniors through four one-hour weekly sessions involving visual aids and completion of bladder records and quizzes; and follow up sessions with senior staff/peer educators to reinforce the previous training. The program was very well received by the participants and approximately 80% felt they had more control over their bladder by the end of the last session.

The interventions that are most effective in reaching the public and triggering the desired behaviour seem to vary between countries and cultures. Television and newspapers work best in Singapore, with a "cured" patient bearing testimony to former suffering and its alleviation having the most impact. In the USA, television advertising targeting OAB, funded primarily by pharmaceutical companies, has yielded a significant response. Nationwide television reaches more people than the circulation of any single newspaper or the distribution of a booklet through physician offices. In March 2008, Japanese National Television broadcast a program about UI during "golden time" (2000 to 2045 hours). The audience rating was 15.6%, the highest in a year (usual rating 12%), and more than 500 calls were received in one night, requesting repeat broadcast and more details about treatment. However, the Internet is rapidly becoming the most effective and quickest way to reach the largest number of people. But there are cultural differences in the how online health information is used, as well as the types of sites users prefer to surf [110].

5. RECOMMENDATIONS FOR CONTINENCE PROMOTION AND AWARENESS (GRADE D)

Based on the literature reviewed in this section, the following recommendations can be made:

- Continence awareness should be part of mainstream and on-going health education and advocacy programs with emphasis on eliminating stigma, raising awareness of effective treatments, promoting HSB and improving QoL.
- Continence awareness programs should include education, health-care, and community service providers.
- Research is needed to provide higher levels of evidence on the effectiveness of continence promotion programs to include:
  - o Identification and understanding of barriers to HSBs
  - o Translation of promotion research into improved clinical practice and identification of methods by which this occurs.
  - o Effectiveness and impact of consumer education initiatives.

IV. CONTINENCE ADVOCACY

1. BACKGROUND

Advocacy is defined as the act or process of defending or maintaining a cause or proposal. Advocacy, as it pertains to incontinence, involves assisting individuals in finding necessary health care and treatment. Organisations consisting of professional and public members promote continence advocacy as a core mission.

There is little doubt that incontinence is a common problem that often goes unreported, with those affected anxious to conceal the problem and reluctant to discuss it. Misconceptions fuel this reluctance, such as the widespread belief that incontinence is normal in some circumstances, especially in women following childbirth or in both sexes after a certain age. Incontinence is associated with a very strong stigma that sets it apart from most other health problems and will inevitably influence behaviours. Whereas many formerly stigmatized health issues such as cancer and women's health are more openly discussed today than previously, incontinence remains for the most part shrouded in silence [133,134]. Yet the effect of incontinence on self-image, emotional well-being and QoL cannot be underestimated. Lowered self-esteem, shame, embarrassment, despair and depression are often reported; incontinence can

affect the ability to form or maintain personal relationships, leading to isolation [135,136,137,138].

In such circumstances, there is a need among the general public for better awareness and understanding of bladder and bowel problems, and of the services and treatments that are available. There is also a need for both practical and emotional support to those affected and for advocacy on their behalf in pursuit of development in treatments and services. In response to these needs, continence advocacy organizations have emerged in many countries.

2. CONTINENCE ADVOCACY WORLDWIDE

A central goal of most continence advocacy organizations is the raising of public awareness and understanding of the types of incontinence, the risk factors for incontinence and treatments, services and management products available. These organizations provide a valuable voice for an often unheard consumer population in political and health-care governance, development and planning processes. In recent years, consumers and clinicians have been involved in identifying and prioritizing important areas of research relating to incontinence in order to inform research development and funding decisions [139,140]. In addition, through advocacy organisations, the consumers of health care have become more closely involved and influential in the activities of clinical professional organisations.

Another major role that has been adopted by many continence organizations is the direct provision of information support to those affected by incontinence and to caregivers. The types of information provided include background information about symptoms, risk factors and conditions, treatments and management strategies, and availability of, and access to, health and social services. Such information is provided through a variety of sources, including regularly produced magazines, internet-based information resources, telephone support lines (often staffed by qualified nursing or counseling staff), and printed media such as leaflets and booklets on a wide variety of topics. Other innovative strategies have included outreach work through travelling information roadshows and events [116]. Organisations also provide emotional supports to people with incontinence by putting them in touch with others similarly affected either through direct contact at meetings or through internet discussion forums.

For the Fifth International Consultation on Incontinence, forty-seven continence organisations in twenty-eight countries were identified, with an additional two international consumer-based organisations (Appendix 1). Continence organisations vary in scale and in nature, from small consumer or clinician groups that focus on quite specific bladder symptoms or conditions, to large and well-funded national organisations that address bladder problems generally. Often the founding and development of such organisations has resulted from the dedication of a small group of sufferers consumers, clinicians or both, who have worked tirelessly to promote awareness and understanding of incontinence among the public or colleagues and to provide better services and supports to those affected. They represent a wide diversity of models, including consumer-led, company-sponsored, consumer-only, professionals-only, and organisations which have deliberately set about trying to bring together all relevant stakeholders in a relatively democratic model. In every part of the world, these organisations play a dynamic role in building both public and professional awareness of this underserved and underreported condition.

a) Funding

The degree of funding available inevitably affects the level of work that organizations can undertake. Whereas in some countries, such as Australia, relatively strong governmental support has been provided for the work of continence support organisations, in other countries such as the USA and UK, financial support has come for the most part through charitable donations from individuals and foundations, or through the support of the pharmaceutical industry and continence products manufacturers. Most continence organisations are poorly capitalized, being either under- or unfunded (i.e., run by volunteers) and are held together initially by either a dedicated consumer advocate or an energized healthcare professional. In most cases, this professional is an urologist or nurse whose patient population includes persons with UI. In developing countries, where the need for improved awareness, support and services is often greatest, the availability of funding for continence advocacy work is particularly challenging.

Lack of funding limits the work of continence organisations, and searching for funding can present a considerable burden in terms of time and skills for an organisation's paid or voluntary staff. The very source of funding can present additional challenges: in most parts of the world, organisations are at least partially, if not totally, dependent upon funding from pharmaceutical and product manufacturers. In order to avoid a perceived or real conflict of interest, organisations are well advised to have clear and robust policies dictating the nature of their relationships with commercial entities, to declare their arrangements fully and, if possible, to ensure that they are not dependent for funding upon only one company.

b) Collaboration

Within countries, some previously separate consumer-led organisations have merged with clinician-led organisations in order to make best use of funding available and to prevent duplication of efforts [133]. In other countries there may be good reasons why this is not possible, while in some circumstances there is merit in the independence of groups focusing on specific areas within the continence field. However, both within countries and internationally, there is much to be gained from the networking and cooperation of organisations.

Duplication of effort in the production of materials and other activities can often be avoided, and although it may not be practical to develop global and uniform strategies for continence promotion and public awareness, much can be learned from the positive and negative experiences of other organisations in other countries. For instance, in 1998, the Asia Pacific Continence Advisory Board member countries including Thailand, Korea, China, Hong Kong, Taiwan, Malaysia, Indonesia, India, Philippines, Singapore and Pakistan joined to develop continence promotion programmes that collaborated with health care professionals and the general public. Their mission was to develop strategies to increase awareness and reduce the social burden of UI in the Asia Pacific Rim.

In addition, the cooperation and coordination of continence organisations on an international level can result in more effective engagement with influential international clinical and research organisations. Professionals (e.g., urologists, urogynaecologists, gynaecologists, geriatricians, primary care practitioners, physiotherapists, nurses) and professional organisations have been instrumental in promoting awareness of continence in all care settings. The International Continence Society (ICS) established the Continence Promotion Committee (CPC) to promote education, services and public awareness about incontinence throughout the world, and to facilitate communication, exchange of information and partnerships between continence organisations, health care professionals, governments, and industry. The CPC's multinational and multidisciplinary representation, which includes representatives of continence organisations from around the world, aims to identify broad issues through an international forum that can facilitate translation at the local and national level. Each year at the ICS's annual meeting, the CPC holds workshops around various themes that have a broad national focus, such as prevention, GP education and promotional strategies. Its relevance, as is the case with each of the national organisations, is to recognize the interface between continence management and continence awareness and promotion. The CPC is also promoting continence awareness through the hosting of public forums in conjunction with the ICS annual meeting and sponsorship of the yearly World Continence Week.

The level of evidence on the impact of national organisations increasing continence awareness is Level 3.

3. RECOMMENDATION FOR CONTINENCE ADVOCACY (LEVEL OF EVIDENCE-3, GRADE D)

Based on the literature reviewed in this section, the following recommendations can be made:

- Research is needed on the activities or effectiveness of organisations that target consumers or the general public.

V. SERVICE DELIVERY, MODELS AND ACCESSING CARE

1. BACKGROUND

There has never been a comprehensive examination of an optimal service or model for delivery of continence care. It is not known whether academic, specialist-led centres will achieve better and more cost-effective results than primary care clinics, domiciliary services or any other model. However, most experts believe that female UI is initially most effectively diagnosed and managed by primary care providers compared to specialist services. A large cross-sectional community mail survey of women with UI in France, Germany, Spain, and the UK found that many women actually prefer to be treated for UI by primary care providers, despite easy access to specialized services [141]. Appropriately trained continence nurses and physical therapists can provide high quality UI care for women; women are satisfied with care provided by continence nurses [142,143,144]. In 2000, the UK Department of Health issued guidance on continence services that outlined a good practice model to achieve more responsive, equitable, effective continence services [145].

In the USA, the primary sources of care for the majority of Medicare patients (primarily an elderly population) are family physicians and primary care physicians [146]. Less than 1 person in 1000 is admitted to an academic, medical centre hospital [147]. Thus, in the USA, elderly persons with UI and FI will probably be seen by primary care physicians for initial assessment. This is unlikely to address the needs of developing countries (such as the Asia Pacific area or in Africa) where dissemination of expertise to rural communities and isolated community health care workers is more logical. Continence services are being implemented in several countries using shared teaching and educational resources through co-operative arrangements of the respective Continence Foundations. Thus, the general practitioner (GP) or family physician plays an important role in the first line treatment of UI that may be treated successfully with conservative treatments in the majority of patients [148,149].

In fact, UI is often a complex and multi-faceted problem, particularly in frail or dependent individuals, and it may require input from a wide variety of disciplines to tackle it effectively. Drennan and colleagues[150] interviewed thirty-two caregivers about their strategies for managing a person with UI and dementia. They recommended that professionals, especially those in primary care, could be more proactive in questioning patients about incontinence and toileting habits to identify counter-productive and harmful strategies. Symptoms typically associated with incontinence may also be indicative of other conditions, as evidenced by the urgency and frequency symptoms of BPS [151,152]. The ICI Committee 19 addresses Bladder Pain Syndrome. While it may not be practical for all specialties to work in close prox-

imity, there is a need to consider carefully specialist roles, responsibility, and which protocols will guide appropriate referrals and ensure good collaboration. It is important that there are neither gaps nor overlaps in the service.

Although some might see multidisciplinary relationships as the ideal, the reality is not always smooth. In some situations, rivalries and competition between disciplines and medical specialties is evident. This may be because of competition for patients and revenue, or because of disputes over the demarcation of the scope of different disciplines (such as the boundary between urology and gynaecology, or between nursing and physiotherapy).

Implementation of integrated service mandates can be challenging due to infrastructure limitations and other barriers. For example, despite national recommendations for multidisciplinary integrated continence services in the UK, audits indicate that this requirement is not yet being met [153,154,155].

2. NEED FOR SERVICES

There are no studies directly comparing the effectiveness of specific delivery systems for continence care. In certain cases, enthusiasts have conducted research, and results may not generalize to the wider setting. Others have combined the expertise of multidisciplinary teams to maximize service delivery. The level of evidence on service delivery models is 4.

A Japanese survey of over 1,000 caregivers of elderly incontinent people in the community found that more than 80% of caregivers are female and over half were more than 60 years old [95]. The caregivers felt that incontinence caused problems with the home getting dirty (10%), extra laundry (9%), need to wake at night (7%), and not being able to leave their homes because of incontinence (9%). When asked what kind of government service they wanted, caregivers replied “health training” (10%), “knowledge about incontinence” (10%), and “supply of a portable toilet” (3%). Only 6% wanted the government to send them professional caregivers and only 4% desired referral to a specialist physician.

Knowledge and attitudes about UI and care certainly may influence consumer choices. Some studies suggest that as QoL worsens, care-seeking increases [156]. In some cultures, particularly those where living with extended family is more common, UI may be viewed as a family issue rather than a disorder affecting just one family member [157]. Family support is often seen as an important component when dealing with UI [158].

Buckley and Lapitan[159] conducted an online survey of 1,040 community-dwelling adults in the UK to examine attitudes and behaviours related to care-seeking for UI, FI, and nocturnal enuresis [159]. Overall, 75% said they would turn to their GP for help. However, a surprising 23% said they did not know where to turn for help. This confirms that there are still major needs for continence promotion and consumer education at the community level.

This can create a dilemma and raises many questions. Should health care professionals attempt to persuade or educate people who do not see UI as a problem that it is an abnormal condition? Should a patient who is “not bothered” by symptoms be treated because the partner or caregiver requests the physician’s assistance? This is concerning as Rodriquez, et al.[160] found that physicians underestimated the degree to which patients were bothered by their symptoms 25% to 37% of the time. Is lack of bother genuine or simply a defense against having to tackle an unpleasant problem? Does early intervention prevent later deterioration in symptoms? Does delay in treatment mean that success rates are lowered? There is scant evidence on any of these issues or on the most acceptable way of providing help.

Using narrative analysis of structured patient interviews, Bradway and Strumpf[161] found that women with UI who sought professional care were more likely to “tell a story,” describe UI as having a negative impact on their sense of self, were older, Caucasian, were in ‘good or excellent’ self-reported health, and had suffered from UI longer compared to those who did not seek care [161]. They also confirmed that many women found that UI impairs their sexual health and intimacy.

In contrast, some studies have shown that compared to general health care, many women prefer to take a more active role in their care for UI. In a survey of 265 Norwegian women with UI, O’Donnell and Hunskaar found that 60% of women wanted to be actively involved in their UI care decisions compared to only 38% for their general health care needs [162]. However, this may also be influenced by the context of care and the education level of the patient [163] .The findings are not universal, and may be more associated with a desire for adequate clinical information rather than a desire to make active treatment decisions [164].

It is the impression of all members of this committee that due to the high percentage of people not seeking help for UI (for all the above mentioned reasons), health care professionals must develop the concept of a “reaching-out” service and to actively provide service for incontinence care. This means promoting awareness, openly discussing and actively detecting UI, while providing simple and efficient therapy. While not all patients with voiding disorders (e.g., bothersome lower urinary tract symptoms including urgency, frequency, nocturia, poor stream and hesitancy) have incontinence, many of these patients will also benefit from a service that will provide assessment, education and relevant treatment prior to the potential onset of incontinence.

3. MODELS OF CARE

Continence care was defined by the Canadian Continence Foundation as “all measures directed

toward the prevention, improvement and or management of UI" (http://www.canadiancontinence.ca/pdf/en_dec2000vol_1.pdf). Models of care for the frail elderly with UI are covered by Committee 11: Incontinence in the Frail Elderly. A report on continence care services worldwide noted that services were scattered, inconsistent and considerable discrepancies exist in their funding. It was concluded that there is a need for accessible (and affordable) continence care and multidisciplinary teamwork [165]. Models of service delivery for FI, BPS/IC and POP have not been defined.

The provision of continence care and services in each country will depend on the organisation and infrastructure of its health services. It is difficult to make specific recommendations that will apply in such a variety of contexts. In addition, UI is so widespread and affects men and women of all ages who receive medical care from a variety of health care providers (e.g., PCP, family physician, geriatrician, gynaecologist, nurse practitioners). This means that there will seldom be one point of entry to continence care. There has been little systematic assessment of continence services aimed at identifying an optimal service. It is not known whether academic, specialist-led centres will achieve better and more cost-effective results than primary care clinics, domiciliary services or any other model. There are no studies directly comparing the effectiveness of specific delivery systems for continence care. A range of service delivery models is described below. The level of evidence on service delivery models is Level 4.

a) Single specialist

This is a service led by a consultant or specialist physician (urologist, gynaecologist or urogyaecologist), often focused around the "urodynamic unit" providing medical or surgical treatment. This is the most common model in developed countries; the best of them have a nurse continence advisor or continence nurse specialist as an integrated part of the service.

b) Nurse specialist or advisor

In some health systems, both UI and FI have traditionally been seen solely as a nursing problem, with little interest or input from other members of a multidisciplinary medical team. Except for a few isolated areas, the main intervention has been trying to help individuals and caregivers cope with symptoms, rather than attempting to treat the underlying cause of the UI. For example, in the UK, it is common for an elderly person presenting with UI to be referred directly to the district nurse "for assessment for pads and pants," with no physical examination or further investigation considered.

There are many examples of nurse-directed models of incontinence care described in the literature. Farrell and colleagues [166] studied a modification of UI care that involved step-wise care delivery, including a continence advisor and nurses, which were found to be as effective as the traditional medical model. In countries such as Australia, New Zealand and the UK, a national network of Continence Nurse Advisors (CNAs) or Continence Nurses liaise, integrate services, and guide individuals through the referral route most appropriate to meet their needs. The efficacy of Continence Nurse Practitioners (CNPs) in the UK was reported by Matharu and associates [167] who studied four hundred and fifty (450) women over 40 years of age who underwent urodynamic studies in the UK after seeing a trained CNP. In patients diagnosed with bladder overactivity, the CNP had prescribed drug therapy to 79% of patients and pelvic floor muscle training (PFMT) to 64.8%. In those with urodynamic stress UI, 88% had appropriately been prescribed PFMT. Nursing assessment has the potential to assign patients the correct conservative treatment thereby shortening waiting times for urodynamics and specialist assessment.

There is more evidence that treatment of incontinent community-dwelling individuals by a "continence nurse" is beneficial in terms of clinical outcomes [168]. Jeffrey and colleagues[144] assessed the clinical effectiveness and patient satisfaction with nurse-led, telephone follow-up of women with lower urinary tract symptoms. Participants were offered telephone follow-up with a nurse instead of a conventional outpatient appointment. Suitability for this option was decided by the doctor who saw the woman at her last visit. In total, 116 women received "telephone consultations" and the mean overall satisfaction score was 77 (maximum score was 100). Only 16 patients (17%) did not prefer telephone follow-up to a clinic visit. The authors concluded that nurse-led telephone follow-up is associated with high satisfaction and has the advantages of consistent follow-up by the same clinician, convenience to the patient and cost-savings [144]. Shaw, Williams, and Assassa[169] conducted a postal survey of people in the UK receiving services for UI by CNPs. Participants expressed satisfaction with nurse-led services because of the interpersonal, technical, communication and information-giving skills of the nurses.

The nurse continence advisor (NCA) may be independent, but is usually associated with community/area health centres, where they may have variable professional support from GPs and family physicians. Continence nurses often work in both hospital and community settings, and the service is focused on primary care. This is particularly true for district nurses. Key roles include patient assessment and implementation of conservative management strategies where appropriate and facilitation of patient access to incontinence product subsidies or schemes.

The Department of Health in the UK has commissioned an evaluation of different models of nursing services, with and without specialist NCAs. It was found that where there is a continence nurse incontinent people are more likely to receive a tar-

geted referral to specialists such as an urologist, are more likely to have had investigations such as urodynamic testing and are more likely to receive appropriate treatment and care for their UI. These patients were also more likely to report satisfaction with the service. In contrast, there are still concerns that general nurses continue to "contain the problem" instead of promoting continence, despite acknowledging its importance [170].

Unfortunately, there is often still an emphasis on containment and simple management of UI rather than on active therapy. Part of this may be due to cost, which has been shown to be lower for containment compared to active continence evaluation, promotion, and treatment [171]. Even in this case, provision of care may be substandard. An audit of the continence services in the UK revealed that rationing of pads and absorbent products was widespread, with most patients limited to four pads per day [172]. In addition, 59% of the continence services surveyed provided pads for children under the age of four, which is outside of the published national guidelines. This indicates a need for improved implementation of continence services with regard to use of pads and products.

In a series of studies performed in Leicestershire UK, the short and long-term outcomes of a new CNP-led service for urinary symptoms (three and six months after implementing the program) were examined and evaluated [173,174,175]. Williams, et al.[175] reported on a randomized, controlled study (RCT) of 3,746 community-dwelling individuals greater than 40 years of age (61% women) who had incontinence, frequency, urgency, and nocturia all impacting QoL. The experimental group was comprised of 2,958 patients. The standard care was the control group (n=788) who accessed GP services and existing continence services in the area. The experimental group received an 8-week primary intervention package by the CNP (21 generalist nurses who trained as CNPs). The CNPs delivered evidence-based behavioral interventions using predetermined care pathways in four visits over an 8-week period. Interventions included advice on diet, fluids, bladder training, pelvic floor muscle awareness and healthy eating. Individuals whose symptoms persisted after primary intervention were offered urodynamic testing. The CNP led service had a 10% higher cure rate than standard care with statistically and clinically significant reductions in urgency, frequency, nocturia and UI. In addition, QoL improvements were greater in users of the CNP-led service and higher levels of patient satisfaction were achieved. This is the first study to show the effectiveness of nursing services on urinary storage symptoms (rather than simply incontinence) and associated QoL. The authors noted that the public health value of a 10% reduction in symptoms is substantial when applied to such a common problem.

An additional number of studies support the efficacy of specialist NCA in the delivery of community continence care [148,176,177,178]. In the USA, urology nurses have been trained as "teachers" to successfully implement behaviour modification programs to groups [179]. Nurses may also play an important role in the evaluation and management of POP, a condition which is often associated with concomitant UI [180].

Regional continence nurses have also been successfully incorporated into primary care practices, however they need to be given both the authority and opportunity for interactions. A survey of 22 district continence nurses found that having regularly scheduled appointments with patients who were actively involved in their assessment and management led to the best nurse provider satisfaction and sense of professionalism [181].

In the USA, there has also been an increase in nurses who specialize in dealing with patients with pelvic floor disorders including UI, FI, POP and BPS/IC/PBS, although there are no academic or clinical proficiency requirements in order to be considered a CNP or "continence nurse specialist." Those nurses who do specialize in continence care have obtained their knowledge and skills through self-motivated activities [182]. Masters prepared or educated "advanced practice registered nurses" (APRNs) have become increasingly interested in, and knowledgeable about, the assessment, diagnosis, and treatment of people suffering with UI. These nurses are developing a nursing subspecialty in the care of individuals with UI and related pelvic floor dysfunction, providing comprehensive assessment and treatment (drug and conservative therapy), and acting as educators and researchers [183].

A 2000 study in the USA demonstrated significantly improved outcomes for three clinical problems, UI, depression, and pressure ulcers, when advanced practice gerontological nurses worked with nursing home (NH) staff to implement scientifically-based protocols [184]. In addition to working with NHs to provide resident evaluation as physician extenders, this research indicates that this service model using an APRN can be an effective link between current research-based knowledge about clinical problems and NH staff. This study also showed that consistent educational efforts with staff and NH residents demonstrated that interventions could improve or stabilize the level of UI in this population.

c) Multidisciplinary resource and referral centre

Multidisciplinary clinics, as service models, have been shown to provide comprehensive continence care. In multidisciplinary clinics, such as a "Pelvic Floor Clinic," the gynaecologist, urologist, colorectal surgeon, and continence nurse work together [185]. Some pelvic floor clinic staffing models also include physical therapists (PTs) and registered dieticians.

An Australian study took all community referrals of those who had been incontinent for at least two months and had at least one episode in the preceding two weeks to a continence clinic [186]. Patients were randomized to conservative treatment or control, with a crossover design. Patients were asked subjective questions about embarrassment, odor, depression, family relationships, isolation, and laundry, on a 4-point scale ranging from no effect to major effect upon life. The questionnaire was completed at the start, and at 2, 4, 8, and 12 months. Seventy-eight patients entered the study and 87% improved with treatment (versus 41% controls). Fifty-two percent were moderately or severely embarrassed at the start of the study period, but at 4 months, only 17% were. Depression decreased from 49% to 22% and isolation from 28% to 12%. Odor and the use of extra laundry also decreased. All benefits were maintained at 12 months. Controls did not improve on these items until crossed over to active treatment, despite feeling better. The authors conclude that conservative treatment in a multidisciplinary community clinic improves continence and well-being.

The Continence Foundation of Australia (CFA), funded by the Australian Government, employs CNAs to answer the National Continence Helpline and to provide advice to consumers and health professionals, including referral advice [187]. Evaluation of this service indicated availability and uptake of information, as well as increased traffic to the Bladder and Bowel website and the National Public Toilet Map. There had also been a general increase in the number of consumers seeking help for their incontinence.

An expansion of this service provision is exemplified by the National Centre for Continence in Israel, which aims to provide an integrated service [188]. The Center's professional team not only treats incontinent patients, but also educates GPs and nurses who come from pre-selected peripheral/outlying clinics. They also provide ongoing support and advice as well as a pathway for tertiary referral. A local team (GP and nurse) is also selected to be in charge of promotion, detection and treatment of incontinence at the clinic. They later become "in charge" of incontinence in their region. This model allows national distribution of continence services with support from the resource centre and provides interdisciplinary exchange, as well as maximum co-operation between Medical Centres and community health services. The national centre is funded by government and industry to provide a "Hotline" for the public, to promote education programmes in nursing and medical schools, hospitals and NHs, and to develop guidelines for diagnosis and management of incontinence by primary healthcare staff.

Multidisciplinary services should initially focus on a step-wise approach to evaluation and management. This need not be limited to tertiary level centers, but can be incorporated into care in local communities when providers with expertise are available [189].

The multidisciplinary model has also been used for delivery of community-based services. One model used a combination of clinic and home visits, multidisciplinary care delivery to targeted client groups, and use of multidisciplinary tools and provider education [190]. Overall, a generalist approach was found to be most effective in this study, although this may depend on the community context and other factors. The model shown in **Figure 1** combines an academic center and community services. Although it was proven feasible, there were significant challenges due to funding and infrastructure [191]. This program in Canada is ongoing, and additional research will be needed to assess overall outcomes.

d) Primary care

Although primary care practitioners can certainly do a large portion of general continence care, the literature notes barriers to care provision and poor adherence to evidence-based recommendations [192,155]. This precludes efficient delivery of continence care and prevents appropriate first-line treatment. Cohen and colleagues [193] found that, among primary care providers, only 25% initiated a discussion of incontinence with their patients. In their cohort, older patients were less likely to be asked about incontinence compared with younger patients. Findings from a USA survey indicate that the majority of primary care practitioners were unlikely to ask about UI [194]. Forty percent recommended pad use for treatment, and only 17% were aware of clinical practice guidelines. The identical situation exists in other countries such as in Europe and Canada [195,196]. Although most primary care practitioners recognize that UI is common, only a minority have an organized plan for its evaluation and management, and report feeling very comfortable dealing with UI. Ten years ago, attempts by the U.S. Agency for Health Care Policy and Research, now known as the Agency for Healthcare Research and Quality (AHRQ), to use physician group interventions to raise awareness through UI guidelines failed to improve screening and management rates in the primary care setting [197]. There have been other innovative methods used to increase UI screening. Yazdany[198] prospectively randomized patient charts (n=88) to receive a chart-alert sticker ("Do you leak urine?") that reminded resident physicians to ask about UI in their general gynaecology clinics. Overall, the rate that resident physicians inquired about incontinence increased with the alert-sticker from 4% to 34%. This method may be more easily implemented in electronic health records.

Many countries have sought to shift the provision of primary care from doctors to nurses in order to reduce the demand for doctors and improve healthcare efficiency. A Cochrane review found that quality of care is similar for nurses and doctors, since nurses tend to provide more health advice and achieve higher levels of patient satisfaction compared to doctors [142]. A RCT in the Netherlands compared usual care for UI in GP clinics to those that included

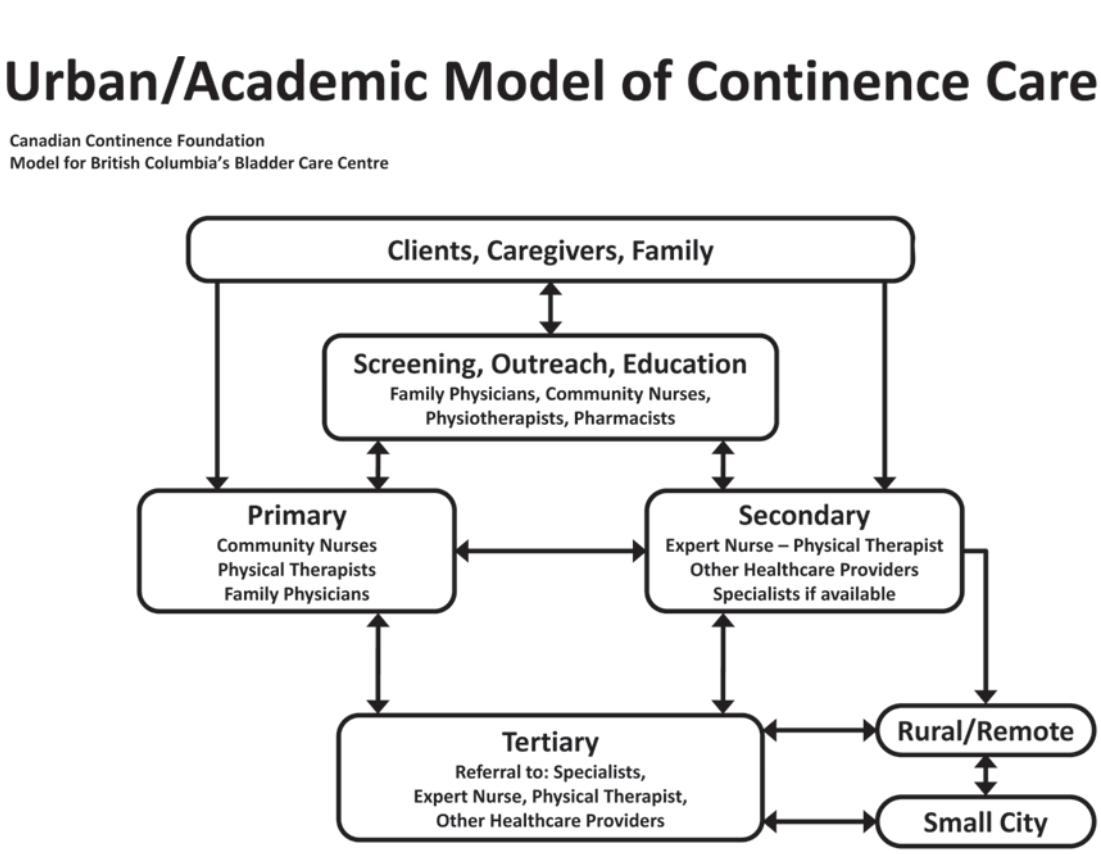


Figure 1. Urban/ Academic Model of Continence Care

a nurse specialist [199,200]. Short-term outcomes revealed better continence rates in those patients seen in clinics that involved care by the nurse practitioners. However, the results were not sustained at the one-year follow-up, and both groups had equivalent continence outcomes. A focus group analysis with the nurse practitioners revealed that they felt competent to provide the needed services and appreciated by the patients [201]. In addition, they felt they added value to the practice, particularly since many of the GPs were seen as lacking interest in UI. Overall, the results do suggest a benefit from this type of multidisciplinary care delivery. Future research will be needed to determine if long-term outcomes can be maintained and if the model may have other unmeasured benefits, such as better cost-effectiveness.

Therefore, primary care practitioners may not be the most appropriate professional to mange UI, and this committee's recommendations include a care delivery model (**see Figure 2**) based on a chronic care approach that has been used successfully in other chronic conditions (e.g., diabetes, CHF, asthma) [202].

There are many factors that can persuade health care planners about the importance of adequate investment in community continence services. The prevalence and the number of incontinent people is likely to increase with an aging and increasingly dependent population and many frail, disabled or elderly people are incontinent for reasons extraneous to the urinary system (such as poor mobility, an inappropriate physical environment or lack of an individualised care regime). It is often best to provide an initial assessment for such individuals in their usual surroundings and to reserve hospital or clinic (specialist or academic) referral for those who do not respond to simple measures such as treatment of constipation, modifying a diuretic medication, or provision of accessible toilet facilities. A number of guidelines have suggested an algorithmic, stepwise approach to UI assessment and treatment, and many conservative treatments have a good success rate in primary care [203,204,205,206].

e) Other service models

In a structured literature review, Chin and colleagues found that primary care clinics for continence led by nurses and allied health professionals were common across the world [207]. Although there were a number of differences that were culture specific, there were also a number of key factors that predicted high quality care across all cultures. These included identification and recruitment of appropriate patients, improving access to care, enhancing engagement with primary care providers, using small teams with adequate training, developing structured referral lines,

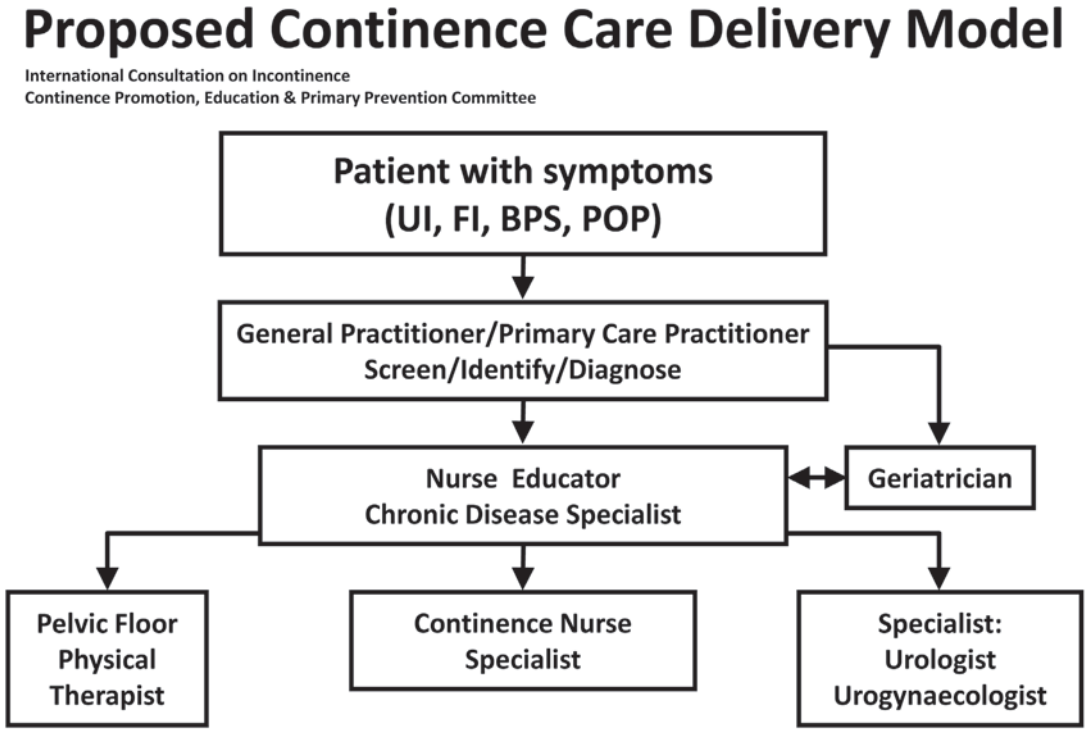


Figure 2. Proposed Continence Care Delivery Model

and working to employ evidence-based practices including guidelines and treatment protocols.

Group intervention models for delivering first-line treatment for UI is feasible [208,112,209] and may be an equally effective and potentially cost-saving approach to this form of therapy [210]. Even simple group education about UI in general, may improve self-care among postmenopausal women with the condition [11]. Another study has shown that non-medical lay instructors can be taught how to instruct patients in proper pelvic floor muscle exercises [211]. This train-the-trainer model may be useful to help disseminate behavioural therapy on a more widespread basis.

Education of other professionals who interact with UI patients, but do not themselves provide direct health care, may also be quite useful. For example, improved education about UI and other lower urinary tract disorders among teachers may help improve not only their own continence health, but that of their students as well [212].

Many consumers seek information from the Internet, although the quality of materials can be highly variable. Some websites include an interactive component, including e-mail of other communication methods that allow users to interact with a health educator or other professional [213]. Computerized education methods have been developed to disseminate consumer education materials about UI [214]. Usability was considered good and these methods may help disseminate continence promotion materials.

1. Acute or sub acute care to community

Patients with UI who receive care in acute care hospitals have been shown to lack appropriate care because of the lack of knowledge amongst acute care nurses about assessment or management of UI [215]. Nursing education must change to improve this situation. The value of tackling this is shown in a retrospective review of 6,773 episodes of care in 54 medical facilities [216]. The discharge destination was altered by the presence or absence of UI – 57% versus 82% respectively being discharged home, and 29% versus 12% being discharged to a NH or other health care venue. In addition, the time in rehabilitation was 185.6 days for those with UI compared with 156.8 days without UI, and geriatric costs in evaluation and management were higher in the UI group. The level of functional independence and motor function also impacted outcome.

Continence promotion, education and treatment may occur in a variety of clinical settings, particularly in relation to other associated clinical conditions. For example, UI occurs commonly after acute stroke. Rehabilitation nurses who work with post-stroke patients could play an important role in continence care, however research shows this may not happen

regularly. A recent multinational qualitative study examined a focus group of rehabilitation nurses in the UK, Sweden and China [217]. They found that only a superficial assessment of continence was routinely performed by most nurses in this setting. The authors noted a focus on containment and social continence although process models of practice were seen in all countries. Other studies have corroborated these findings and reveal the emphasis in the rehabilitation setting is containment rather than continence promotion or active therapy [218]. The results highlight a need for systematic assessment and development of patient-centered care plans.

Heart failure is another common clinical condition, particularly among older adults, that is frequently associated with UI. A recent study of 182 heart failure patients with at least monthly UI revealed that 83% had not asked for help with their incontinence symptoms and 64% were interested in learning more [219]. Many patients, particularly those with concomitant diabetes, were contemplating changing their behaviours and seeking care.

Clinical care around the time of pregnancy and delivery is another potential time for patient education and interventions aimed at preventing or treating UI [220]. Studies have shown that women are generally very receptive to this type of clinical education in the post-partum interval [221]. Additionally, women who were instructed in pelvic floor muscle exercise by a PT during the immediate post-partum period were more likely to continue the exercises at one year after delivery compared to controls [222]. However, in many cases, this opportunity is missed due to lack of training on the part of care providers. A study of nurse midwives in Australia found that the majority do not assess for UI in the peripartum period [223]. In addition, the survey respondents indicated a lack of guidelines for nurse midwives.

2. Elder services (long term care or nursing homes)

There is growth worldwide in the use of APRN "continence" specialists practicing in home care and LTC settings, providing expert consultation in UI and related disorders [183,182]. Many have developed innovative approaches to management of UI in NHs. Bucci [224] developed the CHAMMP (Continence, History, Assessment, Medications, Mobility, Plan) tool to educate NH staff in the USA on a comprehensive continence assessment and to assist in implementation of individualized plans of care. The CHAMMP program improved one facility's Quality Measure Indicator Report. ICI Committee 11 discusses services for frail elders.

Many older adults rely on home care services for a variety of health care needs, including UI. The methods used to implement and deliver services can differ a great deal depending on the care model used in a particular region. Implementation of guidelines is felt to be an important part of this process [225]. This allows care providers to try to put evidence into direct practice. A recent study examined 19 home care agencies in the Netherlands to determine if the quality of care systems influenced outcomes [168]. Most models included designation of the continence nurse and documenting UI-related actions on the patient care record. However, no differences in clinical outcomes were observed in this study of 155 home care teams. The authors concluded that additional research examining specific implemented practices would be required in the future.

Even within the long-term care setting, the focus is too often on containment and use of pads or absorbent products compared to active continence promotion or treatment. A recent Cochrane review supported this finding, and noted that none of the studies reviewed focused on attempts to maintain continence in facility residents [226].

One new innovative model has described the development of individualized continence profiles for use with NH residents [227]. This may help NH staff identify residents who may benefit from various forms of assessment and interventions. Another model has worked to involve NH residents more actively in their fluid intake and continence care. After a 12-week intervention, overall hydration status improved and time spent in wet diapers decreased significantly in a cohort of 153 NH residents who participated in the intervention [228]. Education of staff was felt to be important to the observed success in this study. Within the context of 'person-centered care,' there is a growing need to develop and encourage bladder rehabilitation and prevention with a proactive focus, particularly for older adults [229]. This may help to expand the focus beyond containment only in this population.

Another study found that the best performing long-term care facilities in terms of UI care generally utilized a multidisciplinary process improvement team [230]. In addition, more were likely to use a clinical practice guideline in evaluation and management compared to the poorer performing facilities.

Data have shown that a nurse's level of knowledge and attitudes about UI may influence care within the NH environment [231]. Overall perceptions about physical functioning in older adults may also impact this issue in hospitalized patients [232]. Physical functioning is a complex entity and nurses in this focus group study identified system-level approaches that could be used to prevent additional functional decline in their patients.

Education specifically targeted at family caregivers may also be important in the promotion of continence for community dwelling older adults. A recent report by Jackson and colleagues [233] used focus groups of family caregivers and health care professionals to identify the types of materials and methods of delivery preferred by participants [233]. Most wanted printed materials such as summary brochures or fact sheets with answers to frequently asked questions.

Electronic materials were not as readily desired in this study.

Distance learning techniques have been successfully used to teach and implement programs and strategies for management of UI in NH [234]. This training method might help to improve dissemination of information, particularly in rural and otherwise underserved communities in more remote locations.

3. Models in developing nations

Continence services are a relative luxury, to which countries with a low per capita income are unlikely to devote scarce resources, especially while other population health issues have precedence.

The potential demand for UI services in developing nations far outstrips the resources that are available. The provision of services will depend on dedicated healthcare professionals with support by government or industry, and by a local continence organisation to educate a new generation of service providers who will carry the services to remote communities. Increased use of advanced communication technologies can help to disseminate continence promotion materials among nurses and other health professionals worldwide [235].

In some instances, consideration will have to be given to cultural and social mores and taboos. For example, Ethiopia's Health Minister has stressed the need to develop rural health services to reduce the incidence of fistula and to have first time mothers examined by Traditional Birth Attendants (TBAs). The ICI Committee 18, Vesico vaginal fistula in the developing world, addresses service for this specific condition. It is planned that TBAs will be trained to identify high-risk women and thereby divert expenditure from high cost physicians and urban health services to training community health workers and to health education. Attitudes on female circumcision, contraception and women's health, matters that are often decided by their husbands, obviously have much wider implications than just continence care.

4. RECOMMENDATIONS FOR SERVICE DELIVERY, MODELS AND ACCESSING CARE

Making recommendations for interdisciplinary and multidisciplinary models for continence advocacy and service delivery remains a rather elusive goal. Although there have been more publications since the last ICI, there has been little evidence of substance generated. Implementation is quite difficult, funding is often limited, and there are few studies on outcomes. Based on the literature reviewed in this section, the following recommendations can be made:

- There is a need to move beyond the theory and work on research about the practice of continence care delivery and education. We recommend a care delivery model based on a chronic disease approach. (Grade D)
- There needs to be an increased emphasis on non-physician models of care (nursing, nurse practitioner, continence advisor, physiotherapy, physician assistants, etc.). (Grade C)
- Despite the proliferation of guidelines, there is increasing evidence that practicing clinicians are not following them. Implementation models should be developed on how to translate guidelines into practice. (Grade C)
- There still appears to be a shortage of physician specialists in continence care (urology, gynaecology, etc.) which needs addressed. (Grade D)

VI. PROFESSIONAL EDUCATION

1. BACKGROUND

With the continued advances in health care, increasing public pressure to provide high quality evidence-based care, limited time for health professionals to update their knowledge and the recognised ineffectiveness of passive 'lecture style' education provision, the need for new models to change health care providers behaviour is essential. Nowhere is this more relevant than in the provision of care for those with UI and FI, where educational provision has been inconsistent at best.

Professional education is a key component in the provision and care of individuals with UI and FI. In their state-of-the-science statement on the prevention of faecal and UI, Landefeld et al[8] identified that education of health care providers alone is insufficient to improve detection and treatment of UI and FI. However, they recognise that in order to appropriately detect and evaluate incontinence professional education is required along with outreach and practice-based resources. To date, the education and training of those involved in the provision of continence care has been poor.

There is limited literature on the educational preparation and ongoing training of those health care professionals engaged in continence promotion, care, and referral and even less on the evaluation of education programmes in terms of educational or practice outcomes. It has long been recognised that professional education with reference to UI and FI remains only a small part of the basic training of physicians, nurses, or allied health professionals and on-going training is largely 'ad-hoc' with huge variation in the types, content and quality of such training. An early survey in the UK found minimal attention given to incontinence in both medical and nurse training, and a key recommendation for improving continence care was an increase in the quality and quantity of professional education [236]. This has clearly not occurred. While educational initiatives have been undertaken, they remain fragmented and inconsistent internationally. Most notable is the absence of evidence demonstrating an impact of professional or public education on the burden of suffering posed by OAB and UI. The

ICS has established an Education Committee to promote, organise and co-ordinate all educational advances undertaken under the auspices of the ICS. Details are available on the ICS website (www.icsoffice.org).

There is a paucity of published work on professional education on UI or FI. Similarly there are few studies addressing the effectiveness of education in improving the knowledge of learners, or on whether improved knowledge impacts patient outcomes. Information has been building since the publication of the ICI chapter in 2009,[1] but the level of evidence on the effectiveness of professional education remains at Level 4. This section will examine the available evidence on the effectiveness of professional education on incontinence for different groups of health care professionals.

2. MEDICAL EDUCATION

a) Generalists (family physicians/general practitioners/primary care physicians)

Physicians (general, primary care, and family physicians) have been viewed as having a gate-keeping role in continence provision since they are often the most likely first point of contact when consumers seek formal help for their incontinence. Most physicians have received little education or formal training about incontinence, fail to screen for it, and view the likelihood of successful treatment as low, so most avoid the topic with patients. At the same time, there are no data confirming the benefits of screening as a method to reduce the burden of suffering from UI. A postal survey noted that only 18% of respondents said providers asked them to complete a questionnaire about bladder control during routine office visits, and a majority (69%) felt it would be very helpful in prompting discussion if their physician or health care professional provided a form for them to check off symptoms of incontinence [104].

Traditionally, UI and FI have formed only a very small part of the undergraduate medical curriculum. Education on UI has usually been fragmented across different organ systems, with training scattered between gynaecology, urology, and geriatric medicine. Bladder and pelvic floor anatomy is poorly covered in preclinical training and relevant physiology is rarely mentioned. A survey of urology residency directors, medical student educators in urology, and urology applicants identified UI as one of the eight most commonly cited topics to be included in a core urology curriculum [237]. Minimal training is provided on paediatric continence issues.

Recent studies have shown that there has been an overall decline in the amount of time devoted to urologic education in most medical school curricula [238]. Surveys have shown that general levels of knowledge about common conditions such as hemaeturia and OAB are low. In addition, respondents indicated a low likelihood of seeking urologic consultation for many conditions. A similar study found that exposure to issues of pelvic floor dysfunction in women was extremely limited in medical education, with more than 80% of medical students receiving no formal training in this area during the first two years of training [239]. This represents a critical shortfall in training, particularly since many patients with genitourinary problems will initially present to a primary care provider for evaluation and management.

A survey of program directors for internal medicine residency training programs in the USA was conducted to determine whether they felt their residents should master thirteen core competencies identified to be central to the health care of women (including UI) [240]. Although almost all felt this was an important goal, there was a large discrepancy in whether they actually achieved this level of learning. This indicates there is still a wide educational gap among primary care physicians who are often the first portal into the organized health care community for patients with UI.

There is very little available literature on knowledge among family doctors on FI. A study has recently been undertaken to explore GP awareness of surgical treatment options for FI [241]. A postal questionnaire was mailed to 1,100 GPs in the Yorkshire region in the UK, and a response rate of 48.5% was achieved. The questionnaire assessed basic knowledge of FI and treatment options. Overall knowledge was poor, with the majority unaware of available investigations, treatments and specialist centres. The authors recommend better communication between specialist centres and GPs, as well as CME programme implementation.

There is growing evidence to suggest that traditional ‘lecture style’ medical education is ineffective in changing physician behaviour and, ultimately, patient outcomes [242]. More innovative teaching methods are clearly required. Levine and colleagues [243] used a train-the-trainer model to evaluate the management of a number of common geriatric conditions including incontinence. This model involved training, by an expert faculty, a team of non-expert peer educators. These peer educators used a toolkit to conduct small group learning sessions, which were evaluated immediately after and 6 months after the education sessions. The model used principles of knowledge translation and active teaching using tool kits based on guidelines to train geriatricians. Results showed statistically significant improvements in self-reported knowledge, attitudes and office-based practices. The study concluded that modest changes in practice in relation to geriatric conditions were achieved using this peer-led approach. While such evaluations are promising, these models are difficult to sustain and costly. Perhaps most importantly they point to the need to use innovative teaching methods to ensure that educational efforts actually make a difference.

Web-based training and the use of standardized patient case studies has become very popular in medical education and has been successfully incorporated into residency training programs. In one recent project, training about UI was included with a number of other geriatric syndromes [244]. In fact, those internal medical residents who received the information via web-based methods had better overall test results than those who completed paper-based training.

Some models of physician education have incorporated training on UI into modules on quality care. For example, the Assessing Care of Vulnerable Elders (ACOVE) project in the USA includes UI as one of the target conditions. A recent study looked at implementation of this information into community-based physician education within practice groups [245]. These authors found that dissemination of this information was well received by primary care physicians, and some intended to make changes in their practice related to this new knowledge. Similar studies have also found that primary care physicians specifically educated about UI assessment and interventions were more likely to recommend care for UI to their patients [246,247]. Large-scale dissemination of information using these types of training models might ultimately help improve access to care.

b) Specialist physicians

There is little new published evidence on medical specialist training in the form of effective training interventions. Specialist training in incontinence is not always adequate. Both UI and FI still may be perceived as exclusive to "super-specialists," potentially alienating colleagues.

Even among subspecialists, training may not be ideal. A survey of 163 urodynamic services in the UK found that half the respondents felt their training in urodynamics was inadequate [248]. Marsh and colleagues[249] surveyed 100 gynaecologists and urologists in the UK and found widespread inconsistent and inappropriate diagnosis of PBS/IC [249].

Increased use of advanced surgical technology has led to greater need for procedure specific training. Examples include use of laparoscopic and robotic techniques for treatment of POP. Some of these procedures have a steep learning curve and require additional training for surgeons [250]. Structured training and curricula have been developed for a variety of surgical procedures used to treat UI and POP [251]. Inclusion of this training in residency will lead to increased numbers of physicians who are qualified to offer this type of care to patients suffering from UI. A variety of models have been developed to help teach some basic skills such as cystoscopy or methods for grading the degree of POP. One option includes the use of cadaver labs [252]. Others have used inanimate objects to replicate the female pelvis and teach basic anatomic concepts [253,254]. Script concordance models have been developed to assess clinical reasoning skills related to care for UI in older adults [255]. This may allow better measurement of clinical practice behaviours for this condition.

Ongoing education and utilisation of evidence-based training with incorporation of guidelines has been suggested as a way to maintain high quality standards of treatment, particularly for surgical care of UI [256].

In the USA, there has recently been a push to develop sub-certification for specialists who care for women with UI and associated pelvic floor disorders [257]. This has involved cooperation between the certifying boards in both urology and obstetrics and gynaecology. The field of 'female pelvic medicine and reconstructive surgery' has recently been approved by the relevant certifying boards. This means there will soon be a separate board examination in this field. Continued emphasis on quality education for specialist physicians is needed worldwide [258]. A study of gynaecologists in Germany found that most considered their specific post-graduate training in urologic issues and urogynaecology to have been inadequate. The vast majority of general gynaecologists in this study referred their patients with voiding or incontinence issues to subspecialists in urology or urogynaecology.

3. NURSING PROFESSIONALS

Nurses have a significant role to play in the area of incontinence since they are the largest single group of health care professionals around the world and are often the first to become aware that the patient is experiencing incontinence. Cheater and colleagues[25] found that in the UK, an average community nurse case load will comprise approximately one-third of patients with UI. There have been a number of recent studies that explore the use of new innovative methods of education provision for nurses. Rogalski[259] reports a persisting lack of educational emphasis on common symptoms like UI and recommends a curriculum model based on existing guidelines and best available evidence, which could address this shortfall and would increase the quality of continence service provision.

a) Generalist nurses

There are significant gaps in knowledge and clinical practice adoption related to both UI and FI, although nurses worldwide have played a major role in developing new information and testing interventions [260]. Although nurses can provide effective interventions in the area of UI, there is limited research on effective interventions for FI.

Innovative methods of improving knowledge among nurses have undergone recent evaluation. An important study undertaken by Cheater and colleagues [261] adds to the debate by examining the value of audit and feedback, and educational outreach, which in the past has often focused on doctors' behaviours rather than nurses'. In this study, the researchers

undertook a cluster-randomized trial to evaluate 194 nurses in 157 family practices with 1,078 patients with a diagnosis of UI. They found that when compared to educational materials alone, there were no improvements in care for either educational outreach or audit and feedback (all groups did improve, but differences between groups were not significant). McConnell et al[73] described how advanced practice nurses learned evidence-based approaches to managing complex cases, including incontinence, in NH residents. Advanced practice nursing skills include evidence-based assessment and diagnosis for implementing management. The authors suggest that such practices can enhance both student and facility outcomes, although no systematic evaluation was undertaken.

Ostaszkiewski[262] describes a nursing leadership model to enhance continence care in older adults. Evaluation of the program suggests improved management and assessment of incontinence for individuals sustained after a two-year period. Leadership programs have proved effective in a number of areas in nursing provision. Within these more recent studies, the use of innovative methods of knowledge transfer and education are beginning to be adopted, and such methods used in other areas of professional education may be well suited to UI and FI.

Education related to UI may often be linked to training about other concomitant disorders or conditions. For example, training on prevention and treatment of pressure ulcers or dermatitis may include significant components related to UI [263,264,265]. Training about improved mobility in the geriatric population has also shown this educational link [266]. This can help to disseminate information about continence care and promotion to a wider audience of nurses who have direct patient contact.

Although APRNs may have good levels of knowledge and positive attitudes about treating UI in women, many have difficulty applying this directly to practice in the clinical setting [267]. These authors suggest that there needs to be increased exposure to these topics in clinical experiences during training for graduate nurses.

Programs have focused on nurse education for continence care in specific settings, such as the NH [268]. Competency-based UI education with use of case examples has been used successfully in the training of generalist nurses [269]. Experiential activities have also been used with good results [270].

b) Specialist nurses

Educational courses on incontinence are available for nurses in the UK, USA, Europe and Australia, and are beginning to appear in Asia, notably Hong Kong and Singapore. These courses vary from two to four weeks of face to face didactic courses to distance learning courses lasting 12 months that lead to a post-basic nursing certificate and, in some cases, post-graduate degrees.

In the UK, education programs are documented at the Association for Continence advice website (http://www.aca.uk.com/education_modules.php) and comprise information on 1 day courses, as well as diploma courses, degree modules and masters level study. Such databases of courses offer an excellent overview for students and providers. Likewise, the CFA (http://www.continence.org.au/pages/continence-courses.html) is an excellent resource for nurses to access information and be linked to educational organisations that provide a variety of programs which focus on or incorporate both UI and FI in the curriculum. Many can be continued through to post-graduate tertiary education. A number of these programs can be undertaken externally and therefore are popular with nurses in rural and remote areas, as well as students of nursing who practice in other countries. Clinical support is arranged to complement the theoretical components.

Williams, Assassa, Smith, Shaw[271] conducted a small study in the UK that showed improvements in both knowledge and attitudes of nurses who undertook a specially designed, full-time, 3 month program that included a continence module.

Internationally, there is inconsistency in the provision of specialist education to prepare nurses to practice as experts in the field of incontinence. Innovative web-based learning programs incorporating modern information and communication technology (e-learning) may offer one way of providing standardized programs of study to practitioners.

Beitz and Snarponis[272] describe their innovative on-line learning program which includes continence nursing. They feel that such teaching strategies are acceptable to nurses. As with physicians, it is unlikely that improving nursing knowledge alone will translate into improved clinical practice or into the ultimate goal of improved patient outcomes.

Jha, Moran, Blackwell, and Greenham[273] conducted a small study of women attending gynaecology outpatient departments with incontinence problems. Thirty-five percent (7/20) patients did not need to see a doctor, as they were symptom free following treatment recommendations by continence nurses using an integrated care pathway. The authors felt this process facilitated earlier diagnosis and improved access to specialist services and discharge from secondary care.

The level of knowledge about UI within the general nursing community appears to be less than ideal in both the USA[274,275,276] and Sweden [277]. Many non-specialist nurses (referred to as general nurses) desire, and have a need for, more education about what they can do to better manage incontinent patients. Moreover, the QoL of the incontinent NH resident is often more dependent upon the skill, education, and attitudes of the nursing aide than of the qualified nursing staff.

Improved education of school-based nurses regarding normal bowel and bladder habits of children may help to improve pediatric continence and promote healthy elimination patterns [278]. Although 61% of school nurses surveyed reported they had never received training on the topic, many (43%) had been asked to provide information to their teacher colleagues.

In the USA, although there are a growing number of nurses who are developing expertise caring for incontinent patients, there are no academic or clinical proficiency requirements to be considered a "continence nurse practitioner or specialist."[279] In 1993, the Wound, Ostomy, and Continence Nurses Society developed the first certification program for continence care nurses in the USA. This nursing organization recently published a position statement on the role of continence nurses [280]. The Society of Urologic Nurses and Associates certifies different educational levels of nurses in the area of urology and in urodynamic testing. The norm is that most "continence" nurses in the USA obtain their knowledge and skill through self-motivated activities.

Recently, there has been some debate about the need to provide special education and credentialing to non-baccalaureate nurses regarding UI and associated conditions [281]. However, to date, most of the focus on UI education has been at the baccalaureate and advanced degree levels.

Other discussions have focused on whether specialty training in wound, ostomy and continence nursing should be at the doctoral level. In the USA, the new Doctor of Nursing Practice (DNP) degree may help to fill this training gap [282].

A study of 231 vulnerable elders with complex disease and enrolled in a 'Special Needs Plan' in the USA were shown to benefit from a nurse care management program with nurse practitioners in addition to physician care, as opposed to those who received care from a physician alone [247]. The model has continued to develop and requires further evaluation. A smaller study[168] in the Netherlands demonstrated that there were short-term benefits following referral to a continence nurse, however these benefits were not sustained long-term. Both studies demonstrate the need to further evaluate the effectiveness and sustained benefits of specialist continence nurses. A Cochrane Review[142] that explored the substitution of doctors with nurses showed similar patient health outcomes, at least in the short-term, over the range of care investigated.

Albers-Heitner and colleagues[283] evaluated the cost-effectiveness of involving UI nurse specialists in primary care compared to care-as-usual by GPs [283]. From 2005 until 2008, an economic evaluation was performed alongside a pragmatic multicenter RCT comparing patients with UI receiving care by nurse specialists with patients receiving care-as-usual by GPs in the Netherlands. One hundred eighty-six adult patients with stress, urgency, or mixed UI were randomly allocated to the intervention and 198 to care-as-usual; they were followed for 1 year. Main outcome measures were 'QALYsocietal' (Quality Adjusted Life Years based on societal preferences for health outcomes), the EuroQol-5D, 'QALYpatient' (based on patient preferences for health outcomes) (EuroQol VAS), and 'Incontinence Severity weighted Life Year' (ISLY) based on patient-reported severity and impact of UI (ICIQ-UI SF). Health care resource use, patient and family costs, and productivity costs were assessed. Compared to care-as-usual, nurse specialist involvement yielded slightly more favorable cost-effectiveness results. Based on these results, the authors recommended adopting the nurse specialist intervention in primary care.

c) Nursing assistants

There is also a need to address the training of nursing assistants (NAs) and aides, particularly in the long-term care setting. In the USA and many other countries, one concern is the high turnover rate among first-line caregivers in institutional and homecare settings, making it difficult to maintain desired training levels. Nursing assistants are often the people providing 'hands-on' incontinence care, and yet they often have the least training. Certainly, in terms of published evidence, there are few reports of efforts to train NAs. A cross-sectional study via postal survey to gather self-reported data from nurses and NAs in NHs was conducted in Taiwan [284]. Results indicated UI-related knowledge scale and practice behaviors differed significantly in both groups. The authors recommended that enhancing staff competence in incontinence care was needed in both levels of nursing to improve NH residents with UI. Educational efforts, particularly in the NH setting, must involve not only professional nurses, but NAs and other staff, as well. A study of nurses' knowledge about UI in NHs that used a standardized examination about UI and associated care demonstrated that professional nurses answered about two-thirds of questions correctly, but that baseline knowledge among NAs and aides was much lower [285].

4. PHYSIOTHERAPY AND OTHER ALLIED HEALTH PROFESSIONALS

Physiotherapists or physical therapists (PTs) have long played a part in continence care and the management of UI. In some countries, patient self-referral to specialised PTs has become commonplace. Physiotherapist's involvement in UI appears to be either on the basis of individual interest or through association with women's hospitals or obstetric departments, rather than as part of a general physiotherapy practice [286]. As such, they tend to be highly motivated and enthusiastic.

Generalist PTs have been encouraged to be more aware of the risk factors for incontinence in males and females, to identify patients with risk factors for incontinence and to assist them

in seeking further advice or treatment. The "Red Flags" Project conducted in 2005 was a collaborative effort of the Australian Government's National Continence Management Strategy and the Australian Physiotherapy Association's Continence and Women's Health Group to enhance HSB in people with incontinence visiting generalist PTs.

Throughout the world national physical therapy organizations have established continence physiotherapy sub-groups [287]. The International Organisation of Physical Therapists in Women's Health represents over 20 member countries with PTs practicing continence and women's health physiotherapy and offers professional development programs. A number of specialist continence PTs also treat men and children. Universities in many countries offer short courses or post-graduate continence education programs to PTs that may range from post-graduate degree courses to Masters and PhD programs [288].

The Scope of Practice for continence PTs may include PFMT, bladder training, management of sexual dysfunction, anorectal dysfunction and treatment of pelvic pain syndromes, FI and male continence issues.

Pharmacists have a variety of roles to play in continence care. In Australia, they have been avid consumers of continence education programs. In 2004, the Pharmacy Guild launched an educational and promotional program for their members with appropriate outcome evaluation measures. The public sees pharmacists as important and approachable sources of health information, especially information on medicines that may cause or exacerbate UI and FI. Many retail pharmacies display health promotion literature on a range of subjects, including UI. Pharmacists may also advise the consumer on appropriate continence products. Educational seminars for pharmacists are generally well received. There are a growing number of CME programs for pharmacists on the Internet, either through new products or through sites such as www.worldwidelearn.com.

Regulatory issues are often linked not only to quality of care, but also to reimbursement for clinical care and services. Reimbursement policies for services frequently determine which professionals are able to provide continence care. In the Netherlands, for example, the government pays for up to 14 visits to a PT for incontinence therapy. In the USA, patient's visits to a PT are typically restricted by the need for referral and cost.

5. IMPACT OF CLINICAL GUIDELINES

In the past several years, there has been an explosion in the rate of development and publication of clinical guidelines for UI and associated conditions. Since the last ICI, at least 20 different guidelines or consensus recommendations have been published regarding UI and associated conditions. Many of these have been developed by professional organizations focused on urologic, gynaecologic, geriatric, or related fields. Some have been created and disseminated on behalf of national governing bodies. Several older guidelines have recently been updated using evidence-based methodology.

Most of the guidelines target physician practice, although some do include recommendations specific to PTs, nurses, or other health care professionals. Different guidelines focus on specific clinical areas, and some are gender specific. Some only examine issues related to either the assessment or the treatment of UI. Some of the treatment-centered guidelines are specific for either surgical therapy or conservative therapy. Others look at clinical conditions in specific patient populations including those with underlying neurological disorders, women with POP, or patients who have previously undergone surgical treatment for UI. There can be some confusion, particularly when guidelines present conflicting or even contradictory recommendations about specific issues of evaluation or management. **Table 1** summarizes many of the recently published guidelines.

Guidelines have also been developed for different care settings. In the USA, the Centers for Medicare and Medicaid Services (CMS) issued F-Tag 315 in 2005. This guideline provides recommendations for bladder management in the long-term care setting. Nursing journals have published recommendations on ways to enhance implementation and compliance with the U.S. government regulatory guidelines [289].

Some guidelines have focused on education rather than on care delivery. The International Urogynaecological Association (IUGA) issued a set of guidelines specific for training in the area of female pelvic medicine and reconstructive pelvic surgery [290]. Other professional organizations have issued similar information under the headings of 'consensus statements,' 'recommendations,' and 'curricula.'

Many of the published guidelines focus on younger, healthy, community dwelling adults. Guidelines for evaluation and treatment of UI and FI in children and the elderly population or those with significant comorbidity need to be developed. These will need to take into account issues such as cognitive impairment, which can influence continence status in older adults [291]. Fung,[292] in a study in a large academic Veterans Affairs medical centre in the USA, used guidelines to develop condition-specific computerized templates to serve as guides for clinicians to ask questions and perform elements of a physical exam for two specific medical conditions:

Table I. List of Published Guidelines

Citation	Year	Topic	Professional Organization	Country	Language
Rao, 2004	2004	Diagnosis and management of fecal incontinence.	American College of Gastroenterology Practice Parameters Committee	USA	English
Scottish Intercollegiate Guidelines Network	2004	Management of urinary incontinence in primary care	Scottish Intercollegiate Guidelines Network	Scotland	English
ACOG	2005	Urinary incontinence in women	American College of Obstetrics and Gynecology	USA	English
NICE	2006	Urinary incontinence- the management of urinary incontinence in women	National Institute for Health and Clinical Excellence (NICE)	United Kingdom	English
NICE	2007	Faecal incontinence: the management of faecal incontinence in adults	National Institute for Health and Clinical Excellence (NICE)	United Kingdom	English
Nishizawa O.	2008	Urinary incontinence in the elderly		Japan	Japanese (English translation)
vanPinxteren B	2008	Urinary incontinence in all patients	Dutch College of General Practitioners	The Netherlands	Dutch
Garcia-Gonzalez et al,	2008	Diagnosis and treatment of urinary incontinence in the elderly	Consensus panel	Mexico	Spanish
Ghoniem, 2008	2008	Evaluation and management of stress urinary incontinence in women	International Urogynecological Association (IUGA)	International	English
Fritel et al,	2009	Diagnosis and management of adult female stress urinary incontinence:	French College of Gynaecologists and Obstetricians	France	
Fowler et al,	2009	Bladder management in multiple sclerosis	Consensus panel	United Kingdom	English
Polish Society of Obstetrics & Gynecology	2009	Prevention urinary incontinence and pelvic organ prolapse in women undergoing hysterectomy	Polish Society of Obstetrics & Gynecology	Poland	Polish
Velazquez Sanchez Mdel, P. et al,	2009	Diagnosis and management of urinary incontinence	Consensus panel	Mexico	Spanish
Yamaguchi et al,	2009	Clinical guidelines for overactive bladder	Japanese Urological Association Neurogenic Bladder Society	Japan	English
Aubert et al,	2010	Primary nocturnal enuresis	French Expert Consensus Panel	France	French
Dmochowski et al,	2010	Surgical management of stress urinary incontinence in women	American Urological Association (AUA)	USA	English
Drutz et al,	2010	Training for female pelvic medicine and reconstructive pelvic surgery (education)	International Urogynecological Association (IUGA)	International	English
Hermieu et al,	2010	Synthesis of the guidelines of for the treatment of non-neurological urinary incontinence in women	L"Association Francaise d'Urologie	France	French
	2010	Recommendations for the treatment of non-neurological urinary incontinence in women	L"Association Francaise d'Urologie	France	French
Lovatsis et al,.	2010	Evaluation and treatment of recurrent UI after pelvic floor surgery	Canadian Task Force on Preventive Health Care	Canada	English & French
Radziszewski et al,	2010	Urinary incontinence and overactive bladder in women	Consensus panel	Poland	Polish
NICE	2010	Lower Urinary Tract Symptoms (LUTS)	National Institute for Health and Clinical Excellence (NICE)	United Kingdom	English
NICE	2010	Nocturnal Enuresis, the management of bedwetting in children and young people	National Institute for Health and Clinical Excellence (NICE)	United Kingdom	English
Schröder, et al 2010 Thuroff et al, 2011	2010	EAU Guidelines on Urinary Incontinence	European Association of Urology	International	Spanish
ACOVE		Urinary incontinence in the elderly	ACOVE consensus panel	USA	English
Hanno et al,	2011	Interstitial cystitis / bladder pain syndrome	American Urological Association	USA	English
Gormley, et al, 2012	2012	Diagnosis and Treatment of Overactive Bladder (non-neurogenic) in adults	American Urological Association/Society for Urodynamics and Female Urology	USA	English
Winters, et al, 2012	2012	Adult Urodynamics	American Urological Association/Society for Urodynamics and Female Urology	USA	English

UI and falls. This study demonstrated that a set of templates can be developed within an existing electronic heath record system that can be used to prompt a clinician to obtain elements of a history and to perform physical examination.

In 2006, a national UK guideline was produced on UI in women [293]. Within the document, the area of surgeons' competence is discussed; however, there is no mention of other care providers' education and training (including GPs, nurses, physiotherapists, etc.). In order for services to be delivered effectively, primacy needs to be given to practitioners education and training in such documents.

a) Audits and assessments of guidelines

A number of recently published studies have examined the degree to which clinicians actually follow published guidelines. Many of these have focused on primary care providers.

A postal survey of Dutch general practitioners found that most adhered to guidelines when making the diagnosis of UI [199]. However, implementation of other measures and treatments were less robust. At least 25% reported difficulty adhering to the guideline due to lack of time, staff, diagnostic tools, competency in care delivery, and perceived low motivation on the part of patients. Others have questioned the utility of this specific guideline when viewed from the perspective of urologists [294]. They proposed future research to determine if recommendations for referral to specialists are adequate and if they will be implemented in a manner that will benefit patients. Another study with Dutch general practitioners identified therapeutic nihilism among the physicians and low motivation on the part of patients as major barriers to guideline implementation [86]. Other barriers included lack of time, difficulty explaining therapeutic options, limitations in patient mobility, and increased patient comorbidities.

A survey of primary care clinicians in the UK revealed that 56.8% agreed or strongly agreed that the NICE guideline on UI in women reflected their current practice [295]. However, more than half of clinicians indicated that they had not changed their practice to be fully compliant with the guideline. In another study, general practitioners in the UK identified knowledge limitations, time constraints, and access to resources on UI as important barriers to better implementation of the guidelines [296].

Adherence to guideline recommendations may also be less than optimal among specialist providers. Ismail[297] examined records of women undergoing sling surgery for treatment of stress UI at an academic medical center in the UK [297]. Only 45.3% of the patients had documentation in the medical record that they had previously tried conservative therapies. Documentation of underlying risk factors was highly variable. A similar study among urologists in Spain showed that compliance with guideline recommendations was less than ideal [298].

Rovner et al [299] examined published literature to determine the degree of adherence to the 1997 American Urological Association guidelines for the surgical treatment of stress UI in women [299]. They found that none of the 90 articles examined actually met all of the guideline criteria, although most complied with at least half of the recommendations. This directly influences the quality of literature available for evidence-based reviews and development of future guidelines.

Some components of guidelines may be particularly difficult to implement. For example, the NICE guideline recommendation that women undergoing PFMT should have a pelvic examination with assessment of muscle contractions may be challenging to perform in a busy clinical practice [300].

Studies have also examined the degree of awareness and adherence to guidelines among specific patient populations. Ismail reported on the results of a survey of 223 women in the UK who had recently delivered their first child [297]. According to the NICE guideline, these women should have been taught pelvic floor muscle exercises in the antenatal period. Although 95% reported awareness of the importance of the exercises, many did not have accurate information and only a small minority actually practiced them.

Guideline recommendations are not without controversy. In a retrospective database analysis of 6,276 women, Agur et al[301] noted that of women felt to have pure stress UI based on history alone, at least 25% were found to have other forms of voiding dysfunction based on urodynamics [301]. They concluded that the recommendation in the NICE guideline to avoid urodynamic testing in women with pure stress UI symptoms might be unwise and could miss other important findings, which could influence care.

Recent audits in the UK have shown that the mandate to develop and implement integrated continence care services has not been met [153,302,155].

There is even more limited data on whether adherence to guidelines actually leads to substantive changes in measurable continence outcomes [302]. In cases where organized services were available, overall quality outcomes were better compared to areas where these services were not offered [303].

A recent audit of the NICE guideline in the UK revealed that patient age may be associated with differential implementation of guideline recommenda-

tions for UI evaluation and treatment [304]. In this study, data from 7,846 women treated at either acute hospitals or primary care trusts in the UK, revealed that elderly women were significantly less likely to receive guideline compliant care compared to younger women. Actual levels of adherence by the care providers varied widely depending on the specific recommendation being evaluated. Levels of guideline adherence also appeared to differ between specialists providing care in acute hospital settings compared to general practitioners in the primary care trusts. In response to this finding, a recent editorial analysis asked rhetorically if lack of adherence to published guidelines for UI may actually represent a form of ageism on behalf of clinical providers and patients [305].

DuBeau et al[306] assessed the knowledge and attitudes of NH staff (including directors of nursing and nursing home surveyors) following revised USA government guidelines on continence care (Tag F315 - http://www.cms.hhs.gov/transmittals/downloads/R8SOM.pdf) [306]. They used a questionnaire in a convenience sample of 558 staff attending workshops. The authors report striking deficiencies in knowledge amongst staff and identified managerial structures as barriers to guideline implementation. They suggest such barriers need to be overcome in order to improve the quality of continence care.

Realistically the likelihood of obtaining adequate independent funding for effective professional education on UI and FI is unlikely in the current economic climate.

6. RECOMMENDATIONS FOR PROFESSIONAL EDUCATION (GRADE D)

Based on the literature reviewed in this section, the following recommendations can be made:

- There remains a need for rigorously evaluated continence education programmes which adhere to defined minimum standards for continence specialists and generalists, utilizing web-based and distance learning techniques alongside audit and feedback, train-the trainer models and leadership models, as well as traditional methods.
- Models of education content delivery (professional and patient education) are changing with technology with increased emphasis on Internet, web modules, etc. There needs to be ongoing quality control that includes maintenance of accuracy, methods of delivery, etc.
- There is a need for research on the most effective means to educate professional groups on continence issues. Specifically, there is need for research on:

o The effectiveness of innovative teaching methods in improving knowledge and practice.

o Translation of research into improved clinical practice and identification of methods by which this occurs.

o Mechanisms for increasing professional motivation to acquire education and improve performance.

VII. PRIMARY PREVENTION

1. BACKGROUND

Urinary incontinence is a highly prevalent and chronic condition that can often be prevented by addressing modifiable risk factors through primary prevention [307]. Although the evidence base for FI, PBS/IC, and POP is more limited than that for UI, the conditions share many similarities with respect to risk and treatment, suggesting that similar benefits may derive from population-based strategies [1].

Primary prevention refers to efforts directed to an individual, community or population level, to promote protective health behaviours in order to reduce the risk of these conditions. Since the Fourth ICI, there continues to be an increasing body of evidence linking incontinence with other conditions. These links provide opportunities to benefit from cooperative efforts with other health promotion initiatives. Primary prevention of UI using behavioral modification programs, including lifestyle changes (e.g., weight loss, diet modification) has been investigated in at-risk populations, including older women, childbearing and obese women, and women with diabetes. Obesity and diabetes have now been recognized as independent risk factors for UI [307]. ICI Committee 12: Adult Conservative Management reviews the evidence base for prevention of UI and POP in those persons with associated known risk factors and includes the levels of evidence for the respective interventions. Reference has also been made to prevention in other chapters, including ICI Committee 11: Incontinence in the Frail Elderly. Consequently, the focus of this section will be on the principles of population-based prevention, its application in other health conditions, and suggestions for translation into preventative programs for incontinence.

2. POPULATION-BASED PREVENTION

Recent research has predicted that due to population increases and a rise in the number of older adults, there will be a worldwide increase in the prevalence of UI by 20% by 2018 [308]. This has led to repeated calls to boost efforts to provide better continence education, promotion and prevention strategies throughout the world [235].

Prevention strategies should include education about lifestyle factors and behaviours that increase the probability of incontinence, the normal functioning of the urogenital and gastrointestinal tracts, expected age-related and developmental changes, healthy bladder and bowel habits,

and how to find the appropriate treatment providers [309]. A meta-analysis of physical activity programs found that behavioural interventions (such as goal setting, exercise prescription and self-monitoring) were more effective in increasing levels of physical activity than cognitive interventions (described as health education and the provision of information) [310]. Interventions for UI and FI (e.g., lifestyle changes, bladder and bowel training, PFMT) may also be better suited to behavioural rather than cognitive interventions. In addition, programs developed to raise awareness of continence issues should consider targeting a range of groups, including people of different cultures, ages and genders [106]. Consideration should also be given to targeting specific groups, including those who are socio-economically disadvantaged, as they may be hard to reach through population-based programs [311].

In 2011, the CFA launched a population-based campaign titled “Pelvic Floor First” to address concerns regarding the negative impact of some forms of physical activity on pelvic floor health. The campaign sought to raise awareness of pelvic floor related bladder and bowel health issues and to educate people at risk of UI and FI. Fitness instructors taught ways to minimise strain on the pelvic floor muscle when exercising. The campaign consisted of a dedicated web page (http://www.pelvicfloorfirst.org.au), on-line and printed education materials, screening tools for men and women, referral information and accredited on-line training for fitness professionals. Health consumers could also obtain information materials from the web page as well as links for further support from continence health professionals and the Australian National Continence Helpline.

Community based continence education workshops have been found to increase knowledge of continence issues and continence related QoL in women. In a study of 51 women who attended a 2.5 hour workshop, there was an increase in continence knowledge that was sustained for three months after the workshop [103]. The authors conclude that learning self-management strategies are important to improve pelvic floor health and that education in a public forum may be beneficial for these patients.

In 2011, a panel of experts released a consensus statement, A Healthy Bladder [312]. This follows from consensus work conducted that has examined the evidence base for preventative strategies for incontinence,[313,314] reiterating the ongoing need for primary prevention efforts to be addressed not only by healthcare professionals, but also by policymakers and funding bodies.

Consideration should be given to the setting in which the health promotion program is to be delivered, such as schools, work places, community groups and health care institutions [315]. It is acknowledged that while some nations are successfully implementing primary prevention strategies, others have yet to effectively implement secondary prevention measures, such as assessment and management of continence conditions [316]. In Australia, the UK and the U.S.A, continence organisations have received additional support from national governmental departments and agencies resulting in greater resources being applied to preventative and continence promotion programs. Evaluation and research are essential components of population-based prevention programs[317] and it is necessary to include funding for these as part of the program.

The WHO has stressed the importance of intersectoral collaboration involving governments, local communities and the private sector in efforts to tackle the effects of obesity and lack of physical activity upon chronic health conditions (http://www.who.int/dietphysicalactivity/en/). This type of collaboration may assist in spreading the cost of preventative programs for incontinence. A proposed diabetes population based prevention program found that governments are often reluctant to commit to high expenditure programs when the results may not be apparent until a considerable time later [318]. If a preventative program was developed for a combination of chronic health conditions, such as diabetes and incontinence, there may be economies of scale that would make funding such a program more attractive to governments, particularly when there is evidence that bladder changes and UI can be reversed if diabetes is prevented.

There have been a number of population-based prevention programs throughout the world that have been developed to reduce the incidence of obesity and chronic health problems by promoting physical activity and daily consumption of fruits and vegetables. An evaluation of a program in Australia to increase fruit and vegetable consumption in children found that increased parental knowledge as a result of the program was the strongest predictor of fruit and vegetable intake [319]. Evaluation of data from these programs is likely to benefit researchers and practitioners planning continence prevention programs for adults as well as children. The evidence for population-based prevention strategies remains at Level 4, Grade C.

3. PREVENTION OF UI IN OLDER ADULTS

Older adults are a heterogeneous group, and therefore preventive strategies for older adults need to take into consideration the well aged as well as the frail aged. It is important to involve older people and upcoming generations in health promotion research and health promotion intervention programs targeted at older people [320]. Promoting self-efficacy, such that the individual has a belief that they have the capacity and skills to im-

prove their own health, has been used in research on prevention of older, well-educated women with UI [321]. Self-efficacy improves the ability to cope with symptoms and is linked to motivation, knowledge of the benefits of making changes, and adherence to behavior change [322,323]. Self-efficacy over UI may be enhanced if women are taught self-monitoring techniques, such as adjusting fluid and caffeine intake, resolving constipation, PFMT, and monitoring voiding intervals. Self-efficacy measures, such as the Geriatric Self-Efficacy Index for Urinary Incontinence can be used to determine adherence to behavioural programs developed for the prevention and management of UI [6].

Community continence education of older adults has been advocated in several studies. A descriptive cross-sectional study conducted in China found that community-dwelling older persons often expressed negativity toward UI [158]. They considered UI as shameful, their own fault, and not preventable. Despite these feelings, they indicated that UI was not a sufficiently serious problem to justify treatment. In addition, nearly half of the nurses surveyed reported ignoring the initial onset of UI. Findings from this study indicated a great need for UI education for community-dwelling older persons and community nurses [158]. A similar conclusion, that advocated the need for education, was drawn from a cross-sectional descriptive study of 182 community-dwelling Korean American women [324].

Workshops can be an effective tool for population-based prevention education in older women. Tannenbaum [102] carried out a quasi-experimental prospective cohort study to evaluate the effectiveness of an interactive continence workshop. Ninety incontinent women, ages 55 to 87, were involved in this study. The interventions significantly increased knowledge and attitudes about the condition (94%). Sizeable proportions of participants either initiated self-treatment strategies, such as pelvic floor muscle exercises, scheduled toileting or dietary change (43%), or sought consultation with a health care provider (42%). The authors concluded that interactive continence workshops can promote self-management and consultation seeking among older women with incontinence. Incontinence-related knowledge, attitudes, self-perceived skills and intentions for seeking care improved after attending the workshops [102]. A behavioural modification program delivered to a group of women over 55 years of age reported the preventive effects of increasing pelvic floor muscle strength and increasing time between voids upon continence status, suggesting that preventive strategies are effective in older women [309,325].

Correlations have been found between poor general health and severe UI and/or FI in frail older people [326]. There are a number of strategies (e.g., mobility training, progressive strength training, balance and walking exercises), combined with behavioral interventions (e.g., pelvic floor muscle exercises) that may be successful in improving UI in this population. A systematic review of 3 RCTs and 4 quasi-experimental studies aimed to identify conservative interventions for reducing UI in non-institutionalized frail older adults [327]. With 683 participants involved (75% female), the studies concluded that multi-component behavioral interventions, including pelvic floor muscle exercises and bladder training, can improve UI frequency. However, there is need for more RCTs to demonstrate the efficacy of multidimensional treatments to guide clinical practice in the prevention and management of UI in frail older adults. (LOE 2)

4. PREVENTION OF FAECAL INCONTINENCE

While it appears that people are seeking help more readily for UI, the problem of FI remains under–reported,[241] especially in older people,[328] and few physicians ask patients about it in those persons at-risk [329]. A variety of risk factors associated with FI is reported by Committee 16: FI: Conservative Treatment. Analysis of studies on FI is hampered by a lack of standardised terminology with regards to stool consistency, gas leakage and frequency of incontinent episodes [314,330,331]. In order to be all inclusive, search terms for FI were expanded to include additional terms,(stool consistency, gas leakage, frequency of incontinent episodes,flatus,copracrasia). However, there were fewer matched papers about this area. Only an RCT in China revealed that PFMT is effective on the prevention of copracrasia by sphincter preservation operation on mid-lower rectal cancer. One hundred and fifty-one participants who received the surgery were randomized to two groups. Intervention group (n=75) received PFMT for six months but the control group (n=76) did not. The results from 1, 3, and 6 month follow-ups showed that PFMT contributed a positive effect against the development of FI [332]. (LOE 2) While acknowledging that prevention of FI is important, it is recognized that more research is needed to determine the effectiveness of population-based interventions that focus on the risk factors of FI.

5. RECOMMENDATIONS FOR PRIMARY PREVENTION (GRADE C)

Based on the literature reviewed in this section, the following recommendations can be made.

- Primary prevention studies should not be limited to individual interventions, but also test the impact of population-based public health strategies.
- More high quality, randomised controlled trials are needed to strengthen the effectiveness of population-based primary prevention intervention.

REFERENCES

1. Newman DK, C. H. Ee, et al. . Continence promotion, edue cation & primary prevention. Plymouth, United Kingdom: Health Publications; 2009.
2. Newman DK. Tackling the stigma of incontinence: Promoting continence worldwide. 3rd Ed. ed. London, United Kingdom: Isis Medical Media, LTD; 2010.
3. Newman DK, L. Denis, et al. . Promotion, education and organization for continence care. Plymouth, United Kingdom: Health Publications; 2005.
4. Newman DK, L. Denis, et al. Promotion, education and organization for continence care. Plymouth, United Kingdom: Health Publications; 2002.
5. First International Conference on Health Promotion. 1986. (Accessed at http://www.who.int/hpr/NPH/docs/ottawa_charter_hp.pdf)
6. Tannenbaum C, Shatenstein B. Exercise and nutrition in older Canadian women: opportunities for community intervention. Can J Public Health 2007;98:187-93.
7. Norton C, and L. Dibley. Understanding the taboos about bladder and bowels. Wilmette, Illinois: The Simon Foundation.
8. Landefeld CS, Bowers BJ, Feld AD, et al. National Institutes of Health state-of-the-science conference statement: prevention of fecal and urinary incontinence in adults. Ann Intern Med 2008;148:449-58.
9. Bliss DZ, Norton C, Vodusek DB. Raising awareness about fecal incontinence. Neurourol Urodyn 2010;29:612-5.
10. Kerka S. Health Literacy beyond Basic Skills. ERIC Digest 2003.
11. Hines SH, Sampselle CM, Ronis DL, Yeo S, Fredrickson BL, Boyd CJ. Women's self-care agency to manage urinary incontinence: the impact of nursing agency and body experience. ANS Adv Nurs Sci 2007;30:175-88.
12. Holroyd-Leduc JM, Straus S, Thorpe K, Davis DA, Schmaltz H, Tannenbaum C. Translation of evidence into a self-management tool for use by women with urinary incontinence. Age Ageing 2011;40:227-33.
13. Melville JL, Wagner LE, Fan MY, Katon WJ, Newton KM. Women's perceptions about the etiology of urinary incontinence. J Womens Health (Larchmt) 2008;17:1093-8.
14. Patel K, Bliss DZ, Savik K. Health literacy and emotional responses related to fecal incontinence. J Wound Ostomy Continence Nurs 2010;37:73-9.
15. Baker L, Wagner TH, Singer S, Bundorf MK. Use of the Internet and e-mail for health care information: results from a national survey. JAMA 2003;289:2400-6.
16. Diering CL, Palmer MH. Professional information about urinary incontinence on the World Wide Web: is it timely? Is it accurate? J Wound Ostomy Continence Nurs 2001;28:55-62.
17. Sandvik H. Health information and interaction on the internet: a survey of female urinary incontinence. BMJ 1999;319:29-32.
18. Berger M, Wagner TH, Baker LC. Internet use and stigmatized illness. Soc Sci Med 2005;61:1821-7.
19. Sajadi KP, Goldman HB, Firoozi F. Assessing Internet health information on female pelvic floor disorders. J Urol 2011;186:594-6.
20. Lenhart A, J. Horrigan, et al. . The ever shifting internet population: A new look at internet access and the digital divide. Washington, D. C. ; 2003.
21. Pena-Purcell N. Hispanic's use of internet health information: an exploratory study. J Med Library Association 2008;96:101-7.
22. Sajadi KP, Goldman HB, Firoozi F. Assessing internet health information on female pelvic floor disorders. Journal of Urology;186:594-6.
23. Al-Shammary N, S. Awan, et al. . Internet use before consultation with a health professional. Primary Health Care 2007;17:18-21.
24. Sajadi KP, Goldman HB. Social networks lack useful content for incontinence. Urology 2011;78:764-7.
25. Buckley BS, Lapitan MC, On behalf of the epidemiology committee of the 4th International Consultation on Incontinence P, 2008 (Milsom I, Herbison P, Altman D, Lapitan MC, Nelson R, Sillén U, Thom D). Prevalence of Urinary Incontinence in men, women and children: current evidence. Findings of the 4th International Consultation on Incontinence. Urology 2010;76:265-70.
26. Kinchen KS, Burgio K, Diokno AC, Fultz NH, Bump R, Obenchain R. Factors associated with women's decisions to seek treatment for urinary incontinence. J Womens Health (Larchmt) 2003;12:687-98.
27. Stenzelius K, Westergren A, Hallberg IR. Bowel function among people 75+ reporting faecal incontinence in relation to help seeking, dependency and quality of life. J Clin Nurs 2007;16:458-68.
28. Wennberg A-L, Molander U, Fall M, Edlund C, Peeker R, Milsom I. Lower urinary tract symptoms: lack of change in prevalence and help-seeking behaviour in two population-based surveys of women in 1991 and 2007. BJU International 2009;doi:10.1111/j.1464-410X.2009.08534.x.
29. Shaw C, Brittain K, Tansey R, Williams K. How people decide to seek health care: A qualitative study. International Journal of Nursing Studies 2008;45:1516–24.
30. Diokno AC, Burgio K, Fultz NH, Kinchen KS, Obenchain R, Bump RC. Medical and self-care practices reported by women with urinary incontinence. Am J Manag Care 2004;10:69-78.
31. Johnson TM, 2nd, Kincade JE, Bernard SL, Busby-Whitehead J, DeFriese GH. Self-care practices used by older men and women to manage urinary incontinence: results from the national follow-up survey on self-care and aging. J Am Geriatr Soc 2000;48:894-902.
32. Bliss DZ, Fischer LR, Savik K. Managing fecal incontinence: self-care practices of older adults. J Gerontol Nurs 2005;31:35-44.
33. Croswell E, Bliss DZ, Savik K. Diet and eating pattern modifications used by community-living adults to manage their fecal incontinence. J Wound Ostomy Continence Nurs 2010;37:677-82.
34. Anger JT, Nissim HA, Le TX, et al. Women's experience with severe overactive bladder symptoms and treatment: insight revealed from patient focus groups. Neurourol Urodyn 2011;30:1295-9.
35. Diokno AC, Sand PK, Macdiarmid S, Shah R, Armstrong RB. Perceptions and behaviours of women with bladder control problems. Fam Pract 2006;23:568-77.
36. Koch LH. Help-seeking behaviors of women with urinary incontinence: an integrative literature review. J Midwifery Womens Health 2006;51:e39-44.
37. Horrocks S, Somerset M, Stoddart H, Peters TJ. What prevents older people from seeking treatment for urinary incontinence? A qualitative exploration of barriers to the use of community continence services. Fam Pract 2004;21:689-96.
38. Welch LC, Taubenberger S, Tennstedt SL. Patients' experiences of seeking health care for lower urinary tract symptoms. Res Nurs Health 2011;34:496-507.
39. Visser E, de Bock GH, Kollen BJ, Meijerink M, Berger MY, Dekker JH. Systematic screening for urinary incontinence in older women: who could benefit from it? Scand J Prim Health Care 2012;30:21-8.
40. Sykes D, R. Castro, et al. . Characteristics of female outpatients with urinary incontinence participating in a 6-month observational study in 14 European countries. Maturitas 2005;52:S13-S23.
41. Huang AJ, Brown JS, Kanaya AM, et al. Quality-of-life impact and treatment of urinary incontinence in ethnically diverse older women. Arch Intern Med 2006;166:2000-6.

42. Cetinel B, Demirkesen O, Tarcan T, et al. Hidden female urinary incontinence in urology and obstetrics and gynecology outpatient clinics in Turkey: what are the determinants of bothersome urinary incontinence and help-seeking behavior? Int Urogynecol J 2007;18:659–64.

43. Shaw C, Gupta RD, Bushnell DM, et al. The extent and severity of urinary incontinence amongst women in UK GP waiting rooms. Fam Pract 2006;23:497-506.

44. Rizk DE, Shaheen H, Thomas L, Dunn E, Hassan MY. The prevalence and determinants of health care-seeking behavior for urinary incontinence in United Arab Emirates women. Int Urogynecol J Pelvic Floor Dysfunct 1999;10:160-5.

45. Anthony JS. Self-advocacy in health care decision-making among elderly African Americans. J Cult Divers 2007;14:88-95.

46. Downes L. Motivators and barriers of a Healthy Lifestyle Scale: development and psychometric characteristics. J Nurs Meas 2008;16:3-15.

47. Julliard K, Vivar J, Delgado C, Cruz E, Kabak J, Sabers H. What Latina patients don't tell their doctors: a qualitative study. Ann Fam Med 2008;6:543-9.

48. Berger MB, Patel DA, Miller JM, Delancey JO, Fenner DE. Racial differences in self-reported healthcare seeking and treatment for urinary incontinence in community-dwelling women from the EPI Study. Neurourol Urodyn 2011;30:1442-7.

49. Howard DL, Edwards BG, Whitehead K, Amamoo MA, Godley PA. Healthcare practices among blacks and whites with urinary tract symptoms. J Natl Med Assoc 2007;99:404-11.

50. Li Y, Cai X, Glance LG, Mukamel DB. Gender differences in healthcare-seeking behavior for urinary incontinence and the impact of socioeconomic status: a study of the Medicare managed care population. Med Care 2007;45:1116-22.

51. Geoffrion R. Women's knowlege of pelvic floor disorders. Expert Rev Gynecol 2010;5:471-7.

52. Shah AD, Massagli MP, Kohli N, Rajan SS, Braaten KP, Hoyte L. A reliable, valid instrument to assess patient knowledge about urinary incontinence and pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:1283-9.

53. Shah AD, Shott S, Kohli N, Wu JM, Catlin S, Hoyte L. Do racial differences in knowledge about urogynecologic issues exist? Int Urogynecol J Pelvic Floor Dysfunct 2008;19:1371-8.

54. Kang Y. Knowledge and attitudes about urinary incontinence among community-dwelling Korean American women. Journal of Wound, Ostomy and Continence Nursing 2009;36:194-9.

55. Kang Y, Phillips LR, Lim K. Predictors of help seeking among Korean American women with urinary incontinence. J Wound Ostomy Continence Nurs 2011;38:663-72.

56. Rizk DE, Hassan MY, Shaheen H, Cherian JV, Micallef R, Dunn E. The prevalence and determinants of health care-seeking behavior for fecal incontinence in multiparous United Arab Emirates females. Dis Colon Rectum 2001;44:1850-6.

57. Hemachandra NN, L. C. Rajapaksa, et al. . A «usual oca currence:» stress incontinence among reproductive aged women in Sri Lanka. Soc Sci Med 2009;69:1395-401.

58. Hsieh CH, Su TH, Chang ST, Lin SH, Lee MC, Lee MY. Prevalence of and attitude toward urinary incontinence in postmenopausal women. Int J Gynaecol Obstet 2008;100:171-4.

59. Li FL, Low LP, Lee DT. Chinese women's experiences in coping with urinary incontinence. J Clin Nurs 2007;16:610-2.

60. Rizk DE. Ethnic differences in women's knowledge level and other barriers to care seeking and the true incidence and/or prevalence rate of female pelvic floor disorders. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:1587-8.

61. Rizk DE. Measuring barriers to urinary incontinence care seeking in women: the knowledge barrier. Neurourol Urodyn 2009;28:101.

62. Saleh N, Bener A, Khenyab N, Al-Mansori Z, Al Muraikhi A. Prevalence, awareness and determinants of health care-seeking behaviour for urinary incontinence in Qatari women: a neglected problem? Maturitas 2005;50:58-65.

63. El-Azab AS, Shaaban OM. Measuring the barriers against seeking consultation for urinary incontinence among Middle Eastern women. BMC Womens Health 2010;10:3.

64. Weaver A, Jacques E. Encouraging adolescents to seek continence help. Nurs Times 2008;104:46-8.

65. Carls C. The prevalence of stress urinary incontinence in high school and college-age female athletes in the midwest: implications for education and prevention. Urol Nurs 2007;27:21-4, 39.

66. Andersen JCaBA. Screening for urinary incontinence in female athletes. Althletic Training & Sports Health Care 2011;3:206-7.

67. Fonda D, and D. K. Newman. Tackling the stigma of incontinence – Promoting Continence Worldwide. 2nd Ed. ed. United Kingdom: Isis Medical Media, LTD; 2006.

68. Andersson G, Johansson JE, Garpenholt O, Nilsson K. Urinary incontinence--prevalence, impact on daily living and desire for treatment: a population-based study. Scand J Urol Nephrol 2004;38:125-30.

69. Hagglund D, Wadensten B. Fear of humiliation inhibits women's care-seeking behaviour for long-term urinary incontinence. Scand J Caring Sci 2007;21.

70. Hazewinkel MH, Sprangers MAG, Taminiau-Bloem EF, van der Velden J, Burger MPM, Rooversa J-PWR. Reasons for not seeking medical help for severe pelvic floor symptoms: a qualitative study in survivors of gynaecological cancer. BJOG: An International Journal of Obstetrics and Gynaecology 2010;117:39–46.

71. Mills AL, and J. P. Pierce. Editorial using teachable moments to improve nutrition and physical activity in patients. American Family Physician 2008;77:1510-11.

72. Hope C. Promoting continence positively. J Community Nursing 2007;21:24-7.

73. McConnell ES, Lekan-Rutledge D, Nevidjon B, Anderson R. Complexity theory: a long-term care specialty practice exemplar for the education of advanced practice nurses. J Nurs Educ 2004;43:84-7.

74. Palmer MH, Newman DK. Bladder control educational needs of older adults. J Gerontol Nurs 2006;32:28-32.

75. Gunzler C, Kriston L, Stodden V, Leiber C, Berner MM. Can written information material help to increase treatment motivation in patients with erectile dysfunction? A survey of 1188 men. Int J Impot Res 2007;19:330-5.

76. Eogan M, Daly L, O'Connell PR, O'Herlihy C. Does the angle of episiotomy affect the incidence of anal sphincter injury? BJOG 2006;113:190-4.

77. Boyington AR, M. C. Dougherty, et al. . Analysis of interactive continence health information on the web. J Wound Ostomy Continence Nurs 2005;30:280-6.

78. Zarate-Abbott P, Etnyre A, Gilliland I, et al. Workplace health promotion--strategies for low-income Hispanic immigrant women. AAOHN J 2008;56:217-22.

79. Ishikawa H, Takeuchi T, Yano E. Measuring functional, communicative, and critical health literacy among diabetic patients. Diabetes Care 2008;31:874-9.

80. Elstad EA, Taubenberger SP, Botelho EM, Tennstedt SL. Beyond incontinence: the stigma of other urinary symptoms. J Adv Nurs 2010;66:2460-70.

81. Basu M, Duckett JRA. Barriers to seeking treatment for women with persistent or recurrent symptoms in urogynaecology. BJOG: An International Journal of Obstetrics and Gynaecology 2009;DOI: 10.1111/j.1471-0528.2008.02098.x.

82. Norton NJ. The perspective of the patient. Gastroenterology 2004;126:S175-9.

83. Newman DK. Talking to patients about bladder control problems. Nurse Pract 2009;34:33-45.

84. Garcia JA, Crocker J, Wyman JF, Krissovich M. Breaking the cycle of stigmatization: managing the stigma of incontinence in social interactions. J Wound Ostomy Continence Nurs 2005;32:38-52.

85. Norton C. Nurses, bowel continence, stigma, and taboos. J Wound Ostomy Continence Nurs 2004;31:85-94.

86. Teunissen D, van den Bosch W, van Weel C, Lagro-Janssen T. Urinary incontinence in the elderly: attitudes and experiences of general practitioners. A focus group study. Scand J Prim Health Care 2006;24:56-61.

87. Mohamed AM, Hassouna MS, Kassem MS. Gender differences in factors associated with patients' decisions to seek treatment for urinary incontinence in Alexandria, Egypt. East Mediterr Health J 2010;16:1170-82.

88. Tuckett AG, Hodgkinson B, Hegney DG, Paterson J, Kralik D. Effectiveness of educational interventions to raise men's awareness of bladder and bowel health. Int J Evid Based Healthc 2011;9:81-96.

89. Harris MF, McKenzie S. Men's health: what's a GP to do? Med J Aust 2006;185:440-4.

90. Engstrom G, Walker-Engstrom ML, Loof L, Leppert J. Prevalence of three lower urinary tract symptoms in men-a population-based study. Fam Pract 2003;20:7-10.

91. Muller N. What Americans understand and how they are affected by bladder control problems: highlights of recent nationwide consumer research. Urol Nurs 2005;25:109-15.

92. Diokno AC, Estanol MV, Ibrahim IA, Balasubramaniam M. Prevalence of urinary incontinence in community dwelling men: a cross sectional nationwide epidemiological survey. Int Urol Nephrol 2007;39:129-36.

93. Wolters R, Wensing M, van Weel C, van der Wilt GJ, Grol RP. Lower urinary tract symptoms: social influence is more important than symptoms in seeking medical care. BJU Int 2002;90:655-61.

94. Doshani A, Pitchforth E, Mayne CJ, Tincello DG. Culturally sensitive continence care: a qualitative study among South Asian Indian women in Leicester. Fam Pract 2007;24:585-93.

95. Kitagawa K. Annual report on Health and Welfare 1995-6. Tokyo, Japan: Ministry of Health & Welfare of Japan; 1997.

96. Sexton CC, Coyne KS, Kopp ZS, et al. The overlap of storage, voiding and postmicturition symptoms and implications for treatment seeking in the USA, UK and Sweden: EpiLUTS. BJU Int 2009;103 Suppl 3:12-23.

97. Shaw C, Das Gupta R, Williams KS, Assassa RP, McGrother C. A survey of help-seeking and treatment provision in women with stress urinary incontinence. BJU Int 2006;97:752-7.

98. Rios AAN, Cardoso JR, Rodrigues MAF, de Almeida SHM. The help-seeking by women with urinary incontinence in Brazil. Int Urogynecol J 2011;22:879-84.

99. Berger MB, Patel DA, Miller JM, Delancey JO, Fenner DE. Racial differences in self-reported healthcare seeking and treatment for urinary incontinence in community-dwelling women from the EPI study. Neurourology and Urodynamics;30:1442-7.

100. Guimmarra MJ, B. Haralambous, et al. . The concept of health in older age: views of older people and health professionals. Australian Health Review 2007;31:642-50.

101. Wilson LF. Adolescents' attitudes about obesity and what they want in obesity prevention programs. J Sch Nurs 2007;23:229-38.

102. Tannenbaum C, Drali R, Holroyd-Leduc J, Richard L. Lessons learned: impact of a continence promotion activity for older community-dwelling women. Neurourol Urodyn 2010;29:540-4.

103. Geoffrion R, Robert M, Ross S, et al. Evaluating patient learning after an educational program for women with incontinence and pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2009;20:1243-52.

104. Newman DK. Report of a mail survey of women with bladder control disorders. Urol Nurs 2004;24:499-507.

105. Kelly AM, Byrne G. Role of the continence nurse in health promotion. Br J Nurs 2006;15:198-204.

106. McCallum J, L. Millar, et al. Framework for evaluation of the national continence management strategy. Australasian J Ageing 2007;26:A25-A6.

107. The National Continence Program Action Plan. 2011-2014. (Accessed at http://www.bladderbowel.gov.au/assets/doc/NCPActionPlan.pdf.)

108. National Continence Management Strategy (NCMS). 1998-2010. (Accessed at http://www.bladderbowel.gov.au/ncp/ncms/default.htm.)

109. McFall SL, A. M. Yerkes, et al. . Urinary incontinence and quality of life in older women: a community demonstration in Oklahoma. Family & Community Health 1994;17:64-75.

110. Morahan-Martin JM. How internet users find, evaluate, and use online health information: a cross-cultural review. Cyberpsychol Behav 2004;7:497-510.

111. Newman DK, Wallace J, Blackwood N, Spencer C. Promoting healthy bladder habits for seniors. Ostomy Wound Manage 1996;42:18-22, 4-5, 8.

112. Schirm V, Baumgardner J, Dowd T, Gregor S, Kolcaba K. Development of a healthy bladder education program for older adults. Geriatr Nurs 2004;25:301-6.

113. Norton C, Brown J, Thomas E. Continence: a phone call away. Nurs Stand 1995;9:22-3.

114. Roe B, Wilson K, Doll H. Public awareness and health education: findings from an evaluation of health services for incontinence in England. Int J Nurs Stud 2001;38:79-89.

115. Muller N. What the future holds for continence care. Urol Nurs 2004;24:181-6.

116. Gartley CB. Bringing Mohammed to the mountain: educating the community for continence. Urol Nurs 2006;26:387-93.

117. Jarrett NC, C. D. Bellamy, et al. . Men's health help-seeking and implications for practice. Am J Health Studies 2007;22:88-95.

118. Senekjian L, Heintz K, Egger MJ, Nygaard I. Do Women Understand Urogynecologic Terminology? Female Pelvic Med Reconstr Surg 2011;17:215-7.

119. Australian incontinence data analysis and development. 2006. (Accessed at http://www.aihw.gov.au/publications/index.cfm/title/10201)

120. Digesu GA, Khullar V, Panayi D, Calandrini M, Gannon M, Nicolini U. Should we explain lower urinary tract symptoms to patients? Neurourol Urodyn 2008;27:368-71.

121. Smith AL, Nissim HA, Le TX, et al. Misconceptions and miscommunication among aging women with overactive bladder symptoms. Urology 2011;77:55-9.

122. Hougardy V, Vandeweerd JM, Reda AA, Foidart JM. The impact of detailed explanatory leaflets on patient satisfaction with urodynamic consultation: a double-blind randomized controlled trial. Neurourol Urodyn 2009;28:374-9.

123. Neustaedter EG, Milne J, Shorten K, Weckman B, Tse A, Tange S. How well informed are women who undergo urodynamic testing? Neurourol Urodyn 2011;30:572-7.

124. Levy-Storms L, Schnelle JF, Simmons SF. What do family members notice following an intervention to improve mobility and incontinence care for nursing home residents? An analysis of open-ended comments. Gerontologist 2007;47:14-20.

125. Spencer J. Reducing barriers and improving access to continence care: examining the evidence. Urologic nursing 2009;29:405-14.

126. Wagg AR, Barron D, Kirby M, Stott D, Corlett K. A randomised partially controlled trial to assess the impact of self-help vs. structured help from a continence nurse specialist in women with undiagnosed urinary problems in primary care. Int J Clin Pract 2007;61:1863-73.

127. O'Connell B, Gaskin CJ. Using an educational pamphlet to

promote help-seeking behaviour for urinary incontinence in people visiting their general practitioner. Australian & New Zealand Continence Journal;16:8.

128. O'Connell B, Wellman D, Baker L, Day K. Does a continence educational brochure promote health-seeking behavior? J Wound Ostomy Continence Nurs 2006;33:389-95.

129. Hougardy V, Vandeweerd JM, Reda AA, Foidart JM. The impact of detailed explanatory leaflets on patient satisfaction with urodynamic consultation: A double-blind randomized controlled trial. Neurourology and Urodynamics 2009;28:374-9.

130. Franzen K, Johansson JE, Andersson G, Nilsson K. Urinary incontinence: Evaluation of an information campaign directed towards the general public. Scand J Urol Nephrol 2008;42:534-8.

131. Beguin AM, Combes T, Lutzler P, Laffond G, Belmin J. Health education improves older subjects' attitudes toward urinary incontinence and access to care: a randomized study in sheltered accommodation centers for the aged. J Am Geriatr Soc 1997;45:391-2.

132. Geoffrion R, Robert M, Ross S, et al. Evaluating patient learning after an educational program for women with incontinence and pelvic organ prolapse. International Urogynecology Journal and Pelvic Floor Dysfunction 2009;20:1243-52.

133. Buckley BS. Launching a new charity to support continence patients. Continence UK 2008;2:6.

134. Buckley BS, A. Wagg, et al. Emotional well-being in faecal and urinary incontinence. Continence UK 2007;1:66-70.

135. Broome BA. The impact of urinary incontinence on self-efficacy and quality of life. Health Qual Life Outcomes 2003;1:35.

136. Koch T, Kelly S. Identifying strategies for managing urinary incontinence with women who have multiple sclerosis. J Clin Nurs 1999;8:550-9.

137. Shaw C. A review of the psychosocial predictors of help-seeking behaviour and impact on quality of life in people with urinary incontinence. J Clin Nurs 2001;10:15-24.

138. Shaw C, Tansey R, Jackson C, Hyde C, Allan R. Barriers to help seeking in people with urinary symptoms. Fam Pract 2001;18:48-52.

139. Buckley BS, Grant AM, Glazener CM. Case study: A patient-clinician collaboration that identified and prioritized evidence gaps and stimulated research development. J Clin Epidemiol 2011.

140. Herbison P, Hay-Smith J, Paterson H, Ellis G, Wilson D. Research priorities in urinary incontinence: results from citizens' juries. BJOG 2009;116:713-8.

141. O'Donnell M, Viktrup L, Hunskaar S. The role of general practitioners in the initial management of women with urinary incontinence in France, Germany, Spain and the UK. Eur J Gen Pract 2007;13:20-6.

142. Laurant M, Reeves D, Hermens R, Braspenning J, Grol R, Sibbald B. Substitution of doctors by nurses in primary care. Cochrane Database Syst Rev 2005:CD001271.

143. Festen L, Duggan P, Coates D. Improved quality of life in women treated for urinary incontinence by an authorised continence nurse practitioner. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:567-71.

144. Jeffery S, Doumouchtsis SK, Fynes M. Patient satisfaction with nurse-led telephone follow-up in women with lower urinary tract symptoms. J Telemed Telecare 2007;13:369-73.

145. Good Practice for Continence Care. 2000. (Accessed at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005851.)

146. Mold JW, Fryer GE, Phillips RL, Jr., Dovey SM, Green LA. Family physicians are the main source of primary health care for the Medicare population. Am Fam Physician 2002;66:2032.

147. Green LA, Fryer GE, Jr., Yawn BP, Lanier D, Dovey SM. The ecology of medical care revisited. N Engl J Med 2001;344:2021-5.

148. O'Brien J, Long H. Urinary incontinence: long term effectiveness of nursing intervention in primary care. BMJ 1995;311:1208.

149. Seim A, Hermstad R, Hunskaar S. Female urinary incontinence: long-term follow-up after treatment in general practice. Br J Gen Pract 1998;48:1731-4.

150. Drennan VM, Cole L, Iliffe S. A taboo within a stigma? a qualitative study of managing incontinence with people with dementia living at home. BMC Geriatr 2011;11:75.

151. Greenberg P, Brown J, Yates T, Brown V, Langenberg P, Warren JW. Voiding urges perceived by patients with interstitial cystitis/painful bladder syndrome. Neurourol Urodyn 2008;27:287-90.

152. Peters KM, Carrico DJ, Diokno AC. Characterization of a clinical cohort of 87 women with interstitial cystitis/painful bladder syndrome. Urology 2008;71:634-40.

153. Potter J, Peel P, Mian S, et al. National audit of continence care for older people: management of faecal incontinence. Age Ageing 2007;36:268-73.

154. Wagg A, Lowe D, Peel P, Potter J. Continence care for older people in England and Wales: data from a national audit. J Wound Ostomy Continence Nurs 2008;35:215-20.

155. Wagg A, Potter J, Peel P, Irwin P, Lowe D, Pearson M. National audit of continence care for older people: management of urinary incontinence. Age Ageing 2008;37:39-44.

156. Howard F, Steggall M. Urinary incontinence in women: quality of life and help-seeking. Br J Nurs 2010;19:742, 4, 6, 8-9.

157. Kang Y, Crogan NL. Social and cultural construction of urinary incontinence among Korean American elderly women. Geriatr Nurs 2008;29:105-11.

158. Yuan HB, Williams BA, Liu M. Attitudes toward urinary incontinence among community nurses and community-dwelling older people. J Wound Ostomy Continence Nurs 2011;38:184-9.

159. Buckley BS, Lapitan MC. Prevalence of urinary and faecal incontinence and nocturnal enuresis and attitudes to treatment and help-seeking amongst a community-based representative sample of adults in the United Kingdom. Int J Clin Pract 2009;63:568-73.

160. Rodriguez LV, Blander DS, Dorey F, Raz S, Zimmern P. Discrepancy in patient and physician perception of patient's quality of life related to urinary symptoms. Urology 2003;62:49-53.

161. Bradway C, Strumpf N. Seeking care: women's narratives concerning long-term urinary incontinence. Urol Nurs 2008;28:123-9.

162. O'Donnell M, Hunskaar S. Preferences for involvement in treatment decision-making among Norwegian women with urinary incontinence. Acta Obstet Gynecol Scand 2007;86:1370-6.

163. O'Donnell M, Hunskaar S. Preferences for involvement in treatment decision-making generally and in hormone replacement and urinary incontinence treatment decision-making specifically. Patient Educ Couns 2007;68:243-51.

164. Sung VW, Raker CA, Myers DL, Clark MA. Treatment decision-making and information-seeking preferences in women with pelvic floor disorders. Int Urogynecol J 2010;21:1071-8.

165. Milne JL, Moore KN. An exploratory study of continence care services worldwide. Int J Nurs Stud 2003;40:235-47.

166. Farrell SA, Scott TA, Farrell KA, Irving L, Foren J, Twohig J. Two models for delivery of women's continence care: the step-wise continence team versus the traditional medical model. J Obstet Gynaecol Can 2009;31:247-53.

167. Matharu GS, Assassa RP, Williams KS, et al. Continence nurse treatment of women's urinary symptoms. Br J Nurs 2004;13:140-3.

168. Du Moulin MF, Hamers JP, Paulus A, Berendsen CL, Halfens R. Effects of introducing a specialized nurse in the care of community-dwelling women suffering from urinary incontinence: a randomized controlled trial. J Wound Ostomy Continence Nurs 2007;34:631-40.

169. Shaw C, Williams KS, Assassa RP. Patients' views of a new nurse-led continence service. J Clin Nurs 2000;9:574-82.

170. Dingwall L, McLafferty E. Do nurses promote urinary continence in hospitalized older people?: An exploratory study. J Clin Nurs 2006;15:1276-86.

171. Dingwall L. Promoting effective continence care for older people: a literature review. Br J Nurs 2008;17:166-72.

172. Desai N, Keane T, Wagg A, Wardle J. Provision of continence pads by the continence services in Great Britain: fair all round? J Wound Ostomy Continence Nurs 2008;35:510-4.

173. Williams KS, Assassa RP, Smith NK, et al. Development, implementation and evaluation of a new nurse-led continence service: a pilot study. J Clin Nurs 2000;9:566-73.

174. Williams T, Sims J, Burkhead C, Ward PM. The creation, implementation, and evaluation of a nurse residency program through a shared leadership model in the intensive care setting. Dimens Crit Care Nurs 2002;21:154-61.

175. Williams KS, Assassa RP, Cooper NJ, et al. Clinical and cost-effectiveness of a new nurse-led continence service: a randomised controlled trial. Br J Gen Pract 2005;55:696-703.

176. Borrie MJ, Bawden M, Speechley M, Kloseck M. Interventions led by nurse continence advisers in the management of urinary incontinence: a randomized controlled trial. CMAJ 2002;166:1267-73.

177. Borrie MJ, S. Lyteynec, et al. . Outcomes of a new community-nurse continence service. Ann R Coll Physicians Surg Can 1999;32:346-51.

178. Saltmarche A, D. W., Reid, et al. . A community nurse continence service delivery model - a demonstration project. In: Proceedings of hte International Continence Society meeting; 1992; Halifax, Nova Scotia; 1992. p. 274.

179. Lajiness MJ, Wolfert C, Hall S, Sampselle C, Diokno AC. Group session teaching of behavioral modification program for urinary incontinence: establishing the teachers. Urol Nurs 2007;27:124-7.

180. Richardson K, Hagen S. The role of nurses in the management of women with pelvic organ prolapse. Br J Nurs 2009;18:294-6, 8-300.

181. Hagglund D. District continence nurses' experiences of their continence service in primary health care. J Nurs Manag 2010;18:225-33.

182. Newman DK. The roles of the Continence Nurse Specialist. 2nd Ed. ed. United Kingdom: Isis Medical Media, LTD; 2006.

183. Newman DK, and A. J. Wein. Managing and Treating Urinary Incontinence. 2nd Ed. ed. Baltimore, Maryland: Health Professions Press; 2009.

184. Ryden MB, Snyder M, Gross CR, et al. Value-added outcomes: the use of advanced practice nurses in long-term care facilities. Gerontologist 2000;40:654-62.

185. Nijeholt AAB. The Leiden pelvic floor center: a patient-oriented multidisciplinary diagnostic center. In: Proceedings of the International Continence Society; 1998; Jerusalem; 1998.

186. Fonda D, M. Woodward, et al. . Effect of continence management programme on cost and useage of continence pads. Neurourol Urodyn 1993;12:389-91.

187. Final report for Phase 3 of the National Continence Management Strategy. 2010. (Accessed at http://www.bladderbowel.gov.au/assets/doc/ncms/FinalEvaluationReport3September.pdf.)

188. Gruenwald I, Vardi Y. The Center for Continence: a different concept for an old problem. J Am Geriatr Soc 1999;47:912-3.

189. Chatoor D, Soligo M, Emmanuel A. Organising a clinical service for patients with pelvic floor disorders. Best Pract Res Clin Gastroenterol 2009;23:611-20.

190. St. John W, M. Wallis, et al. . Targeting community-dwelling urinary incontinence sufferers: a multi-disciplinary community based model for conservative continence services. Contemp Nurse 2004;17:211-22.

191. Stothers L, Wilkie D, Lieblich P, Wilson P. Developing a continence care centre using an urban/academic model of continence care. Can J Urol 2008;15:4084-90.

192. Steel N, Bachmann M, Maisey S, et al. Self reported receipt of care consistent with 32 quality indicators: national population survey of adults aged 50 or more in England. BMJ 2008;337:a957.

193. Cohen SJ, Robinson D, Dugan E, et al. Communication between older adults and their physicians about urinary incontinence. J Gerontol A Biol Sci Med Sci 1999;54:M34-7.

194. McFall S, Yerkes AM, Bernard M, LeRud T. Evaluation and treatment of urinary incontinence. Report of a physician survey. Arch Fam Med 1997;6:114-9.

195. Eriksen BC, Sandvik H, Hunskaar S. Management of urinary incontinence in gynecological practice in Norway. Acta Obstet Gynecol Scand 1990;69:515-9.

196. Swanson JG, Skelly J, Hutchison B, Kaczorowski J. Urinary incontinence in Canada. National survey of family physicians' knowledge, attitudes, and practices. Can Fam Physician 2002;48:86-92.

197. Bland DR, Dugan E, Cohen SJ, et al. The effects of implementation of the Agency for Health Care Policy and Research urinary incontinence guidelines in primary care practices. J Am Geriatr Soc 2003;51:979-84.

198. Yazdany T, Wong M, Bhatia NN. Improving resident screening and workup of urinary incontinence in an OB/GYN residency program: a randomized controlled study. Female Pelvic Med Reconstr Surg 2011;17:242-5.

199. Albers-Heitner P, Berghmans B, Joore M, et al. The effects of involving a nurse practitioner in primary care for adult patients with urinary incontinence: the PromoCon study (Promoting Continence). BMC Health Serv Res 2008;8:84.

200. Albers-Heitner PC, Lagro-Janssen TA, Joore MM, et al. Effectiveness of involving a nurse specialist for patients with urinary incontinence in primary care: results of a pragmatic multicentre randomised controlled trial. Int J Clin Pract 2011;65:705-12.

201. Albers-Heitner PC, Lagro-Janssen TA, Venema PP, et al. Experiences and attitudes of nurse specialists in primary care regarding their role in care for patients with urinary incontinence. Scand J Caring Sci 2011;25:303-10.

202. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the Chronic Care Model in the new millennium. Health Aff (Millwood) 2009;28:75-85.

203. Fantl JA, D. K. Newman, et al. . Urinary Incontinence in Adults: Acute and Chronic Management Clinical Practice Guideline, No 2, Update. Rockville, MD: US Department of Health and Human Services; 1996 March

204. Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance. A systematic review of the effect of continuing medical education strategies. JAMA 1995;274:700-5.

205. Viktrup L, Summers KH, Dennett SL. Clinical practice guidelines on the initial assessment and treatment of urinary incontinence in women: a US focused review. Int J Gynaecol Obstet 2004;86 Suppl 1:S25-37.

206. Viktrup L, Summers KH, Dennett SL. Clinical practice guidelines for the initial management of urinary incontinence in women: a European-focused review. BJU Int 2004;94 Suppl 1:14-22.

207. Chin WY, Lam CL, Lo SV. Quality of care of nurse-led and allied health personnel-led primary care clinics. Hong Kong Med J 2011;17:217-30.

208. Diokno AC, Ocampo MS, Jr., Ibrahim IA, Karl CR, Lajiness MJ, Hall SA. Group session teaching of behavioral modification program (BMP) for urinary incontinence: a randomized controlled trial among incontinent women. Int Urol Nephrol 2010;42:375-81.

209. McFall SL, Yerkes AM, Cowan LD. Outcomes of a small group educational intervention for urinary incontinence: episodes of incontinence and other urinary symptoms. J Aging Health 2000;12:250-67.

210. de Oliveira Camargo F, A. M. Rodrigues, et al. . Pelvic floor

muscle training in female stress urinary incontinence: comparison between group training and individual treatment using PERFECT assessment scheme. Int Urogynecol J Pelvic Floor Dysfunct 2009;20:1455-62.

211. Brubaker L, Shott S, Tomezsko J, Goldberg RP. Pelvic floor fitness using lay instructors. Obstet Gynecol 2008;111:1298-304.
212. Lordelo P, Maron F, Barros DG, Barroso DV, Bessa J, Jr., Barroso U, Jr. Lower urinary tract dysfunction in children. What do pre-school teachers know about it? Int Braz J Urol 2007;33:383-8; discussion 8.
213. Boyington AR, Dougherty MC, Liao YM. Analysis of interactive continence health information on the Web. J Wound Ostomy Continence Nurs 2003;30:280-6.
214. Boyington AR, Wildemuth BM, Dougherty MC, Hall EP. Development of a computer-based system for continence health promotion. Nurs Outlook 2004;52:241-7.
215. Williams KS, Crichton NJ, Roe B. Disseminating research evidence. A controlled trial in continence care. J Adv Nurs 1997;25:691-8.
216. Green JP, Smoker I, Ho MT, Moore KH. Urinary incontinence in subacute care--a retrospective analysis of clinical outcomes and costs. Med J Aust 2003;178:550-3.
217. Booth J, Kumlien S, Zang Y, Gustafsson B, Tolson D. Rehabilitation nurses practices in relation to urinary incontinence following stroke: a cross-cultural comparison. J Clin Nurs 2009;18:1049-58.
218. Wright J, McCormack B, Coffey A, McCarthy G. Evaluating the context within which continence care is provided in rehabilitation units for older people. Int J Older People Nurs 2007;2:9-19.
219. Hawkins SY, Park J, Palmer MH. Interest in information about urinary incontinence among diabetic and nondiabetic heart failure patients. J Wound Ostomy Continence Nurs 2010;37:536-41.
220. Whitford HM, Alder B, Jones M. A cross-sectional study of knowledge and practice of pelvic floor exercises during pregnancy and associated symptoms of stress urinary incontinence in North-East Scotland. Midwifery 2007;23:204-17.
221. Chiarelli P, Murphy B, Cockburn J. Acceptability of a urinary continence promotion programme to women in postpartum. BJOG 2003;110:188-96.
222. Chiarelli P, Murphy B, Cockburn J. Promoting urinary continence in postpartum women: 12-month follow-up data from a randomised controlled trial. Int Urogynecol J Pelvic Floor Dysfunct 2004;15:99-105; discussion
223. Butterfield YC, O'Connell B, Phillips D. Peripartum urinary incontinence: a study of midwives' knowledge and practices. Women Birth 2007;20:65-9.
224. Bucci AT. Be a continence champion: use the CHAMMP tool to individualize the plan of care. Geriatr Nurs 2007;28:120-4; quiz 5.
225. Egnatios D, Dupree L, Williams C. Performance improvement in practice: managing urinary incontinence in home health patients with the use of an evidence-based guideline. Home Healthc Nurse 2010;28:620-8; quiz 9-31.
226. Roe B, Flanagan L, Jack B, et al. Systematic review of descriptive studies that investigated associated factors with the management of incontinence in older people in care homes. Int J Older People Nurs 2011.
227. Schmitz G, Hayder D, Braumann A, Muller M, Saxer S. Continence profiles. A way to enhance assessment of urinary continence in German nursing practice. Z Gerontol Geriatr 2010;43:407-8, 10-2.
228. Tanaka Y, Nagata K, Tanaka T, et al. Can an individualized and comprehensive care strategy improve urinary incontinence (UI) among nursing home residents? Arch Gerontol Geriatr 2009;49:278-83.
229. Agnew R, Booth J. Promoting urinary continence with older people: a selective literature review. Int J Older People Nurs 2009;4:58-62.
230. Lawhorne LW, Ouslander JG, Parmelee PA. Clinical practice guidelines, process improvement teams, and performance on a quality indicator for urinary incontinence: a pilot study. J Am Med Dir Assoc 2008;9:504-8.
231. Saxer S, de Bie RA, Dassen T, Halfens RJ. Knowledge, beliefs, attitudes, and self-reported practice concerning urinary incontinence in nursing home care. J Wound Ostomy Continence Nurs 2009;36:539-44.
232. Boltz M, Capezuti E, Shabbat N. Nursing staff perceptions of physical function in hospitalized older adults. Appl Nurs Res 2011;24:215-22.
233. Jackson J, D. Bliss, et al. . PS2-20: The development of educational materials to assist family and friend caregivers and healthcare providers in caring for persons with incontinence and dementia. Clin Med Res 2011;9:158.
234. Rahman AN, Schnelle JF, Yamashita T, Patry G, Prasauskas R. Distance learning: a strategy for improving incontinence care in nursing homes. Gerontologist 2010;50:121-32.
235. Gemmill R, Wells A. Promotion of urinary continence worldwide. Urol Nurs 2010;30:336-40.
236. Health care needs assessment. 2004. (Accessed at http://hcna.radcliffe-oxford.com/contframe.htm.)
237. Kerfoot BP, Turek PJ. What every graduating medical student should know about urology: the stakeholder viewpoint. Urology 2008;71:549-53.
238. Mishail A, Shahsavari M, Kim J, Welliver RC, Jr., Vemulapalli P, Adler HL. Deficits in urological knowledge among medical students and primary care providers: potential for impact on urological care. J Urol 2008;180:2140-7.
239. Mueller ER, Kenton K, Rogers RG, Fenner DE. Are we missing an opportunity to teach future physicians about female pelvic floor disorders? Int Urogynecol J Pelvic Floor Dysfunct 2009;20:1413-5.
240. Spencer AL, Kern LM. Primary care program directors' perceptions of women's health education: a gap in graduate medical education persists. J Womens Health (Larchmt) 2008;17:549-56.
241. Thekkinkattil DK, Lim M, Finan PJ, Sagar PM, Burke D. Awareness of investigations and treatment of faecal incontinence among the general practitioners: a postal questionnaire survey. Colorectal Dis 2008;10:263-7.
242. Mazmanian PE, Davis DA. Continuing medical education and the physician as a learner: guide to the evidence. JAMA 2002;288:1057-60.
243. Levine SA, Brett B, Robinson BE, et al. Practicing physician education in geriatrics: lessons learned from a train-the-trainer model. J Am Geriatr Soc 2007;55:1281-6.
244. Westmoreland GR, Counsell SR, Tu W, Wu J, Litzelman DK. Web-based training in geriatrics for medical residents: a randomized controlled trial using standardized patients to assess outcomes. J Am Geriatr Soc 2010;58:1163-9.
245. Warshaw GA, Modawal A, Kues J, et al. Community physician education in geriatrics: applying the assessing care of vulnerable elders model with a multisite primary care group. J Am Geriatr Soc 2010;58:1780-5.
246. Wenger NS, Roth CP, Shekelle PG, et al. A practice-based intervention to improve primary care for falls, urinary incontinence, and dementia. J Am Geriatr Soc 2009;57:547-55.
247. Wenger NS, Roth CP, Hall WJ, et al. Practice redesign to improve care for falls and urinary incontinence: primary care intervention for older patients. Arch Intern Med 2010;170:1765-72.
248. Hosker GL, Kilcoyne PM, Lord JC, Smith AR. Urodynamic services, personnel and training in the United Kingdom. Br J Urol 1997;79:159-62.
249. Marsh F, Garthwaite MA, Southgate J, Ramage C. Assessing UK specialists' knowledge of the diagnostic criteria for painful bladder syndrome/interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:615-20.
250. Akladios CY, Dautun D, Saussine C, Baldauf JJ, Mathelin C, Wattiez A. Laparoscopic sacrocolpopexy for female genital organ prolapse: establishment of a learning curve. Eur J Obstet Gynecol Reprod Biol 2010;149:218-21.

251. Fialkow M, Mandel L, VanBlaricom A, Chinn M, Lentz G, Goff B. A curriculum for Burch colposuspension and diagnostic cystoscopy evaluated by an objective structured assessment of technical skills. Am J Obstet Gynecol 2007;197:544 e1-6.

252. Bowling CB, Greer WJ, Bryant SA, et al. Testing and validation of a low-cost cystoscopy teaching model: a randomized controlled trial. Obstet Gynecol 2010;116:85-91.

253. Geiss IM, Riss PA, Hanzal E, Dungl A. A simple teaching tool for training the pelvic organ prolapse quantification system. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:1003-5.

254. Parnell BA, Dunivan GC, Geller EJ, Connolly A. A novel approach to teaching the pelvic organ prolapse quantification (POP-Q) exam. Int Urogynecol J 2011;22:367-70.

255. Ruiz JG, Tunuguntla R, Charlin B, et al. The script concordance test as a measure of clinical reasoning skills in geriatric urinary incontinence. J Am Geriatr Soc 2010;58:2178-84.

256. Riss P, Hinterholzer S. Maintaining standards for surgery for female urinary incontinence. Maturitas 2010;65:5-10.

257. DeLancey JO. Current status of the subspecialty of female pelvic medicine and reconstructive surgery. Am J Obstet Gynecol 2010;202:658 e1-4.

258. Muller SC, Strunk T. [Is the training and continuing education for urologists in Germany still up to date?]. Urologe A 2011;50:946-51.

259. Rogalski NM. A graduate nursing curriculum for the evaluation and management of urinary incontinence. Educational Gerontology 2005;31:139-59.

260. Wyman JF, Bliss DZ, Dougherty MC, et al. Shaping future directions for incontinence research in aging adults: executive summary. Nurs Res 2004;53:S1-10.

261. Cheater FM, Baker R, Reddish S, et al. Cluster randomized controlled trial of the effectiveness of audit and feedback and educational outreach on improving nursing practice and patient outcomes. Med Care 2006;44:542-51.

262. Ostaszkiewski J. A clinical nursing leadership model for enhancing continence care for older adults in a subacute inpatient setting. J WOCN 2006;33:624-9.

263. Roosen K, Fulbrook P, Nowicki T. Pressure injury prevention: continence, skin hygiene and nutrition management. Aust Nurs J 2010;18:31-4.

264. Beeckman D, Schoonhoven L, Fletcher J, et al. Pressure ulcers and incontinence-associated dermatitis: effectiveness of the Pressure Ulcer Classification education tool on classification by nurses. Qual Saf Health Care 2010;19:e3.

265. Gray M. Incontinence-related skin damage: essential knowledge. Ostomy Wound Manage 2007;53:28-32.

266. Sackley CM, Rodriguez NA, van den Berg M, et al. A phase II exploratory cluster randomized controlled trial of a group mobility training and staff education intervention to promote urinary continence in UK care homes. Clin Rehabil 2008;22:714-21.

267. Keilman LJ, Dunn KS. Knowledge, attitudes, and perceptions of advanced practice nurses regarding urinary incontinence in older adult women. Res Theory Nurs Pract 2010;24:260-79.

268. McConnell ES, Lekan D, Bunn M, et al. Teaching evidence-based nursing practice in geriatric care settings: the geriatric nursing innovations through education institute. J Gerontol Nurs 2009;35:26-33; quiz 4-5.

269. Collette C, Bravo G, Tu le M. Development of a urinary incontinence educational program using a competency-based approach and case method. J Nurses Staff Dev 2009;25:E5-E10.

270. Karlowicz KA. Evaluation of the Urinary Incontinence Scales to measure change after experiential learning: a pilot study. Urol Nurs 2009;29:40-6.

271. Williams KS, Assassa RP, Smith NK, Shaw C, Carter E. Educational preparation: specialist practice in continence care. Br J Nurs 1999;8:1198-207, 202, 204 passim.

272. Beitz JM, Snarponis JA. Strategies for online teaching and learning: lessons learned. Nurse Educ 2006;31:20-5.

273. Jha S, Moran P, Blackwell A, Greenham H. Integrated care pathways: the way forward for continence services? Eur J Obstet Gynecol Reprod Biol 2007;134:120-5.

274. Jacobs M, Wyman JF, Rowell P, Smith DA. Continence nurses: a survey of who they are and what they do. Urol Nurs 1998;18:13-20.

275. Jirovec MM, Wyman JF, Wells TJ. Addressing urinary incontinence with educational continence-care competencies. Image J Nurs Sch 1998;30:375-8.

276. Connor PA, Kooker BM. Nurses' knowledge, attitudes, and practices in managing urinary incontinence in the acute care setting. Medsurg Nurs 1996;5:87-92, 117.

277. Mansson-Linstrom A, Dehlin O, Isacsson A. Urinary incontinence in primary health care. 1. Perceived knowledge and training among various categories of nursing personnel and care units. Scand J Prim Health Care 1994;12:169-74.

278. Arlen AM, Boyt MA, Cooper CS. School nurse perceptions and knowledge of pediatric toileting. J Pediatr Urol 2012;8:205-8.

279. Thompson DL. Continence certification. J Wound Ostomy Continence Nurs 2010;37:683-5.

280. Wound Ostomy Continence Nursing Society. Position Statement, Role of the Wound, Ostomy Continence Nurse or Continence Care Nurse in Continence Care. J Wound Ostomy Continence Nurs 2009;36:529-31.

281. Doughty D. Education and credentialing for non-baccalaureate nurses: should we do it? J Wound Ostomy Continence Nurs 2007;34:486-8.

282. Mejza B. Will the WOC nurse of the future also be a DNP? J Wound Ostomy Continence Nurs 2009;36:271-4.

283. Albers-Heitner CP, Joore MA, Winkens RA, Lagro-Janssen AL, Severens JL, Berghmans LC. Cost-effectiveness of involving nurse specialists for adult patients with urinary incontinence in primary care compared to care-as-usual: An economic evaluation alongside a pragmatic randomized controlled trial. Neurourol Urodyn 2012;31:526-34.

284. Lin SY, Wang RH, Lin CC, Chiang HY. Competence to provide urinary incontinence care in Taiwan's nursing homes: perceptions of nurses and nurse assistants. J Wound Ostomy Continence Nurs 2012;39:187-93.

285. Saxer S, de Bie RA, Dassen T, Halfens RJ. Nurses' knowledge and practice about urinary incontinence in nursing home care. Nurse Educ Today 2008;28:926-34.

286. Slack A, Hill A, Jackson S. Is there a role for a specialist physiotherapist in the multi-disciplinary management of women with stress incontinence referred from primary care to a specialist continence clinic? J Obstet Gynaecol 2008;28:410-2.

287. Women's Health Physical Therapist, 2012. (Accessed at http://www.womenshealthapta.org/plp/.)

288. International Organization of Physical Therapists in Women's Health, 2012. (Accessed at http://www.wcpt.org/ioptwh.)

289. Doughty D, Kisanga J. Regulatory guidelines for bladder management in long-term care: are you in compliance with F-Tag 315? J Wound Ostomy Continence Nurs 2010;37:399-411; quiz 2-3.

290. Drutz HP. IUGA guidelines for training in female pelvic medicine and reconstructive pelvic surgery (FPMRPS). Updated guidelines 2010. Int Urogynecol J 2010;21:1445-53.

291. Woodford H, George J. NICE guidelines on urinary incontinence in women. Age Ageing 2007;36:349-50.

292. Fung CH. Computerized condition-specific templates for improving care of geriatric syndromes in a primary care setting. J Gen Intern Med 2006;21:989-94.

293. Urinary incontinence: The management of urinary incontinence in women. Commissioned by the National Institute for Health and Clinical Excellence (NICE), 2006.

(Accessed at http://www.nice.org.uk/nicemedia/pdf/CG-40NICEguideline.pdf)

294. Heesakkers JP, Mulders PF. [The practice guideline 'Urinary incontinence' (first revision) from the Dutch College of General Practitioners; a response from the perspective of urology]. Ned Tijdschr Geneeskd 2008;152:2544-5.

295. Basu M, Duckett JR. Barriers to seeking treatment for women with persistent or recurrent symptoms in urogynaecology. BJOG 2009;116:726-30.

296. Shaw C, Atwell C, Wood F, Brittain K, Williams K. A qualitative study of the assessment and treatment of incontinence in primary care. Fam Pract 2007;24:461-7.

297. Ismail SI. Audit of compliance with NICE guidelines on the use of tension-free vaginal tape slings for stress incontinence. J Obstet Gynaecol 2007;27:496-9.

298. Ruiz Cerda JL, S. Arlandis Guzman, et al. . [Analysis of the spanish urologists adherence to the recomendations of the guidelines on diagnostic and treatment of urinary incontinence]. Actas Urol Esp 2007;31:1148-60.

299. Rovner ES, Wright CJ, Messer H. Adherence to the 1997 American Urological Association guidelines for the surgical treatment of stress urinary incontinence. Urology 2008;71:239-42.

300. Pomfret I, Holden C. Implementing guidance on pelvic floor exercises. Nurs Times 2007;103:40-1.

301. Agur W, Housami F, Drake M, Abrams P. Could the National Institute for Health and Clinical Excellence guidelines on urodynamics in urinary incontinence put some women at risk of a bad outcome from stress incontinence surgery? BJU Int 2009;103:635-9.

302. Wagg A, Cardozo L, Chapple C, et al. Overactive Bladder and Continence Guidelines: implementation, inaction or frustration? Int J Clin Pract 2008;62:1588-93.

303. Wagg A, Lowe D, Peel P, Potter J. Do self-reported 'integrated' continence services provide high-quality continence care? Age Ageing 2009;38:730-3.

304. Wagg A, Duckett J, McClurg D, Harari D, Lowe D. To what extent are national guidelines for the management of urinary incontinence in women adhered? Data from a national audit. BJOG 2011;118:1592-600.

305. Griebling TL. Urinary incontinence: Incontinence guidelines--is lack of adherence a form of ageism? Nat Rev Urol 2011;8:655-7.

306. DuBeau CE, L. Dupree, et al. . Knowledge and attitudes of nursing home staff and surveyors about the revised federal guidance for incontinence care. Gerontologist. Gerontologist 2007;47:468-47.

307. Sievert KD, Amend B, Toomey PA, et al. Can we prevent incontinence? ICI-RS 2011. Neurourol Urodyn 2012;31:390-9.

308. Abrams P, Chapple CR, Junemann KP, Sharpe S. Urinary urgency: a review of its assessment as the key symptom of the overactive bladder syndrome. World J Urol 2012;30:385-92.

309. Sampselle CM, Messer KL, Seng JS, Raghunathan TE, Hines SH, Diokno AC. Learning outcomes of a group behavioral modification program to prevent urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2005;16:441-6.

310. Conn VS, Hafdahl AR, Mehr DR. Interventions to increase physical activity among healthy adults: meta-analysis of outcomes. Am J Public Health 2011;101:751-8.

311. Harkins C, Shaw R, Gillies M, et al. Overcoming barriers to engaging socio-economically disadvantaged populations in CHD primary prevention: a qualitative study. BMC Public Health 2010;10:391.

312. Lukacz ES, Sampselle C, Gray M, et al. A healthy bladder: a consensus statement. Int J Clin Pract 2011;65:1026-36.

313. Shamliyan T, Wyman J, Bliss DZ, Kane RL, Wilt TJ. Prevention of urinary and fecal incontinence in adults. Evid Rep Technol Assess (Full Rep) 2007:1-379.

314. NIH State-of-the-Science Conference on Prevention of Fecal and Urinary Incontinence in Adults. 2007. (Accessed at http://consensus.nih.gov/2007/2007IncontinenceSOS030Statementpdf.pdf)

315. Rimer BK, and K. Glanz. Theory at a glance: a guide for health promotion practice Bethesda, Maryland: National Institutes of Health [NIH], National Cancer Institute; 2005.

316. Albers-Heitner P, Berghmans B, Nieman F, Lagro-Janssen T, Winkens R. How do patients with urinary incontinence perceive care given by their general practitioner? A cross-sectional study. Int J Clin Pract 2008;62:508-15.

317. Haby MM, Doherty R, Welch N, Mason V. Community-based interventions for obesity prevention: lessons learned by Australian policy-makers. BMC Res Notes 2012;5:20.

318. Zhuo X, Zhang P, Gregg EW, et al. A nationwide community-based lifestyle program could delay or prevent type 2 diabetes cases and save $5.7 billion in 25 years. Health Aff (Millwood) 2012;31:50-60.

319. Glasson C, Chapman K, James E. Fruit and vegetables should be targeted separately in health promotion programmes: differences in consumption levels, barriers, knowledge and stages of readiness for change. Public Health Nutr 2011;14:694-701.

320. Howat P, Boldy D, Horner B. Promoting the health of older Australians: program options, priorities and research. Aust Health Rev 2004;27:49-55.

321. Messer KL, Hines SH, Raghunathan TE, Seng JS, Diokno AC, Sampselle CM. Self-efficacy as a predictor to PFMT adherence in a prevention of urinary incontinence clinical trial. Health Educ Behav 2007;34:942-52.

322. Gieck DJ, Olsen S. Holistic wellness as a means to developing a lifestyle approach to health behavior among college students. J Am Coll Health 2007;56:29-35.

323. Tannenbaum C, Brouillette J, Korner-Bitensky N, et al. Creation and testing of the Geriatric Self-Efficacy Index for Urinary Incontinence. J Am Geriatr Soc 2008;56:542-7.

324. Kang Y. Knowledge and attitudes about urinary incontinence among community-dwelling Korean American women. J Wound Ostomy Continence Nurs 2009;36:194-9.

325. Diokno AC, Sampselle CM, Herzog AR, et al. Prevention of urinary incontinence by behavioral modification program: a randomized, controlled trial among older women in the community. J Urol 2004;171:1165-71.

326. Stenzelius K, Mattiasson A, Hallberg IR, Westergren A. Symptoms of urinary and faecal incontinence among men and women 75+ in relations to health complaints and quality of life. Neurourol Urodyn 2004;23:211-22.

327. Talley KM, Wyman JF, Shamliyan TA. State of the science: conservative interventions for urinary incontinence in frail community-dwelling older adults. Nurs Outlook 2011;59:215-20, 20 e1.

328. Teunissen D, van Weel C, Lagro-Janssen T. Urinary incontinence in older people living in the community: examining help-seeking behaviour. Br J Gen Pract 2005;55:776-82.

329. Wasserberg N, Haney M, Petrone P, et al. Fecal incontinence among morbid obese women seeking for weight loss surgery: an underappreciated association with adverse impact on quality of life. Int J Colorectal Dis 2008;23:493-7.

330. Varma MG, J. S. Brown, et al. . Reproductive Risks for Inw continence Study at Kaiser (RRISK) Research Group. Fecal incontinence in females older than aged 40 years: who is at risk? . Dis Colon Rectum 2006;49:841-51.

331. Bartlett L, Nowak M, Ho YH. Reasons for non-disclosure of faecal incontinence: a comparison between two survey methods. Tech Coloproctol 2007;11:251-7.

332. Zheng M, H. Zhang, et al. . A research about the effect of PFMT on the prevention of copracrasia by sphincter preservation operation on mid-lower rectal cancer. Modern Clinical Nursing 2009;8:1-3.

Appendix 1 –Directory of Continence Organizations

AUSTRALIA

Continence Foundation of Australia
Level 1
30-32 Sydney Road
Brunswick, VIC 3056
Tel: 03 9347 2522
Fax: 03 9380 1233
website: www.continence.org.au
Email: info@continence.org.au

AUSTRIA

Medizinische Kontinenzgesellschaft Osterreich
Speckbacherstrasse 1 A-6020, Innsbruck
Tel: (43) 512 58 37 03
Helpline: 0810 100 455
Website: www.inkontinenz.at
Email: info@kontinenzgesellschaft.at

BELGIUM

Patientenvereniging PIRUS vzw
Postbus 20 – 9930 Zomergem
Tel: +32 0477 672 477
Email: mail@PIRUS.be
www.PIRUS.be

Urobel Belgian association for urological nurses and associates
Urobel vzw
De Pintelaan 185
9000, Gent
Tel.: 09/332.27.65
Fax: 09/332.27.66
Secretaris: voorzitter.urobel@pandora.be
Website: www.urobel.be

CANADA

The Canadian Continence Foundation
PO Box 417, Peterborough, Ontario, K9J6Z3
Tel: (1) 705-750-4600
Fax: (1) 705-750-1770
Website: www.canadiancontinance.ca

CZECH REPUBLIC

Inco Forum
Česká společnost podpory zdraví
Fakultní Thomayerova nemocnice s poliklinikou
Vídeňská 800
140 59 Praha 4
Telefon: +420 261 083 186
GSM: +420 724 207 874
e-mail: kucerova@cspz.cz
Website: www.incoforum.cz/

DENMARK

Kontinensforeningen
The Danish Continence Society
Vester Farimagsgade 6, 1st floor # 1029
DK-1606 Copenhagen V
Denmark
Tel. +45 33 32 52 74
E-mail: info@kontinens.dk
Web www.kontinens.dk

FRANCE

Association d'Aide aux Personnes Incontinentes
5, Avenue du Marechal Juin
92100 BOULOGNE
Tel: + 33 01 46 99 18 99
Fax: +33 01 46 99 18 85
Website: www.aapi.asso.fr
Email: aapi@9online.fr

GERMANY

Deutsche Kontinenz Gesellschaft e.V.
Friedrich-Ebert-Straße 124
34119 Kassel
Telefon: 05 61 / 78 06 04
Telefax: 05 61 / 77 67 70
e-Mail: info@kontinenz-gesellschaft.de
Website: www.gih.de

HONG KONG

Hong Kong Continence Society
c/o Dept of Medicine and Geriatrics
United Christian Hospital
130 Hip Wo Street, Kwun Tong.
Kowloon, Hong Kong
Tel: 852 237 94822
Fax: 852 234 72325
Email: emfleung@ha.org.hk

HUNGARY

Inko Forum
Levelezeski cim
Budapest, Pf 701/153, 1399
Phone: 06 80 730 007
Website: www.inkoforum.hu

INDIA

Indian Continence Foundation
C/o Ankur,
422, 20th Main, I Block,
Rajajinagar,
Bangalore 560 010
India
Tel: 91 80 4904333
Fax: 91 80 4904334
Website: www.indiancontinencefoundation.org

ITALY

Fondazione Italiana Continenza
(The Italian Continence Foundation)
The New Way
Corso Sempione, 44
20154 Milano
Tel 02 45499282
Fax 02 45499277
e-mail: info@contenuti-web.com
Website: www.contenuti-web.com

Federazione Italiana INCOntinenti (FINCO)
Segreteria/Presidenza
Ia le Orazio Flacco, 24
70124 Bari
Tel: 080-5093389
Fax: 0805619181
Website: www.finco.org

JAPAN

Japan Continence Action Society
103 Juri Heim,
1-4-2 Zenpukuji
Suginami-Ku,
Tokyo,
Japan 1670041
Tel: 81 3 3301 3860
Fax: 81 3 3301 3587
Website: www.jcas.or.jp

KOREA

The Korean Continence Society
28 Yeongun-Dong Jongro-Gu,
Seoul 110-744,
Korea.
Tel : 82-2-2072-2428
Fax : 82-2-742-4665
E-mail : kcsuro@gmail.com
Website: www.kocon.or.kr

MALAYSIA

The Continence Foundation of Malaysia
c/o Room 308
North Tower
Sime Darby Medical Centre
Subang Jaya
No 1 Jalan SS12/1A Subang Jaya
Selangor 47500
Malaysia
Tel: 601 2268 9016

MEXICO

Asociacion de Enfremadades Uroginecologicas /
Sociedad de Incontinência Urinaria
http://www.aci-mexico.com/

NETHERLANDS

PelvicFloorPatientsFoundation(SBP)
Stichting Bekkenbodem Patienten
postbus 183
2950 AD Alblasserdam
Tel: 020-6586520
Website: www.bekkenbodem.net

V&VN
Dutch Association of Incontinence Nurses
Afdeling Continentie Verpleegkundigen en Verzorgenden
Postbus 8212
3503 RE Utrecht
Website: http://continentie.venvn.nl/

Interstitial Cystitis Patients' Association
Interstitial Cystitis Patientenvereniging
Smalleweg 6b
Bunnik
030 656 96 32
info@icpatienten.nl
www.icpatienten.nl

NEW ZEALAND

New Zealand Continence Association
PO Box 270
Drury Auckland 2247

Phone: +64 9 236 0610
Fax: +64 9 236 0788
E-mail: zoe@continence.org.nz
Website: www.continence.org.nz

NORWAY

NOFUS: The Norwegian society for people with Urological Diseases and Incontinence,
postboks 2628
Liamyrane,
N-5828 Bergen, Norway.
Tel. +47 55 240025
E-mail: post@nofus.no
www.nofus.no

POLAND

NTM Forum
(The Polish Continence Organisation)
Ciolka 13 Street
01-445 Warsaw, Poland
e-mail: ntm@ntm.pl
www.ntm.pl

UroConti Association
(patient organization)
Ciolka 13 Street
01-445 Warsaw, Poland
e-mail: zg@uroconti.pl
www.uroconti.pl

SINGAPORE

Society for Continence (Singapore)
45 Jalan Pemimpin
Foo Wah Industrial Building #09-20
Singapore 577197
Tel: (65) 6787 0337
Fax: (65) 6588 1723
e-mail rani.sfcs@pacific.net.sg
Website: www.sfcs.org.sg

SOUTH AFRICA

Continence Association of South Africa (CASA)
P.O.Box 731446
Fairland
2030

SWEDEN

SINOBA
Sinoba Organisation
Norrtullsgaten 5, 3tr
113 29 Stockholm
Email: info@sinoba.se
Website: www.sinoba.se

SWITZERLAND

Schweizerische Gesellschaft für Blasenschwäche
Gewerbestrasse 12 CH-8132 Egg
Tel: 41 44 994 74 30
Fax: 41 44 994 74 31
Website: www.inkontinex.ch
Email: info@inkontinex.ch

THAILAND

Department of Surgery
Ramathibodi Hospital & Medical School
Rama6 Road, Bangkok 10400
Tel: 662-201 1315
Fax: 662-201 1316
Email: ravkc@mahidol.ac.th

SLOVAKIA

Slovakia Inco Forum (InkoForum)
P.O.Box 78
850 00 Bratislava
Tel.: +421 2 67 26 73 40
fax: +421 2 62 24 06 30
e-mail: info@inkoforum.sk
Website: www.incoforum.sk or www.inkoforum.sk

UNITED KINGDOM

Association For Continence (ACA)
Drumcross Hall.
Bathgate,
West Lothian EH48 4JT
Scotland UK
Tel: +44 (0) 1506 811077
Fax: +44 (0) 1506 811477
Website: www.aca.uk.com
Email: aca@fitwise.co.uk

The Bladder and Bowel Foundation
Bladder & Bowel Foundation
SATRA Innovation Park
Rockingham Road
Kettering, Northants, NN16 9JH
Helpline: 0845 345 0165
General enquiries: 01536 533255
Fax: 01536 533240
Email: info@bladderandbowelfoundation.org
www.bladderandbowelfoundation.org

ERIC (Education and Resources for Improving Childhood Continence)
36 Old School House,
Britannia Road,
Kingswood,
Bristol BS15 8DB
Tel: (44) 117 960 3060
Fax: (44) 117 301 2106
Website: www.eric.org.uk

PROMOCON
Helpline +44 (0) 161 6078219
Email: info@disabledliving.co.uk
www.promocon.co.uk

Royal College of Nursing Continence Care Forum
Website: http://www.rcn.org.uk/development/communities/rcn_forum_communities/continence_care

UNITED STATES

American Urological Association Foundation (AUAF)
1000 Corporate Boulevard
Linthicum, MD 21090
Tel: 410-689-3990
Fax: 410-689-3998
Website: http://www.urologyhealth.org

International Foundation for Functional Gastrointestinal Disorders (IFFGD)
P O Box 170864
Milwaukee WI 53217-8076
Tel: 414 964 1799
Fax: 414 964 7176
Website: www.iffgd.org www.aboutincontinence.org
Email: iffgd@iffgd.org

Interstitial Cystitis Association (ICA)
PO Box 17522
Baltimore MD 21297-1522
Website: www.ichelp.org
Email: ICAmail@ichelp.org

The NIDDK Bowel Control Awareness Campaign
c/o National Digestive Diseases Information Clearinghouse
2 Information Way
Bethesda, MD 20892–3570
Phone: 1–800–891–5389
TTY: 1–866–569–1162
Fax: 703–738–4929
Email: nddic@info.niddk.nih.gov
Internet: www.bowelcontrol.nih.gov

National Kidney and Urologic Diseases Information Clearinghouse
2 Information Way
Bethesda, MD 20892–3570
Phone: 1–800–891–5389
TTY: 1–866–569–1162
Fax: 703–738–4929
Email: nddic@info.niddk.nih.gov
Internet: www.bowelcontrol.nih.gov

National Association For Continence (NAFC)
P O Box 1019
Charleston, SC 29402-1019
Toll Free: 1-800-BLADDER (252-3337)
Tel: 843 377 0900
Fax: 843 377 0905
Website: www.nafc.org
Awareness Campaign Website: http://www.bladderhealthawareness.org/

Simon Foundation for Continence
P O Box 815,
Wilmette, Illinois 60091
Tel: (1) 847 864 3913
Fax: (1) 847 864 9758
Website: www.simonfoundation.org

Society of Urologic Nurses & Associates (SUNA)
East Holly Avenue, Box 56, Pitman, NJ 08071-0056
Tel: 888-827-7862
Website: www.suna.org
Email: suna@ajj.com

Wound, Ostomy and Continence Nurses Society (WOCN)
15000 Commerce Parkway, Suite C
Mt. Laurel, NJ 08054
Phone: 1–888–224–WOCN (1–888–224–9626)
Fax: 856–439–0525
Internet: www.wocn.org

OTHER ADVOCACY ORGANIZATIONS

International Painful Bladder Foundation (IPBF)
Email: info@painful-bladder.org
Website: www.painful-bladder.org

World Federation of Incontinent Patients (WPIF)
Website: www.wfip.org

Committee 22

Economics of Urinary & Faecal Incontinence, and Prolapse

Chair

Kate H. Moore, (Australia)

Co-Chair

Todd H. Wagner, (USA)

Members

Leslee Subak, (USA)

Stefan de Wachter, (Netherlands)

Consultant

Thomas Dudding, (England)

Acknowledgement

Teh-wei Hu (USA)

CONTENTS

I. INTRODUCTION

II. BACKGROUND

1. PLACING ECONOMIC ANALYSIS OF CONTINENCE CONDITIONS INTO PERSPECTIVE
2. COUNTRY SPECIFIC ECONOMIC ISSUES
3. COSTS AND TIME

III. TYPES OF ECONOMIC ANALYSES

1. OVERVIEW
2. DECISION ANALYSES
3. STATISTICAL ANALYSIS ISSUES
4. BUDGET IMPACT ANALYSIS

IV. PRACTICAL ASPECTS OF ECONOMIC ANALYSIS

1. HEALTH OUTCOME MEASURES SUITABLE FOR USE IN ECONOMIC ANALYSES
2. “DO IT YOURSELF”: HOW TO PERFORM COST UTILITY ANALYSIS, COMMITTEE RECOMENDATIONS.

V. SUMMARY OF RECENT ECONOMIC ANALYSES

1. SURGERY FOR STRESS INCONTINENCE
2. SURGERY FOR URGE INCONTINENCE
3. OUTPATIENT CONSERVATIVE THERAPIES
4. PHARMACOTHERAPY OF URINARY INCONTINENECE
5. COST IMPLICATIONS OF INCONTINENCE IN NURSING HOME SETTING
6. LONGITUDINAL BURDEN OF URINARY INCONTINENCE DISEASE STUDIES
7. PROLAPSE TREATMENTS, COST IMPLICATIONS
8. FECAL INCONTINENCE

VI . SUMMARY AND FUTURE RESEARCH PRIORITIES

VII. APPENDIX SEARCH STRATEGIES

VIII. REFERENCES

Economics of Urinary & Faecal Incontinence, and Prolapse 2012

Kate H. Moore

Todd H. Wagner, Leslee Subak, Stefan de Wachter, Thomas Dudding, Teh-wei Hu

I. INTRODUCTION

Since writing the first chapter about the economics of incontinence in the initial report of the ICI in 1999, our knowledge about this subject, along with the number of treatment options, has increased substantially. The global economic crisis that began in 2008 has led to contracting budgets, both for individuals and governments, and a heightened interest in maximizing value. Economic tools are useful for understanding the value equation. Often economists are called on to enumerate the costs and benefits, and payers are increasingly using these tools to determine what treatments should be provided in order to maximize their population's health.

The first ICI report focused on stress, urge and mixed incontinence. The last report also included pelvic organ prolapse and faecal incontinence. We have developed, in part due to the ICI, better data for understanding how to manage these conditions. For example, stress incontinence can be readily cured by a variety of conservative and surgical options, but the benefit may decay over time. Similarly, pharmaceutical companies have developed new anticholinergic treatments for the overactive bladder, but these may require prolonged administration with longstanding drug costs. Such pharmacotherapy needs to be accompanied by bladder training, which also requires patient compliance to achieve success. The immediate benefit of Botox injections is well documented, as is the fall off in efficacy over time.

The good news is that this new information is making its way into the economic analyses. The bad news is that economic analyses are becoming more complex and harder to evaluate. Because of their unique aetiologies, it is more accurate to talk about the subtype of incontinence, making the blanket term of "the economics of incontinence" less applicable. This chapter takes account of these considerations, and is arranged according to incontinence subtype.

In the last five to ten years, the "aging" of the post WWII baby boomers is changing the consumption of health care resources. The median lifespan of a woman in OECD countries is now 83 years, and rising, with similar enhanced lifespan in men. Thus patients are living longer and are at greater risk for developing a range of conditions, including urinary and faecal incontinence, as well as prolapse. In order to compete for precious healthcare resources, in this contracted global economy, continence clinicians must construct robust health economic analyses of any new treatments if we hope to see these new treatments implemented for the benefit of our patients. In this chapter we present a summary of the appropriate methods, then present a critical analysis of recent publications.

II. BACKGROUND

1. PERSPECTIVE

When a patient with urinary or faecal incontinence (and to some extent prolapse) walks into a doctor's office in any country, they will have already incurred some personal costs in managing the condition at home, such as pads or laundry expenses. He or she will then have a basic consultation, tests will probably be ordered, a range of outpatient conservative (including pharmacological) treatments may be initiated, or a surgical procedure that may be recommended. These are treatment costs. At some stage, particularly in the elderly, the patient may suffer a urinary tract infection that may be associated with the incontinence/ cystocoele, or may slip and fall in their urine on the way to the toilet. These are the costs associated with treating the consequences of incontinence [1, 2].

The way in which these various costs can be measured varies a great deal from country to country. Although all countries regulate health care to some degree, they do so in very different ways e.g., the regulatory environment within which health care is provided can differ greatly from country to country, the need for private insurance and the coverage they provide is usually very country specific. Different countries also limit the building of hospitals in various ways, and control health care costs such as drug prices to a different extent [3]. Health care systems, whether a nation, province, or organization, can limit the treatments for which they will pay, or set limits on the prices. This has implications for estimating costs.

More importantly, this places an important duty upon researchers to describe explicitly where, when and how the costs were calculated. Researchers in one country need to be able to extract as much economic information as possible from the research carried out on a particular condition in other countries, to save "re-inventing the wheel" whenever possible.

Patients often observe very different "costs" for health care goods and services. In health care, we often think of cost as the amount to produce the good, whereas a charge represents the stated amount on a bill, which often includes profit for the manufacturer. Therefore, different accounting systems can yield very different cost estimates. For example, most of the hospital accounting systems in the U.S. focus on billing and payments. The charges listed on the bill usually overstate costs, on average by a factor of three, and are rarely paid in full by the payer. For example, in a study of the costs of surgery for female fecal incontinence in the US,[4] hospital "charges" were defined as the amount on the hospital bill, but the hospital "costs" were defined as the amount that the hospital actually received in payment. Only after understanding this definition can one make sense of the fact that hospital "charges" for FI surgery rose from $48 million to $57 million over 3 years, but the hospital "costs" increased only slightly from $23 to $24.5 million over the same 3 years [4].

In the U.S., many researchers prefer to use payments as the estimate for cost. Researchers have developed imperfect methods for adjusting charges with a hospital-specific ratio of costs to charges to better estimate costs [5]. Charges, however, are not always available. Integrated health care systems, including Canada and the U.K, do not routinely generate bills. For these systems, researchers have developed methods for generating pseudo-bills and cost estimates [6-8].

Many cost determination methods are used. Most analyses include a combination of "gross costing" and "micro costing" [9]. These terms are similar to the phrases "top-down" and "bottom-up". Accounting and billing systems use activity based micro-costing methods, whereby detailed estimates of time and products (inputs) are combined with unit costs to estimate total costs. Micro-costing (or "bottom-up") is challenging to perform because a single inpatient stay or outpatient procedure might have hundreds or thousands of inputs. For example, Morris et al[10] performed over 3621 observations to determine expenditure on urinary faecal or mixed incontinence in a one month study of 29 patients in a sub-acute care facility. Even when there is just a single input, such as a tablet, the cost can vary by location or the time of purchase if prices fluctuate.

At the other end of the spectrum, gross cost methods ("top-down") identify a limited number of important characteristics such as the Health Care Resource Group (HRGs) in the U.K., Diagnosis Related Groups (DRGs) in the U.S or Australia, and length of stay. However, DRG costing lack precision and can be problematic because this method does not track the actual treatment activities, but are based on an average treatment. For example, in Australia the DRG for Tension Free Vaginal Tape and Colposuspension is the same. In the section of this chapter on Sacral Nerve Stimulation (SNS) for faecal incontinence, the costs for temporary stimulation and permanent implantation vary considerably between Spain[11], Italy[12] and the UK[13] as shown in **Table1**.

Table 1. Comparison of the costs of temporary and permanent SNS between Spain, Italy and the UK.

	Spain (€)	Italy (€)	UK (£)
Temporary SNS	1,484	6,400	510
Permanent SNS	10,700	6,400	8,480

Accounting systems are limited in that they always report the health care payer's costs or charges. If researchers want to estimate societal costs, which are often of most interest,[9, 14] one must include both provider-incurred costs and patient-incurred costs. This distinction is important for urinary incontinence, since most providers do not pay for routine care (e.g., pads and protection). These costs are usually incurred by individuals, and in the year 2000 the routine care costs in the U.S. were $1347 per person for urinary incontinence and $1554 for people with OAB [15].

Thus the conclusion drawn by a researcher may be heavily dependant upon their perspective. For example, a study from the USA analysed Medicare claims for the treatment of urinary incontinence among women aged 65 or older for 3 years (1992, 1995, 1998) including outpatient, inpatient and emergency department visits [16]. Such Medicare claims nearly doubled over the time frame, from $128 million to $234 million, largely due to increased numbers of women treated by office visits and ambulatory (day only) surgery for items such as collagen injections. When the per capita changes were analysed, and inflation was considered, costs had actually declined by 15%. However, the editorial comment following this article points out that Medicare claims have a payer's perspective, do not quantitate pad usage, and cannot record pharmacotherapy for urge incontinence. Since we know that overactive bladder is more common as age increases, such pharmacotherapy is likely to be increasingly important in the over 65 age group, so that the conclusion of a 15% drop in per capita Medicare expenditure is not likely to be valid representation of costs in general. The editors pointed out that the article was mainly representative of patients with stress incontinence as a result. Such methodological issues are important.

In the example described above, the "perspective" that the researchers used was that of Medicare claims. In other words, Medicare was the "payer", not

the patient. This highlights the fact that costs can be evaluated from several different perspectives. The four most commonly used perspectives are (1) overall society costs, which includes all aspects of care and treatment (which this committee recommends), (2) the payer, such as Medicare, (3) the provider, such as a hospital or managed care plan and (4) the patient.

In general, health economists prefer that a societal perspective (include all costs) is used [9, 14]. This facilitates comparison of the cost of illness across different countries. The problem is that different countries use different frameworks for reimbursing some or all of the costs of various conditions, so that international comparisons remain controversial.

2. COUNTRY SPECIFIC ECONOMIC ISSUES

From the perspective of a patient, large costs are often incurred when paying for routine care products, treatments, and long-term care. These patient costs vary by country. For example, in Sweden and Spain, the government (tax based) health insurance covers routine care products. In the UK, age-dependant patient subsidies are available for pads. In Germany and Spain, pad costs are reimbursed if prescribed by a doctor [17]. In Australia, low-income patients can apply for a subsidy to reimburse most of their routine care products, but more wealthy patients must pay all costs. In the USA, such products are rarely covered and can be very expensive [17].

The degree of government subsidy to the patient varies greatly by country. In the UK, most patients use the National Health Service (NHS) so that all office visits, tests, outpatient visits and surgical treatments are free to the patient. Pharmacotherapy does attract a small out of pocket payment for each drug. In Italy and Sweden pads are reimbursed, but not in Germany. Pads are not routinely subsidized, only at the discretion of the local Care Trust. In Australia, about 70% of patients only have government insurance, similar to the UK NHS, but 30% of patients also have private insurance so that inpatient treatments attract a rebate from their health fund. In the USA, adults over age 65 and those with a disability are covered by the Medicare program. This provides coverage for inpatient, outpatient and pharmacotherapy, although patients are generally responsible for sizable co-payments and nursing home care is capped. Those not covered by Medicare often have private insurance or Medicaid (a health insurance program for people with low incomes); nonetheless about 48 million Americans lack any insurance.

In the Netherlands, all legal residents are obliged to purchase a basic health policy (the purchase of a complementary policy covering extra health services remains voluntary). The choice of health insurer and type of health plan is free. The government establishes what is in the basic package and under what conditions people are entitled to care.

In regards to long term care benefits for those in residential care, considerable variation occurs. In the USA, Medicare and Medicaid benefits are time limited for re-imbursements to nursing homes and other assisted living facilities. Usually, after several months, benefits stop and payment must come from private insurance or the patient's pocket. In Australia, low income patients who have no private superannuation (pension fund) can receive the "old age pension" which covers fully funded long term care, albeit in lower-calibre facilities than would be chosen by those who could afford better (similar to the Netherlands system). In Japan, generous long term benefits are provided to long term institutional residents, so that out of pocket payments are reduced.

3. COSTS AND TIME

Costs change over time and researchers need to account for temporal changes in their analysis. The easiest way is to present the costs in a specific year (e.g., 2012). Costs borne in past years should be inflated. In many countries, the governments track and publish inflation indices. In the US, inflation is represented in the Consumer Price Index (e.g., www.stats.bls.gov). In the UK, the Health Service Cost Index or the Retail Price Index, published by the NHS Executive, Leeds, UK, can be used to adjust the costs of health care services (www.statistics.uk.gov).

Caution is needed because general inflation relates to the cost of a consistent set of goods over time, e.g., the goods must be of the same quality over time, and thus the costs observed five years ago can be observed today. If so, then the inflation index is informative. However, medical goods change rapidly as does their quality. For example re-usable laparoscopic equipment has been replaced by disposable equipment that is usually more expensive, and the newer drugs for OAB are generally more expensive. This makes it difficult to determine whether any change in price is due to inflation or due to (real or perceived) improvements in quality. Thus, just inflating costs from many years ago can be misleading. Consequently, many researchers recommend against using price indexes that are developed specifically for medicine because these indexes do not take quality into account. Researchers must also be cognizant of the fact that the published success rates for various treatments change over time. For example, in Adang et al.[18] dynamic graciloplasty is portrayed as having a stable success rate over time in the treatment of faecal incontinence (see **Figure 1**). In fact, we now know that dynamic graciloplasty has a very poor success rate over 10 years, so that the estimated data shown below in **figure 1** from 1998, is no longer accurate.

In addition, many continence treatments have costs that extend into the future. Drug treatments require that patients take drugs in the future. People have time preferences for money and future costs should be discounted to represent the present value. Controversy exists about the appropriate discount rate[19-21] but most international studies use a discount rate of 3% per annum. See Adang et al. [18] for example.

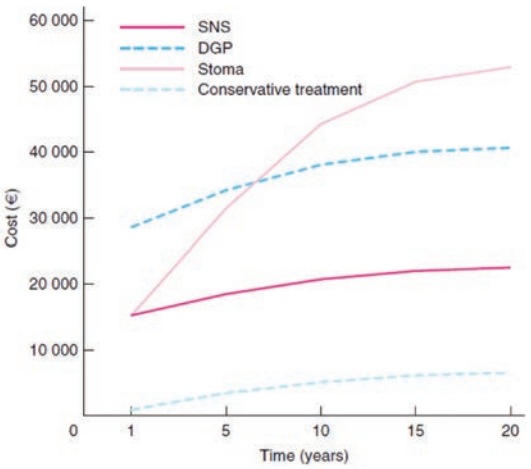


Figure 1. Estimated long-term costs per patient for each treatment: sacral nerve stimulation (SNS), dynamic graciloplasty (DGP), stoma and conservative treatment after 1, 5, 10, 15 and 20 years. Costs are in € and discounted to present values at a 5 per cent rate [18], from analysis by Hetzer et al, 2006 [22].

In summary, defining and measuring costs in health care can be imprecise. Often there is variation across regions and time. This variation needs to be taken into account in the economic analysis and the easiest way is to conduct sensitivity analysis to investigate how different cost estimates can influence the results. By this we mean re-running the analysis with different input parameters. As we describe in the next section, explicitly describing these contextual issues is crucial for interpreting results.

III. TYPES OF ECONOMIC ANALYSIS

1. OVERVIEW

A typology of economic analysis for health and medicine has emerged over the past few decades. This section reviews these studies.

a) Cost of illness (COI)

As already described, COI studies summate the costs related to a condition for a given population. The costs are annualized for a given year (i.e., 2012). A COI is a descriptive analysis. However, COI studies provide little information to decision makers about how to allocate scarce resources for treating conditions, because there is no attempt to measure the "value" of the relevant treatments.

b) Cost minimization analysis (CMA)

CMA compares the costs of alternative health care strategies, assuming that the benefits of the alternatives are equivalent. When the two treatments are truly equivalent in their risks, outcome, and an individual's preference for them, then a cost minimization analysis is sufficient; the cheapest intervention is to be preferred.

c) Cost consequence analysis (CCA)

CCA is a variation on cost-minimization analysis, which involves assessing whether a new treatment results in a greater decrease in health care utilization than another treatment. Thus costs of the intervention are compared to health care utilization, such as the cost per hospitalization averted. There is a naturally appealing rationale for conducting this analysis. Unfortunately, when examined in detail, this rationale boils down to an analysis of whether the new treatment saves money in comparison to the alternative treatment. Accordingly, a cost-utility or cost-benefit analysis provides many advantages over a cost consequence analysis.

d) Cost-effectiveness analysis (CEA)

CEA refers to the broad class of calculations where the effectiveness measure is a general health outcome. CEAs with narrowly focused health outcomes (e.g., incontinence episodes) have well-known limitations. Most notably, the use of narrowly focused health outcomes will miss other important effects. For this reason, there has been widespread agreement on the use of quality adjusted life years (QALYs) as the preferred health outcome in cost-effectiveness analysis. In the US, CEA has become synonymous with cost-utility analysis.

e) Cost-utility analysis (CUA)

CUA refers to a CEA when QALYs are used as the outcome measure. Gold et al.[9] and Drummond et al.[14] have published texts that discuss standard techniques for conducting a CUA. In health and medicine, the CUA is considered to be the gold standard. Utilities capture all potential benefits of an intervention and allow comparisons with other health conditions, making cost-utility analysis a powerful research tool.

Compared to other medical fields, we have insufficient data on utilities in incontinence or on the effect of treatment or change in incontinence severity upon cost utility measures, to date.

Data in a CEA and CUA are represented by an incremental cost-effectiveness ratio (ICER). The ICER represents the average cost of the intervention group minus the average cost of the control group. This amount is then divided by the average utility of the intervention group minus the average utility of the control group (see Section IVb).

f) Cost benefit analysis (CBA)

Involves measuring the benefits in dollars. When everything is measured in dollars, optimal choice can be easily found by addition and subtraction. However, it is difficult to measure benefits in dollars, and many researchers and policymakers are averse to placing a dollar value on life. CBA is rarely used in health.

g) Summary

COI and cost-minimization analyses are simple, yet limited economic tools. Most new treatments offer ad-

ditional benefits at an additional cost. The CBA, CUA and CEA were designed to determine how much money it costs to obtain another unit of effectiveness. Although the CUA is the preferred method, there are many challenges with calculating a QALY. We will discuss these issues in more depth because different methods for calculating QALYs can have a very profound effect on the interpretation of the CEA/CUA.

2. DETAILS OF DECISION ANALYSIS

Decision analysis is a tool that can be used to summarize effectiveness data, costs data, or combine both cost and effectiveness data in a CUA. The value of decision analysis is highlighted by a multi-site clinical trial by Albo and colleagues[23] that compared Burch colposuspension to fascial sling for stress incontinence. They concluded that the fascial sling yielded a higher rate of successful treatment, measured as a composite outcome, but also resulted in greater morbidity. Even in well-designed multi-site clinical trials, the results may be ambiguous. Decision analysis may be used to overcome this ambiguity. Decision analysis is a quantitative probabilistic tool for resolving problems when there is uncertainty with regards to treatment options.

There are two primary decision analytic methods (see below); each has its strengths and weaknesses. The starting point with any decision analysis is a clinical question, such as how to treat women with stress urinary incontinence or how to treat patients with faecal incontinence (see **Fig 2** below from Dudding et al., 2008 [13]). The question should fully and fairly address the clinical questions. One might develop add on questions, such as how to treat women who had surgical failure or sacral nerve implants that become infected or in which leads migrate, but it is often best to address these more specific questions as part of the broader decision analysis.

A benefit of decision analysis is that researchers can combine data from multiple clinical trials and marry that data to observational information (e.g., long-term follow-up data). Decision analytic tools are flexible and can be used to identify the treatment that maximizes quality of life. One can also use the same model to address issues of cost-effectiveness. Hence, one of the first tasks in the decision analysis is to identify the primary outcome. Outcomes such as quality adjusted life years (QALYs), that can reflect treatment and disease, are recommended. By using QALYs, one can overcome conflicting data—for example, the finding that vaginal slings have higher success rates but also greater morbidity. As is discussed elsewhere in this chapter, QALYs value all aspects of quality of life and include mortality. Next, the researcher must

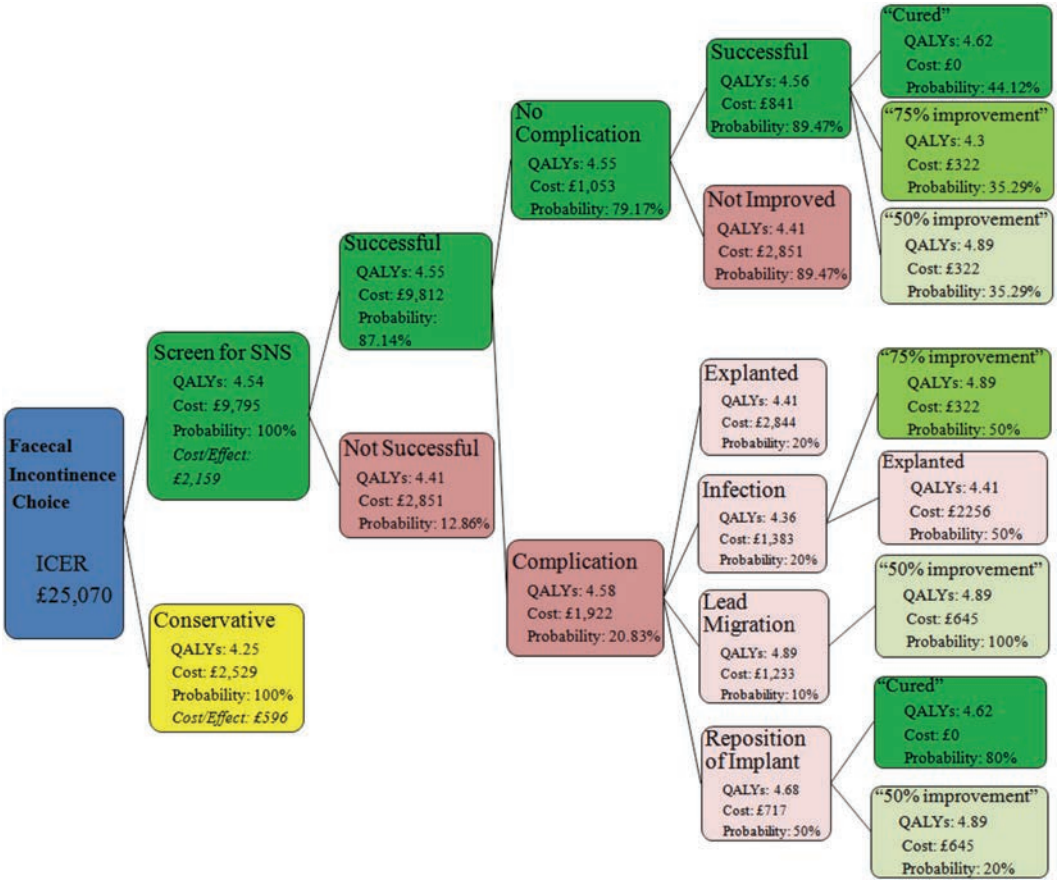


Figure 2. Decision tree for SNS treatment of faecal incontinence modified from Dudding et al (2008) with permission [13]

determine whether the model will include cost information or not. Some decision analytical models focus only on outcomes, while others add cost data to address resource allocation questions.

By combining data from multiple sources, decision analysis can be used to model lifetime costs and benefits. Researchers are often asked to identify the treatment(s) that maximizes lifetime benefits or lifetime cost-effectiveness. Randomized trials, while the gold standard for assessing causation, are time limited, often following participants for less than five years. Decision analysis can extend such data to consider future events, such as surgical failure rates, nursing home admission or life expectancy. Decision analysis can also be used to understand whether the analysis differs by perspective. Payers, providers and patients all have different perspectives, and decision analysis makes it relatively easy to consider each of these perspectives and whether they differ from a society perspective.

a) Steps in a decision analysis

Decision analysis can be boiled down into five steps. The first step involves identifying the structure of the problem and this requires the listing of all decision alternatives, all clinical outcomes, and a sequence of events. After completing step one, step two involves assigning probabilities to all chance events (e.g., death). Step three involves quantifying the benefits (e.g., QALYs) for all outcomes. The fourth step involves the mathematical calculation of expected utility for each strategy (or this can be taken from published data). Step four will often identify the preferred strategy. The final step involves conducting sensitivity analysis to check that the model is robust across a range of clinically meaningful possibilities.

Every decision model involves some assumptions. Frequently, assumptions are needed to incorporate clinical trial data in the model. For example, a common assumption is that the effect shown in a clinical trial is generalizable to the broader population—treating women with TVT will result in effects like those seen in Lier and colleague's paper[24] (discussed later in the chapter). Some assumptions may seem trivial, but it is best to delineate each assumption along the way. Published decision analysis should include a table of assumptions along with other data inputs; frequently this is the first table in the decision analysis.

The clinical question and the structure of the problem (step 1) should provide guidance on the decision model. Frequently decision trees are used because they are simple and address the question at hand. Decision trees are so named because they look like a tree with a trunk, branches and leaves. For example see **Figure 3**, taken from a study of Botox therapy versus clam augmentation cystoplasty by Padmanabhan et al[25], to be discussed later in this chapter.While decision trees are easy to describe and conduct, it is hard to include changes over time in the analysis. Diseases often change over time and people may transition into and out of different health states over time. One strength of Markov models is their ability to include these time-related transitions. We will discuss decision trees first and then Markov models in more detail afterwards.

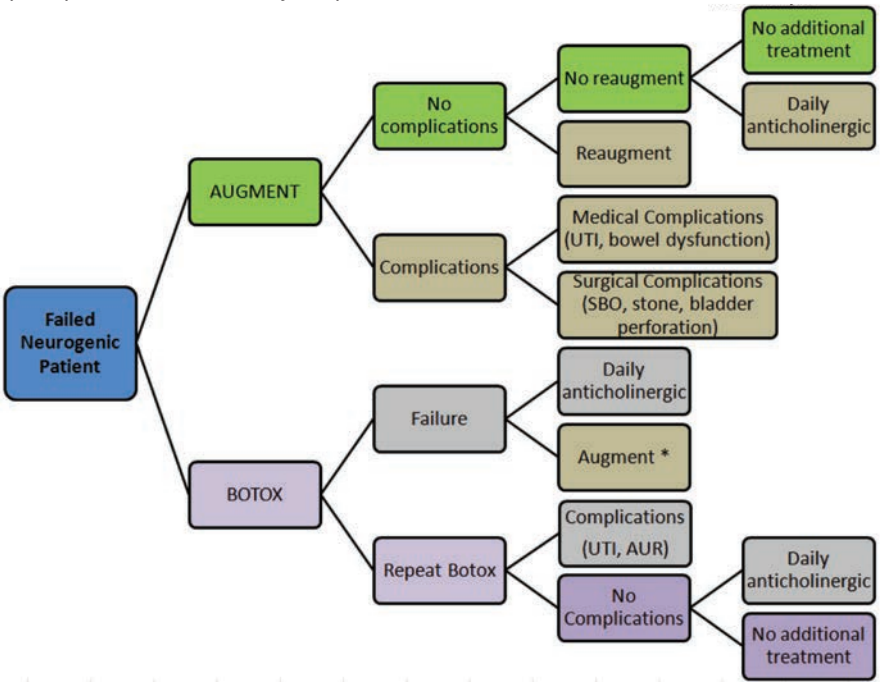


Figure 3. Decision tree for Botox treatment of severely refractory neuropathic DO patients, modified from Padmanabhan et al (2011) [25].
**** indicates the treatment algorithm continues along the augment pathway***

b) Decision Tree

In a decision tree, there is a distinction between a decision node and a chance node. A decision node is a point where a choice is made by the decision maker (typically a physician or patient). For example, for a woman with stress incontinence, the choice to operate (yes or no) would be represented with a decision node. A choice must have at least two options and more than two choices are permitted. However, each choice must be mutually exclusive. A patient cannot choose both operation and no operation. A chance node is a point where chance determines fate. For example, the decision maker chooses to operate or not operate, and hopefully the treatment is successful, but treatment success or failure is a chance node. Not only must chance nodes be mutually exclusive, but they must also be collectively exhaustive (one of the chances must happen and the sum of probabilities for all of the chances must add to 100%).

In addition to chance and decision nodes, there are terminal nodes. These nodes are the final outcome for the pathway taken. Sometimes understanding the nodes makes more sense when looking at the pictorial representation. **Figure 4** shows a hypothetical decision tree for treating a patient with stress incontinence. In this hypothetical situation, we structure the model to have two options: surgery or drugs. It is overly simplistic in that we do not differentiate between drugs.

The main choice is surgery versus medical management. Surgery carries some risks—a small probability of operative death, for example, in the case of clam cystoplasty for refractory detrusor overactivity. The decision nodes are represented by squares while chance nodes are represented by circles. The terminal nodes are cure, no cure, operative death or non-adherence, which is the same as no cure. This is a hypothetical decision model, and most decision models are much more complex. Clearly this model could be expanded to include behavioral treatment and each decision node could be expanded to consider all relevant alternatives (autologous sling, Burch colposuspension, tension-free vaginal tape, trans-obturator tape).

For the next step in the decision model, one must include probabilities at each chance node. We must identify the probability that the disease is cured after operation. Researchers should review the published literature to find this probability and ideally some information about the distribution around this probability (e.g., probability= 58% with a 95% CI 51-68%).

After including probabilities, one must place values next to the terminal nodes. These values must be a single outcome and QALYs are preferred, although life years (unadjusted for quality) are used for some diseases. With outcomes and probabilities, one can then "run" the decision tree. Because there is one decision node with two options, we will be computing expected values for the two options. Running the model involves starting at each endnode and working left or backwards. The expected value for the surgical survival node is 3.8 QALYS. (**Figure 5**)

The expected value for the surgical operative death node is 0. When we combined a 10% chance of operative death (0 QALYS) and a 90% chance of survival (3.8 QALYS), we find the expected value of surgery is 3.42 (**Figure 6**). If we do the calculation for the lower branch, we get the expected value for drug therapy is 3.76 QALYs. Because 3.76 >3.42, we would recommend surgery over drugs IF the sensitivity analysis shows this result to be robust. The decision tree in the example focuses on QALYs for UI treatment and it ignores cost differences, but it could be easily modified to include cost information.

c) Markov Model

The decision tree, as shown above, assumes the chance of events is stable over time. Our knowledge about urinary incontinence suggests otherwise. A person, for example, could get surgery for stress incontinence, but over time we need to include the potential for surgical failure. Markov models are good

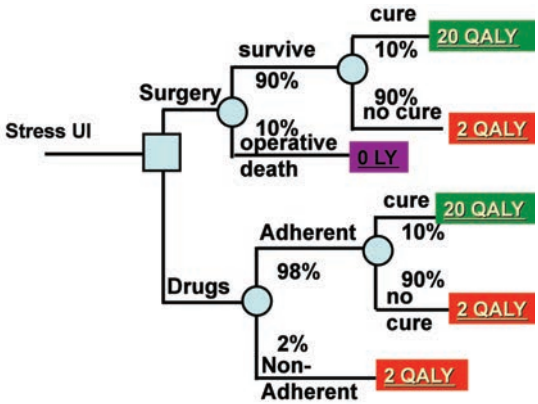


Figure 4. A hypothetical decision tree for treatment of patients with stress incontinence. Squares = decision nodes, Circles = Chance nodes and terminal nodes.

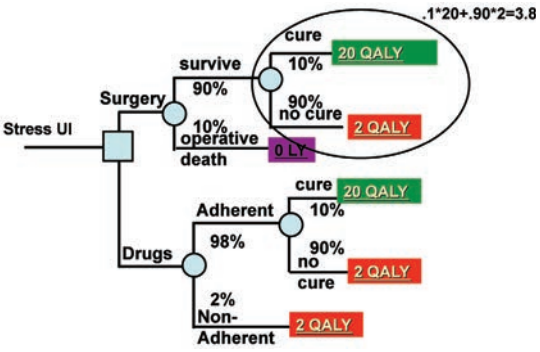


Figure 5. Computation of expected QALY values for the two terminal nodes, after surgery survival.

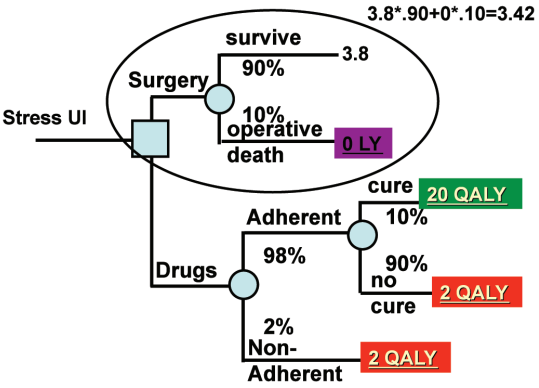


Figure 6. Computation of expected QALY values after surgery for stress incontinence.

for incorporating changes in health states over time. At their core, Markov models are mathematical techniques, derived from matrix algebra, that describe the transitions a cohort of patients make among a number of mutually exclusive health states over time. The model works by cycling to make new calculations for each period of time.

The pictorial depiction of a Markov model is typically shown as a decision state. **Figure 7** shows a very basic four-state Markov model. At each period in time, a person has to be in one and only one of the states. But with each change in time (cycle), the person can move to another state, shown with arrows, depending on the possible states and a probability. If the person dies, they are shown to enter the death state. The person cannot leave this state.

Some aspects of the Markov model construction are similar to a decision tree. Setting up the model is quite similar. One must identify the health states and the transition probabilities. What is quite different is that one must determine the cycle length—the rate at which you allow people to change states. The cycle length should be a clinically meaningful period of time and this choice is also frequently affected by the availability of data. There may be publications showing annual failure rates for surgery and so one could choose an annual cycle. For a Markov model, one needs to know the value for each state. Again, QALYs is the preferred metric. When the model runs, the program keeps track of the amount of time each person spends in each state. Transitions to other states are handled by transition probabilities (i.e. the likelihood of cure or failure). Decisions, such as the decision to change from one treatment to another, can affect transition probability. Models can use cohort simulations where a large hypothetical cohort of patients is run through the model. This does not provide information on the distribution of expected values. Monte Carlo simulations run each patient through the model a large number of times (e.g.,10^4). In doing so, this provides a distribution and variance information on patients.

With Markov models, sensitivity analyses remain a crucial step to test the robustness of the model. Recent advances in sensitivity analyses and in the graphical presentation of data general require the use of specific software. Although some people program Markov models into a spreadsheet, such as Excel, both Tree Age and Decision Maker software, are well known for their ability to streamline decision analysis and provide many advanced features that would be very difficult in Excel.

3. STATISTICAL ANALYSIS

In the last ICI chapter, we discussed alternative statistical techniques, but did not discuss bootstrapping, which has become quite common in cost utility analysis, especially in analyses alongside clinical trials. Bootstrapping is a method of resampling that enables researchers to estimate parameters based on the observed sampling distribution. It is particularly useful when estimating the confident intervals for the incremental cost-effectiveness ratio (ICER). The ICER involves dividing the mean difference in costs by the mean difference in utilities. Statistical software can easily determine whether two samples have different costs or different utilities (e.g., t-test). But software cannot easily calculate the confidence interval around the ratio of these two differences. Bootstrapping involves randomly drawing cases from the sample and replacing the case back in the sample. Resampling is done until the original sample size is met. The same process is then done again and again, typically 4000 times. Thus, by resampling, the analyst can calculate the ICER 4000 times, thereby providing a distribution around the ICER.

4. BUDGET IMPACT ANALYSIS

Providers and payers often have priorities that are not directly addressed by a cost-effectiveness analysis from a societal perspective. Budget impact analysis (BIA) was developed to inform a decision maker on how alternative technology will affect their budget. A BIA will often focus on the decision maker's costs and over a short time frame (e.g., 1-3 years). Other parameters in the model, such as patient characteristics or input costs, can also be tailored specifically for the

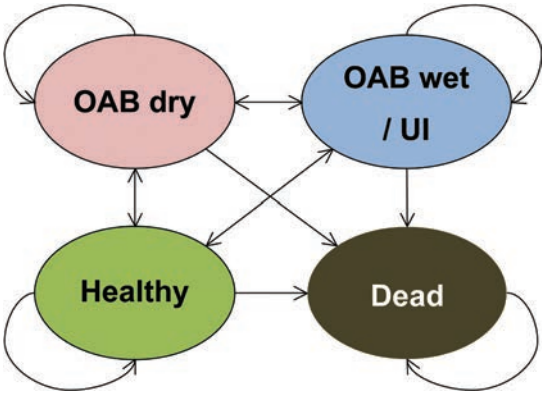


Figure 7. A basic four-state Markov Model

decision maker. Making decision based solely on a BIA can lead to suboptimal societal results. Hence, scientists advocate that a BIA be done in conjunction with a CEA so that decision makers are informed about the broader social implications of their decision. The International Society for Pharmacoeconomics and Outcomes Research (www.ispor.org) has created guidelines for conducting a BIA and these can be found on their website.

IV. PRACTICAL ASPECTS OF ECONOMIC ANALYSIS IN THE CONTINENCE FIELD

1. HEALTH OUTCOME MEASURES SUITABLE FOR USE IN ECONOMIC ANALYSES

There are a number of health outcomes that are used in economic evaluations of incontinence. These include disease-specific outcomes, health status and health value (e.g., QALY). Each is discussed in turn.

a) Incontinence specific outcomes

Cost-Effectiveness in Health and Medicine[9] recommends using QALYs as the effectiveness measure in the CEA. However, the panel also notes that analysts can use a clinical outcome measure. For incontinence, clinical outcome measures include 24-hour pad test, a voiding diary, or urodynamics. These outcomes are attractive for clinicians because they often use these measures in clinical practice.

Clinical outcomes can be very valuable in identifying when a treatment is efficacious. However, using clinical outcomes in a CEA yields results that are limited in scope. A treatment might have improved a person's quality of life, but had little effect on the clinical outcome measure. In this case, the results would be biased. In addition, a CEA with a clinical outcome measure might not be comparable to another CEA with a different clinical outcome measure. A clear advantage of cost utility analysis is that QALYs can be generalized beyond incontinence. For this reason, QALYs and CUAs are the gold standard.

b) Health Status and Quality of Life Measures

There are a number of frequently used and highly regarded general health status measures, such as the SF-36, the Sickness Impact Profile and the Nottingham Health Profile, which describe a person's current health state. Instruments that assess how a person perceives or feels about their health state are called quality of life (QOL) measures.

Chapter 5 in this book reviews generic and disease – specific quality of life measures, which are useful for understanding the effects of a treatment. However, because they cannot be used to create QALYs they are of limited value in economic analysis. An example of an exception is the SF-36 for which Brazier et al. [26] have created a utility scoring system known as the SF-6D.

c) Health value

Although there are several ways of measuring the value of a health state, the most common are willingness to pay (WTP) [27] and the quality-adjusted life year (QALY). We focus on QALYs as they represent the current standard for measuring health value in cost utility analysis.

QALYs denote the relationship between the value of a given health state and the length of time a person lives in that health state. The value of a given health state is measured in 'utilities', where 'utilities' represent preferences for a given health state.

To understand utilities, consider the following: most people would prefer to be healthy over a given time rather than suffer constant urinary or fecal incontinence. Utility measurement refers to valuing these preferences on a perfect health-death scale with endpoints of 1.00 and 0.00, where 1.00 is perfect quality of life (best imaginable) and 0.00 is death equivalent quality of life. For example, the measured utility for urinary incontinence may be 0.60. If treatment improves this to 0.70, then the value of the treatment is 0.70 – 0.60 = 0.10. If this utility gain is maintained over time, say for 10 years, then the gain is 0.10 x 10 = 1.00 QALY. Because utilities are measured on an absolute scale (perfect health to death), they can be used across different health states and therefore can be used to compare the effect of interventions in different health fields, or different interventions within the same field. For example, the QALYs gained from treatment for incontinence could be compared with those gained from treatment for depression. Where treatment costs (including costs to the patient) are known, the treatment providing the lowest incremental cost-per-QALY gained is preferred as this ensures society gains the greatest benefit from the health care dollar.

Direct and indirect methods have been used to elicit utilities [28]. The most common direct elicitation methods for valuation include time trade off (TTO), standard gamble (SG), and the visual analog scale (VAS). For description of these methods, see our previous chapter in this ICI series [29].

1. Instruments measuring utilities suitable for QALY calculation

Multi-attribute utility (MAU) instruments can be used instead of the direct elicitation methods. Simply, a MAU-instrument decomposes HRQoL into health domains (e.g., mobility and emotions). Respondents provide estimates for each attribute, which are then 'valued' and summarized into a utility. The three most commonly used MAU instruments are Quality of Well Being Scale (QWB), Health Utilities Index (HUI) and EQ5D (as reviewed by Hawthorne & Richardson[30]).

Quality of Well-Being Scale (QWB)

The QWB has three dimensions (Mobility, Physical Activity, and Social Activity), with 3–5 levels each,

and 27 illness symptoms [31]. The QWB requires trained interview administration (15–35 minutes), although a shorter version is available; a self-report version is under development. The upper boundary is 1.00, lower boundary is 0.00

Health Utilities Index (HUI)

The HUI uses 12 items that measure 8 domains (Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain). The upper boundary is 1.00, lower boundary is –0.36.

EQ5D

The EQ5D was developed by the Euroqol team from 7 European countries [32, 33]. It has 5 items measuring Mobility, Self-care, Usual Activities, Pain/Discomfort and Anxiety/Depression. The upper boundary is 1.00, lower boundary is –0.59. This has become a very popular instrument in clinical trials because it has been widely used in many languages and it is very brief.

A recent study [34] tested the effect of stress urinary incontinence on quality of life, as measured with the EQ5D. Investigators in the Stress Urinary Incontinence Treatment (SUIT) study, a 12-month, prospective, observational, multicenter study multicountry in four European countries, described the association of SUI symptoms with the EQ5D among 3762 women seeking treatment for symptoms of SUI. Participants had a mean age of 58 years, mean body mass index of 27.7 kg/m2, and had at least one comorbidity in addition to UI. The health state index scores were significantly and independently influenced by the presence of comorbidities affecting quality of life, total number of stress and urge incontinence episodes. In summary, the number of incontinence episodes and type of UI had a significant impact on the EQ-5D index score.

SF-6D

Whenever SF-36 raw scores are available, SF6D utilities can be computed [26]. The SF-6D measures physical functioning, bodily pain, mental health, physical role, emotional role, social functioning, and vitality. The endpoints for the SF-6D are 1.00, and 0.30 for the worst possible health.

The 15D

The 15D was created in Finland. It has 15 items, measuring Mobility, Vision, Hearing, Breathing, Sleeping, Eating, Speech, Elimination, Usual Activities, Mental Function, Discomfort & Symptoms, Depression, Distress, Vitality and Sexual Function [32]. The upper boundary is 1.00, lower boundary is +0.11.

The 15D is a generic, comprehensive, standardized, self-administered measure of HRQOL that can be used both as a profile and single index score measure [35]. The single index score (15D score) on a 0-1 scale and representing the overall HRQOL, is calculated based on population-based preference or utility weights. The 15D scores are shown to be highly reliable, sensitive and responsive to change, and valid for deriving quality-adjusted life years (QALYs) gained for resource allocation purposes. The 15D score is sensitive to urinary incontinence in a cross-sectional study [36, 37] and is sensitive to change in incontinence severity following intervention [24, 38]. A recent population-based survey of over 3700 Finnish adults found that increased severity of urgency and urgency urinary incontinence is associated with statistically significant decreases in the total 15D score and on all 15D dimensions ($p<0.001$ for all) [36].

The Assessment of Quality of Life (AQoL)

The Assesment of Quality of Life (AQoL) includes five dimensions: Illness (not used in utility computation), Independent Living, Social Relationships, Physical Senses and Psychological Well-being [39]. The upper boundary is 1.00, lower boundary is –0.04.

The Rosser Index has two dimensions measuring disability and distress, and measured 29 health states. Values (magnitude estimation) were from a convenience sample of 70 respondents [40]. A revised version in the early 1990s included discomfort as an additional dimension [40]. Administration requires a trained interviewer. The upper boundary is 1.00, and the lower boundary –1.49, which means that health states worse than death are permitted.

Note that many people with incontinence are not cognitively able to complete a MAU or go through a standard utility elicitation process. Some of the MAUs, such as the HUI3, have been validated for use with proxies. Although not always possible, if proxies are expected then proxies should be gathered for all cases, even those patients who complete the utility measure themselves, so that the method is applied in a standard, consistent fashion.

2. "DO IT YOURSELF" - HOW TO CONDUCT A COST UTILITY ANALYSIS: THE COMMITTEE'S RECOMMENDATIONS

The cost utility analysis (CUA) now represents the gold standard for medical decision making. Therefore, the remainder of this section highlights ten key issues that must be addressed in a CUA. These ten principles, summarized below, comprise an appropriate minimum standard for performing and reporting cost utility analyses. The principles were identified from guidelines established by the Panel on Cost-Effectiveness in Health and Medicine convened by the United States Public Health Service [9]. Each principle should be explicitly addressed in every study.

a) The ***Research Question*** must be clearly stated. All CUAs must compare at least two different treatments or interventions. One of these should include the current standard practices. For example when comparing surgeries for stress incontinence, one of the comparators should be a longstanding method, avoid comparing two new methods side by side.

b) The ***Time Frame*** over which costs and benefits are measured should be long enough to capture the economic impact of an intervention and future health outcomes. Pharmacology studies of 12 weeks duration give very little real economic information, and surgical complications/ failures seldom emerge in less than 1-2 years.

c) Perspective: The choice of perspective should be clear. Total society perspective (all payers) is the gold standard. Other perspectives, such as the payer or patient perspective, may be useful but must be stated clearly.

d) Probabilities are needed for each "chance" event, such as chance of cure or chance of an adverse event. The best sources of probabilities come from meta-analyses of randomized clinical trials, or if not available use data from individual clinical trials.

e) Costs: Units of expense and unit costs should be described in detail. Information on the source (e.g., charges, payments) and year of the cost data should be presented. If the costs were inflated and/or converted from another currency, then this must be described.

f) Outcome Measure: Measures of effectiveness depend on the type and objectives of analysis. Quality adjusted life years are the gold standard, as described previously in this chapter.

g) Analytic Model: Each intervention being assessed must be described and possible courses of events identified, including the expected course of disease, treatments, complications, and outcomes. This may be performed using a spreadsheet/ clinical trial path, or Decision Tree, or Markov Model.

h) Discounting: Since the value of both costs and benefits may decrease over time, discounting is used to calculate the present value of money and health states that will occur in the future. Future costs and utilities should be discounted to present value; 3 % per year is a recommended starting point.

i) Incremental Analysis: The purpose of a CUA is to describe the relative value of one health care strategy compared to another. An incremental cost-effectiveness ratio (ICER) is the incremental cost divided by the incremental effectiveness of intervention a compared to intervention b, and is calculated as follows.

$$ICER = \frac{\text{Average Cost intervention A} - \text{Average Cost intervention B}}{\text{Average Utility intervention A} - \text{Average Utility intervention B}}$$

Averages should be used rather than other measures of central tendency, such as medians, because it is important to include the effect of outliers. The leverage of the outliers should be tested in a sensitivity analysis.

j) Sensitivity Analysis: A sensitivity analysis should allow the reader to understand whether the conclusion of the analysis would hold true if either the Costs or the Probabilities (of cure or complications) were to vary substantially. For example if one treatment costs €5,000 and has a cure rate of 90%, and the second treatment costs €2,000 with a cure rate of 80%, then the ICER will assess whether the resultant benefit in QALY/ Quality of Life makes the first treatment worthwhile.

Having reached this conclusion, the researcher should then vary the costs and the cure rates in the model, to see how much variation in real life would be allowed yet still maintain a valid conclusion.

Documenting these boundaries helps define the conditions under which a treatment is preferred. Researchers are developing innovative methods for conducting sensitivity analyses. Probabilistic models that use simulations are becoming more common, although they can be computationally complex. Some journals require probabilistic sensitivity analyses.

V. SUMMARY OF RECENT ECONOMIC ANALYSES

Two trends stand out while reviewing the recent literature. First, many studies are choosing relatively short time frames. This makes it difficult to project the long-term economic consequences. Second, a number of studies are claiming that one treatment is dominant with very small differences in parameter estimates. This raises questions about whether one treatment is non-inferior.

1. SURGERY FOR STRESS INCONTINENCE

Previous reports from this ICI committee[41] on the cost-effectiveness of surgical treatment for stress incontinence can be summarized as:

- minimally invasive surgery (TVT, injectable therapy) are likely to be cost-effective compared to more invasive surgeries like the Burch colposuspension
- studies are limited by poor longer-term data on the effectiveness of less invasive procedures, lack of primary and/or generalizable data on costs, clinical outcomes and utilities and not using a accepted and generalizable outcome (cost per QALY or cost per "cure")
- there is a need for longer-term follow-up data from methodologically rigorous randomized trials to provide a better data to estimate the relative benefits and cost implications

Since the last ICI meeting in 2008, few cost-effectiveness analyses of surgical interventions for stress incontinence which systematically compare costs and outcomes within an RCT framework have been published.

In late 2008, the U.S Urinary Incontinence Treatment Network group estimated costs for incontinence management, health-related quality of life, and willingness to pay for incontinence improvement in women electing to have surgery for stress urinary incontinence [42]. This cross-sectional study included 655 incontinent women enrolled in the Stress Incontinence Surgical Treatment Efficacy Trial (SISTER), a randomized surgical trial. Baseline out-of-pocket costs for incontinence management were calculated by multiplying self-report of resources used (supplies, laundry, dry cleaning) by national resource costs (in 2006 USD). Post-treatment costs were given in a later report.

Health-related quality of life was estimated with the Health Utilities Index (HUI) Mark 3. Participants estimated willingness to pay for 100% improvement in incontinence. Potential predictors of these outcomes were examined by using multivariable linear regression. Mean age was 52 ± 10 years, and mean number of weekly incontinence episodes was 22 ± 21. Mean (SD) and median (interquartile range) estimated personal costs for incontinence management among all women were $14 ± $24 and $8 (interquartile range $3, $18) per week, and 617 (94%) women reported any cost. Costs increased significantly with incontinence frequency. Mixed leak cost more than pure stress incontinence.

The mean and median Health Utilities Index Mark 3 scores were 0.73 ± 0.25 and 0.84 (interquartile range 0.63, 0.92). Women were willing to pay a mean of $118 ± $132 per month for complete resolution of incontinence, and willingness to pay increased significantly with greater expected incontinence improvement, household income, and incontinent episode frequency. Urinary incontinence is associated with high costs, with women reporting expenses of nearly $750 per year out of pocket for incontinence management. Women were also willing to pay a lot - nearly $1,400 per year - for incontinence cure, reflecting the high degree of bother of the condition. Incontinence was also associated with a significant decrement in quality of life.

Subak et al (2010)[43] then studied 491 women who completed 24 months of the Stress Incontinence Surgical Treatment Efficacy Trial (SISTER) who underwent Burch colposuspension or sling surgery. Self-reported out-of-pocket incontinence management costs were measured at 24 months post-operatively. Women quantified the resources used for management of UI including number of supplies for UI and additional laundry and dry cleaning needed each week. Total costs for management of UI were estimated by multiplying these resources by national resource costs (2006 USD). The analysis combined both treatment groups to examine the effects of change in UI over 24 months on cost. Univariate and bivariate changes in cost were analyzed using Wilcoxon signed rank test. Potential baseline predictors of change in cost were examined using multivariate mixed models adjusting for age, ethnicity, baseline BMI, annual income, ≥3 UTIs, POP-Q stage, fecal incontinence, diabetes, prior non-surgical UI treatment, menopause, smoking, treatment group, and accounting for site clusters.

The mean (±SD) age of participants with complete resource use data at baseline and 24 months was 53 ± 10 years. The mean weekly UI frequency was 23 + 21 episodes at baseline, which decreased by 86% at 24 months (P<0.001). Mean weekly cost was $14.88 ± $25 (median $8.42) at baseline which decreased to $4.10 ± $14 (median $0.09) at 24 months (P<0.001). The proportion of women reporting any cost decreased from 95% at baseline to 50% at 24 months (P<.0001). There was a similar reduction in weekly cost for both treatment groups (-$10.83 for Burch vs. -$10.73 for sling; P=0.49). In multivariable analyses, cost decreased by $0.96 ± $0.23 per week for each decrease of 7 UI episodes per week (P<0.001) and was strongly associated with greater improvement in UDI and IIQ scores and decreased 24-hour pad weight (P<0.001 for all). In summary, incontinence management costs decreased by 73% ($580 per woman per year) and were strongly and independently associated with decreasing UI frequency 24 months following Burch or sling.

Lier and colleagues [24] performed a within trial cost-utility analysis in a randomized trial of transobturator tape (TOT) compared with tension-free vaginal tape (TVT) in the surgical treatment of stress urinary incontinence (SUI) among 194 women in Canada. Cure was assessed by objective pad tests. They assessed costs in 2007 Canadian dollars from the public-payer perspective, i.e. 807$ Can for surgical kits, plus day only surgical costs and 12 months of care costs. The 15D utility instrument was used to measure QALYs. At 1 year post-surgery, 81% of TOT patients were dry on 24 hour pad test, versus 77% of TVT patients; 15% of the TOT had groin pain (versus 6% of TVT) but whether this contributed to medical costs over 12 months was not clear. The TOT group had a non-significant average saving of $1133 (95% CI -2793; 442), or 17%, with no difference in average QALYs between groups (95% CI -0.02; 0.01). TOT was cost-saving in over 80% of sensitivity analyses, suggesting that TOT would be cost-effective compared with TVT in the treatment of SUI. However, longer-term assessment of clinical and economic outcomes are needed to confirm the finding and observe for effectiveness, surgical complications, and re-treatment.

Jacklin et al [44] published a decision tree/Markov model in 2010 which proposed to consider the cost

utility of second line treatment for women with stress incontinence who had failed PFMT. The Markov model was controversial, because patients were expected to have either duloxetine or a TVT and then be followed up for 2 years, there was no opportunity for patients not responding to duloxetine to progress to a TVT. However patients failing the initial TVT were able to have a repeat TVT. The purpose of the article was to employ recently published long term followup data for duloxetine (as initial studies only reported to 12 months, with 68% of women estimated to continue therapy, but recent studies showed much poorer continuation rates, i.e. 9% and 8% at 12 months and 2 years). No actual QALY data for the TVT patients were cited from the literature, and QALY date for duloxetine patients was cited from a small study [45].

Unsubstantiated assumptions were made about the QALY loss associated with adverse events from duloxetine therapy. An 8 week course of duloxetine cost £30 (which would be very low cost for this medication in most countries), a TVT cost £2,044. They concluded that TVT is a cost effective second line therapy, but duloxetine, although cheaper, is not cost effective because of high discontinuation rates and lower efficacy. One of the authors was part funded by NICE, a second author had previously been funded by the manufacturers of duloxetine.

Patel et al. [46] compared the operating/bedstay billing costs in 45 patients from South Carolina having surgery for stress incontinence with or without prolapse, who had either commercial mesh kits, or segments of prolene mesh that were sewn in by the surgeon, with or without biomaterials during 2007-2008. Operative billing sheets including operative time, hospital "cost", bedstay time, and the insurance billings were reviewed. Surgeon payment was not included. The definition of cost is unclear and may represent hospital charge rather than cost. In both pure stress incontinence or coexistent prolapse, the surgeon-made prolene mesh operations were less expensive than the surgical kits, not surprisingly. No efficacy data or QALY data were included.

In our last report, Wu et al. [47] had very recently performed a methodologically excellent cost-effectiveness analysis of Burch colposuspension compared with TVT for stress incontinence, using a Markov model to compare costs (2005 USD) and QALy's (measured by the Health Utilities Index) over 10 years from a health care system perspective. In this well done study using state-of-the-art methods, Burch colposuspension was not cost-effective compared with TVT. However, if the tension-free vaginal tape failure rate was to increase over time, Burch may become cost-effective, reinforcing the need for long-term follow-up in surgical trials and cohorts.

In our last chapter, we reported a study regarding open vs. laparoscopic colposuspension by Dumville et al [48], which the Committee pointed out was a good example of the importance of evaluating costs over a long time frame to allow cost effectiveness to emerge. In the initial economic analysis of the two procedures at 6 months, healthcare costs were higher for the laparoscopic arm than for the open Burch arm (£1805 vs. £1433; differential mean cost £372; 95% CI 274, 471) due to increased theater costs. QALYs were slightly higher in the laparoscopic arm relative to the open arm (0.005; 95% CI -0.012, 0.023). The ICER was £74,400 at 6 months. At 24 months, higher mean QALY's persisted in the laparoscopic arm and modeling showed the ICER was reduced to £9300. While laparoscopic colposuspension was not cost effective compared with open colposuspension during the first 6 months following surgery, it may be cost effective over 24 months.

In the last report, we discussed the multicentre RCT of Manca et al (2003)[49] who assessed the cost effectiveness of TVT with open colposuspension for primary stress incontinence at 6 months, in 344 women from 24 centres in the UK and Ireland. The EQ-5D was used to measure QALYs. The TVT had lower mean costs and higher mean QALYs at 6 months, which persisted over 95% of sensitivity analyses. The 2 year and 5 year follow-up of this study has since been published but no further economic analysis appears to have been reported.

2. SURGERY FOR URGE INCONTINENCE

a) Studies regarding Botulinum Toxin A Injections (Botox A)

Three studies comparing Botox A with other treatments have been published since our last report. Wu et al (2009) from the USA performed a Markov model analysis of Botox A versus anticholinergic medication [50]. The model was conducted over a two year time frame, and assumed that 33% of patients would comply with anticholinergic therapy over this time. The Botox treatment cycles were more expensive (US$ 4,400) than the anticholinergic medication (US$ 2,560), but the Botox was more effective (QALY gain 1.63 versus 1.50), yielding an ICER of $14,377.

Wefer et al (2009) from Germany evaluated Botox A injections in 214 patients with neuropathic detrusor overactivity [51]. 300 IU of Botox were injected in each patient (which is common practice in neuropathic DO, but varies from some clinical practice in Idiopathic DO which 200IU are often given). The injections were given as inpatients. Pad costs per day were reduced from €2.11 per day to €1.05, and medications for urinary tract infection fell by half (from €162 per annum to €80 per annum). Unfortunately no QALY measurements were performed.

Robinson et al. (2010)[52] undertook a Markov model study comparing Botox with percutaneous tibial nerve stimulation (PTNS), over a 2 year time frame in refractory idiopathic detrusor overactivity. Repeat botox injections were assumed to occur every 8 months; 20% of patients were assumed to perform clean intermittent self-catheterization for 4 months.

QALY data was assumed from the literature. PTNS was cheaper than Botox (£1,700 versus £4,067) and had a lower ICER (£50,133 versus £111,953) but neither would satisfy UK NICE guidelines for cost-effectiveness (i.e. not less than £30,000 per QALY).

Padmanabham et al (2011) from USA performed a decision tree analysis of Botox injections versus Clam Cystoplasty[25] (which is an arguable model, since Sacral Nerve Stimulation has largely overtaken clam cystoplasty in the western world). Nevertheless, this was a group of severely refractory neuropathic DO patients, who were performing clean intermittent self catheterization (CISC) but still had upper tract dilatation and recurrent urinary tract infection (UTI). Their decision tree is shown in **Figure 3** (earlier in this chapter). Botox 300 IU was injected every 6 months for 5 years, the cost of each injection was US$ 2,800, equaling 28,000 over 5 years. The Clam Cystoplasty cost US $33,000. In their model, it was assumed that 10% of patients would fail Botox, of whom 85% would go on to have a Clam Cystoplasty (this model is controversial in the modern day climate).

No QALY data were provided, but the authors concluded that if the durability of Botox benefits exceeded 5.1 months, then the cost effectiveness of Botox dominated, so long as the complication rate of the Clam Cystoplasty was less than 14%. The first proviso appears quite reasonable, but the complication rate of Clam cystoplasty is known to be higher than 14%, and the 1% mortality is not mentioned (which would have adversely affected any QALY data taken from a real life study).

b) Sacral nerve stimulation

Sacral Nerve Stimulation (SNS) is a minimally invasive FDA approved second line treatment for refractory overactive bladder (OAB) dry and wet. Currently five papers describe different aspects of cost analysis and cost-effectiveness of SNS, some with comparison to other treatment strategies for OAB [53-57].

Aboseif et al[53] in the U.S.A. retrospectively reviewed the costs related to SNS for a period extending from one year pre- to one year post-implantation. In a heterogeneous group of patients, also including patients with urinary retention and chronic pelvic pain, a one year SNS treatment reduced 92% of outpatient doctor visits and diagnostic and therapeutic procedure costs, along with a 30% reduction in drug costs [53]. This however did not include the costs of the neuromodulation implant itself, nor the surgical implantation costs. QALYs were not ascertained.

A cost analysis evaluation was also conducted in a large multicenter cohort study in France,[56] which included 190 OAB wet patients and neuropathic DO, as well as another 85 patients with OAB wet plus faecal incontinence (double incontinence). Treatment costs included insertion of preliminary tined leads under GA as an outpatient then permanent implant as an inpatient, with Botox injections given as an inpatient. Health-related travel costs were also included in the analysis, which extended from the pre-test evaluation, over the temporary stimulation procedure until two years after the implant procedure.

The median overall cost per OAB wet patient for the first two years was €16,403, which was on average €8,525 more per patient compared to patients on alternative treatments, which comprised conservative measures (medication and diapers/pads), botulinum toxin injection, enterocystoplasty or urinary diversion. Importantly, devices and hospital stays accounted for 40% and 52% of the total cost respectively. Although the authors provided a limited cost-effectiveness analysis over the two year period, the interpretation of the results are difficult because of the heterogeneity of the study population, surgical procedures and the lack of clear descriptions of the cost-effectiveness parameters. Their data, however, suggest that SNS for OAB wet is not cost-effective over the two years period. This is in agreement with the data from Siddiqui et al[57] (see below), and not surprising since the initial costs are very high due to the device costs. Interestingly, their data suggest that SNS may be cost-effective even in the short term for patients with double incontinence [56]. This deserves attention in future research.

Siddiqui et al [57] performed a cost-effectiveness analysis of SNS vs intravesical Botulinum Toxin A in patients with idiopathic “OAB wet” in the US. A two year period was chosen for evaluation because no long-term data were available for Botulinum Toxin A. The base case scenario included a staged implant procedure for SNS using the tined lead, and office injections of 200 units Botulinum Toxin A. For the SNS strategy, no data were provided on the procedure (local vs general anesthesia; outpatient vs inpatient clinic). The relevant base case estimates are provided in **table 2**. Based upon their Markov decision model, the base case SNS treatment was more expensive ($15,743 vs $4,392) but also more effective (1.73 vs 1.63 QALYs) than Botulinum Toxin A. During the two year period, SNS was not cost-effective with an ICER of $116,427 [57]. As stated above, the relevance of a cost-effectiveness analysis over a two years period with a costly implant device is questionable.

Two cost-effectiveness studies have considered the longer term, comparing SNS and Botulinum Toxin A in the Netherlands[55] and Spain [54]. The parameter estimates are provided in **Table 2**. In the Netherlands, Leong et al. (2011)[58] showed that SNS becomes cost-effective from the fourth year post-implant on, given an ICER threshold of 40,000€/QALY [55]. These data are based upon two procedures under general anesthesia (1) a staged SNS procedure involving a tined lead test phase in the operating theatre on an outpatient basis, followed by an inpatient stay for device implant; (2) inpatient stay for Botulinum Toxin A injection in the operating theatre.

Table 2. Comparison of studies conducted in the USA, Netherlands and Spain regarding SNS and Botox therapy

		Siddiqui et al (2009)		Leong et al (2011)		Arlandis et al (2011)	
Base Parameter Estimates (years)		2		5 (with 10 year analysis)		10	
Country of Origin		USA		Netherlands		Spain	
Sacral Nerve Stimulation	**Success rates (%)**	Tined lead placement (TLP) (all success go to implant)	75	TLP	75	TLP	80
						1 year	90
				1 year	90	5 year	75
						10 year	75
	Implant longevity	2 year	90	Yearly drop-out	4.3	Not stated	
	Battery replacement	Not stated		7 years (3 months loss of effect)		Not stated	
	Probability of Complication (%)	16 months	19	Not stated		Not stated	
		Conservatively managed	33				
	Probability Requiring Surgical Revision (%)	66 (5% refused)		16 (Removal of device: 7.5%)		Not stated	
	Battery life (years)	Not stated		7		7	
	Base economic case	Staged implant tined lead. Explantation when multiple complications require > 1 surgical revision within 3 mos		SNM test and implant at operating room (45 minutes) for IPG implant inpatient stay		Not stated	
Botox	**Success rates (%)**	79		79		1 year	80
						5 years	59
						10 years	50
	Amount of Botox	200u		200u		100u (BoNT)	
	Base economic case	Office based injections		Operating room (30 min with inpt stay)		Not stated	
	Discount rate/year (%)	3		4		3	
	Discount rate QALYS/year	Not stated		1.5		Not stated	
	Threshold cost effectiveness	50-000 to 10000 $/QALY		<40000 €/QALY		Not stated	
	QALYS	Not stated		Success (continence)		0.95	Success 0.793
				Failure (leaking)		0.73	Failure 0.573
	Failure treatment SNS-Botox (%)	Not stated		Opt for other treatment:		75	Opt for other treatment 77-79
				No further treatment		25	Cystoplasty 5
							Conservative treatment 16

These data are in agreement with the Spanish study by Arlandis et al.,[54] which showed SNS to be cost-effective from five years post-implant on, given an ICER threshold of 30,000€/QALY. These results are based on (1) a staged SNS procedure involving a tined lead test phase; (2) 100 units Botulinum Toxin A. No further data were provided on the procedure (inpatient vs outpatient; local vs general anesthesia). In both studies,[54, 55] several estimates or assumptions had to be made due to the lack of long-term data beyond 1 year for Botulinum Toxin A injections and 5 year for SNS therapy, such as therapy transition rates after failure and drop out rates. To what extent these data are reliable and valid is currently unknown.

Furthermore, both studies quote a one year success rate for SNS of 90%, based upon Van Voskuilen et al,[59] that describes the effect of SNS in 39 patients with OAB over 15.5 months follow up. However, in that study 10 patients were lost to follow and were excluded from the analysis. Therefore the 90% success rate

may be an overestimation, and the worst scenario, considering the ten lost to follow up patients as failures would give a 61% success rate. How this would influence the cost-effectiveness evaluation is unknown. A similar consideration applies for the 5 years success rate of 70% based upon Van Kerrebroeck et al[60] which considers patients lost to follow up as last observation carried forwards.

Sensitivity analyses for several parameters estimated by expert opinion have been performed. In the Netherlands, SNS over a 5 years period remained cost-effective (ICER < 40,000€/QALY) when the estimated dropout rate of 4.3% for both treatments was changed to 2% or 6%, and when utility value for incontinence was changed from 0.73 to 0.80. SNS was no longer cost-effective over 5 years in the following cases:

a. when Botulinum Toxin injections were done under local anesthesia (which is common practice in several countries),

b. when the Peripheral Nerve Evaluation test for SNS screening is used (because of the lower success rate of 55% compared to 75% for Tined Lead screening),

c. when bilateral testing is done

d. when the new and smaller stimulator (Interstim II) is used [55].

Because there is no standard protocol of Botulin Toxin A injection, a different protocol using 200 units every 14 months was evaluated in the Arlandis study, which proved cost-effective on the ICER < € 30000/QALY threshold [54].

3. OUTPATIENT CONSERVATIVE THERAPIES

An important study regarding the baseline "cost of illness" for women with stress or urge leak was detailed in our last chapter (Subak et al.[61]).

A more recent study of the "Cost of Illness"[62] included 528 women with UI weekly or more enrolled in the Reproductive Risks for Incontinence Study at Kaiser population-based study. Similar to the prior studies, routine care costs were calculated with the use of national resource costs ($2005). Potential predictors of these outcomes were examined by multivariable linear regression. Among women with weekly UI, 69% reported incontinence-related costs. Median weekly cost was $1.83 (25%-75% interquartile range [IQR], $0.50, $5.23) and women spent a mean of >$250 per year out-of-pocket for UI routine care. Costs increased with incontinence severity (P < .001) and body mass index (P < .001) were 2.2-fold higher for African American versus white women (P < .0001) and 42% higher for women with mixed versus stress incontinence (P < .05).

Since costs for incontinence management increase with leakage severity, data are needed to explore whether effective treatment will be associated with decreased incontinence costs.

Recently, Subak et al.[63] performed a planned secondary analysis among overweight and obese women, who were enrolled in a clinical trial of a weight loss intervention. The purpose was to estimate the effect of a decrease in incontinence frequency on incontinence management costs [63]. The study included 338 obese and overweight women with at least 10 weekly urinary incontinence episodes at baseline. They enrolled in a randomized clinical trial to determine the effect of an 18-month weight loss and maintenance intervention compared to a structured education program, upon the frequency of incontinence.

Quantities of resources used for incontinence management, including pads, protection, additional laundry and dry cleaning were reported by participants. They estimated direct costs for urinary incontinence management ("cost") by multiplying resources used by national resource costs (in 2006 U.S. dollars). For the total cohort (combined randomization groups), mean (±SD) age was 53 ± 10 years and baseline weight was 97 +17 kg. Mean weekly urinary incontinence frequency was 24+18 at baseline, which decreased by 37% at 6 months and 60% at 18 months follow-up (both P<0.001).

At baseline, adjusted mean cost was $7.76 ± $14 per week. Costs increased significantly with greater incontinence frequency. Mean cost decreased by average of 54% at 6 months and 81% at 18 months (both P < 0.001). In multivariable analyses, cost independently decreased by 23% for each decrease of 7 urinary incontinence episodes per week, 21% for each 5 kg of weight lost, and was strongly associated with greater improvement in UDI and IIQ scores at 18 months (P < 0.001 for all). In this cohort of obese and overweight women enrolled in the clinical trial, management cost for urinary incontinence decreased by over 80% at 18 months ($327 per woman per year) and was strongly and independently associated with decreasing incontinence frequency. This suggests that effective incontinence treatment will be associated with decreasing costs of incontinence management

Although not primary data, Imamura et al (2010) published a comprehensive review of the cost effectiveness of non-surgical treatments for women with stress incontinence [64]. In this report, a group of senior clinicians and other experts obtained funding from the Medical Research Council of the UK to evaluate 88 studies of conservative treatment involving 37 distinct treatment regimes, in a total of 9,721 participants. QALY data were taken from a study by Haywood et al[65] which employed the EQ-5D [64]. In brief, the authors found that a treatment strategy of Pelvic Floor Muscle Training (more than 4 visits) along with lifestyle advice, followed by a TVT where necessary, was the least costly strategy, at £1644 per person, and was the most effective, with a cost utility of 16.20 QALY per annum. This strategy had a 70% likelihood of being the most cost effective across a wide range of sensitivity analyses.

A smaller review of cost effectiveness evaluations for pelvic floor exercise interventions, which included data from 3 older studies (from 1996, 2003, 2006) has also recently appeared [66].

In the last Chapter, we reported an abstract from Ho et al. [67] in Australia who performed a "bottom up" study of the short and long-term treatment costs of conservative and surgical management of childbirth-related stress and mixed urinary incontinence (UI). This report has now been published in full [68]. Costs of treatment episodes during conservative and surgical management were calculated for a cohort of 150 women and related to cure. At 6-13 years follow up, personal and treatment expenditure was measured using a postal questionnaire. During active treatment, patients with stress UI treated conservatively incurred a median cost of AU$658 per capita (IQR 476 – 1191 AU$) compared to a median cost of $6,870 per capita for surgical treatment (IQR 6,320 – 7,508 AU$). Similar cost difference was seen for the two treatment options in mixed incontinence. Of regular clinic attendees, 39% of conservatively treated and 78% of surgically treated patients were cured.

At 6-13 years follow up(82 women with a known address), 43 (52%) responded to the survey, of whom 46% remained cured. The median treatment cost for the total group of postnatal incontinence (irrespective of continence status) was AU$885.80 per capita per annum (IQR 338- 2,589 AU$). The costs per cure are shown in **Table 3**, in Australian dollars.

4. PHARMACOTHERAPY OF URINARY INCONTINENCE

a) Economics of pharmaceutical therapies

Although pharmaceutical companies must show that a new drug is safe and efficacious prior to approval and marketing, the requirement for economic studies (ie whether the new drug is cost-effective compared to standard treatment), varies from country to country.

The U.S. Food and Drug Administration does not require any economic data in its review of a new drug. Instead it leaves economic questions to the purchasers (e.g., insurance companies, government purchasers or individuals), similar to the Netherlands. In the UK, however, the National Institute for Health and Clinical Excellence (NICE) requires economic review. They have denied approvals for new drugs that have an incremental cost effectiveness ratio greater than £30,000 per QALY. In Australia, manufacturers must prove cost-effectiveness in order to achieve listing on the Pharmaceutical Benefit Scheme (whereby patients pay a subsidized cost for the drug). However, only therapeutic efficacy and safety must be shown in order for it to be available in Australia as a non-subsidized "private" prescription.

In response to the regulatory requirements, drug developers routinely conduct economic evaluations. In the UK, such efforts are done as part of the NICE review. In the US, developers present economic data to purchasers for post approval marketing. Many purchasers (as in Australia) have formularies, or lists of medications that they are willing to pay for, and the economic evaluation is frequently part of the request to place the new drug on the formulary.

In the next sections, we review the recent literature on the economics of drugs for incontinence and overactive bladder.

1. Pharmacotherapy for stress incontinence

Mihaylova et al. (2010) assessed the cost-effectiveness of duloxetine compared with conservative therapy in women with SUI [69]. Cost and outcome data from a 12-month, prospective, observational, multicenter, multicountry study were used (the Stress Urinary Incontinence Treatment (SUIT) study). Costs were assessed in 2007 £ from the healthcare plus patient perspective; outcomes were measured in quality adjusted life years using the EQ-5D. Duloxetine alone and with conservative treatment (not explicitly defined but varied by physician practice) were associated with incremental quality-adjusted life-years (QALYs) of about 0.03 over a year compared with conservative treatment alone or with no treatment. Conservative treatment alone did not show an effect on QALYs. Duloxetine either dominated (lower

Table 3. Costs per cure, modified from Ho et al. (2012) [68]

	Costs of pure stress incontinence (A$)	**Costs of mixed incontinence (A$)**	**Treatment duration (days)**
Conservative treatment	Median = 658 (IQR = 476-1191) n = 84	Median = 772 (IQR = 531-985) n = 43	Median = 156 (IQR = 69-367)
Surgical treatment	Median = 6,870 (IQR = 6320-7508) n = 12	Median = 6,894 (IQR = 6733-7206) n = 11	Median = 902 (IQR = 408-1552)
Conservative treatment cost per patient cured	4,073	2,415	
Surgical treatment cost per patient cured	9,415	8,587	

cost and greater change in QALY) or had an incremental cost-effectiveness ratio (ICER) below £900 per QALY gained, compared with no treatment and with conservative treatment alone. Duloxetine plus conservative therapy had an ICER below £5500 (compared with no treatment or conservative treatment alone). Duloxetine compared with duloxetine plus conservative therapy showed similar outcomes but an additional cost for the combined intervention. While limited by the observational design, the study suggests that initiating duloxetine therapy in SUI is a cost-effective treatment alternative.

(NOTE: Duloxetine failed the US approval for stress urinary incontinence due to concerns over liver toxicity and suicidal events. It is approved for SUI in Europe, where it is recommended as an add-on medication in stress urinary incontinence instead of surgery.)

In a similar vein, we reported in our last chapter that Brunenberg[70] conducted a Markov model to assess the cost-effectiveness of duloxetine alone and duloxetine after inadequate response to pelvic floor muscle training [PFMT] compared with PFMT or no treatment for women 50 years of age or older, which narrowly focused upon pharmacotherapy and PFMT for stress incontinence, with no consideration of surgery.

Das Gupta and colleagues[45] also developed a model to assess the cost-effectiveness of duloxetine for moderate to severe SUI, but they assumed that drug treatment was fully effective. Thus duloxetine studies published to date have methodological limitations.

2. Pharmacotherapy for Urge Incontinence

There are five commonly used medical treatments for overactive bladder: Oxybutynin (ditropan) as a tablet or as Oxytrol patches; tolterodine (Detrol), darifenacin (Enablex), trospium (Sanctura), solifenacin (Vesicare), and a sixth recent introduction, Fesoteridine (not yet widely used).

Many economic evaluations are funded by drug developers and compare the investigational drug to placebo or to an older compound that has known problems with side effects (e.g., immediate release oxybutynin). In the Fourth ICI report [41] we reported one study by Ko et al. [71] who conducted an independently funded economic evaluation of five antimuscarinic drugs (in eight formats) for overactive bladder (see **Figure 8**). They concluded that solifenacin had the lowest costs and highest effectiveness, compared to immediate-release (IR) oxybutynin, extended-release (ER) oxybutynin, transdermal oxybutynin, IR tolterodine, (ER) tolterodine, trospium, and darifenacin. However, their study did not meet minimum standards for cost-effectiveness analysis [9, 14]. It also focused on the payer's perspective (rather than a societal perspective), had a short time frame

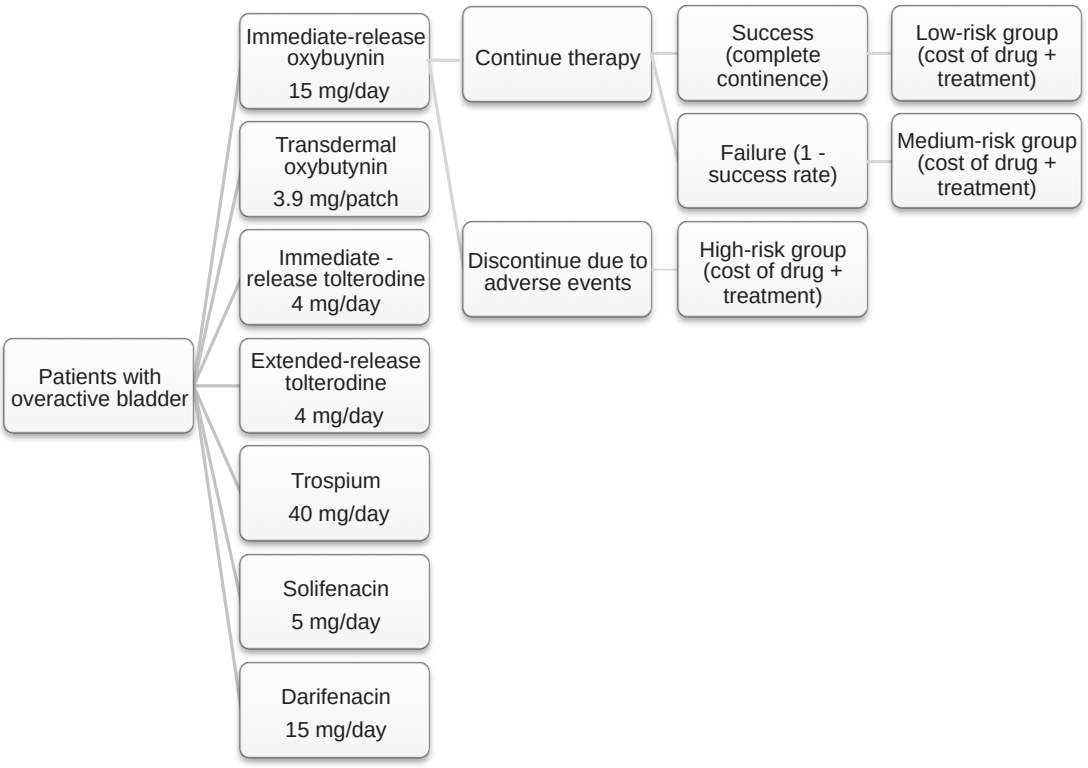


Figure 8. Decision-analysis model used to compare cost-effectiveness of antimuscarinic agents for the treatment of overactive bladder. Modified from Ko et al. (2006)[72].

of 3 months, and used complete continence as the main effectiveness measure (rather than QALYs). Given these limitations, we recommended that these results must be interpreted cautiously and that additional studies using standard methods were needed.

3. Solifenacin Studies

Milsom et al[72] performed a cost effectiveness analysis of Solifenacin flexible dosing (5-10 mg) versus tolterodine 4 mg Sustained release in 4 Nordic Countries. The efficacy data was based upon the STAR RCT (Chapple et al, 2005[73]) and 2 other RCTs of solifenacin versus tolteridine and placebo. QALYs were not included in the original trials, but the EQ5D was estimated from original HRQOL data collected in 1997. The cost differences between solifenacin and tolteridine ranged from €6 to €127. The authors concluded that Flexible dose Solifenacin was more cost effective than Tolteridine 4 mg. This study was supported by Astellas.

Herschorn et al[74] undertook a Markov model based upon the VECTOR study, which compared Solifenacin 5 mg/ day versus Oxybutynin 15 mg / day in Canada. The withdrawal rate due to side effects of oxybutynin (19%) was much greater than that for solifenacin (3%). No QALY data was included in the original VECTOR study. Their 8 week efficacy data was projected over 1 year, which is an arguable model. Solifenacin yielded a cost saving of Can $ 1,830 per annum, giving an ICER of Can $14,000. This study was also funded by Astellas.

Cardozo et al[76] performed a decision tree analysis of solifenacin, versus fesoteridine, oxybutynin ER, propiverine, tolteridine ER and IR in the UK. In this one year model, success was individually defined for frequency, urgency and urge incontinence. The model was problematic (**Fig 9**), in that it assumed if the patient had no success on a drug that was only available in one dose, then the patient was given no further treatment. The original study did not include QALY data, which were calculated from willingness to pay data published by Kobelt in 1998 [77]. The calculation of QALYs from willingness to pay is not a standard methodology and created confusion among the Economics Committee members. Because oxybutynin was so much cheaper than the other drugs (20% of total costs, versus 60-70% of total costs for the other therapies), oxybutynin was dominant for 2 of the 3 outcomes.

In 2005, Getsios and colleagues[78] published a review of the economic studies for overactive bladder, highlighting many of the limitations including a lack of comparisons of drugs to behavioral training.

4. Darifenacin hydrobromide (Enablex)

Darifenacin was approved by the FDA in 2004, based on Phase II and III controlled clinical trials with over 8,800 patients. Short term efficacy (12 week) as well as longer term effects (24 and 52 week) were evaluated [79]. Abrams and colleagues [80] found that darifenacin was associated with significant improvements in quality of life as measured by the King's Health Questionnaire at 12 weeks relative to placebo. Chancellor et al. [79] found that darifenacin and darifenacin combined with a behavioral modification plan both resulted in improvements in symptoms and quality of life, as measured by the Overactive Bladder Questionnaire (OAB-q), but there were no differences between the two groups. Unfortunately, neither the Abrams nor the Chancellor study measured utilities. Besides the Ko [71] article discussed above, there is little data on the cost-effectiveness of darifenacin.

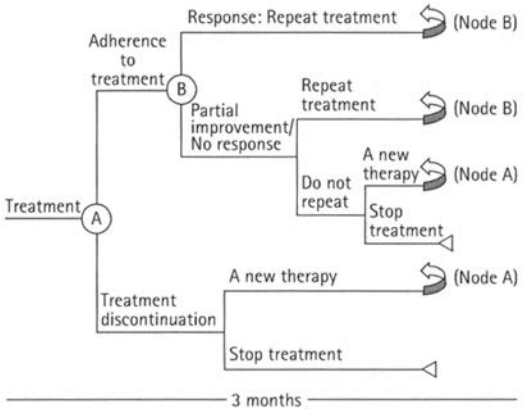


Figure 9. Solifenacin vs fesoteridine, oxybutyin ER, propiverine, tolteridine ER and IR in UK. Reproduced from Cardozo et al. (2010)[77] with permission.

5. Tolterodine (Detrol)

In late 2008, Burgio et al (The UTIN group) conducted a clinical trial of 10 weeks of open-label, extended-release tolterodine alone (n = 153) or combined with behavioral training (n = 154), followed by discontinuation of therapy and follow-up at 8 months [81]. Among 237 participants completing the trial, the rate of successful discontinuation of therapy at 8 months was the same in the combination therapy and drug therapy alone groups (41% in both groups; difference, 0 percentage points [95% CI, -12 to 12 percentage points]). A higher proportion of participants who received combination therapy than drug therapy alone achieved a 70% or greater reduction in incontinence at 10 weeks (69% vs. 58%; difference, 11 percentage points [CI, -0.3 to 22.1 percentage points]). Women in the combination therapy group reported better outcomes over time on the UDI and the OAB-Q (both P <0.001) for patient satisfaction and perceived improvement but not health-related quality of life. They concluded that the addition of behavioral training to drug therapy may reduce incontinence frequency during active treatment but did not improve the ability to discontinue drug therapy and maintain improvement in urinary incontinence. Economic evaluations are ongoing.

Two studies evaluating the cost-effectiveness of tolterodine versus percutaneous tibial nerve stimulation (PTNS) have recently been published. In 2009, Robinson et al[82] undertook a cost minimization study of PTNS versus tolterodine ER 4mg, involving 1-2 year follow-up, from the perspective of the NHS. In the model, the two treatments were assumed to have equivalent efficacy (based on unpublished data), and adverse effects were considered to be cost neutral. The patients having tolterodine were followed for 2 years, the duration of follow-up for PTNS was not clearly stated. Tolterodine appeared to be the cheaper treatment but alteration of the variables in the model had a large effect.

In 2010, Chen et al[83] performed a very similar evaluation of PTNS versus tolterodine, cost-utility values were obtained from the literature [84], yielding an ICER of $70, 754 per QALY, thus PTNS was not cost effective in the treatment of OAB over a 1-year period.

6. Trospium Chloride (Sanctura)

Besides the Ko[71] article discussed above, there is little published data on the cost-effectiveness of trospium chloride.

5. COST IMPLICATIONS OF INCONTINENCE IN NURSING HOME SETTING

Two key aspects of cost of care for nursing homes are (1) cost of nursing home admissions attributable to urinary incontinence, and (2) the treatment cost of urinary incontinence. In the last 4 years, no new studies were found regarding this aspect of the economics of incontinence, therefore our previous findings are briefly summarized.

Additional nursing home admissions cost is often a major component in the total cost of urinary incontinence. In a 2001 study [16] the cost estimate was $2.4 billion in 1995 dollars. In a 2004 study [15], the cost estimate was $4.0 billion in 2000 dollars. In a 2006 study,[85] the attributable fraction (AF) statistics from published data was shown to be $6.0 billion in 2004 dollars. The Attributable Fraction (AF) statistics are obtained by using incontinence prevalence rates for those admitted to nursing homes, as compared to those who were not admitted to nursing homes. It shows that reimbursement for treatment of UI in the community might help or delay institutionalization and offset some costs of staying in nursing homes. The AF method has been used in the economic cost of mental illness, smoking, and cancer diseases. The new estimated magnitude shows that reimbursement for treatment of UI in the community might help or delay institutionalization and offset some costs of staying in nursing homes.

Holroyd-Leduc et al. [86] conducted a population-based prospective cohort study (from 1993-1995) in over 6,500 elderly (>age70) patients. After adjusting for confounders, UI was not an independent predictor for death, nursing home admission, or functional decline. Within nursing homes, labor costs are a major component of caring for incontinent patients. These costs are studied via time/motion observation, correlated with severity and type of incontinence. In 49 long-term care facilities in North Carolina, USA, it was found that the incremental labor costs (per shift) were $3.31 for patients with occasional UI and $5.61 for patients with frequent UI [87], in keeping with Morris et al[10].

Bliss et al. [88] addressed the cost/effectiveness of incontinence-related treatment of skin condition in 16 US nursing homes. Four regiments of different moisture barriers were applied. Time and motion measurements included skin products and time spent. Using acrylate barrier film spray achieved cost savings of between $854 to $1,862 per resident, with better skin protection than the use of an ointment or cream.

6. LONGITUDINAL BURDEN OF DISEASE STUDIES

For the first time in the last ICI report, we found a number of studies that measure the cost of incontinence over the long-term time frame. As pointed out by Birnbaumn et al.[89], the study of “the lifetime cost of illness” is a recent area of research. These authors combined case-control methods (to calculate annual medical costs of stress incontinence, etc) with knowledge of the incidence of the conditions, assuming “steady state conditions” of the costs, to project the lifetime costs of each disorder.

As regard the impact of incontinence upon employed women, Fultz et al. [90] sent a postal questionnaire to 2326 employed women, 37% had leaked urine in the past month. The impact of incontinence upon ability to concentrate, performance of physical activities, self confidence, and ability to complete tasks without interruption increased with the severity of the leak and affected nearly 75% of all those with severe leak status. Similarly, Wu et al. [91] focused upon the work loss burden of women with OAB. The number of days absent was 15% higher among 3077 OAB employees compared to 6154 controls. OAB subjects had 4.4 more days off work than non-OAB subjects, yielding an annual excess cost of $1220 per OAB employee.

In the last chapter, Reeves et al. [92] employed a theoretical model based upon a large “EPIC” prevalence study of OAB [93] to derive the future cost burden for OAB in five European countries. They calculated an annual per capita expense of €269-706 per annum.

A more detailed analysis of OAB costs in Germany [94] that included psychiatric costs of OAB-related depression, and nursing care, indicated an annual per capita expense of €609-1170 per annum in that country.

Since the last report, this same group of authors obtained updated data for the treatment costs of “OAB wet” and “OAB dry” [95]. They also provided new data about the non-treatment costs of OAB, such as lost productivity, depression, sleep disturbance, falls

and fractures, skin infections and UTIs. The manuscript lists 23 website links that were used to access unit costs for each of the six developed countries (Canada, Germany, Italy, Spain, Sweden and UK). A summary of the costs in each country is shown in **Table 4** [95], with summary data in **Table 5** [95]. Overall, the annual treatment costs of OAB in six countries is shown to be ≈ €3.9 billion, with additional costs for nursing home stays (€4.7 billion per year) and loss productivity due to work absenteeism (€1.1 billion per year). The estimated total cost therefore for the ≈25 million patients with OAB in these countries is €9.7 billion.

Cisternas et al [96] undertook an analysis of the economic burden of overactive bladder syndrome in Medicare beneficiaries in the USA[96]. They obtained data for all Medicare claims for patients over age 65 during 2003-2004, compared with non-OAB subjects. Multiple regression analysis was used to estimate costs attributable to OAB after adjusting for demographic characteristics and comorbidities. They used a narrow definition of OAB (detrusor overactivity, urge incontinence, frequency with polyuria) and also a broader definition of OAB (that included incontinence without sensory awareness, nocturnal enuresis, continuous leakage, etc).

Costs were based on the amount of money reimbursed to providers by Medicare (which generally yields 80% of "allowed amounts") that includes inpatient stays, skilled nursing facilities, outpatient visits and procedures such as cystoscopy. **Figure 10** shows the prevalence of the two definitions of OAB compared to other chronic conditions. The prevalence of OAB in this over 65 group was 9-14% for the two definitions.

The mean annual expenditure attributable to OAB ranged from US$825 – 1184 per subject, which comprised 9-12% of all their medical expenditure.

Table 4. Estimated costs per patient with OAB per annum, reproduced from Irwin, 2009 [95] with permission

	Costs (€)*						
Excess Direct Costs	**UK**	**Canada**	**Germany**	**Italy**	**Spain**	**Sweden**	**Total**
Prescription Medication Treatments for Urinary Symptoms+	33	62	81	91	35	89	391
Incontinence Pad Use+	48	56	66	102	102	80	454
Clinical Depression+	204	118	251	82	82	197	934
Diagnostics+	5	5	3	1	1	34	49
Medical consultations – GP+	225	129	31	32	49	184	650
Total	515	370	432	297	255	584	2,453
Sequelae Direct Costs **							
UTI **	6	7	11	5	3	21	53
Skin Infections **	3	3	3	2	1	10	22
Fractures **	4	9	6	2	3	4	28
Total	13	19	21	9	7	35	104
Other Costs							
Nursing Home Admissions for Individuals > 60 yrs old **	381	385	1038	1580	30	562	3,976

***** costs for OAB with UUI***
****costs averaged across all OAB patients***
+excess costs or costs directly related to OAB

Table 5. Total excess costs for OAB in six Western countries, modified from Irwin, 2009 [95]

		Cost € (millions)		
		OAB "dry"	**OAB "wet"**	**Total OAB**
Country	Canada	127.3	251.8	379.1
	Germany	648.7	543.3	1,192.0
	Italy	282.7	289.6	572.3
	Spain	194.9	171.8	366.7
	Sweden	126.5	206.5	332.9
	UK	412.9	594.5	1,007.4
Costs	Total Costs*	1,792.9	2,057.6	3,850.5
	Total nursing home	NA†	4,668.6	4,668.6
	Total lost productivity	857.8	237.8	1,095.6

**Excluding nursing home and productivity costs*
†Not costed

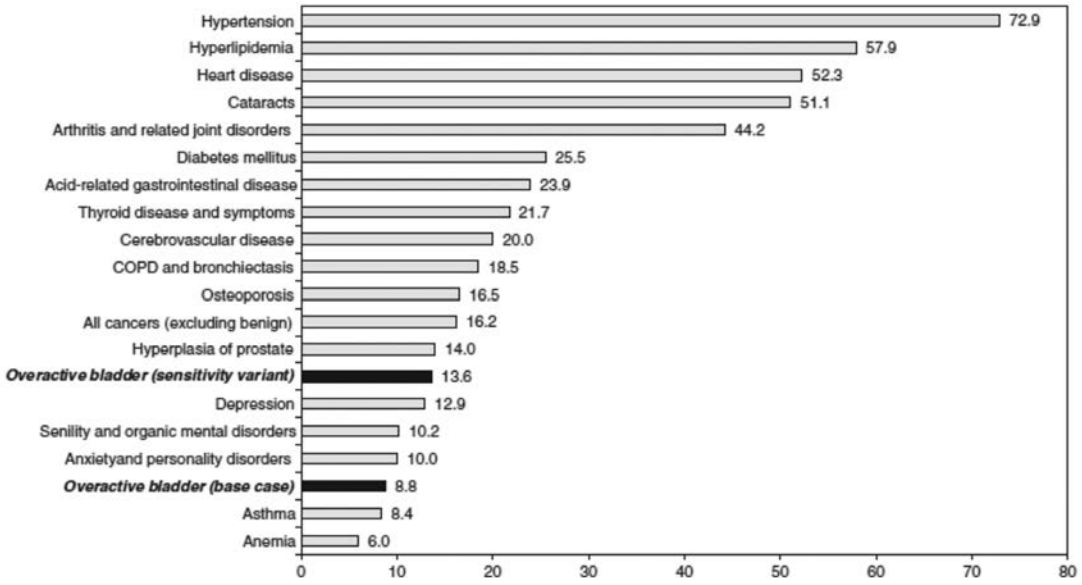


Figure 10. Treated prevalence (%) of OAB compared to other common chronic conditions (each subject may have more than one diagnosis), Medicare enrollees 2003-2004, reproduced with permission from Cisternas et al. (2009)[96].

The total cost of OAB expenditure was 1.8- 3.9 Billion US $ per year. These authors also considered the consequences of incontinence. For example, The OAB cohort had a higher occurrence of events such as falls/ fractures (46% OAB versus 34% non-OAB; RR = 1.4) urinary tract infections (42% OAB versus 17% non-OAB, RR = 2.4), and depression (21% OAB versus 12% non-OAB, RR = 1,8) all p< 0.001. The authors pointed out that this is the first study to evaluate the treatment costs of OAB in over-65 year individuals using "real-world" Medicare claims data.

In the last 4 years, the Committee found 3 publications reporting a new trend towards conducting Internet studies of the Burden of Disease associated with OAB. Because of difficulties in achieving telephone surveys, researchers have moved towards internet surveys, however the Committee feels that such method can be subject to considerable bias.

For example, Kannan et al[97] reported an internet survey in 2009 that was actually conducted in 2006, in which 62,833 American subjects who were members of an industry-based feedback panel were questioned as to whether they had LUTS or OAB. The survey compared 13,954 men and women with LUTS/OAB (comprising 24% of the survey population) with age matched subjects having similar comorbidities. They found that subjects with LUTS/OAB had approximately US $ 1,000 more health care costs per annum. They concluded that the projected costs of LUTS/OAB were US$ 51 Billion per annum more than age/comorbidity matched controls. However, in Discussion, the authors admitted that the study was quite biased towards subjects who were connected to the internet, yet not fully employed, i.e. having sufficient time to enroll in the Industry Feedback Panel.

A similar internet study was reported by Onukwugha et al [98], derived from the Epi LUTS study, which yielded a projected LUTS/OAB cost of 24.9 billion US$. Neither of these projected costs agrees with other cost estimates from non-internet based studies.

Finally Ganz et al [99] performed an overall estimate of the costs of OAB, which used a panel of expert urologists in Boston USA, via a Delphi technique to obtain consensus on the model. The authors accumulated all known costs for OAB, including patients in nursing homes. They projected costs based upon known projected prevalence figures, with respect to the ageing of "baby boomers" (**Figure 11**) showing a projected marked increase in OAB costs as this cohort "swells" the numbers of elderly in the community.

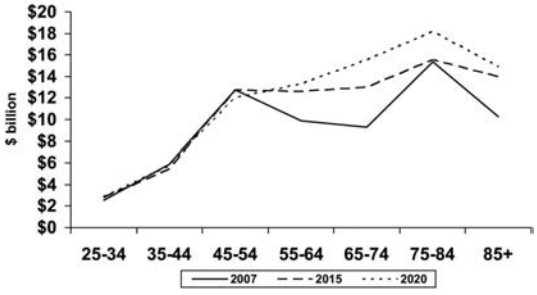


Figure 11. Total national costs of overactive bladder, United States. Reproduced from Ganz et al., 2010[99] with permission.

7. PROLAPSE TREATMENTS, COST IMPLICATIONS

Despite the high prevalence of pelvic organ prolapse and frequency of surgery for prolapse, there are minimal data on costs or cost-effectiveness of medical care for this condition

In the previous chapter, we reported an important cost of illness study from 2001, regarding the annual treatment cost of surgery for pelvic organ prolapse in the U.S. [100]. Treatment costs of pelvic organ prolapse surgery were US$1,012 million (1997 US$; 95% CI 775-1,251 million). Hospitalization accounted for a majority of the total cost (71%) with the remainder being physician services (29%). Twenty-one percent of pelvic organ prolapse operations included urinary incontinence procedures (US$218 million). The annual treatment costs of operations for pelvic organ prolapse are substantial and similar to other surgical interventions for women (breast cancer, gynecologic cancer, urinary incontinence).

In 2009, Subramanian et al. [101] estimated the rate, type and costs of surgical interventions for pelvic organ prolapse (POP) in Germany, France, and England. They identified hospital admissions for pelvic floor surgery in 2005 from national hospital activity databases in each country: the German Hospital Episode, the French Medical Care Program Information System, and the National Health Service England Hospital Episode Statistics. Costs to the payer were estimated using the Diagnosis-Related Group reimbursement rates for each country. In 2005, the number (rate) of admissions for POP surgery was 36,854 (0.87 per 1000 women) in Germany, 36,679 (1.14 per 1000 women) in France, and 28,959 (1.13 per 1000 women) in England. Admissions for POP surgery constituted 10.4%, 16.7% and 16.9% of all admissions for female genital tract therapeutic interventions in Germany, France and England, respectively. At least 20% of hysterectomies were performed for the primary indication of POP. 57.4%, 45.0%, and 40.1% of all admissions for POP surgery included a hysterectomy. The costs to payers were €144,236,557, €83,067,825, and €81,030,907 in Germany, France, and England, respectively. These data effectively document the substantial burden and costs associated with POP surgery in the three countries studied using generalizable data and appropriate methods.

A multicentre international randomized controlled trial of pelvic floor physiotherapy for mild to moderate prolapse (the POPPY study) was published as an abstract in 2011[102]. A total of 447 women were randomized to either 5 physiotherapy visits over 16 weeks, or were given written instructions about lifestyle advice re constipation, obesity etc. Although the POPSS quality of life test [103] was employed, and showed significant benefit for physiotherapy treatment, the authors had not been able to find a QALY test that was responsive to change for prolapse treatment in the literature. The net cost of active physiotherapy treatment was £127 per patient, yielding an average decrease in POP-SS of 1.52 points. This would approximately equate to a 10% improvement in quality of life for one year, yielding a cost per QALY of £16,000.

In 2011, Hullfish and colleagues from the UK [104] developed a Markov model to compare the relative cost effectiveness of treatments for post-hysterectomy pelvic organ prolapse (POP), including expectant management, use of a pessary, and surgery. They used probabilities from published studies and expert consensus and generalizable national costs from national charge data from the 2007 Healthcare Costs and Utilization Project Nationwide Inpatient Sample adjusted for all payor cost to charge ratio. They could not identify published HRQOL or utility scores for POP conditions, so estimated these based on a range of 1.0 for repaired POP without complications to 0.0 for major complication or re-operation. Over a 1 year timeframe, initial pessary use was the least expensive and had the lowest QALY. Vaginal reconstructive surgery had the highest QALY. Unfortunately, the results were not presented as incremental analyses so they are difficult to interpret. Sensitivity analysis demonstrated that these baseline results depended on several key estimates in the model: probabilities of POP complications, surgery following pessary use, and late complications following surgery, utility of pessary use, and the cost of robotic assisted surgery.

In 2011, Murray et al. [105] investigated the cost of traditional anterior colporrhaphy (AC), hand-cut mesh, and mesh kit anterior vaginal prolapse (AVP) repair using a decision analysis model. The model included mean operating room (OR) times, mesh extrusion rates, and recurrence rates obtained from a meta-analysis and Medicare reimbursement for surgeon fees and office visits, and hospital costs of supplies, OR time, and room and board. Non-kit mesh repair was $3,380, AC $3,461, and mesh kit $4,678. One-way sensitivity analyses demonstrated recurrence rate of AC would need to be 28% to be cost equivalent to non-kit mesh repair and the non-kit mesh cost must be < $480 (basecase $400) to remain less expensive than AC. Mesh kit repair did not reach cost equivalence, even with an OR time of 0 minutes. Two-way sensitivity analysis comparing mesh extrusion and AC recurrence demonstrated AC is less costly if recurrence is <20% or extrusion >25%.

As per our previous report, a Cochrane review of surgeries for the management of pelvic organ prolapse emphasized the importance of CEA and CUA [106]. They observed that abdominal sacrocolpopexy is associated with a lower rate of recurrent vault prolapse and dyspareunia than the vaginal sacrospinous colpopexy yet these benefits must be balanced against a longer operating time, longer time to return to activities of daily living and increased cost of the abdominal approach. Similarly, the use of mesh or graft

inlays at the time of prolapse repair may reduce the risk of recurrence and the addition of a continence procedure to a prolapse repair operation may reduce the incidence of postoperative urinary incontinence. Yet, these benefits needs to be balanced against possible differences in costs and adverse effects, which have not been assessed and, like surgical treatment for stress incontinence, are inherently appropriate for CEA since there may be differences between procedures in costs, clinical outcome and health-related quality of life.

Maher et al. [2004] performed a randomized trial of abdominal sacral colpopexy vs. vaginal sacrospinous colpopexy to treat vaginal vault prolapse among 95 women [107]. Secondary outcomes included the impact on cost (measured as Australian bed and operating theater costs) and general- and incontinence-specific quality of life. Two years after the operation, the subjective and objective success rates were similar between groups. The abdominal approach was associated with a longer operating time, a slower return to activities of daily living, and a greater cost than the sacrospinous colpopexy (P<.01). Both surgeries significantly improved the patient›s quality of life (P<.05). These data suggest that formal cost-utility analysis would be beneficial to further compare these two common procedures for pelvic organ prolapse. Additional data with generalizable costs and utility measures and long-term efficacy outcomes are needed.

In the chapter of this text regarding surgery for pelvic organ prolapse (Chapter 15), the authors give further references that provide surgical cost data for a variety of procedures, such as laparoscopic sacrocolpopexy, robotic sacrocolpopexy, versus abdominosacrocolpopexy, and laparoscopic sacrocolpopexy versus total vaginal mesh procedures. Readers are referred to that chapter for details, however no Utility measures were provided in these reports.

8. FECAL INCONTINENCE

a) Cost of illness

In the previous chapter, several cost of illness studies regarding faecal incontinence were reported. However these studies mainly employed previously collected databases[108, 109], or focused upon inpatients [10], subjects with constipation as the main complaint [108], women with faecal incontinence after obstetric injury [110]. Few conducted face-to-face direct enquiry of the personal costs of leakage of faeces[10]. Most did not employ a validated measure of severity [10, 108-110]. Deutekom et al[111] from the Netherlands did measure treatment and non-treatment costs along with the Vaizey continence score, no QALYs were measured and the relationship between cost and severity was not explored.

In 2011, Parkin et al[112] conducted personal interviews with a consecutive sample of 54 ambulatory home dwelling men (5) and women (49) patients who presented with faecal incontinence to a tertiary outpatient Unit, to collect cost data prior to the onset of treatment in relation to baseline severity as measured by St Marks score[113], maximum score 24 points.

Costs were determined by administering a 3 page questionnaire, modelled on the DBICI questionnaire for urinary incontinence[114]. Interviews were conducted face to face, taking approximately 15 minutes each. The information included basic personal hygiene costs (pads, laundry, wipes, cleansers), medication costs (loperamide, creams & stool bulking agents etc) and diagnostic costs (including medical attendance, anorectal physiology, colonoscopy). Following each interview, the personal hygiene items used by patients were costed from known tables compiled by visiting local pharmacies and suppliers. Costs were recorded in AU$.

The median age was 69.5 (IQR 61.5-74) and the major personal expense was for pads and personal hygiene items (median 70.89 per annum, IQR 0.63-310.68). Medicare costs included medical consultation and rebates for physiology testing and endoscopy (median $576.92 IQR). There was no relationship between these overall costs and incontinence severity. The Spearman rank correlation showed no significant relation between total personal costs and severity (r=0.21). When the costs just for pads and creams alone was evaluated, a relationship became apparent (r= 0.34, p=0.05, **Figure 12**).

b) Prevention

The cost effectiveness of two sphincter preserving treatments for anal fistula (anal fistula plug versus endoanal advancement flap) in the treatment of cryptoglandular fistulae to prevent faecal incontinence was studied by Adamina et al in 2010 [115]. The primary end-points were absence of drainage and fistula openings on physical examination at 6 months and absence of abscess formation at any time during follow-up.

This was a microcosting analysis of treatment costs, adjusted for inflation. Non-medical costs and lost productivity costs were not assessed, sensitivity analyses were performed. The study was flawed in that the success rates of healing in advancement flap group were lower than the majority of published studies on this technique. Cost-effectiveness was based on healing and complication rates, with no direct measurement of faecal incontinence. Use of the anal fistula plug saved $1,588 US per healed fistula.

Tan et al (2008) studied the cost effectiveness of primary sphincteroplasty versus delayed sphincteroplasty for anal sphincter injury, in the prevention of faecal incontinence [116]. They constructed a decision tree analysis over 10 years. QALYs were derived from SF36, but no direct QALY tests were measured. The primary sphincteroplasty was associated with a gain of 5.72 QALYs for a cost of £2,750,

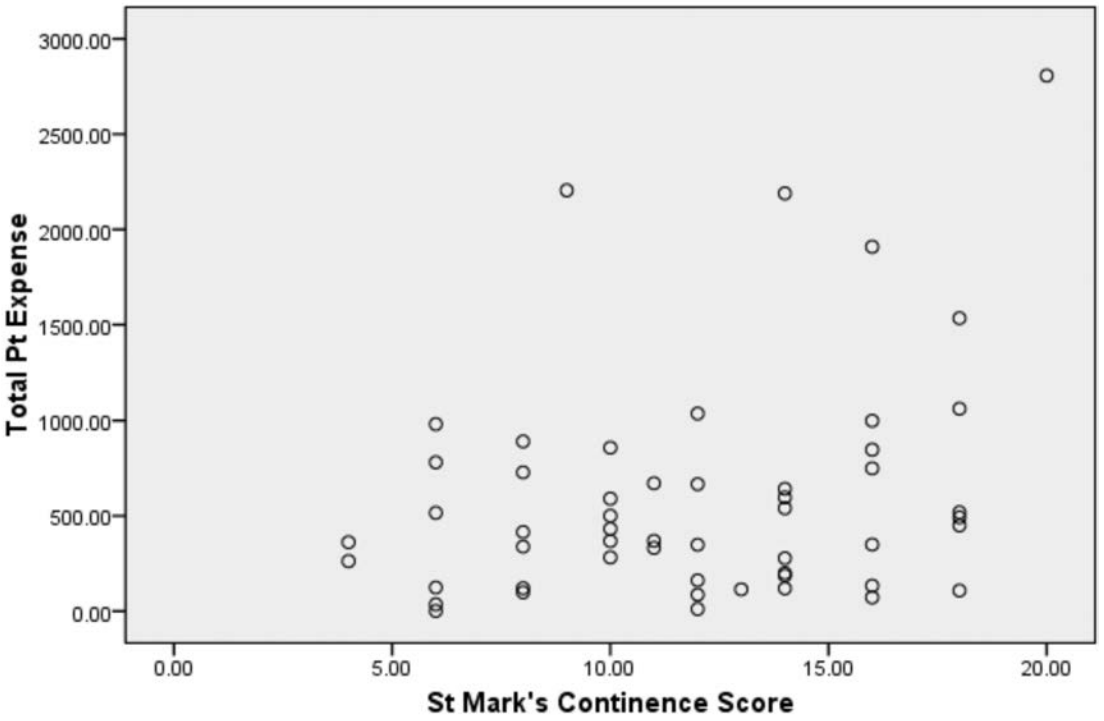


Figure 12. Total personal costs vs incontinence severity St Mark's score

the delayed sphincteroplasty yielded a QALY gain of 3.73 for a cost of £2,667, thus the primary sphincteroplasty was judged to be cost effective.

c) Treatment costs

Reflecting the increased use of sacral nerve stimulation (SNS) as a first-line surgical treatment for patients with faecal incontinence, recent cost-effectiveness analyses have primarily focused on this therapy. Brosa et al (2008) performed a cost effectiveness study of Sacral Neuromodulation for the treatment of faecal incontinence[11]. In their decision tree, they employed two decision pathways, firstly, for patients with an intact anal sphincter (IAS) and secondly for patients with a structurally deficient anal sphincter (SDAS) who had previously undergone a sphincteroplasty. Two of the authors worked for the Medtronics company (international makers of sacral neuromodulation equipment), and "4 authors received an unrestricted grant from Medtronics".

Because recent NICE guidelines recommend Sacral Nerve Stimulation (SNS) as first line therapy in patients with an intact sphincter, and as second line therapy in those with a deficient sphincter[117], their aim was to evaluate the previous scenario (no option to perform SNS) with a new decision tree that included SNS. QALYs were obtained from Deutekom et al [118], [ie for patients with faecal incontinence QALY = 0.68, for patients with no faecal incontinence QALY = 0.87]. Costs were obtained from Spanish Health Costs Database[119]. Temporary SNS evaluation cost €1,484, whilst permanent SNS cost €10,700. Other treatments in the model were more expensive, such as Dynamic graciloplasty €12,000 and Artificial Anal Sphincter €12,000 (taken from Spanish DRG figures).

The timeline for the model was 5 years, with 3% discount rate per annum. Prevalence figures and Medtronics sales forecast were used to estimate numbers of patients likely to receive SNS over the next 5 years, to perform Budget Impact Analysis. Monte Carlo simulation analysis was performed for a cohort of 1,000 patients (i.e. Bootstrapping, see Methods of this chapter) to test sensitivity.

The results of their decision tree analysis showed that patients obtained an additional symptom free year of 0.31 and 0.34 per patient per 5 years in the two pathways respectively. In patients with an intact sphincter, SNS had a cost of €16,181 per QALY gained; for those with a deficient sphincter, SNS cost €22,195 per QALY gained. Budget Impact Analysis on the basis of 75-100 expected patients per annum would yield a budget impact of 0.1% in patients with faecal incontinence.

The authors commented that dynamic graciloplasty in 123 patients yielded complications in 74% of patients with a total of 189 complications [120]. Artificial anal sphincter was performed in 112 patients with 51 patients required a total of 73 further reoperations with 41 (36.6%) subjects requiring device removal [121]. No corresponding figures for reoperation rates were given for those undergoing SNS.

The relationship between the Markov model developed in the above paper by Brosa et al [11], and a patient cohort study published by a similar group of authors [122] also from Spain in the same year, is unclear. In the paper from Munoz-Duyos et al.,[122] patient level cost data is given for 57 temporary evaluations under local anaesthetic in 47 patients, giving a success rate of 61% (which is lower than many other publications). Permanent SNS devices were implanted in 29 patients, who were followed for a median of 3 years.

The study was reported on an intention to treat basis over a five-year time horizon. Only treatment costs were evaluated. The actual Markov model was not provided. Costs were not discounted. No sensitivity analysis was performed. It is unclear how the QALY were determined, as no QALY tests were administered, and data arising from calculating QALYs from SF36 were quoted as being derived from the paper by Brosa et al [11]. Thus it appears that this report from Munoz-Duyos [2008] was in some aspects a duplicate of the earlier Brosa paper [11, 122].

Despite this paper being entitled a "cost effectiveness study" there was little individual cost data given, for example, the temporary evaluation cost was €397, and the SNS permanent device cost was €10,178. Mainly, group totals of costs were given, for example, operating room costs of €26,000 for all the temporary evaluations, and €17,000 for all SNS implantations in the study group. Thus the majority of costs were associated with implantation of the permanent SNS device (due to upfront device costs).

In patients with an anatomically intact anal sphincter, SNS versus maximum conservative treatment had an ICER of €16 181 per QALY gained, well within the €30 000 per QALY threshold accepted in Spain.

In 2010, Indinnimeo et al. [12] from Italy, published a cost effectiveness study of SNS based on the decision tree model of Brosa (who was a co-author of this paper also)[11]. The decision tree parameters appeared to be identical, based on the same NICE guidelines, but cost data from the Italian NHS reimbursement list were substituted. For example, the cost of temporary evaluation of SNS was €6,400, the cost of permanent implantation of SNS was €6,400, the cost of dynamic graciloplasty was €8,760 and the cost of artificial anal sphincter was €4,620 (as shown in **Table 1**, earlier in this chapter).

Clinical data were obtained from published studies and from "expert" panel consensus. Note should be made that one of the authors worked for Medtronic Italia and that some data on SNS were taken from a review in which the majority of patients were implanted using an open surgical rather than percutaneous technique. Treatment success was defined as "the cessation of the patient to seek further treatment due to a satisfactory reduction of incontinent episodes with the therapy". Measurement of success was based on outcome at 6-month follow-up and it was assumed that loss in efficacy over time for each treatment was equal. The committee felt that this may have biased the results, as generally (for example) the efficacy of sphincter repair declines with time (80% ‹success› at 1 year, 50% at 5 years, 20% at ten-years [123]). In contrast, loss of efficacy with SNS is more likely to occur in the first year (in the absence of device failure).

There were several difficulties regarding the design of the decision tree. Firstly, the study assumed that all patients with a structurally deficient anal sphincter should undergo sphincter repair. Structural deficiency was defined as damage up to 120 degrees in radial extent affecting partial or full length of the internal or external anal sphincter, or both.

No reference was given to sphincter function in assessing the role of sphincteroplasty.

The Committee felt that in real life, those with partial length defects or isolated internal anal sphincter defects would not be considered for sphincteroplasty; only patients with full length defects with adequate residual muscle bulk and function would generally be considered for sphincter repair.

Generally, the indications for sphincter repair or dynamic graciloplasty are end-stage faecal incontinence in the presence of a substantial muscular defect and / or neural defect of the anal sphincter. However, the Decision Tree analysis assumed that all patients (even those with intact anal sphincters) would undergo one of these operations, which seems to make the model flawed in the case of patients with an intact anal sphincter.

Secondly, the model also assumed that of those undergoing a neo-sphincter procedure, 95% would undergo dynamic graciloplasty and only 5% artificial anal sphincter. The Committee felt that artificial anal sphincter is more readily performed in current clinical practice, with the recent understanding of poor long-term outcome of dynamic graciloplasty. Only 65 DG were performed in 21 European Centres in 2011 (Personal correspondance Medtronic Inc.). Finally, the model indicates that colostomy achieved 100% continence. In practice patients may still be incontinent of mucous which can cause considerable morbidity and impact upon quality of life.

The cost utility analysis revealed an ICER (€ per QALY gained) of €28,285 in those with sphincter defects, and €38,662 in those with intact sphincters. These results were within €40,000 acceptability threshold of the Italian NHS. Their Budget Impact Analysis appeared to give a low estimate of the total number of patients being treated with SNS (that is 86 to 115 patients per year over five year period in a population of 48 million people).

Mitchell et al [2011] performed economic analysis of the use of local anaesthetic (LA) versus general anaesthetic (GA) for insertion of temporary test electrodes (single electrode helical wires were used rather than tined quadripolar leads) [124]. Because LA was used, determining the optimal site for electrode placement was based upon sensory perception of the stimulus effect, rather than motor response. However, one third of patients undergoing SNS are known to have poor sensory localization and are unable to define the exact location of the stimulus making electrode placement difficult [125].

This was a retrospective cohort study of 111 consecutive age and sex matched patients, 42% of patients had LA which cost £613, and 58% had GA which cost £743, yielding a saving of £130 for the LA cases.

All were planned as day case procedures, but 89% of LA patients went home that day versus 62% of GA cases. A greater proportion of patients had success in the GA group (77% versus 64%). The small sample size resulted in a modest effect and a large standard error with non-significant effects. Reduced cost with the LA procedure was not correlated with effectiveness, so it is difficult to make conclusions about the outcome of study.

In late 2009, Dudding et al [13] performed a cohort analysis of 70 consecutive patients treated with SNS at a single UK institution over a ten-year period [1996-2006] with subsequent followup for approximately 2 years, which was then projected over a 7 year time horizon. Unlike the previous publications, these authors collected data prospectively at the patient level for baseline cost information and evaluated actual success, failure and complications, which comprised the Decision Tree analysis (as previously shown in **Fig**. **2**, Decision Analysis).

All of the patients had failed standard conservative therapy, and these costs were assessed at baseline, for comparison with subsequent intervention with SNS. A societal perspective was taken and sensitivity analysis was performed.

Treatment and non-treatment costs were assessed. The treatment costs were taken from UK national tariff and health resource group codes. Face to face data on routine care costs was not collected but careful calculations of typical costs of pad usage, loperamide consumption, outpatient visits etc were undertaken.

The non-treatment costs were derived from publications regarding time off work [110, 126, 127] and loss of work productivity[111, 128], from non-British sources, yielding a figure of £912 per patient per annum (which may not have been applicable to the UK population studied).

QALY data were calculated from conversion of elements of the Short-form 36 questionnaire, which is a standard methodology [26], although it must be noted that the SF-36 was not designed for economic evaluations. Inconsistencies can occur with this conversion which makes it possible for a patient with a better health state to record a lower QALY value than a patient with a worse health state [129].

Because the study included a self-selected group of patients who had failed to benefit from conservative treatments, it may not be representative of all patients who undergo conservative management for faecal incontinence (many of whom do achieve success from conservative treatment).

All procedures were performed under general anaesthesia, but the costing for short stay procedures was such that this had little economic effect. The cost for temporary evaluation was £510, the cost of permanent SNS implant was £8,480. **Figure 2** shows the clinical pathway with resultant success rates and complication rates of this patient cohort (earlier in this chapter). Complications occurred in nearly 20% of patients (several were mild but required some form of medical intervention); these were carefully costed in the manuscript at the patient level. The basic conservative regime cost £596 per QALY gained, and SNS cost £2159 per QALY gained. Sensitivity analysis was performed to assess robustness of the model and rates were discounted by 3.5%. Including all treatment and non-treatment costs the ICER for SNS was £25,070 per QALY gained. This equates to £1038 more per year to treat patients with SNS for a median reduction in 286 incontinent episodes (£3.63 per episode reduced). Lost productivity make up a large proportion of the total cost of faecal incontinence and this was reflected in this study. When lost productivity was included, the ICER was reduced to £12,959 per QALY gained for SNS versus conservative therapy.

In conclusion the ICER of £25,070 per QALY gained was within the £30,000 per QALY threshold recommended by the UK National Institute of Clinical Excellence as an effective use of UK NHS funding (**Figure 2**).

In 2009, Dudding and Nugent[130] published an abstract which compared the costs of using a permanent quadripolar tined lead electrode for temporary testing as part of a staged implant versus the single electrode helical wire as part of a two-stage procedure. This was a decision tree analysis based upon published literature, which took into account success, failure and complication rates. On an intention to treat basis of 100 patients, a saving of £27.78 per patient can be made by adopting a staged implant strategy. They concluded that a permanent quadripolar electrode should be used for temporary SNS.

VI. SUMMARY AND FUTURE RESEARCH PRIORITIES

In the four years since the last ICI consensus conference, some high quality economic analyses of surgery for stress incontinence treatments have been published. The Committee notes that evidence regarding cost utility of outpatient therapies for stress incontinence remains limited, aside from the recent economic study of obesity treatment for this condition. However the economic analysis of therapy for overactive bladder syndrome requires greater effort, to encompass longer time frames and wider use of QALYs that can yield cost utility analysis (CUA). The Committee was disappointed to find that most of the recent economic studies of anticholinergic therapy did not include collection of raw QALY data.

In the last 4 years, the implementation of Sacral Nerve Stimulation for refractory detrusor overactivity has been the subject of several economic analyses, which are indeed important. However the Committee reiterates the need to collect primary data for QALY outcomes in future studies of this technique.

In the field of prolapse, it is not yet known whether any currently available QALYs are sensitive to treatment benefit, so that CUA may still not be feasible in this area. The recent POPPY study is to be commended for including patient-level cost data and quality of life information about conservative treatment.

As regards faecal incontinence, research into Cost of Illness remains rather preliminary, so that broader more long term studies are still needed. It is encouraging to see economic analyses of Sacral Nerve Stimulation in this field as well, however more data about Cost Utility in Faecal Incontinence is urgently needed.

As regards methodology, researchers need to consider carefully how they construct the model parameters for Decision Tree Analysis and Markov Models, so that "real life" assumptions are made. The gold standard remains Cost Utility Analysis in parallel with Randomized Controlled Trials, and we urge all clinicians to consider cost and QALYs as important outcome measures.

VII. APPENDIX – SEARCH STRATEGIES

We performed a comprehensive computerized medical literature search (PubMed) for the years 2007-2012 to identify all economic, health-related quality of life and cost-effectiveness analyses published on urinary incontinence, fecal incontinence or pelvic organ prolapse. Our initial search strategy was very broad and meant to be very sensitive but not specific. We performed a search for the following Medical Subject Headings (MeSH) and keywords: cost-effectiveness analysis, health care costs, quality-adjusted life years, costs and cost analysis, sickness impact profile, or utilities and urinary incontinence, overactive bladder, fecal incontinence, anal incontinence, uterine prolapse or pelvic organ prolapse. The initial searches were reviewed to identify articles appropriate for more detailed evaluation. Inclusion criteria were: urinary or fecal incontinence or prolapse as primary disease, data on costs available. Studies were excluded when they were a review or case-report.

REFERENCES

1. Darkow T, Fontes CL, Williamson TE. Costs associated with the management of overactive bladder and related comorbidities. Pharmacotherapy. 2005: 25:511-9
2. Wagner TH, Hu TW, Bentkover J, et al. Health-related consequences of overactive bladder. Am J Manag Care. 2002: 8:S598-607
3. Kanavos P, Reinhardt U. Reference pricing for drugs: is it compatible with U.S. health care? Health Aff. 2003: 22:16-30
4. Sung VW, Rogers ML, Myers DL, Akbari HM, Clark MA. National trends and costs of surgical treatment for female fecal incontinence. Am J Obstet Gynecol. 2007: 197:e1-5
5. Shwartz M, Young DW, Siegrist R. The ratio of costs to charges: how good a basis for estimating costs? Inquiry. 1995: 32:476-81
6. Wagner TH, Chen S, Barnett PG. Using average cost methods to estimate encounter-level costs for medical-surgical stays in the VA. Med Care Res Rev. 2003: 60:15S-36S
7. Barnett PG. Research without billing data. Econometric estimation of patient-specific costs. Med Care. 1997: 35:553-63
8. Jacobs P, Roos NP. Standard cost lists for healthcare in Canada. Issues in validity and inter-provincial consolidation. Pharmacoeconomics. 1999: 15:551-60
9. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds Cost-effectiveness in health and medicine. Oxford: Oxford University Press 1996
10. Morris AR, Ho MT, Lapsley H, Walsh J, Gonski P, Moore KH. Costs of managing urinary and faecal incontinence in a sub-acute care facility: a "bottom-up" approach. Neurourol Urodyn. 2005: 24:56-62
11. Brosa M, Munoz-Duyos A, Navarro-Luna A, et al. Cost-effectiveness analysis of sacral neuromodulation (SNM) with Interstim for fecal incontinence patients in Spain. Curr Med Res Opin. 2008: 24:907-18
12. Indinnimeo M, Ratto C, Moschella CM, Fiore A, Brosa M, Giardina S. Sacral neuromodulation for the treatment of fecal incontinence: analysis of cost-effectiveness. Dis Colon Rectum. 2010: 53:1661-9
13. Dudding TC, Meng Lee E, Faiz O, et al. Economic evaluation of sacral nerve stimulation for faecal incontinence. Brit J Surg. 2008: 95:1155-63
14. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Second edn, Oxford: Oxford University Press, 1997
15. Hu TW, Wagner TH, Bentkover JD, Leblanc K, Zhou SZ, Hunt T. Costs of urinary incontinence and overactive bladder in the United States: a comparative study. Urology. 2004: 63:461-5
16. Wilson L, Brown JS, Shin GP, Luc KO, Subak LL. Annual direct cost of urinary incontinence. Obstet Gynecol. 2001: 98:398-406
17. Monz B, Hampel C, Porkess S, et al. A description of health care provision and access to treatment for women with urinary incontinence in Europe -- a five-country comparison. Maturitas. 2005: 52 Suppl 2:S3-12
18. Adang EM, Engel GL, Rutten FF, Geerdes BP, Baeten CG.

Cost-effectiveness of dynamic graciloplasty in patients with fecal incontinence. Dis Colon Rectum. 1998: 41:725-33; discussion 33-4

19. Krahn M, Gafni A. Discounting in the economic evaluation of health care interventions. Med Care. 1993: 31:403-18

20. Ganiats TG, Carson RT, Hamm RM, et al. Population-based time preferences for future health outcomes. Med Decis Making. 2000: 20:263-70

21. Olsen JA. On what basis should health be discounted? J Health Econ. 1993: 12:39-53

22. Hetzer FH, Bieler A, Hahnloser D, Lohlein F, Clavien PA, Demartines N. Outcome and cost analysis of sacral nerve stimulation for faecal incontinence. Brit J Surg. 2006: 93:1411-7

23. Albo ME, Richter HE, Brubaker L, et al. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007: 356:2143-55

24. Lier D, Ross S, Tang S, Robert M, Jacobs P, for the Calgary Women's Pelvic Health Research G. Trans-obturator tape compared with tension-free vaginal tape in the surgical treatment of stress urinary incontinence: a cost utility analysis. BJOG. 2011: 118:550-6

25. Padmanabhan P, Scarpero HM, Milam DF, Dmochowski RR, Penson DF. Five-year cost analysis of intra-detrusor injection of botulinum toxin type A and augmentation cystoplasty for refractory neurogenic detrusor overactivity. World J Urol. 2011: 29:51-7

26. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002: 21:271-92

27. Johannesson M, O'Conor RM, Kobelt-Nguyen G, Mattiasson A. Willingness to pay for reduced incontinence symptoms. Br J Urol. 1997: 80:557-62

28. Torrance G. Measurement of health state utilities for economic appraisal: a review. Journal of Health Economics. 1986: 5:1-30

29. Hu TW, Wagner TH, Hawthorne G, Moore KH, Subak L, eds Abrams P, Cardozo L, Khoury S, Wein A, Economics of Incontinence. Plymouth: Health Publication Ltd. 2005,p 75-95

30. Hawthorne G, Richardson J. Measuring the value of program outcomes: a review of multiattribute utility measures. Expert Rev Pharmacoecon Outcomes Res. 2001: 1:215-28

31. Kaplan R, Anderson J, Gamiats T. the Quality of Well-Being Scale: rationale for a single quality of life index. In Walker S, Rosser R eds, Quality of Life Assessment: Key Issues in the 1990s. Dordrecht Kluwer Academic Publishers, 1993

32. Sintonen H, Pekurinen M. A fifteen-dimensional measure of health-related quality of life (15D) and its applications. In Walker S, Rosser R eds, Quality of Life Assessment: Key Issues in the 1990s. Dordrecht Kluwer Academic Publishers, 1993

33. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001: 33:337-43

34. Tincello D, Sculpher M, Tunn R, et al. Patient Characteristics Impacting Health State Index Scores, Measured by the EQ-5D of Females with Stress Urinary Incontinence Symptoms. Value Health. 2010: 13:112-8

35. Sintonen H. The 15D instrument of health-related quality of life: properties and applications. Ann Med. 2001: 33:328-36

36. Vaughan CP, Johnson Ii TM, Ala-Lipasti MA, et al. The Prevalence of Clinically Meaningful Overactive Bladder: Bother and Quality of Life Results from the Population-Based FINNO Study. Eur Urol. 2011: 59:629-36

37. Saarni SI, Harkanen T, Sintonen H, et al. The Impact of 29 Chronic Conditions on Health-related Quality of Life: A General Population Survey in Finland Using 15D and EQ-5D. Qual Life Res. 2006: 15:1403-14

38. Stach-Lempinen E, Kujansuu P, Laippala R, MetsÃ¤noja B. Visual Analogue Scale, Urinary Incontinence Severity Score and 15 DÃ—Psychometric Testing of Three Different Health-related Quality-of-life Instruments for Urinary Incontinent Women. Scand J Urol Nephrol. 2001: 35:476-83

39. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. Qual Life Res. 1999: 8:209-24

40. Rosser R. A health index and output measure. In Walker S, Rosser R eds, Quality of Life Assessment: Key Issues in the 1990s. Dordrecht Kluwer Academic Publishers, 1993

41. Abrams P, Cardozo L, Khoury S, Wein A, eds Incontinence. 4th ed. Paris: 4th International Consultation on Incontinence 2009

42. Subak LL, Brubaker L, Chai TC, et al. High costs of urinary incontinence among women electing surgery to treat stress incontinence. Obstet Gynecol. 2008: 111:899-907

43. Subak LL, Brubaker L, Chai T, et al. Urinary incontinence management costs decrease following burch or sling surgery for stress incontinence. Female Pelvic Med Reconstr Surg. 2010: 16:s51-s2

44. Jacklin P, Duckett J, Renganathan A. Analytic model comparing the cost utility of TVT versus duloxetine in women with urinary stress incontinence. Int Urogynecol J. 2010: 21:977-84

45. Gupta RD, Caiado M, Bamber L. An evaluation of the cost-effectiveness of duloxetine as a treatment for women with moderate-to-severe stress urinary incontinence. J Med Econ. 2006: 9:1-25

46. Patel BN, Smith JJ, Badlani GH. Minimizing the cost of surgical correction of stress urinary incontinence and prolapse. Urology. 2009: 74:762-4

47. Wu JM, Visco AG, Weidner AC, Myers ER. Is Burch colposuspension ever cost-effective compared with tension-free vaginal tape for stress incontinence? Am J Obstet Gynecol. 2007: 197:62.e1-5

48. Dumville JC, Manca A, Kitchener HC, et al. Cost-effectiveness analysis of open colposuspension versus laparoscopic colposuspension in the treatment of urodynamic stress incontinence. BJOG. 2006: 113:1014-22

49. Manca A, Sculpher MJ, Ward K, Hilton P. A cost-utility analysis of tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence. BJOG. 2003: 110:255-62

50. Wu JM, Siddiqui NY, Amundsen CL, Myers ER, Havrilesky LJ, Visco AG. Cost-Effectiveness of Botulinum Toxin A Versus Anticholinergic Medications for Idiopathic Urge Incontinence. The Journal of Urology. 2009: 181:2181-6

51. Wefer B, Ehlken B, Bremer J, et al. Treatment outcomes and resource use of patients with neurogenic detrusor overactivity receiving botulinum toxin A (BOTOX) therapy in Germany. World J Urol. 2009: 28:385-90

52. Robinson D, Jacklin P, Cardozo L. What's needling us about the management of refractory overactive bladder? An economic analysis of the use of Percutaneous Nerve Stimulation and Botulinum Toxin. Neurourol Urodyn. 2010: 29:1063-5

53. Aboseif SR, Kim DH, Rieder JM, et al. Sacral neuromodulation: cost considerations and clinical benefits. Urology. 2007: 70:1069-73; discussion 73-4

54. Arlandis S, Castro D, Errando C, et al. Cost-effectiveness of sacral neuromodulation compared to botulinum neurotoxin a or continued medical management in refractory overactive bladder. Value Health. 2011: 14:219-28

55. Leong RK, de Wachter SG, Joore MA, van Kerrebroeck PE. Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder. BJU Int. 2010: 108:558-64

56. Leroi AM, Lenne X, Dervaux B, et al. Outcome and cost

analysis of sacral nerve modulation for treating urinary and/or fecal incontinence. Ann Surgery. 2011: 253:720-32

57. Siddiqui NY, Amundsen CL, Visco AG, Myers ER, Wu JM. Cost-effectiveness of sacral neuromodulation versus intravesical botulinum A toxin for treatment of refractory urge incontinence. J Urol. 2009: 182:2799-804

58. Leong RK, de Wachter SG, Joore MA, van Kerrebroeck PE. Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder. BJU Int. 2011: 108:558-64

59. Van Voskuilen AC, Oerlemans DJ, Weil EH, van den Hombergh U, van Kerrebroeck PE. Medium-term experience of sacral neuromodulation by tined lead implantation. BJU Int. 2007: 99:107-10

60. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol. 2007: 178:2029-34

61. Subak LL, Brown JS, Kraus SR, et al. The “costs” of urinary incontinence for women. Obstet Gynecol. 2006: 107:908-16

62. Subak L, Van Den Eeden S, Thom D, Creasman JM, Brown JS, Reproductive Risks for Incontinence Study at Kaiser Research G. Urinary incontinence in women: Direct costs of routine care. Am J Obstet Gynecol. 2007: 197:596. e1-9

63. Subak LL, Pinto AM, Wing RR, et al. Decrease in urinary incontinence management costs in women enrolled in a clinical trial of weight loss to treat urinary incontinence. Obstet Gynecol. 2012: In Press, May 2012

64. Imamura M, Abrams P, Bain C, et al. Systematic review and economic modelling of the effectiveness and cost-effectiveness of non-surgical treatments for women with stress urinary incontinence. Health Technol Assess. 2010: 14:1-188

65. Haywood KL, Garratt AM, Lall R, Smith JF, Lamb SE. EuroQol EQ-5D and condition-specific measures of health outcome in women with urinary incontinence: reliability, validity and responsiveness. Qual Life Res. 2008: 17:475-83

66. Roine E, Roine RP, Rasanen P, Vuori I, Sintonen H, Saarto T. Cost-effectiveness of interventions based on physical exercise in the treatment of various diseases: a systematic literature review. Int J Technol Assess Health Care. 2009: 25:427-54

67. Ho T, Eastwood A, Kuteesa W, Short A, Moore KH. Incontinence after childbearing; Longitudinal analysis of direct costs of conservative and surgical therapy. Neurourol Urodyn. 2006: 25:513-4

68. Ho MT, Eastwood A, Kuteesa W, Short A, Moore KH. Incontinence after childbearing: long-term analysis of direct costs of conservative and surgical therapy. Aust NZ Continence J. 2012: 18:10-9

69. Mihaylova B, Pitman R, Tincello D, et al. Cost-effectiveness of duloxetine: the Stress Urinary Incontinence Treatment (SUIT) study. Value Health. 2010: 13:565-72

70. Brunenberg DE, Joore MA, Veraart CP, Berghmans BC, van der Vaart CH, Severens JL. Economic evaluation of duloxetine for the treatment of women with stress urinary incontinence: a Markov model comparing pharmacotherapy with pelvic floor muscle training. Clin Ther. 2006: 28:604-18

71. Ko Y, Malone DC, Armstrong EP. Pharmacoeconomic evaluation of antimuscarinic agents for the treatment of overactive bladder. Pharmacotherapy. 2006: 26:1694-702

72. Milsom IAN, Axelsen S, Kulseng-Hansen S, Mattiasson A, Nilsson CG, WickstrØM J. Cost-effectiveness analysis of solifenacin flexible dosing in patients with overactive bladder symptoms in four Nordic countries. Acta Obstet Gynecol Scand. 2009: 88:693-9

73. Chapple CR, Martinez-Garcia R, Selvaggi L, et al. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. European Urology. 2005: 48:464-70

74. Herschorn S, Vicente C, Piwko C. Canadian cost-effectiveness analysis of solifenacin compared to oxybutynin immediate-release in patients with overactive bladder. J Med Econ. 2010: 13:508-15

75. Speakman M, Khullar V, Mundy A, Odeyemi I, Bolodeoku J. A cost-utility analysis of once daily solifenacin compared to tolterodine in the treatment of overactive bladder syndrome. Curr Med Res Opin. 2008: 24:2173-9

76. Cardozo L, Thorpe A, Warner J, Sidhu M. The cost-effectiveness of solifenacin vs fesoterodine, oxybutynin immediate-release, propiverine, tolterodine extended-release and tolterodine immediate-release in the treatment of patients with overactive bladder in the UK National Health Service. BJU Int. 2010: 106:506-14

77. Kobelt G, Jonsson L, Mattiasson A. Cost-effectiveness of new treatments for overactive bladder: the example of tolterodine, a new muscarinic agent: a Markov model. Neurourol Urodyn. 1998: 17:599-611

78. Getsios D, El-Hadi W, Caro I, Caro JJ. Pharmacological management of overactive bladder : a systematic and critical review of published economic evaluations. Pharmacoeconomics. 2005: 23:995-1006

79. Chancellor MB, Kianifard F, Beamer E, et al. A comparison of the efficacy of darifenacin alone vs. darifenacin plus a Behavioural Modification Programme upon the symptoms of overactive bladder. Int J Clin Pract. 2008: 62:606-13

80. Abrams P, Kelleher C, Huels J, Quebe-Fehling E, Omar MA, Steel M. Clinical relevance of health-related quality of life outcomes with darifenacin. BJU Int. 2008: 102:208-13

81. Burgio KL, Kraus SR, Menefee S, et al. Behavioral therapy to enable women with urge incontinence to discontinue drug treatment: a randomized trial. Ann Intern Med. 2008: 149:161-9

82. Robinson D, Jacklin P, Cardozo L. Is cost the Achilles heel of posterior tibial nerve stimulation? A cost minimisation comparison with antimuscarinic therapy in the management of OAB. Neurourol Urodyn. 2009: 28:879-81

83. Chen HW, Bercik RS, Werner EF, Thung SF. Cost-effectiveness of percutaneous tibial nerve stimulation versus extended release tolterodine for overactive bladder. J Urol. 2012: 187:178-84

84. Wu JM, Fulton RG, Amundsen C. Quality of life for different overactive bladder severities and treatments. Female Pelvic Med Reconstr Surg. 2010: 16:s151

85. Morrison A, Levy R. Fraction of nursing home admissions attributable to urinary incontinence. Value Health. 2006: 9:272-4

86. Holroyd-Leduc JM, Mehta KM, Covinsky KE. Urinary incontinence and its association with death, nursing home admission, and functional decline. J Am Geriatr Soc. 2004: 52:712-8

87. Shih YC, Hartzema AG, Tolleson-Rinehart S. Labor costs associated with incontinence in long-term care facilities. Urology. 2003: 62:442-6

88. Bliss DZ, Zehrer C, Savik K, Smith G, Hedblom E. An economic evaluation of four skin damage prevention regimens in nursing home residents with incontinence: economics of skin damage prevention. J Wound Ostomy Cont. 2007: 34:143-52; discussion 52

89. Birnbaum H, Leong S, Kabra A. Lifetime medical costs for women: cardiovascular disease, diabetes, and stress urinary incontinence. Women Health Iss. 2003: 13:204-13

90. Fultz N, Girts T, Kinchen K, Nygaard I, Pohl G, Sternfeld B. Prevalence, management and impact of urinary incontinence in the workplace. Occup Med-Oxford. 2005: 55:552-7

91. Wu EQ, Birnbaum H, Marynchenko M, Mareva M, Williamson T, Mallett D. Employees with overactive bladder: work loss burden. J Occup Environ Med. 2005: 47:439-46

92. Reeves P, Irwin D, Kelleher C, et al. The current and future burden and cost of overactive bladder in five European countries. Eur Urol. 2006: 50:1050-7

93. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study.[Erratum appears in BJU Int 2001 Nov;88(7):807]. BJU Int. 2001: 87:760-6

94. Klotz T, Bruggenjurgen B, Burkart M, Resch A. The economic costs of overactive bladder in Germany. Eur Urol. 2007: 51:1654-62; discussion 62-3

95. Irwin DE, Mungapen L, Milsom I, Kopp Z, Reeves P, Kelleher C. The economic impact of overactive bladder syndrome in six Western countries. BJU Int. 2009: 103:202-9

96. Cisternas MG, Foreman AJ, Marshall TS, Runken MC, Kobashi KC, Seifeldin R. Estimating the prevalence and economic burden of overactive bladder among Medicare beneficiaries prior to Medicare Part D coverage. Curr Med Res Opin. 2009: 25:911-9

97. Kannan H, Radican L, Turpin RS, Bolge SC. Burden of illness associated with lower urinary tract symptoms including overactive bladder/urinary incontinence. Urology. 2009: 74:34-8

98. Onukwugha E, Zuckerman IH, McNally D, Coyne KS, Vats V, Mullins CD. The total economic burden of overactive bladder in the United States: a disease-specific approach. Am J Manag Care. 2009: 15:S90-7

99. Ganz ML, Smalarz AM, Krupski TL, et al. Economic costs of overactive bladder in the United States. Urology. 2010: 75:526-32

100. Subak LL, Waetjen LE, van den Eeden S, Thom DH, Vittinghoff E, Brown JS. Cost of pelvic organ prolapse surgery in the United States. Obstet Gynecol. 2001: 98:646-51

101. Subramanian D, Szwarcensztein K, Mauskopf JA, Slack MC. Rate, type, and cost of pelvic organ prolapse surgery in Germany, France, and England. Eur J Obstet Gyn R B. 2009: 144:177-81

102. Hagen S, Stark D, Glazener C, et al. A multicentre randomised controlled trial of pelvic floor muscle training intervention for women with pelvic organ prolapse. Neurourol Urodyn. 2011: 30:983-4

103. Hagen S, Glazener C, Sinclair L, Stark D, Bugge C. Psychometric properties of the pelvic organ prolapse symptom score. BJOG. 2009: 116:25-31

104. Hullfish KL, Trowbridge ER, Stukenborg GJ. Treatment strategies for pelvic organ prolapse: a cost-effectiveness analysis. Int Urogynecol J. 2011: 22:507-15

105. Murray S, Haverkorn RM, Lotan Y, Lemack GE. Mesh kits for anterior vaginal prolapse are not cost effective. Int Urogynecol J. 2011: 22:447-52

106. Maher C, Baessler K, Glazener CM, Adams EJ, Hagen S, Glazener CMA. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2007:CD004014

107. Maher CF, Qatawneh AM, Dwyer PL, Carey MP, Cornish A, Schluter PJ. Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study. Am J Obstet Gynecol. 2004: 190:20-6

108. Dunivan GC, Heymen S, Palsson OS, et al. Fecal incontinence in primary care: prevalence, diagnosis, and health care utilization. Am J Obstet Gynecol. 2010: 202:493.e1-6

109. Sung VW, Washington B, Raker CA. Costs of ambulatory care related to female pelvic floor disorders in the United States. Am J Obstet Gynecol. 2010: 202:483.e1-4

110. Mellgren A, Jensen LL, Zetterstrom JP, Wong WD, Hofmeister JH, Lowry AC. Long-term cost of fecal incontinence secondary to obstetric injuries. Dis Colon Rectum. 1999: 42:857-65; discussion 65-7

111. Deutekom M, Dobben AC, Dijkgraaf MG, Terra MP, Stoker J, Bossuyt PM. Costs of outpatients with fecal incontinence. Scand J Gastroentero. 2005: 40:552-8

112. Parkin K, Patton V, Lubowski D, Moore KH. A prospective "bottom up" study of the direct personal and investigation costs of faecal incontinence in ambulatory men and women in relation to severity. Neurourol Urodyn. 2011: 30:1098-9

113. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. Gut. 1999: 44:77-80

114. Dowell CJ, Bryant CM, Moore KH, Simons AM. Calculating the direct costs of urinary incontinence: a new test instrument. BJU Int. 1999: 83:596-606

115. Adamina M, Hoch JS, Burnstein MJ. To plug or not to plug: a cost-effectiveness analysis for complex anal fistula. Surgery. 2010: 147:72-8

116. Tan EK, Jacovides M, Khullar V, Teoh TG, Fernando RJ, Tekkis PP. A cost-effectiveness analysis of delayed sphincteroplasty for anal sphincter injury. Colorectal Dis. 2008: 10:653-62

117. Faecal incontinence: the management of faecal incontinence in adults. London: National Institute for Health and Clinical Excellence www.nice.org.uk/CG049; 2007

118. Deutekom M, Terra MP, Dobben AC, et al. Impact of faecal incontinence severity on health domains. Colorectal Dis. 2005: 7:263-9

119. Gisbert R, Brosa M. Base de Datos de Costes Sanitarios eSalud. Barcelona http:www.oblikue.com, 2006

120. Rongen MJ, Uludag O, El Naggar K, Geerdes BP, Konsten J, Baeten CG. Long-term follow-up of dynamic graciloplasty for fecal incontinence. Dis Colon Rectum. 2003: 46:716-21

121. Wong WD, Congliosi SM, Spencer MP, et al. The safety and efficacy of the artificial bowel sphincter for fecal incontinence: results from a multicenter cohort study. Dis Colon Rectum. 2002: 45:1139-53

122. Munoz-Duyos A, Navarro-Luna A, Brosa M, Pando JA, Sitges-Serra A, Marco-Molina C. Clinical and cost effectiveness of sacral nerve stimulation for faecal incontinence. Brit J Surg. 2008: 95:1037-43

123. Dudding TC, Vaizey CJ, Kamm MA. Obstetric anal sphincter injury: incidence, risk factors, and management. Ann Surgery. 2008: 247:224-37

124. Mitchell PJ, Cattle K, Saravanathan S, Telford KJ, Kiff ES. Insertion under local anaesthetic of temporary electrodes for sacral nerve stimulation testing is reliable and cost effective. Colorectal Dis. 2011: 13:445-8

125. McLennan MT. The role of electrodiagnostic techniques in the reprogramming of patients with a delayed suboptimal response to sacral nerve stimulation. Int Urogynecol J. 2003: 14:98-103

126. Malouf AJ, Chambers MG, Kamm MA. Clinical and economic evaluation of surgical treatments for faecal incontinence. Brit J Surg. 2001: 88:1029-36

127. Miner PB, Jr. Economic and personal impact of fecal and urinary incontinence. Gastroenterology. 2004: 126:S8-13

128. The Management of Faecal Incontinence in Adults: Final Scope, 2005. London: NICE; 2005

129. Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. J Clin Epidemiol. 1998: 51:1115-28

130. Dudding T, Nugent K. Staged versus dual procedure sacral nerve stimulation for faecal incontinence: A cost analysis. Colorectal Dis. 2009: 11 (suppl 2):26

Committee 23

Research Methodology

Chair

L. Brubaker

Members

I. Nygaard (US)

K. Bo (Norway)

D.G. Tincello (UK)

Y. Homma (Japan)

J. Cook (UK)

M.S. Choo (Korea)

J. Kusek (US)

S. Meikle (US)

C. Payne (US)

CONTENTS

I. INTRODUCTION

1. LEVELS OF EVIDENCE
2. PRIMARY GUIDING ETHICAL PRINCIPLES
3. INFORMED CONSENT IS AN ETHICAL CORNERSTONE OF HUMAN SUBJECT RESEARCH.
4. SPECIFIC INFORMED CONSENT IS REQUIRED FOR RESEARCH PARTICIPATION.
5. THE INVESTIGATOR HAS AN ETHICAL RESPONSIBILITY TO TAKE RESPONSIBILITY FOR ALL ASPECTS OF THE RESEARCH.
6. ENSURING PARTICIPANT SAFETY IS PARAMOUNT.
7. HIGH QUALITY DATA MANAGEMENT IS KEY TO PROVIDING VALID AND ETHICAL RESEARCH RESULTS. (41).
8. USEFUL WEBSITES:
9. FINANCIAL CONFLICTS OF INTEREST

II. DEFINING THE RESEARCH QUESTIONS

III. EXPERIMENTAL STUDIES

1. RANDOMIZED CONTROLLED TRIALS
2. NON-RANDOMIZED CONTROLLED CLINICAL TRIAL(S)
3. PRAGMATIC AND EXPLANATORY TRIALS
4. DRUG TRIALS ARE CATEGORIZED ACCORDING TO THE FOLLOWING DEFINITIONS (30, 50).
5. BIAS, BLINDING AND EFFECTS ON VALIDITY

IV. ELIGIBILITY CRITERIA

V. SAMPLING STRATEGIES

VI. DATA COLLECTION

VII. OUTCOME MEASURES

1. PRIMARY OUTCOMES
2. SECONDARY OUTCOME
3. TYPES OF OUTCOME MEASURES

VIII. SATISTICAL CONCERNS

1. SAMPLE SIZE CONSIDERATIONS
2. SAMPLE SIZE CALCULATION
3. THE TARGET DIFFERENCE

IX. ANALYSIS

X. REPORTING RESEARCH RESULTS

XI. SPECIAL CONCERNS FOR SPECIFIC STUDIES

1. BEHAVIORAL AND PHYSIOTHERAPY TRIALS
2. EXPERIMENTAL DEVICES AND MATERIALS
3. SURGICAL STUDIES
4. PHARMACOTHERAPY TRIALS

XII. COST ANALYSIS

XIII. RECOMMENDATIONS FOR SPECIFIC PATIENT GROUPS

1. MEN WITH LUTS
2. WOMEN WITH LUTS
3. FRAIL OLDER AND DISABLED PEOPLE
4. CHILDREN
5. NEUROGENIC POPULATIONS
6. RECOMMENDATIONS FOR RESEARCH IN POPULATIONS AFFECTED BY FAECAL INCONTINENCE
7. RECOMMENDATIONS FOR RESEARCH IN POPULATIONS AFFECTED BY BLADDER PAIN SYNDROME (INCLUDING INTERSTITIAL CYSTITIS)
8. RECOMMENDATIONS FOR RESEARCH IN POPULATIONS AFFECTED BY PELVIC ORGAN PROLAPSE

XIV. CONCLUSIONS

Research Methodology

L. Brubaker

I. Nygaard, K. Bo, D.G. Tincello, Y. Homma, J. Cook, M.S. Choo, J. Kusek , S. Meikle, C. Payne

I. INTRODUCTION

This chapter provides general recommendations for good research practice, including principles of clinical trial design and statistical methodology. In addition, we present specific recommendations applicable to trials for certain types of treatments and certain subgroups of patients.

1. LEVELS OF EVIDENCE

Most contributions to this consultation used the Oxford Centre for Evidence-based Medicine Levels of Evidence and Grades of Recommendation (http://www.cebm.net/levels_of_evidence.asp). However, as these are not an appropriate metric for recommendations in this chapter, the Research Committee used the following categories.

- High: Supported by strong evidence (multiple strong publications)
- Medium: Supported by moderate evidence (limited/moderate level publications)
- Low: Expert/Panel opinion

The report endorses consistent use of the methodology and approved terminology that will not only facilitate incontinence research by producing high quality studies but also facilitate communication about research. Recognized published guidelines produced by the International Continence Society (ICS) [1-15] and Society for Female Urology and Urodynamics (SUFU) [16-18] are useful examples of standardized terminology that advances communication in research.

Research is defined as "systematic investigation designed to develop or contribute to generalizable knowledge" [19] and participants accept risks to advance scientific knowledge and to benefit others [20]. The aim of clinical research in functional urology and urogynaecology is to evaluate treatments intended to prevent and/or significantly reduce symptoms of lower urinary tract dysfunction. The research methodology presented herein is intended to facilitate production of high-impact, high-quality research which will provide evidence needed to inform clinical practice, stimulate other investigators, generate new research ideas, and lead to a better understanding of physiology and pathophysiology of the human health and disease.

Although it is beyond the scope of this section to review the rules of conducting human subject research in depth and extensive coverage is available elsewhere [21-25], all investigators should understand the difference between "research" and "clinical practice". At a minimum, criteria for an ethical research study should meet the following criteria:

- the study should well planned, scientifically sound with clearly defined aims;
- clinical research should be prospectively registered whenever possible;
- the study should be feasible with a realistic chance for completion;
- there should be a reasonable assumption that new knowledge will be provided at the end of the study; and
- there should be an expectation that the results will be published to advance scientific knowledge [21, 26].

Human subject research protocols must be approved by an Institutional Review Boards (IRB), although IRB approval should be regarded only as a minimal ethical standard for research. Ultimately it is responsibility of the investigator to ensure the research is ethically acceptable.

2. PRIMARY GUIDING ETHICAL PRINCIPLES

There are 3 primary guiding ethical principles for human research outlined by the 1979 Belmont Report on "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" [27]. These principles are essential for ethical clinical research and are briefly reviewed in the following section.

a) Respect for Persons recognizes the voluntary nature of research participation and includes informed consent without undue influence.

b) Beneficence requires investigators to maximize

benefits and reduce risks to the subject. The primary concern of the investigator should be the safety of the research participant and careful consideration of the risk/benefit ratio; this includes an ongoing responsibility to monitor research and medical literature as the research proceeds. The investigator needs to critically consider within the expert medical community if there is clinical equipoise for the proposed interventions in their trial. Is one treatment no better than another? Are the research risks reasonable in relation to anticipated benefits? It is the responsibility of the investigator to ensure risks are minimized and potential benefits enhanced as well as that the knowledge gained outweighs the risaks [26]. Of note, invalid research cannot be ethical no matter how favorable the risk–benefit ratio for study participants.

c) Justice requires that the benefits and risks be distributed fairly (i.e. not only using people without access to health care, prisoners, or those impaired). Justice is of particular concern in Phase I testing of pharmacuetical agents and in early investigation of surgical devices/implants. Payment offered for participation in such drug trials may be extremely attractive to poor and disenfranchised subjects. Early device studies may target countries with lax regulatory environment even if there is little intent to market the device there in the long term.

3. INFORMED CONSENT IS AN ETHICAL CORNERSTONE OF HUMAN SUBJECT RESEARCH.

Peer review of protocols by a multidisciplinary team may include members of the scientific community, clinicians, pharmacists, the public/patient groups, the legal profession and individuals who can provide an ethical perspective. Each member of this team reviews the protocol from their particular type of expertise and in doing so aids in safeguarding patient health and well-being.

4. SPECIFIC INFORMED CONSENT IS REQUIRED FOR RESEARCH PARTICIPATION.

The length and depth of detail in consent forms vary widely between institutions. In the extreme, they involve exhaustive pages of information, which explain every alternative treatment with its pros and cons in detail. A general list of requirements for a consent form includes: name of the investigators and contact numbers, a detailed description of the new treatment and its known side effects, rationale for why the new therapy may be preferred to standard therapy. A summary table of the results of previous studies using the drug can be helpful when available. A statement that the patient may decline to be in the study with no subsequent consequence to their ongoing medical care is generally provided and whether or not remuneration is expected. Additionally, there should be a statement about payment for medical care required during the course of the study if there is an adverse event associated with the intervention. An understanding that the patient will be randomly assigned to treatment should be included when relevant, written using terms that are meaningful to potential participants [28-29].

5. THE INVESTIGATOR HAS AN ETHICAL RESPONSIBILITY TO TAKE RESPONSIBILITY FOR ALL ASPECTS OF THE RESEARCH.

This will insure that the work is done rigorously and to maintain the integrity of the research [30]. International Committee of Medical Journal Editors (ICMJE) now requires that information about trial design be placed into an accepted clinical trials registry prior to participant enrollment [31]. For more information, see more extensive information available elsewhere [30, 32-35]. A list of registries acceptable to the ICMJE can be found on their website. One objective of trial registration is to reduce publication bias given that trials with positive findings are more likely to be published than those with negative findigs. An important feature of one registry, clinicaltrials.gov, is a results database [36].

Consider this pragmatic, simple test to use when resolving an ethical research dilemma: “Imagine what you are preparing to do will be reported the next day on the front page of your local newspaper. If you are comfortable having colleagues, friends, and family know what you did, chances are you acted responsibly”.

6. ENSURING PARTICIPANT SAFETY IS PARAMOUNT.

An independent data safety monitor (DSM) or data safety monitoring board (DSMB) is important to evaluate the study on an ongoing basis to determine early evidence of significant harm or benefit [37-38]. Depending on the size, complexity, and risks of a trial, the DSMB is comprised of experts needed to monitor interim data to ensure the safety of the participants. The DSMB should be established prior to initiation of the trial. In addition to reviewing results of the study for safety monitoring they may evaluate interim analyses to ensure that a treatment is not producing unacceptable levels of side effects and/or efficacy [29, 37]. A priori stopping rules or boundaries are established to assess if the study should continue or be terminated due to futility (that is, no conclusion will be drawn due to low enrollment, few outcome events, or high drop out rates etc.), reaching an endpoint, or identifying increased risks. Guidelines for stopping the study should be agreed upon, prior to the start of the trial [30]. Interim analyses (in particular those based on efficacy) will have implications for the study power. Specialist statistical advice and support will be essential to address these issues [39, 40]. Investigators must not be aware of the results of interim analyses, however, since this may cause bias by influencing how vigorously any given patient is recruited into or followed up in the study, and most importantly, runs the risk of a type

II error (ie mistakenly concluding benefit when there is none). Nevertheless, emergency procedures for unblinding a patient's allocation are required in case of a severe side effect or concomitant serious illness where knowledge of treatment assignment is essential for patient management and safety.

7. HIGH QUALITY DATA MANAGEMENT IS KEY TO PROVIDING VALID AND ETHICAL RESEARCH RESULTS [41].

In addition, ethical conduct of research includes timely and complete reporting. Clear guidelines for authorship have been established by medical journals [42]. Beginning with the research contract, authorship rules should be established according to accepted guidelines. In general, authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

8. USEFUL WEBSITES:

- The National Reference Center for Bioethics Literature (http://bioethics.georgetown.edu/nrc/index.htm)
- International Bioethics Organizations Database (http://bioethics.georgetown.edu/databases/Organizations/index.htm)
- International Committee of Medical Journal Editors (http://www.icmje.org)

9. FINANCIAL CONFLICTS OF INTEREST

Many investigators are involved in testing new drugs or devices developed by industry and have the potential to significantly supplement to personal income. It is acceptable for investigators to receive contracted financial support to perform this research and a principled partnership between industry and investigators is essential if we are to preserve medical progress [43]. Financial conflict of interest policies have been developed due to ethical concerns about potential biases that may influence trial design, conduct, over interpretation of positive results or not publishing negative results [30, 44]. It is important that investigators do not receive money directly (personal income) from industry sponsors but rather through a research contract through an appropriate entity with research oversight capabilities. Disclosure of these relationships helps maintain scientific integrity and preserve public trust in the scientific process. This is a rapidly evolving area and investigators are encouraged to clearly understand and disclose such relationships.

An investigator's institution may have additional definitions and reporting requirements for financial conflict of interest disclosures. There are many potential relationships between physicians and industry; it is preferable that the nature of the relationship and its financial magnitude if any, be fully defined rather than categorized (i.e. "consultant") so that the reader can appropriately assess the disclosure.

II. DEFINING THE RESEARCH QUESTIONS

The investigator(s) should take a deliberate approach to formulate the specific research question, based on a careful review of related clinical research and relevant studies that are well designed and clinically relevant. The research reviews provided by the Cochrane Incontinence Group (http://healthsci.otago.ac.nz/dsm/wch/obstetrics/cure) provide an excellent starting point for most major incontinence topics. Based on a thorough literature review, the investigator clearly describes the primary research question(s), summarizes the background information, and formulates the rationale, objectives and hypotheses for the study. The investigator(s) should formulate the simplest study design which will provide the highest quality of evidence to test the given hypothesis in a cost and time-efficient manner. Whenever possible, basic or translational research should occur as part of the clinical research study in order to advance discovering of underlying mechanisms or pathophysiology. This balance between breadth and depth greatly increases the yield of the research effort [45].

III. EXPERIMENTAL STUDIES

1. RANDOMIZED CONTROLLED TRIALS

Experimental studies have the potential to provide a higher level of evidence than observational studies. The randomized double-blind clinical trial (RCT) is considered the gold standard study design. Properly planned and executed, the RCT is the optimal approach to limiting allocation bias [46]. The study participants are assigned to a treatment group by a random (chance) mechanism that ensures adequate concealment so that neither the study participant nor the investigator can influence treatment group assignment in order to reduce allocation bias. Subject assignment must be concealed during enrollment (for example, by separating allocation from the process of recruiting subjects, and by using remote randomization such as by telephone or web-based procedures), and wherever possible treatment allocation must be concealed during the trial (for example, using blinding with or without placebo). In order to minimize bias, the randomization process must be concealed from those recruiting subjects to the trial [48- 49). This can be achieved most effectively by the use of central telephone randomization.

In drug studies, a pharmacy can maintain identical treatment drug and placebo already randomly allocated into individual subject portions. These are distributed consecutively as subjects are enrolled in the study. In some studies, blinding of subjects and health care providers may not be possible, for example in trials of some surgical procedures or health care delivery methods. In almost all cases, however, the personnel collecting outcome data should be unaware (blinded) to the subjects' treatment allocation. RCTs require ethical equipoise and are usually expensive to conduct optimally.

The purpose of randomization is to produce groups that are, on average, comparable. A per-protocol analysis retains this property only in the unlikely situation when non-compliance is unrelated both to the patient's underlying state of health and the treatment received [50]. The intention-to-treat approach in pragmatic trials retains the full benefits of randomization and has the advantage that the comparison will more closely reflect the relative effectiveness of the treatments when applied in real clinical practice, where non-compliance is a common occurrence [51].

a) Simple randomization can use computer-generated random numbers, either prepared specifically for the trial or using existing tables of random numbers where the digits of 0-9 appear with equal likelihood in each entry. Treatments are assigned to odd or even numbers. As the total number of subjects in the trial increases, the balance of numbers and characteristics of subjects between the groups improves. In small trials, however, balance is not assured by simple randomization. Appreciable imbalances in subjects per group may be particularly important in a multicenter study where imbalances in assignment can occur within individual institutions.

b) Block randomization is one method used to prevent imbalances in subject numbers assigned to each group, particularly when the number of subjects in the trial is small. With block randomization, the total sample size is divided into blocks of a given size. Within each block, the group is assigned so that there are equal numbers allocated to each group. To prevent investigators from learning the block size and being able to guess order of assignment, the block size can be varied, usually at random from a small number of alternatives. In any case, blocking prevents serious imbalances in characteristics across groups when used in conjunction with stratification as described below.

c) Stratified randomization

Most disease states have factors known to influence the outcome of treatment, for example symptom severity or gender. A form of randomization that accounts for such factors is called stratified randomization [46-47]. Stratified randomization ensures equal distribution of subjects with a particular characteristic in each group when blocking is employed within strata. Stratification is usually restricted to a small number of factors, in particular those most likely to influence outcome. Despite its complexity, stratified randomization is usually helpful in a multicenter trial, so that both the numbers of subjects in each group and the important factors influencing the outcome can be balanced within each site. An alternative method exists to cater for more factors at once, known as minimization, where the characteristics of individuals already randomized alter in a systematic manner the chances of a given subject being allocated to the different trial groups, so as to maximize the resulting balance of these factors [46-47, 52].

Although the classical RCT involves the study of parallel groups, other options are possible and may overcome some of the limitations of the classical approach [53]:

d) Parallel Group Trials

This design generally includes one group of subjects assigned active treatment and a second (parallel) group a placebo or another treatment not believed to be an active treatment. The key feature of this design is that both groups (treatment and comparison group) are assembled and followed at the same time. In clinical trials of drugs the dose of the drug tested may be either a single dose or multiple doses to determine clinical benefit and/or minimize side-effects. More complex study designs can in some circumstances be worth considering – for example, factorial trials where two or more interventions can be investigated simultaneously [54-55], and cluster randomized trials whereby groups of participants (defined by some common feature, e.g. members of the same health maintenance organization, clinic, etc.) rather than individuals are randomly allocated to the trial arms [56]. This strategy might be employed when studying an intervention requiring policy changes in an institution, with a hospital, clinic, or health care system being the unit of randomization.

e) Crossover Trials

Subjects receive both the treatment being studied and the placebo/alternative treatment, with random order of treatment assignment. The benefit of crossover studies is that they eliminate the effect of variation between groups of participants seen in parallel trials, that is each subject serves as his/her own control. Crossover studies are particularly well suited for small studies, where the course of the disease under study is believed to be stable, and where the primary objective is to measure a short-term change in the outcome (e.g. urinary symptoms) in response to treatment. The duration of treatment required before the anticipated effect may be observed is critical in determining whether the crossover study design is appropriate – too long a period time before an effect becomes evident, and the disease state may vary before the study

participant has completed all arms of the trial; too short, and it may not be possible to detect the effect during the period of data collection. Carryover of treatment effects from one treatment period (or observation period if a placebo follows treatment) to another, make this a challenging study design to implement in many cases. To avoid a carryover effect, a washout period should be included, in which participants receive either placebo or no treatment. A run-in period in which signs and symptoms of the illnesses studied are monitored may be necessary before treatment begins to ensure that only those whose disease state is stable are entered into the study. Given all thesefeatures and limitations, this design is unlikely to be widely applicable in studies of interventions for incontinence.

There are two types of clinical trial designs that show the similarity of medical treatments: non-inferiority trials and equivalence trials.

f) Non-inferiority trials

the primary objective of a non-inferiority trial is to demonstrate that the new treatment is not unacceptably worse than that of the standard treatment. This design may be appropriate when one treatment is less costly , may offer advantages related to improved quality of life, or has fewer side-effects, and the current belief is that both treatments have a a similar effect on the disease or condition of interest . A key feature of this type of trial design is the ability to rule out a non-inferiority margin; that is, a minimum threshold for an unacceptable loss of efficacy [57-59]. As an example, if prior independent studies found similar effects of pelvic floor exercises and a drug in the treatment of stress incontinence, one might set up a study to demonstrate that no important difference in clinical effect was present between the two treatments by direct comparison. Currently there is considerable uncertainty about the design of non-inferiority trials as it relates to U.S. and European drug regulatory bodies [60-62]such that there have been recommendations to consider alternative designs [57]. Non-inferiority trials have been infrequently used in studies of urinary incontinence. A recent example is the Value of Urodynamic Evaluation (ValUE) trial, a non-inferiority randomized trial of preoperative urodynamic investigation in women undergoing stress urinary incontinence surgery [63].

g) Equivalence trials

The goal of an equivalence trial is to show that the experimental treatment is not more inferior and not more superior to a standard treatment by a given amount [64-66]. The clinically important difference between the standard treatment group and the new therapy is established prior to start of the study (Fleming TR 2000), and it is shown, by formal statistical testing, that the difference between the control and study treatments are not large in either direction (more beneficial or less beneficial). A recent trial of midurethral sling surgery illustrates this type of study design [67].

h) Superiority trials

The most common study design for clinical trials of urinary incontinence and for many other diseases/ conditions is the superiority trial where the goal is, in its most simple form, to show one treatment is better than another (or no treatment, placebo). The general approach is to establish a priori a clinically meaningful effect that you wish to detect. Once conducted, determining superiority requires that the findings permit the investigator to reject the null hypothesis that the two distributions of the treatment effect are equal, in favor of the new treatment being better than the control [58].

2. NON-RANDOMIZED CONTROLLED CLINICAL TRIAL(S)

This category includes trials in which treatment allocation is known to the investigator prior to obtaining informed research consent (for example, day of clinic appointment). This approach often results in baseline characteristics of the treatment groups being significantly different, decreasing the ability to interpretate trial results. Because of this major shortcoming, this type of study should be used rarely, if at all.

3. PRAGMATIC AND EXPLANATORY TRIALS

There is an important distinction between pragmatic and explanatory trials [68- 69], and correspondingly, between intention-to-treat and per-protocol approaches to data analysis [50, 70]. This distinction has a number of facets. In pragmatic trials the interventions are designed to be as close as possible to treatment options in clinical practice (including multiple patient management choices) and entry criteria are usually relatively liberal in comparison with explanatory trials. In addition, pragmatic trials may involve a wide variety of outcome domains, including patient-completed questionnaires, and an economic evaluation of outcomes. As a result of intention-to-treat data analysis, pragmatic trials will tend to yield lower estimates of treatment differences than explanatory trials. It may be of interest to gauge the effect of treatment given full compliance; therefore, full data analysis ideally incorporates both intention-to-treat and per-protocol approaches [50]. The primary analysis, though, should follow the intention-to-treat principle.

Data from pragmatic trials are analyzed by intention-to-treat, according to the group to which subjects were randomized, regardless of the extent of compliance with the intended treatment. In explanatory trials, data are analyzed accounting for compliance. This per-protocol approach may exclude serious non-compliers, analyze data according to treatment actually received, or allow for degree of compliance in a statistical model.

At first sight, the explanatory approach appears more attractive. However, there are considerable limitations to the explanatory approach, particularly when the intention is to draw inferences from the trial to wider clinical practice (generalizability).

4. DRUG TRIALS ARE CATEGORIZED ACCORDING TO THE FOLLOWING DEFINITIONS [30, 50].

a) Phase I studies

The first studies of a drug in humans, often open label and uncontrolled, concentrating on safety and frequently but not exclusively carried out in healthy volunteers. Pharmacokinetic and tolerance information is obtained from Phase I trials.

b) Phase II studies

The first attempts to investigate treatment efficacy, often the first use of the drug in subjects and focusing on short-term outcomes. A common objective of Phase II studies is dose finding in terms of efficacy. Two sub-types may usefully be distinguished: Phase IIA studies where single treatments are considered in relation to a minimum response prior to further investigation; Phase IIB where direct comparisons are made between interventions, albeit on a small scale and not necessarily involving randomization [71].

c) Phase III studies

Large-scale, authoritative randomized studies performed once the most likely effective and tolerated treatment regimens have been established. The objective is often to establish that the intervention is suitable for registration/approval with the appropriate regulatory authority. Trials are conducted after submission of a new drug application (NDA), but before the product's approval for market launch. Phase IIIB trials (between submission for approval and receipt of marketing authorization) may supplement or complete earlier trials, or seek different kinds of information (for example, quality of life or marketing). Phase III trials are also used to investigate the effectiveness and cost-effectiveness of various interventions – that is, non-drug including organizational issues – and not necessarily with reference to regulatory authorities. All Phase III trials should be subject to a formal sample size calculation – for instance to obtain sufficiently precise estimates of the comparisons between treatments or to have a reasonable chance (power) of detecting a difference if one exists (see section II C 7 below).

d) Phase IV studies

These investigations are usually carried out after registration/approval, to investigate the drug's safety and efficacy in different populations. Such post-marketing surveillance studies are typically larger and simpler than regulatory studies; they may lack a control group and are often conducted using surveys.

5. BIAS, BLINDING AND EFFECTS ON VALIDITY

Bias can be introduced at many stages of a study including patient selection, randomization, assessment of outcomes, and statistical analysis and interpretation. Bias occurs because of previously conceived ideas held by those involved, which consciously or unconsciously affect their actions and observations. In addition to observer bias, an amount of observer error is inherent in outcome measures that require clinical interpretation.

a) Blinding

In order to minimize bias, research design should strive for the highest practical level of blinding. Blinding is the process by which key elements of knowledge are withheld that can otherwise lead to bias. Blinding should not be confused with concealment of allocation, referring to withholding knowledge of assignment in advance, which is a prerequisite for the validity of any trial [48, 72]. While blinding is important, its effect is lower than that of concealment of allocation [73]. In most drug studies placebo pills allow blinding of all relevant participants.

b) Unblinded trials

They are conducted in an open manner where both subjects and study investigators are aware of which treatment has been assigned. While certain types of therapy may require investigation in this manner (e.g., some surgical trials), there remains considerable opportunity for bias. Both subjects and investigators may have preconceived ideas regarding the benefits of a particular treatment that can influence the reporting of symptoms and/or their outcome.

c) Single blind trial

Commonly, in a single blind trial, 'single blinding' may refer to blinding the outcome assessor (but not the subject); this is common in trials in which blinding the subject is not possible (such as pelvic muscle exercise trials). It is important to specify who is blinded to which aspects of study execution, rather than using only the vague term "blinded".Hence, in these studies the only possible blinded person is the assessor. It may be advantageous for the clinical staff to be aware of the assignment to allow them to monitor the health and safety of individuals, since the potential effects of the treatment (side effects) will often be known in advance. Single blinding ameliorates biased reporting of symptoms and/or side effects by subjects. However, clinical staff can influence data collection and change other aspects of subjects' care when they know which study treatment subjects are receiving.

d) Double blind trials

In double blind trials, both parties who could influence outcome are unaware of group assignment. Often this is just the subjects and the clinical team responsible for their care. Selection of an appropriate external comparison group is challenging and factors unknown or not measured by the investigators may adversely influence the findings.

IV. ELIGIBILITY CRITERIA

Eligibility criteria impact every aspect of a study's progress, from recruitment to analysis to acceptance of the study's results by the community. Yet, in the planning phase of a study, this vital aspect is often given short shrift. Eligibility criteria will differ, depending on the main goal of a study. For a Phase I trial, designed to understand safety of an intervention, eligibility criteria should be very narrow, and should focus on minimizing risk and maximizing ability to demonstrate proof of concept. A Phase II trial, designed to test the efficacy of a treatment in a fairly ideal population, will have broader eligibility criteria, but will exclude individuals in whom it is highly unlikely a treatment will be helpful, or highly likely that a treatment might be harmful. If a treatment shows promise at this point, eligibility criteria for a Phase III trial are as broad as possible, to test the effectiveness of the treatment in as real world of a setting as possible, thus maximizing generalizability. Conclusions can only be as broad as the eligibility criteria allow. Thus, a drug found to be effective in a study that included only healthy middle-aged people can be recommended for that group, but not for older people, children, people with medical conditions, or other groups excluded by the eligibility criteria.

While some **exclusion criteria** are necessary to reduce risk to potential participants, it is important to include individuals in whom the treatment would likely be used once widespread. For example, in testing a new drug for urgency incontinence, that is excreted by the kidneys, it is important to exclude people with high serum creatinine levels, but equally important to include older individuals with multiple co-morbidities in specific studies, as these are also likely to benefit from a drug for urgency incontinence once released.

Particularly in longer-term studies of pelvic floor disorders, some exclusion criteria are needed to maximize potential for follow-up. Such studies often exclude people likely to move or die during the study period, people with conditions that impair adherence (such as drug or alcohol dependence, severe mental illness or homelessness) or factors that make follow-up more difficult (such as lack of a telephone). For ethical reasons, it is important to either exclude people with significant cognitive impairment (such that informed consent is impossible) or to plan a consent process with a legally authorized representative in mind. However, all exclusions impact the generalizability of the conclusions and so such trade-offs must be carefully thought through.

Additionally, inclusion criteria related to the condition of study must be considered in concert with the consideration of the primary outcome measure. If an inclusion measure defines "disease", it is essential that the outcome measure does not include this same measure or cut-point as "success". For example, if a surgical trial comparing two treatments for pelvic organ prolapse defines prolapse as >/= stage II (and excludes from enrollment only women with </= Stage I prolapse) and the primary outcome measure defines successful treatment as prolapse at or above the hymen, then women enrolled with maximal prolapse at points 0 or -1 may be considered successfully treated when in fact, their condition has subjectively not changed. It is also important to note that a given condition, such as stress urinary incontinence, will be present or absent depending on which outcome measure is used to define it. Avoid using one outcome measure to exclude women from a study and then a different outcome measure defining the same condition as the primary outcome measure.

V. SAMPLING STRATEGIES

Every study must address its sampling strategy, that is, the selection of participants. In principle, sampling should involve random selection. In practice, however, this ideal is rarely met outside of large-scale epidemiological studies. For example, RCTs are drawn from a subset of the population, often limited to those with access to academic medical centers plus the willingness and ability to participate. Where this is the case, it is crucial to provide descriptive information about the study sample, so that its representativeness can be judged. Guidelines for reporting of RCTs include requirements to state the study population, give details of inclusion and exclusion criteria, and present clearly the numbers of eligible subjects who were not randomized and the reasons [32, 48- 49].

A study may require a sample that is representative of the community overall or one representative of patient groups suffering the condition/ disease. In principle, this is achieved by taking a simple random sample from a known population. In practice, a list of all eligible individuals is obtained and then a sample is drawn by a method in which each member of the population has an equal probability of selection ('epsem'). Even in ideal circumstances, however, some sophistication on this basic method is usually desirable or necessary. For example, in stratified sampling, subjects are arranged into subgroups and the sampling is performed within each subgroup separately. This ensures that the sample is representative of the population in terms of these subgroup character-

istics. In multi-stage random sampling, the population is first divided into primary sampling units (such as hospital, health center, or surgeon), and a sample of primary units is selected. The secondary sampling units, usually individual subjects, are selected within the primary sampling units. A special case of multi-stage random sampling is cluster sampling where all individuals within each primary unit are included. Standard procedures for sampling should be followed [56, 74].

It is important to note that, while the technicalities of random selection of subjects for a study are closely related to the random allocation of subjects in an RCT (and indeed there are similar issues in trials relating to stratification and clustering)[56], there is an important distinction in the objectives of the two procedures. First, the (ideally random) selection from the population of eligible subjects concerns the external validity or generalizability of the study findings (RCT or otherwise). Independent of this, the random allocation of subjects in an RCT is concerned with the internal validity or comparability of the trial groups. It is usually obvious whether the study can be performed at a single institution, or whether a multicenter study will be required. Single institution studies have the benefit of being less complicated from a logistical perspective. While multicenter trials are more complex to manage and are usually more expensive, they provide larger numbers of participants in a shorter period of time, and increase the generalizability of research findings.

VI. DATA COLLECTION

Although the number of questions in a single study should be limited, it is still relevant to record as many as observations as is possible without jeopardizing recruitment or retention with onerous demands. Strong consideration should be given to collection of the following data groups [16],[75].

a) Baseline data:

b) Observations:

1. Patient's observation/Subjective measures
2. Clinician's observation/Objective measures

c) Tests

1. Quantification of symptoms—bladder diary, and
2. Pad tests for incontinence outcomes
3. Urodynamics

d) Follow-up

e) Quality of life measures

f) Socioeconomics

It is useful to consider collection of the following variables:

- Age
- Race/ethnicity
- Gender
- Body mass index (height and weight)
- For women – obstetric history, including parity and menopausal status
- Smoking status
- Co-morbidities such as cardiovascular, respiratory and neurologic conditions and diabetes
- Medication use
- Past surgical history
- Level of education
- Mental and physical status
- Prior treatment for pelvic floor disorders, including behavioural, pharmacological and/or surgical interventions
- Sexual function

VII. OUTCOME MEASURES

Specific discussions of the most appropriate outcome measures for particular studies of incontinence and pelvic organ prolapse are discussed elsewhere in this consultation. The purpose here is to define the general concepts of primary and secondary outcomes, which are relevant to both sample size determination and data analysis. The distinction between these two sets of outcomes depends on the context of the trial, and should be decided at the planning stage of the study. Primary and secondary outcomes should not be confused with the distinction between primary and secondary analyses of trial data.

1. PRIMARY OUTCOMES

Primary outcomes are those viewed by the researchers to be of central interest. Sample size calculations are based on anticipated changes in the primary outcomes. The final study population may or may not be sufficient to allow robust comparisons of secondary outcomes. Trial results that are based on the primary outcomes can lead to reseponsible alterations in standards of patient care.

The number of primary outcomes in a particular trial will depend on the nature of the interventions and the number of independent domains. The number of primary outcomes is usually limited to three. Sample size calculation is based on the primary outcomes. The number and nature of outcome domains in a particular study will vary depending on the study's perspective. Careful selection of outcome measures

that are valid and clinically relevant is intrinsic to the success of research; usually no single measure can fully express the outcome of an intervention.

2. SECONDARY OUTCOME

Secondary outcomes can be relatively large in number. They are not the focus of the main study objectives and are rarely used directly in sample size estimation. Secondary outcomes are exploratory, i.e., as hypothesis-generating exercises for which independent confirmation is essential or used to monitor: e.g. safety, side-effects, costs or patient acceptance.

3. TYPES OF OUTCOME MEASURES

Traditionally, a patient's success after a particular treatment was reported by the physician, using subjective information that differed from physician to physician. Given the mismatch between physicians' and patients' perceptions of treatment effectiveness, this type of physician reported outcome measure has been largely replaced with patient-reported outcomes (PROs). The Food and Drug Administration defines a PRO as any report of the status of a patient's condition that comes from the patient, without interpretation of the response by the clinician or anyone else.

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf)

There is emerging consensus that PROs are most appropriate when describing success or failure of therapies. However, physician-reported outcomes can yield valuable information about mechanistic effects of therapies and are also vital in developing predictive data for future use. As an example, a patient's report of a bulge is a reasonable outcome measure for a study of surgical treatment for POP. However, if, over time, women with stage II POP after treatment who were initially asymptomatic became symptomatic, it would be pertinent to include prolapse stage, as an anatomic outcome measure, in the definition of success.

Other types of physician reported outcome measures (often called "objective outcomes"), used frequently in pelvic floor disorder research, include results obtained from urodynamic testing (e.g., presence or absence of detrusor overactivity incontinence), radiologic imaging (e.g., various angles measured during pelvic ultrasonography), physical examination (e.g., the POP-Q system for assessing pelvic organ prolapse), laboratory values, biomarkers, etc. , as well as tests collected by the patient but interpreted by the physician (such as pad tests and bladder diaries).

The primary types of PROs include [76].

- **Disease/condition specific**: measure patients' perceptions of a specific condition. These cannot be administered to people without the condition under study.
- **Population specific:** specific to a certain population (for example, women or men or elderly) with or without a given condition.
- **Dimension specific:** assess one aspect of health status. The primary dimensions studied include:
  - Physical function (e.g., activities of daily living)
  - Symptoms (e.g., urinary incontinence)
  - Psychological well-being (e.g., depression)
  - Social well-being (e.g., sexual function)
  - Cognitive function (e.g., mental status evaluation)
  - Role activities (e.g., household or work activities)
  - Personal constructs (e.g., body image)
- **Generic measures:** measure broad aspects of health which can be used to compare across populations (The SF- 36 is a commonly used measure). These are often less responsive to clinically significant changes in health than condition-specific instruments
- **Utility measures:** (e.g., EuroQol) incorporate preferences or values attached to individual health states. This type of instrument produces evidence for the overall value of health states to society and can be used in cost-utility analysis.
- **Summary items:** participants summarize an overall picture of their status in one item (for example, the transitional item queried in the SF 36: "Compared to one year ago, how would you rate your health in general now: excellent, very good, good, fair, poor?"
- **International Classification** of Functioning, Disability and Health (ICF), WHO 2001
- **Unified and standard language** and framework for discription of health and health-related states
- **Body, Individual, Society**
  - Body functions and structures
  - Activities and participation
- **Body functions:** physiological and psycological functions of body systems
- **Body structures:** anatomical parts
- **Impairments:** problems in body function or structure such as significant deviation or loss

- **Activity:** execution of a task or action by an individual
- **Participation:** involvement in a life situation

While not yet in wide use, web-based resources for administering computerized adaptive tests are being developed. One example is the Patient Reported Outcomes Measurement Information System (PROMIS) system (www.nihpromis.org). Using this type of testing, researchers can lower participant burden substantially. For example, in a measure of physical function, someone who endorses inability to dress themselves would not be asked the next series of questions in a typical validated physical function questionnaire about walking or exercising; someone who endorses ability to run marathons would not be asked questions about less strenuous activities. Nascent work has begun on the use of the PROMIS system in pelvic floor disorders [77].

Investigators should strive to use validated outcomes measures whenever possible. A fully validated outcome measure is demonstrated to 1) be reproducible when administered to the same person twice, 2) yield results that align with other gold standard measures (content validity), 3) change with successful treatment (be responsive to change), and 4) measure what it is intended to measure (face validity). (A full discussion of psychometric properties needed to validate a questionnaire can be found elsewhere in this consultation.) Much progress has been made in this area over the last decade, and therefore, when planning a study, the default position should always be choosing a validated outcome tool as a primary outcome measure. However, it is important to note that just because a questionnaire is "valid" does not mean it can be used in any population in any language. Researchers must take care to use instruments in the populations for which they were intended.

Adverse event recording and analysis is an important aspect of outcome measures, especially when the benefits may be offset by harms. Adverse event assessment should be systematiclly included in every interventional study. The Clavien-Dindo system for structured reporting and analysis of surgical complications has been used in several studies comparing pelvic floor interventions[78]. In this system, complications are classified into one of four categories based on the type of therapy needed to correct the complication.

The timing of outcome assessment should reflect the study question. Studies reporting efficacy of incontinence treatment should follow subjects for a minimum of one year. Although early follow-up can provide important insights about adverse events, a great deal more emphasis needs to be placed on long term effectiveness. The follow-up time for a trial should be at a fixed time (for logistical reasons, this is in practice often a short time window) relative to randomization rather than when treatment was actually received, since again this is the only way of ensuring a valid comparison. The planned timing of follow-up at a fixed time relative to randomization should, however, allow for any likely delays in receiving treatment, e.g., due to surgical waiting lists.

VIII. SATISTICAL CONCERNS

1. SAMPLE SIZE CONSIDERATIONS

There is no single answer for sample size determination; often the calculation proceeds around a 'circle of specifications' (involving, say, power, targeted difference in effect size and population available for study). Furthermore, the ideal of the target being the minimum for clinical significance cannot always be met; rather, the aim in practice is to produce a convincing argument (among the researchers themselves, and also to funding bodies and regulatory agencies) that the sample size has an adequate chance of detecting differences that are (a) feasible, and (b) worthwhile detecting in clinical terms. A common failing is selecting a target difference that is too large, often derived from differences that have been observed or published previously rather than based on considered clinical judgment. Preliminary investigations into the levels of treatment effects that patients themselves consider worthwhile should be carried out much more commonly than is the case at present.

Sample size should be calculated in the planning stage of all studies. There are many formal equations to assist in this process, details of which will not be given here [70-71, 79-80]. Rather, the emphasis for this discussion is on the concepts involved and the information required for the calculations to proceed.

2. SAMPLE SIZE CALCULATION

One approach to sample size calculation is based on the required precision of an estimate, which is relevant to both descriptive and analytical investigations. The basic issue is one of precision (measured by the standard error, SE) or margin of error (which depends on the SE but is more specifically defined as half the width of the 95% confidence interval [CI] around the estimate). The higher the level of precision specified in advance (i.e., the smaller the SE and the narrower the CI), the larger the sample size will need to be. However, the margin of error depends on the nature of the primary outcome variable, i.e., whether it is a continuous variable (such as maximum urinary flow rate) or a binary variable (such as the presence or absence of self-reported urgency incontinence). For a continuous variable, the variability (standard deviation) of the measure must be estimated for relevant subjects; this may

be derived from some combination of clinical experience, the literature, or a pilot study. The larger the variability, the larger the sample size required. For a binary variable, its prevalence must be estimated in the population to be studied, since the SE for such variables depends on their prevalence.

A second approach, based on power, is the most commonly used and requires that the study have adequate probability (power) of detecting a given (target) magnitude of effect. It requires similar prior information, including estimates of the variability for continuous measures and the magnitude of proportions for binary variables. In addition, it requires specification of three other quantities: the significance level, the power, and the target difference. Significance is a statistical term that tells how certain one can be that a difference or relationship exists. It does not necessarily imply that the result is clinically relevant, just that the result is likely to be accurate. The significance level, termed alpha, is conventionally, though not necessarily, set at 5%. Power is defined as the probability that the study will detect (as statistically significant at the alpha level specified) a given target difference between the groups, if such a difference exists. Power is commonly specified in the range of 80% to 90%, which implies a risk of not detecting the target difference of between 20% and 10%, respectively. For a trial involving anything other than minor risks and expenditure, a power closer to 90% than 80% would seem preferable [32], which leads to a larger sample size (as does a stricter alpha level of, say, 1%). This is most pertinent when a lack of statistical significance is obtained in a small trial, particularly when the sample size was not planned using a power calculation [47]. This is the basis for the adage that "the absence of evidence is not evidence of absence"[25]. A planned unequal allocation to the trial groups also requires an inflation of the sample size [47], as does interim analyses. By multiplying the number of significance tests performed, studies with interim analyses generally require stricter significance levels at each analytical point [50, 70].

3. THE TARGET DIFFERENCE

This is the last, and arguably the most important, quantity that must be specified for the power-based approach to sample size calculation. The target difference is defined as the minimum difference between treatment groups considered to be clinically significant. Clinical significance is an entirely different concept from statistical significance. Investigators must estimate the clinical significance as the magnitude of difference (in means or proportions) that would lead to a change in clinical management for the target group of patients. For example, a study might propose that a 20% difference in incontinence episode frequency is a clinically meaningful response. Ideally, such an assumption would be based on surveys of patient behavior but in practice the decision is often based on clinical judgement. In any case, the smaller the clinically significant target difference, the larger the required sample size. Statistical significance means that the observed difference, whatever its magnitude, cannot reasonably be considered as being due to chance. Statistical significance (denoted by the p-value) represents the strength of evidence against the null hypothesis [81]. The degree of clinical significance can be inferred only with the additional information of a confidence interval for the comparison between groups. A very large trial may achieve a high level of statistical significance with a very small effect size and therefore be of little clinical significance. A trial designed in such a way poses ethical challenges because many extra subjects are exposed to risk without meaningful benefit.

With each approach, appropriate adjustment for attrition (loss to follow-up) should be performed. This is commonly achieved by simply increasing the planned sample size in proportion to the anticipated attrition (i.e. to predict the reduced effective sample size that will be available for the analysis).

IX. ANALYSIS

The analytic plan should be consistent with study aims and the a priori analytic plan should be included at the time of the protocol entry into a clinical trials registration system. Currently, high tier journals will often request the statistical analysis plan and protocol at the time of the review of the report. This section will not contain any technical details of statistical methods, which are available in standard texts [47, 82-83], but rather will summarize concepts of data analysis.

It is established practice that the **primary analyses** (for both primary and secondary outcomes) of an RCT should be on an intention-to-treat basis [48, 72]. **Secondary analyses** incorporating non-compliance and/or which treatment was actually received may be justified in addition to the primary analyses. In practically all situations, hypothesis tests should be two-sided (i.e., allowing for the possibility that the difference could have been in either direction, that is benefit or harm), rather than one-sided. One-sided tests are only appropriate if a difference in one direction is not just unlikely, but would not be of interest, such a demonstrating only superiority of a new drug.

Regardless of the type and complexity of statistical techniques used in analysis, the general underlying principles behind hypothesis testing and estimation apply. In particular, the statistical significance of a hypothesis test should be interpreted critically. The actual p-value should be considered, rather than just whether or not it is below an arbitrary threshold such as 5% [48]; indeed, the p-value is better considered a measure of the strength of evidence against the null hypothesis, on a continuum or 'shades-of-grey

[83-84]. The direction and magnitude of the trial comparison should be presented with an appropriate confidence interval to indicate the possible clinical significance and precision of the comparison [48, 85].

Appreciable **loss to follow-up** in a trial (which is not the same as adherence with intended treatment, lack of efficacy, or the observation of adverse events) may present serious problems both in terms of generalizability of the findings to the wider population and, in the case of differential loss to follow-up across treatment groups, to the validity of the comparisons. Indeed, strictly speaking any missing outcome data means that not all of those allocated to the various randomization groups can be included in the analysis [86], and this might lead to the conclusion that the term 'intention-to-treat' should only be used if follow-up is complete. Under current guidelines, **intention-to-treat** relates more to the broad strategy adopted by the researchers for data analysis [39, 87]. Results should always be accompanied by a full and clear statement of how deviations from intended treatment and missing outcome measures have been handled in the analysis. The discussion should include how missing outcome data may have affected the conclusions [86]. Sensitivity analyses can be used to test the exclusion of, or assumptions about, missing values; practical examples of such analyses are becoming more common [88]. Another design strategy, modified intent to treat (MITT), is common in drug trials. It requires the participant to take at least a single dose of the study medication in order to be included in the analysis.

It is essential that a statistical analysis plan be developed for the trial prior to implementation. The CONSORT statement provides an outline of the various stages of data analysis for RCTs [32, 72]. Here we present the underlying concepts of data analysis at a particular follow-up time relative to randomization, and considers initially the simplest case of a clinical trial with two treatment groups. Multiple treatment groups will be covered briefly, but repeated measurements of outcomes and interim analyses involve considerably more complex methods of planning and analysis, for which expert help is essential [71, 89].

- **Stage of data analysis**

The first stage of data analysis is to address the representativeness of randomized subjects compared to the target population of eligible patients. The number of eligible patients who were and were not randomized should be provided, along with reasons for excluding potential study participants. This aspect of the findings of the trial will only prove useful if all eligible patients are considered: in practice there is a tendency for researchers to avoid approaching certain potentially eligible patients (selective pre-screening), for any of a wide variety of reasons, and this behavior may introduce bias in which subjects from the target population are included in the study. The presentation of this information is facilitated by use of the CONSORT flow diagram [48, 72]. Use of the CONSORT guidelines is associated with improved quality of reporting of trials generally [32]. Descriptive statistics should also be given of important characteristics of health care professionals approached for involvement in recruiting subjects to the trial, both for those taking part and those declining.

The second stage of data analysis is to compare the two groups at randomization (baseline) including demographic, prognostic, and outcome variables. A common error at this point is to rely on statistical testing for these comparisons [47, 50, 70]. If the randomization procedure has been performed correctly, then any statistically significant differences in baseline characteristics are likely due to chance. Statistical testing of this kind is not a test of the comparability of trial groups; rather, it is a test of the allocation procedure [47, 50, 70]. It may be seriously misleading, particularly if lack of a statistically significant difference for a given characteristic is taken to imply comparability. Baseline comparability is best assessed by simply obtaining descriptive statistics for the groups and making a judgment as to whether any observed differences are likely to be influential or not. If differences are likely to be influential, they should be considered in the analyses. Notable exceptions to this are baseline measures of the outcome variables, which should be considered in the analysis regardless of the situation at baseline, since removing variance in the outcome measure that is purely attributable to differences between individuals at baseline has potentially marked benefits in terms of precision and power [50]. Investigators should consider stratifying the randomization on any strongly prognostic variable (for reasons of efficiency rather than bias). Since there are practical limitations as to how many variables a trial can stratify for, a technique known as minimization may also be considered [46, 74]. Any variables stratified or minimized at randomization should be allowed for in the analysis [50]. In incontinence research, variables such as prior failure of therapy in drug and surgical studies or the degree of anatomic support in surgical or injectable trials or degree/amount of incontinence might be considered important enough to stratify, or to include in the analysis if unequally distributed.

The next stage of data analysis is to perform the primary (comparative) analyses for the outcome variables. First, though, it is essential to derive and report actual numeric data – even if simply in the form of descriptive statistics – rather than just reporting for instance a percentage change, even if the latter are relevant and provided as well. Graphs can be misleading, especially when subsections of the scales are magnified, and should be used to supplement or clarify the numerical data,

not to replace it. Primary outcomes should initially be analyzed by intention-to-treat comparisons of the groups as randomized, both using hypothesis tests for statistical significance and CIs for comparisons between the groups to assess clinical and statistical significance, usually adjusting for baseline measurements of the outcome variable. With a small number of primary outcomes, multiple testing is not a concern. However, when a large number of statistical tests are performed for secondary outcomes, corrections to the observed p-values should at least be considered.

The most commonly used procedure for multiple testing of many outcomes is the **Bonferroni correction** [47, 50, 82]. The Bonferroni correction is fairly conservative in reducing the risk of a statistically significant effect occurring purely by chance, at the cost of reduced power for individual outcomes. This is particularly pertinent when, as is usually the case, the outcomes are positively associated with one another. While there are alternative procedures that improve this deficiency, none of them are entirely satisfactory [50]. It is emphasized that whatever strategy is adopted to deal with multiple testing, the major errors are to rely solely on p-values rather than present confidence interals "CI"s as well, to over-simplify the presentation of p-values to just non-significant"NS" or "p<0.05" rather than to quote the actual p-values, and above all to report selectively the results of significance tests.

Another example of a **"multiplicity"** is where there are more than two treatment groups, e.g., when different doses of a drug are being investigated or when more than one 'active' procedure is being compared with placebo [50]. Similar issues to multiple testing of different outcomes are involved here, but there are a greater variety of commonly used procedures available to deal with the central concern of finding a difference purely by chance. Standard methods for dealing with this multiple comparisons problem include the procedures attributed to Tukey, Newman-Keuls and Dunnett [90].

Secondary analyses of trial data include per-protocol analyses with adjustments using regression methods for pertinent process measures such as degree of adherence with the allocated treatments. Secondary analyses also include **planned subgroup analyses,** such as the investigation of different intervention effects across age, ethnic, or disease severity groups. Subgroups should be analyzed by using appropriate interaction terms in regression models [48, 70]. Using interaction terms rather than performing repeated, separate, subgroup-specific analyses considerably reduces the risk of false positive findings [91-92]. Subgroup analyses should be carried out sparingly, specified in advance (preferably with a clinical rationale), and above all should not be reported selectively [48, 92-93]. This last point relates not just to subgroup analyses but to all stages of reporting randomized trials. Pre-specification of the primary outcomes in the study protocol and analysis plan, along with clear statements about all the outcomes considered is essential to avoid selective reporting. The large volumes of data accumulated in major multicenter RCTs almost guarantee that something "significant" can be identified by "data-mining". If not identified by the investigators as an a priori item of interest such findings should be viewed with great skepticism.

X. REPORTING RESEARCH RESULTS

Over that past decade, progress has been made in reporting research results. However, faster progress would occur if investigators would follow the reporting recommendations. As part of the "Enhancing the QUAlity and Transparency Of health Research" **(EQUATOR)** Network project, a website was developed at www.equator-network.org. On the website, the Consolidated Standards of Reporting Trials **(CONSORT)** statement provides guidelines for reporting the design, detailed methods, and results of RCTs. For studies of diagnostic tests the Standards for Reporting of Diagnostic Accuracy **(STARD)** [94] statement fills the same role and information is also included on the EQUATOR website. Guidelines for reporting meta-analyses are described by the Quality of Reporting of Meta-analyses (QUORUM-37) and Epidemiologic research reporting guidelines are contained in STROBE, Strengthen the Reporting of Observational Studies in Epidemiology [38, 72].

The CONSORT statement is specifically designed to provide standards for reporting RCTs [48, 72]. It includes a checklist of items that should be included by authors preparing manuscripts. Adherence to these guidelines and the use of flow diagrams in particular is associated with improved quality in reporting of RCTs [95]. Errors in presentation of statistical information are extensively covered in many textbooks [47, 82]. This section will emphasize the most important points on reporting of RCTs, to ensure an objective and comprehensive presentation of the trial itself, and also to facilitate any subsequent synthesis of research evidence including formal meta-analyses of RCTs. Meta-analyses are themselves the subject of separate reporting guidelines: the QUORUM statement [96]. However, such guidelines are not a panacea [97]; deficiencies in reporting are still common [72]. [98]

The CONSORT statement for reporting **parallel group randomized trials** have recently been updated Statements have also been issued for pragmatic trials [99-102] and noninferiority and equivalence trials. The CONSORT statement includes a checklist of items and a comprehensive set of characteristics of a clinical trial to assist investigators to write reports of their findings, journal editors and

reviewers in the review of manuscript submitted for publication and permit consumers of the literature to critically appraise articles. Clear statements about the objectives of the trial, intended study population, and planned comparisons. Subgroup or covariate analyses should be clearly specified and justified. The method of randomization should be stated, as should the unit of randomization; in most cases, this will be the individual participant but occasionally an aggregate group of subjects will be allocated jointly in a cluster randomized design [56]. Cluster randomized designs are also now the subject of separate reporting guidelines [103], and involve particular complications in terms of data analysis [104]. For all trials, specifications for the sample size calculation (primary outcomes, target differences, etc.) should be stated and justified. In addition, the precision actually obtained in a study must be presented. This requires confidence intervals as well as the observed p-values, at least for primary outcomes but preferably for all outcomes. The principal confidence intervals should be for comparisons between the groups, rather than for differences in the outcomes within the trial groups [47, 50]. Results should include a trial flow diagram, with numbers and reasons for the exclusion of eligible subjects, the number randomized, and subsequent losses to follow-up [32]. Protocol deviations should be described and explained [70]. Harms of the trial should be described for each treatment group. Finally, the discussion should include a brief summary of the trial's findings, possible explanations for the results, interpretation of the findings in light of the literature, limitations of the trial including internal and external validity, and the clinical and research implications of the study[48].

Recommendations on Study Conduct and Statistical Methods

- The role of quality RCTs as providing the strongest level of evidence in incontinence research should be fully acknowledged by researchers, journal reviewers, and editors. **HIGH**
- Careful attention to the planning and design of all research, especially RCTs, is of the utmost importance. **HIGH**
- Appropriate expertise in biostatistics and clinical trial design should be employed at the design phase of a RCT and thereafter on an ongoing basis. **HIGH**
- The design, conduct, analysis and presentation of RCTs must be fully in accordance with the CONSORT Statement. **HIGH**
- The design, conduct, analysis and presentation of observational studies should follow STROBE guidelines. **HIGH**
- The design, conduct, analysis and presentation of meta-analyses should follow QUORUM guidelines. **HIGH**
- Reporting studies of diagnostic tests, including urodynamics, should follow the STARD state¬ment guidelines. **HIGH**

XI. SPECIAL CONCERNS FOR SPECIFIC STUDIES

1. BEHAVIORAL AND PHYSIOTHERAPY TRIALS

a) Terminology

The lack of consistent terminology severely hampers our ability to build a body of literature about conservative interventions. The terms "behavioral therapy", "lifestyle intervention", "conservative treatment", "non-surgical treatment", "physiotherapy", "biofeedback", and pelvic floor muscle exercise" are often used interchangebly and incorrectly to describe both the same, and different interventions. While such therapies are discussed elsewhere in this consultation, we here advance this committee's opinion about appropriate terminology:

b) Behavioral interventions

According to Oxford Advanced American Dictionary the term behavioral is «the way someone behaves, especially towards other people», and behavioral science is the study of human behavior. We recommend that behavioral science be limited to studies that evaluate how people do or do not behave as desired.

c) Lifestyle interventions

Lifestyle interventions for UI are discussed elsewhere in this consultation and have traditionally included change in diet, intake of caffeine and carbonated soft drinks, fluid restriction, weight loss, smoking cessation and advice of increasing general physical activity level. Behavioral science can be used to understand how and why people change life-style to, for example, adhere to exercise and weight loss programs, but it should not be used as term to replace specific therapies such as physiotherapy or pelvic floor muscle training.

d) Physiotherapy

Physiotherapy refers to assessment, prevention and treatment given by an authorized physiotherapist (ICS physiotherapy committee www.icsoffice.org). It involves "using knowledge and skills unique to physiotherapists" and, "is the service only provided by, or under the direction and supervision of a physiotherapist" (WCPT 1999). This implies that the term physiotherapy should only be used in trials where the professional providing the intervention is a physiotherapist. We recommend describing the actual intervention instead of using the term physiotherapy: eg pelvic floor muscle training

with or without biofeedback, electrical stimulation, pelvic floor muscle training with vaginal cones or resistance device etc. This accurately describes the intervention and is neutral towards profession. Publications should report the actual profession of the interventionist (e.g., physiotherapist, general practitioner, urogynecologist, urologist, midwife, nurse, fitness instructor), rather than using the vague term, "therapist".

e) Biofeedback

Biofeedback encompasses "a group of experimental procedures where an external sensor is used to give an indication on bodily processes, usually in the purpose of changing the measured quality" [105]. Biofeedback equipment was developed within the area of psychology, mainly for measurement of sweating, heart rate and blood pressure under different forms of stress. Today, a variety of biofeedback apparatuses are commonly used in clinical practice to assist with PFMT, and the biofeedback can be either visual, auditory or both. In many textbooks the term "biofeedback" has been used to classify a method as different from PFMT. However, biofeedback is not a treatment on its own. It is an adjunct to training. For example, it may measure the response from a single PFM contraction or provide visual feedback during attempts to relax the muscles. Hence, a more precise terminology is PFM training or relaxation with or without biofeedback.

In addition to traditional biofeedback apparatuses, other instruments can offer valuable feedback. Vaginal and anal surface EMG, urethral, vaginal or anal squeeze pressure measurements, ultrasound and MRI can all be used to make the patients more aware of muscle function, and to enhance and motivate patients' effort during training [106].

f) Conservative interventions/treatments

Conservative interventions include all of the above, and this term includes everything except medication and surgery. As several studies have found that more than 30% of women with pelvic floor dysfunction are not able to perform a correct PFM contraction at the first consultation [107-110] it is mandatory to report how ability to perform a correct contraction was assessed before commencing an exercise trial. Also in electrical stimulation research one should report in which way response to the stimulation was assessed.

Although there is level A, grade 1 evidence for some of the conservative interventions such as PFMT for SUI, a variety of new conservative methods to treat the condition are frequently suggested in clinical practice and in the literature. These new methods are often presented as being effective, but are usually a hypothesis based on theories, data from small experimental laboratory studies/ small clinical series, or associations found in large epidemiological studies. If the clinicians like the approach, it soon enters clinical practice and textbooks without any further critical testing [113]. A model for how new therapies ideally should enter clinical practice has been proposed [114]. In this model the new idea should go through at least the 4 first stages before they enter practice:

Clinical observation and laboratory studies

- Clinical exploration
- Pilot studies
- Randomized controlled trials
- Refinement, eg dose-response issues
- Active dissemination of the method if it has proven to be effective

It is important that the patients participating in the 3 first stages before the RCT are given full information that they are participating in an experimental treatment, and that the clinician does not know if this new approach is effective. The patients also need to be informed if there are other proven effective treatments available.

g) Reporting of trial characteristics

In addition to reporting the specific type of intervention (eg.PFMT with biofeedback compared to PFMT alone or electrical stimulation) and the profession adminstering the intervention, the intervention needs to be described in such detail that other investigators can reproduce the intervention. This includes:

- Ability to perform a correct PFM contraction.
- Frequency: number of home training sessions and supervised training sessions (eg every day, 3 times/week)
- Number of repetitions and sets (eg. 12 sets x 3 times/ day)
- Duration: length of each training session (eg. 20 minutes), and duration of the total training period (eg, 3 months, 6 months)
- Intensity: In exercise science, this is usually reported as % of one repetition maximum for strength training. In pelvic floor muscle training it is often described as attempts to reach maximum contractions or utilizing submaximal contractions. Another description of intensity is the holding time in seconds, eg: 6-8 sec
- Adherence: the degree to which participants follow the prescribed protocol, usually reported as a percentage of the total possible.

Educational material provided, such as DVDs, brochures and booklets should be described.

Assessment: All devices used for assessments (eg manometers, dynamometers, ultrasound and EMG) must be described in detail, and their re-

sponsiveness (ability to detect small changes), reliability and validity should be reported [111].

h) Adherence vs effectiveness

It is important to note that adherence is not the same as the effectiveness of a program, as it is possible to have high adherence, but still little effect of training. Hence, when reporting the effect of conservative interventions it is ideal to measure also the exposure variable that the treatment is expected to change (eg muscle strength, ability to relax etc). This variable should not be confused with the primary or secondary outcomes of the intervention (eg leakage measured with pad testing, number of leakage episodes or QoL).

In many areas of conservative interventions there are high quality RCTs, systematic reviews and meta-analysis showing statistically significant and clinically relevant differences between the intervention and the untreated control group or other interventions. Of conservative therapies, PFMT for SUI/MUI has the strongest evidence to support its use; further, the more intensive the program (more supervision, higher dosage of training) the better the effect. Therefore, when comparing new methods and innovations with established PFMT, it is important to compare the new intervention with the current best evidence, meaning the effective arm of the reported RCTs. Unfortunately it is common to compare new methods with an ineffective training protocol, thereby overestimating the effect of the new method and claiming that it is equal to or better than "the old method". When comparing different methods the dosage also needs to be the same in both treatment arms, eg when comparing PFMT with and without biofeedback, the number of supervised sessions, length of the sessions, frequency of home treatment and duration of the intervention must be the same.

i) Adverse events and cost

There are few adverse effects or complications reported after conservative interventions, but they do exist, eg in electrostimulation [112], and adverse effects or lack of adverse effect, and inconvenience to the patients should be reported. Although seldom harmful, conservative treatments are time consuming and can be costly for participants and paying parties because of the need for close follow up during the interventions. Cost effectiveness studies are crucial to fully understand where conservative therapies fit in the treatment armamentarium.

j) Outcome measures

The need for use of responsive, reliable and valid outcome measures in research is covered elsewhere in this chapter. The RCTs published in conservative treatment have applied a huge variety of outcome measures, making systematic reviews and meta-analysis difficult or impossible to conduct. Therefore, in future research it is important to use established and recommended outcome measures. In addition to description and use of responsive, reliable and valid primary and secondary outcome measures, future studies should include description and assessment of adherence to the intervention protocol, measurement of the independent variable (the intervention; eg strength training, relaxation training) and measurement of the possible underlining mechanisms of how the treatment works. It is usually not possible to blind the participants or those providing the intervention, but the assessors of outcome should always be blinded to group allocation.

k) Specific and non-specific effects

There have been some concerns that the effect of conservative treatments can be attributed to non-specific effects such as the extra attention of the therapist. The role of the therapist is to educate, motivate and empower the patient to be able to perform the actual program, secure high adherence, and minimize drop-outs. In patient reported outcomes and reports on quality of life it may be difficult to separate the effect of the attention and the actual effect. However, the effect of the attention is less likely to affect outcomes such as muscle strength, urodynamic assessments, pad testing and morphological changes measured by ultrasound and MRI. To minimize bias, all assessments should be conducted by investigators blinded to treatment allocation; the logistics of this should be addressed during the planning phase of the study. In a high quality RCT, Dumoulin et al address the problem of attention in physiotherapy research [115]. Women with persistent UI, three months after childbirth were randomized to either two different training regimens or a control group receiving relaxation massage for the back and limbs for the same amount of time as the supervised training groups. 70% were cured on pad testing in both treatment groups while there was no effect on urine loss in the relaxation massage group. Participants in the massage control group had improvement in disease specific quality of life.

l) Power calculations and number of participants

Some of the RCTs on conservative treatments are flawed by small sample sizes, this being especially evident in electrostimulation studies and may account for negative effects caused by type II errors. It is important that future studies use results of previous published studies to make appropriate power calculations that incorporate estimates of drop-outs and loss to follow-up to decide the optimal number of participants needed. Recruiting large numbers of participants may come at the expense of the rigor of the intervention [116]. Weak interventions (eg non-optimal training dosages or

suboptimal electrostimulation parameters) are unlikely to be effective and do not yield the true effect of an intervention. In meta-analyses, adding RCTs with large sample sizes but weak and ineffective interventions, can dilute the effect of smaller RCTs with higher methodological and interventional quality [116].

m) Long term studies

To date there are no quality criteria for how to report long term follow-up studies or how to conduct meta-analyses of long term studies. Challenges in long term follow-up studies include cross over to the more effective treatment after cessation of the original RCT, co-interventions during the follow-up period, recurrent events (eg new pregnancy), competing events (other diseases leading to incontinence) and loss to follow up. For conservative interventions it is expected that any training effect will diminish over time if no maintenance training is conducted or the pre- or co-contraction of the pelvic floor muscles has not reached an automatic level during the original trial. In order to control for as many of the above mentioned factors as possible, it is recommended that the long term follow up study should be planned together with the original RCT. Loss to follow-up and adherence to the protocol during the follow-up period must be reported [106, 111-117].

Recommendations for conservative treatment trials:

- Use correct terminology to describe the intervention. HIGH
- Report details of ability to perform correct contraction, dose-response issues and adherence. HIGH
- Use recommended outcome measures with high responsiveness, reliability and validity. HIGH
- Compare new methods with the best available intervention. HIGH
- Use power calculation in planning of the study. Avoid large sample sizes and weak (ineffective dosages) interventions. HIGH
- For long-term follow-up studies report crossover, co-interventions, recurrent and competing events, adherence in the follow-up period and loss to follow-up

2. EXPERIMENTAL DEVICES AND MATERIALS

Surgical research presents unique challenges to efforts at optimizing patient care. It is important to create a pathway for real advances while simultaneously protecting patient safety. When new procedures are substantially different from prior operations there should be a broad based preliminary exploration leading to a comparative trial if warranted. At the same time, many minor modifications of surgical procedures are inappropriate for randomized trials and if required, surgical progress would be slowed [118].

a) Randomisation

It has been argued that the first patient in whom a procedure is performed should be randomized [119-120]. Alternatively, it has been suggested that case series for new procedures are allowed until the procedure finds its intended use and to avoid doing studies while those performing the procedures are on the “learning curve”. Typically, new surgical procedures for incontinence have been reported as case series [121-122]. Not only do surgical case series provide the lowest level of evidence for treatment effects, case series may be “harmful”. An accumulation of “positive” case series may present a premature certainty about benefits of a procedure and make it even more difficult to perform randomized trials [123-124]. Influential members of the surgical community may endorse a new procedure and if the procedure is considered better it may be difficult to get surgeons and patients to randomize or a trial may appear to be unethical with a “proven” procedure [119, 123, 125].

b) Adoption by clinicians

Therefore, devices often are widely adopted by clinicians based on anecdotal data, marketing, or small case series. This raises a unique problem for trials in this area: 1) Surgeon buy-in can be difficult to obtain as some surgeons (“early adopters”) may perceive that the newest therapy is best and thus be unwilling to randomize patients to receive the traditional therapy, 2) Other surgeons (“late adopters”) may perceive that the data available do not support use of the newest therapy and thus be unwilling to randomize patients, 3) Patients may be unwilling to be randomized to traditional therapy because they are influenced by marketing forces propelling the newest devices to the forefront, and 4) Device companies frequently modify their materials or technique recommendations; therefore, by the end of the 3-5 years it typically takes to complete the earliest outcome assessment for a surgical randomized trial, the device tested is no longer the same as the device used in the trial. Thus, the results may be discounted as being no longer applicable.

c) Recruitment procedures

An important area of concern in surgical and device studies is patient recruitment procedures. Both in this regard and for all components of a study, we strongly support reporting according to the CONSORT guideline for randomized trials and the STROBE guidelines for observational studies. Subjects should be enrolled in a manner that minimizes selection bias. The protocol should detail the procedure by which consecutive patients meeting

the inclusion criteria are selected. All situations in which a patient meets the inclusion/exclusion criteria but is not offered enrollment by the investigator should be documented. The number of patients who decline enrollment should be stated, along with the reasons. It is vital that clinician researchers do not "cherry pick" from their patients, that is, that they do not limit recruitment to those patients considered to have the greatest chance of cure or lowest chance of risk. The study population should be as generalizable as possible. There should be a complete accounting of all participants in the study including the reasons for subject withdrawal.

Participants must be well informed about what is known and not known about devices or procedures being tested. They should not be led to assume that because a device is on the market, it is "safe and effective", as gaining knowledge about this is the purpose of the trial.

3. SURGICAL STUDIES

Cross-sectional studies of surgical procedures by type can provide estimates of prevalence, variation by age, race, and region as well as morbidity and mortality [126-127]. This type of information raises important health policy questions regarding physician practices, patient preferences for incontinence treatment, and differential access to and the utilization of care.

Case series are the most common study design found in the surgical literature, especially for new "innovative" surgical procedures. This is true despite the fact that case series cannot account for selection bias on the part of both the patient and surgeon, non-reporting bias of failures or loss to follow-up, lack of long-term follow-up, and provide the lowest level of evidence for treatment effects. Observational studies can provide important information about effectiveness and complications of surgical procedures, and also are very helpful in designing and selecting potential randomized clinical trials.

The randomized controlled trial is the accepted "gold standard" for research of treatment effects. In all surgical specialties, there has been growing concern regarding the limited number of randomized controlled trials for surgical procedures, poor methodological standards in those that have been performed, and a perception that surgeons are reluctant to rigorously test new surgical interventions [119, 123, 128-129]. A number of reasons for the paucity of surgical trials have been suggested including the lack of a regulatory board similar to the Food & Drug Administration responsible for the development of new medications [130].

The body of literature of surgical randomized trials in pelvic floor disorders is small, though increasing. However, many RCTs have serious limitations including a sample size too small to detect differences between groups, lack of blinding of the participants and/or individuals assessing the outcomes, short follow-up, inclusion of limited number of surgeons only, poor description of the technique, and lack of standardized outcome measures. Multi-center treatment networks are useful to overcome some of these limitations.

Differential drop out after randomization (or for cohort studies, after the intervention) can introduce bias. In a large and methodologically sound randomized controlled trial comparing the tension-free vaginal tape (TVT) and colposuspension, a large number of women withdrew from the colposuspension arm after randomization [131-132]. The loss of participants after randomization introduced bias in favor of the TVT because the drop outs had less severe incontinence resulting in the colposuspension group having more severe incontinence. It has been suggested that participants were only willing to continue if they were randomized to the "new and better" TVT procedure [132- 133]. Accounting for subjects "lost to follow-up" must also be detailed as per the CONSORT and STROBE recommendations. In the UK TVT RCT, drop out after surgery was similar for both procedures. In contrast, in two large study comparing two incontinence procedures performed by the Urinary Incontinence Treatment Network, randomization was done in the operating room after the patient was anesthetized and therefore no participant was lost to randomization [134],[67].

For studies of specific surgical procedures, the technique should be described in such detail that it could easily be reproduced in another study. **Standardization of the procedure** may vary depending on the research question [135]. Surgical trials using a small number of highly skilled surgeons are analogous to medical trials where only compliant patients are randomized, reflecting efficacy of the procedure in an ideal setting. It may be more generalizable to a mixture of skill level among surgeons in the community, and so reflect effectiveness of the procedure in usual practice [124].

Masking of participants as to their assigned intervention and those assessing the outcome is particularly important for surgical trials for incontinence because there may be enthusiasm by the patient or surgeon for a new procedure, many outcomes are based on the patient's own assessments such as symptom and quality of life scores, and the intervention is primarily for improvement of symptoms [118].

For new surgical procedures, important issues of adequate informed consent and conflicts associated with incentives for developing, starting and using new procedures have been raised. **Informed consent for a new procedure must include**:

- acknowledgement that the procedure is new and has not been shown to be more effective than a traditional approach
- discussion of potential complications, especially any integrally related to the procedure or device
- disclosure that information on complications are limited, and
- disclosure that the long-term benefits are unclear [122].

Incentives for adopting new procedures prior to sufficient evidence can arise from self-interest by attracting patients to one's practice, industry marketing, and patient desire for "cutting edge" techniques. Industry sponsorship or a surgeon's financial interest must be disclosed.

Organizations and treatment networks have been established to address many issues related to surgical interventions. Examples include the UK National Institute of Clinical Excellence (NICE www.nice.org.uk), the Australian Safety and Efficacy Register of New Interventional Procedures-Surgical (ASERNIP-S www.surgeons.org/asernip-s), and the US treatment networks: Urinary Incontinence Treatment Network (UITN http://www. niddk.nih.gov/patient/uitn/uitn.htm) for the NIDDK and the Pelvic Floor Disorders Network (PFDN). The NICE and ASERNIP-S provide systematic reviews of new operations, assessment of effectiveness, and recommendations that the technique has sufficient data for widespread use, or that the techniques appear unsafe, or that further audit/research are required before its widespread usage. The UITN and PFDN were established to provide the infrastructure for multicenter large randomized controlled trials for incontinence and prolapse.

Recommendations for Surgical and DeviceTrials:

- The safety and serious side effects of new operations must be completely defined with adequate follow-up so that risks can be weighed against efficacy. At a minimum, this requires more use of large scale, independent, prospective, multicenter cohort studies when RCTs are not practical. **HIGH**
- Safety and serious side effects of incontinence devices must be completely defined with adequate follow-up, especially for use of implantable devices and biologic materials, so that risks can be weighed against efficacy.**HIGH**
- Valid informed research consent is required in all trials of surgical interventions, which is separate from the consent to surgery. **HIGH**
- We recommend ongoing research into the usefulness of pre- and post-operative predictive testing (such as urodynamics, ultrasound, MRI, etc) in surgical trials. **HIGH**
- Reports of successful treatment should be limited to subjects with a minimum (not mean) of one year follow-up and should include a patient perspective measure. Specific assumptions about subjects lost to follow-up should be stated. **HIGH**
- Randomization for surgical trials should occur at the time of surgery to minimize dropouts and switch of procedure **HIGH**
- Long-term follow-up of RCT cohorts in an observational cohort is recommended. **HIGH**

4. PHARMACOTHERAPY TRIALS

Although many RCTs have been published in recent years on pharmacotherapy for urinary incontinence a great deal more remains to be learned. The trials have almost all been limited to 8-12 weeks of treatment giving very little information about long term safety and efficacy of drug therapy. Inclusion criteria are often stringent, such that the study population of healthy middle-aged people bears little resemblance to the patients for whom providers wish to prescribe medication. There is less than adequate information about special patient groups—men, children, neurogenic patients, and especially the frail elderly. Because incontinence creates such an impact on the older population, good studies to define the utility and safety of drug therapy are greatly needed in this group.

An issue of special relevance in trials of pharmaceutical agents (although germane to other treatment modalities) is the controversy regarding placebos in clinical trials. Regardless of whether a drug is effective or not, simply giving a drug to a patient may produce a beneficial response. To assess if a drug has an effect over and above the placebo response, it is usually tested against an inactive substance (placebo). In incontinence studies, the placebo effect may be quite large, anywhere from 30-50% in recent published studies. To account for this, investigators and regulators have generally demanded a placebo arm in most clinical trials of medication. While this may be acceptable to participants for short trials, it is neither ethical nor feasible to withhold treatment for longer periods of time. Further, clinicians and patients generally want to know how a new drug compares with established treatment.

Masking, while desired in all types of trials, is especially important in pharmacological trials. Further, it is feasible to do in such trials (as opposed to surgical or conservative interventions, in which masking may not always be possible) and thus should be prioritized. However, the identical appearance of two pills does not guarantee that participants will be unaware of group assignment. Side effects

common with anti-cholinergic therapy, such as dry mouth, may unmask participants. Studies should assess the degree to which masking was successfully maintained.

Recommendations for Pharmacotherapy Trials

- As effective drug therapy is available for most forms of incontinence, active drug comparator arms are recommended for most trials. **HIGH**
- Very little is known about the safety, efficacy and tolerability of drug therapy beyond 12 week trials. A concerted effort is needed to create this type of information base. Long-term follow-up of RCT cohorts in an observational cohort is recommended **HIGH**

XII. COST ANALYSIS

Economic and health policy outcomes are gaining increasing importance, as policy makers deliberate the values of different therapies. The financial burden on the health care system, the patient and patient's family of various treatment options makes cost an important outcome to measure. We recommend that cost analyses be planned with clinical studies whenever possible. Costs may be influenced by economic and political factors that are subject to change at any time; however, when basic units of work, time, and resources are carefully defined, models of costs remain useful even if market forces change in an unforeseen manner.

In health and medicine, economic analyses are descriptive and/or comparative. Descriptive data include the socioeconomic cost caused by the disease and its current treatment, whereas comparative data provide an economic evaluation of different treatment strategies and interventions where costs are compared to health outcomes.

There are several relevant types of cost analysis, some of which require a high level of expertise to conduct:

- **Cost of illness analysis** (COI) typically quantifies the burden of medical expenses (direct costs) and the resulting value of lost productivity (indirect costs) attributable to a specific condition such as an illness or injury [136], [132].
- **Cost effectiveness analysis** (CEA) measures the costs and consequences of two or more diagnostic or treatment pathways related to a single common effect or health outcome. It then summarizes the results in ratios that demonstrate the cost of achieving a unit of health effect for different types of patients and for variations of the intervention [137], [133].
- **Cost utility analysis** (CUA) is a form of cost effectiveness analysis in which particular attention is paid to the quality of health outcome related to treatment. In CUA, health effects are expressed in terms of quality-adjusted life years (QALYs) [138], [107]. A QALY is a measure of health outcome that assigns to a given period of time a weighting that corresponds to the health-related quality of life during that period, and then aggregates these weights across time periods. The QALY is important because it considers both quantity and quality of life.
- **Cost benefit analysis** estimates the net social benefit of an intervention by comparing the benefit of the intervention with the cost, with all benefits and costs measured in dollars [24], [134]. Health outcomes are converted into monetary values using "willingness to pay" (the value an individual would pay for reduction in illness severity) or "risk of death" or "human capital" methods (an individual's value to society based on productivity or future wages) [139- 140], [135-136].

Recommendations on Cost Analysis in Incontinence:

- Cost analysis should be incorporated into clinical studies whenever possible [137]. **HIGH**

XIII. RECOMMENDATIONS FOR SPECIFIC PATIENT GROUPS

1. MEN WITH LUTS

When considering men with LUTS, one must consider some unique factors which may influence urinary tract symptoms independently of any intervention, and so confound any data. These are the presence of the prostate gland which can cause bladder outlet obstruction (BOO), and the rarity of sphincter incompetence except in men who have undergone surgery for benign or malignant prostatic disease. For short term outcomes after intervention studies, these factors are unlikely to be relevant, but longer term follow up, and large observational or epidemiological studies may need to take these factors and changes over time into account when analyzing data. The prostate gland may complicate research outcomes as a result of outflow obstruction (either at baseline, or development of a new problem during follow up studies). Also, for patients with prostate cancer (either at the time of enrolment, or during follow up of longer studies), it is likely that both the disease, and the treatment given (surgery or radiotherapy) may alter urinary tract function and symptoms independently of any intervention in the study and thus confound the outcomes. , Overall, about 2/3 of men with LUTS have urethral obstruction and over 50 % have detrusor overactivity, al-

though a much smaller number have urinary incontinence due to detrusor overactivity [141].

If prostate size is considered to be a variable that could affect outcomes, measurement of prostate volume should be made before and after treatment. The method used to measure volume and its reliability and validity should be provided if available or their absence indicated. Any associations between outcomes and change in prostate size should be tested for using appropriate methods and reported. Consideration should be given to stratifying participants by prostate volume when there is suspicion that response to therapy may be size dependent.

Insofar as about 2/3 of men with LUTS have bladder outlet obstruction (BOO), any research protocol in men should consider inclusion of a method to screen for it. At the least, maximum free urinary flow rates and measurement of post-void residual urine should be recorded before and after treatment and the effect of therapy on these parameters should be documented simultaneously with assessment of the primary outcome variables. Synchronous pressure-flow studies are generally desirable and should be included whenever feasible. Several pressure-flow nomograms have been proposed to diagnose obstruction in men. The ICS nomogram is recommended and it is important to specify which if any nomogram is being used [142]

Recommendations for Research in Men:

- Measurement of prostate size should be performed before and after treatment (at the same time as continence outcome measures where possible) whenever prostate size is considered to be a potentially important variable, or to change during the intervention and follow up. **HIGH**
- Maximum free flow rate and measurement of post-void residual urine should be recorded pre-treatment and the effect of therapy on these parameters should be documented simultaneously with assessment of the primary outcome variables. **HIGH**
- Participants should be stratified by prostate size at randomization when size is considered to be a potentially important determinant of treatment outcome. **LOW**

2. WOMEN WITH LUTS

a) Hormonal effects

Our knowledge of hormonal influences on the lower tract remains limited. Recent RCTs and prospective cohort studies have demonstrated that hormone replacement therapy (HRT) does not improve or may worsen incontinence [143-145). It therefore seems appropriate that information about menstrual and hormonal status should be an integral part of the baseline history. New studies designed to examine the influence of hormones on incontinence (if considered ethical by an appropriate review board) should include details of hormonal status (premenopausal, postmenopausal without HRT, post-menopausal with HRT), the route and type of HRT (oestrogen only, combined sequential, combined continuous), and whether or not oophorectomy has been performed.

b) Obstetric History

The influence of vaginal childbirth on the structure and function of the female pelvis is the focus of much recent and ongoing research but the complex interactions remain incompletely understood. While it is clear that childbirth, and particularly vaginal childbirth increases the risk of incontinence and pelvic organ prolapse, the potential effect of further childbirth on previous or current treatments of incontinence (especially surgery) has yet to be determined.

Potentially confounding variables include: number and route of deliveries (vaginal/Cesarean), use of forceps or vacuum, infant birthweight and head circumference, duration of second stage of labor, use of episiotomy and any vaginal or perineal trauma, and epidural anaesthesia. The importance of these variables will depend upon the specific study design; for randomised studies the allocation process should balance these between groups, but consideration should be given to stratifying or minimizing the randomization against one or more of these important factors, depending on the exact intervention. For epidemiological or observational research each of these factors should be collected and included in univariate and multivariate analyses.

c) Pelvic Organ Prolapse

The effect of pelvic organ prolapse on lower urinary tract function remains poorly understood. Pelvic organ prolapse may potentially affect lower urinary tract function by obstruction of the urethral outflow, and thereby mask sphincter weakness (so called “occult” stress incontinence). Emerging evidence suggests that prolapse may contribute to the symptoms of OAB and correction of the prolapse may modulate these symptoms. Thus, it is important to include assessment of pelvic organ prolapse in incontinence research on women. A validated assessment method for prolapse should be used to identify the stage of proplase; the Pelvic Organ Prolapse Quantification System (POP-Q) [9] is recommended. Research protocols should be developed, either excluding women with prolapse severity beyond a specified stage, or the analysis plan should include stratification for stage of prolapse in randomization, and adjustment for prolapse stage in any analysis. For larger studies where regression analyses are planned, stage of prolapse should be considered a mandatory factor for inclusion. Prolapse should be graded at the same time as the outcome assessment for incontinence and LUTS is performed.

Recommendations for research in women:

- Specific information about menopausal status, hysterectomy, parity/obstetric history, and hormonal status should be included in baseline clinical trial data and controlled for in specified analyses in the research protocol. **HIGH**
- High quality, symptom and bother scores (e.g.,ICIQ-FLUTS, KHQ, PISQ, ICIQ-FLUTSsex) validated in women should be employed when assessing outcomes **HIGH**
- Standardized assessment of pelvic organ prolapse (by POPQ) should be performed before treatment and at the time of other outcome assessments in all research where prolapse and continence outcomes are being assessed. **HIGH**
- Criteria for cure/improvement/failure from incontinence treatment should be defined in the protocol based on patient perception as well as objective and semi-objective instruments such as validated questionnaires, diaries and pad tests. **HIGH**
- Assessment of the impact of treatment on sexual function should be performed with other outcome assessment when appropriate. **MEDIUM**

3. FRAIL OLDER AND DISABLED PEOPLE

There are a number of unique and pertinent research issues for this population.

In the frail elderly, important variables include:

- **Demographic information:** Advancing age, white race, and women [145-148) are associated with an increase risk of incontinence and each of these variables should be adjusted for in most analyses.
- **Medical Conditions:** Medical conditions related and unrelated to the lower urinary tract have been shown to increase the risk of incontinence in older women and are especially important to assess in the frail older population [147, 149-151]. Prior hysterectomy has also been suggested as a potential risk factor for incontinence in older women [152-153].
- **Medication Inventory:** Certain medications may exacerbate incontinence and therefore a complete medication inventory is essential [151, 153-155].
- **Physical function:** Mobility is often impaired in the frail elderly and impacts urinary control [156], therefore mobility should be assessed using validated instruments such as the Bartel Orcats or ADL scales [156-157]. Data on walking aids or wheelchairs, gait speed, and manual dexterity may also be collected.
- **Cognitive function:** Cognitive function impairment and/or dementia increase the risk of incontinence [158]. The Mini-Mental Status Scale Examination [130] assesses global cognitive function, and the Confusion Assessment Method (CAM) [159] is a standardized assessment for delirium. A battery of neuropsychological tests to measure subtle impairments in cognitive function include the Buschke Selective Reminding Test (verbal learning and memory) [160], the Digit Symbol (incidental memory, visual scanning and motor speed) [161], and the Trails A (attention and visual) [162].

Outcome measures should be selected for applicability to the frail elderly. Commonly used self-reported measures of frequency of urinary symptoms, severity, or level of bother may not be possible in the cognitively impaired frail elderly patient. Similarly, voiding diaries that have been shown to be valid and reliable in assessing urinary frequency, nocturia, and incontinence episodes by type [138, 162-164] may not be feasible or reliable. Motivated and trained staff, caregivers, or family members may be able to adequately collect diary data; however, this has not been validated.

In nursing home or inpatient settings, **wet checks by staff** at set intervals have been used in a number of studies. There are limitations to the measurement including visually determining what is “wet” because of new absorbent materials and staff reports not always being reliable or valid, due to underreporting [165-166]. To overcome the limitation of defining wetness and underreporting, 24-hour **pad weighing tests** [167-168] may be used. Pad weighing tests and wet checks are feasible and can provide important outcome data if staff is well trained and checks are often [14]. New outcome measures specific to the frail older population such as increased socialization or decreased caregiver burden need to be developed.

4. CHILDREN

The conduct of clinical research in children is generally more difficult than in adults. Four overriding issues separate pediatric research from the general recommendations. First, physiology varies widely within the group referred to as “children”, differs from adults, and changes with time. Because children are growing, any treatment, especially pharmacological and surgical therapy, may affect them profoundly in the long term. This is particularly true of the immature brain, nervous system and other incompletely developed systems. Second, compliance with therapy is more complicated as children may depend on caregivers to administer treatment in many studies. Third, reporting of symptoms and outcomes may be difficult. Symptoms reported by a caregiver may not be interpreted in the same way as the child. Finally, the issue of informed consent is complex with children.

Urinary incontinence in children falls into four main categories: neurogenic (myelomeningocele and other less common neurogenic etiologies), **monosymptomatic nocturnal enuresis, detrusor overactivity,** and **dysfunctional voiding without neurologic disease.** This issue of age groups is most crucial in children with myelomeningocele. These children are often on medication beginning at a very young age and continuing for many years; the long-term safety of medications in children must be established in all age groups. Therapy for other causes of incontinence in children tends to start at a later age, by which time size is the main difference between children. We recommend that clinical studies have long-term (five years or more), open label extension arms to monitor safety, particularly focusing on normal growth and development and the effects on treatment of liver and central nervous system function.

Assessment of compliance with therapy is always difficult, and even more so with children. Compliance with voiding diaries, a significant issue in the adult population, may be even more problematic with children. The social and family interactions between the child and parent or carer can influence the accuracy of data collection and treatment compliance, both positively and negatively.

Outcome measures are not as well developed in children as in adults. Validated, age-specific symptom and disease-specific quality of life instruments must be developed for the pediatric population. Early efforts in this area have been reported for dysfunctional voiding [169] and daytime incontinence [170]; much more work remains to be done. Invasive urodynamics can be used when deemed appropriate (specifically in the neurogenic population); however, the test-retest reproducibility of urodynamic investigations in children is still under investigation.

Recommendations for Research in Children:

- Long-term follow-up is of critical importance in the pediatric population in order to ascertain the effect of a treatment on normal growth and development. **HIGH**
- Research is needed to develop standardized outcome measures including validated, age-specific symptom and disease-specific quality of life outcome measures. **MEDIUM**

5. NEUROGENIC POPULATIONS

a) Classification

Classification of NLUTD has three primary aims—to aid in discriminating or identifying an unknown underlying neurological disease process, to characterize the nature of the dysfunction so as to develop a treatment plan, and to assess the risk of secondary effects (e.g. on the upper tract) which may influence the necessity and aggressiveness of treatment. The latter two are clearly relevant to research in neurogenic incontinence and must be reflected in study design and patient description.

It is difficult to find a classification system of NLUTD as a base for research that is satisfactory for each of the three aims. The published systems have been reviewed in detail [171]. Both the disease process and the site of the neurologic lesion(s) are relevant in the study of NLUTD, yet even this information is inadequate to predict the functional characteristics for an individual patient. There is no one method that meets the broad needs of classification in this group. Typical or classic cases are often well described but it is especially difficult to describe mixed and incomplete lesions. Thus, classification systems necessarily oversimplify or become extremely cumbersome. Finally, it must be acknowledged that the complexity of neurologic diseases and variations in individual behavior almost always call for a customized approach to therapy, further complicating research in the neurogenic patient. All of these factors complicate study design as it becomes difficult to create workable inclusion and exclusion criteria that apply to other than a narrow segment of the neurogenic population. Ideally a broad population of potentially relevant participants would be enrolled in research studies with full characterization of both the neurologic condition and the nature of the lower urinary tract dysfunction so as to allow for subgroup analysis.

b) History and evaluation:

Study planning is best undertaken with the cooperation of urologist, neurologist, and other clinicians, who have a specific interest and special training in the neurogenic patient. Baseline data collected by history in subjects with neurogenic lower urinary tract disorders should include:

- bladder volumes by diary or examination (maximum voided or catheterized volume, post voiding residual urine, total capacity);
- mechanism of bladder evacuation: normal (volitional), spontaneous involuntarily (“reflex”), Credé, sterile intermittent catheter (SIC), clean intermittent catheter (CIC), intermittent catheter by second person, or suprapubic or urethral catheter;
- use of external appliances (e.g., diaper or pad use, condom catheter, urethral catheter, suprapubic tube);
- the typical time span of continence (continence interval) following last bladder evacuation and maximal continent bladder volume.
- bowel function, sexual function, and specific neurologic deficits
- the evolution of the condition of (changes in)

the upper tract should be included in the outcomes evaluation of treatment for NLUTD.

Where possible these factors should be controlled for in analyses, and stratified for in randomization for interventional studies, or patients with certain factors should be excluded. The details will depend on the research question to be asked.

c) Urodynamics:

Baseline urodynamics are recommended for research studies of neurogenic incontinence, because the symptomatic response is usually of lesser relevance, compared to objective response in NLUTD, especcially where NDO or reduced compliance is involved in the dysfunction. Neurogenic disorders commonly cause complex and generalized lower tract dysfunction, often with combined bladder and urethral sphincter abnormalities.

Recommendations for Research in Populations Affected by Neurogenic Lower Urinary Tract Dysfunction:

- Detailed urodynamic studies are recommended for classification of neurogenic lower urinary tract disorders in research studies because the nature of the lower tract dysfunction cannot be accurately predicted from clinical data. Videourodynamic studies are preferred but are not mandatory. **LOW**
- An area of high priority for research is the development of a classification system to define neurogenic lower urinary tract disorders. Relevant features could include the underlying diagnosis, the symptoms, more precise documentation of the neuromuscular lesion by clinical neurophysiologic testing, and the nature of the urodynamic abnormality. **LOW**

6. RECOMMENDATIONS FOR RESEARCH IN POPULATIONS AFFECTED BY FAECAL INCONTINENCE

- High quality, validated, symptom and bother scores (e.g., ICIQ-BS, Wexner score, FQIL, Manchester Questionnaire, FISI) should be employed when assessing outcomes **HIGH**
- Due to the high concordance of faecal and urinary incontinence, and the potential for urinary incontinence therapy to affect bowel function, data on faecal incontinence should be collected at the outset and during trials of urinary incontinence whenever practical. **HIGH**

7. RECOMMENDATIONS FOR RESEARCH IN POPULATIONS AFFECTED BY BLADDER PAIN SYNDROME (INCLUDING INTERSTITIAL CYSTITIS)

- Broader entry criteria should be used to reflect the full spectrum of the BPS/IC patient population. **MEDIUM**
- The primary endpoint of BPS/IC trials should be patient driven and the Global Response Assessment is recommended. A wide spectrum of secondary endpoints will be useful in defining the effect of treatments. **MEDIUM**

8. RECOMMENDATIONS FOR RESEARCH IN POPULATIONS AFFECTED BY PELVIC ORGAN PROLAPSE

- A validated standardized assessment of prolapse (eg POP-Q) should be used for baseline and outcome assessments. **HIGH**
- Complete reporting of outcomes including a validated assessment of anatomy, functional status, and complications is essential. **HIGH**
- Complications/adverse events (especially for mesh) must be explicitly and completely
- Long term outcomes (> 2 years) of intervention studies are needed **HIGH**

XIV. CONCLUSIONS

The 2012 Consultation examined and classified available data in order to determine the level of evidence that supports our care of incontinent patients. This committee's contribution was to provide guidance to facilitate high quality research for the next Consultation. All quality research, be it prospective or retrospective, clinical or preclinical, begins with a clear research question and benefits from detailed planning—establishing a clear and relevant hypothesis, developing a trial of appropriate magnitude to accept or reject the hypothesis, and defining methods of adequate sensitivity and specificity to produce credible data.

REFERENCES

1. Abrams P, Blaivas JG, Stanton SL, Andersen JT. The standardisation of terminology of lower urinary tract function. the international continence society committee on standardisation of terminology. Scand J Urol Nephrol Suppl. 1988;114:5-19.
2. Bates P, Bradley WE, Glen E, Melchior H, Rowan D, Sterling A, et al. The standardization of terminology of lower urinary tract function. Eur Urol. 1976;2(6):274-6.
3. Bates P, Glen E, Griffiths D, Melchior H, Rowan D, Sterling A, et al. Second report on the standardization of terminology of lower urinary tract function. procedures related to the evaluation of micturition: Flow rate, pressure measurement, symbols. Act Urol Jpn. 1977;27:1563-6.
4. Bates P, Bradley WE, Glen E, Griffiths D, Melchior H, Rowan D, et al. Third report on the standardisation of terminology of lower urinary tract function. procedures related to the evaluation of micturition: Pressure flow relationships, residual urine. Euro Urol. 1980;6:171-.
5. Fourth report on the standardisation of terminology of lower urinary tract function. terminology related to neuromuscular dysfunction of the lower urinary tract. produced by the international continence society. Br J Urol. 1981 Aug;53(4):333-5.
6. Abrams P, Blaivas JG, Stanton SL, Andersen J, Fowler CJ, Gerstenberg T, et al. Sixth report on the standardisation of terminology of lower urinary tract function. procedures related to neurophysiological investigations: Electromyography, nerve conduction studies, reflex latencies, evoked potentials and sensory testing. Br J Urol. 1987;59(4):300-4.
7. Rowan D, James ED, Kramer AE, Sterling AM, Suhel PF. Urodynamic equipment: Technical aspects. produced by the international continence society working party on urodynamic equipment. J Med Eng Technol. 1987 Mar-Apr;11(2):57-64.
8. Andersen J, Blaivas J, Cardozo L, Thuroff J. Lower urinary tract rehabilitation techniques: Seventh report on the standardization of terminology of lower urinary tract function. Int Urogynecol J. 1992;3:75 - 80.
9. Bump R, Mattiasson A, Bo K, Klarskov P, Smith ARB, Brubaker L, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obset Gynecol. 1996;175:10-7.
10. Griffiths D, Hofner K, van Mastrigt R, Rollema HJ, Spangberg A, Gleason D. Standardization of terminology of lower urinary tract function: Pressure-flow studies of voiding, urethral resistance, and urethral obstruction. international continence society subcommittee on standardization of terminology of pressure-flow studies. Neurourol Urodyn. 1997;16(1):1-18.
11. Mattiasson A, Djurhuus JC, Fonda D, Lose G, Nordling J, Stohrer M. Standardization of outcome studies in patients with lower urinary tract dysfunction: A report on general principles from the standardisation committee of the international continence society. Neurourol Urodyn. 1998;17(3):249-53.
12. Lose G, Fantl JA, Victor A, Walter S, Wells TL, Wyman J, et al. Outcome measures for research in adult women with symptoms of lower urinary tract dysfunction. Neurourol Urodyn. 1998;17(3):255-62.
13. Nordling J, Abrams P, Ameda K, Andersen JT, Donovan J, Griffiths D, et al. Outcome measures for research in treatment of adult males with symptoms of lower urinary tract dysfunction. Neurourol Urodyn. 1998;17(3):263-71.
14. Fonda D, Resnick NM, Colling J, Burgio K, Ouslander JG, Norton C, et al. Outcome measures for research of lower urinary tract dysfunction in frail older people. Neurourol Urodyn. 1998;17(3):273-81.
15. Tjandra J, Chan M, Yeh C, Murray-Green C. Sacral nerve stimulation is more effective than optimal medical therapy for severe fecal incontinence: A randomized, controlled study. Dis Colon Rectum. 2008;51:494-502.
16. Blaivas JG, Appell RA, Fantl JA, Leach G, McGuire EJ, Resnick NM, et al. Standards of efficacy for evaluation of treatment outcomes in urinary incontinence: Recommendations of the urodynamic society. Neurourol Urodyn. 1997;16(3):145-7.
17. Blaivas JG, Appell RA, Fantl JA, Leach G, McGuire EJ, Resnick NM, et al. Definition and classification of urinary incontinence: Recommendations of the urodynamic society. Neurourol Urodyn. 1997;16(3):149-51.
18. Blaivas JG. Outcome measures for urinary incontinence. Urology. 1998 Feb;51(2A Suppl):11-9.
19. Protection of human subjects [Internet].: Department of Health and Human Services; 2005. Available from: http://www.hhs.gov/ohrp/.
20. Federman D, Hanna K, Rodriguez LL. Responsible research: A systems approach to protecting research participants. Washington, DC: The National Academices Press; 2002.
21. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA. 2000 May 24-31;283(20):2701-11.
22. Sung NS, Crowley WF,Jr, Genel M, Salber P, Sandy L, Sherwood LM, et al. Central challenges facing the national clinical research enterprise. JAMA. 2003 Mar 12;289(10):1278-87.
23. Barnbaum DR, Byron M. Research ethics: Text readings. Upper Saddle River, NJ: Prentice Hall; 2001.
24. Gallin J. Principles and practices of clinical research. 2002: Academic Press; 2002.
25. Shamoo AE, Resnik DB. Responsible conduct of research. New York, NY: Oxford University Press; 2003.
26. Weijer C, Miller PB. When are research risks reasonable in relation to anticipated benefits? Nat Med. 2004 Jun;10(6):570-3.
27. Ethical priciples and guidelines for the protection of human subjects of research [Internet].: The Belmont Report; 1979. Available from: http://ohsr.od.nih.gov/guidelines/belmont.html
28. Donovan J, Mills N, Smith M, Brindle L, Jacoby A, Peters T, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. commentary: Presenting unbiased information to patients can be difficult. BMJ. 2002 Oct 5;325(7367):766-70.
29. Featherstone K, Donovan JL. Random allocation or allocation at random? patients' perspectives of participation in a randomised controlled trial. BMJ. 1998 Oct 31;317(7167):1177-80.
30. Hulley ST, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clinical research. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2007.
31. Laine C, Horton R, DeAngelis CD, Drazen JM, Frizelle FA, Godlee F, et al. Clinical trial registration — looking back and moving ahead. N Engl J Med. 2007 06/28; 2012/02;356(26):2734-6.
32. Statistical considerations in the design of clinical trials [Internet].: International Conference on Harmonisation; May 29, 2001. Available from: http://www.ifpma.org/pdfifpma/e9.pdf.
33. Friedman LM, Furberg CD, DeMets DL. Fundalmentals of clinical trials. 3rd ed. New York: Springer Verlag; 1998.
34. Pagano M, Gauvreau K. Principles of biostatistics. 2nd ed. Pacific Grove, CA: Duxbury Press; 2000.

35. Vittinghoff E, Glidden DV, Shiboski SC. Regression methods in biostatistics. Springer; 2005.

36. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database--update and key issues. N Engl J Med. 2011 Mar 3;364(9):852-60.

37. Hicks LK, Laupacis A, Slutsky AS. A primer on data safety monitoring boards: Mission, methods, and controversies. Intensive Care Med. 2007 Oct;33(10):1815-8.

38. Slutsky AS, Lavery JV. Data safety and monitoring boards. N Engl J Med. 2004 Mar 11;350(11):1143-7.

39. Grant A, et al. Issues in data monitoring and interim analysis of trials. Health Technol. Vol. 9(7) DOI 10.3310/hta9070

40. Sydes MR, Altman DG, Babiker AB, Parmar MK, Spiegelhalter DJ, DAMOCLES Group. Reported use of data monitoring committees in the main published reports of randomized controlled trials: A cross-sectional study. Clin Trials. 2004 Feb;1(1):48-59.

41. Society for Clinical Data Management. Good clinical data management practices. 2nd ed. Hillsborough, NJ: ; 2002.

42. Lundberg GD, Glass RM. What does authorship mean in a peer-reviewed medical journal? JAMA. 1996 Jul 3;276(1):75.

43. Task force on financial conflicts of interest in clinical research protecting subjects, preserving trust, promoting progress II: Principles and recommendations for oversight of an institutions's financial interests in human subjects research [Internet].; 2002.

44. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: A systematic review. JAMA. 2003 Jan 22-29;289(4):454-65.

45. Spilker B. Guide to clinical studies and developing protocols. New York: Raven Press; 1984.

46. Pocock S. Clinical trials: A practical approach. Chichester: Wiley; 1983.

47. Altman D. Practical statistics for medical research. London: Chapman & Hall; 1991.

48. Simon R, Thall P. Phase II trials. In: Armitage P, Colton T, editors. Encyclopedia of Biostatistics. 1st ed. Chichester, UK: Wiley; 1998. p. 3370-6.

49. A proposal for structured reporting of randomized controlled trials. the standards of reporting trials group. JAMA. 1994 Dec 28;272(24):1926-31.

50. Senn S. Statistical issues in drug development. Chirchester: Wiley; 1997.

51. Peters T, Wildschut H, Weiner C. Epidemiologic considerations in screening. In: Wildschut H, Weiner CP, Peters TJ, editors. When to screen in obstetrics and gynecology. London: WB Saunders; 1996.

52. Rosenberger WF, Lachin JM. Randomization in clinical trials: Theory and practice. Colton T, editor. New York: Wiley; 2002.

53. Armitage P. Statisticals methods in medical research. Oxford: Blackwell Science; 1994.

54. McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials: A systematic review. JAMA. 2003 May 21;289(19):2545-53.

55. Montgomery AA, Peters TJ, Little P. Design, analysis and presentation of factorial randomised controlled trials. BMC Med Res Methodol. 2003 Nov 24;3:26.

56. Donner A, Klar N. Design and analysis of cluster randomization trials in health research. London: Arnold; 2000.

57. Fleming TR, Odem-Davis K, Rothmann MD, Li Shen Y. Some essential considerations in the design and conduct of non-inferiority trials. Clin Trials. 2011 08;8(4):432-9.

58. Schumi J, Wittes J. Through the looking glass: Understanding non-inferiority. Trials. 2011;12:106.

59. Kaul SD,George A. Good enough: A primer on the analysis and interpretation of noninferiority trials. Ann Intern Med. 2006 July 4;145(1):62-9.

60. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Guidance for industry non-inferiority clinical trials. Silver Spring, Maryland: U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research; 2010.

61. Committee for Medicinal Products for Human Use, editor. Guideline on the choice of the non-inferiority margin. London, England: Eruopean Medicines Agency; 2005.

62. European Medicines Agency, editor. Choice of control group in clinical trials. London, England: ; 2001.

63. Nager CW, Brubaker L, Daneshgari F, Litman HJ, Dandreo KJ, Sirls L, et al. Design of the value of urodynamic evaluation (ValUE) trial: A non-inferiority randomized trial of preoperative urodynamic investigations. Contemporary Clinical Trials. 2009 Nov;30(6):531-9.

64. Siegel JP. Equivalence and noninferiority trials. Am Heart J. 2000 Apr;139(4):S166-70.

65. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: The importance of rigorous methods. BMJ. 1996 Jul 6;313(7048):36-9.

66. Powers JH. Noninferiority and equivalence trials: Deciphering 'similarity' of medical interventions. Stat Med. 2008 Feb 10;27(3):343-52.

67. Richter HE, Albo ME, Zyczynski HM, Kenton K, Norton PA, Sirls LT, et al. Retropubic versus transobturator midurethral slings for stress incontinence. N Engl J Med. 2010 Jun 3;362(22):2066-76.

68. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. J Chronic Dis. 1967;20(637):648.

69. Newell DJ. Intention-to-treat analysis: Implications for quantitative and qualitative research. Int J Epidemiol. 1992 Oct;21(5):837-41.

70. Matthews J. An introduction to randomized controlled clinical trials. 1st ed. London: Arnold; 2000.

71. Friedman LM, Furberg CD, DeMets DL. Fundamentals of clinical trials. 3rd ed. Springer Verlag; 1998.

72. Moher D, Jones A, Lepage L, CONSORT Group (Consolitdated Standards for Reporting of Trials). Use of the CONSORT statement and quality of reports of randomized trials: A comparative before-and-after evaluation. JAMA. 2001 Apr 18;285(15):1992-5.

73. Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. Ann Intern Med. 2002 Feb 5;136(3):254-9.

74. Egger M, Juni P, Bartlett C, CONSORT Group (Consolidated Standards of Reporting of Trials). Value of flow diagrams in reports of randomized controlled trials. JAMA. 2001 Apr 18;285(15):1996-9.

75. Hilton P, Robinson D. Defining cure. Neurourol Urodyn. 2011;30(5):741-745.

76. Fitzpatrick R, Davey C, Buxton MJ, Jones DR. Evaluating patient-based outcome measures for use in clinical trials. Health Technol Assess. 1998;2(14):i,iv, 1-74.

77. Sung VW, Marques F, Rogers RR, Williams DA, Myers

DL, Clark MA. Content validation of the patient-reported outcomes measurement information system (PROMIS) framework in women with urinary incontinence. Neurourol Urodyn. 2011;30(4):503-9.

78. Dindo D, Demartines N, Claiven PA. Classification of surgical complications. A new proposal with evlaution in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.

79. Campbell MJ, Julious SA, Altman DG. Estimating sample sizes for binary, ordered categorical, and continuous outcomes in two group comparisons. BMJ. 1995 Oct 28;311(7013):1145-8.

80. Machin D. Sample size tables for clinical studies. 2nd ed. Oxford: Blackwell Science; 1997.

81. Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests? BMJ. 2001 Jan 27;322(7280):226-31.

82. Bland M. An introduction to medical statistics. 2nd ed. Oxford: Oxford University Press; 1995.

83. Sterne J. Commentary: Null points--has interpretation of significance tests improved? Int J Epidemiol. 2003 Oct;32(5):693-4.

84. Kirkwood B, Sterne J. Essential medical statistics. 2nd ed. Oxford: Blackwell Science; 2003.

85. Hoenig JM, Heisey DM. Null points - has interpretation of significance tests improved. J Am Stat. 2001;55:19-24.

86. Hollis S, Campbell F. What is meant by intention to treat analysis? survey of published randomised controlled trials. BMJ. 1999 Sep 11;319(7211):670-4.

87. Lewis JA, Machin D. Intention to treat--who should use ITT? Br J Cancer. 1993 Oct;68(4):647-50.

88. Richards SH, Bankhead C, Peters TJ, Austoker J, Hobbs FD, Brown J, et al. Cluster randomised controlled trial comparing the effectiveness and cost-effectiveness of two primary care interventions aimed at improving attendance for breast screening. J Med Screen. 2001;8(2):91-8.

89. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ. 1990 Jan 27;300(6719):230-5.

90. Zar J. Biostatistical analysis. 2nd ed. New Jersey: Prentic Hall; 1984.

91. Brookes ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: Risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol. 2004 Mar;57(3):229-36.

92. Brookes S. Subgroup analyses in randomized trials: Risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol;In press.

93. Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G. Subgroup analyses in randomised controlled trials: Quantifying the risks of false-positives and false-negatives. Health Technol Assess. 2001;5(33):1-56.

94. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD initiative. Fam Pract. 2004 Feb;21(1):4-10.

95. Moher D, Schulz KF, Altman DG. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001 Apr 14;357(9263):1191-4.

96. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. quality of reporting of meta-analyses. Lancet. 1999 11/27;354(9193):1896-900.

97. Raz S, Erickson DR. SEAPI QMM incontinence classification system. Neurourol Urodyn. 1992;11(3):187-99.

98. Cavadas V, Frederico B, Carvalho F, Osorio L, Gomes M, Silva-Ramos M. The quality of reporting of randomized controlled tirals in pelvic organ prolapse. Int Urogynecol J. 2011;22:1117-11125.

99. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: An extension of the CONSORT statement. BMJ. 2008 Nov 11;337:a2390.

100. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ, CONSORT Group. Reporting of noninferiority and equivalence randomized trials: An extension of the CONSORT statement. JAMA. 2006 Mar 8;295(10):1152-60.

101. Campbell MK, Elbourne DR, Altman DG, CONSORT group. CONSORT statement: Extension to cluster randomised trials. BMJ. 2004 Mar 20;328(7441):702-8.

102. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, CONSORT Group. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: Explanation and elaboration. Ann Intern Med. 2008 Feb 19;148(4):295-309.

103. Altman DG. Better reporting of randomised controlled trials: The CONSORT statement. BMJ. 1996 Sep 7;313(7057):570-1.

104. Peters TJ, Richards SH, Bankhead CR, Ades AE, Sterne JA. Comparison of methods for analysing cluster randomized trials: An example involving a factorial design. Int J Epidemiol. 2003 Oct;32(5):840-6.

105. Schwartz G, Beatty J, editors. Biofeedbak: Theory and research. New York: Academic Press; 1977.

106. Bo K. Pelvic floor muscle training for stress urinary incontinence. In: Bo K, Berghumans B, Morkved S, Van Kampen M, editors. Evidence-based physical therapy for the pelvic floor. Philadelphia, Pa: Churchill Lingstone Elsevier; 2007. p. 171-87.

107. Kegel AH. Stress incontinence and genital relaxation; a nonsurgical method of increasing the tone of sphincters and their supporting structures. . 1952;Ciba Clin Symp(4):35-51.

108. Benvenuti F, Caputo GM, Bandinelli S, Mayer F, Biagini C, Sommavilla A. Reeducative treatment of female genuine stress incontinence. Am J Phys Med. 1987;66(4):155-68.

109. Bump RC, Hurt WG, Fantl JA, Wyman JF. Assessment of kegel pelvic muscle exercise performance after brief verbal instruction. American Journal of Obstetrics & Gynecology. 1991;165(2):322,7; discussion 327-9.

110. Larsen S, Oseid S. Knowledge about and ability to correct pelvic floor muscle exercises in women with urinary stress incontinence. Neurourol Urodynam. 1988;7(3):261-2.

111. Bo K, Sherburn M. Evaluation of female pelvic-floor muscle function and strength. Phys Ther. 2005 Mar;85(3):269-82.

112. Indrekvam S, Hunskaar S. Side effects, feasibility, and adherence to treatment during home-managed electrical stimulation for urinary incontinence: A norwegian national cohort of 3,198 women. Neurourology & Urodynamics. 2002;21(6):546-52.

113. McKinlay JB. From "promising report" to "standard procedure": Seven stages in the career of a medical innovation. Milbank Mem Fund Q Health Soc. 1981 Summer;59(3):374-411.

114. Bo K, Herbert RD. When and how should new therapies become routine clinical practice? Physiotherapy. 2009 Mar;95(1):51-7.

115. Dumoulin C, Lemieux MC, Bourbonnais D, Gravel D, Bravo G, Morin M. Physiotherapy for persistent postnatal stress urinary incontinence: A randomized controlled trial. Obstet Gynecol. 2004 Sep;104(3):504-10.

116. Herbert RD, Bo K. Analysis of quality of interventions in systematic reviews. BMJ. 2005 Sep 3;331(7515):507-9.

117. World Confederation for Physical Therapy, editor. Description of physical therapy. London: ; 1999.

118. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: Problems and possible solutions. BMJ. 2002 Jun 15;324(7351):1448-51.

119. McLeod RS, Wright JG, Solomon MJ, Hu X, Walters BC, Lossing A. Randomized controlled trials in surgery: Issues and problems. Surgery. 1996 May;119(5):483-6.

120. Chalmers TC. Randomization of the first patient. Med Clin North Am. 1975 Jul;59(4):1035-8.

121. Nygaard I, Holcomb R. Reproducibility of the seven-day voiding diary in women with stress urinary incontinence. International Urogynecology Journal. 2000;11(1):15-7.

122. Gates E. Ethical considerations in the incorporation of new technologies into gynecologic practice. Clinical Obstetrics & Gynecology. 2000 September;43(3):540-50.

123. Hall JC, Mills B, Nguyen H, Hall JL. Methodologic standards in surgical trials. Surgery. 1996 Apr;119(4):466-72.

124. Baum M. Reflections on randomised controlled trials in surgery. Lancet. 1999 Apr;353 Suppl 1:SI6-8.

125. Frader J, Caniano D, editors. Research and innovation in surgery. Houston, Tx: Oxford University Press; 1998.

126. Korn AP, Learman LA. Operations for stress urinary incontinence in the united states, 1988-1992. Urology. 1996 Oct;48(4):609-12.

127. Waetjen LE, Subak LL, Shen H, Lin F, Wang TH, Vittinghoff E, et al. Stress urinary incontinence surgery in the united states. Obstetrics & Gynecology. 2003;101(4):671-6.

128. Solomon MJ, Laxamana A, Devore L, McLeod RS. Randomized controlled trials in surgery. Surgery. 1994 Jun;115(6):707-12.

129. Solomon MJ, McLeod RS. Should we be performing more randomized controlled trials evaluating surgical operations? Surgery. 1995 Sep;118(3):459-67.

130. Folstein, M.F., Folstein, S.E., McHugh,P.R. "Mini-mental state:" a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.

131. Ward K, Hilton P, United Kingdom and Ireland Tension-free Vaginal Tape Trial Group. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ. 2002 Jul 13;325(7355):67.

132. Hilton P. Trials of surgery for stress incontinence?thoughts on the ?humpty dumpty principle? BJOG: An International Journal of Obstetrics & Gynaecology. 2002;109(10):1081-8.

133. Maddern GJ, Middleton PF, Grant AM. Urinary stress incontinence. BMJ. 2002 Oct 12;325(7368):789-90.

134. Tennstedt S, et al. Design of the SISTEr (stress incontinence surgical treatment efficacy trial) study: A randomized surgical trial comparing the burch colposuspenion and the autologous rectal fascial sling. Am J Obset Gynecol. In press.

135. McLeod RS. Issues in surgical randomized controlled trials. World J Surg. 1999 12;23(12):1210-4.

136. Finkelstein E, Corso P. Cost-of-illness analyses for policy making: A cautionary tale of use and misuse. Expert Rev Pharmacoecon Outcomes Res. 2003 Aug;3(4):367-9.

137. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. panel on cost-effectiveness in health and medicine. JAMA. 1996 Oct 9;276(14):1172-7.

138. Brown JS, McNaughton KS, Wyman JF, Burgio KL, Harkaway R, Bergner D, et al. Measurement characteristics of a voiding diary for use by men and women with overactive bladder. Urology. 2003 Apr;61(4):802-9.

139. Chang RW, Pellisier JM, Hazen GB. A cost-effectiveness analysis of total hip arthroplasty for osteoarthritis of the hip. JAMA. 1996 Mar 20;275(11):858-65.

140. Subak LL, Caughey AB. Measuring cost-effectiveness of surgical procedures. Clinical Obstetrics & Gynecology. 2000;43(3):551-60.

141. Fusco F, Groutz A, Blaivas JG, Chaikin DC, Weiss JP. Videourodynamic studies in men with lower urinary tract symptoms: A comparison of community based versus referral urological practices. Journal of Urology. 2001;166(3):910-3.

142. Griffiths CJ, Harding C, Blake C, McIntosh S, Drinnan MJ, Robson WA, et al. A nomogram to classify men with lower urinary tract symptoms using urine flow and noninvasive measurement of bladder pressure. J Urol. 2005 Oct;174(4 Pt 1):1323,6; discussion 1326; author reply 1326.

143. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T, et al. Postmenopausal hormones and incontinence: The heart and Estrogen/Progestin replacement study. Obstet Gynecol. 2001 Jan;97(1):116-20.

144. Jackson S, Shepherd A, Brookes S, Abrams P. The effect of oestrogen supplementation on post-menopausal urinary stress incontinence: A double-blind placebo-controlled trial. Br J Obstet Gynaecol. 1999 Jul;106(7):711-8.

145. Grodstein F, Lifford K, Resnick NM, Curhan GC. Postmenopausal hormone therapy and risk of developing urinary incontinence. Obstet Gynecol. 2004 Feb;103(2):254-60.

146. Fultz NH, Herzog AR, Raghunathan TE, Wallace RB, Diokno AC. Prevalence and severity of urinary incontinence in older african american and caucasian women. J Gerontol A Biol Sci Med Sci. 1999 Jun;54(6):M299-303.

147. Wetle T, Scherr P, Branch LG, Resnick NM, Harris T, Evans D, et al. Difficulty with holding urine among older persons in a geographically defined community: Prevalence and correlates. J Am Geriatr Soc. 1995 Apr;43(4):349-55.

148. Thom D, Brown J. Reproductive and hormonal risk factors for urinaty incontinence: Review of the clinical and epidemiologic literature. Journal of the American Geriatrics Society. 1998;46:1411-7.

149. Brown JS, Seeley DG, Fong J, Black DM, Ensrud KE, Grady D. Urinary incontinence in older women: Who is at risk? study of osteoporotic fractures research group. Obstetrics & Gynecology. 1996;87(5 Pt 1):715-21.

150. Brown JS, Grady D, Ouslander JG, Herzog AR, Varner RE, Posner SF. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. heart & Estrogen/Progestin replacement study (HERS) research group. Obstetrics & Gynecology. 1999;94(1):66-70.

151. Diokno AC, Brock BM, Herzog AR, Bromberg J. Medical correlates of urinary incontinence in the elderly. Urology. 1990 Aug;36(2):129-38.

152. Brown JS, Sawaya G, Thom DH, Grady D. Hysterectomy and urinary incontinence: A systematic review.[comment]. Lancet. 2000;356(9229):535-9.

153. Marshall HJ, Beevers DG. Alpha-adrenoceptor blocking drugs and female urinary incontinence: Prevalence and reversibility. Br J Clin Pharmacol. 1996 Oct;42(4):507-9.

154. Fantl JA, Wyman JF, Wilson M, Elswick RK, Bump RC, Wein AJ. Diuretics and urinary incontinence in community-dwelling women. Neurourol Urodyn. 1990;9(1):25-34.

155. Menefee SA, Chesson R, Wall LL. Stress urinary incontinence due to prescription medications: Alpha-blockers and angiotensin converting enzyme inhibitors. Obstet Gynecol. 1998 May;91(5 Pt 2):853-4.

156. Katz S. The index of ADL: A standard measurement of biological and psychological function. JAMA. 1963;185:914-9.

157. Mahoney fi, barthel dw. Functional evaluation: The barthel index. Md State Med J. 1965 Feb;14:61-5.

158. Ouslander J, Johnson T, Nasr S, Schnelle J, Miller M. Atrial natriuretic peptide levels in geriatric patients with nocturia and nursing home residents with nighttime incontinence. Journal of the American Geriatrics Society. 1999;47(12):1439-44.

159. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990 Dec 15;113(12):941-8.

160. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology. 1974 Nov;24(11):1019-25.

161. Wechsler D. Wechsler adult intelligence scale - revised. New York: Psychological Corp; 1988.

162. Homma Y, Ando T, Yoshida M, Kageyama S, Takei M, Kimoto K, et al. Voiding and incontinence frequencies: Variability of diary data and required diary length. Neurourol Urodyn. 2002;21(3):204-9.

163. Groutz A, Blaivas JG, Chaikin DC, Resnick NM, Engleman K, Anzalone D, et al. Noninvasive outcome measures of urinary incontinence and lower urinary tract symptoms: A multicenter study of micturition diary and pad tests. Journal of Urology. 2000;164(3 Pt 1):698-701.

164. Locher JL, Goode PS, Roth DL, Worrell RL, Burgio KL. Reliability assessment of the bladder diary for urinary incontinence in older women. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2001;56(1):M32-5.

165. Ouslander JG, Palmer MH, Rovner BW, German PS. Urinary incontinence in nursing homes: Incidence, remission and associated factors. J Am Geriatr Soc. 1993 Oct;41(10):1083-9.

166. Colling J, et al. Continence program for care dependent elderly (final report). 1995. Report No.: NIH-NCNR-NR01554.

167. Siltberg H, Victor A, Larsson G. Pad weighing tests: The best way to quantify urine loss in patients with incontinence. Acta Obstet Gynecol Scand Suppl. 1997;166:28-32.

168. Griffiths DJ, McCracken PN, Harrison GM. Incontinence in the elderly: Objective demonstration and quantitative assessment. Br J Urol. 1991 May;67(5):467-71.

169. Farhat W, Bagli DJ, Capolicchio G, O'Reilly S, Merguerian PA, Khoury A, et al. The dysfunctional voiding scoring system: Quantitative standardization of dysfunctional voiding symptoms in children. J Urol. 2000 Sep;164(3 Pt 2):1011-5.

170. Sureshkumar P, Craig JC, Roy LP, Knight JF. A reproducible pediatric daytime urinary incontinence questionnaire. J Urol. 2001 Feb;165(2):569-73.

171. Campbell MF. Campbell's urology. 8th ed. Philadelphia, PA: WB Saunders Company; 2004.

2013

Co-Sponsored by

INTERNATIONAL CONSULTATION ON UROLOGICAL DISEASES (ICUD)

EUROPEAN ASSOCIATION OF UROLOGY (EAU)

In collaboration with

the Major International Associations of Urology, Gynecology and Urodynamics

and other medical associations

5th International Consultation on Incontinence

Recommendations of the International Scientific Committee:

Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse and Faecal Incontinence

P. Abrams, K.E. Andersson, W Artibani, L. Birder, D. Bliss, L. Brubaker, L. Cardozo, C. Chapple, A. Cottenden, D. de Ridder, R. Dmochowski, C. Dumoulin, M. Drake, C. Fry, P. Hanno, , S. Herschorn, C. Kelleher, H. Koelbl, S. Khoury, R. Madoff, C. Maher, I. Milsom, K.H. Moore, K.N. Moore, D. Newman, R. Nijman, P. Rosier, D. Staskin, J. Thuroff, A. Tubaro, D. Vodusek, A. Wein,

and the Members of the Committees

INTRODUCTION

The 5th International Consultation on Incontinence met from February 23rd – 25th 2012 in Paris and was organised by the International Consultation on Urological Diseases and the EAU, in order to develop consensus statements for the diagnosis, evaluation and treatment of urinary incontinence, faecal incontinence, pelvic organ prolapse and bladder pain syndrome.

The consensus statements are evidence based following a thorough review of the available literature and the global subjective opinion of recognised experts serving on focused committees. The individual committee reports were developed and peer reviewed by open presentation and comment. The Scientific Committee, consisting of the Chairmen of all the committees then refined the final consensus statements.These consensus statements published in 2013 will be periodically re-evaluated in the light of clinical experience, technological progress and research.

CONTENTS

1. DEFINITIONS
2. EVALUATION
3. MANAGEMENT RECOMMENDATIONS

I. URINARY INCONTINENCE IN CHILDREN

II. URINARY INCONTINENCE IN MEN

III. URINARY INCONTINENCE IN WOMEN

IV. FISTULAE

V. PELVIC ORGAN PROLAPSE

VI. URINARY INCONTINENCE IN NEUROLOGICAL PATIENTS

VII. BLADDER PAIN SYNDROME

VIII. FAECAL INCONTINENCE IN NON-NEUROLOGICAL PATIENTS

IX. FAECAL INCONTINENCE IN NEUROLOGICAL PATIENTS

X. URINARY AND FAECAL INCONTINENCE IN FRAIL OLDER MEN AND WOMEN

4. RECOMMENDATIONS FOR PROMOTION, EDUCATION, AND PRIMARY PREVENTION
5. RECOMMENDATIONS FOR BASIC SCIENCE RESEARCH
6. RECOMMENDATIONS FOR EPIDEMIOLOGY
7. RECOMMENDATIONS FOR CLINICAL RESEARCH

Annex 1 : Bladder Charts and Diaries

Annex 2 : International Consultation on Incontinence Modular Questionnaire (ICIQ) - ICIQ UI SF (short-form)

1. Definitions

The consultation agreed to use the current International Continence Society definitions (ICS) for lower urinary tract dysfunction (LUTD) including incontinence, except where stated. These definitions appeared in the journal Neurourology and Urodynamics (2002; 21:167- 178 and 2006; 25: 293) or can be viewed on the ICS website: www.icsoffice.org

The following ICS definitions are relevant:

1. Lower Urinary Tract Symptoms (LUTS)

LUTS are divided into ***storage*** symptoms and ***voiding*** symptoms.

Urinary incontinence is a storage symptom and defined as the complaint of any involuntary loss of urine. This definition is suitable for epidemiological studies, but when the prevalence of bothersome incontinence is sought, the previous ICS definition of an "Involuntary loss of urine that is a social or hygienic problem ", can be useful.

Urinary incontinence may be further defined according to the patient's symptoms

- ***Urgency Urinary Incontinence*** is the complaint of involuntary leakage accompanied by or immediately preceded by urgency.
- ***Stress Urinary Incontinence*** is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.
- ***Mixed Urinary Incontinence*** is the complaint of involuntary leakage associated with urgency and also with effort, exertion, sneezing and coughing.
- ***Nocturnal Enuresis*** is any involuntary loss of urine occurring during sleep.
- ***Post-micturition dribble*** and ***continuous urinary leakage*** denotes other symptomatic forms of incontinence.

Overactive bladder is characterised by the storage symptoms of urgency with or without urgency incontinence, usually with frequency and nocturia.

2. Urodynamic Diagnosis

- ***Overactive Detrusor Function***, is characterised by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked.

The overactive detrusor is ***divided*** into:

  - ***Idiopathic Detrusor Overactivity***, defined as overactivity when there is no clear cause
  - ***Neurogenic Detrusor Overactivity*** is defined as overactivity due to a relevant neurological condition.

- ***Urodynamic stress incontinence*** is noted during filling cystometry, and is defined as the involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction.

3. Bladder Pain Syndrome *

- ***Bladder pain syndrome*** is defined as an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptom(s) of more than 6 weeks duration, in the absence of infection or other identifiable causes.

4. Pelvic Organ Prolapse

- ***Uro-genital prolapse*** is defined as the symptomatic descent of one or more of : the anterior vaginal wall, the posterior vaginal wall, and the apex of the vagina (cervix/uterus) or vault (cuff) after hysterectomy. Uro-genital prolapse is measured using the POP-Q system.
- ***Rectal prolapse*** is defined as circumferential full thickness rectal protrusion beyond the anal margin.

5. Anal Incontinence *

- ***Anal incontinence***, defined as "any involuntary loss of faecal material and/or flatus" and may be divided into:
  - ***Faecal incontinence***, any involuntary loss of faecal material
  - ***Flatus incontinence***, any involuntary loss of gas (flatus)

** To date, these definitions are not included in the current ICS terminology*

2. Evaluation

The following phrases are used to classify diagnostic tests and studies:

- ***A highly recommended*** test is a test that should be done on every patient.
- ***A recommended test*** is a test of proven value in the evaluation of most patients and its use is strongly encouraged during initial evaluation.
- ***An optional test is a test*** of proven value in the evaluation of selected patients; its use is left to the clinical judgement of the physician
- ***A not recommended test*** is a test of no proven value.

This section primarily discusses the ***Evaluation of Urinary Incontinence*** with or without ***Pelvic Organ Prolapse*** (POP) and ***Anal Incontinence.***

The recommendations are intended to apply to children and adults, including healthy persons over the age of 65.

These conditions are highly prevalent but often not reported by patients. Therefore, the Consultation strongly recommends case finding, particularly in high risk groups.

I. HIGHLY RECOMMENDED TESTS DURING INITIAL EVALUATION

The ***main recommendations*** for this consultation have been abstracted from the extensive work of the 23 committees of the 5th International Consultation on Incontinence (ICI, 2012).

Each committee has written a report that reviews and evaluates the published scientific work in each field of interest in order to give ***Evidence Based*** recommendations. Each report ends with detailed recommendations and suggestions for a programme of research.

The main recommendations should be read in conjunction with the management algorithms for children, men, women, the frail older person, neurogenic patients, bladder pain, pelvic organ prolapse, and anal incontinence

The ***initial evaluation*** should be undertaken, by a clinician, in every patient presenting with symptoms/signs suggestive of these conditions.

1. History and General Assessment

Management of a disease such as incontinence requires caregivers to ***assess*** the sufferer in a holistic manner. Many factors may influence a particular individual's symptoms, some may cause incontinence, and may influence the choice and the success of treatment. ***The following components of the medical history are particularly emphasized:***

a) Review of Systems:

- Presence, severity, duration and bother of any urinary, bowel or prolapse symptoms. Identifying symptoms in the related organ systems is critical to effective treatment planning. It is useful to use validated questionnaires to assess symptoms.
- Effect of any symptoms on sexual function: validated questionnaires including impact on quality of life are a useful part of a full assessment.
- Presence and severity of symptoms suggesting neurological disease

b) Past Medical History:

- ***Previous conservative, medical and surgical treatment,*** in particular, as they affect the genitourinary tract and lower bowel. The effectiveness and side effects of treatments should be noted.
- ***Coexisting diseases*** may have a profound effect on incontinence and prolapse sufferers, for example asthma patients with stress incontinence will suffer greatly during attacks. Diseases may also precipitate incontinence, particularly in frail older persons.
- ***Patient medication:*** it is always important to review every patient's medication and to make an assessment as to whether current treatment may be contributing to the patient's condition.
- ***Obstetric and menstrual history.***
- ***Physical impairment:*** individuals who have compromised mobility, dexterity, or visual acuity may need to be managed differently

c) Social History:

- ***Environmental issues:*** these may include the social, cultural and physical environment.

- ***Lifestyle***: including exercise, smoking and the amount and type of food/fluid intake.

d) Other Treatment Planning Issues:

- ***Desire for treatment*** and the extent of treatment that is acceptable
- ***Patient goals*** and expectations of treatment
- ***Patient support*** systems (including caregivers).
- ***Cognitive function***: all individuals need to be assessed for their ability to fully describe their symptoms, symptom bother and quality of life impact, and their preferences and goals for care. They must be able to understand proposed management plans and to discuss, where appropriate, alternative treatment options. In some groups of patients formal testing is essential e.g. cognitive function testing for individuals for whom the clinician has concerns regarding memory deficits and/or inattention/confusion, and depression screening for individuals for whom the clinician has concerns about abnormal affect. Proxy respondents, such as family and caregivers, may be used to discuss history, goals of care, and treatment for individuals with dementia, but only if the individual is incapable of accurate reporting or weighing treatment decisions.

2. Physical Examination

The ***more complicated*** the history and the more extensive and/or invasive the proposed therapy, the ***more complete*** the examination needs to be. Depending on the patient's symptoms and their severity, there are a number of components in the examination of patients with incontinence and/or pelvic organ prolapse.

Physical examination should be performed regardless of whether the patient is a child, a woman, a man, someone with neurological disease or a frail elderly person.

a) General status:

- Mental status
- Obesity (BMI)
- Physical dexterity and mobility

b) Abdominal/flank examination: for masses, bladder distention, relevant surgical scars

c) Pelvic examination:

- Examination of the perineum and external genitalia including tissue quality and sensation.
- Vaginal (half-speculum) examination for pelvic organ prolapse (POP)
- Bimanual pelvic and anorectal examination for pelvic mass, pelvic floor muscle function, etc
- Stress test for urinary incontinence.

d) Neurological testing (see chapter on assessment)

3. Urinalysis

In patients with urinary symptoms a ***urinary tract infection*** is a readily detected, and easily treatable cause of LUTS, and urine testing is highly recommended. Testing may range from dipstick testing, to urine microscopy and culture when indicated.

Conclusion

For simple treatments, particularly non-invasive and inexpensive therapies, management may start without the need for the further investigations listed below.

II. RECOMMENDED FURTHER ASSESSMENT PRIOR TO, OR DURING, SPECIALIST ASSESSMENT

The tests below are recommended when the **appropriate indication(s) is present**. Some recommended tests become highly recommended in specific situations.

This section should also be read in conjunction with the relevant committee reports.

1. Further Symptom and Health-Related QoL Assessment

In patients with ***urinary symptoms*** the use of a ***simple frequency volume chart*** or ***bladder diary*** (examples in Annex 1) is highly recommended to document the frequency of micturition, the volumes of urine voided, incontinence episodes and the use of incontinence pads.

The use of the ***highest quality questionnaires*** (Grade A, where available) is recommended for the assessment of the patient's perspective of symptoms of incontinence and their impact on quality of life.

The ICIQ is highly recommended (Grade A) for the basic evaluation of the patient's perspective of urinary incontinence, with other Grade A questionnaires recommended for more detailed assessment. ***Further development is required in the areas*** of pelvic organ prolapse, bladder pain syndrome, and for specific patient groups, as only Grade B questionnaires are currently available (see Annex 1).

2. Renal Function Assessment

Standard ***biochemical tests for renal function*** are recommended in patients with urinary incontinence and a possibility of ***renal impairment.***

3. Uroflowmetry

Uroflowmetry with the measurement of post void residual urine is recommended as a screening test for symptoms suggestive of urinary voiding dysfunction or physical signs of POP or bladder distension.

4. Estimation of Post Void Residual Urine (PVR)

In patients with ***suspected voiding dysfunction***, PVR should be part of the initial assessment if the result is likely to influence management, for example, in neurological patients.

5. Imaging

Although ***routine imaging is not recommended,*** imaging of the lower urinary tract and pelvis is ***highly recommended*** in those with ***urinary symptoms*** whose initial evaluation indicates a possible co-existing lower tract or pelvic pathology. Initial imaging may be by ultrasound, or plain X ray.

Imaging of the upper urinary tract is highly recommended in specific situations. These include:

- Haematuria,
- Neurogenic urinary incontinence e.g. myelodysplasia, spinal cord trauma,
- Incontinence associated with significant post-void residual,
- Co-existing loin/kidney pain,
- Severe pelvic organ prolapse, not being treated
- Suspected extra-urethral urinary incontinence,
- Children with incontinence and UTIs, where indicated
- Urodynamic studies which show evidence of poor bladder compliance.

In anorectal conditions, anal US or MRI prior to anal sphincter surgery is highly recommended, when obvious anatomic defects are not evident. Defaecating proctography or dynamic MRI is recommended in suspected rectal prolapse which cannot be adequately confirmed by physical examination.

6. Endoscopy

Although ***routine*** cysto-urethroscopy is not recommended, LUT endoscopy is ***highly recommended:***

- When initial testing suggests other pathologies, e.g. haematuria
- When pain or discomfort feature in the patient's LUTS, these may suggest an intravesical lesion
- When appropriate in the evaluation of vesicovaginal fistula and extra-urethral urinary incontinence (in childbirth fistulae, endoscopy is often unnecessary).

In anorectal conditions, proctoscopy or flexible sigmoidoscopy should routinely be performed in the evaluation of patients with faecal incontinence. Colonoscopy, air contrast barium enema or CT colography is highly recommended in the presence of unexplained change in bowel habit, rectal bleeding or other alarm symptoms or signs (see Basic Assessment chapter).

7. Urodynamic Testing

a) Urodynamic evaluation is recommended

- When the results may ***change management***, such as prior to most invasive treatments for UI and POP,
- After ***treatment failure***, if more information is needed in order to plan further therapy,
- As part of both initial and long-term ***surveillance*** programmes in some types of neurogenic lower urinary tract dysfunction,
- In "***complicated incontinence***" (for details please see relevant subcommittee reports).

b) The aims of Urodynamic Evaluation are

- To reproduce the patient's symptoms and correlate these with urodynamic findings
- To assess bladder sensation
- To detect detrusor overactivity
- To assess urethral competence during filling
- To determine detrusor function during voiding
- To assess outlet function during voiding
- To assess residual urine

8. Small bowel follow-through, CT entography or capsule endoscopy.

These tests are recommended in the presence of unexplained diarrhoea or when Crohn's disease is suspected.

III. OPTIONAL DIAGNOSTIC TESTS

1. Additional Urodynamic Testing

Video-urodynamics may be useful in the management of UI in children, in patients who fail surgery and in some neurogenic patients, to obtain additional anatomical information. Both US and X-ray imaging can be used.

If a more ***detailed estimate of urethral function*** is required, then the following optional tests may give useful information:

- Urethral pressure profilometry
- Abdominal leak point pressures
- Video-urodynamics
- Electromyography

If initial urodynamics have failed to demonstrate the cause for the patient's incontinence then the following tests are optional:

- repeated routine urodynamics
- ambulatory urodynamics

2. Pad Testing

Pad testing is an optional test for the routine evaluation of urinary incontinence and, if carried out, a 24 hr test is suggested.

3. Neurophysiological Testing and Imaging

The ***information*** gained by clinical examination and urodynamic testing may be ***enhanced*** by ***neuro-physiological testing*** of striated muscle and nervous pathways.

Appropriately trained personnel should perform these tests. The following neuro-physiological tests can be considered in patients with peripheral lesions prior to treatment for lower urinary tract or anorectal dysfunction.

- Concentric needle EMG
- Sacral reflex responses to electrical stimulation of penile or clitoral nerves.

Pudendal nerve latency testing is ***not recommended.***

Further imaging of the central nervous system, including spine, by myelography, CT and MRI may prove useful if simple imaging, for example by spinal X-rays in patients with suspected neurological disease, proves normal.

4. Further Imaging

Cysto-urethrography, US, CT and ***MRI*** may have an indication :

- Suspected pelvic floor dysfunction
- Failed surgery, such as recurrent posterior vaginal wall prolapse or failed sling surgery
- Suspected fixed urethra

5. Cysto-urethroscopy

This is an ***optional test*** in patients with complicated or recurrent UI (e.g. after failed SUI surgery)

6. Anorectal physiology testing

Anorectal manometry is useful to assess resting and squeeze anal pressures.

3. Management Consensus statements

The consensus statements are derived from the ***detailed work in the committee reports*** on the management of incontinence in children, men, women, the frail elderly and neurological patients, as well as those with obstetric fistula, pelvic organ prolapse, bladder pain syndrome, and faecal incontinence. The management of incontinence is presented in ***algorithm form*** with accompanying ***notes.***

The Consultation recognises that no algorithm can be applied to every patient and each patient's management must be individualised.

There are algorithms for

I. Urinary Incontinence in Children
II. Urinary Incontinence in Men
III. Urinary Incontinence in Women
IV. Fistulae
V. Pelvic Organ Prolapse
VI. Urinary Incontinence in Neurological Patients
VII. Bladder Pain Syndrome
VIII. Faecal Incontinence in Non-Neurological Patients
IX. Faecal Incontinence in Neurological Patients
X. Urinary and Faecal Incontinence in Frail Older Men and Women

These algorithms are divided into two for groups I to III, VII and X. The two parts, initial ***management*** and ***specialised management*** require a little further explanation.

Although the management algorithms are designed to be used for patients whose predominant problem is incontinence, there are many other patients in whom the algorithms may be useful such as those patients with urgency and frequency, so-called "***OAB dry***"

➦ The algorithms for *initial management*

are intended for use by all ***clinicians*** including health care assistants, nurses, physiotherapists, generalist doctors and family doctors as well as by specialists such as urologists, geriatricians and gynaecologists. The consultation has attempted to phrase the recommendations in the basic algorithms in such a way that they may be readily used by clinicians in all countries of the world, both in the developing and the developed world.

➦ The *specialised* algorithms

are intended for use by ***specialists***. The specialised algorithms, as well as the initial management algorithms are ***based on evidence where possible,*** and on the ***expert opinion*** of the 400 healthcare professionals who took part in the Consultation. In this consultation, committees ascribed levels of evidence to the published work on the subject and devised grades of recommendation to inform patient management.

It should be noted that these algorithms, dated ***December 2012***, represent the Consultation ***consensus at that time***. Our knowledge, developing from both a research base and because of evolving expert opinion, will inevitably ***change with time.*** The Consultation does not wish those using the algorithms to believe they are "carved in tablets of stone": there will be changes both in the relatively short term and the long term.

◆ Essential components of basic assessment

Each algorithm contains a core of recommendations in addition to a number of essential components of basic assessment listed in sections I to III.

- General assessment
- Symptom assessment
- Assessment of quality of life impact
- Assessment of the desire for treatment
- Physical examination
- Urinalysis

◆ Joint decision making

The patient's desires and goals for treatment : Treatment is a matter for discussion and joint decision making between the patient and his or

her health care advisors. This process of consultation includes the specific need to assess whether or not the sufferer of incontinence wishes to receive treatment and, if so, what treatments he or she would favour. Implicit in this statement is the assumption that the health care provider will give an ***appropriate explanation of the patient's problem*** and the ***alternative lines of management,*** and the indications and the ***risks of treatment.*** The assumption that patients almost always wish to have treatment is flawed, and the need to consult the patient is paramount.

In each algorithm, treatments are listed in ***order of simplicity,*** the least invasive being listed first. This order does not imply a scale of efficacy or cost, two factors which need to be considered in choosing the sequence of therapy. The order is likewise not meant to imply a suggested sequence of therapy, which should be determined jointly by the treating health care provider and the patient, considering all the relevant factors listed above.

In the ***initial management algorithms***, treatment is ***empirically based,*** whilst the ***specialised management*** algorithms usually rely on precise diagnosis from urodynamics and other testing.

The assumption is made that patients will be reassessed at an appropriate time to evaluate their progress.

◆ Use of Continence Products

The possible role of c***ontinence products*** should be considered at each stage of patient assessment and treatment, and if treatment is not (fully) successful, subsequent management.

- ***Firstly***, intermittent catheterisation or indwelling catheter drainage often have a role to play in addressing urinary retention.
- ***Secondly,*** assisted toileting using such devices as commodes, bedpans, and handheld urinals may help to achieve ***dependent continence****** where access, mobility and/or urgency problems undermine a patient's ability to maintain ***independent continence****, be it urinary and / or faecal.
- ***Finally,*** containment products (to achieve ***contained incontinence****) for urine and / or faeces find an essential role in enhancing the quality of life of those who:
- Elect not to pursue treatment options
- Are awaiting treatment
- Are waiting for treatment to take effect
- Are unable to be (fully) cured

Further guidance and care algorithms on which products might be suitable for a given patient are given in Committee 20.

** Useful terms suggested by Fonda & Abrams. (Cure sometimes, help always – a "continence paradigm" for all ages and conditions. Fonda D and Abrams P, Neurology & Urodynamics 25: 290-292, 2006).*

I. URINARY INCONTINENCE IN CHILDREN

A. INITIAL MANAGEMENT

Children present specific management problems for a variety of reasons: assessment requires help from their parents and caregivers; consent to treatment may be problematic; and cooperation in both assessment and treatment may be difficult.

1. Initial *assessment should involve a detailed investigation of voiding and bowel habits using bladder/bowel diaries and structured and validated questionnaires*.

The child's social environment and general and behavioural development should also be formally assessed and recorded. Physical examination should be done to detect a palpable bladder, faecal loading and exclude anatomic and neurogenical causes. Urine analysis and culture is sufficient to exclude the presence of infection. If possible, the child should be observed voiding.

➦ ***Referrals for specialist treatment are recommended for children who have complicated incontinence associated with:***

- Recurrent and febrile urinary infection
- Voiding symptoms or evidence of poor bladder emptying
- Urinary tract anomalies
- Previous pelvic surgery
- Neuropathy or neuropathic origin
- Bowel dysfunction not responsive to treatment
- Comorbid behavioural (e.g. ADHD and ODD) and emotional disorders.

➦ ***Initial treatment is recommended for the remaining patients who have:***

- Nocturnal enuresis without other symptoms (mono-symptomatic enuresis).
- Daytime symptoms of frequency, urgency, voiding postponement, straining, interrupted voiding, urgency incontinence with or without night-time wetting.

2. Treatment

➦ Initial treatment for ***mono-symptomatic nocturnal*** enuresis should include:

- parental and child counselling and motivation
- review of bladder diary with attention to night-time polyuria
- a choice between either bed wetting alarm (Grade A) and anti-diuretic hormone analogues of desmopressin (Grade A). It may be a parental and child choice if advantages and disadvantages are well explained.

➦ ***Daytime incontinence*** should be managed holistically including:

- counselling, timed voiding, behaviour modification and bowel management when necessary (Grade B);
- antimuscarinics may be used if there are symptoms that suggest bladder overactivity (Grade A)

Initial Management of Urinary Incontinence in Children

HISTORY/ SYMPTOM ASSESSMENT

Nocturnal enuresis (monosymptomatic)

Daytime ± Nighttime wetting ± Urgency / frequency

"Complicated" Incontinence associated with:

- Urinary tract anomaly
- Neuropathy
- Pelvic surgery
- Voiding (emptying) symptoms
- Recurrent urinary infection
- Bowel dysfunction not responsive to treatment
- Comorbid behavioral and emotional disorders

CLINICAL ASSESSMENT

General assessment (see relevant chapter)
- Physical examination: abdominal, perineal, ext. genitalia, back/spine, neurological
- Assess bowel function -> if constipated, treat and reassess
- Urinalysis ± Urine culture -> if infected, treat and reassess
- Assess post-void residual urine by abdominal examination (optional : by ultrasound)

PRESUMED DIAGNOSIS

MONOSYMPTOMATIC NOCTURNAL ENURESIS

URGENCY INCONTINENCE

RECURRENT INFECTION

DYSFUNCTIONAL VOIDING

Any other abnormality detected e.g. Post void residual

TREATMENT *

- Explanation/education
- Enuresis Diary
- Alarm
- Desmopressin

Failure

- Explanation/education
- Fluid/voiding regime
- Bladder training
- Antimuscarinics
- Alarm (bed wetting)

Failure

SPECIALISED MANAGEMENT

* At any stage of the patient's care pathway, management may need to include continence products

I. URINARY INCONTINENCE IN CHILDREN

B. SPECIALISED MANAGEMENT

➦ ***Two groups of children*** with ***"complicated" incontinence*** should have specialist management from the outset (Fig. 2).

- Children whose incontinence is due to, or associated with, ***urinary tract anomalies*** and **neuropathy.**
- ***Children*** without urinary tract anomalies, but with ***recurrent febrile infection*** and, proven or suspected, ***lower urinary tract dysfunction***.

➦ Children who ***fail the basic treatment***, but who have neither neurogenic nor anatomical problems, should also receive specialist management.

Children with comorbid behavioural and emotional disorders require referral to mental health services, as compliance and treatment outcomes are lower.

Assessment and treatment should follow evidence-based practice parameters and guidelines

1. Assessment

➦ As part of further assessment, the measurement of ***urine flow*** (in children old enough), together with the pelvic ***ultrasound estimate of residual urine*** and appearance of the bladder wall and rectum are highly recommended. An evaluation of the ***upper urinary tracts with ultrasound is also highly recommended.***

Those who do not improve ***with treatment*** and have neither neurogenic nor anatomical problems ***should be reassessed*** using micturition charts, symptom scores, urinalysis, uroflowmetry and residual urine determination.

If there are recurrent and febrile infections, upper tract imaging and possibly a VCUG should be considered. However, endoscopy is rarely indicated.

➦ ***Urodynamics should be considered:***

- If the type and severity of lower tract dysfunction ***cannot be explained by clinical findings.***
- If ***invasive treatment*** is under consideration, for example, stress incontinence surgery if there is sphincteric incompetence, or bladder augmentation if there is detrusor overactivity.
- ***If upper tract dilatation exists*** and is thought to be due to bladder dysfunction.

Invasive urodynamic studies are generally not recommended if the child has normal upper tract imaging and is to be treated by noninvasive means.

➦ ***Spinal Imaging*** (US/X-ray/MRI) may be needed if a bony abnormality or neurological condition is suspected.

2. Treatment

The treatment of incontinence associated with ***urinary tract anomalies*** is complex and cannot easily be dealt with in an algorithm. In many children ***more than one pathophysiology*** demands treatment. If there are ***complex congenital abnormalities present***, the treatment is mostly surgical and it should be individualised according to the type and severity of the problem (please see Children's Committee Report).

Care should be given by specialist children's nurses and therapists.

➦ ***Initial treatment should be non-surgical.***

- ***For stress urinary incontinence*** (SUI): pelvic floor muscle training (Grade C).
- ***For suspected bladder overactivity*** (OAB): fluid/voiding regimes and antimuscarinics (Grade A).
- ***For voiding dysfunction:*** timed voiding, voiding re-education, pelvic floor muscle relaxation (+/- biofeedback), intermittent catheterisation (when PVR >30% of bladder capacity) (Grade B/C).
- ***For bowel dysfunction:*** high fibre diet and laxatives as appropriate.

The child's progress should be assessed and, if quality of life is still significantly impaired, or if the upper urinary tracts are at risk, ***surgical treatment*** is likely to be necessary.

➦ ***If surgical treatment is required,*** then urodynamic studies are recommended to confirm the diagnosis.

- ***For SUI***, sling surgery, bulking agent injection and AUS may be considered.
- ***For DO/poor compliance,*** botulinum toxin (for DO, and off-label) and bladder augmentation may be performed.
- ***If the child cannot do IC*** then a Mitrofanoff channel may be needed.

Specialised Management of Urinary Incontinence in Children

EXPERT HISTORY & PHYSICAL EXAMINATION

Incontinence without suspicion of urinary tract anomaly

Incontinence with suspicion of urinary tract anomaly

CLINICAL ASSESSMENT

- Urinalysis: if UTI, treat and reassess as appropriate
- Treat bowel dysfunction and reassess
- Renal / bladder ultrasound
- Assess post void residual
- Flow rates ± electromyography
- Behavioural Evaluation

if abnormal -->

Consider:
- Micturating cystogram
- Renal scintigram
- Urodynamics
- Cystourethroscopy
- Spinal imaging

DIAGNOSIS

- STRESS URINARY INCONTINENCE
- DETRUSOR OVERACTIVITY / POOR COMPLIANCE
- VOIDING DYSFUNCTION
- ANATOMICAL CAUSES OF URINARY INCONTINENCE

TREATMENT *

- Pelvic floor muscle training
  - Failure
  - AUS
  - Sling
  - Bulking agent injection
- Fluid/ voiding regime
- Antimuscarinics
- Bowel management.
  - Failure
  - Botulinum toxin
  - Bladder augmentation
- Timed voiding
- Pelvic floor relaxation ± biofeedback.
- Pharmacotherapy
  - Antimuscarinics
  - α-blockers
- Intermittent cath.
- Bowel management
- Antibiotic if infection
  - Failure
  - Mitrofanoff if IC fails
- Correct anomaly (see : surgical treatment in children)

* At any stage of the patient's care pathway, management may need to include continence products

II. URINARY INCONTINENCE IN MEN

A. INITIAL MANAGEMENT

1. Initial Assessement should identify :

➦ ***Complicated" incontinence group***

Those with pain or with haematuria, recurrent infections, suspected or proven poor bladder emptying (for example due to bladder outlet obstruction), or incontinence following pelvic irradiation or radical surgery, are recommended for ***specialised management.***

Poor bladder emptying may be suspected from symptoms, physical examination or if imaging has been performed by X-ray or ultrasound after voiding.

➦ ***Four other main groups*** of men should be identified by initial assessment as being suitable fo***r initial management.***

- Those with ***post-micturition dribble*** alone,
- Those with **overactive bladder** (OAB) symptoms: urgency with or without urgency incontinence, together with frequency and nocturia
- Those with ***stress incontinence*** (most often post-prostatectomy),
- Those with ***mixed*** urgency and stress incontinence (most often post-prostatectomy)

2. Management

➦ For men with ***post-micturition dribble,*** this requires no assessment and can usually be treated by teaching the man how to do a strong pelvic floor muscle contraction after voiding, or manual compression of the bulbous urethra directly after micturition. (Grade B)

➦ For men with ***stress, urgency*** *or* ***mixed*** urgency / stress incontinence, initial treatment should include appropriate lilfestyle advice, pelvic floor muscle training, scheduled voiding regimes, behavioural therapies and medication. In particular:

- Lifestyle interventions (Grade D)
- Supervised pelvic floor muscle training for men with post radical prostatectomy SUI (Grade B)
- Scheduled voiding regimes for OAB (Grade C)
- Antimuscarinic drugs for OAB symptoms with or without urgency incontinence (Grade B) if the patient has no evidence of significant post-void residual urine
- α-adrenergic antagonists (a-blockers), can be added if it is thought that there may also be bladder outlet obstruction. (Grade C)

➦ ***Should initial treatment be unsuccessful*** after a reasonable period of time (for example, 8-12 weeks), ***specialist advice*** is highly recommended.

Clinicians are likely to wish to treat the ***most bothersome symptom*** first in men with symptoms of ***mixed*** incontinence.

Initial Management of Urinary Incontinence in Men

HISTORY

- Post-micturition dribble
- Incontinence on exertion (usually post-prostatectomy)
- Incontinence with mixed symptoms
- Urgency / frequency, with or without urgency incontinence
- "Complicated" incontinence
  - Recurrent or "total" incontinence
  - Incontinence associated with:
    - Pain
    - Haematuria
    - Recurrent infection
    - Prostate irradiation
    - Radical pelvic surgery

CLINICAL ASSESSMENT

- General assessment (see relevant chapter)
- Urinary symptom assessment and symptom score (including frequency-volume chart and questionnaire)
- Assess quality of life and desire for treatment
- Physical examination: abdominal, rectal, sacral, neurological
- Urinalysis ± urine culture -> if infected, treat and reassess
- Assessment of pelvic floor muscle function
- Assess post-void residual urine

Any other abnormality detected e.g. significant post void residual

PRESUMED DIAGNOSIS

- STRESS INCONTINENCE presumed due to sphincteric incompetence
- MIXED INCONTINENCE Treat most bothersome symptom first
- URGENCY INCONTINENCE presumed due to detrusor overactivity

MANAGEMENT *

- Urethral milking
- Pelvic floor muscle contraction

DISCUSS TREATMENT OPTIONS WITH THE PATIENT

- Lifestyle interventions
- Pelvic floor muscle training ± biofeedback
- Scheduled voiding (bladder training)
- Incontinence products
- Antimuscarinics (OAB ± urgency incontinence) and α-adrenergic antagonists (if suspected bladder outlet obstruction)

Failure

SPECIALISED MANAGEMENT

* At any stage of the patient's care pathway, management may need to include continence products

II. URINARY INCONTINENCE IN MEN

B. SPECIALISED MANAGEMENT

The specialist may first **reinstitute initial management** if it is felt that previous therapy had been inadequate.

1. Assessment

➦ Patients with "***complicated" incontinence*** referred directly to specialised management, are likely to require ***additional testing,*** such as cytology, cystourethoscopy and urinary tract imaging.

If these tests prove normal then those individuals can be treated for incontinence by the initial or specialised management options as appropriate.

If symptoms suggestive of detrusor overactivity, or of sphincter incompetence ***persist,*** then ***urodynamic*** studies are advisable in order to arrive at a precise diagnosis, prior to invasive treatment.

2. Treatment

When basic management has failed

and if the patient's incontinence markedly disrupts his quality of life then ***invasive therapies*** should be considered.

➦ ***For sphincter incompetence*** the recommended option is the artificial urinary sphincter (Grade B). Other options, such as a male sling, may be considered (Grade C).

➦ ***For idiopathic detrusor overactivity***, (with intractable overactive bladder symptoms) the recommended therapies are: Botulinum toxin A (Grade B), neuromodulation (Grade C), and bladder augmentation (Grade C).*

**Note: At the time of writing, botulinum toxin for idiopathic DO is being used "off-label".*

➦ When incontinence has been shown to be associated with ***poor bladder emptying*** and ***detrusor underactivity,*** it is recommended that effective means are used to ensure bladder emptying, for example, intermittent catheterisation (Grade B/C).

➦ ***If incontinence is associated with bladder outlet obstruction***, then consideration should be given to surgical treatment to relieve obstruction (Grade B). α-blockers and/or 5α- reductase inhibitors would be an optional treatment (Grade C). There is increased evidence for the safety of antimuscarinics for overactive bladder symptoms in men, chiefly in combination with an □-blocker (Grade B).

Specialised Management of Urinary Incontinence in Men

HISTORY/ SYMPTOM ASSESSMENT

CLINICAL ASSESSMENT

DIAGNOSIS

TREATMENT *

Post-prostatectomy incontinence

Incontinence with urgency / frequency

"Complicated" Incontinence :
- Recurrent incontinence
- Incontinence associated with:
  - Prostate or pelvic irradiation
  - Radical pelvic surgery

- Consider urodynamics and imaging of the urinary tract
- Urethrocystoscopy (if indicated)

STRESS INCONTINENCE due to sphincteric incompetence

MIXED INCONTINENCE Treat major component first

URGENCY INCONTINENCE due to detrusor overactivity (during filling)

Consider:
- Urethrocystoscopy
- Further imaging
- Urodynamics

with coexisting bladder outlet obstruction

with coexisting underactive detrusor (during voiding)

Lower urinary tract anomaly/ pathology

If initial therapy fails:
- Artificial urinary sphincter
- Male sling (see chapter 13)

- α-blockers, 5ARI
- Correct anatomic bladder outlet obstruction
- Antimuscarinics

If initial therapy fails:
- Botulinum toxin A
- Neuromodulation

- Intermittent catheterisation
- Antimuscarinics

- Correct anomaly
- Treat pathology

* At any stage of the patient's care pathway, management may need to include continence products

III. URINARY INCONTINENCE IN WOMEN

A. INITIAL MANAGEMENT

1. Initial assessment should identify :

➦ ***"Complicated" incontinence group.***

Those with pain or haematuria, recurrent infections, suspected or proven voiding problems, significant pelvic organ prolapse or who have persistent incontinence or recurrent incontinence after pelvic irradiation, radical pelvic surgery, previous incontinence surgery, or who have a suspected fistula, should be refered to a specialist.

➦ **Three other main groups** of patients should be identified by initial assessment.

- Women with ***stress incontinence*** on physical activity
- Women with ***urgency, frequency*** with or without urgency incontinence
- Those women with ***mixed*** urgency and stress incontinence

Abdominal, pelvic and perineal examinations should be a routine part of physical examination. Women should be asked to perform a "stress test" (cough and strain to detect leakage likely to be due to sphincter incompetence). Any pelvic organ prolapse or urogenital atrophy should be assessed. Vaginal or rectal examination allows the assessment of voluntary pelvic floor muscle function, an important step prior to the teaching of pelvic floor muscle training.

2. Treatment

➦ For women with ***stress, urgency or mixed*** urinary incontinence, initial treatment should include appropriate lifestyle advice, pelvic floor muscle training, PFMT), scheduled voiding regimes, behavioural therapies and medication. In particular:

- ***Advice*** on caffeine reduction (Grade B) and weight reduction (Grade A)
- ***Supervised pelvic floor muscle training*** (Grade A), ***supervised vaginal cones training*** for women with stress incontinence (Grade B)
- ***Supervised bladder training*** (Grade A) for OAB.
- ***If oestrogen deficiency*** and/or ***UTI*** is found, the patient should be treated at initial assessment and then reassessed after a suitable interval using vaginal oestrogens. (Grade B).
- ***Antimuscarinics*** for OAB symptoms with or without urgency incontinence (Grade A); duloxetine* may be considered for stress urinary incontinence (Grade B)

PFMT should be based on sound muscle training principles such as specificity, overload progression, correct contraction confirmed prior to training, and use of the Knack for 12 weeks before reassessment and possible specialist referral.

Clinicians are likely to wish to treat the ***most bothersome symptom first*** in women with symptoms of mixed incontinence. (Grade C).

➦ Some women with significant ***pelvic organ prolapse*** can be treated by vaginal devices that treat both incontinence and prolapse (incontinence rings and dishes).

** Duloxetine is not approved for use in United States. It is approved for use in Europe for severe stress incontinence (see committee report on pharmacological management for information regarding efficacy, adverse events, and 'black box' warning by the Food and Drug Administration of the United States).*

Initial Management of Urinary Incontinence in Women

HISTORY

Incontinence on physical activity

Incontinence with mixed symptoms

Incontinence / frequency with urgency

Complicated incontinence

- Recurrent incontinence
- Incontinence associated with:
  - Pain
  - Haematuria
  - Recurrent infection
  - Significant voiding symptoms
  - Pelvic irradiation
  - Radical pelvic surgery
  - Suspected fistula

CLINICAL ASSESSMENT

- General assessment (see relevant chapter)
- Urinary symptom assessment (including frequency-volume chart and questionnaire)
- Assess quality of life and desire for treatment
- Physical examination: abdominal, pelvic and perineal
- Cough test to demonstrate stress incontinence if appropriate
- Urinalysis ± urine culture -> if infected, treat and reassess *If appropriate*
- Assess oestrogen status and treat as appropriate
- Assess pelvic floor muscle function
- Assess post-void residual urine

PRESUMED DIAGNOSIS

STRESS INCONTINENCE presumed due to sphincteric incompetence

MIXED INCONTINENCE Treat most bothersome symptom first

OAB -with or without URGENCY INCONTINENCE presumed due to detrusor overactivity

- If other abnormality found e.g.
- Significant post void residual
- Significant pelvic organ prolapse
- Pelvic mass

TREATMENT *

- Life style interventions.
- Pelvic floor muscle training for SUI, MUI, or OAB
- Bladder retraining for OAB
- Antimuscarinics (OAB ± urgency incontinence) or Duloxetine** (SUI)

- Other adjuncts, such as electrical stimulation
- Vaginal devices

Failure

SPECIALISED MANAGEMENT

** Subject to local regulatory approval (see black box warning).

* At any stage of the patient's care pathway, management may need to include continence products

III. URINARY INCONTINENCE IN WOMEN

B. SPECIALISED MANAGEMENT

1. Assessement

Women who have "***complicated" incontinence*** (see initial algorithm) may need to have additional tests such as cytology, cystourethroscopy or urinary tract imaging. If these tests are normal then they should be treated for incontinence by the initial or specialised management options as appropriate.

➦ Those women who have ***failed initial management*** and whose quality of life is impaired are likely to request further treatment. If initial management has been given an adequate trial then ***interventional therapy may be desirable.*** Prior to intervention ***urodynamic testing*** is highly recommended, when the results may change management. It is used to diagnose the type of incontinence and therefore inform the management plan. Within the urodynamic investigation urethral function testing by urethral pressure profile or leak point pressure is optional.

➦ Systematic assessment for ***pelvic organ prolapse*** is highly recommended and it is suggested that the POP-Q method should be used in research studies. Women with co-existing pelvic organ prolapse should have their prolapse treated as appropriate

2. Treatment

➦ ***If urodynamic stress incontinence is confirmed*** then the treatment options that are recommended for patients with ***some degree of bladder-neck and urethral mobility*** include the full range of non-surgical treatments, as well as retropubic suspension procedures, (Grade A) and bladder neck/sub-urethral sling operations:(Grade A). The ***correction of symptomatic*** pelvic organ prolapse may be desirable at the same time.

For patients with ***limited bladder neck mobility,*** bladder neck sling procedures, (Grade A) injectable bulking agents (Grade B) and the artificial urinary sphincter (Grade B) can be considered.

➦ **Refractory *urgency incontinence*** (overactive bladder) secondary to idiopathic detrusor overactivity may be treated by botulinum toxin A (Grade C)*, neuromodulation (Grade A) or bladder augmentation (Grade C).

➦ Those patients with ***voiding dysfunction*** leading to significant post-void residual urine (for example, >30% of total bladder capacity) may have bladder outlet obstruction or detrusor underactivity. Prolapse is a common cause of voiding dysfunction.

** At the time of writing, botulinum toxin is being used "off-label" and with caution.*

Specialised Management of Urinary Incontinence in Women

HISTORY/ SYMPTOM ASSESSMENT

- Incontinence on physical activity
- Incontinence with mixed symptoms
- Incontinence with urgency / frequency

"Complicated" incontinence:
- Recurrent incontinence
- Incontinence associated with:
  - Pain
  - Haematuria
  - Recurrent infection
  - Voiding symptoms
  - Pelvic irradiation
  - Radical pelvic surgery
  - Suspected fistula

CLINICAL ASSESSMENT

- Assess for pelvic organ mobility / prolapse
- Consider imaging of the UT/ pelvic floor
- Urodynamics (see notes)

DIAGNOSIS

- URODYNAMIC STRESS INCONTINENCE (USI)
- MIXED INCONTINENCE USI/DOI
  Treat. most bother-some symptom first
- DETRUSOR OVERACTIVITY INCONTINENCE (DOI)
- INCONTINENCE associated with poor bladder emptying
  - *Bladder outlet obstruction*
  - *Underactive detrusor*

Consider:
- Urethrocystoscopy
- Further imaging
- Urodynamics

Lower urinary tract anomaly / pathology

TREATMENT *

If initial therapy fails :
- Stress incontinence surgery
  - bulking agents
  - tapes and slings
  - colposuspension

If initial therapy fails :
- Botulinum toxin
- Neuromodulation
- Bladder augmentation

- Correct anatomic bladder outlet obstruction (e.g. genito-urinary prolapse)
- Intermittent catheterization

- Correct anomaly
- Treat pathology

* At any stage of the patient's care pathway, management may need to include continence products

IV. FISTULAE

GENERAL INTRODUCTION

In the developing world fistulae are often a consequence of poor peri-natal care. The epidemiology, aetiology, diagnosis, treatment and prevention have been described in detail during the recent International Consultation on Obstetric Fistula.

In contrast to the field of obstetrical fistulae where the numbers of patients are high, the prevalence of non-obstetrical fistulae seems to be much lower. The published series have small patient numbers, are usually retrospective and have a low level of evidence. The published obstetrical series show impressive numbers and demonstrate the level of skill that many of the fistula surgeons have obtained while working in difficult and isolated situations.

Both committees are convinced that obstetric fistula surgeons in the developing world and reconstructive pelvic surgeons in the developed countries can learn a lot from each other.

PART I: OBSTETRIC FISTULA

INTRODUCTION

Epidemiological studies on obstetric fistulae are inadequate.

The incidence of fistulae is expressed per 1,000 deliveries and would appear to be between 0.1% rising to 1.5 per 1,000 pregnancies in rural areas.

The major risk factors appear to be age at first marriage, short stature, pregnancy with a male child rather than a female child, failure to attend ante-natal care, low socio-economic status, low social class, lack of employment and illiteracy.

The consequences of obstetric fistulae include divorce (16-92%), social isolation, worsening poverty, malnutrition, sexual dysfunction and mental illness (including anxiety/depression), insomnia, general ill health and thoughts of worthlessness and suicide.

ASSESSMENT

Early detection of fistulae could improve by examining all women after their delivery or Caesarian section who suffered prolonged labour and who are at risk of developing an obstetric fistula.

Associated pathologies should be actively searched for and should be taken into account in the treatment plan: all components of the 'obstructed labour injury complex' should be examined.

Classification of fistulae is recommended. Although many classification systems exist, the committee recommends the use of the Waaldijk classification, since it is supported by the largest amount of data. It involves precise measurements of the distances between the external urinary meatus and the distal edge of the fistulae, together with the widest diameter of the fistulae. Fistulae are classified into types 1, 2 and 3. Type 3 fistulae are those fistulae other than vesico-vaginal fistulae (VVF) and include recto-vaginal fistulae (VVF) and uretero-vaginal fistulae. **(Grade C)**

The formal classification of the fistulae should be done under anaesthesia when the patient is on the operation table, just before surgery.

MANAGEMENT OF NEW AND ESTABLISHED VVFs

Management of VVF depends on whether the fistulae is diagnosed within two or three months of its occurrence or whether the woman presents late with an established fistula. (Algorithm 1)

Early fistulae (less than 75 days after obstructed labour). There is evidence that early catheter care will result in the cure of a significant minority of VVFs. **(Grade C)**

Established fistulae (>75 days after obstructed labour) and those that fail catheter treatment should be treated surgically by a fistula surgeon. **(Grade C)**

TREATMENT

If catheter drainage fails, then fistula repair will be necessary. There are certain principles behind fistula repair:

- Necrotic tissue must be removed prior to fistula repair.
- Fistula repair must only be undertaken by a properly trained surgeon.
- Adequate post-operative care is essential.
- Proper follow-up should be arranged.

A vaginal approach under spinal anaesthesia is preferred.

A tension-free single layer closure of the bladder wall and closure of the vaginal wall in a separate layer are advocated. A Martius flap in primary obstetric fistula repair is not recommended.

In principle most fistulae can be dealt with by vaginal approach, but an abdominal approach can be useful in some cases (e.g. concomitant reconstructive procedures). Advanced training and surgical skills are prerequisites for treating this type of fistula.

When reporting on outcome after fistula repair, authors should make a clear distinction between fistula closure rates and post-operative stress incontinence rates and the time at which the follow-up was organized.

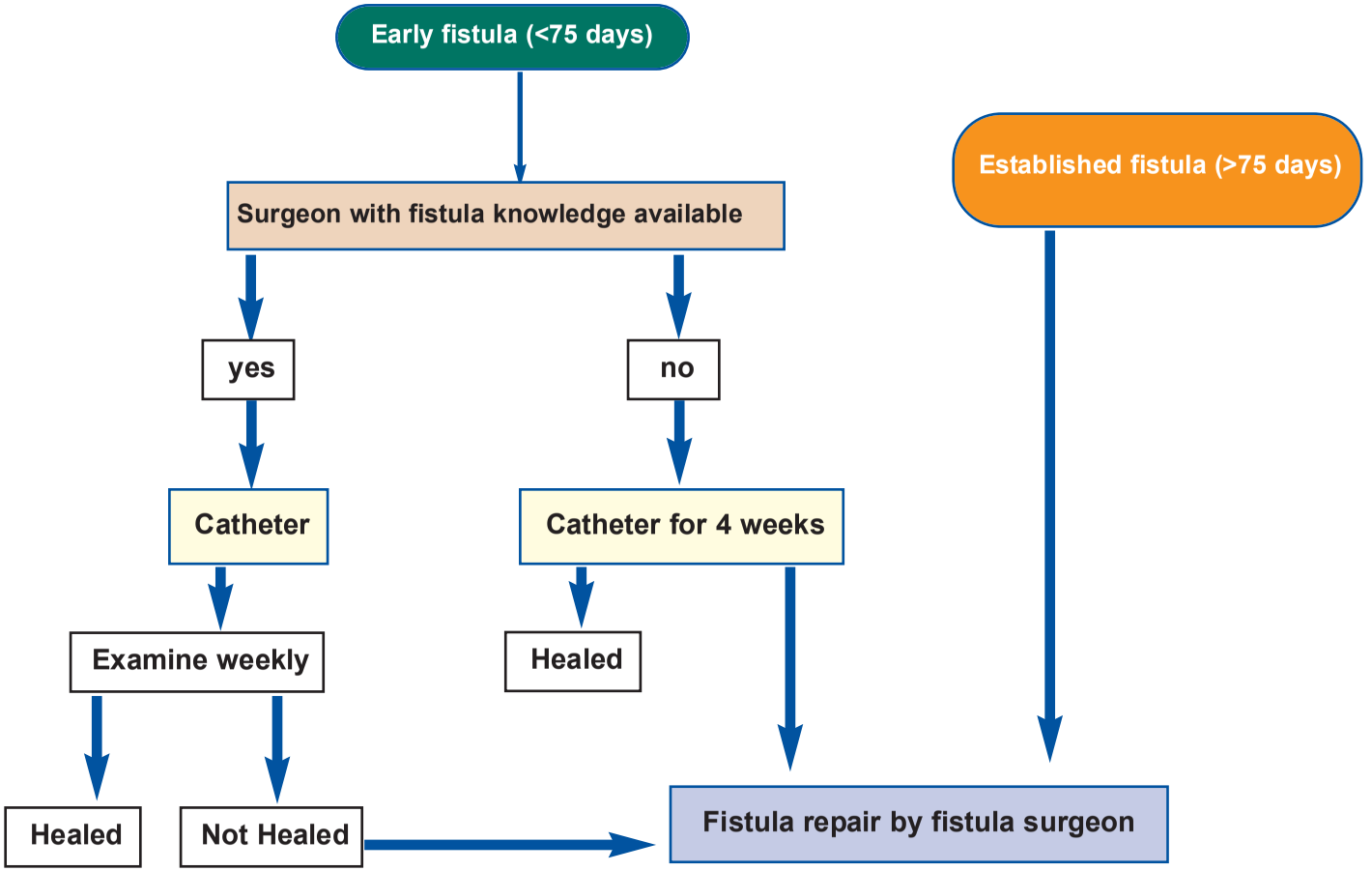
Prevention of post-operative stress incontinence must be added to the surgical procedure if the urethral closing mechanism is involved. This can be done by a good repair of the pubocervical fascia and refixation or by adding a sling procedure.

MANAGEMENT OF THE COMPLICATIONS OF VVF

The complications of vesico-vaginal fistulae are many but include:

- Persistence or recurrence of urinary incontinence
- Persistence of lower urinary tract symptoms or occurrence of new lower urinary tract symptoms, including overactive bladder
- Urinary tract infections
- Upper urinary tract symptoms, including loin pain
- Dyspareunia and sexual dysfunction
- Infertility
- Neurological symptoms
- Psychological problems and mental illness

MANAGEMENT OF OBSTETRIC VESICOVAGINAL FISTULAE *



* At any stage of the patient's care pathway, management may need to include continence products

PART II: NON-OBSTETRIC FISTULAE

INTRODUCTION

Iatrogenic urogenital fistulae are known complications of pelvic surgery and oncological treatments such as radiotherapy, chemotherapy or a combination of both. In the oncological context, fistulae may also occur as a result of primary or recurrent malignancy. The development of fistula following radiotherapy for primary treatment should trigger a search for evidence of tumour recurrence (Grade D)

- Urogenital fistulae are more frequent in women who have undergone hysterectomy.
- The risk of injury to the bowel or urinary tract and of subsequent fistula formation is higher in women with malignant disease undergoing radical surgery than in women with benign disease undergoing simple surgical procedures
- Several modifications to conventional radical hysterectomy have been described, although they have not consistently been shown to mitigate the risk of urinary fistula postoperatively.
- Data on exenterative surgery are inconsistent, although the risk of fistula formation may be higher following exenteration for recurrent disease as compared to that following radical hysterectomy for the primary treatment of malignancy.
- The rate of visceral injury and fistula formation is inconsistently reported following laparoscopically assisted radical hysterectomy, but may be somewhat higher than following open surgery.
- Local ablative treatments applied in gynaecological oncology, whilst apparently relatively low risk as single treatments, may carry considerable risk for fistula formation when repeated.
- The rate of fistula formation following radiotherapy for gynaecological cancer appears to be of the same order as that following surgical treatment.
- The risk of fistula formation following radiotherapy for locally recurrent malignancy is higher than following its use in primary disease.
- The use of neoadjuvant or adjuvant therapies is likely to be associated with a greater risk of fistula development than the primary treatment alone.
- The most common non-obstetric causes of fistulae involving the gastro-intestinal tract are diverticular disease, Crohn's disease, malignancy and radiotherapy.

ASSESSMENT OF FISTULAE

- Leakage of stool, urine, or possibly both is the hallmark sign of a fistulae.The leakage is usually painless, may be intermittent if it is position dependent, or may be constant. Unfortunately, intraoperative diagnosis of a GU or GI injury is made in only about half of the cases that result in fistulae.
- CT and cystoscopy appear more consistent in the confirmation and location of possible intestino-vesical fistulae, than other investigations (Grade C)
- Level 3 evidence indicates that the routine use of cystoscopy with dye testing at gynaecological surgery has high sensitivity, specificity and negative predictive value in the detection of ureteric injury, although false positive tests do occur. The clinical and cost-effectiveness of routine cystoscopy remains to be established. (Grade C)
- Ureteric injury or fistulae may be suspected in patients following pelvic surgery if a fluid leak or pelvi-calyceal dilatation occurs postoperatively. (Grade D)
- Uretero-arterial fistula may be suspected in patients presenting with haematuria with a history of relevant pelvic surgery and indwelling ureteric stent. (Grade D)
- Elevated levels of creatinine in drainage fluid following pelvic surgery are suggestive of a urinary tract injury. (Grade D)

MANAGEMENT OF VESICOVAGINAL FISTULAE

The literature relating to surgical fistulae is extensive, but of limited quality.

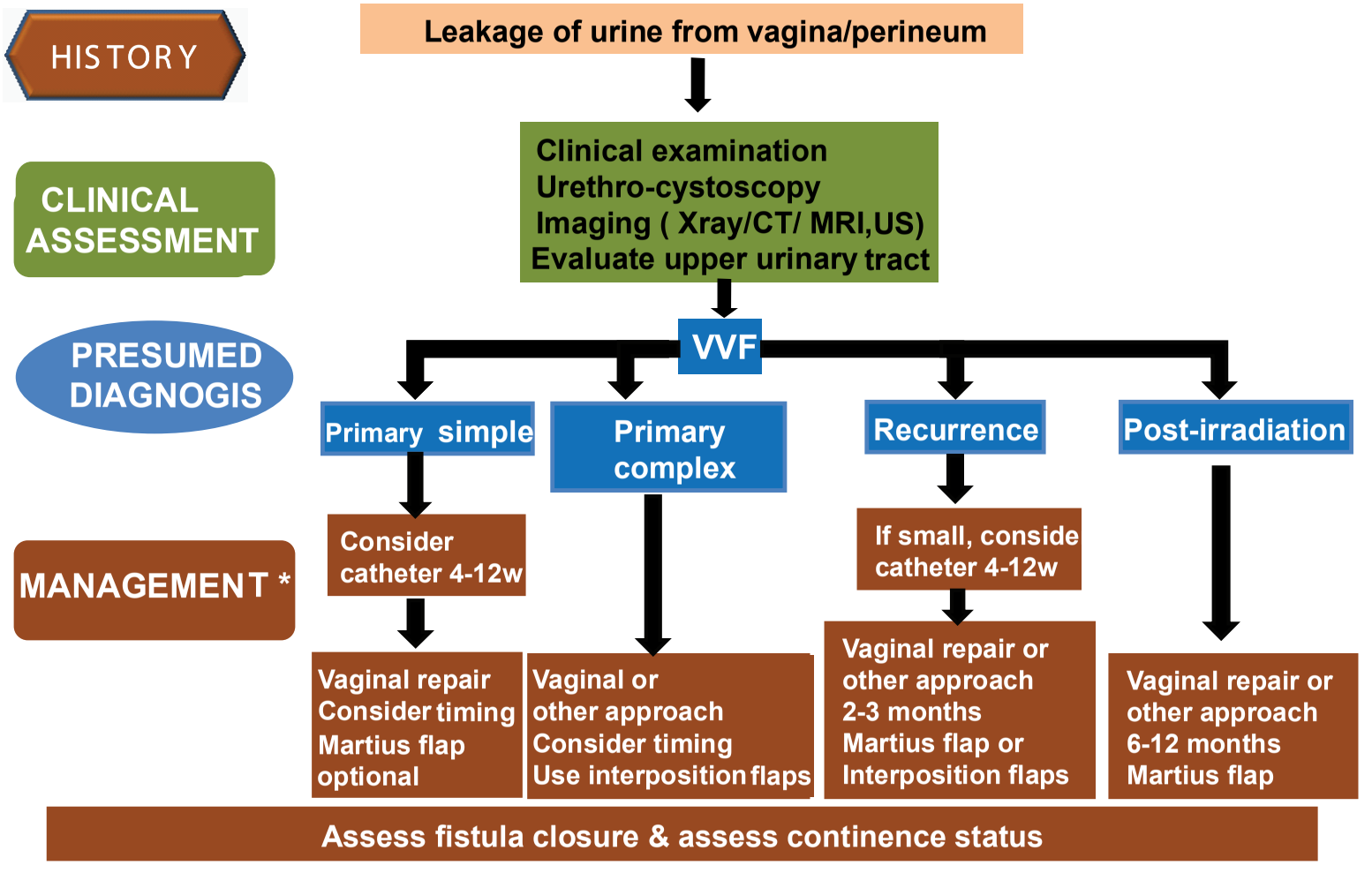
- Spontaneous closure of surgical fistulae does occur, although it is not possible to establish the rate with any certainty; if a vesicovaginal fistulae is diagnosed within six weeks of surgery, indwelling catheterisation can be considered for a period of up to 9 weeks (*i.e.* up to 12 weeks after the causative event). (Grade C)

- Attention should be given as appropriate to skin care, nutrition, rehabilitation, counselling and support prior to and following fistulae repair. (Grade D)
- Perioperative antibiotic prophylaxis should follow local policies. (Grade D)
- There is no benefit from mechanical or laxative bowel preparation prior to colonic surgery; it is reasonable that this recommendation be extrapolated to apply to fistulae surgery. (Grade B)
- There is no proven benefit to delayed repair of vesicovaginal fistulae; the timing of repair should be tailored to the individual patient and surgeon requirements, but can be undertaken as soon as any oedema, inflammation, tissue necrosis, infection are resolved. (Grade B)
- There are no high quality data to indicate greater cure rates for any one technique as compared to others ; level 3 evidence indicates similar success rates for vaginal and abdominal, and for transvesical and transperitoneal approaches. (Grade C)
- Surgeons involved in fistulae surgery should have appropriate training, skills, and experience to select an appropriate procedure for each patient. (Grade D)
- The majority of vesico-vaginal and all urethro-vaginal fistulae can be repaired vaginally, regardless of aetiology. (Grade C)
- Where concurrent ureteric re-implantation or augmentation cystoplasty are required, the abdominal approach is necessary.(Grade D)
- A variety of interpositional grafts can be used in either abdominal or vaginal procedures, although there is little evidence to support their use in any specific setting. (Grade C)
- Conventional and robotically-assisted laparoscopic approaches have both been shown to be feasible in selected cases; the indications for, or optimal patient for these techniques is not yet clear. (Grade C)
- A period of continuous bladder drainage is crucial to successful fistulae repair; there are no high level data to support any particular type, route, or duration of catheterisation; current practice suggests: 10-14 days for simple and/or post-surgical fistulae; 14-21 days for complex and/or post-radiation fistulae. (Grade D)

RADIATION FISTULAE

- Whilst diversion is used more widely in radiation-associated fistulae of all types as compared to non-radiated fistulae, there is low level evidence that repair procedures can achieve successful fistulae closure and continence in appropriately selected cases. (Grade C)
- Where urinary and/or faecal diversions are required, attempts should be made to avoid using irradiated tissues wherever possible, and to minimise the potential for anastomotic complications. (Grade C)
- There is low level evidence to support the use of interposition grafts when repair of radiation-associated fistulae is undertaken.(Grade C)
- In patients with intractable urinary incontinence from radiation-associated fistulae, where life expectancy is very short, ureteric occlusion might be considered; there is insufficient evidence to recommend any particular technique. (Grade D)

MANAGEMENT OF IATROGENIC VESICOVAGINAL FISTULAE



* At any stage of the patient's care pathway, management may need to include continence products

MANAGEMENT OF FISTULAE INVOLVING BOWEL

- There is limited evidence to support a non-surgical or conservative surgical approach in colo-vesical fistulae where there are minimal symptoms or evidence of limited bowel involvement. (Grade C)
- There is only limited low level evidence to support a non-surgical approach in colo-vesical fistulae associated with diverticular disease; nevertheless, in the frail elderly, or in patients who have limited symptoms of urinary infection or urinary diarrhoea it is reasonable to consider a trial of conservative management. (Grade D)
- A one-stage approach to surgery for intestino-vesical fistulae is appropriate in many cases, but should be limited to those patients whose nutritional state is good, and where there is no evidence of additional intra-abdominal pathology (*e.g.* severe inflammation, radiation injury, advanced malignancy, intestinal obstruction) or major co-morbidity. (Grade B)
- A laparoscopic approach to one-stage management has been shown to be feasible, although there is no high level evidence to allow comparison of outcomes with open surgery. (Grade D)

MANAGEMENT OF URETERIC FISTULAE

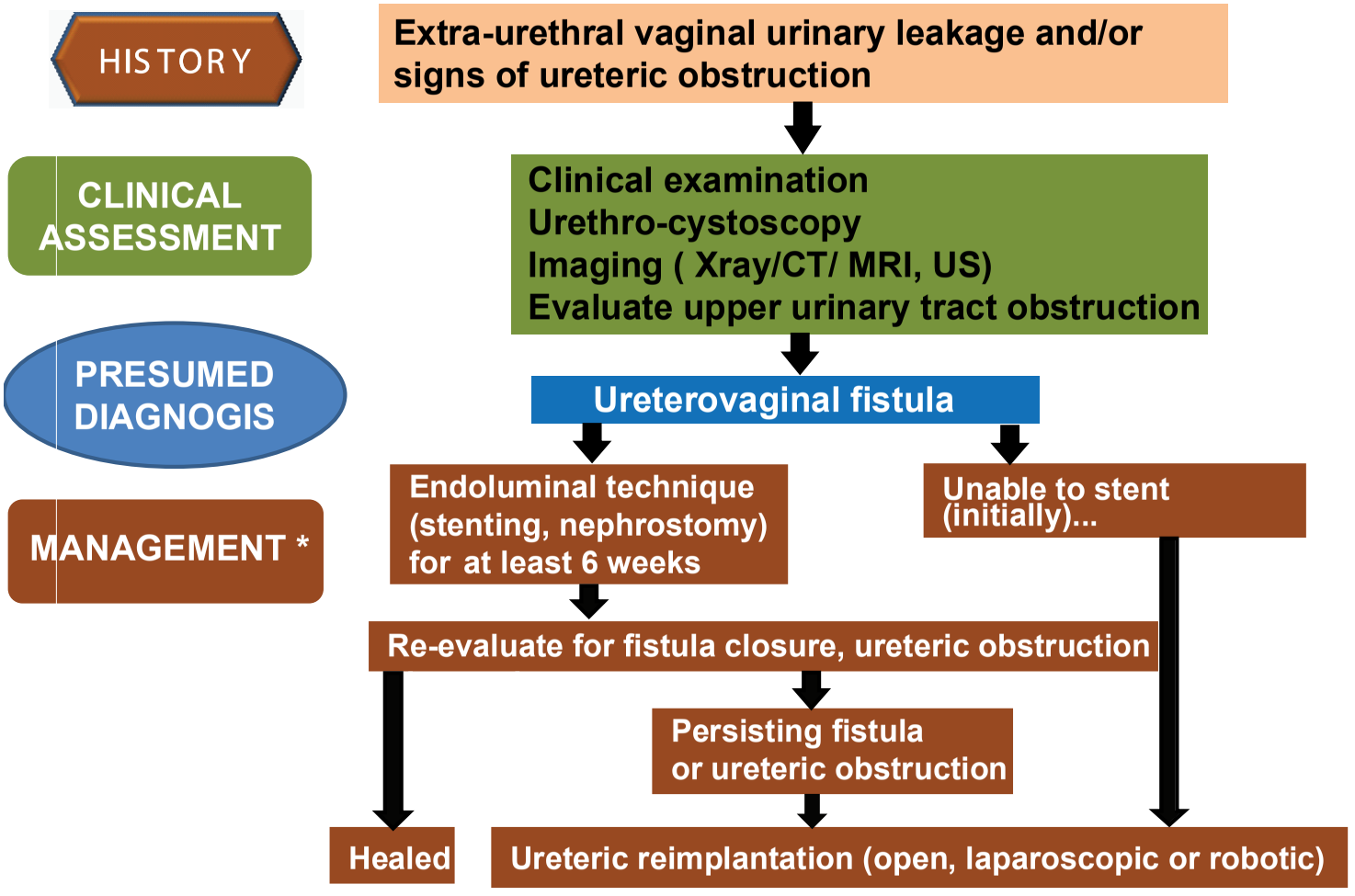
- Surgeons undertaking complex pelvic surgery should be competent at identifying, preserving and repairing the ureter. (Grade D)
- Ureteric stents are not required as prophylaxis against injury during routine gynaecological surgery, while their role in more extensive surgery remains to be established. (Grade B)
- Most upper urinary tract fistulae should be initially managed by conservative or endoluminal techniques where such expertise and facilities exist. (Grade B)
- Persistent ureterovaginal fistulae should be repaired by an abdominal approach using open, laparoscopic or robotic techniques according to availability and competence. (Grade D)
- For patients with ureteric fistulae associated with advanced pelvic cancer and poor performance status, palliation by nephrostomy tube diversion and endoluminal distal ureteric occlusion is an option. (Grade C)

MANAGEMENT OF URETHRO-VAGINAL FISTULAE

Recommendations

- Urethrovaginal fistulae are preferably treated by a vaginal approach. (Grade C)
- A variety of autologous tissue interposition techniques have been described, but their value remains uncertain. (Grade C)
- Urethrovaginal fistulae repair may be complicated by stress incontinence, urethral stricture and urethral shortening necessitating long-term follow-up. (Grade C)

MANAGEMENT OF IATROGENIC URETERIC FISTULAE



* At any stage of the patient's care pathway, management may need to include continence products

V. PELVIC ORGAN PROLAPSE

I. INTRODUCTION

Pelvic organ prolapse includes ***urogenital*** and ***rectal*** prolapse. Treatment for pelvic organ prolapse should be reserved for ***symptomatic women***, except in rare, selected, cases.

1. ASSESSMENT

Symptom enquiry may reveal a variety of symptoms. Symptom severity ***may not correlate*** with the severity of the anatomical changes.

Physical examination should:

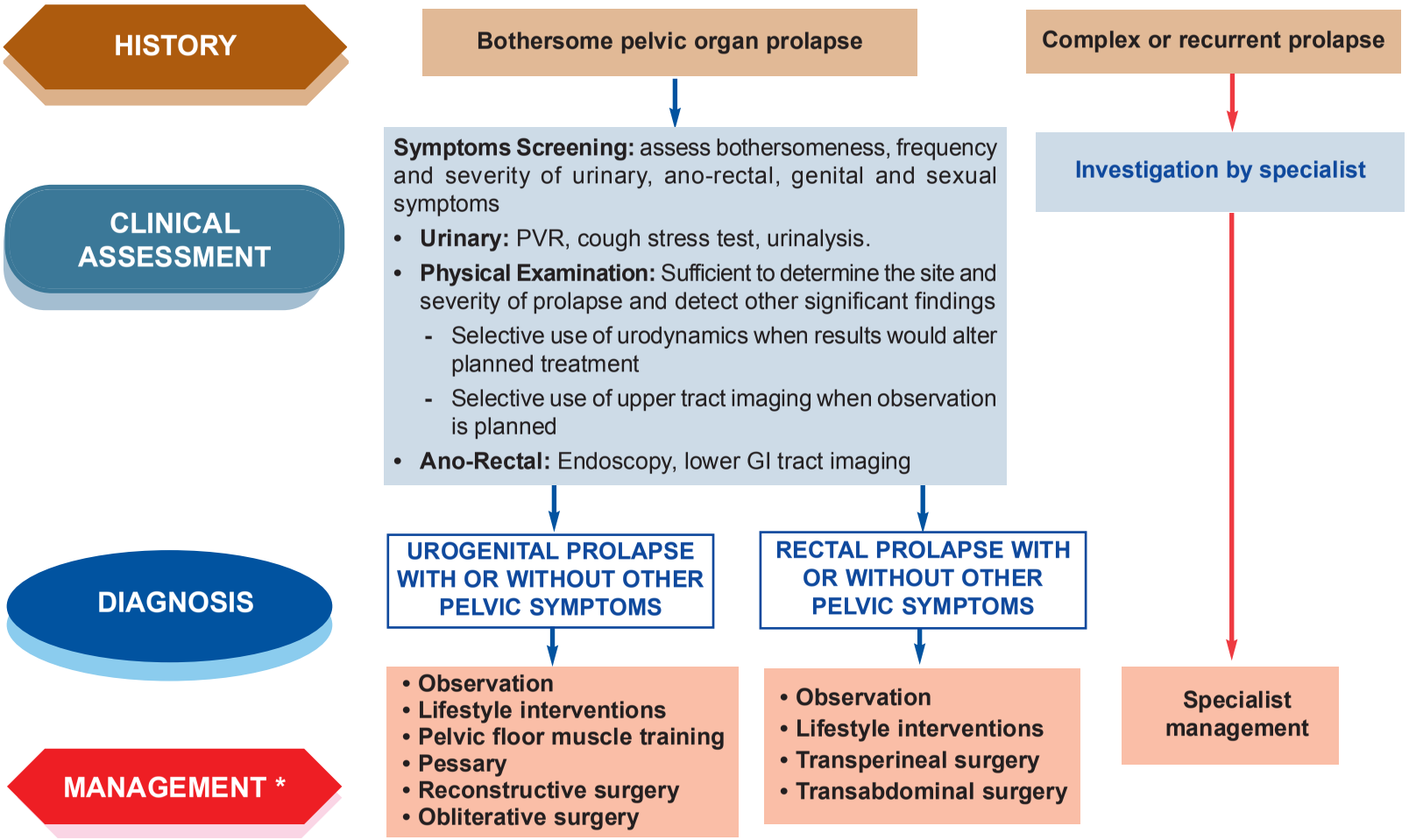
- define the severity of maximum anatomical support defect,
- assess pelvic floor muscle function and
- determine if epithelial/mucosal ulceration is present.

Post void residual should be measured; nearly all elevated post void residuals resolve with treatment of urogenital prolapse. ***Imaging of the upper tract*** is indicated when treatment of vaginal prolapse beyond the hymen is observation only (i.e. no pessary or surgery).

2. MANAGEMENT

- ***Observation*** is appropriate when medically safe and preferred by the patient (Grade C).
- ***Pelvic floor muscle training may:***
  - reduce the symptoms of urogenital prolapse (Grade A), although topographic change is not expected
  - prevent or slow deterioration of anterior urogenital prolapse (Grade B)
- ***Pessaries,*** when successfully fitted, may improve protrusion symptoms (Grade B). Regular follow up is mandatory. ***Support pessaries*** that concurrently treat stress incontinence should be considered when appropriate.
- ***Local oestrogens*** may benefit hypoestrogenic women for the prevention and/or treatment of vaginal epithelial ulceration (Grade C).
- ***Reconstructive surgery*** should aim to optimise anatomy and function (see full text for grades of recommendation for specific surgical techniques). Pre and postoperative pelvic floor muscle training may promote quality of life and fewer symptoms after surgery for urogenital prolapse (Grade C).
- ***Obliterative surgery*** is reserved for selected women who agree to permanent vaginal closure (Grade B).

Management of Pelvic Organ Prolapse
(including urogenital prolapse and rectal prolapse)



* At any stage of the patient's care pathway, management may need to include continence products

VI. URINARY INCONTINENCE IN NEUROLOGICAL PATIENTS

A. Initial Management

I. STRONG GENERAL RECOMMENDATIONS

- Patients with known neurological disease often need evaluation to exclude bladder dysfunction, not only if symptoms occur, but as a standard assessment as ***neurogenic bladder*** has a high prevalence in this disease (for prevalence figures see chapter)
- ***A possible neurological*** cause of " idiopathic " incontinence should always be considered. Diagnostic steps to evaluate this include basic assessments, such as history and physical examination, urodynamics and specialised tests.
- ***Incontinence in neurological*** patients does ***not necessarily relate*** to the neurologic pathology. ***Other diseases*** such as prostate pathology, pelvic organ prolapse, might have an influence. These have to be ruled out.
- ***Extensive diagnostic evaluation*** is often useful and necessary to tailor an individual treatment based on complete neurofunctional data. This ***may not be needed in every patient*** e.g. patients with suprapontine lesions or in patients where treatment will consist merely of bladder drainage due to bad medical condition or limited life expectancy.
- There is often a need to manage ***bladder*** and ***bowel*** together

II. INITIAL ASSESSMENT

- The management of neurological urinary incontinence depends on an ***understanding of the likely mechanisms*** *producing incontinence.* This can in turn depend on the ***site and extent of the nervous system abnormality.***
- Therefore neurogenic incontinence patients can be divided into those having:
  - ***peripheral lesions*** (as after major pelvic surgery) including those with lesions of the cauda equina (eg.lumbar disc prolapse);
  - ***sacral spinal cord lesions involving the sacral micturition centre***
  - ***suprasacral spinal cord lesions*** (suprasacral infrapontine spinal cord lesions);
  - ***central lesions of the brain or brain stem*** (stroke, Parkinson's disease).
- ***History*** and ***physical examination*** are important in helping ***distinguish*** these groups.

III. INITIAL TREATMENT

➦ Patients with ***peripheral nerve lesions*** (e.g. denervation after pelvic surgery) and patients with ***spinal*** cord lesions (e.g. traumatic spinal cord lesions) should get ***specialised management*** (A)

➦ Initial treatment for patients with incontinence due to ***suprapontine pathology***, like stroke; need to be assessed for degree of mobility and ability to cooperate. Initial recommended treatments are behavioural therapy (C) and anti-muscarinic drugs for presumed detrusor overactivity (A). Continence products (B) or catheters (C) may be necessary for non-cooperative or less mobile patients.

Initial Management of Neurogenic Urinary Incontinence

HISTORY, level of lesion

- **Peripheral nerve lesion (e.g. radical pelvic surgery). Sacral cord/cauda equina lesion (e.g. lumbar disc prolapse)**
- **Suprasacral infrapontine and pontine lesions e.g. trauma, multiple system atrophy.**
- **Suprapontine cerebral lesion (e.g. Parkinson's disease, stroke, multiple sclerosis**

CLINICAL ASSESSMENT

- Further history
- General assessment including of home circumstances
- Urinary diary and symptom score
- Assessment of functional ability, quality of life and desire for treatment
- Physical examination: assessment of sensation in lumbosacral dermatomes, anal tone and voluntary contraction of anal sphincter, bulbocavernosus and anal reflexes, gait, mobility, contractures, hand fuction.
- Urine analysis + culture (if infected: treat as necessary)
- Urinary tract imaging, serum creatinine : if abnormal to specialised management
- Post void residual (PVR) assessment by abdominal examination or optional by ultrasound

This assessment will give basic information, but does not yield precise neurourological diagnosis

PRESUMED DIAGNOSIS

Stress urinary incontinence due to sphincter incompetence with negligible PVR

Urinary incontinence due to detrusor overactivity

- **Urinary incontinence associated with poor bladder emptying (significant PVR)**
- **With negligible PVR**

MANAGEMENT *

- Behavioural modification
- External appliances

Failure

- Intermittent catheterisation ** with or without
- Antimuscarinics

Failure

Depending on cooperation and mobility :
- Behavioural modification,
- Antimuscarinics,
- Continence products,
- Indwelling catheter

Failure

Specialised management preferable for more " tailored " treatment

* At any stage of the patient's care pathway, management may need to include continence products

** Some patients omit IC through personal choice or inability to self catheterise

VI. URINARY INCONTINENCE IN NEUROLOGICAL PATIENTS

B. Specialised Management

I. ASSESSMENT

- Most patients with neurogenic urinary incontinence require specialised assessment : ***urodynamic studies should be used*** with videourodynamics if available when surgical interventions are planned or when the “bladder may be unsafe”.
- ***Upper tract imaging*** is needed in some patients and more detailed renal function studies will be desirable if the upper tract is considered in danger: high bladder pressure, upper urinary tract dilatation, recurrent or chronic upper tract infection, (major) stones, (major) reflux.
- In patients with ***peripheral lesions*** clinical ***neurophysiological testing*** may be helpful for better definition of the lesion

II. TREATMENT

Also for specialised management conservative treatment is the mainstay (A). Management of neurogenic urinary incontinence has several therapeutic options. The algorithm details the recommended options for different types of neurological dysfunction of the lower urinary tract. The dysfunction does not necessarily correspond to one type/level of neurological lesion but ***must depend*** mostly on ***urodynamic findings***. One should always ascertain that the management is ***urodynamically safe*** (low pressure, complete emptying)

It is recommended to look at ***urinary*** and ***bowel*** function ***together*** if both systems are affected, as symptoms and treatment of one system can influence the other and vice versa (A).

As therapeutic approaches can differ in various neurological diseases, the most prevalent diseases are discussed separately in the chapter

III. TREATMENT MODALITIES (often in combination)

➦ Conservative

- Intermittent catheterisation (A)
- Behavioural treatment(C)
- Timed voiding (C)
- Continence products (B)
- Antimuscarinics(A)
- Alpha 1 adrenergic blockers (C)
- Intravesical electrical stimulation (C)
- Bladder expression (B)
- Triggered voiding (C)
- Indwelling catheter (C)

➦ Surgical treatment

- Artificial sphincter (A)
- Bladder neck Sling (B)
- Sub-urethral tapes (D)
- Bulking agents (D)
- Bladder neck closure (D)
- Stents intraurethral (B)
- TUI sphincter (B)
- Botulinum toxin for : sphincter(C) detrusor (A)
- Sacral deafferentation (B)
- Sacral anterior root stimulator (B)
- Enterocystoplasty (B)
- Autoaugmentation (D)

Specialised Management of Neurogenic Urinary Incontinence

LEVEL AND EXTENT OF LESION, HISTORY AND CLINICAL ASSESSMENT

- Peripheral nerve lesion (e.g. radical pelvic surgery) conus cauda equina lesion (e.g. lumbar disc prolapse)
- Suprasacral infrapontine and pontine lesion (e.g. trauma, multiple sclerosis)
- Suprapontine cerebral lesion (e.g. Parkinson's disease, stroke, multiple sclerosis)

SPECIALISED ASSESSMENT

- Urodynamic testing (usually videourodynamics.
- Urinary tract imaging

DIAGNOSIS

- Stress UI due to sphincteric incompetence
- Incontinence associated with poor bladder emptying due to detrusor underactivity / sphincter overactivity
- UI due to detrusor overactivity
  - With DSD
  - No DSD

CONSERVATIVE TREATMENT

- Timed voiding Ext. appliances
- IC
- α-1 blockers
- Straining
- IC + AM
- IDC + AM
- Bot tox to detrusor + IC
- Behavioural
- IC + AM
- Triggered voiding
- Indwelling cath. + AM
- Continence products + AM
- Botulinum toxin to detrusor

AM = antimuscarinics
SDAF = sacral deafferentation
SARS = sacral anterior -roots stim

SURGICAL TREATMENT *

- Artificial sphincter
- Bladder neck sling
- Antologous sling
- Bulking agents
- Bladder neck closure
- (Synthetic midurethral tapes)**
- Stents intraurethral
- TUI sphincter
- Botulinum toxin to sphincter *
- SDAF + IC
- SDAF + SARS
- Enterocystoplasty
- [Autoaugmentation]

IC = intermittent catheterization
PVR = postvoid residual
TUI = transurethral incision
DSD = Detrusor sphincter dyssynergia
IDC = indueting catheter

** if urethral hypermobility is the cause of SUI; the long-term risks of tapes in the neurogenic population are undefined

* Intravesical botulinum injections undertaken according to national licensing. Sphincteric botulinum injections are not currently licensed.

Stoma/diversion may be an option in selected cases

* At any stage of the patient's care pathway, management may need to include continence products

VII. BLADDER PAIN SYNDROME

I. DEFINITION

Bladder Pain Syndrome in the absence of a universally agreed definition, the European Society for the Study of Interstitial Cystitis (ESSIC) definition is given along with the definition of the American Urological Association

- **ESSIC :** *Chronic pelvic pain, pressure or discomfort of greater than 6 months duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.*
- **American Urological Association Guideline Definition:** *An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes.*

II. BLADDER PAIN SYNDROME (BPS)

1. NOMENCLATURE

The scientific committee of the International Consultation voted to use the term ***"bladder pain syndrome"*** for the disorder that has been commonly referred to as interstitial cystitis (IC). The term painful bladder syndrome was dropped from the lexicon. The term IC implies an inflammation within the wall of the urinary bladder, involving gaps or spaces in the bladder tissue. This does not accurately describe the majority of patients with this syndrome. Painful Bladder Syndrome, as defined by the International Continence Society, is too restrictive for the clinical syndrome.

Properly defined, the term Bladder Pain Syndrome appears to fit in well with the taxonomy of the International Association for the Study of Pain (IASP) (see below), and focuses on the actual symptom complex rather than what appears to be long-held misconception of the underlying pathology.

Bladder Pain Syndrome

Bladder pain syndrome is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. There is no proven infection or other obvious local pathology. Bladder pain syndrome is often associated with negative cognitive, behavioural, sexual, or emotional consequences as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.

2. HISTORY / INITIAL ASSESSMENT

Males or females whose symptoms meet the requirements of the definition of bladder pain syndrome should be evaluated. The presence of commonly associated disorders including irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia in the presence of the cardinal symptoms of bladder pain syndrome also suggests the diagnosis. Abnormal gynecological findings in women and well-characterized confusable diseases that may explain the symptoms must be ruled out.

➦ The initial assessment consists of a frequency/volume chart, focused physical examination, urinalysis, and urine culture. Urine cytology, cystoscopy, and urodynamic evaluation are recommended if clinically indicated and/or the diagnosis is in doubt. Patients with urinary infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and microscopic or gross haematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms, are they diagnosed with BPS. **Grade of recommendation: C**

3. INITIAL TREATMENT

- patient education,
- dietary manipulation,
- non-prescription analgesics,
- stress reduction,
- pelvic floor muscle relaxation techniques comprise the initial treatment of BPS. In the patient with findings suggesting pelvic floor dysfunction, pelvic floor muscle physical therapy with myofascial trigger point release and intravaginal Thiele massage is often an effective therapeutic intervention.

The treatment of pain needs to be addressed directly, and in some instances referral to an anaesthesia/pain ***centre can be an appropriate early step in conjunction with ongoing treatment of the syndrome***.

Treatment should be focused on the most bothersome or distressing symptoms(s).

➦ ***When conservative therapy fails or symptoms are severe*** and conservative management is unlikely to succeed,

- oral medication, or
- intravesical treatment can be prescribed.

It is recommended to initiate a ***single form*** of therapy and observe results, adding other modalities or substituting other modalities as indicated by degree of response or lack of response to treatment. **Grade of recommendation: C**

4. SECONDARY ASSESSMENT

➦ **If initial oral or intravesical therapy fails**, *or before beginning such therapy based on clinician judgment,* it is reasonable to consider ***further evaluation*** which can include urodynamics, pelvic imaging, and cystoscopy with bladder distention and possible bladder biopsy under anaesthesia.

Findings of ***detrusor overactivity*** suggest a trial of antimuscarinic therapy.

The presence of a ***Hunner's lesion*** suggests therapy with transurethral resection, fulguration of the lesion, or direct steroid injection into the lesion. ***Distention*** itself can have therapeutic benefit in 30-50% of patients, though benefits rarely persist for longer than a few months. **Grade of recommendation: C**

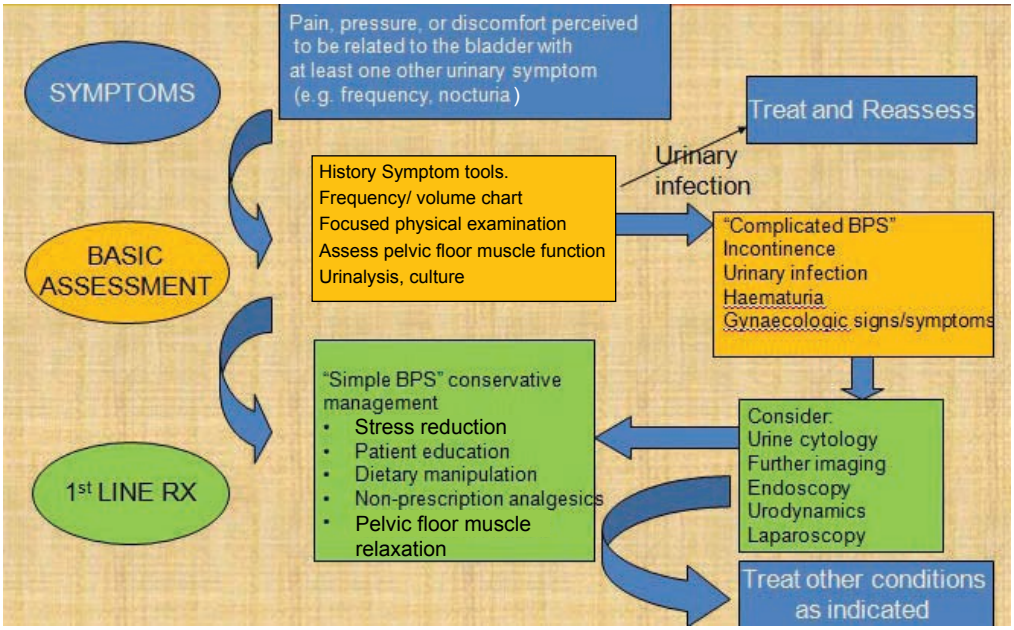
5. REFRACTORY BPS

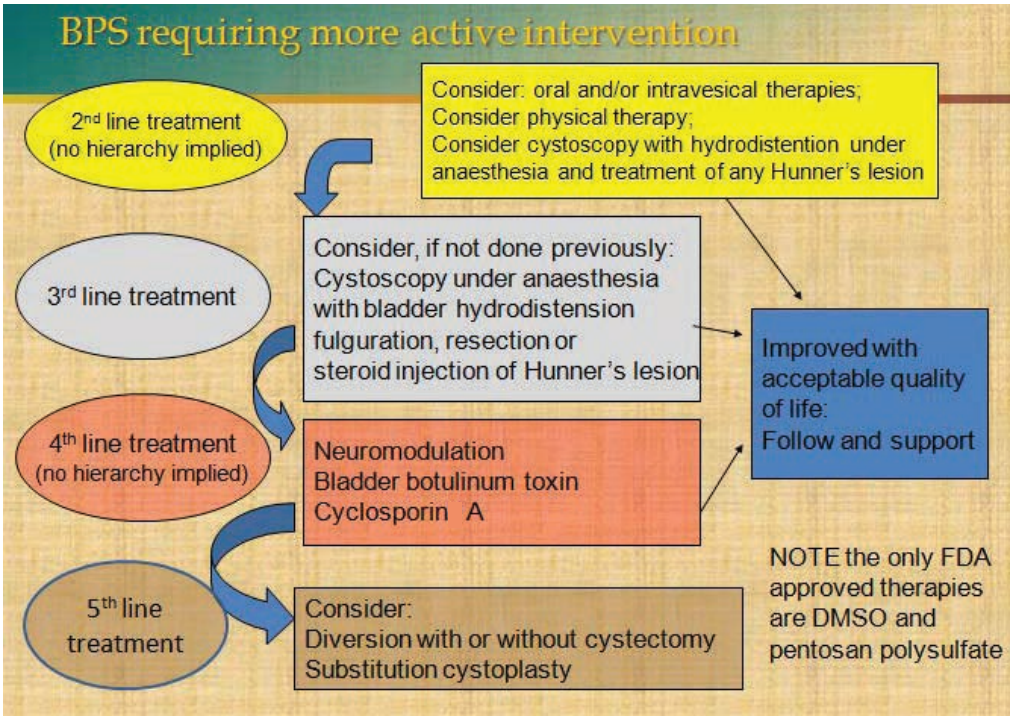
➦ Those patients with ***persistent, unacceptable symptoms*** despite oral and/or intravesical therapy are candidates for ***more aggressive modalities.*** Many of these are best administered within the context of a ***clinical trial if possible.*** These may include neuromodulation, intradetrusor botulinum toxin, oral cyclosporine A, or clinical trials of newly described pharmacologic management techniques. At this point, most patients will benefit from the expertise of an anaesthesia pain clinic.

➦ ***The last step in treatment*** is usually some type of ***surgical intervention*** aimed at increasing the functional capacity of the bladder or diverting the urinary stream.

- ***Urinary diversion*** with or without cystectomy has been used as a last resort with good results in selected patients.
- ***Augmentation*** or ***substitution cystoplasty*** seems less effective and more prone to recurrence of chronic pain in small reported series. **Grade of recommendation: C**

Bladder Pain Syndrome





- Pain management is a primary consideration at every step of algorithm
- Patient enrollment in appropriate research trial is reasonable option at any point
- Evidence supporting neuromodulation, cyclosporin A, and botulinum toxin for BPS indication is limited. These interventions are appropriate only for practitioners with experience treating BPS and willing to provide long-term care post-intervention

VIII. FAECAL INCONTINENCE IN NON-NEUROLOGICAL PATIENTS

INITIAL MANAGEMENT

I. INITIAL CLINICAL ASSESSMENT

Patients with faecal incontinence present with a variety of symptom complexes. As many people are reluctant to admit to having faecal incontinence, it is important to proactively enquire about it, especially in known high risk groups (such as older community-living individuals, post partum women who might have had an obstetric injury, and patients with loose stools).

- ***History*** will include bowel symptoms including loose stools, severity and types of incontinence, systemic disorders, neurological disorders, and anorectal surgeries (e.g., haemorrhoidectomy), obstetrical history for women, medications, diet, chronic straining, cognitive status, and effects of symptoms on quality of life.
- ***Types of incontinence:*** *urgency faecal incontinence,* often a symptom of external anal sphincter dysfunction; *flatus incontinence* (leakage of rectal gas) may indicate rectal sensory impairment and/or internal anal sphincter dysfunction; and *soiling after defaecation*, typically related to a defect in the internal sphincter or poor closure of external sphincter due to rectal prolapse or stage III/IV haemorrhoids.
- ***Physical examination*** will include anal inspection, abdominal palpitation, a brief neurological examination, digital rectal examination and usually proctosigmoidoscopy or colonoscopy.
- ***Further diagnostic testing*** needs to be considered if the patient has symptoms such as an unexplained change in bowel habit, weight loss, anaemia, rectal bleeding, severe or nocturnal diarrhoea, or an abdominal or pelvic mass and bowel pathology when organic conditions such as cancer, inflammatory bowel disease (IBD), a recto-vaginal fistula, full thickness rectal prolapse, or cloacal deformity are suspected. ***Condition specific management*** is indicated for these patients.

Reversible factors (such as inadequate access to toilets and side effects of medications resulting in loose stools) should be assessed and addressed at the outset.

II. INITIAL INTERVENTIONS

➦ Initial management can often be performed in primary care. After environmental factors and local or systemic pathology have been excluded, ***initial interventions include:***

- Discussion of **options** and **goals** of management with the patient
- Provision of patient or caregiver **information** and **education** (Grade A)
- Adjustment of **diet** and fluid advice, **fibre** intake (Grade A)
- Establishing a **regular bowel habit** (Grade C) or **urgency training** if relevant (Grade C)
- **Anti-diarrhoeal** medication can help if stools are loose (Grade B)
- **Rectal Irrigation** to achieve complete rectal evacuation of faeces (Grade B)
- Use of **continence products** including various types and sizes of absorbent pads, briefs, etc., to contain leaked faeces and prevent skin damage

III. SECONDARY INTERVENTIONS

- If initial interventions fail to improve symptoms after 8-12 weeks, consideration should be given to referral to an **incontinence specialist** (e.g., gastroenterologist, continence nurse, advisor physiotherapist, or colorectal surgeon) for other interventions or further assessment.
- **Pelvic floor muscle training (PFMT) – c**ontraction of pelvic floor muscles multiple times per day to improve strength of contraction and increase awareness of anorectal muscle function. (Grade C)
- **Biofeedback therapy** – behavioural treatment designed to enhance the strength of sphincter contraction and improve rectal sensation using specialised equipment. Biofeedback therapy can be combined with PFMT to improve strength. (Grade B)

IV. SECONDARY ASSESSMENT

- A variety of anorectal investigations, including manometry, anal ultrasound, and possibly MRI, defaecagraphy, and neuro-physiological testing can help to define structural or functional abnormalities of anorectal function and guide management if initial and/or secondary interventions are ineffective

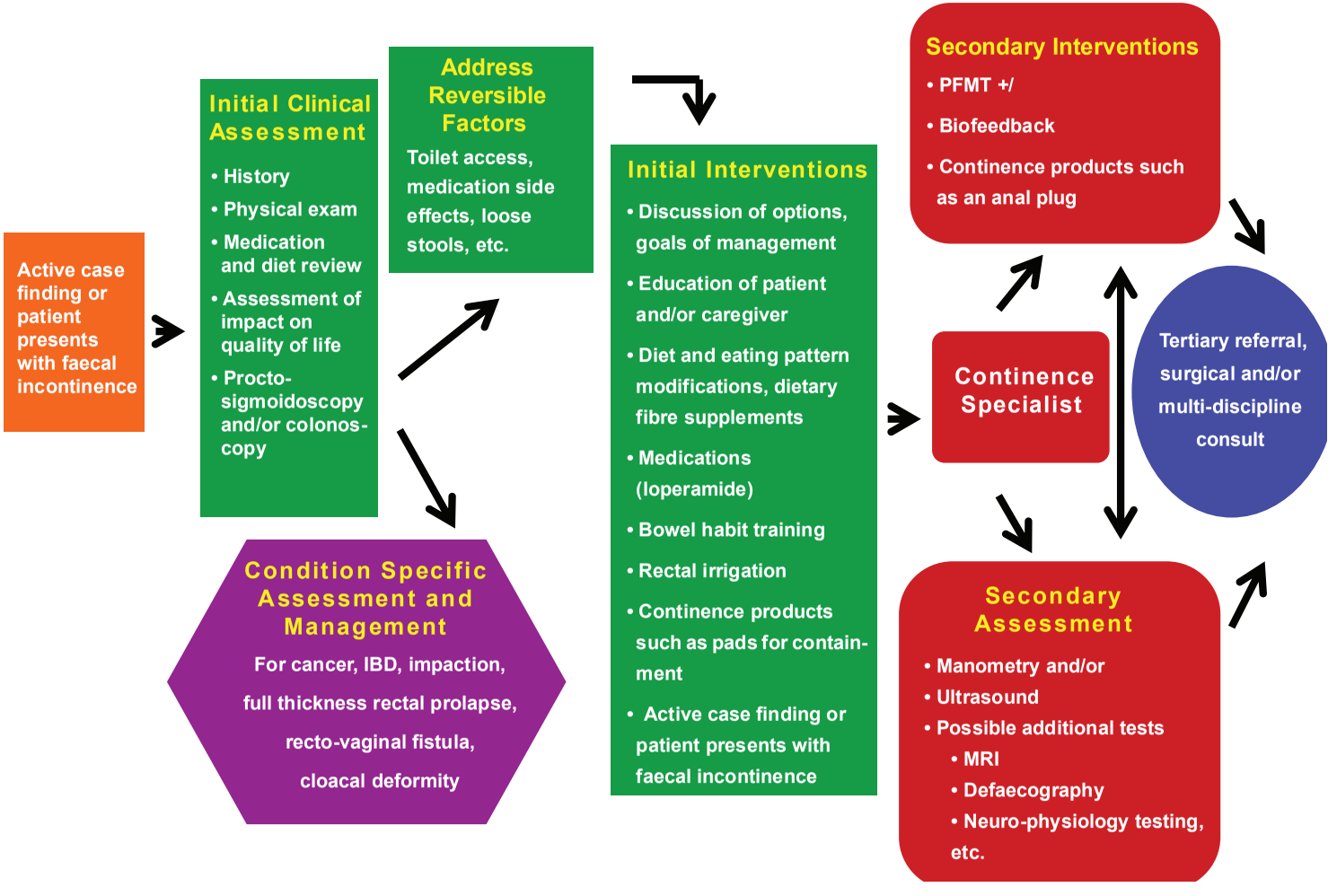
V. TERTIARY REFERRAL, SURGICAL OR MULTI-DISCIPLINARY CONSULTATION

- **Faecal** incontinence that fails to respond to initial and secondary management requires specialised consultation by a gastroenterologist, colorectal surgeon, urogynecologist, and/or a multi-disciplinary team.

RESEARCH RECOMMENDATIONS

- Data should be collected on faecal incontinence whenever practical as part of research on urinary incontinence.
- Development of techniques for diagnosing FI and its severity using new and available technologies
- Well designed and adequately powered studies are needed to evaluate all treatment modalities currently available including
    - Effectiveness of lifestyle modifications including weight loss, exercise, modifying diet and eating pattern and supplementing dietary fibre as primary and adjuvant management strategies
    - Comparative effectiveness trial comparing instrumented biofeedback training to neuromodulation for the treatment of FI
    - Effectiveness of tibial nerve stimulation
- Studies are needed to develop interventions for supporting coping and self-management of faecal incontinence, odour, and urgency and increasing care seeking

Initial Management of Faecal Incontinence



VIII. FAECAL INCONTINENCE

Surgery for Faecal Incontinence

I. INITIAL ASSESSMENT AND MANAGEMENT

The reader is referred to the relevant sections on "Dynamic Testing" and "Conservative Treatment for Faecal Incontinence." In general, patients referred for surgical management of faecal incontinence must either have failed conservative therapy or not be candidates for conservative therapy due to severe anatomic or neurological dysfunction.

Prior to surgical management of faecal incontinence, the integrity of the anal sphincter complex should be assessed. This assessment is best performed with endoanal ultrasound, though pelvic MRI may also be useful. Ancillary tests include anal manometry, electromyography, and defaecography.

- Patients with rectal prolapse, rectovaginal fistulae, and cloacae often have associated faecal incontinence. Initial therapy should be directed at correction of the anatomic abnormality (in the case of rectovaginal fistula or cloaca, this surgical repair may include overlapping sphincteroplasty.) If the patient has persisting faecal incontinence, she should undergo repeat assessment, including especially endoanal ultrasound.

II. SPECIALISED MANAGEMENT

The surgical approach to the incontinent patient is influenced by the presence and magnitude of an anatomic sphincter defect. If no defect is present, or if the sphincter defect is minimal, options include SNS and injection therapy.

- For patients with moderate sphincter defects, sphincteroplasty, SNS or injection therapy can each be considered. For patients with large sphincter defects (>120 degrees), sphincteroplasty is likely the best option, though a PNE trial for SNS can be considered.
- Patients with sphincter defects of greater than 180° or major perineal tissue loss require individualised treatment. In some cases, initial reconstruction can be performed. Should incontinence persist, alternatives include stimulated muscle transposition, artificial anal sphincter implantation, or sacral nerve stimulation.

III. SALVAGE MANAGEMENT

For patients who remain incontinent following sphincteroplasty, repeat endoanal ultrasound should be undertaken to reassess the status of the repair. If no defect is present, or if the sphincter defect is minimal (<30 degrees), options include SNS and injection therapy. If there is a large persisting sphincter defect, repeat sphincteroplasty can be considered.

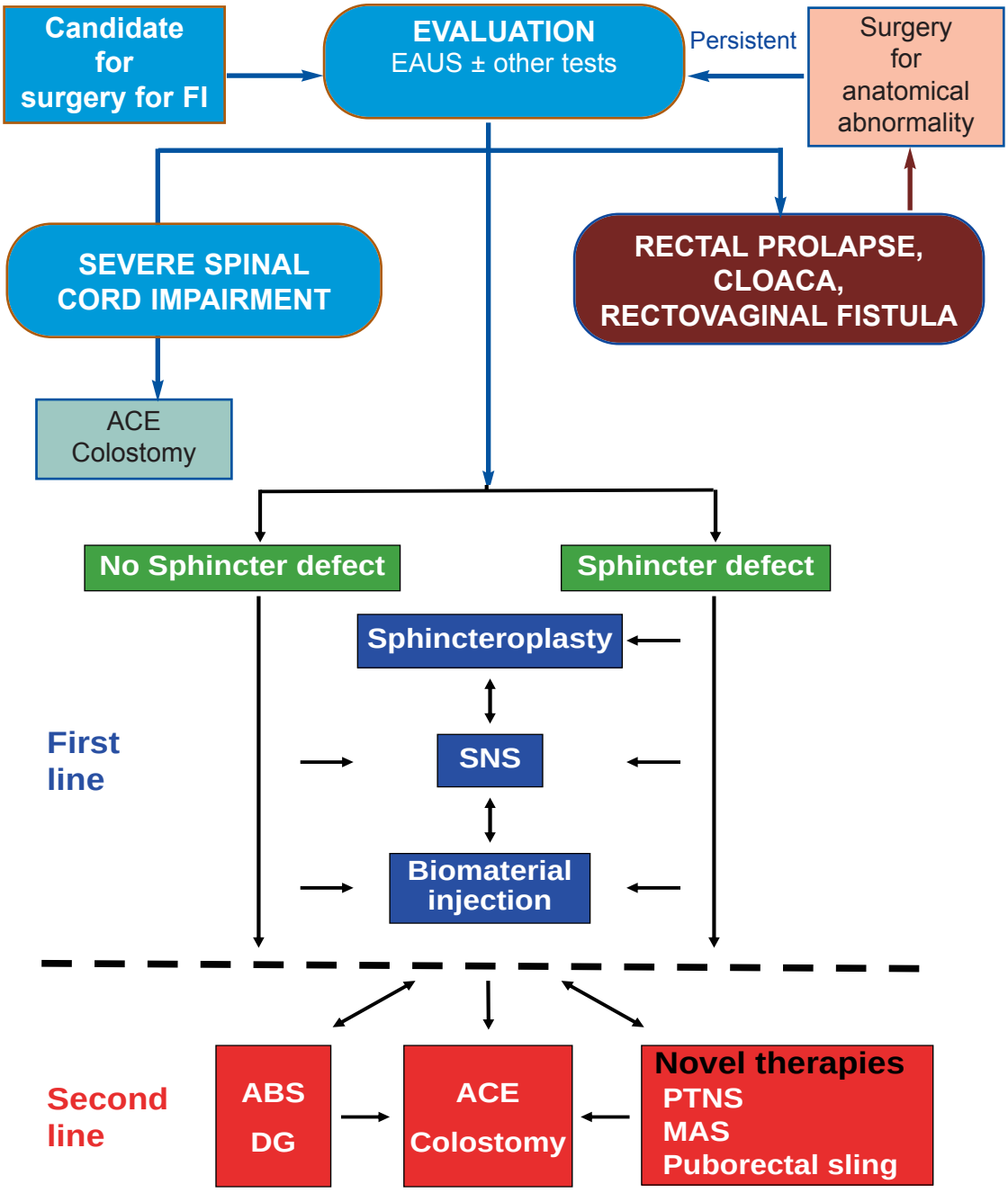
Patients who have failed sacral nerve stimulation can be considered for injection therapy or sphincteroplasty if a sphincter defect is present. Other alternatives include stimulated graciloplasty and implantation of an artificial anal sphincter.

Patients who fail surgical therapy for faecal incontinence, or who do not wish to undergo extensive pelvic reconstruction, should consider placement of an end sigmoid colostomy. While this procedure does not restore continence, it does restore substantial bowel control and appears to improve social function and quality of life. Novel therapies can also be considered under protocol: PTNS, the magnetic anal sphincter and sling procedures.

IV. SPECIAL SITUATIONS

Individuals with severe spinal cord dysfunction (due, e.g., to injury or congenital abnormality) should be considered for an Antegrade Continence Enema (ACE) procedure or colostomy.

Surgical Management of Faecal Incontinence *



EAUS: endoanal ultrasonography, ACE: antegrade continence enema,
SNS: sacral nerve stimulation, ABS: artificial bowel sphincter,
DG: dynamic graciloplasty, PTNS: posterior tibial nerve stimulation,
MAS : magnetic anal sphincter

* At any stage of the patient's care pathway, management may need to include continence products

IX. FAECAL INCONTINENCE IN NEUROLOGICAL PATIENTS

A. INITIAL MANAGEMENT

➦ Patients with ***known neurological disease*** may present with symptoms related to neurologic bowel dysfunction – difficulty in defaecation, constipation and faecal incontinence which disturb their activities of daily living and quality of life. Many have permanent impairments and functional limitations and disabilities, which are due to neurological deficits and complications

I. INITIAL ASSESSMENT

➦ ***History taking***: this includes

- Neurological diagnosis and functional level
- Previous and present lower gastrointestinal (LGIT) function and disorders
- Severity of neurogenic bowel dysfunction
- Current bowel care and management including diet, fluid intake, medications affecting bowel functions
- Co-morbidity / complication e.g., urinary incontinence, autonomic dysreflexia, pressure ulcers, sexual dysfunction
- Patient's satisfaction, needs, restrictions and quality of life
- Environmental factors and barriers and facilitators to independent bowel management.

➦ ***Physical examination***:

- Cognitive functions; motor, sensory and sacral reflexes – voluntary anal sphincter contraction, deep perianal sensation, anal tone, anal and bulbocavernosus reflexes
- Spasticity of the lower limbs
- Abdominal palpation for faecal loading and rectal examination

➦ ***Functional assessment***:

- hand and arm use, fine hand use, mobility – maintaining body position, transfer and walking ability.

➦ ***Environmental factors assessment***:

- toilet accessibility; devices for bowel care and mobility; caregivers' support and attitude;

II. BASIC INVESTIGATIONS:

Stool exam, plain abdomen XRay

III. INITIAL TREATMENTS

- ***Patient education and goals-setting*** - complete defaecation on a regular basis and faecal continence based on right time, right place, right trigger and right consistency
- ***Adequate fibre diet and fluid intake***; appropriate trigger according to preservation of sacral (anorectal) reflex – digital rectal stimulation; suppository and enema; if no anorectal reflex, manual evacuation; abdominal massage can also be helpful
- ***Prescribe medications*** – stool softener, laxative, prokinetic agents, anti-diarrhoea drugs as neccessary
- Assistive techniques may be necessary for
  - defaecation – irrigation
  - for incontinence – anal plug

The diagram does not apply to management in acute neurological patients that need regular bowel emptying.

Initial Management of Neurogenic Faecal Incontinence

HISTORY, level of lesion

- Sacral cord/cauda equina lesion (e.g. lumbar disc prolapse). Peripheral nerve lesion (e.g. radical pelvic surgery)
- Suprasacral infrapontine and pontine lesion (e.g. trauma, multiple sclerosis)
- Suprapontine lesions (e.g. Parkinson)

CLINICAL ASSESSMENT

- History taking including diagnosis, pre-morbid bowel function and sensation and their disorders, current bowel and bladder programme, co-morbid diseases/disorders, QOL and needs
- Physical & neurological examination including cognitive function, voluntary anal contraction, sensation, sacral reflexes, digital rectal examination, abdominal palpation for faecal impaction
- Functional assessment including hand and arm use, fine hand use, balance, transfer and walking
- Environmental factors assessment including toilet accessibility, assistive device, caregivers' support and attitude
- Basic investigation: stool exam, plain film abdomen in selected patients (diarrhoea, impaction not felt on rectal examination)

This assessment will give basic information but does not permit a precise diagnosis of neurogenic bowel dysfunction

PRESUMED DIAGNOSIS

- Incontinence due to sphincter incompetence
- Incontinence due to lack of cognitive function, sensory awareness disorders, unable to control by voluntary anal contraction
- " False incontinence " due to faecal impaction

TREATMENT *

- Manual evacuation
  Assistive device – anal plug
  mini-enema, transanal/transrectal irrigation
- Digital rectal stimulation
  Chemical stimulant: suppository, mini-enema, stool softener, laxative; given by patient/caregiver
- Faecal disimpaction incl. enemas and transanal/transrectal irrigation

Necessary in all

Patient education, adequate fibre diet and fluid intake; regular bowel care, preferably ± 3 times a week

Specialised management preferable for more " tailored " treatment

* At any stage of the patient's care pathway, management may need to include continence products

IX. FAECAL INCONTINENCE IN NEUROLOGICAL PATIENTS

B. SPECIALISED MANAGEMENT

I. ASSESSMENT

- ***Some patients*** with neurogenic faecal incontinence will need ***specialised assessment,*** especially if initial management is unsuccesful to look for comorbidity and certainly before performing invasive treatment
- ***Do not assume*** that all symptoms are ***due to neuropathy,*** e.g. women with neurological pathology might have had childbirth injury to the sphincter
- **Special investigations**: manometry, endoanal ultrasound, (dynamic) MRI, (needle) EMG. These specific bowel functional tests and electro-diagnostic tests must be considered ***optional*** as their value in neurological pathology is not sufficiently demonstrated so far.

II. TREATMENTS

➦ ***Also for specialised management, conservative treatment for neurological faecal incontinence is the mainstay***

➦ ***Management of neurological*** incontinence does not include very extensive treatment modalities and many conservative interventions are still empirical.

- Transanal irrigation (C)
- Electrical stimulation sphincter, (C)
- Percutaneous neuromodulation : further research is required

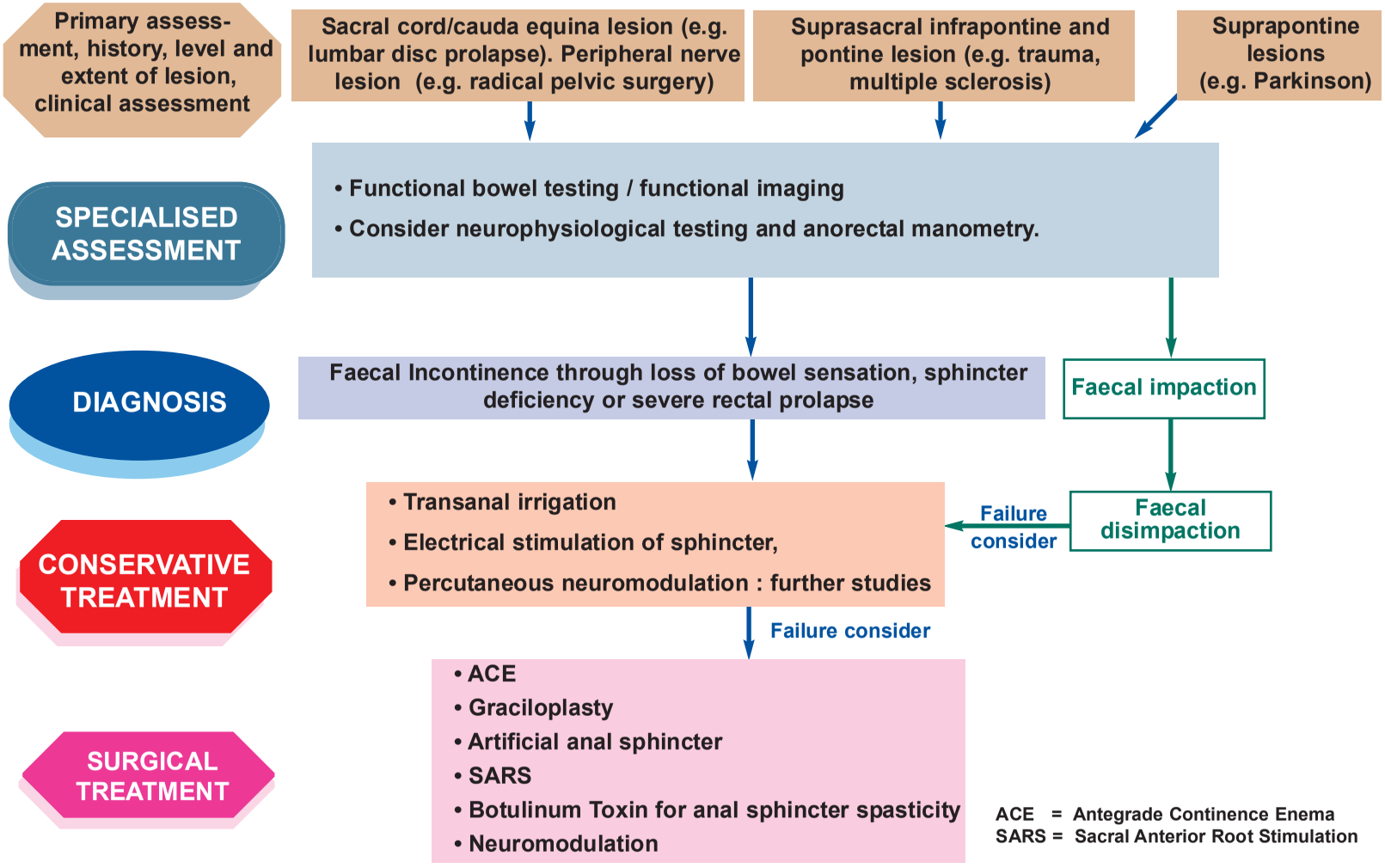
➦ Surgical management of neurogenic faecal incontinence has different options which need a very strict patient selection

- Antegrade Continence Enema ACE (C)
- Graciloplasty (C)
- Artificial sphincter (C)
- Sacral Anterior Root Stimulation SARS (C)
- Botulinum Toxin (C)
- Neuromodulation (C)

➦ It is recommended to look at urinary and bowel function together if both systems are affected, as symptoms and treatment of one system can influence the other and vice versa (A).

➦ As therapeutic approach can differ in different neurological diseases, the most prevalent diseases are discussed separately in the chapter.

Specialised Management of Neurogenic Faecal Incontinence *



Stoma/diversion may be an option in selected cases

* At any stage of the patient's care pathway, management may need to include continence products

X. URINARY AND FAECAL INCONTINENCE IN FRAIL OLDER MEN AND WOMEN

There is no reason to suspect why interventions which have proven efficacy in the community dwelling elderly should not also be effective in frail older people. Clinicians should, however, take due regard of the practicality, potential benefits and dangers of employing any single intervention in this population. Frail older people do require a different approach addressing the potential role of co-morbid disease, current medications (prescribed, over the counter and/or naturopathic), and functional and cognitive impairment in urinary and faecal incontinence. The extent of the investigation and management should take into account the degree of bother to the older person and/or caregiver, the goals for care, the degree that the older person is able to undertake any intervention and the overall prognosis and life expectancy. Effective management to meet the goals of care should be possible for most frail older people.

I. HISTORY AND SYMPTOM ASSESSMENT

- Active case finding for urinary and faecal incontinence should be done in all frail older people (Grade A). History should include comorbid conditions and medications that could cause or worsen incontinence. Physical examination should include a rectal examination for faecal loading or impaction (Grade C), functional assessment (mobility, transfers, manual dexterity, dressing and undressing ability, ability to toilet) (Grade A), a screening test for depression (Grade B), and cognitive assessment (to assist in planning and management, (Grade C)). The mnemonic DIPPERS (see urinary and faecal incontinence algorithms) covers some of these comorbid conditions. Note that urogenital atrophy does not, in itself, cause urinary incontinence and should not be treated for this purpose (Grade B). The patient and / or caregiver should be asked about the degree of bother of urinary incontinence and/or faecal incontinence(Grade B); goals for urinary and faecal incontinence care (dryness, decrease in specific symptoms, quality of life, reduction of comorbidity, lesser care burden) (Grade B); and likely cooperation with management (Grade C).
- Evaluation for bowel “alarm” symptoms (rectal bleeding, positive blood screening from stool studies, obstructive symptoms, recent onset of constipation, weight loss, and a change in stool calibre) will need more extensive evaluation (Grade A)
- Urinalysis is recommended for all patients, primarily to screen for haematuria (Grade C). Treatment of otherwise asymptomatic bacteriuria/pyuria is not beneficial (Grade C), and it may cause harm by increasing the risk of antibiotic resistance and severe adverse effects. e.g., *Clostridium difficile colitis* (Grade C).
- Stool studies may not be needed in all patients with faecal incontinence. Patients with diarrhoea, especially those with more acute onset diarrhoea, may need to be tested for infectious causes of their diarrhoea. Other stool studies could involve testing for malabsorption syndromes.
- The utility of the Clinical Stress test in this population is uncertain (Grade D).
- Wet checks can assess urinary incontinence frequency in long-term care residents (Grade C):

  A post voiding residual volume (PVR) test is impractical in many care settings and there is no consensus for the definition of what constitutes a “high” PVR in any population. A PVR measurement is **not** recommended in the routine initial assessment of frail older people with urinary incontinence.
- However, there is compelling clinical experiential evidence for PVR testing in selected frail older people with: diabetes mellitus (especially long standing); prior urinary retention or high PVR; recurrent UTIs; medications that impair bladder emptying (e.g., opiates); severe constipation; persistent or worsening urgency urinary incontinence despite antimuscarinic treatment; or prior urodynamics showing detrusor underactivity and/or bladder outlet obstruction (Grade C). Treatment of contributing comorbidity may reduce PVR. Trial with catheter may be considered for PVR > 200-500 ml if the PVR is felt to contribute to UI or urinary frequency (Grade C).
- **Nocturia** Assessment of frail elders with bothersome nocturia should identify potential underlying causes including nocturnal polyuria (by bladder diary/frequency-volume chart or wet checks; oedema on examination) (Grade C),primary sleep problems (e.g., sleep apnoea); and low voided volumes (e.g., from high PVR).
- Stool impaction/ loading. If suspected on digital rectal examination, an abdominal x-ray may be necessary to further evaluate the degree and location of impaction /loading in frail older adults.

II. CLINICAL DIAGNOSIS

The most common types of Urinary Incontinence in frail older people are urgency, stress, and mixed urinary incontinence. Frail older people with urgency urinary incontinence also may have detrusor underactivity and high PVR (without outlet obstruction). There is no evidence that antimuscarnincs are less effective or cause retention in this situation (Grade D).

The most common types of faecal incontinence in frail older people are related to urgency and passive leakage. Passive leakage can refer to leakage, seepage and staining following bowel movements that are not associated with faecal urgency and may also occur with faecal impaction. Because constipation and impaction often contribute to faecal incontinence in older adults, these are considered separately in the algorithm.

III. INITIAL MANAGEMENT

- Initial treatment should be individualised and influenced by goals of care, treatment preferences and estimated remaining life expectancy, as well as the most likely clinical diagnosis (Grade C). In some frail older persons the only possible outcome may be containment; management with continence products, especially for people with minimal mobility (require assistance of $\geq$ 2 people to transfer), advanced dementia (unable to state their name), and /or nocturnal urinary and faecal incontinence.
- Conservative and behavioural therapy for UI includes lifestyle changes (Grade C), bladder training for more fit alert persons (Grade B), and prompted voiding for frailer, more impaired older people (Grade A).
- For the select cognitively intact older person with UI or FI, pelvic floor muscle therapy can be considered, but there are few studies (Grade C). Antimuscarinics may be added to conservative therapy of urgency UI (Grade A-C, depending on agent).
- For the select cognitively intact older with FI, biofeedback may be considered, but few studies exist among frail older adults.
- Alpha-blockers may be cautiously considered in frail men with suspected prostatic outlet obstruction (Grade C). All drugs should be started at the lowest dose and titrated with regular review until either care goals are met or adverse effects are intolerable.
- DDAVP (vasopressin) has a high risk of severe hyponatraemia in frail older persons and should not be used outside specialist centres (Grade A).
- Improving stool consistency can be done with dietary fibre and supplementary fibre in older adults (Grade C). In older adults with diarrhoea, loperamide may be considered at low doses to improve stool consistency. However, close monitoring for constipation and impaction is needed.

IV. ONGOING MANAGEMENT AND REASSESSMENT

Optimal urinary and faecal incontinence management is usually possible with the above approaches. If initial management fails to achieve the desired goals the next steps are reassessment and treatment of contributing comorbidity and/or functional impairment.

V. SPECIALISED MANAGEMENT

If frail older people have either other significant factors (e.g., pain, haematuria, bowel “alarm” symptoms), UI or FI symptoms that cannot be classified as urgency, stress, or mixed or overflow or other complicated comorbidity which the primary clinician cannot address (e.g. dementia, functional impairment), then specialist referral should be considered. Referral may also be appropriate when there is been insufficient response to initial management. The type of specialist will depend on local resources and the reason for referral: surgical specialists (urologists, gynecologists, colorectal surgeons), gastroenterologists, geriatricians or physical therapist (functional and cognitive impairment); or continence nurse specialists (homebound patients). Referral decisions should consider goals of care, patient/caregiver desire for invasive therapy and estimated remaining life expectancy.

Age *per se* is not a contraindication to UI or FI surgery (Grade C), but before surgery is considered, all patients should have:

- evaluation and treatment for any comorbidity, medications, and cognitive or functional impairments contributing to UI that could compromise surgical outcome (e.g., dementia that precludes patient ability to use artificial sphincter) (Grade C)
- adequate trial of conservative therapy, including pharmacological therapies where relevant (Grade C)
- discussion (including the caregiver) to ensure that the anticipated surgical outcome is consistent with goals of care in the context of the patient’s remaining life expectancy (Grade C)
- urodynamic testing or anorectal manometry, because clinical diagnosis may be inaccurate (Grade B)
- preoperative assessment and perioperative care to establish risk for and to minimize common geriatric post-operative complications such as delirium and infection (Grade A), dehydration and falls (Grade C).

Management of Urinary Incontinence in Frail Older Men & Women

HISTORY/SYMPTOM ASSESSMENT

CLINICAL ASSESSMENT

- **D**elirium
- **I**nfection
- **P**harmaceuticals
- **P**sychological
- **E**xcess urine output
- **R**educed mobility
- **S**tool impaction

(and their factors)

Avoid overtreatment of asymptomatic bacteriura

CLINICAL DIAGNOSIS

* These diagnoses may overlap in various combinations, e.g., Mixed UI, DHIC (see text)

INITIAL MANAGEMENT *

(if Mixed UI, initially treat most bothersome symptoms)

ONGOING REASSESSMENT and MANAGEMENT

Active Case Finding in all Frail Elderly people

- **Assess, treat and reassess potentially treatable conditions, including relevant comorbidities and ADLs (see text)**
- **Assess QoI, desire for Rx, goals for Rx, patient & caregiver preferences**
- **Targeted physical examination (cognition, mobility, neurological and digital rectal examination)**
- **Urinalysis**
- **Consider bladder diary or wet checks, especially if nocturia is present. PVR in specific patients (see text)**

UI associated with:

- Pain
- Haematuria
- Recurrent symptomatic UTI
- Pelvic mass
- Pelvic irradiation
- Pelvic / LUT surgery
- Prolapse beyond introitus (women)
- Suspected fistula

URGENCY UI*

- **Lifestyle interventions**
- **Behavioural therapies**
- **Consider trial of antimuscarinic drugs**

SIGNIFICANT PVR*

- **Treat constipation**
- **Review medications**
- **Consider trial of alpha-blocker (men)**
- **Catheter drainage if PVR 200-500 ml, then reassess (see text)**

STRESS UI*

- **Lifestyle interventions**
- **Behavioural therapies (See text)**

*** Other**

If insufficient improvement, reassess for and treat contributing comorbidity ± functional impairment

If continued insufficient improvement, or severe associated symptoms are present, consider specialist referral as appropriate per patient preferences and comorbidity (see tex)

* At any stage of the patient's care pathway, management may need to include continence products

Management of Faecal Incontinence in Frail Older Men & Women

HISTORY/SYMPTOM ASSESSMENT

Active Case Finding in all Frail Elderly people

FI associated with:
- Pain
- Rectal bleeding
- Change in stool calibre
- Weight loss
- Chronic diarrhoea
- Faecal impaction
- Inflammatory bowel disease
- Pelvic irradiation
- Malabsorption syndromes
- Prolapse beyond introitus (women)
- Suspected fistula

CLINICAL ASSESSMENT

Rx reversible causes:
- Delirium
- Infection
- Pharmaceuticals
- Psychological
- Excess stool output (diarrhoea)
- Reduced mobility
- Stool impaction (and their factors)

- Assess, treat and reassess potentially treatable conditions, including relevant comorbidities and ADLs (see text)
- Assess QoI, desire for Rx, goals for Rx, pt & caregiver preferences
- Targeted physical examination (cognition, mobility, neurological and digital rectal examination)
- Urinalysis
- Consider bowel diary and clean checks, especially if nocturia is present. PVR is specific patients (see text)

CLINICAL DIAGNOSIS

** These diagnoses may overlap in various combinations, e.g., Urgency-related,passive/seepage, and impaction (see text)

Urgency FI**

Constipation/ Faecal Impaction*

Passive FI*

*** Other**

INITIAL MANAGEMENT *

- Lifestyle interventions
- Behavioural therapies
- Biofeedback
- Improve stool consistency

- Treat constipation (osmotic laxatives) If impacted, Glycerine or Bisacodyl suppositories. Phospate enemas if severe.
- Review medications that may contribute to constipation
- Consider biofeedback if dyssynergic defaecation is suspected

- Lifestyle interventions
- Behavioural therapies
- Biofeedback
- Improve stool consistency

ONGOING REASSESSMENT and MANAGEMENT

If insufficient improvement, reassess for and treatment of contributing comorbidity ± functional impairment

If continued insufficient improvement, or severe associated symptoms are present, consider specialist referral as appropriate per patient preferences and comorbidity (see tex)

* At any stage of the patient's care pathway, management may need to include continence products

4. Recommendations for Further Research in Epidemiology

1. Longitudinal study designs are needed to: (i) estimate the incidence and remission rates of urinary incontinence (UI) anal incontinence (AI) and pelvic organ prolapse (POP) and to (ii) describe the natural course of these conditions and (iii) to investigate risk factors and possible protective factors. In addition similar studies regarding other lower urinary tract symptoms (LUTS) should be initiated.
2. Although there is today more information regarding prevalence, incidence, and other epidemiological data in developing countries further information is still needed. It is recommended that fundamental research regarding prevalence, incidence and other epidemiological data in developing countries should be encouraged, and tailored to the cultural, economic and social environment of the population under study.
3. Some potential risk and protective factors deserve more attention. For example, the role of pregnancy and childbirth in the development of UI, AI and POP must be studied in a fashion that links population-based methods to clinical assessment of pregnancy, delivery and birth trauma and follows women over many years. Such a design is necessary because the effect of pregnancy and childbirth may become clear only years later when the woman is older and because the woman will not then be able to report the exact nature of the tear, episiotomy, etc.
4. There should be more emphasis on the associations between UI, AI and POP and specific diseases like stroke, diabetes, and psychiatric diseases.
5. The variation of disease occurrence in groups of different racial origin yet similar environmental exposures, lend support to the presumed genetic influence on the causation of UI, AI and POP. This again provides circumstantial evidence for a genetic contribution to pelvic floor muscle disorders since most of these studies have been unable to control for heritability in relation to the complex interaction of environmental factors.

   The aetiology of UI, AI and POP is widely recognised to be multifactorial, yet the complex interaction between genetic predisposition and environmental influences is poorly understood. Genetic components require further investigation. Twin studies provide a possible means of studying the relative importance of genetic predisposition and environmental factors. By comparing monozygotic female twins with identical genotype, and dizogytic female twins who on average share 50 percent of their segregating genes, the relative proportions of phenotypic variance resulting from genetic and environmental factors can be estimated. A genetic influence is suggested if monzygotic twins are more concordant for the disease than dizygotic twins whereas evidence for environmental effects comes from monozygotic twins who are discordant for the disease.

5. Recommendations for Further Basic Science Research

1. Integrate data from reductionist experiments to inform the formulation of better systems-based approaches in the investigation of the pathology of the lower urinary tract (LUT), the genital tract (GT) and the gastro-intestinal tract (GIT).
2. Encourage greater emphasis on basic research to characterise tissues receiving relatively little attention: ie the lower gastrointestinal tract; the bladder neck and urethra.
3 Generate improved experimental approaches to investigate the pathophysiology of the LUT and GIT by:
   - developing fully-characterised animal models
   - using human tissue from well-characterised patient groups.
   - developing emerging areas such as: tissue engineering; protein structure modelling
   - increasing collaborations between biological, physical and mathematical sciences.
4. Use genome-wide bioinformatic surveys to generate testable hypotheses regarding the physiological and pathophysiological functions of the LUT and GIT
5. Develop centres of excellence in LUT and GIT research
   - integrate expertise from university departments, academic medical units and industry
   - encourage translational approaches to research.
   - develop inter-institutional research-training programmes to allow new researchers the opportunity to better interact and exchange ideas

6. Bring about a greater emphasis on the importance of research to medical trainees through:

- establishing research training as a core component of medical training
- increased access to support funds, especially scholarships and personal awards
- organisation of focused multidisciplinary research meetings, either stand-alone or as dedicated sessions during international conferences
- greater interaction between medical centres and Higher Education Institutions (HEIs)
- allow researchers-in-training better access to international meetings through reduced registration charges and travel grants.
- Lobby research-funding organisations about the medical and social importance of LUT and GIT disorders.

7. Increase emphasis on research into lower urinary tract and gastro-intestinal tract in HEIs through:

- greater representation on grant-funding agencies
- encouragement of submission to high impact-factor journals and recognition of research published in specialty journals
- more integrated teaching and training opportunities

6. Recommendations

Continence Promotion, Education and Primary Prevention

Continence promotion, service delivery, education, and primary prevention involves informing and educating the public and health care professionals that urinary and faecal incontinence are not inevitable, but are treatable or at least manageable. In addition, other bladder disorders such as bladder pain syndrome and pelvic organ prolapse can be treated successfully. Progress continues to be made in the promotion of continence awareness through advocacy programmes and public access to information on a worldwide basis. Professional education of these conditions has increased. However, screening and help-seeking behaviour have not noticeably improved. Published studies focus on developing better models of existing service provision and education, rather than testing new strategies to increase screening. There have been advances in primary prevention of urinary incontinence.

CONTINENCE AWARENESS AND PROMOTION

- Continence awareness should be part of mainstream and on-going health education and advocacy programmes with emphasis on eliminating stigma, raising awareness of effective treatments, promoting help-seeking behaviour and improving QoL.
- Continence awareness programmes should include education, health-care, and community service providers.
- Research is needed to provide higher level of evidence on the effectiveness of continence promotion programmes to include:
  - º Identification and understanding of barriers to help-seeking behaviours
  - º Translation of promotion research into improved clinical practice and identification of methods by which this occurs.
  - º Effectiveness and impact of consumer education initiatives.

CONTINENCE ADVOCACY AND MODELS OF SERVICE DELIVERY

- There is a need to move beyond the theory and work on research about the practice of continence care delivery and education. We recommend a care delivery model based on a chronic disease approach.
- There needs to be an increased emphasis on non-physician models of care (nursing, nurse practitioner, continence advisor, physiotherapy, physician assistants, etc.).
- Despite the proliferation of guidelines, there is increasing evidence that they are not being followed by practicing clinicians. Implementation models should be developed on how to translate guidelines into practice.
- There still appears to be a shortage of physician specialists in continence care (urology, gynaecology, etc.) and this needs to be addressed. (**Grade D)**
- Research is needed on the activities or effectiveness of organisations that target consumers or the general public.

PROFESSIONAL EDUCATION

- There remains a need for rigorously evaluated continence education programmes which adhere to defined minimum standards for continence specialists and generalists, utilising web-based and distance learning techniques alongside audit and feedback, train-the trainer models and leadership models as well as traditional methods.
- Models of education content delivery (professional and patient education) are changing with technology with increased emphasis on internet, web modules, etc. There needs to be ongoing quality control that includes maintenance of accuracy, methods of delivery, etc.
- There is a need for research on the most effective means to educate professional groups on continence issues to include:
  - The effectiveness of innovative teaching methods in improving knowledge and practice.
  - Translation of research into improved clinical practice and identification of methods by which this happens.
  - Mechanisms for increasing professional motivation to acquire education and improve performance.

PRIMARY PREVENTION:

- Primary prevention studies should not be limited to individual interventions, but also test the impact of population-based public health strategies **(Grade C)**
- More high quality randomised controlled trials are needed to strengthen the effectiveness of population-based primary prevention intervention.

7. Recommendations for Clinical Research Methodology

PART I: RECOMMENDATIONS ON STUDY CONDUCT AND STATISTICAL METHODS

The role of quality RCTs as providing the strongest level of evidence in incontinence research should be fully acknowledged by researchers, journal reviewers, and editors. HIGH

Careful attention to the planning and design of all research, especially RCTs, is of the utmost importance. HIGH

Appropriate expertise in biostatistics and clinical trial design should be employed at the design phase of a RCT and thereafter on an ongoing basis. HIGH

The design, conduct, analysis and presentation of RCTs must be fully in accordance with the CONSORT Statement. HIGH

The design, conduct, analysis and presentation of observational studies should follow STROBE guidelines. HIGH

The design, conduct, analysis and presentation of meta-analyses should follow QUORUM guidelines. HIGH

Reporting studies of diagnostic tests, including urodynamics, should follow the STARD statement guidelines. HIGH

PART II: RECOMMENDATIONS ON RESEARCH CONDUCT

RECOMMENDATIONS FOR CONSERVATIVE TREATMENT TRIALS

Use correct terminology to describe the intervention. HIGH

Report details of ability to perform correct contraction, dose-response issues and adherence. HIGH

Use recommended outcome measures with high responsiveness, reliability and validity. HIGH

Compare new methods with the best available intervention. HIGH

Use power calculation in planning of the study. Avoid large sample sizes and weak (ineffective dosages) interventions. HIGH

For long-term follow-up studies report cross-over, co-interventions, recurrent and competing events, adherence in the follow-up period and loss to follow-up.

RECOMMENDATIONS FOR SURGICAL AND DEVICE TRIALS

- The safety and serious side effects of new operations must be completely defined with adequate follow-up so that risks can be weighed against efficacy. At a minimum, this requires more use of large scale, independent, prospective, multicenter cohort studies when RCTs are not practical. HIGH
- Safety and serious side effects of incontinence devices must be completely defined with adequate follow-up, especially for use of implantable devices and biologic materials, so that risks can be weighed against efficacy.HIGH
- Valid informed research consent is required in all trials of surgical interventions, which is separate from the consent to surgery. HIGH
- We recommend ongoing research into the usefulness of pre- and post-operative predictive testing (such as urodynamics, ultrasound, MRI, etc) in surgical trials. HIGH
- Reports of successful treatment should be limited to subjects with a minimum (not mean) of one year follow-up and should include a patient perspective measure. Specific assumptions about subjects lost to follow-up should be stated. HIGH
- Randomisation for surgical trials should occur at the time of surgery to minimize drop-outs and switch of procedure HIGH
- Long-term follow-up of RCT cohorts in an observational cohort is recommended HIGH

RECOMMENDATIONS ON COST ANALYSIS IN INCONTINENCE

- Cost analysis should be incorporated into clinical studies whenever possible (137). HIGH

Part III: RECOMMENDATIONS FOR SPECIFIC PATIENT GROUPS

IIIa: MEN WITH LUTS

- Measurement of prostate size should be performed before and after treatment (at the same time as continence outcome measures where possible) whenever prostate size is considered to be a variable, or to change during the intervention and follow up. HIGH
- Maximum free flow rate and measurement of post-void residual urine should be recorded pre-treatment and the effect of therapy on these parameters should be documented simultaneously with assessment of the primary outcome variables. HIGH
- Participants should be stratified by prostate size at randomization when size is considered to be a potentially important determinant of treatment outcome. LOW

IIIb: WOMEN WITH LUTS

- Specific information about menopausal status, hysterectomy, parity/obstetric history, and hormonal status should be included in baseline clinical trial data and controlled for in specified analyses in the research protocol. HIGH
- High quality, symptom and bother scores (e.g.,ICIQ-FLUTS, ICIQ-SM, KHQ, PISQ, ICIQ-FLUTSsex) validated in women should be employed when assessing outcomes. HIGH
- Standardized assessment of pelvic organ prolapse should be performed before treatment and at the time of other outcome assessments in all research where prolapse and continence outcomes are being assessed. HIGH
- Criteria for cure/improvement/failure from incontinence treatment should be defined in the protocol based on patient perception as well as objective and semi-objective instruments such as validated questionnaires, diaries and pad tests. HIGH
- Assessment of the impact of treatment on sexual function should be performed with other outcome assessment when appropriate. MEDIUM

IIIc: CHILDREN

- Long-term follow-up is of critical importance in the paediatric population in order to ascertain the effect of a treatment on normal growth and development. HIGH
- Research is needed to develop standardised outcome measures including validated, age-specific symptom and disease-specific quality of life outcome measures. MEDIUM

IIId: NEUROGENIC POPULATIONS

- Detailed urodynamic studies are recommended for classification of neurogenic lower urinary tract

disorders in research studies because the nature of the lower tract dysfunction cannot be accurately predicted from clinical data. Videourodynamic studies are preferred but are not mandatory. LOW

- An area of high priority for research is the development of a classification system to define neurogenic disorders. Relevant features could include the underlying diagnosis, the symptoms, more precise documentation of the neuromuscular lesion by clinical neurophysiologic testing, and the nature of the urodynamic abnormality. LOW

IIIf: POPULATIONS AFFECTED BY BLADDER PAIN SYNDROME (INCLUDING INTERSTITIAL CYSTITIS)

- Broader entry criteria should be used to reflect the full spectrum of the BPS/IC patient population. MEDIUM
- The primary endpoint of BPS/IC trials should be patient driven and the Global Response Assessment is recommended. A wide spectrum of secondary endpoints will be useful in defining the effect of treatments. MEDIUM

IIIg: POPULATIONS AFFECTED BY PELVIC ORGAN PROLAPSE

- A validated standardised assessment of prolapse (eg POP-Q) should be used for baseline and outcome assessments. HIGH
- Complete reporting of outcomes including a validated assessment of anatomy, functional status, and complications is essential. HIGH
- Complications/adverse events (especially for mesh) must be explicitly and completely reported in any research. HIGH
- Long term outcomes (> 2 years) of intervention studies are needed. HIGH

IV. RECOMMENDATIONS FOR ETHICS IN RESEARCH

Continuity in clinical direction from design through authorship is mandatory. Investigators should be involved in the planning stage and a publications committee should be named at the beginning of the clinical trial. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals, from the International Committee of Medical Journal Editors should be followed. Authorship requires:

- Substantial contributions to conception and design or acquisition of data or analysis and interpretation of data,
  - Drafting the article or revising it critically for important intellectual content,
  - Final approval of the version to be published
- Authors should provide a description of what each contributed and editors should publish that information.
- Authors should have access to all raw data from clinical trials, not simply selected tables

Clinical trial results should be published regardless of outcome. The sponsor should have the right to review manuscripts for a limited period of time prior to publication but the manuscript is the intellectual property of its authors, not the sponsor.

- All authors should be able to accept responsibility for the published work and all potential conflicts of interest should be fully disclosed

International Consultation on Incontinence Modular Questionnaire (ICIQ)

The scientific committee which met at the end of the 1st ICI in 1998 supported the idea that a universally applicable questionnaire should be developed, that could be widely applied both in clinical practice and research.

The hope was expressed that such a questionnaire would be used in different settings and studies and would allow cross-comparisons, for example, between a drug and an operation used for the same condition, in the same way that the IPSS (International Prostate Symptoms Score) has been used.

An ICIQ Advisory Board was formed to steer the development of the ICIQ, and met for the first time in 1999. The project's early progress was discussed with the Board and a decision made to extend the concept further and to develop the ICIQ Modular Questionnaire to include assessment of urinary, bowel and vaginal symptoms. The first module to be developed was the ICIQ Short Form Questionnaire for urinary incontinence: the ICIQ-UI Short Form. The ICIQ-UI Short Form has now been fully validated and published [2].

Given the intention to produce an internationally applicable questionnaire, requests were made for translations of the ICIQ-UI Short Form at an early stage, for which the Advisory Board developed a protocol for the production of translations of its modules. The ICIQ-UI Short Form has been translated into 30 languages to date. Two further, newly developed and fully validated, modules have been finalised since the third consultation and are now being incorporated into clinical practice and research, and translated accordingly for international use. The ICIQ-VS[7] provides evaluation of vaginal symptoms and the ICIQ-B [3] can be used to assess bowel symptoms including incontinence. Both questionnaires also provide assessment of the impact of these symptoms on quality of life (**Table 1**).

Where high quality questionnaires already existed within the published literature, permission was sought to include these within the ICIQ in order to recommend them for use. Eleven high quality modules have been adopted into the ICIQ which are direct (unchanged) derivations of published questionnaires (Table 1).

www.ICIQ.net provides details of the validation status of the modules under development for urinary symptoms, bowel symptoms and vaginal symptoms and provides information regarding the content of existing modules. Information regarding production of translations and the ICIQ development protocol is also available for those interested in potential collaborations to continue development of the project.

ICIQ-UI on Urinary Incontinence Questionnaire (short form)

Initial number **CONFIDENTIAL** DAY MONTH YEAR
Today's date

Many people leak urine some of the time. We are trying to find out how many people leak urine, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1 Please write in your date of birth: DAY MONTH YEAR

2 Are you *(tick one)*: Female ☐ Male ☐

3 How often do you leak urine? *(Tick one box)*

never ☐	0
about once a week or less often ☐	1
two or three times a week ☐	2
about once a day ☐	3
several times a day ☐	4
all the time ☐	5

4 We would like to know how much urine you think leaks.
How much urine do you usually leak (whether you wear protection or not)?
(Tick one box)

none ☐	0
a small amount ☐	2
a moderate amount ☐	4
a large amount ☐	6

5 Overall, how much does leaking urine interfere with your everyday life?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

ICIQ score: sum scores 3+4+5 ☐☐

6 When does urine leak? *(Please tick all that apply to you)*

never – urine does not leak ☐
leaks before you can get to the toilet ☐
leaks when you cough or sneeze ☐
leaks when you are asleep ☐
leaks when you are physically active/exercising ☐
leaks when you have finished urinating and are dressed ☐
leaks for no obvious reason ☐
leaks all the time ☐

Thank you very much for answering these questions.

Table 1. Fully validated ICIQ modules and derivation

MODULES AVAILABLE FOR USE	
ICIQ – MLUTS (IC*Smale* Short Form [4])	Urinary symptoms (male)
ICIQ – FLUTS (BFLUTS Short Form [5])	Urinary symptoms (male)
ICIQ-VS [2]	Vaginal symptoms
ICIQ-B [3]	Bowel symptoms
ICIQ - UI Short Form [1]	Urinary incontinence short form
ICIQ – N (IC*Smale* [6]/ BFLUTS [7])	Nocturia
ICIQ – OAB (ICSmale [6]/ BFLUTS [7])	Overactive bladder
ICIQ – MLUTS Long Form (IC*Smale* [6])	Urinary symptoms long form (male)
ICIQ – FLUTS Long Form (BFLUTS [7])	Urinary symptoms long form (female)
ICIQ – LUTSqol (KHQ [8])	Urinary symptoms quality of life
ICIQ – Nqol (N-QOL [9])	Nocturia quality of life
ICIQ – OABqol (OABq [10])	Overactive bladder quality of life
ICIQ – MLUTSsex (IC*Smale* [6])	Sexual matters related to urinary symptoms (male)
ICIQ – FLU7])	(female)

REFERENCES

1. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, et al. ICIQ: a brief and robust measure for evaluating symptoms and impact of urinary incontinence. Neurourology and urodynamics 2004. 23: 322-330.
2. Price N, Jackson SR, Avery K, Brookes ST, Abrams P. Development and psychometric evaluation of the ICIQ vaginal symptoms questionnaire: the ICIQ-VS. BJOG 2006. 113: 700- 712.
3. Cotterill N, Norton C, Avery K, Abrams P, Donovan J. A patient-centrered approach to developing a comprehensive symptom and quality of life assessment of anal incontinence. Diseases of the colon and rectum 2008. 51: 82-87.
4. Donovan J, Peters TJ, Abrams P, Brookes ST, De La Rosette JJMCH, et al. Scoring the short form ICSmaleSF questionnaire. Journal of Urology 2000. 164: 1948-1955.
5. Brookes ST, Donovan J, Wright M, Jackson S, Abrams P. A scored form of the Bristol Female Lower Urinary Tract Symptoms questionnaire: data from a randomized controlled trial of surgery for women with stress incontinence. American Journal of Obstetrics and Gynaecology 2004. 191: 73-82.
6. Donovan J, Abrams P, Peters TJ, Kay H, Reynard J, et al. The ICS-'BPH' study: the psychometric validity and reliability of the ICSmale questionnaire. BJU International 1996. 77: 554-562.
7. Jackson S, Donovan J, Brookes ST, Eckford S, Swithinbank L, et al. The bristol female lower urinary tract symptoms questionnaire: development and psychometric testing. BJU International 1996. 77: 805-812.
8. Kelleher CJ, Cardozo L, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. British Journal of Obstetrics and Gynaecology 1997. 104: 1374-1379.
9. Abraham L, Hareendran A, Mills I, Martin M, Abrams P, et al. Development and validation of a quality-of-life measure for men with nocturia. Urology 2004. 63: 481-486.
10. Coyne KS, Revicki D, Hunt TL, Corey R, Stewart WF, et al. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire the OAB-q. Quality of life research 2002. 11: 563-574.

Annex 1 : Bladder Charts and Diaries

The ICS defines three types of Bladder Charts and Diaries which can be used to collect data:

Micturition Time Chart

• times of voiding and

• incontinence episodes

Frequency Volume Chart

• times of voiding with voided volumes measured,

• incontinence episodes and number of changes of incontinence pads or clothing.

Bladder Diaries

• the information above, but also

• assessments of urgency,

• degree of leakage (slight, moderate or large) and descriptions of factors leading to symptoms such as stress leakage, eg. running to catch a bus

It is important to assess the individual's fluid intake, remembering that fluid intake includes fluids drunk plus the water content of foods eaten. It is often necessary to explain to a patient with LUTS that it may be important to change the timing of a meal and the type of food eaten, particularly in the evenings, in order to avoid troublesome nocturia.

The micturition time and frequency volumes charts can be collected on a single sheet of paper (Fig. 1). In each chart/diary, the time the individual got out of bed in the morning and the time they went to bed at night should be clearly indicated.

Each chart/diary must be accompanied by clear instructions for the individual who will complete the chart/diary: the language used must be simple as in the suggestions given for patient instructions. There are a variety of designs of charts and diaries and examples of a detailed bladder diary are given. The number of days will vary from a single day up to one week.

INSTRUCTIONS FOR COMPLETING THE MICTURITION TIME CHART

This chart helps you and us to understand why you get trouble with your bladder. The diary is a very important part of the tests we do, so that we can try to improve your symptoms. On the chart you need to record:

1. When you get out of bed in the morning, show this on the diary by writing 'GOT OUT OF BED'.
2. The time, eg. 7.30am, when you pass your urine. Do this every time you pass urine throughout the day and also at night if you have to get up to pass urine.
3. If you leak urine, show this by writing a 'W' (wet) on the diary at the time you leaked
4. When you go to bed at the end of the day show it on the diary - write 'WENT TO BED'.

INSTRUCTIONS FOR USING THE FREQUENCY VOLUME CHART

This chart helps you and us to understand why you get trouble with your bladder. The diary is a very important part of the tests we do, so that we can try to improve your symptoms. On the chart you need to record:

1. When you get out of bed in the morning, show this on the chart by writing 'Got out of bed'.
2. The time, eg. 7.30am when you pass your urine. Do this every time you pass urine throughout the day and also at night if you have to get up to pass urine.
3. Each time you pass urine, collect the urine in a measuring jug and record the amount (in mls or fluid ozs) next to the time you passed the urine, eg. 1.30pm - 320 mls.
4. If you leak urine, show this by writing 'W' (wet) on the diary at the time.
5. If you have a leak, please add 'P' if you have to change a pad and 'C' if you have to change your underclothes or even outer clothes. So, if you leak and need to change a pad, please write 'WP' at the time you leaked.
6. At the end of each day please write in the column on the right the number of pads you have used, or the number of times you have changed clothes.

When you go to bed at the end of the day show it on the diary - write 'Went to Bed'

INSTRUCTIONS FOR USING THE BLADDER DIARY

This diary helps you and us to understand why you get trouble with your bladder. The diary is a very important part of the tests we do, so that we can try to improve your symptoms. On the chart you need to record:

1. When you get out of bed in the morning, show this on the diary by writing 'GOT OUT OF BED'.
2. During the day please enter at the correct time the drinks you have during the day, eg. 8.00am - two cups of coffee (total 400 ml).
3. The time you pass your urine, eg. 7.30am. Do this every time you pass urine throughout the day and night.
4. Each time you pass urine, collect the urine in a measuring jug and record the amount (in mls or fluid ozs) next to the time you passed the urine, eg. 1.30pm/320ml.
5. Each time you pass your urine, please write down how urgent was the need to pass urine:

'O' means it was not urgent.
+ means I had to go within 10 minutes.
++ means I had to stop what I was doing and go to the toilet.

6. If you leak urine, show this by writing an 'W' on the diary at the time you leaked.
7. If you have a leak, please add 'P' if you have to change a pad and 'C' if you have to change your underclothes or even outer clothes. So if you leak and need to change a pad, please write 'WP' at the time you leaked.
8. If you have a leakage please write in the column called 'Comments' whether you leaked a small amount or a large amount and what you were doing when you leaked, eg. 'leaked small amount when I sneezed three times'.
9. Each time you change a pad or change clothes, please write in the 'Comments' column.
10. When you go to bed at the end of the day show it on the diary - write 'Went to Bed'.

Frequency - Volume chart - Standard Version - 7 days

Name: Pierre Smith

Date	7:00 am	Mid-day	Midnight	6:00am	Pads used
16th APRIL	UP 150 200 50 250 275 200 150 BED 2.30 5.30 7.30 7.30 9.30 WC 11.00 3.00 6.00 9.30 11.45 12 2.70 2.50				1
17th	UP 260 210 230 150 220 250 50 BED 275 200 7.30 10.00 1.00 3.30 7.30 9.30 11 11 1.30 4.00				0
18th	UP 300 150 200 275 100 150 175 125 BED 400 7.00 9.00 11.15 2.15 4.15 6.30 8.00 10.30 11 4.30				0
19th	UP 250 300 310 75 200 50 250 BED 260 220 200 7.30 10.30 2.15 3.00 W 5.50 9.00 10.15 10.30 12.00 2.30 5.00				0
20th	UP 150 250 275 175 200 250 100 100 BED 350 7.30 10.30 2.00 4.30 7.15 9.45 11.00 0.45 1 5.00				0
21st	UP 200 100 175 75 200 220 300 BED 350 300 8 9.00 WC 11.00 11.45 2.30 5.30 7.30 10 200 3.30 6.00				1
22nd	UP 150 220 150 290 300 110 150 BED 350 7.30 9.30 11.00 2.15 5.00 7.00 WC 9.30 11 (200) 4.30				1

No. of drinks per day: 7

BLADDER DIARY Detailed version - one day

Name: Maria Schmidt Date: 18th April 1998

	Urine passed Time/Amount		Urgency?	Leakage?	Comments?	Drinks - time, type and amount
	6:00 am					
GOT UP	7.15	200	0	—		8.00–2 cups coffee 400mls.
	7.30	100	+	—		
	11.30	275	++	W	Wet pants	11.00 can coke
	12:00 noon					
	12.30	150	+	—		12.30 1 glass water – 250mls
	3.00	220	0	—		3.30
	3.45	—	—	W	sneezed 3 times	cup tea – 200ml
	5.30	175	0	—		
	6:00 pm					6.30
	7.45	200	—	—		glass water – 250mls.
	9.30	175	—	—		8.00 glass wine – 100 mls
BED	10.30	100	—	—		10.00 mug cocoa – 250 ml
	12:00 midnight					
	3.30	250	—	—		

Detailed Contents

Committee 1
Epidemiology of Urinary Incontinence (UI) and other Lower Urinary Tract Symptoms (LUTS), Pelvic Organ Prolapse (POP) and Anal Incontinence (AI)

A. INTRODUCTION 17
B. BASIC EPIDEMIOLOGICAL CONSIDERATIONS 17
C. EPIDEMIOLOGY OF ENURESIS AND UI IN CHILDREN 18
I. GENERAL COMMENTS AND DEFINITIONS 18
II. PREVALENCE OF NOCTURNAL ENURESIS (NE) 19
1. PREVALENCE OF ALL NIGHT WETTING (MNE+ NMNE) ACCORDING TO AGE 19
2. PREVALENCE OF MONOSYMPTOMATIC ENURESIS (MNE) 21
3. PREVALENCE OF NE VERSUS GENDER 21
4. PREVALENCE OF NE VERSUS ETHNICITY 21
5. PREVALENCE OF NE VERSUS FREQUENCY OF WET NIGHTS AND AGE 21
III. POTENTIAL RISK FACTORS FOR NE 21
1. DAYTIME UI AND LUT DYSFUNCTION 21
2. FAMILY HISTORY 21
3. PSYCHOPATHOLOGY 22
4. DEVELOPMENTAL DELAY AND ADHD 23
5. SLEEP AND AROUSAL 23
6. SOCIO-CULTURAL FACTORS 23
7. OTHER RISK FACTORS 23
IV. PREVALENCE OF FUNCTIONAL INCONTINENCE IN CHILDREN 23
1. PREVALENCE OF OVERACTIVE BLADDER (OAB) 24
2. COMORBIDITY 24
a) Prevalence of NE 24
b) Prevalence of Bowel problems 24
V. POTENTIAL RISK FACTORS FOR DAY WETTING 25
1. FAMILY HISTORY 25
2. PSYCHOPATHOLOGY 25
3. MINOR NEUROLOGICAL DYSFUNCTION AND DEVELOPMENTAL DELAY 26
4. OTHER RISK FACTORS FOR DAY UI 26
VI. SUMMARY POINTS 26
D. EPIDEMIOLOGY OF UI IN WOMEN 27
I. GENERAL COMMENTS AND DEFINITIONS 27
II. PREVALENCE 28
III. INCIDENCE AND REMISSION 28
IV. RISK FACTORS 32
1. AGE 32
2. OBESITY AND ADIPOSITY 33
3. PARITY, PREGNANCY AND MODE OF DELIVERY 34
4. ETHNICITY AND RACE 37
5. MENOPAUSAL REPLACEMENT THERAPY 37
6. HYSTERECTOMY 37
7. DIET 39
8. SOCIOECONOMIC STATUS 39
9. SMOKING 39
10. PHYSICAL ACTIVITY 39
11. COMORBIDITIES: DIABETES, UTI, COGNITIVE IMPAIRMENT, ISCHAEMIC HEART DISEASE, PHYSICAL IMPAIRMENT AND DEPRESSION 40
V. SUMMARY POINTS 41
VI. FUTURE DIRECTIONS 42
E. EPIDEMIOLOGY OF UI IN MEN 43
I. GENERAL COMMENTS 43
II. PREVALENCE 43
1. TYPES OF INCONTINENCE 43
2. SEVERITY OF INCONTINENCE 45
3. RACE/ETHNICITY 45
4. INCIDENCE AND REMISSION 45
III. POTENTIAL RISK FACTORS FOR UI 45
1. AGE 45
2. LOWER URINARY TRACT SYMPTOMS (LUTS) AND INFECTIONS 46
3. FUNCTIONAL AND COGNITIVE IMPAIRMENT, PHYSICAL ACTIVITY 46
4. NEUROLOGICAL DISORDERS 47
5. DIABETES 47
IV. FACTORS OF UNCLEAR ASSOCIATION WITH UI IN MEN 47
V. SUMMARY POINTS 47
F. EPIDEMIOLOGY OF OVERACTIVE BLADDER AND NOCTURIA 48
I. OVERACTIVE BLADDER 48
1. GENERAL COMMENTS AND DEFINITIONS 48
2. PREVALENCE OF OVERACTIVE BLADDER 48
3. INCIDENCE OF OVERACTIVE BLADDER 49
4. RISK FACTORS FOR OVERACTIVE BLADDER 50
a) Age 50
b) Gender 50
c) Obesity 50
d) Life style 50
e) Race/ethnicity and socioeconomic status 51
f) Reproductive factors and pelvic surgery 51
g) Specific conditions 51
II. NOCTURIA 52
1. PREVALENCE OF NOCTURIA 52
2. INCIDENCE OF NOCTURIA 52
3. RISK FACTORS FOR NOCTURIA 53
a) Age 53
b) Gender 54
c) Obesity 54
d) Life-style 54
e) Race/Ethnicity and socioeconomic status 54
f) Reproductive factors and pelvic surgery 54
g) Specific conditions 55
4. SUMMARY POINTS 56
5. FUTURE NEEDS 57
G. EPIDEMIOLOGY OF POP 57
I. GENERAL COMMENTS AND DEFINITIONS 57
II. PREVALENCE OF POP 57
III. INCIDENCE 59
IV. POTENTIAL RISK FACTORS 59
1. BOWEL DYSFUNCTION AND PELVIC ORGAN PROLAPSE 59
2. PELVIC SURGERY AND POP 60
3. OBSTETRIC FACTORS AND POP 61
4. MISCELLANEOUS RISK FACTORS AND POP 62
V. SUMMARY POINTS 63
H. THE GENETIC EPIDEMIOLOGY OF UI AND POP IN ADULT WOMEN 63
I. FAMILY STUDIES 63
II. TWIN STUDIES 65
III. SEGREGATION ANALYSES 66
IV. LINKAGE STUDIES 66
V. GENE ASSOCIATED STUDIES 66
VI. SUMMARY POINTS 70
I. EPIDEMIOLOGY OF ANAL INCONTINENCE 70
I. GENERAL COMMENTS AND DEFINITIONS 70

1. ASCERTAINMENT OF ANAL INCONTINENCE 70
2. DATA SOURCES AND LEVEL OF EVIDENCE 71
II. PREVALENCE 71
1. ADULTS 72
2. CHILDREN 72
III. INCIDENCE 72
IV. RISK FACTORS 73
1. AGE 73
2. GENDER 73
3. OBESITY 73
4. CHILDBIRTH AND MODE OF DELIVERY 73
5. NURSING HOME RESIDENCE 74
6. DIARRHOEA 74
7. SURGERY 74
8. SPECIFIC NEUROLOGICAL AND OTHER DISEASES 76
9. CONSTIPATION 76
10. COHORTS INITIATED BEFORE CLINICAL AI ASSESSED FOR SUBSEQUENT DEVELOPOMENT OF AI 76
V. PREVENTION 76
VI. SUMMARY POINTS 77
VII. FUTURE NEEDS 77
J. WHY DO PREVALENCE ESTIMATES DIFFER? 77
I. GENERAL PROBLEMS IN SURVEY RESEARCH 77
II. DIFFERENT DEFINITIONS AND MEASUREMENT 77
III. SUMMARY POINTS 78
K. HELP SEEKING BEHAVIOUR 79
I. URINARY INCONTINENCE 79
II. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE 79
III. SUMMARY POINTS 79
L. EPIDEMIOLOGY AND CLINICAL WORK: FROM RESPONDENT TO PATIENT 79
I. WORLDWIDE ESTIMATES OF CURRENT AND FUTURE INDIVIDUALS (≥20 YEARS) WITH LOWER URINARY TRACT SYMPTOMS INCLUDING URINARY INCONTINENCE AND OVERACTIVE BLADDER 80
II. SUMMARY POINTS 83
M. RECOMMENDATIONS FOR FURTHER RESEARCH 83
I. URINARY INCONTINENCE 83
II. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE 84
REFERENCES 85

Committee 2
Cell Biology

I. INTRODUCTION 111
II. INTERSTITIAL CELLS: THEIR ROLES IN MUSCLE AND SUBUROTHELIAL LAYERS 111
1. IMMUNOHISTOCHEMICAL MARKERS USED TO CHARACTERIZE BLADDER INTERSTITIAL CELLS 112
2. STRUCTURAL IMMUNOHISTOCHEMICAL MARKERS USED TO IDENTIFY INTERSTITIAL CELLS 113
a) Suburothelial interstitial cells 113
b) Surface muscle interstitial cells 114
c) Intramuscular interstitial cells 114
d) Muscle coat interstitial cells 115
3. FUNCTIONAL CHARACTERISTICS OF INTERSTITIAL CELLS 115
a) Suburothelial interstitial cells 115
b) Interstitial cells in the detrusor layer 115
III. THE UROTHELIUM – STRUCTURE AND FUNCTION 117
1. RELEASE OF TRANSMITTERS 118
a) Stimuli for release 118
b) Transmitter chemicals, ATP 118
c) Transmitter chemicals, acetylcholine 119
2. UROTHELIAL ION TRANSPORT AND PERMEABILITY 119
a) Urothelial ion transport 119
b) Urinary tract infections 120
3. FUNCTIONAL INTERACTIONS WITH THE DETRUSOR LAYER 120
a) Urothelium-derived relaxing factors 120
b) Contractile activity of the mucosa 120
c) Interaction between mucosa and detrusor 121
IV. DETRUSOR SMOOTH MUSCLE CONTRACTILE ACTIVATION 122
1. SMOOTH MUSCLE CELLS 122
2. CONTRACTILE PROTEIN ISOFORMS AND THE CONTRACTILE MACHINERY 123
a) Myosin 123
b) Actin isoforms 124
c) Actin-associated proteins in the thin filaments 124
3. CONTRACTILE ACTIVATION OF SMOOTH MUSCLE 124
a) Receptor-mediated activation of detrusor smooth muscle 124
b) Molecular mechanisms for activation of the contractile machinery 125
c) Role of the Ca2+-sensitization pathway in the regulation of the myosin-mediated pathway for smooth muscle contraction 125
d) The role of thin filament-mediated regulation of contraction 126
e) Smooth muscle relaxation 126
f) Alterations to contractile and regulatory proteins in lower urinary tract dysfunction 127
4. SPONTANEOUS ACTIVITY 127
a) The origin of spontaneous activity 127
b) The myogenic hypothesis 128
c) The neurogenic hypothesis 129
5. ELECTRICAL ACTIVITY AND ION CHANNELS 129
V. THE OUTFLOW TRACT 129
1. TRIGONE 129
a) Developmental origins of the trigone and insertion of the vesicoureteral junctions 130
b) Superficial and deep trigone 131
2. THE URETHRA AND SPHINCTER MECHANISMS 131
a) Bladder-urethral coordination 131
b) The internal sphincter 132
c) External urethral sphincter (EUS) 134
d) Consequences of EUS dysfunction and treatments 134
3. PROSTATE 134
a) Prostatic lobes and their cellular components 134
b) Prostatic innervation and its role in seminal fluid secretion and emission 135
c) Benign prostatic hyperplasia (BPH), prostatitis and therapeutic approaches 136
VI. NOVEL MOLECULAR TARGETS FOR OAB AND DETRUSOR OVERACTIVITY 137
1. INTRODUCTION 138
2. SEVEN TRANSMEMBRANE SPANNING RECEPTORS (7-TM, METABOTROPIC RECEPTORS) 138
a) Acetylcholine (ACh)-muscarinic receptors 138
b) Adrenergic β-receptors 139
c) Cannabinoids, GPR18, GPR55, GPR119 139
d) GABAB 140

e) Glutamate metabotropic receptors 140
f) Prostanoid receptors 140
g) Tachykinins 141
3. LIGAND-GATED ION-CHANNELS 143
4. ION-CHANNELS 143
a) Acid-sensing (proton-gated) ion channels (ASICs) 144
b) Epithelial sodium channels (ENaC) 145
c) K+ channels 145
d) Transient receptor potential (TRP) cation channels 146
VII. BIOMARKERS FOR OAB AND DO 150
1. INTRODUCTION 150
2. URODYNAMIC FINDINGS 151
3. URINARY BIOMARKERS 152
a) Cytokines and chemokines 152
b) Prostaglandins in OAB 152
c) Urine ATP and nitric oxide (NO) 152
d) Urinary nerve growth factor (NGF) in OAB 152
4. SERUM BIOMARKERS 153
a) C-reactive protein (CRP) 153
5. BLADDER WALL IMAGING BIOMARKERS 153
a) Ultrasonography 153
b) Near-infrared spectroscopy (NIRS) and DO 154
6. CONCLUSION 154
VIII. THE LOWER GASTROINTESTINAL TRACT (ANUS AND RECTUM) AS RELEVANT TO FAECAL INCONTINENCE 155
1. INTRODUCTION 155
2. BASIC PHYSIOLOGY OF THE RECTUM AND ANUS 155
a) The internal anal sphincter (IAS) 155
3. INNERVATION OF THE RECTUM AND ANUS 156
a) Parasympathetic innervation 156
b) Sympathetic innervation 156
c) Non-adrenergic, non-cholinergic (NANC) innervation 157
d) Sensory innervation 157
4. SMOOTH MUSCLE AND INTERSTITIAL CELLS 157
a) Smooth muscle 157
b) Interstitial cells 158
5. FUTURE DIRECTIONS FOR RESEARCH 159
IX. RECOMMENDATIONS FOR RESEARCH CONCERNING LOWER URINARY TRACT (LUT) AND LOWER GASTROINTESTINAL TRACT RESEARCH (LGIT) 159
X. ABBREVIATIONS AND NOMENCLATURE 160
REFERENCES 162

Committee 3
Neural Control

OVERVIEW 181
I. UROTHELIUM 181
1. ANATOMY AND BARRIER FUNCTION 182
2. UROTHELIAL CELLS AND REPAIR 182
3. UROTHELIAL HETEROGENEITY 184
4. ROLES FOR UROTHELIAL CELLS IN VISCERAL SENSATION 184
a) Urothelial-Neuronal Signaling 185
b) Involvement of the Urothelium in "Sensing" Chemical and Mechanical Stimuli 185
5. CLINICAL SIGNIFICANCE OF THE SENSORY WEB 187
II. AFFERENT NEURONES 188
1. OVERVIEW: PROPERTIES OF AFFERENT NEURONES 188
2. PATHWAYS TO THE SPINAL CORD 188
3. FUNCTIONAL PROPERTIES OF BLADDER AFFERENTS 189
4. MODULATING AFFERENT SENSITIVITY 191
a) Nitric oxide 191
b) Purinergic Signalling 192
c) Cholinergic Mechanisms 192
d) Botulinum Toxin 193
e) Transient Receptor Potential (TRP) Cation Channels 193
f) Cannabinoids 194
g) Adrenoreceptors 194
5. CROSS TALK BETWEEN THE BLADDER AND BOWEL 195
III. NEURAL CONTROL OF FEMALE PELVIC FLOOR MUSCLES AND RHABDOSPHINCTERS 195
1. STRUCTURAL ELEMENTS OF THE PELVIC FLOOR 195
2. PERIPHERAL INNERVATION OF THE FEMALE LEVATOR ANI (LA) MUSCLES 196
a) LA Motor Neurons 198
b) LA Afferent Innervation 198
3. REFLEX ACTIVATION OF PELVIC FLOOR MUSCLES 198
4. PERIPHERAL INNERVATION OF URETHRAL AND ANAL RHABDOSPHINCTERS 200
a) Urethral and Anal Rhabdosphincter Motor Neurons 200
b) Afferent Innervation of the Urethral and Anal Rhabdosphincters 202
5. REFLEX ACTIVATION OF URETHRAL AND ANAL RHABDOSPHINCTERS 202
6. INHIBITION OF URETHRAL RHABDOSPHINCTER (URS) REFLEXES DURING VOIDING 204
7. SUPRASPINAL ACTIVATION OF RHABDOSPHINCTERS AND PELVIC FLOOR MUSCLES 204
8. NEUROCHEMICAL ANATOMY OF RHABDOSPHINCTER MOTOR NEURONS 206
a) Pharmacology of Urethral and Anal Rhabdosphincters 206
9. LA AND RHABDOSPHINCTER NEUROPATHY 208
IV. EFFERENT PATHWAYS TO THE BLADDER 210
1. PREGANGLIONIC NEURONS 210
2. GANGLIA 210
3. TERMINAL NERVE FIBERS 211
4. TRANSMITTERS 212
a) Glutamate 212
b) Glycine/ gamma amine butyric acid 212
c) Serotonin 212
d) Adrenergic 212
e) Substance P 213
f) Purinergic 213
5. PELVIC ORGAN INTERACTIONS AT THE EFFERENT NEURAL LEVEL 213
a) Bladder and Outlet 213
b) Bladder and Bowel 214
c) Bladder and Prostate/Uterus 214
6. EFFERENT INHIBITION 214
7. PERIPHERAL EXCITATORY MECHANISMS 215
V. PONTINE-MIDBRAIN CONTROL OF BLADDER FUNCTION 216
1. AFFERENT PATHWAYS LINKING THE BLADDER AND URETHRA TO THE PONS AND MIDBRAIN 217
2. DEFINING THE CENTRAL CIRCUITRY REGULATING BLADDER FUNCTION BY TRANSNEURONAL TRACING 218
3. BARRINGTON'S NUCLEUS: THE PONTINE MICTURITION CENTER (PMC) 218
4. BARRINGTON'S NUCLEUS, THE LOCUS COERULEUS AND CENTRAL RESPONSES TO BLADDER INFORMATION 220
a) Normal Function 220
b) Pathological Consequences 220
5. SUPRASPINAL INPUTS TO BARRINGTON'S NUCLEUS 222
6. DEFENSIVE STRATEGIES AND MICTURITION 223
7. COORDINATION OF BLADDER WITH OTHER PELVIC VISCERA BY BARRINGTON'S NUCLEUS 223
8. THE PONTINE CONTINENCE CENTRE (PCC) 224

9. NEUROTRANSMITTERS & MODULATORS WITHIN BRAINSTEM NETWORKS CONTROLLING BLADDER 224
VI. FOREBRAIN CONTROL OF BLADDER FUNCTION 225
1. BACKGROUND 225
2. ROLE AND IMPORTANCE OF CEREBRAL CONTROL OF VOIDING 225
3. CORTICAL AND SUBCORTICAL CENTRES INVOLVED IN BLADDER CONTROL. EVIDENCE FROM OBSERVATIONS OF LESIONS AND FROM FUNCTIONAL BRAIN IMAGING IN HUMANS 227
a) Frontal Lobes 227
b) Anterior Cingulate Gyrus (ACG), Supplementary Motor Cortex (SMA) and Insula 228
c) Periaqueductal Grey (PAG) 232
d) Hypothalamus 232
e) Pons 232
f) Other Regions 232
4. VOIDING 233
5. WORKING MODEL OF BRAIN / BLADDER CONTROL 233
a) The Normal Continence Mechanism 235
b) A Back-up Continence Mechanism 235
c) Limbic or Paralimbic Circuits 235
d) Voiding 235
6. CONCLUSION: CORTICAL CONTROL OF BLADDER FUNCTION 235
VII. ABNORMAL LOWER URINARY TRACT FUNCTION 236
1. ABNORMALITIES INVOLVING AFFERENT SIGNALING 236
a) Bladder Pain Syndrome / Interstitial Cystitis (BPS/IC) 236
b) Pelvic Organ Cross-talk 237
2. INVOLVING ABNORMAL URINE STORAGE 237
a) Overactive Bladder / Detrusor Overactivity 237
b) Stress Urinary Incontinence 239
3. INVOLVING ABNORMAL VOIDING 239
a) Bladder Outflow Obstruction 239
4. CO-MORBID DISORDERS 240
REFERENCES 241

Committee 4
Pathophysiology of Urinary Incontinence, Faecal Incontinence and Pelvic Organ Prolapse

PREFACE 263
A. THE OVERACTIVE BLADDER 263
I. INTRODUCTION 263
II. MECHANISMS UNDERLYING INCREASED AFFERENT ACTIVITY 265
1. THE UROTHELIUM-BASED HYPOTHESIS 265
2. MYOGENIC HYPOTHESIS 266
3. OTHER LOCAL FACTORS 267
a) Ischaemia 267
b) Inflammation 267
III. MECHANISMS INVOLVED IN ABNORMAL HANDLING OF THE AFFERENT SIGNALS IN THE BRAIN 268
1. NEUROGENIC DETRUSOR OVERACTIVITY 268
a) Suprapontine lesions 268
b) Spinal cord lesions 268
B. PREGNANCY, CHILDBIRTH AND THE PELVIC FLOOR 269
I. DAMAGE TO FUNCTIONS SUSTAINED BY THE PELVIC FLOOR 269
1. POSTPARTUM URINARY INCONTINENCE 269
2. ANAL INCONTINENCE 270
3. PELVIC ORGAN PROLAPSE 271
II. EFFECT OF PREGNANCY ON PELVIC FLOOR FUNCTION 272
1. EFFECT ON THE COLLAGEN 272
2. NATURAL HISTORY 272
3. FAMILIAL PREDISPOSITION 273
III. PATHOPHYSIOLOGICAL MECHANISM OF BIRTH INJURY TO THE PELVIC FLOOR 274
1. MUSCLE TRAUMA 274
2. NERVE INJURY 276
IV. PERINEAL TRAUMA 276
1. EPIDURAL ANALGESIA DURING LABOUR 276
2. ROLE OF EPISIOTOMY 277
V. CONCLUSION AND RECOMMENDATION 279
C. PATHOPHYSIOLOGY OF STRESS INCONTINENCE IN WOMEN: URETHRAL STRUCTURE, SUPPORT AND FUNCTION 279
I. THE FEMALE UROGENITAL DIAPHRAGM: URETHRAL SPHINCTER LOCATION 280
II. EFFECT OF CHILDBIRTH, VAGINAL PROLAPSE AND URETHRAL POSITION ON URINARY CONTINENCE 282
1. PUDENTAL NERVE 282
2. CARDINAL AND UTERO-SACRAL LIGAMENTS 282
3. THE VAGINA 282
4. LEVATOR MUSCLES 282
III. EMERGING CONCEPTS OF URETHRA WEAKNESS AND ISD 283
IV. HYPERMOBILITY VS. ISD: FROM DICHOTOMY TO CONTINUUM 283
1. DIRECT STUDIES OF URETHRAL FUNCTION 284
a) Studies of urethral position 284
b) Studies of urethral pressure and resistance 284
c) Electrophysiological studies of urethral function 284
d) Genetic factors 284
2. ROLE OF ADVANCED IMAGING IN UNDERSTANDING PATHOPHYSIOLOGY 285
a) Magnetic resonance imaging 285
b) Real time ultrasonography 285
V. CONCLUSIONS 287
D. PELVIC ORGAN PROLAPSE 287
I. PATHOPHYSIOLOGY OF PELVIC ORGAN PROLAPSE 287
1. INHERITANCE, GENETIC AND ETHNIC PREDISPOSITION 288
2. ALTERATION OF COLLAGEN, ELASTIN AND SMOOTH MUSCLE OF THE VAGINAL AND SUPPORTIVE TISSUE 291
3. NEUROLOGICAL FACTORS 293
4. PREGNANCY AND PELVIC FLOOR MUSCLE REMODELLING 294
5. CHILDBIRTH 294
6. OBSTETRIC AND MATERNAL FACTORS 296
7. AGE 297
8. HORMONES 297
9. OBESITY 297
10. CONSTIPATION 297
11. CHRONIC PELVIC FLOOR STRESS 298
12. PREVIOUS OPERATIONS 298
13. THE BONY PELVIS 298
14. ASSOCIATED PELVIC FLOOR CONDITIONS 298
a) Bladder function 298
b) Anorectal function 300
c) Sexual function 301

II. CONCLUSION AND RECOMMENDATIONS 301
E. PATHOPHYSIOLOGY OF FAECAL INCONTINENCE 302
I. STRUCTURE AND FUNCTION OF THE ANO-RECTUM 302
1. MUSCLES 302
a) Internal anal sphincter (IAS) 302
b) External anal sphincter (EAS) 302
c) Conjoined longitudinal muscle 303
d) Puborectalis muscle (PR) 303
e) Levator ani 303
2. NERVE STRUCTURE AND SENSATION 303
3. CEREBRAL CORTEX 304
4. REFLEXES 304
a) Rectoanal inhibitory reflex (RAIR) 304
b) Cough reflex 304
c) Rectoanal contractile reflex (sensori-motor response) 304
5. RECTUM 304
6. ANAL ENDOVASCULAR CUSHIONS 304
7. STOOL CONSISTENCY 305
8. PHYSICAL MOBILITY 305
II. CONTINENCE MECHANISM 305
III. DEVELOPMENT OF INCONTINENCE 305
1. PASSIVE INCONTINENCE 305
2. URGENCY INCONTINENCE 305
IV. RISK FACTORS FOR FECAL INCONTINENCE 306
1. AGING 306
2. GENDER 306
3. DIABETES 306
4. GASTROINTESTINAL DISORDERS 307
a) Diarrhoea 307
b) Rectal urgency 307
c) Constipation/impaction 307
d) Irritable bowel syndrome 307
5. NEUROLOGICAL/PSYCHIATRIC CONDITIONS 307
a) Dementia 307
b) Depression 308
c) Spinal Cord Injury 308
d) Stroke 308
6. NUTRITION 308
a) Obesity 308
b) Vitamin D 308
7. OBSTETRICAL INJURY 308
8. PHYSICAL MOBILITY 309
9. RADIATION 309
10. RECTAL PROLAPSE 309
a) Mucosal, internal and full thickness rectal prolapse 309
11. SURGERY 309
a) Anorectal surgery 309
b) Rectal resection 310
c) Hysterectomy 310
d) Cholecystectomy 310
12. SMOKING 310
13. URINARY INCONTINENCE 310
V. SUMMARY AND RESEARCH RECOMMENDATIONS 310
F. CHILDBIRTH AND FAECAL INCONTINENCE 310
I. NEUROGENIC TRAUMA 311
II. MECHANICAL TRAUMA 311
1. UNRECOGNISED ("OCCULT") ANAL SPHINCTER TRAUMA 311
2. RECOGNISED OBSTETRIC ANAL SPHINCTER INJURIES 316
III. INSTRUMENTAL VAGINAL DELIVERY 318
IV. EPISIOTOMY 319
V. DELIVERY TECHNIQUES 319
VI. TRAINING 320
VII. IRRITABLE BOWEL SYNDROME (IBS) 320
VIII. CONCLUSIONS AND RECOMMENDATIONS 320
G. PATHOPHYSIOLOGY OF INCONTINENCE IN MEN 320
I. CONTINENCE MECHANISM IN THE MALE 321
II. INCONTINENCE ASSOCIATED WITH BPH AND ITS TREATMENT 323
III. CONTINENCE ASSOCIATED WITH RADICAL PROSTATECTOMY 325
1. INCIDENCE 325
2. RECOVERY OF CONTINENCE AFTER RADICAL PROSTATECTOMY 326
3. RISK FACTORS 327
4. AETIOLOGY AND PATHOPHYSIOLOGY OF POST RADICAL PROSTATECTOMY INCONTINENCE: SPHINCTER VS.BLADDER DYSFUNCTION 327
IV. INCONTINENCE RELATED TO RADIATION THERAPY FOR PROSTATE CANCER 329
V. CONCLUSIONS 330
H. CAUSE OF TRANSIENT INCONTINENCE IN OLDER ADULTS 330
I. URINARY INCONTINENCE 330
1. QUALITY OF DATA 330
2. RESULTS OF LITERATURE REVIEW 330
a) Delirium 331
b) Urinary infection 331
c) Atrophic vaginitis 331
d) Medications 331
e) Diuresis 332
f) Restricted mobility 332
g) Nocturia 332
h) Faecal impaction 332
II. FAECAL INCONTINENCE 332
1. BACKGROUND 332
2. CAUSES 332
a) Altered mental status 333
b) Impaired mobility 333
c) Stool consistency 333
d) Diarrhoea 333
e) Constipation 333
III. SUMMARY 334
IV. RECOMMENDATIONS 334
V. RESEARCH PRIORITIES 334
REFERENCES 335

Committee 5
5A. Initial Assessment of Urinary Incontinence in Adult Male and Female Patients (5A)
5B. Patient-Reported Outcome Assessment (5B)

I. INTRODUCTION 363
II. GENERAL INFORMATION 363
1. TERMINOLOGY 363
a) Types of urinary incontinence 364
b) Bladder storage symptoms 364
c) Bladder sensation 364
d) Voiding and postmicturition symptoms 364
2. ASSESSMENT OF SUB-POPULATIONS REVIEWED BY OTHER COMMITTEES 365
3. EVIDENCE BASED RECOMMENDATIONS 365
III. INTIAL ASSESEMENT 365

1. PURPOSE OF INTIAL ASSESSMENT (EXPERT OPINION OF THE COMMITTEE) 365
2. INTIAL ASSESSMENT – GENERAL RECOMMEDATIONS 366
3. INTIAL ASSESSEMENT – GENERAL RESEARCH RECOMMENDATIONS 367
IV. GENERAL POPULATIONS 367
1. INITIAL ASSESSMENT OF URINARY INCONTINENCE 367
a) History 367
b) Diaries 368
c) Urinalysis 369
d) Post Voiding Residual in the Female and Male Patient 370
V. SPECIFIC POPULATIONS: EVALUATION OF THE FEMALE PATIENT 372
1. ESTABLISHING THE TYPE OF URINARY INCONTINENCE IN WOMEN 372
a) The reliability of simple history questions for women 372
b) Accuracy of the general physical examination in women 373
2. PELVIC ASSESSMENT: PELVIC FLOOR STRENGTH AND PELVIC ORGAN PROLAPSE 374
a) Assessment of pelvic floor muscle strength 374
b) Assessment of Pelvic Prolapse 375
3. GENERAL RECOMMENDATIONS IN THE FEMALE PATIENT 377
4. RESEARCH RECOMMENDATIONS IN THE FEMALE PATIENT 378
VI. SPECIFIC POUPULATION: EVALUATION OF THE MALE PATIENT 378
1. CHARACTERISTICS OF MALE INCONTINENCE 378
a) Prevalance of OAB (male) 378
b) Prevalance of Incontinence after surgery (male – the prostate) 379
2. GENERAL MEDICAL HISTORY (MALE) 380
3. SYMPTOM ASSESSMENT (MALE) 380
4. PHYSICAL EXAMINATION (MALE) 381
5. URINALYSIS AND URINE CYTOLOGY (MALE) 382
6. MEASUREMENT OF THE SERUM CREATININE (MALE) 382
7. MEASUREMENT OF THE SERUM PROSTATESPECIFIC ANTIGEN (PSA) (MALE) 382
8. RECOMMENDATIONS 383
9. FUTURE RESEARCH 383
REFERENCES 383

5B. PATIENT-REPORTED OUTCOME ASSESSMENT 389

I. INTRODUCTION 389
1. SELECTING PRO MEASURES FOR CLINICAL TRIALS AND CLINICAL PRACTICE 389
2. SELECTING PRO MEASURES FOR RESEARCH STUDIES 390
a) Study Design 390
b) Study Population 390
c) Intervention 390
3. TYPES OF PRO MEASURES 391
4. LITERATURE SEARCH STRATEGY 391
II.THE MEASUREMENT OF PATIENT-REPORTED OUTCOMES (PROS) OF INCONTINENCE, OTHER LOWER URINARY TRACT SYMPTOMS, AND BOWEL PROBLEMS 391
1. PRO QUESTIONNAIRE DEVELOPMENT AND VALIDATION 391
a) Determining Questionnaire Intent and Purpose 392
b) Developing the Items 393
c) Determining the Mode of Administration of a Questionnaire 393
d) Questionnaires' Psychometric Properties 393
e) Linguistic and Cultural Validation 394
f) Regulatory Oversight 395
g) Questionnaire Development - A Conclusion 395
III. RECOMMENDED PRO QUESTIONNAIRES 395
IV. INTERNATIONAL CONSULTATION ON INCONTINENCE MODULAR QUESTIONNAIRE (ICIQ):WHAT IS THE ICIQ? 396
1. AIMS AND OBJECTIVES 396
2. ICIQ MODULES 398
a) Core Modules 398
b) Specific Patient Group Modules 398
c) Optional Modules 398
d) Post-treatment Module 398
3. GUIDANCE FOR USE OF THE ICIQ 398
4. ICIQ QUESTIONNAIRE IMPLEMENTATION 400
5. CONCLUSION 400
V. PATIENT-REPORTED OUTCOME (PRO) QUESTIONNAIRES TO ASSESS THE IMPACT OF URINARY INCONTINENCE, OAB AND LOWER URINARY TRACT SYMPTOMS 400
1. HEALTH-RELATED QUALITY OF LIFE MEASURES 401
2. PATIENT SATISFACTION AND GOAL ATTAINMENT SCALING 401
3. SCREENING TOOLS 402
4. ASSESSING SYMPTOM BOTHER AND OVERALL BOTHER 402
5. ASSESSING THE IMPACT OF URGENCY 402
VI. QUESTIONNAIRES TO ASSESS SYMPTOMS AND HEALTH-RELATED QUALITY OF LIFE IMPACT OF PELVIC ORGAN PROLAPSE 402
VII. QUESTIONNAIRES TO ASSESS SYMPTOMS AND HRQL IMPACT OF FAECAL INCONTINENCE 403
VIII. QUESTIONNAIRES TO ASSESS SEXUAL FUNCTION/SEXUAL HEALTH AND URINARY SYMPTOMS 403
IX. QUESTIONNAIRES FOR SPECIFIC PATIENT GROUPS 404
1. OLDER PEOPLE 404
a) The Urge Impact Scale (URIS) [Grade B] 405
b) Caregivers 405
2. CHILDREN 405
3. SPINAL CORD INJURED/NEUROLOGICAL IMPAIRMENT 405
4. PROSTATE/BLADDER CANCER 405
5. LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATE DISEASE 406
6. SUMMARY 406
X. RECOMMENDATIONS FOR RESEARCH 406
REFERENCES 423

Committee 6
Urodynamic Testing

I. INTRODUCTION 431
A. URODYNAMICS 431
I. WHAT IS URODYNAMICS? 431
II. WHAT SHOULD BE THE ROLE OF URODYNAMIC STUDIES IN CLINICAL PRACTICE? 432
III. THE TESTS OF CONVENTIONAL URODYNAMICS 433
1. UROFLOWMETRY 433
2. FILLING CYTOMETRY 433
3. PRESSURE-FLOW STUDIES (VOIDING CYSTOMETRY) 433
4. URETHRAL PRESSURE PROFILOMETRY 434

5. ABDOMINAL LEAK POINT PRESSURE 434
IV. TECHNOLOGICAL INNOVATIONS IN URODYNAMICS 434
1. AIR-CHANGED CATHETERS FOR PRESSURE MEASUREMENT 434
2. OBJECTIVE ASSESSMENT OF BLADDER SENSATION 434
3. NON-INVASIVE PRESSURE (& FLOW) MEASUREMENTS 435
4. URETHRAL RETRO-RESISTANCE PRESSURE 436
5. URETHRAL PRESSURE REFLECTOMETRY 437
6. ULTRASOUND IMAGING 437
B. URODYNAMICS: NORMAL VALUES, RELIABILITY AND DIAGNOSTIC PERFORMANCE 437
I. REPRODUCIBILITY OF FILLING CYSTOMETRY AND AMBULATORY URODYNAMICS 437
1. INTER-OBSERVER, TEST-RETEST AND PRACTICE VARIATION 437
2. SHORT-TERM (WITHIN-SESSION) REPRODUCIBILITY 438
3. INTERMEDIATE-TERM REPRODUCIBILITY 439
4. LONG-TERM REPRODUCIBILITY 439
5. REPRODUCIBILITY OF AMBULATORY URODYNAMICS 440
II. CYSTOMETRY: NORMAL VALUES 440
1. NORMAL VALUES: FILLING CYSTOMETRY AND AMBULATORY URODYNAMICS 440
2. COMPLIANCE 441
3. NORMAL SENSATIONS AND BLADDER CAPACITY 441
4. DETRUSOR (OVER-) ACTIVITY IN NORMAL SUBJECTS 442
5. INFLUENCE OF CATHETER ON VOIDING 442
III. REPRODUCIBILITY, RELIABILITY AND NORMAL VALUES OF URETHRAL PRESSURE MEASUREMENTS 443
1. NORMATIVE AND COMPARATIVE DATA FOR MAXIMUM URETHRAL CLOSURE PRESSURE 443
2. RELIABILITY OF URETHRAL PRESSURE VARIABLES 443
3. AGING 443
4. OTHER PARAMETERS AFFECTING THE MEASUREMENT OF URETHRAL CLOSURE PRESSURE 443
IV. LEAK POINT PRESSURE 444
1. INTRODUCTION 444
2. RELIABILITY OF LEAK POINT PRESSURE MEASUREMENTS 444
a) Diagnosis 444
b) Treatment 445
c) Within-patient variability 445
V. DIAGNOSTIC PERFORMANCE OF FILLING CYSTOMETRY AND AMBULATORY MONITORING 446
1. SENSITIVITY AND SPECIFICITY OF FILLING CYSTROMETRY IN OVERACTIVE BLADDER SYNDROME 446
a) Detrusor overactivity incontinence 446
b) Detrusor overactivity alone 447
c) Overactive bladder syndrome and detrusor overactivity 447
d) Distinguishing or defining characteristics of detrusor overactivity 450
e) Provocative manoeuvres 451
2. AMBULATORY URODYNAMICS: SENSITIVITY AND SPECIFICITY 452
3. THE ADJUNCT USE OF IMAGING AND ELECTROMYOGRAPHY 453
VI. THERAPEUTIC PERFORMANCE OF FILLING CYTOMETRY AND AMBULATORY MONITORING 453
1. PREDICTION OF TREATMENT RESPONSE 453
a) Filling cystometry 453
b) Ambulatory monitoring 453
C. CLINICAL APPLICATIONS OF URODYNAMIC STUDIES 454
I. PATIENT EVALUATION: WOMEN 454
1. INTRODUCTION 454
2. STRESS URINARY INCONTINENCE 455
a) Urethral pressures and severity of stress urinary incontinence 455
b) Aspects of urodynamic studies relevant to therapy for stress urinary incontinence 456
c) Prediction of failure of surgery 457
d) Voiding difficulties after surgery 457
e) Postoperative urgency 458
f) The role of urodynamic studies in predicting occult stress urinary incontinence in women due to be treated for pelvic organ prolapse 459
3. URGENCY URINARY CONTINENCE 459
a) Pathophysiology and severity of urgency urinary incontinence 459
b) Prediction of treatment response 460
4. RECOMMENDATIONS FOR URODYNAMIC STUDIES IN WOMEN WITH URINARY INCONTINENCE 460
II. PATIENT EVALUATION: MEN 461
1. INTRODUCTION 461
2. URODYNAMIC TESTING OF DETRUSOR OVERACTIVITY AND OVERACTIVE BLADDER IN MEN 461
3. LOWER URINARY TRACT SYMPTOMS RELATED TO MALE LOWER URINARY TRACT DYSFUNCTION: DETRUSOR OVERACTIVITY AND BLADDER OUTLET OBSTRUCTION 462
4. POST-PROSTATECTOMY INCONTINENCE 463
a) General 463
b) Transurethral resection of the prostate and Open Prostatectomy for benign disease 464
c) Radical Prostatectomy and Radiotherapy 464
d) Artificial urinary sphincter and male sling 466
5. NEUROLOGICAL LESIONS RELATED TO MALE INCONTINENCE 467
a) Nocturnal enuresis 467
b) Stroke 468
c) Parkinson's disease 468
d) Diabetes Mellitus (DM) 469
e) Recommendations for urodynamic investigation for men suffering from nocturnal enuresis, stroke, Parkinson's disease or DM 469
III. NEUROGENIC LOWER URINARY TRACT DYSFUNCTION 470
1. INTRODUCTION 470
2. WHAT IS USUALLY EVALUATED? 470
3. SPECIAL TESTS 470
4. NEUROGENIC DETRUSOR OVERACTIVITY INCONTINENCE 470
5. DETRUSOR-SPHINCTER DYSSYNERGIA 471
6. LEAKAGE ASSOCIATED WITH CHRONICRESIDUAL/ RETENTION OF URINE ('OVERFLOW INCONTINENCE') 471
7. REPRODUCIBILITY AND RELIABILITY OF TESTS 471
8. DOES URODYNAMIC TESTING HELP TO SELECT (OPTIMAL) TREATMENT? 471
IV. PATIENT EVALUATION: CHILDREN 472
1. INTRODUCTION 472
2. NEUROGENIC BLADDER DYSFUNCTION 473
a) Myelodysplasia 473
b) Occult spinal dysraphism 474
c) Sacral agenesis 475
d) Spinal cord injury 476
e) Cerebral palsy 477
f) Tumours 477
3. ANORECTAL MALFORMATION OR IMPERFORATE ANUS 477

4. ANATOMIC ABNORMALITIES 478
a) Posterior urethral valves 478
b) Bladder exstrophy and persistent Cloacal anomalies 479
c) Ectopic ureterocele 480
d) Vesicoureteral reflux 480
e) Urethral stricture 481
5. FUNCTIONAL DISORDERS OF THE LOWER URINARY TRACT 481
a) Diurnal incontinence 481
b) Enuresis (nocturnal) 482
6. TECHNICAL CONCERNS: RELIABILITY AND REPRODUCIBILITY OF TESTS 483
V. PATIENT EVALUATION: FRAIL ELDERLY 484
1. INTRODUCTION 484
2. ROUTINE EVALUATION 485
a) Urinary urgency incontinence 485
b) Stress urinary incontinence 486
3. EVIDENCE FOR REPRODUCIBILITY AND RELIABILITY OF URODYNAMIC TEST IN THE GERIATRIC OR FRAIL ELDERLY POPULATION 486
a) Filling cystometry 486
b) Post-void residual urine 486
c) Pressure-flow studies 486
4. EVIDENCE THAT PERFORMING URODYNAMIC TESTING IMPROVES CLINICAL OUTCOMES IN THE GERIATRIC POPULATION 487
5. THE PRACTICAL INDICATIONS FOR URODYNAMIC STUDIES AND WHICH TESTS ARE NEEDED 487
a) Post-void residual urine 487
b) Uroflowmetry 487
c) Pressure-flow studies 487
6. THE URODYNAMIC PARAMETERS IMPORTANT IN VARIOUS GERIATRIC CONDITIONS 487
a) Parkinson's Disease 487
REFERENCES 489

Committee 7
Imaging, Neurophysiological Testing and Other Tests

A. INTRODUCTION 509
B. IMAGING IN URINARY INCONTINENCE AND PELVIC FLOOR DYSFUNCTION 510
I. IMAGING OF THE UPPER URINARY TRACT 510
1. INDICATIONS 510
2. TECHNIQUES 511
a) Ultrasonography 511
b) Intravenous Urography 511
c) Computerised tomography 512
d) Magnetic resonance imaging 513
e) Isotopes 513
f) Conclusions 513
g) Consensus Statement 513
h) Suggested Research Areas 514
II. IMAGING OF THE LOWER URINARY TRACT 514
1. X-RAY IMAGING 514
a) Female Cystourethrography 514
2. ULTRASONOGRAPHY 521
a) Types Of Ultrasonography 521
b) Standardisation 522
c) The Urethra And Bladder Neck 522
d) Bladder Neck 524
e) Determination of the Post Void Residual Urine and Bladder Wall Thickness 525
f) Pelvic Floor Muscles 527
g) Pelvic Organ Prolapse 531
h) Ultrasonography In Relation To Pregnancy And Delivery 534
i) Pelvic Floor Surgery 535
j) Conclusions 537
k) Consensus Statement 537
l) Future Research Areas 537
3. MRI (THE EVOLVING ROLE OF MRI IN THE ASSESSMENT OF THE FEMALE PELVIC FLOOR) 538
a) Technique 538
3. THREE DIMENSIONAL MRI 540
a) Normal Pelvic Floor Functional Anatomy 540
b) Pathophysiology of pelvic floor disorders 544
c) Pelvic Organ Prolapse 549
d) Assessing Treatment Outcome 554
e) Conclusions 555
f) Consensus Statement 555
g) Future Research Areas 555
III. SPECIAL ISSUES 556
1. POST-VOID RESIDUAL 556
a) Measuring PVR 556
b) Conclusions 557
c) Consensus Statements 558
d) Future Research Areas 558
2. OPEN BLADDER NECK AND PROXIMAL URETHRA AT REST 558
a) Conclusions 559
b) Consensus Statements 559
c) Future Research Areas 559
3. FEMALE URETHRAL DIVERTICULA 559
a) Conclusions 560
b) Consensus Statements 560
c) Future Research Areas 560
4. IMAGING OF THE NERVOUS SYSTEM 560
a) Lumbosacral Spine x-rays 560
b) CT, MRI, SPECT and PET 560
c) Consensus Statements 562
d) Future Research Areas 562
5. ENDOSCOPY OF THE LOWER URINARY TRACT 563
a) Evaluation of the Female Bladder Outlet 563
b) Evaluation of the Bladder 564
c) Extra-Urethral Urinary Incontinence 564
d) Intraoperative Lower Urinary Tract Evaluation 564
e) Evaluation of the Male Bladder Outlet 564
f) Evaluation of Urethral Sphincter In Post-Prostatectomy Incontinence 565
g) Consensus Statements 565
h) Future Research Areas 565
C. Imaging in Anal Incontinence 565
I. INDICATIONS 565
II. IMAGING MODALITIES 565
1. ULTRASONOGRAPHY 565
a) Endoanal Ultrasound (EAUS) 566
b) 3 Dimensional Endoanal Ultrasonography (3-d eaus) 566
c) Transvaginal Ultrasonography 567
d) Transperineal Ultrasonography 567
e) Translabial Ultrasonography 567
f) Integrated Multicompartmental Pelvic Floor Ultrasonography 567
g) Dynamic Anorectal Endosonography (DAE) 568
h) Sonoelastography 568
2. MRI 568
3. EVACUATION DEFAECOGRAPHY (PROCTOGRAPHY) 569
III. SPHINCTERIC DISORDERS 570
1. THE INTERNAL ANAL SPHINCTER (IAS) 570
2. THE EXTERNAL ANAL SPHINCTER 571
IV. CONCLUSIONS 572
V. CONSENSUS STATEMENTS 572
VI. FUTURE RESEARCH AREAS 572
D. PAD TESTING 573
I. DEFINITION 573
II. INDICATION AND METHODOLOGY 573
III. OFFICE-BASED PAD TESTING 573

1. SHORT PAD TEST 573
a) Quantification: 573
b) Reproducibility: 574
2. ONE-HOUR PAD TEST 574
a) Quantification 574
b) Reproducibility 574
c) Validity 574
d) Bladder volume 574
e) Diagnosis 574
f) Sensitivity to change 575
3. TWO-HOUR PAD TEST 575
IV. HOME BASED PAD TESTING 575
1. 12-HOUR PAD TEST 575
a) Quantification 575
2. 24-HOUR PAD TEST 575
a) Quantification 575
b) Reproducibility 575
c) Diagnosis 575
d) Validity 575
3. 48-HOUR PAD TEST 575
a) Quantification: 575
4. COMMENTS 576
5. ROLE OF THE INVESTIGATION 577
V. CONCLUSIONS 577
VI. CONSENSUS STATEMENTS 577
VII. FUTURE RESEARCH AREAS 578
E. NEUROPHYSIOLOGY 578
I. INTRODUCTION 578
1. CLASSIFICATION OF CLINICAL NEUROPHYSIOLOGICAL TESTS 578
2. BIOLOGICAL CORRELATES OF ELECTROPHYSIOLOGICAL TESTS 578
a) Conduction Tests: Nerve Conduction, Evoked Potential and Reflex Studies 578
b) Electromyography (EMG) 578
3. GENERAL METHODOLOGICAL CONSIDERATIONS 579
a) Equipment 579
b) Recording 579
II. CLINICAL NEUROPHYSIOLOGICAL TESTS 580
1. SOMATIC MOTOR SYSTEM TESTS 580
a) Electromyography (EMG) 580
b) Pudendal Nerve Conduction Tests 587
c) Anterior Sacral Root (Cauda Equina) Stimulation 587
d) Motor Evoked Potentials 588
2. SENSORY SYSTEM TESTS 588
a) Sensory Measurements During Cystometry 588
b) Assessment of Anorectal Sensation 589
c) Quantitative Sensory Testing 589
d) Sensory Neurography 589
e) Somatosensory Evoked Potentials (SEP) 589
3. SACRAL REFLEXES 590
a) Sacral Reflex on Electrical Stimulation 590
b) Sacral Reflex on Mechanical Stimulation 591
4. AUTONOMICAL FUNCTION TESTS 592
a) Tests in Generalised Autonomic Neuropathy 592
b) Dartos reflex 592
c) Smooth Muscle Electromyography 592
d) Sympathetic Skin Response (SSR) 592
III. EVIDENCE BASED USE OF CLINICAL NEUROPHYSIOLOGICAL TESTS 592
1. USEFULNESS OF CLINICAL NEUROPHYSIOLOGICAL TESTS IN EVALUATION OF INDIVIDUAL PATIENTS 593
2. USEFULNESS OF CLINICAL NEUROPHYSIOLOGICAL TESTS IN RESEARCH 593
IV. CONSENSUS STATEMENT 593
1. CLINICAL NEUROPHYSIOLOGICAL TESTING 593
2. TECHNICAL STANDARDS 593
3. FUTURE RESEARCH AREAS 593
F. OTHER INVESTIGATIONS 594
I. URINALYSIS 594
1. CONSENSUS STATEMENT 594
2. FUTURE RESEARCH AREAS 594
II. BLOOD TESTS 594
III. TISSUE ANALYSIS 594
1. CONSENSUS STATEMENT 596
2. FUTURE RESEARCH AREAS 596
G. CONCLUSIONS 596
REFERENCES 598

Committee 8
Pharmacological Treatment of Urinary Incontinence

A. Introduction 625
I. PUBLICATION SEARCHES 625
II. CENTRAL NERVOUS CONTROL 626
III. PERIPHERAL NERVOUS CONTROL 626
IV. PATHOGENESIS OF BLADDER CONTROL DISORDERS 629
V. BLADDER CONTRACTION 629
VI. MUSCARINIC RECEPTORS 630
B. Drugs used for treatment of overactive bladder symptoms/detrusor overactivity 632
I. ANTIMUSCARINIC (ANTICHOLINERGIC) DRUGS 632
1. ANTIMUSCARINICS WITH "SPECIFIC" ACTION 635
a) Atropine sulfate 635
b) Darifenacin hydrobromide 635
c) Fesoterodine fumarate 637
d) Imidafenacin 638
e) Propantheline bromide 639
f) Solifenacin succinate 640
g) Tolterodine tartrate 642
h) Trospium chloride 645
2. ANTIMUSCARINICS WITH "MIXED" ACTION 646
a) Oxybutynin chloride 646
b) Propiverine hydrochloride 649
c) Flavoxate hydrochloride 651
3. CLINICAL USE OF ANTIMUSCARINICS 652
II. DRUGS ACTING ON MEMBRANE CHANNELS 653
1. CALCIUM ANTAGONISTS 653
2. POTASSIUM CHANNEL OPENERS 654
III. A-ADRENOCEPTOR (AR) ANTAGONISTS 655
IV. B-ADRENOCEPTOR AGONISTS 656
V. PHOSPHODIESTERASE (PDE) INHIBITORS 660
VI. ANTIDEPRESSANTS 662
1. IMIPRAMINE 662
2. DULOXETINE 663
VII. CYCLOOXYGENASE (COX) INHIBITORS 663
VIII. TOXINS 664
1. BOTULINUM TOXIN 664
a) Mechanism of action of BONT 664
b) BoNT/A effects on bladder histology 665
c) BoNT/A injection protocol 666
d) Effect of Bont/A on NDO adult patients 666
e) BONT/A and UTI in adult NDO patients 668
f) BONT/A in IDO patients 668
g) BONT/A in children and elderly patients 670
h) Effect of BoNT/A on quality of life 671

i) Side effects of bladder wall injection of BoNT/A 672
j) Effectiveness of repeated injections in NDO and IDO patients 673
k) Cost-effectiveness of BoNT/A 674
l) Comparisons between different BoNT/A brands 674
m) BONT/B 674
n) BONT/A in IC/PBS 675
2. CAPSAICIN AND RESINIFERATOXIN (RTX) 676
a) Rationale for intravesical vanilloids 676
b) Intravesical capsaicin 676
c) RTX in NDO 676
d) RTX in IDO 676
e) RTX and urgency 677
f) Intravesical RTX and IC/PBS 677
IX. OTHER DRUGS 677
1. BACLOFEN 677
X. COMBINATIONS 678
1. A1-AR ANTAGONISTS WITH ANTIMUSCARINICS 678
2. COMBINED ANTIMUSCARINICS 679
3. ANTIMUSCARINICS AND 5A-REDUCTASE INHIBITORS 680
4. A1-AR ANTAGONISTS WITH 5A-REDUC TASE INHIBITORS 680
XI. FUTURE POSSIBILITIES 680
1. PERIPHERALLY ACTING DRUGS 680
a) Vitamin D3 receptor analogues 680
b) TRP channel antagonists 681
c) Prostanoid receptor agonists/antagonists 682
d) Intraprostatic Injections of drugs 682
e) Cannabinoids 684
2. CENTRALLY ACTING DRUGS 686
a) Gonadotropin-releasing hormone antagonists 686
b) Gabapentin 687
c) Tramadol 687
d) NK1-receptor antagonists 687
C. Drugs used for treatment of stress incontinence in women 688
I. A-ADRENOCEPTOR AGONISTS 689
II. B-ADRENOCEPTOR AGONISTS 690
III. B –ADRENOCEPTOR ANTAGONISTS 690
IV. SEROTONIN-NORADRENALINE UPTAKE INHIBITORS 690
1. IMIPRAMINE 690
2. DULOXETINE 690
D. Stress urinary incontinence in men 693
E. Drugs to treat overflow incontinence/ acute urinary retention 694
F. Hormonal treatment of urinary incontinence 695
I. OESTROGENS 695
1. OESTROGENS AND THE CONTINENCE MECHANISM 695
2. OESTROGENS FOR STRESS URINARY INCONTINENCE 695
3. OESTROGENS FOR URGENCY URINARY INCONTINENCE AND OVERACTIVE BLADDER SYMPTOMS 696
4. EVIDENCE REGARDING OESTROGENS AND INCONTINENCE FROM LARGE CLINICAL TRIALS 696
II. OTHER HORMONES 697
III. DESMOPRESSIN 698
G. Considerations in the Elderly 701
I. ANTIMUSCARINIC AGENTS 701
1. EFFICACY AND TOLERABILITY 701
2. COGNITIVE SAFETY 701
II. DESMOPRESSIN – EFFICACY AND SAFETY IN THE ELDERLY 703
III. BOTULINUM TOXIN A IN OLDER ADULTS 703
IV. OTHER 703
REFERENCES 704

Committee 9
Diagnosis and Management of Urinary Incontinence in Childhood

A. Introduction 731
I. NORMAL DEVELOPMENT OF BLADDER AND SPHINCTER CONTROL 731
II. NORMAL VALUES 732
1. NORMAL BLADDER CAPACITY 732
2. NORMAL VOIDING 733
3. NORMAL VOIDING PRESSURES 733
4. NORMAL URINARY FLOW RATES 733
B. Evaluation in children who wet 734
I. HISTORY TAKING 734
II. PHYSICAL EXAMINATION 735
III. URINALYSIS 735
IV. NON-INVASIVE DIAGNOSTIC TECHNIQUES 735
1. FREQUENCY / VOLUME CHARTS: BLADDER DIARY 735
2. QUANTIFICATION OF URINE LOSS 736
3. SCORING SYSTEMS 736
4. QUANTIFICATION OF CONSTIPATION 736
5. URINARY FLOW 736
6. ULTRASOUND IMAGING OF UPPER AND LOWER URINARY TRACT 737
a) Post-void residual volume 738
b) Ultrasound-flow-ultrasound 738
7. INVASIVE DIAGNOSTIC TECHNIQUES 739
a) Voiding Cystourethrogram 739
b) (Video)-Urodynamics 740
c) Cystoscopy 741
C. Nocturnal enuresis 741
I. DEFINITION 741
II. SEVERITY 741
III. PREVALENCE 743
IV. INHERITANCE 743
V. GENDER AND MONOSYMPTOMATIC NE 743
VI. CLASSIFICATION 744
1. PRIMARY VERSUS SECONDARY NOCTURNAL ENURESIS 744
2. MONO-SYMPTOMATIC VERSUS NON-MONO-SYMPTOMATIC NE 744
VII. PATHOPHYSIOLOGY OF MONOSYMPTOMATIC NE 744
1. INCREASED NOCTURNAL URINE OUTPUT 744
2. DETRUSOR OVERACTIVITY DURING THE NIGHT 746
3. LACK OF AROUSAL FROM SLEEP/CNS FUNCTION 746
VIII. TREATMENT OF NOCTURNAL ENURESIS 747
1. EVALUATION 748
a) The frequency volume chart (FVC) 748
b) Symptoms of nocturnal enuresis 748
2. PHYSICAL EXAMINATION 749
3. LABORATORY EXAMINATION 749
4. THE MANAGEMENT OF NE DEPENDS ON: 749
5. EVIDENCE BASED RECOMMENDATIONS FOR TREATMENT 750
6. PHARMACOLOGICAL TREATMENT 750
a) Desmopressin 750
b) Antimuscarinic drugs for OAB 751

c) Tricyclic antidepressants 751
7. ENURESIS ALARM 752
8. DRY BED TRAINING 752
9. AROUSAL TRAINING 753
10. ACUPUNCTURE 753
11. COMBINED TREATMENT WITH ALARM AND DESMOPRESSIN 753
12. INHIBITORS OF PROSTAGLANDIN SYNTHESIS 754
13. NON RESPONDERS 754
14. CONCLUSION 754
D. Children with both day and night time incontinence 755
I. PREVELANCE 756
II. INTRODUCTION TO CLINICAL ASSESSMENT 757
III. CONFOUNDING FACTORS: LOWER URINARY TRACT DYSFUNCTION, RECURRENT URINARY TRACT INFECTION AND VESICOURETERIC REFLUX (VUR) 758
IV. CLASSIFICATION 759
1. OVERACTIVE BLADDER IN CHILDREN 759
2. DYSFUNCTIONAL VOIDING 760
3. DETRUSOR UNDERACTIVITY 761
4. VOIDING POSTPONEMENT 761
5. GIGGLE INCONTINENCE 761
6. VESICOVAGINAL ENTRAPMENT 762
7. ELIMINATION SYNDROME 762
V. PRINCIPLES OF NON PHARMACOLOGICAL TREATMENT FOR ALL DIFFERENT STATES 763
1. BLADDER REHABILITATION AND UROTHERAPY 763
2. ADJUNCTIVE BIOFEEDBACK 764
3. CLEAN INTERMITTENT (SELF) CATHETERISATION 764
4.NEUROMODULATION 765
5. ALARM TREATMENT 767
6. CONCLUSION 767
VI. PHARMACOLOGICAL TREATMENT 767
1. ANTIMUSCARINIC THERAPY 767
a) Oxybutynin 767
b) Tolterodine 768
c) Terodiline 769
d) Trospium and propiverine 769
e) Solifenacin 769
f) Botulinum toxin 769
g) Alpha-adrenergic blockade 769
VII. CONCLUSION CHILDREN WITH BOTH DAY AND NIGHT TIME INCONTINENCE 770
E. NEUROGENIC DETRUSOR-SPHINCTER DYSFUNCTION 770
I. INTRODUCTION 770
II. PRESENTATION OF NEUROGENIC DETRUSOR SPHINCTER DYSFUNCTION IN CHILDREN 770
III. CLASSIFICATION: PATTERN RECOGNITION 771
IV. MANAGEMENT 772
1. ASSESSMENT 772
2. TREATMENT 772
F. SURGICAL MANAGEMENT OF URINARY INCONTINENCE IN CHILDREN 774
I. ABNORMALITIES OF STORAGE 775
II. ABNORMALITIES OF SPHINCTERIC FUNCTION 775
III. BYPASS OF SPHINCTERIC MECHANISM 776
IV. EVALUATION AND DIAGNOSIS 776
V. INDICATIONS FOR SURGICAL PROCEDURES TO CORRECT URINARY INCONTINENCE 776
1. STORAGE FUNCTION 776
2. SPHINCTER FUNCTION DURING STORAGE 776
3. PROCEDURES TO BYPASS THE SPHINCTER 777
VI. BLADDER RESERVOIR CONSTRUCTION 777
1. URETEROSIGMOIDOSTOMY 777
2. BLADDER AUGMENTATION, BLADDER REPLACEMENT AND CONTINENT URINARY DIVERSION, USING INTESTINE 777
3. WHICH INTESTINAL SEGMENT SHOULD BE UTILIZED? 778
a) Stomach 778
b) Ileum / Colon 778
c) General principles 778
d) Bladder augmentation techniques 779
e) Auto-augmentation 779
f) Seromuscular patch 779
g) Ureteral bladder augmentation 780
h) Experimental Methods 780
VII. BLADDER OUTLET SURGERY 781
1. URETHRAL ENHANCEMENT 781
2. BULKING AGENTS 781
3. ARTIFICIAL URINARY SPHINCTER 781
4. FASCIAL SLINGS 782
5. BLADDER NECK CLOSURE 783
6. BLADDER OUTLET RECONSTRUCTION 783
7. ALTERNATIVE CONTINENCE CHANNELS 784
a) The Mitrofanoff principle 784
b) The Ileo-cecal valve 785
c) Kock pouch 785
d) Artificial Sphincter 785
e) Where to place the cutaneous stoma 785
VIII. COMPLICATIONS OF CONTINENCE SURGERY IN CHILDREN 785
1. STORAGE AND EMPTYING COMPLICATIONS 785
2. RESERVOIR RUPTURE 786
3. METABOLIC COMPLICATIONS 786
4. EFFECTS ON THE GASTROINTESTINAL TRACT 787
5. RENAL FUNCTION 787
6. INFECTIONS AND STONES 787
7. GROWTH 788
8. PREGNANCY 789
9. MALIGNANCY 789
10. PSYCHOLOGICAL CONSEQUENCES AND QUALITY OF LIFE 790
IX. CONSENSUS STATEMENT ON SURGICAL TREATMENT OF URINARY INCONTINENCE IN CHILDREN 790
G. PSYCHOLOGICAL ASPECTS OF URINARY INCONTINENCE, ENURESIS AND FAECAL INCONTINENCE 790
I. INTRODUCTION 791
II. CLINICAL BEHAVIOURAL DISORDERS 791
III. CLINICAL BEHAVIORAL DISORDERS IN CHILDREN WITH ENURESIS AND URINARY INCONTINENCE 792
1. EPIDEMIOLOGICAL STUDIES 792
a) Nocturnal Enuresis 792
b) Urinary Incontinence (Daytime Wetting) 794
2. CLINICAL STUDIES 794
a) Nocturnal Enuresis 794
b) Urinary Incontinence (Daytime Wetting) 795
IV. CLINICAL BEHAVIORAL DISORDERS IN CHILDREN WITH FAECAL INCONTINENCE 796
1. EPIDEMIOLOGICAL STUDIES 796
2. CLINICAL STUDIES 796

V. SUBCLINICAL SIGNS AND SYMPTOMS OF WETTING CHILDREN 798
1. IMPACT ON CHILDREN 798
2. IMPACT ON PARENTS 798
VI. GENERAL PRINCIPLES 799
1. ASSESSMENT 799
a) Screening Questionnaires 799
b) Child Psychiatric Assessment 799
2. OF PSYCHOLOGICAL DISORDER 801
3. UROTHERAPY 801
4. NON-SPECIFIC APPROACHES 802
5. COUNSELLING 802
6. COGNITIVE-BEHAVIOURAL THERAPY 802
7. BASELINE AND OBSERVATION 802
8. BIOFEEDBACK 802
9. ALARM TREATMENT 803
VII. CONCLUSION AND SUMMARY 804
REFERENCES 804

Committee 10
Neurologic Urinary and Faecal Incontinence

A. Introduction 829
B. Pathophysiology 831
I. SUPRAPONTINE LESIONS 831
II. PONTINE LESIONS 831
III. SUPRASACRAL SPINAL CORD LESIONS 831
IV. SACRAL (CONUS MEDULLARIS) LESIONS 832
V. SUBSACRAL LESIONS (CAUDA EQUINA OR PERIPHERAL NERVES) 832
C. Neurological urinary incontinence 832
I. EPIDEMIOLOGY 832
1. NEUROLOGICAL LESION BY DISEASE LOCATION 832
a) Diseases Affecting Brain/Brainstem 832
b) Diseases of the spinal cord 833
c) Peripheral nerve problems 834
d) Other 835
II. SPECIFIC DIAGNOSTICS 835
1. HISTORY 835
2. PHYSICAL EXAMINATION 836
3. URODYNAMIC TESTS 836
a) Electromyography (EMG) during cystogram 836
b) Filling parameters 837
c) Filling technique 838
d) The outlet during voiding 838
e) Bladder sensation 838
f) Complications of urodynamic testing 838
4. SPECIAL TESTS 839
a) Bladder-cooling reflex; the ice water test (IWT) 839
b) Bethanechol supersensitivity test (BST) 840
c) Electrodiagnostic tests 840
III. CONSERVATIVE TREATMENT 843
1. OVERVIEW ACCORDING TO TYPE OF LESION 843
a) Supraspinal lesions 843
b) Suprasacral lesions 843
c) Lower motor neuron lesions 843
2. SPECIFIC INTERVENTIONS 844
a) Behavioral therapy 844
b) Catheters and appliances 846
IV. PHARMACOTHERAPY 849
1. DRUGS FOR NEUROGENIC STORAGE DYSFUNCTION 849
a) Bladder relaxants 849
b) Intravesical bladder relaxants 850
c) Drugs for sphincter deficiency 854
2. DRUGS FOR TREATING VOIDING DYSFUNCTION 854
a) Alpha-adrenergic antagonists 854
b) Botulinum toxin 854
c) Cholinomimetics 855
V. ELECTROSTIMULATION 855
1. ELECTRICAL NEUROMODULATION 855
a) Anogenital Stimulation 856
b) Pudendal Nerve Stimulation 856
c) Dorsal Genital Nerve (DGN) stimulation 856
d) Posterior tibial nerve stimulation 857
e) Repetitive transcranial magnetic stimulation 857
f) Deep brain stimulation 857
2. ELECTRICAL STIMULATION OF THE PELVIC FLOOR MUSCULATURE 858
3. INTRAVESICAL ELECTRICAL STIMULATION (IVES) 858
VI. SURGICAL TREATMENT OF URINARY INCONTINENCE 859
1. SACRAL NEUROMODULATION 859
a) Hypotheses on the modes of action of neuromodulation 859
b) Treatment of neurogenic detrusor overactivity incontinence 859
c) Sacral neuromodulation for urinary retention in neurological bladder dysfunction 861
2. DENERVATION PROCEDURES FOR TREATING REFLEX URINARY INCONTINENCE DUE TO DETRUSOR OVERACTIVITY 862
a) Peripheral bladder denervation 862
b) Isolated rhizotomy of ventral and/or dorsal sacral roots 862
c) Rhizotomy of posterior sacral roots and stimulation of the anterior sacral roots 863
3. SURGERY FOR INCONTINENCE ASSOCIATED WITH POOR BLADDER EMPTYING DUE TO DETRUSOR UNDERACTIVITY 865
a) Surgical treatment of detrusor external sphincter dyssynergia 865
b) Bladder neck incision (BNI) for detrusor-bladder neck dyssynergia (DBND) 871
4. SURGERY TO INCREASE DETRUSOR STRENGTH 872
5. STRESS URINARY INCONTINENCE (SUI) DUE TO SPHINCTERIC INCOMPETENCE 872
a) Bulking agents 873
b) Autologous Sling Procedures 874
c) Suburethral tapes 875
d) Artificial urinary sphincter (AUS) 875
e) Surgery of the bladder neck 876
f) Complete bladder neck or urethral closure 878
6. SURGICAL ALTERNATIVES EXCLUDING DENERVATION PROCEDURES TO TREAT REFLEX INCONTINENCE DUE TO NEUROGENIC DETRUSOR OVERACTIVITY 878
a) Bladder augmentation using intestinal segments 878
b) Autoaugmentation by detrusor myotomy 883
c) Bladder augmentation using biomaterials 884
d) Cutaneous continent urinary diversion 885
e) Non-continent cutaneous urinary diversion 889
D. Neurological faecal incontinence 894
I. EPIDEMIOLOGY 894
II. NEUROPHYSIOLOGY OF BOWEL DYSFUNCTION 894
III. ASSESSMENT 895
IV. CONSERVATIVE TREATMENT 895
1. BOWEL PROGRAM /BOWEL CARE 895
2. SPECIFIC TECHNIQUES 896
a) Diet 896
b) Toileting 896
c) Digital rectal stimulation 896
d) Manual stool extraction 896
3. CHEMICAL STIMULANTS 896
4. ASSISTIVE TECHNIQUES FOR DEFECATION 897

a) Abdominal massage 897
b) Anal stimulation with water streams 897
c) Transanal / Transrectal irrigation (TAI) 897
5. APPLIANCE/ASSISTIVE TECHNIQUES FOR FAECAL INCONTINENCE 897
a) Anal plug 897
b) Neuromodulation /Electrostimulation/Magnetic stimulation 897
c) Quality of life 898
V. SURGICAL TREATMENT 898
1. SACRAL NERVE STIMULATION 899
2. ANTEGRADE CONTINENCE ENEMA (ACE) 901
3. DYNAMIC GRACILOPLASTY 903
4. ARTIFICIAL ANAL SPHINCTER 903
5. COLOSTOMY 906
6. POSTANAL REPAIR 907
E. Specific neurological diseases 907
I. DEMENTIAS 907
1. DEMENTIA AND URINARY INCONTINENCE 907
2. ALZHEIMER'S DISEASE 907
a) Epidemiology and prevalence 907
b) Pathology and disease-specific urinary tract problems 908
c) Diagnosis and treatment 908
d) Guidance for further research 909
3. VASCULAR DEMENTIA 909
a) Epidemiology and prevalence 909
b) Diagnosis 909
c) Pathology and disease-specific urinary tract problems 910
d) Disease specific diagnosis and treatment 910
e) Recommendations for further research 911
4. DEMENTIA WITH LEWY BODIES 911
a) Epidemiology and prevalence 911
b) Pathology and disease-specific urinary tract problems 911
c) Disease specific diagnosis and treatment 912
5. FRONTOTEMPORAL DEMENTIA (FTD) 912
a) Epidemiology and prevalence 912
b) Pathology and disease-specific urinary tract problems 912
c) Diagnosis and treatment 912
6. CONSTIPATION AND FECAL INCONTINENCE IN DEMENTIA 912
7. NORMAL PRESSURE HYDROCEPHALUS 913
a) Epidemiology and prevalence 913
b) Pathology and disease-specific urinary tract problems 913
c) Diagnosis and treatment 913
II. MULTIPLE SYSTEM ATROPHY 914
1. EPIDEMIOLOGY AND PREVALENCE 914
2. PATHOLOGY AND DISEASE-SPECIFIC URINARY TRACT PROBLEMS 914
3. DIAGNOSIS AND TREATMENT 915
4. FAECAL INCONTINENCE 916
III. PARKINSON'S DISEASE 917
1. URINARY INCONTINENCE 921
a) Pathology and disease-specific urinary tract problems 917
b) Specific diagnosis and treatment 918
2. CONSTIPATION AND FAECAL INCONTINENCE 919
a) Pathology and disease-specific problems 919
b) Disease-specific diagnosis and treatment 920
IV. CEREBRAL LESIONS AND CEREBROVASCULAR ACCIDENTS 921
1. URINARY INCONTINENCE 921
a) Pathology and disease specific LUT problems 921
b) Disease-specific diagnosis and management 922
V. MENINGITIS-RETENTION SYNDROME 923
VI. ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) 925
VII. SPINAL CANAL STENOSIS 926
1. CAUDA EQUINA SYNDROME 927
2. LUMBAR DISC PROLAPSE 927
VIII. NEUROPATHIES AND MUSCLE DISORDERS 928
1. GUILLAIN BARRE SYNDROME 928
a) Urinary dysfunction 928
b) Bowel dysfunction 929
2. FAMILIAL AMYLOID POLYNEUROPATHY 930
3. FAMILIAL DYSAUTONOMIA 930
4. CHARCOT-MARIE-TOOTH DISEASE 930
5. AUTONOMIC NEUROPATHIES 930
a) Acute Idiopathic Autonomic Neuropathy 930
b) Autoimmune Autonomic Ganglionopathy 930
c) Pure Autonomic Failure 931
6. DISORDERS OF THE NEUROMUSCULAR JUNCTION 931
7. MUSCLE DISORDERS 931
a) Muscular Dystrophies 931
b) Mitochondrial cytopathy 931
8. PERIPHERAL NEUROPATHY DUE TO IATROGENIC LESIONS (FOCAL NEUROPATHY) 931
a) Hysterectomy (simple and radical) 932
b) Abdominoperineal resection and total mesorectal excision 932
IX. MULTIPLE SCLEROSIS 934
1. EPIDEMIOLOGY 934
2. URINARY DYSFUNCTION IN MS 934
a) Infectious complications 935
b) Alterations of the bladder 935
c) Bladder cancer 935
d) Complications of the upper urinary tract 936
e) Risk factors in urological complications 936
f) The role of urodynamics in multiple sclerosis 936
3. COLORECTAL DYSFUNCTION IN MS 937
a) Epidemiology 937
b) Pathophysiology of MS-related digestive disorders 938
X. SPINAL CORD LESIONS 938
1. URINARY INCONTINENCE 938
a) Epidemiology and prevalence 938
b) Pathology and disease-specific LUT problems 938
c) Disease specific management 942
d) Guidance for further research 944
2. FAECAL INCONTINENCE 945
a) Epidemiology and prevalence 945
b) Pathology and disease specific lower gastrointestinal (LGIT) problems 946
c) Conservative bowel management 946
d) Guidance for further research 947
XI. MYELOMENINGOCOELE 947
1. URINARY INCONTINENCE 947
2. BOWEL PROBLEMS 949
XII. SYSTEMIC AND OTHER CONDITIONS 950
1. SYSTEMIC LUPUS ERYTHEMATOSIS 950
a) Urinary incontinence 950
2. HERPES ZOSTER 951
3. HIV 952
a) Urinary incontinence 952
b) Faecal incontinence 952
4. NEUROSYPHILIS 953
5. DIABETES MELLITUS 953
a) Urinary incontinence 953
b) Faecal Incontinence 954
LIST OF ABBREVIATIONS 955
REFERENCES 956

Committee 11
Incontinence in the Frail Elderly

A. General considerations 1003
I. INTRODUCTION 1003
II. SEARCH STRATEGIES 1004
III. DEFINING THE FRAIL OLDER POPULATION 1004
1. FRAILTY 1004

2. IMPACT OF UI ON MORBIDITY AND INSTITUTIONALISATION 1005

B. Urinary Incontinence in frail older people 1005

I. AETIOLOGY AND ASSESSMENT 1005

1. BACKGROUND 1005

2. QUALITY OF THE DATA 1005

3. UI AS A GERIATRIC SYNDROME 1005

4. AGE-RELATED CHANGES RELEVANT TO UI IN THE FRAIL ELDERLY 1006

a) Bladder 1006

b) Urethra 1008

c) Pelvic floor 1009

d) Vagina 1010

e) Prostate 1010

f) Other changes 1011

5. FACTORS OUTSIDE THE LOWER URINARY TRACT CAUSING OR CONTRIBUTING TO UI 1011

a) Medications 1011

b) Co-morbid conditions and functional impairment 1011

c) Neurological and psychiatric disorders 1014

d) Depression 1014

e) Falls 1015

f) Stroke 1015

g) Recommendations for research 1015

h) Recommendations for practice 1015

6. ENVIRONMENTAL FACTORS 1015

a) The physical environment 1016

b) Processes and quality of care 1016

c) Assessment 1017

d) Knowledge 1017

e) Processes of care that reduce functional status 1017

f) Lack of toileting assistance 1017

g) Staffing levels and skill mix 1019

h) Use and misuse of continence aids 1019

i) Recommendations for research 1021

j) Recommendations for practice 1021

II. ASSESSMENT OF THE FRAIL OLDER PERSON WITH UI 1021

1. COMPONENTS 1021

a) Identification of frail older persons 1021

b) Primary care assessment 1022

c) Cough stress test 1022

d) Postvoid residual measurement 1022

e) Urodynamic testing 1022

f) Ultrasound estimation of bladder weight 1022

2. SUMMARY OF EVIDENCE 1023

3. RECOMMENDATIONS FOR EVALUATION (SEE ALGORITHM) 1023

III. FACTORS IN MANAGEMENT 1023

1. BACKGROUND 1023

2. ROLE OF COMORBIDITY IN MANAGEMENT DECISIONS 1023

3. DEFINING OUTCOMES FOR TREATMENT 1023

4. ROLE OF REMAINING LIFE EXPECTANCY IN TREATMENT DECISIONS 1024

5. PREFERENCES FOR CARE 1024

6. COSTS AND BENEFITS OF UI TREATMENT IN FRAIL ELDERLY 1025

a) Estimating Costs 1025

b) Benefit and effectiveness of treatment 1026

7. ISSUES IN DRUG TREATMENT 1027

a) Age-related changes in pharmacology 1027

b) Availability of low dose agents 1027

c) Inappropriate polypharmacy 1027

d) Adverse drug effects 1027

e) Drug interactions 1029

f) Potentially inappropriate drugs for older persons 1029

8. SPECIAL ISSUES UNIQUE TO FRAIL OLDER MEN 1030

9. SUMMARY OF THE EVIDENCE 1031

IV. TREATMENT OF URINARY INCONTINENCE IN THE FRAIL ELDERLY 1031

1. LIFESTYLE INTERVENTIONS 1031

a) Quality of data and results 1031

b) Summary of the evidence 1031

2. BEHAVIOURAL INTERVENTIONS 1031

a) Quality of data 1032

b) Efficacy 1032

c) Summary of evidence 1035

d) Interventions with caregivers and long term care staff 1035

3. INTERVENTIONS WITH LONG TERM CARE STAFF AND CAREGIVERS 1035

a) Quality of data 1036

b) Results 1036

c) Recommendations for practice 1039

4. PHARMACOLOGICAL TREATMENT 1040

a) Background 1040

b) Quality of data 1040

c) Results 1041

d) Summary of the evidence 1046

e) Recommendations for practice 1047

5. SURGICAL TREATMENT IN THE FRAIL ELDERLY 1047

a) Background 1047

b) Incontinence surgery in frail elderly women 1048

c) Incontinence surgery in frail elderly men 1049

d) General issues in surgical care of the frail elderly 1049

e) Summary of evidence 1049

f) Recommendations for management 1050

g) Recommendations for research 1050

6. CATHETERS 1050

a) Background 1050

b) Quality of the data 1050

c) Rates of IDC use in frail older adults 1051

d) IDC for end of life care 1052

e) Management recommendations 1052

f) Intermittent catheterisation as an alternative to IDC in frail older adults 1053

g) Research recommendations 1053

V. NOCTURIA IN THE OLDER ADULT 1053

1. BACKGROUND 1053

2. QUALITY OF THE DATA 1053

3. PREVALENCE, INCIDENCE, AND IMPACT 1054

4. PATHOPHYSIOLOGY 1055

5. DIAGNOSTIC ASSESSMENT 1055

6. TREATMENT 1056

a) Behavioural approaches and treatment of comorbidity 1056

b) Pharmacotherapy 1057

c) Surgical and procedural treatments 1059

7. SUMMARY OF EVIDENCE 1060

8. RECOMMENDATIONS FOR MANAGEMENT 1060

9. RECOMMENDATIONS FOR RESEARCH FOR NOCTURIA IN THE ELDERLY [636] 1060

VI. MODELS OF CARE FOR THE FRAIL ELDERLY WITH UI 1060

1. BACKGROUND 1060

2. HOME CARE 1060

3. CONTINENCE NURSE ADVISORS AND NURSE-LED MODELS 1061

4. COLLABORATIVE PRACTICES BETWEEN ADVANCE PRACTICE NURSES AND PHYSICIANS 1061

5. INSTITUTIONAL LONG TERM CARE 1062

6. OTHER INSTITUTIONAL SETTINGS 1063

7. RESEARCH RECOMMENDATIONS 1064

C. FAECAL INCONTINENCE 1065

I. BACKGROUND 1065

II. PREVALENCE AND RISK FACTORS FOR FAECAL INCONTINENCE 1065

1. PREVALENCE ESTIMATES FOR FAECAL INCONTINENCE 1065

2. PREVALENCE AND INCIDENCE ESTIMATES OF FI IN COMMUNITY-DWELLING OLDER ADULTS 1065

3. PREVALENCE ESTIMATES OF FI IN HOSPITALIZED OLDER ADULTS 1067

4. PREVALENCE AND INCIDENCE ESTIMATES OF FI IN LONG-TERM CARE RESIDENTS 1067
5. FAECAL INCONTINENCE IN OLDER ADULTS – THE "HIDDEN" PROBLEM 1067
6. RISK FACTORS ASSOCIATED WITH FI IN OLDER ADULTS 1068
III. THE AGEING LOWER BOWEL AND PATHOPHYSIOLOGY IN OLDER ADULTS WITH FAECAL INCONTINENCE 1068
1. QUALITY OF DATA 1068
2. ANORECTAL FUNCTION IN HEALTHY OLDER ADULTS 1068
3. CAUSES OF FAECAL INCONTINENCE IN OLDER ADULTS 1070
4. EVALUATION OF FAECAL INCONTINENCE IN OLDER ADULTS 1072
5. TREATMENT OF FI IN OLDER ADULTS 1073
a) Quality of data 1073
b) Multi-component treatments for FI 1073
c) Treatment of FI in nursing home settings 1074
d) Treatment of FI in stroke survivors 1074
e) Sacral Neuromodulation/Percutaneous tibial nerve stimulation for FI in older adults 1074
6. SUMMARY OF EVIDENCE ON THE TREATMENT OF FI IN FRAIL OLDER PEOPLE 1074
7. RECOMMENDATIONS - TREATMENT OF FI IN FRAIL OLDER PEOPLE (ALL GRADE C) 1075
8. AREAS FOR FURTHER RESEARCH ON FI IN FRAIL OLDER PEOPLE 1075
REFERENCES 1076

Committee 12
Adult Conservative Management

I. INTRODUCTION 1103
A. UI IN WOMEN 1103
I. LIFESTYLE INTERVENTIONS 1103
1. PREVENTION 1103
2. TREATMENT 1103
a) Weight loss 1103
b) Physical activity 1104
c) Physical Forces (exercise and work) 1105
d) Smoking 1106
e) Dietary factors 1106
f) Constipation 1107
g) Other 1108
3. OTHER LUTS 1108
4. FACTORS AFFECTING OUTCOME 1108
II. PELVIC FLOOR MUSCLE TRAINING (PFMT) 1108
1. RATIONALE AND PRINCIPLES 1108
a) Biological rationale for PFMT for SUI 1108
b) Biological rationale for PFMT for UUI 1109
c) Principles of skeletal muscle strengthening 1109
d) Principles of behaviour change 1110
2. PREVENTION AND TREATMENT (PREGNANT AND POSTNATAL WOMEN ONLY) 1110
a) Is PFMT effective in the prevention of UI in childbearing women? 1111
b) Is PFMT effective in the treatment of UI in childbearing women? 1113
c) Is PFMT effective in the mixed prevention and treatment of UI in childbearing women? 1114
3. PREVENTION (OTHER WOMEN) 1116
a) Is PFMT effective in the prevention of UI? 1116
4. TREATMENT (WOMEN) 1116
a) Is PFMT better than no treatment, a placebo or a control group treatment? 1116
b) Is one type of PFMT programme better than another? 1120
c) Is PFMT better than other treatments? 1129
d) Does the addition of PFMT to other treatments add benefit? 1134
5. OTHER LUTS 1135
6. FACTORS AFFECTING OUTCOME 1136
a) Age 1136
b) Other 1136
III. WEIGHTED VAGINAL CONES (VCS) 1137
1. PREVENTION 1137
2. TREATMENT 1138
a) Are VCs better than no treatment, placebo or control treatments? 1138
b) Are VCs as effective as other treatments? 1138
c) Are VCs combined with PFMT better than PFMT alone? 1144
3. OTHER LOWER URINARY TRACT SYMPTOMS (LUTS) 1144
4. FACTORS AFFECTING OUTCOME 1144
IV. ELECTRICAL STIMULATION (ESTIM) 1144
1. PREVENTION 1152
2. TREATMENT 1152
a) Is EStim better than no active treatment (placebo, sham, control or no treatment) for treatment of UI? 1152
b) Is one type of EStim better than another in the treatment of UI? 1154
c) Is EStim better than other treatments for UI? 1154
d) Does the addition of EStim to other treatments add any benefit in the treatment of UI? 1156
3. OTHER LUTS 1158
4. FACTORS AFFECTING OUTCOME 1158
V. MAGNETIC STIMULATION (MSTIM) 1158
1. PREVENTION 1160
2. TREATMENT 1160
a) Is MStim better than no active treatment (placebo, control or no treatment)? 1160
b) Is one approach to MStim better than another? 1163
c) Is MStim better than other treatments? 1163
d) Does the addition of MStim to other treatments add any benefit in the treatment of UI? 1163
VI. SCHEDULED VOIDING REGIMENS 1164
1. PREVENTION 1165
2. TREATMENT 1165
a) What is the most appropriate bladder training (BT) protocol? 1166
b) Is BT better than no treatment, placebo or control treatments? 1167
c) Is BT better than other treatments? 1168
d) Can any other treatment be added to BT to add benefit? 1169
e) Does the addition of BT to any other treatment add benefit? 1170
f) Timed voiding 1171
3. OTHER LUTS 1171
4. FACTORS AFFECTING OUTCOME 1172
a) Age 1172
b) Other 1172
VII. COMPLEMENTARY AND ALTERNATIVE MEDICINES 1172
VIII. SUMMARY AND RECOMMENDATIONS 1173
1. SUMMARY 1173
2. RECOMMENDATIONS FOR PRACTICE 1173
a) Lifestyle Intervention 1173
b) PFMT (principal recommendation) 1173
c) PFMT (other recommendation) 1173
IX. FUTURE RESEARCH DIRECTIONS 1174
a) Lifestyle Intervention: 1174
b) Pelvic floor muscle training (PFMT) 1175
c) Vaginal cones (VC) 1175
d) Electrical stimulation (EStim) and magnetic stimulation (MStim) 1175
e) Scheduled voiding regimes, especially bladder training (BT) 1175
B. PELVIC ORGAN PROLAPSE (POP) 1175
I. LIFESTYLE INTERVENTIONS 1176

1. PREVENTION 1176
a) Quality of data 1176
b) Results 1179
c) Summary 1181
2. TREATMENT 1181
II. PHYSICAL THERAPIES 1181
1. PREVENTION 1181
a) Quality of data 1181
b) Results 1181
c) Summary 1182
2. TREATMENT 1182
a) Quality of data 1182
b) Results 1185
c) Summary 1186
d) Recommendations 1186
III. PESSARIES 1186
1. QUALITY OF DATA 1187
2. OUTCOME 1189
a) Patient reported outcomes 1189
IV. SUMMARY AND RECOMMENDATIONS 1191
1. RECOMMENDATIONS FOR PRACTICE 1191
2. FUTURE RESEARCH DIRECTIONS 1191
a) Lifestyle interventions 1191
b) Pelvic floor muscle training (PFMT) 1191
c) Pessaries 1195
C. URINARY INCONTINENCE IN MEN 1195
I. LIFESTYLE INTERVENTIONS 1196
II. PELVIC FLOOR MUSCLE TRAINING (PFMT) 1196
1. PREOPERATIVE RP PFMT 1196
2. PREOPERATIVE AND/OR POSTOPERATIVE RP PFMT, POST RP CONTINENCE STATUS NOT ESTABLISHED PRIOR TO INTERVENTION 1196
a) Preoperative PFMT instruction with postoperative home PFMT versus control 1196
b) Pre-operative PFMT instruction followed by supervised post-operative PFMT versus post-operative PFMT 1201
c) Post-operative PFMT immediately after catheter removal (no pre-operative instruction) 1201
3. POSTOPERATIVE RP PFMT FOR INCONTINENT MEN 1202
a) PFMT with digital rectal feedback (DRE) after radical prostatectomy 1202
b) PFMT with BF after radical prostatectomy 1203
c) PFMT plus or minus BF with EStim or MStim after radical prostatectomy 1204
d) PFMT compared to other interventions after radical prostatectomy 1206
4. PREOPERATIVE TURP PFMT 1206
5. PREOPERATIVE AND/OR POSTOPERATIVE TURP PFMT 1206
6. POSTOPERATIVE TURP PFMT FOR INCONTINENT MEN 1207
7. PFMT FOR OTHER LUTS 1207
a) PFMT for post micturition dribble (PMD) 1207
8. FACTORS AFFECTING OUTCOME 1207
III. ELECTRICAL STIMULATION (ESTIM) 1207
1. PREVENTION OF UI 1208
2. TREATMENT OF UI 1208
a) Is EStim better than no treatment, placebo or control treatments? 1208
b) Is one approach to EStim better than another? 1208
c) Is EStim better than other treatments? 1209
d) Does the addition of EStim to other treatments add benefit? 1209
3. OTHER LUTS 1209
4. FACTORS AFFECTING OUTCOME 1209
a) Age 1209
b) Other 1209
IV. MAGNETIC STIMULATION (MSTIM) 1209
1. PREVENTION OF UI 1210
2. TREATMENT OF UI 1210
a) Is MStim better than no treatment, placebo or control treatment? 1210
b) Is one approach to MStim better than another? 1210
c) Is MStim better than other treatments? 1210
V. SCHEDULED VOIDING REGIMENS 1210
1. PREVENTION OF UI 1210
2. TREATMENT OF UI 1210
a) Bladder training 1210
b) Timed voiding 1210
3. OTHER LUTS 1211
4. FACTORS AFFECTING OUTCOME 1211
a) Age 1211
b) Other 1211
VI. COMPLEMENTARY AND ALTERNATIVE MEDICINES 1211
1. PREVENTION OF UI 1211
2. TREATMENT UI 1211
a) What is the most effective acupuncture protocol? 1211
b) Acupuncture versus no treatment, sham acupuncture or any other treatment 1211
3. OTHER LUTS 1211
4. FACTORS AFFECTING OUTCOME 1211
VII. SUMMARY 1212
1. RECOMMENDATIONS FOR PRACTICE 1212
2. FUTURE RESEARCH DIRECTIONS 1212
a) Lifestyle interventions 1212
b) Pelvic floor muscle training (PFMT) 1212
c) Electrical stimulation (EStim) and magnetic stimulation (MStim) 1213
d) Scheduled voiding regimens 1213
APPENDIX 1 1214
TERMINOLOGY 1214
APPENDIX 2 1214
REVIEW OF THE LITERATURE/SEARCH TERMS 1214
REFERENCES 1215

Committee 13
Surgical Treatment of Urinary Incontinence in Men

I. INTRODUCTION 1231
II. EVALUATION PRIOR TO SURGICAL THERAPY 1232
III. INCONTINENCE AFTER RADICAL PROSTATECTOMY FOR PROSTATE CANCER 1234
1. INCIDENCE AND PREVALENCE 1234
2. RISK FACTORS 1235
3. PATHOPHYSIOLOGY 1238
4. SURGICAL AND MINIMALLY INVASIVE TREATMENTS 1239
a) Urethral Bulking Agents 1239
b) Male Sling 1240
c) Adjustable Balloons 1245
d) Artificial Urinary Sphincter 1246
5. TIMING OF SURGICAL INTERVENTION 1248
IV. INCONTINENCE AFTER PROSTATECTOMY FOR BENIGN DISEASE 1248
1. INCIDENCE AND RISK FACTORS 1248
2. TIMING OF SURGICAL INTERVENTION 1249
3. SURGICAL TREATMENT OPTIONS 1249
a) Artificial Sphincter 1249
b) Injectable Agents 1249
c) Male Sling Procedures 1250
V. INCONTINENCE AFTER EXTERNAL BEAM RADIOTHERAPY ALONE AND IN COMBINATION WITH SURGERY FOR PROSTATE CANCER 1250

1. SURGICAL TREATMENT 1251
VI. INCONTINENCE AFTER OTHER TREATMENT FOR PROSTATE CANCER AND NEOBLADDER FOR BLADDER CANCER 1251
1. BRACHYTHERAPY 1251
2. CRYOSURGICAL ABLATION OF THE PROSTATE 1251
3. HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) 1251
4. INCONTINENCE AFTER NEOBLADDER CONSTRUCTION 1253
VII. TRAUMATIC INJURIES OF THE URETHRA AND PELVIC FLOOR 1253
VIII. CONTINUING PEDIATRIC PROBLEMS INTO ADULTHOOD: THE EXSTROPHY-EPISPADIAS COMPLEX AND OTHER CONGENITAL ANOMALIES 1254
1. EARLY MANAGEMENT OF EXSTROPHY AND EPISPADIAS 1254
2. LATE BLADDER FUNCTION 1255
3. MANAGEMENT OF INCONTINENCE 1256
a) Investigation 1256
b) Medical Management 1256
c) Bulking Agents For The Bladder Outflow 1256
d) Surgical Management 1257
e) Diversion 1257
4. RECOMMENDATIONS 1258
IX. DETRUSOR OVERACTIVITY AND REDUCED BLADDER CAPACITY 1258
1. REFRACTORY URGENCY INCONTINENCE AND IDIOPATHIC DETRUSOR OVERACTIVITY 1258
a) Botulinum toxin A injection in the bladder 1260
b) Electrical stimulation and neuromodulation 1263
c) Surgical treatment by detrusor myectomy and augmentation 1265
2. REDUCED BLADDER CAPACITY 1265
X. URETHROCUTANEOUS AND RECTOURETHRAL FISTULAE 1266
1. URETHROCUTANEOUS FISTULA (UCF) 1266
a) Acquired UCF 1266
b) Management of UCF 1266
2. RECTOURETHRAL FISTULAS (RUF) 1266
a) Congenital RUF 1267
b) Acquired RUF 1267
c) Diagnosis of RUF 1269
d) Therapy of RUF 1269
e) Surgical Approaches 1270
f) Summary 1275
XI. THE ARTIFICIAL URINARY SPHINCTER (AUS) 1275
1. AVAILABILITY AND COST 1275
2. INDICATIONS 1275
3. SURGICAL TECHNIQUES 1276
4. COMPLICATIONS 1276
a) Incontinence 1276
b) Mechanical failure 1278
c) Erosion and/or infection 1278
d) Rare complications 1278
5. DURABILITY OF AUS COMPONENTS 1278
6. DIAGNOSTIC PROCEDURES RELATED TO ARTIFICIAL SPHINCTER FAILURE 1279
7. TREATMENT OF COMPLICATIONS 1281
a) Atrophy of the urethra 1281
b) Mechanical failure 1281
c) Infection 1281
d) Erosion 1281
8. CONSENSUS PROTOCOL FOR FOLLOW-UP OF PATIENTS WITH AUS 1282
XII. SUMMARY AND RECOMMENDATIONS 1282
1. EVALUATION OF MALE INCONTINENT PATIENTS 1282
2. INCONTINENCE POST-PROSTATECTOMY FOR BPO AND POST-RADICAL PROSTATECTOMY FOR PROSTATE CANCER 1282
3. INCONTINENCE FOLLOWING OTHER TREATMENTS FOR PROSTATE CANCER 1283
4. INCONTINENCE FOLLOWING PELVIC TRAUMA (LEVEL OF EVIDENCE 3; GRADE OF RECOMMENDATION C) 1283
5. INCONTINENCE IN ADULT EPISPADIAS-EXSTROPHY COMPLEX (LEVEL OF EVIDENCE 3; GRADE OF RECOMMENDATION C) 1283
6. REFRACTORY URGENCY INCONTINENCE AND DETRUSOR OVERACTIVITY 1283
7. REDUCED CAPACITY BLADDER 1283
8. URETHROCUTANEOUS FISTULA AND RECTOURETHRAL FISTULA (LEVEL OF EVIDENCE 3; GRADE OF RECOMMENDATION C) 1283
9. MANAGEMENT OF AUS COMPLICATIONS (LEVEL OF EVIDENCE 3; GRADE OF RECOMMENDATION C) 1283
10. NEW TECHNOLOGIES (LEVEL OF EVIDENCE C; GRADE OF RECOMMENDATION D) 1284
REFERENCES 1284

Committee 14
Surgery for Urinary Incontinence in Women

A. Introduction 1309
I. SURGERY FOR STRESS INCONTINENCE (INCLUDING COMPLICATIONS) 1309
1. URETHRAL BULKING AGENTS 1309
2. RETROPUBIC MID-URETHRAL SLINGS (MUS) 1311
a) Retropubic MUS vs. no treatment 1312
b) Retropubic MUS vs. open colposuspension 1312
c) Retropubic MUS vs. laparoscopic colposuspension 1315
d) Retropubic MUS vs. traditional sling 1316
e) Retropubic MUS vs. retropubic MUS 1316
f) Retropubic MUS vs. transobturator mus 1317
g) Other studies 1322
h) CONCLUSIONS / RECOMMENDATIONS 1323
3. TRANSOBTURATOR MID-URETHRAL SLINGS 1323
a) Evolution of the TOT including proposed advantages 1323
b) Initial prospective cohort trials 1324
c) Transobturator Outside-in versus Inside-out 1325
d) Comparator Trials: Transobturator versus Retropubic MUS in the Index Patient 1325
e) Comparator Trials: Transobturator versus Retropubic MUS in patients with Intrinsic Sphincter Deficiency (ISD) 1326
f) Complications of Obturator Slings 1327
g) Transobturator Slings in Special Populations 1327
h) Conclusion and recommendation 1330
4. SINGLE INCISION MINI SLINGS (SIS) 1330
5. TRADITIONAL SLING PROCEDURES 1331
a) Traditional sling vs. bulking agent 1332
b) Traditional sling vs. colposuspension 1335
c) Traditional sling vs. traditional sling 1336
d) Traditional sling vs. midurethral sling 1338
e) CONCLUSIONS / RECOMMENDATIONS 1339
6. LAPAROSCOPIC COLPOSUSPENSION 1339
a) Laparoscopic versus open colposuspension 1339
b) Laparoscopic colposuspension versus other techniques 1341
c) Different techniques of laparoscopic colposuspension 1341
d) Cost effectiveness of laparoscopic colposuspension 1341
e) Complications of laparoscopic colposuspension 1341
f) Longevity of laparoscopic colposuspension 1342
g) Summary 1342
h) Recommendations 1342

II. STRESS INCONTINENCE AND PELVIC ORGAN PROLAPSE 1342
1. OVERT SUI WITH POP 1343
2. OCCULT SUI WITH POP 1344
3. NO OVERT OR OCCULT SUI AND POP 1344
4. UUI AND POP 1346
5. CONCLUSIONS 1346
III. NEUROMODULATION 1346
1. SACRAL NEUROMODULATION 1346
a) Recent Cochrane review 1346
b) Long term results 1347
c) Conclusion and Recommendations 1350
2. PERCUTANEOUS TIBIAL NERVE STIMULATION (PTNS) 1350
a) Efficacy 1350
b) PTNS vs Placebo (sham device) 1350
c) PTNS vs tolterodine ER 1351
d) Long term data 1351
e) Mode of action 1352
f) Neurogenic DO 1352
g) CONCLUSION AND RECOMMENDATIONS 1352
IV. ENTEROCYSTOPLASTY 1352
V. AUTO AUGMENTATION 1353
VI. URETHRAL DIVERTICULUM 1354
1. PREOPERATIVE STAGING 1354
2. TREATMENT 1354
3. RECOMMENDATIONS 1356
VII. ARTIFICIAL URINARY SPHINCTER IN WOMEN 1356
VIII. CONFOUNDING VARIABLES 1358
1. INTRODUCTION 1358
2. AGE 1358
3. RACE 1359
4. OBESITY 1359
5. PSYCHIATRIC ILLNESS 1359
6. ACTIVITY 1359
7. PREVIOUS CONTINENCE SURGERY 1359
8. CONCOMITANT HYSTERECTOMY 1360
9. SEVERITY AND DURATION OF SYMPTOMS 1360
10. DETRUSOR OVERACTIVITY AND STRESS INCONTINENCE 1360
11. URETHRAL OCCLUSIVE FORCES 1360
12. SURGEON'S EXPERIENCE 1361
13. ADJUVANT OESTROGEN THERAPY 1361
IX. CLINICAL TRIAL OUTCOMES USED IN STRESS URINARY INCONTINENCE RESEARCH 1361
REFERENCES 1364

Committee 15
Pelvic Organ Prolapse Surgery

I. INTRODUCTION 1379
II. PREVALENCE AND INCIDENCE OF POP 1379
III. OUTCOME ASSESSMENT 1381
1. OUTCOME ASSESSMENT: ANATOMY 1382
2. OUTCOME ASSESSMENT: SYMPTOMS 1382
3. OUTCOME EVALUATION: QUALITY OF LIFE 1383
4. OUTCOME ASSESSMENT: REOPERATION 1383
a) Primary prolapse surgery/different site 1383
b) Repeat surgery 1384
c) Surgery for Complications 1384
d) Surgery for non-prolapse related conditions 1384
5. DEFINING TREATMENT SUCCESS 1384
IV. ANTERIOR COMPARTMENT SURGERY 1385
1. NATIVE TISSUE REPAIRS 1385
2. SYNTHETIC GRAFTS IN ANTERIOR COMPARTMENT SURGERY 1387
3. BIOLOGIC GRAFTS ANTERIOR COMPARTMENT SURGERY 1390
V. UTERINE PRESERVATION DURING POP SURGERY 1393
1. PATIENT SELECTION 1393
2. VAGINAL HYSTEROPEXY 1393
a) The Manchester procedure 1393
b) Sacrospinous Hysteropexy 1394
c) Vaginal Mesh Hysteropexy 1395
3. ABDOMINAL HYSTEROPEXY 1395
a) Abdominal Sacral Hysteropexy 1396
b) Laparoscopic sacral hysteropexy 1396
c) Laparoscopic Uterosacral Hysteropexy 1397
d) Hysterectomy at time of sacral colpopexy 1398
4. PREGNANCY AND HYSTEROPEXY 1398
VI. APICAL SUPPORT PROCEDURES 1400
1. SACROSPINOUS LIGAMENT SUSPENSION (SSLS) 1400
2. UTEROSACRAL LIGAMENT SUSPENSION (USLS) 1400
3. MAYO/MCCALL'S CULDOPLASTY 1403
4. LEVATOR MYORRHAPHY 1403
5. ILIOCOCCYGEUS FASCIA FIXATION 1403
6. TRANSVAGINAL MESH APICAL PROLAPSE 1404
7. SACRAL COLPOPEXY 1405
a) Abdominal Sacral Colpopexy (ASC) 1405
b) Abdominal sacral colpopexy (ASC) versus sacrospinous ligament suspension (SSLS) 1405
c) Laparoscopic Sacral Colpopexy (LSC) 1405
d) Robotic Sacral Colpopexy(RSC) 1408
8. OBLITERATIVE PROCEDURES: LEFORT COLPOCLEISIS, TOTAL COLPOCLEISIS 1409
VII. SURGERY FOR POSTERIOR VAGINAL WALL PROLAPSE 1411
1. ANATOMY OF THE POSTERIOR VAGINAL WALL 1411
2. ANATOMIC DEFECTS THAT MAY CONTRIBUTE TO PROLAPSE OF THE POSTERIOR VAGINAL WALL 1411
3. MIDLINE PLICATION OR TRADITIONAL POSTERIOR COLPORRAPHY 1412
4. SITE SPECIFIC DEFECT REPAIR 1412
5. TRANSANAL REPAIR OF RECTOCELE 1413
6. GRAFT AUGMENTED RECTOCELE 1414
7. MODIFIED SACROCOLPOPEXY 1414
VIII. PELVIC ORGAN PROLAPSE SURGERY AND BLADDER FUNCTION 1415
1. CONTINENT WOMEN UNDERGOING POP SURGERY. WHAT IS THE RISK OF DE NOVO SUI AND IS CONTINENCE SURGERY REQUIRED? 1415
2. POP SURGERY AND STRESS URINARY INCONTINENT WOMEN 1416
3. SHOULD WOMEN UNDERGOING POP SURGERY WITH OCCULT SUI IDENTIFIED PRE-OPERATIVELY UNDERGO CONTINENCE SURGERY AT TIME OF POP SURGERY? 1417
4. OVERACTIVE BLADDER (OAB) SYMPTOMS 1417
5. VOIDING PROBLEMS 1418
IX. COMPLICATIONS AND METHODS OF PREVENTION 1420
1. CLASSIFICATION OF COMPLICATIONS 1420
2. REOPERATION AFTER VAGINAL MESH SURGERY 1420
3. REOPERATION AFTER ABDOMINAL SURGERY 1421
4. VAGINAL MESH EXPOSURE 1421
5. VISCERAL (BLADDER, RECTUM) MESH EXPOSURE 1422
6. INFECTION, ABSCESS, CELLULITIS, SPONDYLODISCITIS 1422
7. PAINFUL MESH CONTRACTION 1422
8. OTHER COMPLICATIONS 1423
9. METHODS OF PREVENTION 1423
a) Influence of non specific factors on mesh-related complications (obesity, smoking, age, sexual activity) 1423

b) Oestrogen therapy 1423
c) Antibiotic prophylaxis 1423
d) Mesh implantation and visceral injury 1423
e) Surgeon training 1423
10. VAGINAL MESH SURGERY 1423
a) Choose the right mesh for vaginal surgery 1423
b) Interest in mesh kits 1424
c) Concomitant hysterectomy 1424
d) Surgical incision 1424
11. ABDOMINAL SACROCOLPOPEXY 1424
a) Choice of surgical route for sacrocolpopexy 1424
b) Choose the right mesh for abdominal surgery 1424
c) Choose the right fixation to the promontory, vaginal wall and levator ani 1425
d) Concomitant hysterectomy 1425
12. PERITONEAL CLOSURE 1425
13. TREATMENT OF VAGINAL MESH EXPOSURE 1425
X. PELVIC ORGAN PROLAPSE AND SEXUAL FUNCTION 1426
1. SEXUAL FUNCTION AFTER PROLAPSE SURGERY WITHOUT MESH 1427
2. SEXUAL FUNCTION AFTER PROLAPSE SURGERY WITH MESH 1427
XI. ECONOMIC EVALUATION 1429
REFERENCES 1430

Committee 16
Assessment and Conservative Management of Faecal Incontinence and Quality of Life in Adults

I. INTRODUCTION 1445
II. CLINICAL ASSESSMENT 1445
1. SEARCH STRATEGY 1446
2. HISTORY 1446
a) Type of incontinence 1446
b) Etiology 1446
3. PHYSICAL EXAMINATION 1446
a) General, perianal, and digital rectal exam 1446
b) Proctoscopy 1447
c) Vaginal examination 1447
d) Recommendations for practice 1447
e) Recommendations for research 1447
III. SPECIALIZED TESTING 1447
1. ANORECTAL MANOMETRY 1447
a) Indications 1447
b) Equipment and testing 1448
c) Anal resting pressure 1448
d) Squeeze increase 1448
e) Recto-anal inhibitory reflex 1448
f) Rectal sensation and compliance 1448
g) Recommendations for practice 1448
h) Recommendations for research 1448
2. ENDOANAL ULTRASOUND IMAGING 1449
a) Introduction 1449
b) Endoanal ultrasonography technique 1449
c) Endoanal ultrasonography in faecal incontinence 1449
d) Alternative Ultrasound Modalities in Faecal Incontinence 1450
e) Summary of Evidence 1450
f) Recommendations for practice 1450
g) Recommendations for research 1450
3. MAGNETIC RESONANCE IMAGING 1450
a) Introduction 1450
b) Normal anal sphincter anatomy at MRI 1450
c) Anal sphincter defects on MRI 1450
d) Anal sphincter atrophy at MRI 1451
e) Role of MRI in the assessment of faecal incontinence 1451
f) Recommendations for practice 1451
g) Recommendations for research 1451
4. DEFECOGRAPHY 1451
a) Introduction 1451
b) Examination technique 1451
c) Parameters studied at defecography 1452
d) Recommendations for practice 1452
e) Recommendations for research 1452
5. CLINICAL NEUROPHYSIOLOGIC TESTING 1452
a) Introduction 1452
b) Types of neurophysiologic testing for faecal incontinence 1452
c) Elelectromyography 1453
d) Pudendal nerve conduction testing 1453
e) Sensory system testing 1453
f) Anal mucosal electrosensitivity 1453
g) Recommendations for practice 1453
h) Recommendations for research 1453
IV. EDUCATION AND LIFESTYLE INTERVENTIONS 1453
1. BACKGROUND 1453
2. SEARCH 1454
3. REVIEW OF EVIDENCE ON THE EFFECT OF EDUCATION AND LIFESTYLE CHANGES ON FAECAL INCONTINENCE 1454
a) Weight loss 1454
b) Smoking 1454
c) Medication side-effects 1454
d) Toilet facilities 1455
e) Patient and care-giver education and attitudes 1455
f) Complementary therapies 1455
g) Summary of evidence on education and lifestyle interventions in faecal incontinence 1456
h) Recommendations for practice 1456
i) Recommendations for research 1456
V. DIET AND FLUIDS 1456
1. INTRODUCTION 1456
2. LITERATURE SEARCH 1456
a) Criteria for considering studies for this review 1457
3. REVIEW OF EVIDENCE ON DIET AND FLUIDS 1457
a) Diet modification 1457
b) Fluids 1458
c) Lactose, yogurt, sorbitol, fructose, caffeine, and alcohol 1458
d) Prebiotics, probiotics, and synbiotics 1458
e) Dietary fibre 1458
VI. BOWEL MANAGEMENT AND RETRAINING PROGRAMMES 1461
1. BACKGROUND 1461
2. SEARCH 1461
3. REVIEW OF EVIDENCE ON BOWEL MANAGEMENT AND RETRAINING PROGRAMMES 1462
a) Bowel habit and toileting 1462
b) Resisting urgency 1462
c) Evacuation training 1462
d) Rectal irrigation 1462
e) Combinations of therapies 1463
f) Summary of evidence on bowel management and retraining programs 1463
g) Recommendations for practice 1463
h) Recommendations for research 1463
VII. TREATMENT WITH MEDICATION 1463
1. GOALS 1463
2. SEARCH METHODS 1464
3. REVIEW OF EVIDENCE ON MEDICATIONS FOR FAECAL INCONTINENCE 1464
a) Treatment of diarrhoea-associated faecal incontinence with antidiarrhoeal drugs 1464
b) Drugs for increasing anal canal pressure in patients with passive faecal incontinence 1466
c) Drug treatment of constipation-associated faecal incontinence 1466
VIII. PELVIC FLOOR MUSCLE EXERCISES, BIOFEEDBACK, AND ELECTRICAL STIMULATION 1467

1. PELVIC FLOOR MUSCLE TRAINING 1467
2. BIOFEEDBACK 1467
3. ELECTRICAL STIMULATION 1467
4. METHODS 1467
5. SUMMARY OF ICI 2008 ASSESSMENT 1468
a) ICI 2008 assessment of pelvic floor muscle exercises 1468
b) ICI 2008 assessment of biofeedback therapy [173] 1468
c) ICI 2008 assessment of tibial nerve transcutaneous electrical stimulation from non-implantable devices 1469
6. UPDATE: REVIEW OF EVIDENCE FOR 2008-2012 1469
7. TIBIAL NERVE PERCUTANEOUS STIMULATION 1471
8. SUMMARY OF EVIDENCE 1471
9. RECOMMENDATIONS FOR PRACTICE 1471
10. RECOMMENDATIONS FOR RESEARCH 1471
IX. QUALITATIVE RESEARCH ON THE EXPERIENCE OF FAECAL INCONTINENCE AND QUALITY OF LIFE 1471
1. BACKGROUND 1471
2. CRITERIA FOR EVALUATION 1472
a) Type of study – The qualitative evidence pyramid 1472
b) Criteria for evaluation of qualitative studies 1472
c) Levels of evidence 1473
d) Grades of recommendation 1473
3. SEARCH METHOD 1473
4. REVIEW OF EVIDENCE ON THE EXPERIENCE OF FAECAL INCONTINENCE AND QUALITY OF LIFE 1473
5. LIVING WITH FAECAL INCONTINENCE AND RELATIONSHIPS – SUMMARY OF EVIDENCE 1474
a) Recommendations for practice 1475
b) Recommendations for research 1475
6. LIVING WITH FAECAL INCONTINENCE AND TIME AND PLANNING – SUMMARY OF EVIDENCE 1475
a) Recommendations for practice 1476
b) Recommendations for research 1476
7. LIFE LIVING WITH FAECAL INCONTINENCE AND BODILY SYMPTOMS, SELF ESTEEM AND BODY IMAGE – SUMMARY OF EVIDENCE 1476
a) Recommendations for practice 1477
b) Recommendations for research 1477
8. LIVING WITH FAECAL INCONTINENCE AND SEXUALITY – SUMMARY OF EVIDENCE 1477
a) Recommendations for practice 1477
b) Recommendations for research 1478
9. LIVING WITH FAECAL INCONTINENCE AND DIET ISSUES – SUMMARY OF EVIDENCE 1478
a) Recommendations for practice 1478
b) Recommendations for research 1478
X. ALGORITHM 1478
REFERENCES 1479

Committee 17
Surgery For Faecal Incontinence

I. INTRODUCTION 1489
II. SURGERY FOR ADULT FAECAL INCONTINENCE 1490
1. SPHINCTER REPAIR 1490
2. SPHINCTEROPLASTY 1491
3. POST-ANAL REPAIR 1493
4. NON-STIMULATED MUSCLE TRANSPOSITION 1494
5. STIMULATED MUSCLE TRANSPOSITION 1494
6. ARTIFICIAL ANAL SPHINCTER 1496
a) Functional Results of ABS 1497
b) Surgical Risks and Postoperative Complications of ABS 1498
7. SACRAL NERVE STIMULATION 1499
a) Technique 1499
b) Patient Selection and Indications 1499
c) Mechanism of Action 1500
d) Outcome 1501
e) Quality of Life 1503
f) Cost Benefit 1504
g) Safety 1504
8. POSTERIOR TIBIAL NERVE STIMULATION 1505
a) Introduction 1505
b) Techniques 1505
c) Patient Selection and Indications 1505
d) Mechanism of Action 1506
e) Outcome 1506
f) Quality of Life 1506
g) Safety 1506
9. INJECTABLE BIOMATERIALS 1506
10. COLOSTOMY 1510
11. PUBORECTAL SLING 1511
III. SURGERY FOR PAEDIATRIC FAECAL INCONTINENCE 1512
1. ANORECTAL MALFORMATIONS 1512
2. OTHER CAUSES OF FAECAL INCONTINENCE 1513
3. OTHER OPERATIONS 1513
IV. CONCLUSIONS 1514
1. SPHINCTER REPAIR (GRADE B) 1514
2. SPHINCTEROPLASTY (GRADE B) 1514
3. POST-ANAL REPAIR (GRADE C) 1514
4. NON-STIMULATED MUSCLE TRANSPOSITION (GRADE C) 1514
5. STIMULATED MUSCLE TRANSPOSITION (GRADE C) 1514
6. ARTIFICIAL ANAL SPHINCTER (GRADE B) 1514
7. SACRAL NERVE STIMULATION (GRADE B) 1514
8. POSTERIOR TIBIAL NERVE STIMULATION (GRADE D) 1514
9. INJECTABLE BIOMATERIALS (GRADE C) 1514
10. COLOSTOMY (GRADE C) 1514
11. PUBORECTAL SLING (GRADE D) 1514
12. SURGERY FOR PAEDIATRIC FAECAL INCONTINENCE (GRADE C) 1514
V. RESEARCH PRIORITIES 1515
1. BASIC SCIENCE AND PATHOPHYSIOLOGY (METTRE 1. 2. ETC EN CORPS 9) 1515
2. CELLULAR THERAPY 1515
3. OUTCOME MEASURES 1515
4. CLINICAL TRIALS 1515
5. DECISION AND COST-BENEFIT ANALYSIS 1515
6. TREATMENT DELIVERY 1515
REFERENCES 1516

Committee 18
Fistula

GENERAL INTRODUCTION 1529
A. Obstetrical fistula 1529
I. INTRODUCTION 1529
II. WOMEN, FISTULA SURGEONS, NGOS AND GOVERNMENTS 1529
1. EPIDEMIOLOGY OF VVF 1530
2. PREVENTION OF VVF 1530
3. UNMET NEEDS IN VVF 1532
4. MANAGEMENT OF NEW AND ESTABLISHED VVFS 1533
5. CLASSIFICATION OF VVF 1533
6. MANAGEMENT OF THE COMPLICATIONS OF VVF 1535
7. SOCIAL RE-INTEGRATION OF TREATED WOMEN 1536
B. Non-obstetrical fistula 1538
I. INTRODUCTION 1538
II. EPIDEMIOLOGY 1538
1. POST-GYNAECOLOGICAL SURGERY 1538
2. ONCOLOGICAL FISTULA 1540
3. CANCER SURGERY 1540

4. RADIATION FISTULA 1541
5. CHEMOTHERAPY 1543
6. COMBINATION THERAPIES 1543
III. URETERIC FISTULA 1543
IV. FISTULA INVOLVING THE GI TRACT 1543
V. DIAGNOSIS OF FISTULA 1545
1. CLINICAL DIAGNOSIS 1545
a) The role of cystoscopy in preventing and diagnosing VVF 1546
b) Imaging 1546
2. DIAGNOSIS OF GI FISTULA 1546
3. RECOMMENDATIONS 1547
VI. MANAGEMENT OF VESICO-VAGINAL FISTULA 1547
1. CONSERVATIVE MANAGEMENT 1547
a) Immediate management by catheterisation or defunctionalizing 1547
b) Pharmacotherapies to assist fistula closure 1548
c) Palliation and skin care 1549
d) Nutrition 1549
e) Physiotherapy 1549
f) Antimicrobial therapy 1549
g) Bowel preparation 1549
h) Counselling 1549
2. SURGICAL MANAGEMENT 1550
a) Timing of surgery 1550
b) Outcomes from treatment and follow-up 1550
c) Surgical approaches 1551
c) Adjuvant Techniques in the Repair of VVF: Tissue Interposition 1555
3. POST-OPERATIVE MANAGEMENT 1555
a) Catheter type 1555
b) Duration 1555
4. MANAGEMENT OF RADIATION FISTULA 1558
a) Diversion procedures 1558
b) Repair techniques 1558
c) Interposition grafts 1559
d) Other management approaches 1559
VII. MANAGEMENT OF GI FISTULA 1560
1. LITERATURE REVIEW 1560
2. NON-SURGICAL MANAGEMENT 1560
3. SURGICAL MANAGEMENT 1561
4. RECOMMENDATIONS 1562
VIII. MANAGEMENT OF URETERIC FISTULA 1562
1. GENERAL PRINCIPLES 1562
2. EVIDENCE QUALITY 1562
3. EVIDENCE SUMMARY 1562
a) Management of Specific Fistula 1562
IX. MANAGEMENT OF URETHRO-VAGINAL FISTULA 1565
1. INTRODUCTION 1565
2. AETIOLOGY 1565
3. DIAGNOSIS 1565
4. SURGICAL REPAIR 1565
a) Vaginal approach 1565
b) Posterior approach 1568
c) Abdominal approach 1568
5. COMPLICATIONS 1568
6. FOLLOW UP 1568
7. RECOMMENDATIONS 1568
REFERENCES 1569

Committee 19
Bladder Pain Syndrome

I. INTRODUCTION 1583
1. EVIDENCE ACQUISITION 1583
2. DEFINITION 1583
II. HISTORY/NOMENCLATURE/ TAXONOMY 1584
1. HISTORICAL NOTES 1584
2. NOMENCLATURE AND TAXONOMY 1586
III. EPIDEMIOLOGY 1588
1. EARLY EPIDEMIOLOGICAL STUDIES: 1589
2. PATIENT SELF REPORT SURVEYS: 1589
3. PHYSICIAN DIAGNOSES STUDIES 1589
4. SYMPTOM BASED SURVEYS 1590
5. INCIDENCE: 1591
6. OTHER CONSIDERATIONS 1591
a) Children 1591
b) Men 1592
c) Overlapping Non bladder syndromes 1592
d) Progression 1592
IV. ETIOLOGY 1592
1. MAST CELL ACTIVATION 1593
2. INCREASED PERMEABILITY OF THE UROTHELIUM DUE TO UROTHELIAL DYSFUNCTION/GAG-LAYER DEFECTS 1593
3. INHIBITION OF UROTHELIAL BLADDER CELL PROLIFERATION 1593
4. AUTOIMMUNE MECHANISMS 1593
5. INFECTION 1594
6. NEUROBIOLOGY/PELVIC CROSS-TALK 1594
7. TOXIC AGENTS 1594
8. HYPOXIA 1594
9. THE ROLE OF GENETICS IN BPS 1595
10 . CONCLUSIONS: 1595
V. PATHOLOGY 1595
VI. DIAGNOSIS 1598
1. HISTORY 1598
2. PHYSICAL EXAMINATION 1598
3. PAIN MAPPING 1598
4. LABORATORY TESTING 1598
5. SYMPTOM EVALUATION 1599
6. URODYNAMICS 1599
7. POTASSIUM TESTING 1599
8. CYSTOSCOPY AND HYDRODISTENSION 1600
a) Inspection 1601
b) Classification 1601
c) How useful is hydrodistention? 1601
9. MORPHOLOGY 1602
a) Biopsies 1602
b) Number of biopsies 1602
c) Biopsy handling 1602
d) Mast cell counting 1602
e) The pathology report 1602
10. BIOMARKERS 1603
11. CONFUSABLE DISEASES 1603
VII. CLASSIFICATION 1604
VIII. CONSERVATIVE TREATMENT 1605
1. BEHAVIORAL MODIFICATION 1605
2. PHYSICAL THERAPY 1605
3. STRESS REDUCTION 1606
4. DIETARY MANIPULATION 1606
IX. ORAL THERAPY 1606
1. ANALGESICS 1607
2. ANTIDEPRESSANTS 1608
a) Amitriptyline 1608
b) Doxepin, desipramine, duloxetine 1608
3. ANTIHISTAMINES 1608
a) Hydroxyzine 1608
b) Cimetidine 1609
4. IMMUNOSUPPRESSANTS 1609
a) Cyclosporine 1609
b) Suplatast Tosilate 1609
c) Azathioprine and Chloroquine derivatives 1609
d) Corticosteroids 1609
5. SODIUM PENTOSANPOLYSULFATE 1609
6. OTHER ORAL MEDICATIONS THAT HAVE BEEN USED FOR BPS 1610
a) L-arginine 1610
b) Quercetin 1611

c) Antibiotics *1611*
d) Methotrexate *1611*
e) Montelukast *1611*
f) Nifedipine *1611*
g) Misoprostol *1611*
h) Tanezumab *1612*
X. INTRAVESICAL / INTRAMURAL THERAPY 1612
1. DMSO (DIMETHYL SULFOXIDE) 1612
2. HEPARIN 1612
3. HYALURONIC ACID 1613
4. CHONDROITIN SULFATE 1613
5. PENTOSAN POLYSUFATE 1613
6. VANILLOIDS (CAPSAICIN, RESINIFERATOXIN) 1614
7. BACILLUS CALMETTE-GUERIN (BCG) 1614
8. OXYBUTYNIN 1614
9. LIDOCAINE 1614
10. BOTULINUM TOXIN (INTRAMURAL) 1614
XI. NEUROMODULATION 1615
XII. PAIN EVALUATION AND TREATMENT 1616
1. EVALUATION OF PAIN: 1616
2. PHARMACOLOGIC MANAGEMENT OF CHRONIC PELVIC PAIN 1616
a) Non-acidic antipyretic analgesics *1617*
b) Acidic antipyretic analgesics *1617*
c) Neuropathic analgesics *1617*
XIII. SURGICAL THERAPY 1619
1. HYDRODISTENTION 1620
2. TRANSURETHRAL RESECTION 1620
3. CYSTOLYSIS – PERIPHERAL DENERVATION 1620
4. SYMPATHETIC DENERVATION 1620
5. PARASYMPATHETIC DENERVATION 1620
6. BOWEL SURGERY 1621
a) Bladder augmentation-cystoplasty *1621*
b) Cystoplasty with Supratrigonal Resection *1621*
c) Cystoplasty with Subtrigonal Cystectomy *1621*
7. URINARY DIVERSION WITH OR WITHOUT TOTAL CYSTECTOMY AND URETHRECTOMY 1621
XIV. CLINICAL SYMPTOM SCALES 1622
XV. OUTCOME ASSESSMENT 1625
1. THE PROBLEM 1625
2. THE PLACEBO ISSUE 1626
3. OUTCOME INTERPRETATION 1628
4. IMMPACT RECOMMENDATIONS 1628
XVI. PRINCIPLES OF MANAGEMENT 1628
1. HARMONIZATION 1628
XVII. RECOMMENDATIONS OF INTERNATIONAL CONSULTATION ON INCONTINENCE: 1629
1. HISTORY / INITIAL ASSESSMENT 1629
2. INITIAL TREATMENT 1629
3. SECONDARY ASSESSMENT 1629
4. REFRACTORY BPS 1629
XVIII. FUTURE DIRECTIONS IN RESEARCH 1633
XIX. SUMMARY 1634
1. DEFINITION 1634
2. BLADDER PAIN SYNDROME (BPS) 1634
a) Nomenclature *1634*
b) History / Initial Assessment *1634*
c) Initial Treatment *1634*
d) Secondary Assessment *1635*
e) Refractory BPS *1635*
REFERENCES 1636

Committee 20
Management Using Continence Products

I. INTRODUCTION 1653
II. OVERALL GUIDELINES FOR SELECTING CONTINENCE PRODUCTS 1654
1. PRODUCT CATEGORIES 1654
2. IDENTIFYING THE NEEDS 1654
3. PATIENT ASSESSMENT FACTORS 1656
4. MAIN USER GROUPS 1658
5. CHOOSING BETWEEN PRODUCT CATEGORIES 1658
6. SUMMARY 1658
7. RECOMMENDATIONS 1658
III. PRODUCT EVALUATION METHODOLOGY 1658
1. RESEARCH QUESTIONS 1658
a) Comparisons *1658*
b) Product representation *1664*
2. RESEARCH DESIGN 1664
a) Sample size and study power *1665*
b) Outcome variables *1665*
3. SUMMARY AND RECOMMENDATIONS 1666
4. RESEARCH PRIORITIES 1666
IV. HANDHELD URINALS 1666
1. FEMALE HANDHELD URINALS 1666
2. MALE HANDHELD URINALS 1667
3. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION 1667
4. RECOMMENDATIONS 1668
5. PRIORITIES FOR RESEARCH 1668
V. COMMODES AND BEDPANS 1668
1. RESULTS 1668
2. SUMMARY 1670
3. RECOMMENDATIONS 1670
4. PRIORITIES FOR RESEARCH 1670
VI. ABSORBENT PRODUCTS 1670
1. INTRODUCTION 1670
2. ABSORBENT PRODUCT CATEGORIES 1671
3. ABSORBENT PRODUCT MATERIALS 1675
4. ABSORBENT PRODUCT CAPACITY AND USER REQUIREMENTS 1675
5. ABSORBENT PRODUCTS FOR WOMEN WITH LIGHT URINARY INCONTINENCE 1676
a) Quality of data *1676*
b) Results *1676*
c) Summary *1678*
d) Recommendations *1678*
e) Research priorities *1679*
6. ABSORBENT PRODUCTS FOR MEN WITH LIGHT URINARY INCONTINENCE 1679
a) Recommendations *1679*
b) Research priorities *1679*
7. ABSORBENT PRODUCTS FOR MEN AND WOMEN WITH MODERATE-HEAVY URINARY INCONTINENCE 1679
a) Quality of data *1681*
b) Results *1681*
c) Summary *1683*
d) Recommendations *1684*
e) Research priorities *1684*
8. DISPOSABLE UNDERPADS 1684
a) Summary *1686*
b) Recommendations *1686*
c) Research priorities *1686*
9. WASHABLE UNDERPADS 1686
a) Summary *1686*
b) Recommendations *1686*
c) Research priorities *1686*
10. ABSORBENT PADS FOR CHILDREN WITH URINARY AND / OR FAECAL INCONTINENCE 1686
a) Summary and recommendations *1687*
b) Research priorities *1687*
11. PADS FOR FAECAL INCONTINENCE 1687
a) Recommendations *1687*
b) Research priorities *1687*
12. GENERAL RECOMMENDATIONS ON PAD SELECTION 1687
13. RECOMMENDATIONS RELATING TO WASHABLE PADS 1688

VII. SHEATHS 1689
1. PRODUCT CATEGORIES AND FEATURES 1689
2. QUALITY OF DATA 1689
3. RESULTS 1689
4. SUMMARY 1691
5. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION 1692
6. RECOMMENDATIONS 1692
7. PRIORITIES FOR RESEARCH 1692
VIII. URINE DRAINAGE BAGS AND ACCESSORIES 1692
1. PRODUCT CATEGORIES AND FEATURES 1692
2. QUALITY OF DATA 1693
3. RESULTS 1693
a) Evaluations of urine drainage bags 1693
b) Urine drainage bag suspension systems 1695
c) Infection and cross-infection issues for management of urine drainage systems for indwelling catheters. 1696
d) Long-term management of urine drainage systems and reuse of components 1697
e) Urinary drainage bag features intended to reduce the risk of cross infection 1698
f) Purple urine bag syndrome 1698
4. SUMMARY 1699
5. GENERAL POINTS FROM THE LITERATURE, INCLUDING EXPERT OPINION 1699
6. RECOMMENDATIONS 1699
7. PRIORITIES FOR RESEARCH 1699
IX. BODYWORN URINALS 1699
1. FEMALE BODYWORN URINALS 1699
2. MALE BODYWORN URINALS AND DRIBBLE CONTAINERS 1699
3. PRIORITIES FOR RESEARCH 1700
X. MECHANICAL DEVICES FOR WOMEN WITH URINARY INCONTINENCE 1700
1. DEVICES THAT OCCLUDE AT THE EXTERNAL MEATUS 1701
a) Quality of data and results 1701
b) Summary 1702
c) Recommendations 1702
d) Priorities for research 1702
2. INTRAURETHRAL DEVICES 1702
a) Quality of data and results 1703
b) Summary 1704
c) Recommendations 1704
d) Priorities for research 1704
3. INTRAVAGINAL DEVICES 1704
a) Quality of data and results 1704
b) Summary 1707
c) Recommendations 1707
d) Priorities for research 1707
4. OVERVIEW OF MECHANICAL DEVICES FOR WOMEN 1707
a) Overall summary 1707
b) Overall recommendations 1708
c) Overall priorities for research 1708
XI. MECHANICAL DEVICES FOR MEN WITH URINARY INCONTINENCE 1708
1. QUALITY OF DATA 1708
2. RESULTS 1708
3. SUMMARY 1709
4. RECOMMENDATIONS 1709
5. PRIORITIES FOR RESEARCH 1709
XII. CATHETERS 1709
1. INTERMITTENT CATHETERISATION 1709
a) Quality of data 1711
b) User characteristics: 1711
c) Catheter characteristics 1712
d) Associated risks / problems 1714
e) Catheter management 1716
f) Comparisons between intermittent and indwelling catheterisation 1718
g) Catheter use over time in persons with SCI 1718
h) Summary 1719
2. INDWELLING CATHETERISATION 1720
a) Quality of Data 1720
b) Prevalence of indwelling catheters use 1722
c) User characteristics 1724
d) Routes of catheter insertion 1724
e) Catheter characteristics 1725
f) Catheter materials 1725
g) Catheter size – catheter gauge, length and balloon size 1726
h) LTC–associated risks / problems: catheter-associated urinary tract infection (CAUTI) 1727
i) LTC-associated risks and problems: recurrent catheter blockage 1733
j) LTC-associated risks and problems: urethral trauma, bladder calculi and bladder cancer 1736
k) Catheter management strategies 1737
l) Levels of evidence relating to catheter-associated risks and complications 1745
m) Urinary catheters versus other care strategies 1746
3. CATHETER-RELATED QUALITY OF LIFE 1746
a) Changes in Bladder Management 1747
b) Embarrassment 1747
c) Sexuality 1748
d) Catheter-related Pain 1748
e) Adjustment to a Catheter 1749
f) Self-management 1749
g) Summary 1749
4. OVERALL RECOMMENDATIONS RELATING TO CATHETERS 1750
a) Intermittent catheters 1750
b) Indwelling catheters 1750
c) Catheter valves 1751
5. PRIORITIES FOR RESEARCH 1751
a) General 1751
b) Intermittent catheters 1751
c) Indwelling catheters 1751
d) Catheter valves 1752
e) Quality of life 1752
XIII. PRODUCTS FOR PREVENTING OR CONTAINING FAECAL INCONTINENCE 1752
1. PRODUCTS TO PREVENT OR CONTAIN LEAKED STOOL 1752
2. QUALITY OF DATA 1754
3. RESULTS 1755
a) Anal Plugs 1755
b) Rectal Trumpet 1756
c) Rectal Catheter Systems 1756
d) Anal Pouch 1757
4. SUMMARY 1758
5. RECOMMENDATIONS 1758
6. PRIORITIES FOR RESEARCH 1758
XIV. SKIN HEALTH AND CONTINENCE PRODUCTS 1758
1. BACKGROUND 1758
a) The role of urine and faeces in skin irritation 1759
b) Prevalence of incontinence-associated dermatitis / perineal dermatitis 1760
c) Pressure ulcers and incontinence 1761
2. CLINICAL STUDIES OF THE IMPACT OF PRODUCTS AND PRODUCT MATERIALS ON SKIN HEALTH 1762
a) Quality of data 1762
b) Results 1763
3. CLINICAL STUDIES OF SKIN-CARE PRODUCTS AND NURSING PRACTICES TO MAINTAIN OR IMPROVE SKIN HEALTH 1764
a) Quality of data 1765
b) Results 1765
4. SUMMARY 1767
5. RECOMMENDATIONS 1767
6. PRIORITIES FOR RESEARCH 1767
XV. ODOUR CONTROL PRODUCTS 1768

1. PRODUCTS FOR URINARY INCONTINENCE 1768
2. PRODUCTS FOR FAECAL INCONTINENCE 1768
3. RECOMMENDATIONS 1769
4. PRIORITIES FOR RESEARCH 1769
REFERENCES 1770

Committee 21
Continence Promotion, Education & Primary Prevention

I. LITERATURE SEARCH 1789
II. INTRODUCTION 1789
III. CONTINENCE PROMOTION AND AWARENESS 1790
1. BACKGROUND 1790
2. RAISING AWARENESS AND UNDERSTANDING 1790
3. HELP-SEEKING (CARE-SEEKING) BEHAVIOR 1791
a) Barriers to seeking care 1792
b) Gender-specific disparity 1793
c) Symptom impact and bother 1794
4. CONTINENCE PROMOTION PROGRAMS 1794
a) Creating public awareness 1795
b) Program evaluation 1796
5. RECOMMENDATIONS FOR CONTINENCE PROMOTION AND AWARENESS (GRADE D) 1797
IV. CONTINENCE ADVOCACY 1797
1. BACKGROUND 1797
2. CONTINENCE ADVOCACY WORLDWIDE 1798
a) Funding 1798
b) Collaboration 1798
3. RECOMMENDATION FOR CONTINENCE ADVOCACY (LEVEL OF EVIDENCE-3, GRADE D) 1799
V. SERVICE DELIVERY, MODELS AND ACCESSING CARE 1799
1. BACKGROUND 1799
2. NEED FOR SERVICES 1800
3. MODELS OF CARE 1800
a) Single specialist 1801
b) Nurse specialist or advisor 1801
c) Multidisciplinary resource and referral centre 1802
d) Primary care 1803
e) Other service models 1804
4. RECOMMENDATIONS FOR SERVICE DELIVERY, MODELS AND ACCESSING CARE 1807
VI. PROFESSIONAL EDUCATION 1807
1. BACKGROUND 1807
2. MEDICAL EDUCATION 1808
a) Generalists (family physicians/general practitioners/primary care physicians) 1808
b) Specialist physicians 1809
3. NURSING PROFESSIONALS 1809
a) Generalist nurses 1809
b) Specialist nurses 1810
c) Nursing assistants 1811
4. PHYSIOTHERAPY AND OTHER ALLIED HEALTH PROFESSIONALS 1811
5. IMPACT OF CLINICAL GUIDELINES 1812
a) Audits and assessments of guidelines 1814
6. RECOMMENDATIONS FOR PROFESSIONAL EDUCATION (GRADE D) 1815
VII. PRIMARY PREVENTION 1815
1. BACKGROUND 1815
2. POPULATION-BASED PREVENTION 1815
3. PREVENTION OF UI IN OLDER ADULTS 1816
4. PREVENTION OF FAECAL INCONTINENCE 1817
5. RECOMMENDATIONS FOR PRIMARY PREVENTION (GRADE C) 1817
REFERENCES 1818
APPENDIX 1. Drectory of continence organizations 1826

Committee 22
Economics of Urinary & Faecal Incontinence, and Prolapse

I. INTRODUCTION 1831
II. BACKGROUND 1831
1. PERSPECTIVE 1831
2. COUNTRY SPECIFIC ECONOMIC ISSUES 1833
3. COSTS AND TIME 1833
III. TYPES OF ECONOMIC ANALYSIS 1834
1. OVERVIEW 1834
a) Cost of illness (COI) 1834
b) Cost minimization analysis (CMA) 1834
c) Cost consequence analysis (CCA) 1834
d) Cost-effectiveness analysis (CEA) 1834
e) Cost-utility analysis (CUA) 1834
f) Cost benefit analysis (CBA) 1834
g) Summary 1834
2. DETAILS OF DECISION ANALYSIS 1835
a) Steps in a decision analysis 1836
b) Decision Tree 1837
c) Markov Model 1838
3. STATISTICAL ANALYSIS 1838
4. BUDGET IMPACT ANALYSIS 1838
IV. PRACTICAL ASPECTS OF ECONOMIC ANALYSIS IN THE CONTINENCE FIELD 1839
1. HEALTH OUTCOME MEASURES SUITABLE FOR USE IN ECONOMIC ANALYSES 1839
a) Incontinence specific outcomes 1839
b) Health Status and Quality of Life Measures 1839
c) Health value 1839
2. "DO IT YOURSELF" - HOW TO CONDUCT A COST UTILITY ANALYSIS: THE COMMITTEE'S RECOMMENDATIONS 1840
V. SUMMARY OF RECENT ECONOMIC ANALYSES 1841
1. SURGERY FOR STRESS INCONTINENCE 1841
2. SURGERY FOR URGE INCONTINENCE 1843
a) Studies regarding Botulinum Toxin A Injections (Botox A) 1843
b) Sacral nerve stimulation 1844
3. OUTPATIENT CONSERVATIVE THERAPIES 1846
4. PHARMACOTHERAPY OF URINARY INCONTINENCE 1847
a) Economics of pharmaceutical therapies 1847
5. COST IMPLICATIONS OF INCONTINENCE IN NURSING HOME SETTING 1850
6. LONGITUDINAL BURDEN OF DISEASE STUDIES 1850
7. PROLAPSE TREATMENTS, COST IMPLICATIONS 1853
8. FECAL INCONTINENCE 1854
a) Cost of illness 1854
b) Prevention 1854
c) Treatment costs 1855
VI. SUMMARY AND FUTURE RESEARCH PRIORITIES 1858
VII. APPENDIX – SEARCH STRATEGIES 1858
REFERENCES 1858

Committee 23
Research Methodology

I. INTRODUCTION 1865
1. LEVELS OF EVIDENCE 1865
2. PRIMARY GUIDING ETHICAL PRINCIPLES 1865

3. INFORMED CONSENT IS AN ETHICAL CORNERSTONE OF HUMAN SUBJECT RESEARCH 1866
4. SPECIFIC INFORMED CONSENT IS REQUIRED FOR RESEARCH PARTICIPATION. 1866
5. THE INVESTIGATOR HAS AN ETHICAL RESPONSIBILITY TO TAKE RESPONSIBILITY FOR ALL ASPECTS OF THE RESEARCH 1866
6. ENSURING PARTICIPANT SAFETY IS PARAMOUNT 1866
7. HIGH QUALITY DATA MANAGEMENT IS KEY TO PROVIDING VALID AND ETHICAL RESEARCH RESULTS [41] 1867
8. USEFUL WEBSITES 1867
9. FINANCIAL CONFLICTS OF INTEREST 1867
II. DEFINING THE RESEARCH QUESTIONS 1867
III. EXPERIMENTAL STUDIES 1867
1. RANDOMIZED CONTROLLED TRIALS 1867
a) Simple randomization 1868
b) Block randomization 1868
c) Stratified randomization 1868
d) Parallel Group Trials 1868
e) Crossover Trials 1868
f) Non-inferiority trials 1869
g) Equivalence trials 1869
h) Superiority trials 1869
2. NON-RANDOMIZED CONTROLLED CLINICAL TRIAL(S) 1869
3. PRAGMATIC AND EXPLANATORY TRIALS 1869
4. DRUG TRIALS ARE CATEGORIZED ACCORDING TO THE FOLLOWING DEFINITIONS [30, 50] 1870
a) Phase I studies 1870
b) Phase II studies 1870
c) Phase III studies 1870
d) Phase IV studies 1870
5. BIAS, BLINDING AND EFFECTS ON VALIDITY 1870
a) Blinding 1870
b) Unblinded trials 1870
c) Single blind trial 1870
d) Double blind trials 1871
IV. ELIGIBILITY CRITERIA 1871
V. SAMPLING STRATEGIES 1871
VI. DATA COLLECTION 1872
a) Baseline data 1872
b) Observations 1872
c) Tests 1872
d) Follow-up 1872
e) Quality of life measures 1872
f) Socioeconomics 1872
VII. OUTCOME MEASURES 1872
1. PRIMARY OUTCOMES 1872
2. SECONDARY OUTCOME 1873
3. TYPES OF OUTCOME MEASURES 1873
VIII. SATISTICAL CONCERNS 1874
1. SAMPLE SIZE CONSIDERATIONS 1874
2. SAMPLE SIZE CALCULATION 1874
3. THE TARGET DIFFERENCE 1875
IX. ANALYSIS 1875
X. REPORTING RESEARCH RESULTS 1877
XI. SPECIAL CONCERNS FOR SPECIFIC STUDIES 1878
1. BEHAVIORAL AND PHYSIOTHERAPY TRIALS 1878
a) Terminology 1878
b) Behavioral interventions 1878
c) Lifestyle interventions 1878
d) Physiotherapy 1878
e) Biofeedback 1879
f) Conservative interventions/treatments 1879
g) Reporting of trial characteristics 1879
h) Adherence vs effectiveness 1880
i) Adverse events and cost 1880
j) Outcome measures 1880
k) Specific and non-specific effects 1880
l) Power calculations and number of participants 1880
m) Long term studies 1881
2. EXPERIMENTAL DEVICES AND MATERIALS 1881
a) Randomisation 1881
b) Adoption by clinicians 1881
c) Recruitment procedures 1881
3. SURGICAL STUDIES 1882
4. PHARMACOTHERAPY TRIALS 1883
XII. COST ANALYSIS 1884
XIII. RECOMMENDATIONS FOR SPECIFIC PATIENT GROUPS 1884
1. MEN WITH LUTS 1884
2. WOMEN WITH LUTS 1885
a) Hormonal effects 1885
b) Obstetric History 1885
c) Pelvic Organ Prolapse 1885
3. FRAIL OLDER AND DISABLED PEOPLE 1886
4. CHILDREN 1886
5. NEUROGENIC POPULATIONS 1887
a) Classification 1887
b) History and evaluation 1887
c) Urodynamics 1888
6. RECOMMENDATIONS FOR RESEARCH IN POPULATIONS AFFECTED BY FAECAL INCONTINENCE 1888
7. RECOMMENDATIONS FOR RESEARCH IN POPULATIONS AFFECTED BY BLADDER PAIN SYNDROME (INCLUDING INTERSTITIAL CYSTITIS) 1888
8. RECOMMENDATIONS FOR RESEARCH IN POPULATIONS AFFECTED BY PELVIC ORGAN PROLAPSE 1888
XIV. CONCLUSIONS 1888
REFERENCES